National Clinical Guideline Centre

Draft for consultation, December 2014

# Type 1 diabetes in adults

## Type 1 diabetes: diagnosis and management of type 1 diabetes in adults

*Clinical guideline <...>*

*Appendix G*

*December 2014*

*Draft for consultation*

*Commissioned by the National Institute for Health and Care Excellence*

Royal College of Physicians | The Royal College of Surgeons of England | Royal College of General Practitioners | Royal College of Nursing | NICE accredited

**Disclaimer**
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.



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# Appendix G: Clinical evidence tables

## G.1 Diagnosis

### G.1.1 Distinguishing between different types of diabetes

#### G.1.1.1 Population: Adults only (n≥50)

**Table 1: AMROUCHE 2008 (100)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Ch Amrouche, H. Jamoussi Kamoun, N. Trabelsi, and S. Blouza Chabchoub. Latent autoimmune diabetes in Tunisian adults (LADA): identification of autoimmune markers. *Tunis Med* 86 (4):316- | Observational: cross-sectional study<br><br>Tunisian study | Total N=100 T2D<br><br>**Inclusion criteria:**<br>• T2D<br>• Age at disease onset >30 years<br>• Insulin Tx required >6 months to 1st 6 years after Dx<br>• Insulin required after failure of oral therapy<br>• Spontaneous ketosis under maximal doses of a-diabetic oral Tx<br><br>**Exclusion criteria:**<br>• Age >80 yrs<br>• Diabetes caused by any | • ADULTS<br>• DIABETES TYPE:<br>○ T2D | | • **T2D:**<br>○ GADA<br>○ IA-2<br>○ ICA<br><br>**Cut-offs for positivity**<br>None given | n/a | **T2D** | | **Funding:** None mentioned<br><br>**Risk of bias:**<br>• n/a |
| | | | | **T2D** N=107 | | | GADA+ | 18% | |
| | | | | | | | IA-2, % | 42% | |
| | | | | | | | ICA, % | 49% | |
| | | | Age, years (SD) | 53 (10.5) | | | Presence of GAD65 was SS higher when ICA was absent | | |
| | | | Age at onset of diabetes, years (SD) | 43.4 (10) | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| 318, 2008.<br><br>REF ID: AMROUCHE 2008 | | endocrinopathy or pancreatopathy<br>• MODY or mitochondrial diabetes<br>• Diabetes with chromosomal abnormalities<br>• Ketoacidosis within 1st 6 months of diabetes<br>• Insulin requirement after 6 yrs of diabetes<br>• Any other indication of insulin Tx | | | | | |

**Table 2: ANDERSEN 2014 xxxxx (318)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| M. K. Andersen, M. Sterner, T. Forsen, A. Karajamaki, O. Rolandsson, C. Forsblom, P.-H. Groop, K. Lahti, P. M. Nilsson, L. Groop, and T. Tuomi. Type 2 diabetes susceptibility gene variants | Observational : cross-sectional study<br><br>several Scandanavian registries used, but genotyping done on patients. | n=1317 adults<br>n=911 LADA<br>n=406 type 1 diabetes<br>(study also assessed non-diabetic controls – not included here)<br><br>Inclusion criteria:<br>LADA or type 1 diabetes<br>Diagnosis at >35 years of age<br>LADA diagnosis: GADA | ADULTS<br>DIABETES TYPE:<br>type 1 diabetes<br>LADA | | Type 1 diabetes:<br>Fasting C-pep<br><br>Cut-offs for positivity<br>C-pep: detection limit 0.01 nM | Baseline | Type 1 diabetes adults | | Funding: A number of non-pharma grants.<br><br>Risk of bias:<br>n/a |
| | | | | | | | fC-pep, nmol/litre | 0.04 | |
| | | | | | | | | | |
| | | | Type 1 diabetes adults<br>n=406 | | | | LADA adults | | |
| | | | Age | 55 years | | | fC-pep, nmol/litre | 0.73 | |
| | | | Age of onset | 45 years | | | | | |
| | | | Male | 48% | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| predispose to adult-onset autoimmune diabetes. Diabetologia 57 (9):1859-1868, 2014.<br><br>REF ID: ANDERSEN 2014 | | and sufficient B-cell function at time of diagnosis, indicated by no insulin treatment and/or C-peptide level >0.2 nmol/litre.<br>type 2 diabetes diagnosis: initial diagnosis of type 1 diabetes by treating physician, fasting C-peptide <0.2 nmol/litre at time of investigation, and initiation of permanent insulin treatment within 6 months from diagnosis.<br><br>Exclusion criteria: None given | HbA1c, % (SD) | 8.5% | | | | | |
| | | | LADA adults n=911 | | | | | | |
| | | | Age | 61 years | | | | | |
| | | | Age of onset | 56 years | | | | | |
| | | | Male | 53% | | | | | |
| | | | HbA1c, % | 7.5% | | | | | |

**Table 3: ARSLAN 2014 (319)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| D Arslan, A Merdin, D Tural, M Temizel, O Akin, S Gunduz, | Observational: retrospective case-series | n=52 type 1 diabetes | ADULTS<br>DIABETES TYPE:<br>type 1 diabetes | Type 1 diabetes:<br>GAD<br>ICA | At diagnosis | Type 1 diabetes adults | | Funding: None mentioned.<br><br>Risk of bias: |
| | | | | | | GAD+ and/or ICA+ | 62% | |
| | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A Murat Tatli, F Avci, and M Uysal. The effect of autoimmunity on the development time of microvascular complications in patients with type 1 diabetes mellitus. Med Sci Monit 20:1176-1179, 2014.<br><br>REF ID: ARSLAN 2014 | Turkey | Inclusion criteria:<br>type 1 diabetes (ADA criteria)<br>Developed microvascular complications(retinopathy, neuropathy, nephropathy)<br>Had been tested for markers: GAD, and ICA.<br><br>Exclusion criteria:<br>None given | | Type 1 diabetes adults n=52 | Cut-offs for positivity<br>Compared to reference range. | | | | n/a retrospective |
| | | | Age mean, (SD) | 34 years (8) | | | | | |
| | | | Male | 42% | | | | | |
| | | | Disease duration, range | 0-12 months | | | | | |

**Table 4: ARIKAN 2005 xxxxx (102)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| Ender Arikan, Tevfik Sabuncu, Esref M. Ozer, and Husrev Hatemi. The | Observational Cross-sectional study. Study carried out in | n=54 adult participants (39 females and 15 males) with type 2 diabetes | Adult with:<br>type 2 diabetes<br>LADA identified from GADA-positive patients. | Serum C peptide (nmol/litre)<br>GADA | Not stated | Patients who were GADA positive had significantly earlier diabetes onset age than did the GADA-negative patients. | Funding: Not given |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| clinical characteristics of latent autoimmune diabetes in adults and its relation with chronic complications in metabolically poor controlled Turkish patients with Type 2 diabetes mellitus. J.Diabetes Complications 19 (5):254-258, 2005.<br><br>REF ID: ARIKAN 2005 | Turkey | referred to a hospital due to poor glycaemic control. (n=37 type 2 diabetes and n=17 LADA – GAD+)<br><br>Inclusion criteria: None given<br>Exclusion criteria: None given | Classification of diabetes: GADA-positive patients were identified as LADA patients.<br><br>Comparison of the data between GADA-positive and – negative patients | | | (defined as LADA)<br><br>Cut-offs for positivity<br><br>Serum C-PEPTIDE: not given<br><br>GADA-positive: >1.5 U/ml | | GADA positive patients had significantly lower BMI and lower serum C-peptide value than the GADA-negative patients.<br><br>GAD+: 17/54 (31.5%) | Risk of bias: n/a |
| | | | | GAD+ (LADA) n=17 | GAD- (type 2 diabetes) n=37 | | | | |
| | | | Age (years) | 56.6± 6.7 | 59.8± 6.7 | | | | |
| | | | Age at onset, (years) | 45.1± 5.8 | 50.8± 8.0 | | | | |
| | | | Retinopathy (%) | 61.5 | 28.6 | | | | |
| | | | Nephropathy (%) | 84.6 | 50.0 | | | | |
| | | | Neuropathy (%) | 60.0 | 40.0 | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

**Table 5: BARKER 2014 xxxxx (300)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A. Barker, A. Lauria, N. Schloot, N. Hosszufalusi, J. Ludvigsson, C. Mathieu, D. Mauricio, M. Nordwall, B. Van Der Schueren, T. Mandrup-Poulsen, W. A. Scherbaum, I. Weets, F. K. Gorus, N. Wareham, R. D. Leslie, and P. Pozzilli. Age-dependent decline of beta-cell function in type 1 diabetes after diagnosis: a multi-centre longitudinal study. Diabetes Obes. Metab. 16 (3):262-267, 2014.<br><br>REF ID: BARKER 2014 | Observational: prospective case-series<br><br>7 European registries | n=1665 adults subgroup<br>Total n=3929 type 1 diabetes adults, young people, and children<br><br>Inclusion criteria:<br>type 1 diabetes (ADA and WHO criteria)<br><br>Exclusion criteria:<br>None given | ADULTS subgroup (age at onset >18 years)<br>DIABETES TYPE:<br>type 1 diabetes | | Type 1 diabetes:<br>Fasting C-pep<br>Stimulated C-pep (results not given in study due to very small number of stim C-pep mmts made)<br><br>Cut-offs for positivity<br>C-pep: detection limit 0.01 nM | Baseline, 1 and 5 years | Type 1 diabetes adults | | Funding: Centro Internazionale Studi Diabete.<br><br>Risk of bias:<br>n/a<br>lots of missing data at follow-up |
| | | | | Type 1 diabetes adults<br>n=1665 | | | Baseline f-C-pep, nM (SD) | 0.30 (0.38)<br>n=1655 | |
| | | | | | | | 1-year C-pep, nM (SD) | 0.30 (0.36)<br>n=455 | |
| | | | | | | | 5-year C-pep, nM (SD) | 0.17 (0.33)<br>n=202 | |
| | | | Age of onset (baseline) | Mean 29.3 years (SD 8.0) | | | | | |
| | | | Male | n=818 | | | | | |
| | | | HbA1c, % (SD) | 11.1 (2.8) | | | | | |

**Table 6: BODALSKA 2006 xxxxx (52)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| J. Bodalska-Lipinska, A. Szadkowska, and L. Markuszewski. Principles of diagnosis of latent autoimmune diabetes in adults (LADA). Diabetol.Dosw.Klin. 6 (2):69-74, 2006.<br><br>REF ID: BODALSKA 2006 | Observational cross-sectional study | n=56 participants with newly diagnosed type 2 diabetes were studied.<br><br>Inclusion criteria:<br>None given<br><br>Exclusion criteria:<br>None given | Adult with:<br>type 2 diabetes<br>Immune-mediated type 1 diabetes – Latent Autoimmune Diabetes in Adults (LADA)<br><br>13 female aged 19-62 years (46.4±12.9 years) and 43 men aged 23-67 years (46-9±9.9 years). | ICA: units JDF (Juvenile Diabetes Foundation)<br>GADab: arbitrary units (AU)<br>(IA-2ab)<br>FC peptide.<br><br>Cut-offs for positivity<br>ICA+: ≥ 5 j JDF<br><br>GADab: sens/spec 75.4% and 98%. Ninety nine percentile (5.2 AU) in control group was the threshold for negative results.<br><br>IA-2ab: sens/spec 60.5% and 99%. Ninety nine percentile (8.1 AU) in control group was the threshold for negative result.<br><br>Fasting plasma C- | Not stated | | | | Funding: Not given<br><br>Risk of bias:<br>n/a |
| | | | | | | Whole population (n=56) | | | |
| | | | | | | ICA+<br><br>Titre (JDF U) | n (%)<br><br>Mean ± SD<br>Range | 11/56 (19.6)<br><br>36.2±45.7<br>0-40 | |
| | | | | | | GAD+<br><br>Titre (AU) | n (%)<br><br>Mean ± SD<br><br>Range | 3/56 (5.3)<br><br>89.3±52.9<br>0-128 | |
| | | | | | | IA-2+<br><br>Titre (AU) | n (%)<br><br>Mean ± SD<br><br>Range | 3/56 (5.3)<br><br>36.2±45.7<br>0-89 | |
| | | | | | | C-peptide [pmol/ml] | Mean ± SD<br><br>Range | 1.05±0.94<br>0.32-2.7 | |
| | | | | | | The group of 14 patients, which did not meet the diagnostic standards of type 2 diabetes, was classified as immune-mediated type 1 diabetes | | | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| | | | | peptide: detection threshold was 0.025pmol/litre. | | | |

**Table 7: BELL 2004 xxxxx (108)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| David S. H. Bell and Fernando Ovalle. The role of C-peptide levels in screening for latent autoimmune diabetes in adults. Am.J.Ther. 11 (4):308-311, 2004.<br><br>REF ID: BELL 2004 | Observational cross-sectional study. | Total n=78 (n=39 LADA and n=39 type 2 diabetes).<br><br>Inclusion criteria for participants with LADA:<br>Insidious onset of diabetes after age 30<br>Initial diagnosis of type 2 diabetes so that insulin was not used in the 12 months after diagnosis<br>Presence of anti-GAD Abs<br><br>Exclusion criteria:<br>None given<br><br>Baseline characteristics<br>LADA (n=39) type 2 diabetes | Adult with:<br>type 2 diabetes<br>LADA. | Random serum C peptide<br>Anti-GAD antibody titre (GAD-GS)<br><br>Cut-offs for positivity<br><br>Random serum C-peptide: normal fasting range, 0.8-4.ong/dL | Not stated | LADA:<br><br>Mean C-peptide: 1.0±0.2 ng/mL (range, 0-4.3)<br><br>type 2 diabetes:<br>Mean C-peptide: 5.1 ± 0.4 ng/mL (range, 1.0-11.8 ng/mL).<br><br>SS difference from LADA<br><br>All participants with type 2 diabetes had a C-peptide level within or above the normal range. | Funding:<br>Not given<br><br>Risk of bias:<br>n/a |

| Reference | Study type | Number of patients | | | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | (n=39) | | | | | | |
| | | Age (y) | 60.1±1.9 | 60.1±1.69 | | | | | | |
| | | Duration of type 2 diabetes (y) | 10.0±1.9 | 10.6±1.0 | | | | | | |
| | | | | | | | | | | |

**Table 8: HAMPE 2013 (302)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| CS. Hampe, Murray E. Maitland, Lisa K. Gilliam, Thanh H. T. Phan, Ian R. Sweet, Jared R. Radtke, Vasile Bota, Bruce R. Ransom, and Irl B. Hirsch. High titres of autoantibodies to glutamate decarboxylase in type 1 diabetes patients: epitope analysis | Observational : cross-sectional study<br><br>USA | n=100 type 1 diabetes<br><br>Inclusion criteria:<br>Adults ≥18 years<br>Clinical diagnosis of type 1 diabetes<br>Sc insulin treatment<br><br>Exclusion criteria:<br><18 years<br>Serious illness affecting immune system<br>Immunosuppressive | Type 1 diabetes adults<br>DIABETES TYPE:<br>type 1 diabetes | | Type 1 diabetes:<br>GAD65<br><br>Cut-offs for positivity<br>GAD65 (high titre): at least 10x greater than median of entire cohort | n/a | Type 1 diabetes adults | | Funding: NIH and ADA.<br><br>Risk of bias:<br>n/a<br>no missing data |
| | | | Type 1 diabetes adults and young people<br>n=187 | | | | GAD65+ | 45% | |
| | | | Age median, (range) | 16 years (2 - 62) | | | GAD65+ patients titre, U/ml, median | 400 U/mL (range 142-250,000) | |
| | | | Male | n=44 | | | High titre (≥2000 U/mL) | n=10 | |
| | | | Disease duration, median (range) | 25 years (2-60) | | | There was NS correlation between GAD65 titre and age at onset, duration of diabetes, gender, or age at sampling. | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| and inhibition of enzyme activity. Endocr Pract 19 (4):663-668, 2013.<br><br>REF ID: HAMPE 2013 | | medication | Age at onset, median (range) | 16 years (2-62) | | | | | |
| | | | | | | | | | |
| | | | Drop-outs/missing data: none | | | | | | |

**Table 9: HAWA 2013 (303)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes (baseline) | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| MI. Hawa, Hubert Kolb, Nanette Schloot, Huriya Beyan, Stavroula A. Paschou, Raffaella Buzzetti, Didac Mauricio, et al and Action LADA consortium. Adult-onset autoimmune diabetes in Europe is | Observational: cross-sectional study<br><br>9 European countries | n=114 type 1 diabetes and n=377 LADA (total n=6156 patients met inclusion criteria and were then diagnosed)<br><br>Inclusion criteria:<br>Adult-onset diabetes<br>Age 30-70 years<br>Primary diabetes<br>Diagnosis in past 5 years<br>≥2 recorded f-blood glucose mmts ≥7 mmol/litre | ADULTS<br>DIABETES TYPE:<br>type 1 diabetes (started insulin at diagnosis, and all Ab+)<br>LADA (free of insulin >6 months post-diagnosis, and Ab+) | | | Type 1 diabetes:<br>GAD<br>IA-2A<br>ZnT8A<br><br>LADA:<br>GAD<br>IA-2A<br>ZnT8A<br><br>Cut-offs for positivity<br>Determined by using standard | n/a | Type 1 diabetes | | Funding: EU and DeveloGen<br><br>Risk of bias:<br>n/a<br>no missing data |
| | | | | Type 1 diabetes n=114 | LADA n=377 | | | GAD high titre | 79.8% | |
| | | | | | | | | GAD+/IA-2A+, and ZnT8A+ | 13.2% | |
| | | | | | | | | | | |
| | | | | | | | | LADA | | |
| | | | | | | | | GAD high titre | 78.5% | |
| | | | Age, years mean | 44.1 | 51.9 | | | GAD+/IA-2A+, and ZnT8A+ | 9.0% | |
| | | | M/F % | 52% | 50% | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes (baseline) | Comments |
|---|---|---|---|---|---|---|---|---|---|
| prevalent with a broad clinical phenotype: Action LADA 7. Diabetes Care 36 (4):908-913, 2013<br><br>REF ID: HAWA 2013 | | LADA = age 30-70 years with diabetes-associated auto-Abs, did not require insulin treatment for ≥ 6 months post-diagnosis<br>type 1 diabetes = diabetes and diabetes-associated auto-Abs, and Insulin started at diagnosis or ≤1 month.<br><br>Exclusion criteria:<br>Insufficient dataset<br>Current pregnancy<br>Renal disease with raised creatinine or proteinuria<br>Acute illness | Age at onset, mean years | 41.8 | 49.7 | curve end-point | | Type 1 diabetes patients vs. LADA:<br>type 1 diabetes were younger, lower age of onset.<br>NS difference in number of patients with high GAD titre. | |
| | | | BMI, mean | 25.6 | 28.6 | | | | |
| | | | Duration of disease, mean years | 1.93 | 2.37 | | | | |
| | | | Drop-outs/missing data: none | | | | | | |

**Table 10: HOPE 2013 (320)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| S. V. Hope, A. G. Jones, E. Goodchild, M. Shepherd, R. E. J. Besser, B. Shields, T. | Observational : cross-sectional study | n=191 type 2 diabetes<br><br>Inclusion criteria:<br>Insulin treated type | ADULTS<br>DIABETES TYPE:<br>type 2 diabetes | type 2 diabetes:<br>UCPCR<br><br>Cut-offs for | n/a | type 2 diabetes adults | | Funding: NIHR and other non-pharma sponsors. |
| | | | | | | UCPCR, ≤0.2 nmol/mmol | n=24 (13%) | |
| | | | | | | | | |
| | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| McDonald, B. A. Knight, and A. Hattersley. Urinary C-peptide creatinine ratio detects absolute insulin deficiency in Type 2 diabetes. Diabet Med 30 (11):1342-1348, 2013.<br><br>REF ID: HOPE 2013 | UK | 2 diabetes diagnosis: age ≥45 years, clinical diagnosis of type 2 diabetes, insulin treatment not started within 1 year of diagnosis<br><br>Exclusion criteria:<br>None reported | type 2 diabetes adults n=191 | | positivity<br>UCPCR: ≤0.2 nmol/mmol | | | | Risk of bias:<br>n/a<br>a few missing data (small, <10%) |
| | | | Age median, (IQR) | 73.5 years (67 - 78) | | | | | |
| | | | Male | 63% | | | | | |
| | | | Disease duration, median (IQR) | 13.5 years (9-19) | | | | | |
| | | | Age at onset, median (IQR) | 58 years (50 - 65) | | | | | |
| | | | Missing data: | n=3 | | | | | |
| | | | Drop-outs/missing data: none | | | | | | |

**Table 11: HUANG 2013 (304)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| G Huang, Yufei Xiang, Lingling Pan, Xia Li, Shuoming Luo, and Zhiguang Zhou. Zinc transporter 8 autoantibody (ZnT8A) could help differentiate | Observational: cross-sectional study<br><br>China – 46 centres | n=3062 type 2 diabetes newly diagnosed<br><br>Inclusion criteria:<br>Adults ≥30 years age at onset<br>Newly diagnosed (≤1 year)<br>type 2 diabetes | type 2 diabetes adults<br>DIABETES TYPE:<br>type 2 diabetes and LADA within the type 2 diabetes group | | type 2 diabetes and LADA:<br>GADA<br>IA-2A<br>ZnT8<br><br>Cut-offs for positivity<br>Healthy control | n/a | type 2 diabetes adults | | Funding: A number of non-pharma sources.<br><br>Risk of bias:<br>n/a<br>no missing data |
| | | | type 2 diabetes adults n=3062 | | | | ZnT8 | 1.99% | |
| | | | Age median, (range) | 51.3 years (30 - 88) | | | GADA | 6.43% | |
| | | | | | | | IA-2A | 1.96% | |
| | | | | | | | ZnT8+ /GADA+ | 0.20% | |
| | | | | | | | ZnT8+/IA-2A+ | 0.26% | |
| | | | | | | | GADA+/IA-2A+ | 0.32% | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| latent autoimmune diabetes in adults (LADA) from phenotypic type 2 diabetes mellitus. Diabetes.Metab .Res.Rev. 29 (5):363-368, 2013.<br><br>REF ID: HUANG 2013 | | (WHO criteria)<br>No incidence of ketosis or ketoacidosis within 6 months of disease onset<br>Insulin independence for ≥6 months<br><br>Exclusion criteria:<br>Secondary diabetes mellitus<br>Pregnant<br>Malignant disease | Male | n=1782 | group values used | | ZnT8+ /GADA+/IA-2A+ | 0.49% | |
| | | | | | | | For LADA diagnosis: ZnT8 and/or GADA | 7.74% | |
| | | | | | | | For LADA diagnosis: ZnT8 and/or IA-2A | 3.20% | |
| | | | Drop-outs/missing data: none | | | | For LADA diagnosis: GADA and or IA-2A | 7.58% | |
| | | | | | | | For LADA diagnosis: GADA and or IA-2A and or ZnT8 | 8.62% | |
| | | | | | | | There was a NS but declining trend in ZnT8 positivity with age. | | |

**Table 12: MAHADEB 2014 (305)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| YP. Mahadeb, D Gruson, Martin Buysschaert, and Michel P. Hermans. What are the characteristics of phenotypic type | Observational : cross-sectional study<br><br>USA | n=524 type 2 diabetes<br><br>Inclusion criteria:<br>type 2 diabetes (criteria of | type 2 diabetes adults<br>DIABETES TYPE:<br>type 2 diabetes | type 2 diabetes:<br>GADA<br><br>Cut-offs for positivity<br>GADA (high titre): | n/a | type 2 diabetes adults | | Funding: NIH and ADA.<br><br>Risk of bias: n/a<br>no missing data |
| | | | | | | GADA+ | 5.7% | |
| | | | | | | GADA+ patients titre, IU/litre, median (IQR) | 29.4 IU/litre (15.0 – 42.9) | |
| | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 2 diabetic patients with low-titre GAD65 antibodies? Acta Diabetol. 51 (1):103-111, 2014.<br><br>REF ID: MAHADEB 2014 | | Expert Committee on the Diagnosis and Classification of Diabetes)<br><br>Exclusion criteria:<br>None given | type 2 diabetes adults and young people<br>n=524 | | based on healthy individuals. LADA cases were considered as those with GADA titres >59UI/litre (UKPDS cut-off)<br><br>Low titre GADA+ = 10-59UI/litre (based on UKPDS and healthy individuals value in this study). | | There was NS difference between GADA+ and GADA- for age, and diabetes duration. | | consecutive recruitment |
| | | | Age mean | 65 years | | | | | |
| | | | Male | 66% | | | | | |
| | | | Disease duration, mean | 14 years (1SD 9 years) | | | | | |
| | | | | | | | | | |
| | | | Drop-outs/missing data: none | | | | | | |

**Table 13: MARASCHIN 2013 (306)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| JF Maraschin, LS Weinert, N Murussi, V Witter, T da Costa Rodrigues, ER Rossato, and SP Silveiro. Influence of age at diagnosis and duration of diabetes on the positivity of | Observational: cross-sectional study<br><br>Brazil | n=92 type 1 diabetes group<br>n=298 overall recruited in 3 different population groups (type 1 diabetes, healthy, gestational diabetes) | Type 1 diabetes adults<br>DIABETES TYPE:<br>type 1 diabetes | | Type 1 diabetes:<br>GADA<br>C-peptide<br><br>Cut-offs for positivity<br>GADA (high titre): based on the recruited group of healthy controls. | n/a | Type 1 diabetes adults | | Funding: FIPE.<br><br>Risk of bias: n/a<br>no missing data<br>consecutive recruitment |
| | | | | | | | GADA+ | n=44 (48%) | |
| | | | | | | | C-peptide, nmol/litre (SD) | 0.17 (0.03) | |
| | | | Type 1 diabetes adults<br>n=92 | | | | | | |
| | | | Age mean (SD) | 35 (10) years | | | | | |
| | | | Male | 53% | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| glutamic acid decarboxylase antibody in South-Brazilian type 1 diabetes mellitus. Ann.Clin.Biochem. 50 (patient 3):262-266, 2013.<br><br>REF ID: MARASCHIN 2013 | | Inclusion criteria:<br>type 1 diabetes group: clinical diagnosis based on history of documented DKA, insulin use up to 3 years after diagnosis, fasting baseline C-pep <0.3 nmol/litre.<br><br>Exclusion criteria:<br>None given | Disease duration, years, mean (SD) | 16 (9) | | | | | |
| | | | Age at diagnosis, mean (SD) | 20 (9) | | | | | |
| | | | BMI, kg/m2. Mean (SD) | 24 (3) | | | | | |
| | | | Drop-outs/missing data: none | | | | | | |

**Table 14: MURAO 2008 xxxxx (128)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| S Murao, S | Observational | Total n= 57 | ADULT (age>20 years) | LAD: | 5 years | LADA: A – (n=31) | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| Kondo, J Ohashi, Y Fujii, I Shimizu, M Fujiyama, K Ohno, et al. Anti-thyroid peroxidase antibody, IA-2 antibody, and fasting C-peptide levels predict beta cell failure in patients with latent autoimmune diabetes in adults (LADA)--a 5-year follow-up of the Ehime study. Diabetes Res.Clin.Pract. 80 (1):114-121, 2008.<br><br>REF ID: MURAO 2008 | study – prospective case-series | LADA.<br><br>n=42/57 completed the 5 year follow-up.<br><br>Inclusion criteria for LADA patients:<br>Presence of GADAb.<br>Without insulin therapy both at the time of registration and 12 months after the diagnosis.<br><br>Exclusion criteria:<br>None mentioned | DIABETES TYPE:<br>LADA<br><br>Age of LADA patients (n=57) according to the time of registration<br><br>Group A<br>Age at diabetes onset (years): 56.0 (50.5-59)<br><br>Group B<br>Age at diabetes onset (years): 58.5 (47-67)<br><br>Group C<br>Age at diabetes onset (years): 42 (41-57) | Fasting C-peptide<br>Postprandial C-peptide<br>GADAb<br>IA-2A<br><br>Cut-offs for positivity<br><br>Postprandial C-peptide: criterion for beta cell failure was <0.33 nmol/litre postprandial C-peptide<br><br>GADAb+: >1.5 u/ml<br><br>IA-2A: Not reported | follow up. | FC peptide (nmol/litre): 0.63 (0.42-0.77)<br>GADAb ≥ 10U/ml: 5<br>IA-2Ab alone: 0 (0.0)<br>LADA: B – (n=6)<br>FC peptide (nmol/litre): 0.82 (0.65-1.28)<br>GADAb ≥ 10U/ml: 1<br>IA-2Ab alone: 0. (0.0)<br>LADA: C – (n=5)<br>FC peptide (nmol/litre): 0.83 (0.77-0.93)<br>GADAb ≥ 10U/ml: 2<br>IA-2Ab alone: 1 (20.0) | Supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Science, Sports and Technology.<br><br>Risk of bias: n/a |

**Table 15: PASCHKE 2013 (307)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes (baseline) | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| A Paschke, Agata Grzelka, Agnieszka Zawada, and Dorota Zozulinska-Ziolkiewicz. Clinical characteristics and autoantibody pattern in newly diagnosed adult-onset autoimmune diabetes. Pol.Arch.Med. Wewn. 123 (7-8):401-408, 2013.<br><br>REF ID: PASCHKE 2013 | Observational: cross-sectional study<br><br>Poland | n=344 LADA<br><br>Inclusion criteria:<br>Newly diagnosed diabetes<br>diagnosis within ≤3 months before hospitalisation<br>Age of onset ≥18 years<br>Positivity for ≥1 anti-islet autoantibodies (ICA, GADA, IA-2A) ≥ 6 months post-diagnosis<br><br>Exclusion criteria:<br>None mentioned | ADULTS<br>DIABETES TYPE:<br>LADA (split by age at diagnosis) | | | LADA:<br>GAD<br>IA-2A<br>ICA<br>C-peptide<br><br>Cut-offs for positivity<br>Determined by using JDF reference sample | n/a | LADA | | Funding: None mentioned |
| | | | | Age <35 (but >18 years) n=278 | Age ≥35 n=66 | | | C-peptide, fasting, ng/ml (SD) | <35years: 1.15 (0.89)<br>>35 years: 1.06 (0.61) | |
| | | | | | | | | C-peptide, stimulated, ng, ng/ml (SD) | <35years: 2.14 (1.69)<br>>35 years: 1.59 (0.76) | |
| | | | | | | | | 1 Ab | n=64 (19%) | |
| | | | | | | | | 2 Abs | n=112 (33%) | |
| | | | | | | | | 3 Abs | n=168 (49%) | Risk of bias:<br>n/a<br>no missing data<br>retrospect data collection from patient records |
| | | | | | | | | GADA+ | 90.7% | |
| | | | | | | | | ICA | 79.1% | |
| | | | | | | | | IA-2A | 60.5% | |
| | | | Age at onset, years mean (SD) | 25.2 (4.9) | 42.6 (7.1) | | | The most common 2-Ab combination was GADA + ICA | | |
| | | | Male % | 68% | 55% | | | The presence of multiple auto-Abs was associated with younger age, lower fasting and stimulated C-pep, and shorter duration of symptoms. | | |
| | | | BMI, mean | 22.9 | 23.4 | | | | | |
| | | | Duration of disease, mean weeks (SD) | 8.2 (11.9) | 6.5 (5.2) | | | | | |
| | | | Drop-outs/missing data: none | | | | | | | |

**Table 16: ROGOWICZ 2014 (323)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A Rogowicz-Fontczak, D Zozulilska-Ziolkiewicz, Monika Litwinowicz, Pawel Niedzwiecki, Krystyna Wyka, and Bogna Wierusz-Wysocka. Are zinc transporter type 8 antibodies a marker of autoimmune thyroiditis in non-obese adults with new-onset diabetes? EUR.J.ENDOCRINOL. 170 (4):651-658, 2014.<br><br>REF ID: ROGOWICZ 2014 | Observational: cross-sectional study<br><br>Poland | n=80 diabetes (n=56 LADA)<br><br>Inclusion criteria:<br>Diagnosis of diabetes (WHO criteria)<br>Newly diagnosed<br>Non-obese<br>Caucasian race<br>Age 35 – 65 years.<br><br>Exclusion criteria:<br>BMI ≥30 kg/m2<br>Cancer<br>Hepatic failure<br>Diagnosed HepB or HepC virus<br>Renal failure<br>Chronic pancreatitis<br>Anaemia<br>Use of drugs affecting glucose metabolism<br>History of alcohol abuse | ADULTS<br>DIABETES TYPE:<br>LADA | | LADA:<br>GAD<br>ICA<br>IA-2A<br>ZnT8<br>Fasting C-peptide<br>Stimulated C-peptide<br><br>Cut-offs for positivity<br>ICA: >5 JDF units<br>GAD: >10 U/ml<br>IA-2A: >20 U/ml<br>ZnT8: WHO standard curve | At diagnosis | LADA adults | | Funding: Poznan University of Medical Sciences, Poland.<br><br>Risk of bias: n/a |
| | | | | LADA adults n=56 | | | Fasting C-pep, ng/ml (SD) | 1.1 (0.6) | |
| | | | Age mean | 42years | | | Stim C-pep, ng/ml (SD) | 1.7 (1.0) | |
| | | | Male | 59% | | | GADA+ | 83.9% | |
| | | | HbA1c, % (SD) | 11.4 (2.4) | | | ICA | 62.5% | |
| | | | | | | | IA-2A | 42.8% | |
| | | | | | | | ZnT8A | 33.0% | |
| | | | | | | | ZnT8+ /GAD+ | 84.2% | |
| | | | | | | | ZnT8+ /ICA+ | 89.4% | |
| | | | | | | | ZnT8+ /IA-2A | 47.3% | |
| | | | | | | | ZnT8-/GAD+ | 83.8% | |
| | | | | | | | ZnT8- /ICA+ | 51.4% | |
| | | | | | | | ZnT8- /IA-2A | 41.6% | |
| | | | | | | | Titres, median: | | |
| | | | | | | | GADA (U/ml) | 522.3 (ZnT8+)<br>282.8 (ZnT8-) | |
| | | | | | | | ICA (JDF) | 80 (ZnT8+)<br>20 (ZnT8-) | |
| | | | | | | | IA-2A (U/ml) | 19.1 (ZnT8+)<br>17.3 (ZnT8-) | |

**Table 17: ROH 2013 xxxxx (308)**

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MO Roh, Chan Hee Jung, Bo Yeon Kim, Ji Oh Mok, and Chul Hee Kim. The prevalence and characteristics of latent autoimmune diabetes in adults (LADA) and its relation with chronic complications in a clinical department of a university hospital in Korea. Acta Diabetol. 50 (2):129-134, 2013.<br><br>REF ID: ROH 2013 | Observational: retrospective case-series<br><br>Korea<br><br>patients were diagnosed based on the presence of GADA markers and so the useful data for this study is the titres of the | Total n=323<br>n=37 type 1 diabetes<br>n=17 LADA<br>n=268 type 2 diabetes<br><br>Inclusion criteria:<br>type 1 diabetes (insulin dependent < 6 months after diagnosis)<br>LADA (GADA+ but insulin independent during first 6 months from DX irrespective of age<br>type 2 diabetes (GADA- and insulin independent ≥6 months from | ADULTS<br>DIABETES TYPE:<br>LADA<br>type 1 diabetes<br>type 2 diabetes | | | | LADA:<br>Stim C-peptide<br>fC-PEPTIDE<br>GAD<br><br>Type 1 diabetes:<br>Stim C-peptide<br>fC-PEPTIDE<br>GAD<br><br>type 2 diabetes:<br>Stim C-peptide<br>fC-PEPTIDE<br>GAD<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): ≤0.6ng/ml<br>GADA+: not reported | n/a | Type 1 diabetes | | Funding: None mentioned |
| | | | | Type 1 diabetes n=37 | LADA n=17 | type 2 diabetes n=268 | | | GADA titre, U/ml, median (range) | 0.08 (0.01 – 91.9) | |
| | | | | | | | | | fC-peptide titre, ng/ml, median (range) | 0.33 (0.01 – 2.13) | |
| | | | | | | | | | StimC-petide titre, ng/ml, median (range) | 0.83 (0.01 – 7.22) | |
| | | | Age, years (SD) | 29 (10.7) | 40.2 (14.0) | 48.7 (16.1) | | | LADA | | Risk of bias:<br>n/a<br>no missing data<br>retrospect data collection from patient records |
| | | | | | | | | | GADA titre, U/ml, median (range) | 6.0 (1.5 – 114.85) | |
| | | | | | | | | | fC-peptide titre, ng/ml, median (range) | 0.39 (0.01 – 9.67) | |
| | | | Age at onset, years (SD) | 26.1 (11.4) | 32.8 (8.1) | 44.6 (13.8) | | | StimC-petide titre, ng/ml, median (range) | 0.62 (0.01 – 8.64) | |
| | | | | | | | | | type 2 diabetes | | |
| | | | Disease duration, years, | 1.5 (0-19) | 4 (0-17) | 1 (0-43) | | | GADA titre, U/ml, median (range) | 0.07 (0.01 – 1.41) | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | markers | diagnosis).<br><br>Exclusion criteria:<br>None given | median (range) | | | | | | fC-peptide titre, ng/ml, median (range) | 2.18 (0.01 – 14.3) | |
| | | | | | | | | | StimC-petide titre, ng/ml, median (range) | 5.33 (0.01 – 28.2) | |

**Table 18: SHISHIKURA 2014 (324)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| K. Shishikura, K. Tanimoto, S. Sakai, Y. Tanimoto, J. Terasaki, and T. Hanafusa. Association between skeletal muscle mass and insulin secretion in patients with type 2 diabetes mellitus. Endocr.J. 61 | Observational: cross-sectional study<br><br>Japan | n=138 type 2 diabetes<br><br>Inclusion criteria:<br>type 2 diabetes<br>Attending hospital for treatment<br><br>Exclusion criteria: | Adults<br>DIABETES TYPE:<br>type 2 diabetes | | type 2 diabetes:<br>Stimulated C-peptide<br><br>Cut-offs for positivity<br>C-peptide: not mentioned. | n/a | type 2 diabetes adults | | Funding: None mentioned<br><br>Risk of bias: n/a<br>no missing data<br>consecutive recruitment |
| | | | type 2 diabetes adults<br>n=138 | | | | Stim C-peptide, mg/mL | Male: 4.9<br>Female: 4.1 | |
| | | | Age mean | 62 years | | | | | |
| | | | Male | 62% | | | | | |
| | | | BMI | 25 kg/m2 | | | | | |
| | | | Medication use | None: 9%<br>Oral hypoglycaemic agent: 42% | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| (3):281-287, 2014.<br><br>REF ID: SHISHIKURA 2014 | | Detection of anti-GADA<br>History of gastrectomy<br>Using a cardiac pacemaker or implanted defibrillator<br>Use of steroid hormones<br>Renal insufficiency<br>cachexia | | Insulin: 23%<br>Agent + insulin: 25% | | | | | |
| | | | Drop-outs/missing data: none | | | | | | |

**Table 19: SORGJERD 2012 xxxxx (87)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| E. P. Sorgjerd, F. Skorpen, K. Kvaloy, K. Midthjell, and V. Grill. Time dynamics of autoantibodies | Observational: prospective case-series study<br><br>Nord- | HUNT 2: n=120 type 1 diabetes and n=120 LADA. | Adult with:<br>type 1 diabetes<br>LADA<br>type 2 diabetes<br><br>Classification of diabetes: | FC-peptide,<br>GADA<br>IA-2A (the latter only in HUNT3). | Prospective data obtained (HUNT2 to HUNT3; 10-13 years | Pattern of antibody positivity in LADA influences phenotype: 17/161 LADA cases were positive for antibodies other than GADA.<br>1/17 of these cases was GADA-. LADA cases positive | Funding: The Liaison committee of the Central Norway Regional |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: the HUNT study, Norway. Diabetologia 55 (5):1310-1318, 2012.<br><br>REF ID: SORGJERD 2012 | Trondelag county in Norway | HUNT 3: n=147 TID and 85 LADA<br><br>HUNT2 and HUNT3: n=302 type 2 diabetes.<br>The HUNT study consists of three health surveys performed in 1984-1986 (HUNT 1), 1995-1997 (HUNT2) and 2006-2008 (HUNT3). The cases that formed the basis of this analysis were collected from HUNT2 and HUNT3 surveys.<br><br>Adult | type 1 diabetes if they started insulin treatment within 12 months of diagnosis and were: (1) antibody-positive, or (2) antibody-negative but with fasting C-peptide levels<150pmol/litre.<br>Type 1 diabetes cases were divided into two subgroups based on the median onset, which was 24 years. Groups were termed young-onset type 1 diabetes and adult-onset TID.<br>LADA if they were antibody positive and had not been treated with insulin within 12 months of diagnosis. No age limit was set for LADA.<br>type 2 diabetes if GADA-negative and had not been treated with insulin within 12 months of diagnosis.<br><br>Comparison of clinical characteristics in HUNT2 for LADA patients who participated both in HUNT2 and HUNT3 and who became either antibody-negative or stayed antibody-positive at HUNT3 | Additional antibody measurements:<br>Serum samples from diabetic cases classified as LADA or type 1 diabetes were analysed for 1A-2A (if not done already in HUNT3) as well as for ZnT8A.<br>Serum samples from HUNT2 were used to analyse antibodies in cases classified as LADA and type 1 diabetes inn HUNT3 but with no diagnosis of diabetes in HUNT2.<br><br>Cut-offs for positivity<br><br>Fasting serum C- | follow-up) on 44 LADA, 59 type 1 diabetes and 302 type 2 diabetes cases from HUNT2 and 31 LADA and 24 type 1 diabetes incident cases from HUNT3 | for 2 or 3 Abs (10%, n=16) had a higher GADA titre (p<0.001) and higher non-fasting blood glucose (p=0.011) vs. those positive only for 1 Ab.<br><br>A majority of diagnosed LADA cases lose antibody positivity: After 10-13 years, in HUNT3, a majority of LADA cases (26 of 44, 59%) were now negative for all three antibodies.<br><br>Twenty eight cases out of 59 type 1 diabetes (47%) were already antibody-negative in HUNT2, whereas 31 cases (53%) were antibody-negative in HUNT3. In contrast to LADA, only three cases (6%) with type 1 diabetes who were positive in HUNT2 had lost positivity in HUNT3.<br><br>Comparing LADA patients who became antibody-negative with those with type 2 diabetes: LADA patients had less preserved C-peptide levels compared with those with type 2 diabetes (median [min-max]: 492 [30-1,354] vs 700.5 | Health Authority and the ntnu and the liaison committee of St Olav's Hospital Trust and the faculty of Medicine NTNU<br><br>Risk of bias:<br>n/a |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | population aged >20 years). No age limit was set for LADA.<br><br>Exclusion criteria:<br>None given | | | | PEPTIDE: <150 pmol/litre<br><br>GADA-negative: Ab- index (ai) relative to a standard serum. Lower limit was 0.01 ai; no upper limit was defined. An index of ≥ 0.08 antibody index (ai) was considered positive.<br><br>IA-2A+: A value of ≥ 0.11 ai was considered positive (method range, 0.01-3.00 ai).<br><br>ZnT8A: A value of >0.08 ai was considered positive (method range >0.01ai) | | [30-2,059]; p=0.009). | | |
| | | | | Antibody-negative, HUNT3 n=26 | Antibody-positive, HUNT3 n=18 | | | Ab- HUNT3 | | |
| | | | Sex (male), % (n) | 46.2 (12) | 55.6 (10) | | | C-peptide (pmol/litre) | 492 (30-1,384) | |
| | | | Age at onset, (years) | 53.5 (42-75) | 44.5 (21-60) | | | GADA titre (ai) | 0.11 (0.08-0.46) | |
| | | | Duration of diabetes (years) | 7.5 (1-20) | 8.0 (1-43) | | | IA-2A titre (ai) | <0.01 (<0.01-0.07) | |
| | | | | | | | | ZnT8A titre (ai) | 0.01 (<0.01-0.04) | |
| | | | Clinical characteristics of incident LADA cases from HUNT3 who were either antibody-negative or antibody-positive in HUNT2. | | | | | Ab+ HUNT3 | | |
| | | | | | | | | C-peptide (pmol/litre) | 118.5 (30-588) | |
| | | | | | | | | GADA titre (ai) | 0.51 (0.07-2.43) | |
| | | | | | | | | IA-2A titre (ai) | 0.01 (<0.01-0.93) | |
| | | | | | | | | ZnT8A titre (ai) | 0.01 (<0.01-0.93) | |
| | | | | | | | | LADA Ab- | | |
| | | | | Antibody-negative | Antibody-positive | | | C-peptide (pmol/litre) | 986 (290-2,144) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n=10 | n=21 | | | | | |
| | | | Sex (male), % (n) | 50 (5) | 52.4 (11) | | | GADA titre (ai) | 0.12 (0.08-1.09) | |
| | | | | | | | | IA-2A titre (ai) | 0.018 (<0.01-0.06) | |
| | | | Age at onset, (years) | 70 (57-80) | 55 (31-79) | | | ZnT8A titre (ai) | <0.01 (<0.01-0.18) | |
| | | | | | | | | LADA Ab+ | | |
| | | | | | | | | C-peptide (pmol/litre) | 587 (48-1496) | |
| | | | | | | | | GADA titre (ai) | 1.17 (0.1-2.09) | |
| | | | | | | | | IA-2A titre (ai) | 0.02 (<0.01 to >3.0) | |
| | | | | | | | | ZnT8A titre (ai) | 0.01 (<0.01-0.46) | |

**Table 20: WILMOT 2013 (309)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| H. Wilmot-Roussel, D. J. Levy, C. Carette, S. Caillat-Zucman, C. Boitard, J. | Observational: cross-sectional<br><br>France | n=430<br><br>Inclusion criteria:<br>type 1 diabetes<br>At least 10 | Type 1 diabetes adults<br>DIABETES TYPE:<br>type 1 diabetes | Type 1 diabetes:<br>GAD<br>IA-2<br><br>Cut-offs for | n/a | Type 1 diabetes adults | | Funding: None mentioned<br><br>Risk of bias: n/a |
| | | | | | | No Ab+ | n=189 (44%) | |
| | | | | | | 1 Ab+ (GAD+ or IA-2+) | n=180 (42%) | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Timsit, and D. Dubois-Laforgue. Factors associated with the presence of glutamic acid decarboxylase and islet antigen-2 autoantibodies in patients with long-standing type 1 diabetes. Diabetes Metab. 39 (3):244-249, 2013.<br><br>REF ID: WILMOT 2013 | | years duration type 1 diabetes diagnosis: age <20 years, and/or presence of ketosis, and/or presence of autoAbs at onset of diabetes, and strict insulin dependency from onset.<br><br>Exclusion criteria:<br>None given | Type 1 diabetes adults n=92 | | positivity<br>Not mentioned. | | 2 Ab+ (GAD+ and IA-2+) | n=61 (14%) | no missing data<br>retrospect data collection consecutive patients in the centre |
| | | | | | | | ≥1 Ab+ | n=241 (56%) | |
| | | | Age median (range) | 33 (18 - 83) years | | | Among patients with a single detected AB+, GAD was SS more prevalent than IA-2 (71% vs 29%), p<0.0001 | | |
| | | | Male | n=206 | | | | | |
| | | | Disease duration, years, median (range) | 19 (10 - 65) | | | | | |
| | | | Age at diagnosis, median (range) | 12 (1 – 70) years | | | | | |
| | | | HbA1c %, median (range) | 7.9 (4.8 – 15.8) | | | | | |
| | | | Drop-outs/missing data: none | | | | | | |

**Table 21: ZAMPETTI 2012A xxxxx (310)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| S Zampetti, M | Observati | Total n=686 | ADULTS | LADA: | n/a | LADA | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Capizzi, M Spoletini, G Campagna, G Leto, L Cipolloni, C Tiberti, E Bosi, A Falorni, R Buzzetti, and NIRAD Study Group. GADA titre-related risk for organ-specific autoimmunity in LADA subjects subdivided according to gender (NIRAD study 6). J.Clin.Endocrinol. Metab. 97 (10):3759-3765, 2012.<br><br>REF ID: ZAMPETTI 2012A | onal: cross-sectional study<br><br>Italy (NIRAD cohort)<br><br>LADA patients were diagnosed based on the presence of GADA markers and so the useful data for this study is the titres of the markers | n=236 LADA<br>n=450 type 2 diabetes<br><br>Inclusion criteria:<br><br>Exclusion criteria:<br>None given | DIABETES TYPE:<br>LADA<br>type 2 diabetes | | | GAD<br>IA-2<br>ZnT8<br><br>type 2 diabetes:<br>GAD<br>IA-2<br>ZnT8<br><br>Cut-offs for positivity<br><br>IA-2+: not reported<br>ZnT8+: not reported<br>GADA+: 99th percentile of control subjects; low titre = ≤32 a.u.; high titre = >32 a.u. (32 a.u. = 300 WHO units) | | | | NovoNordisk, and ONLUS of Societa Italiana di Diabetologia.<br><br>Risk of bias: n/a<br>no missing data |
| | | | | LADA n=236 | type 2 diabetes n=450 | | | High GADA titre | n=116 | |
| | | | | | | | | Low GADA titre | n=120 | |
| | | | | | | | | IA-2 | n=98 (42%) | |
| | | | | | | | | ZnT8 | n=44 (32%) | |
| | | | Age at onset, years (SD) | 50.4 (12.9) | 51.6 (10.8) | | | type 2 diabetes | | |
| | | | | | | | | IA-2 | 13 (2.9%) | |
| | | | Male | n=123 | n=234 | | | ZnT8 | 7 (1.6%) | |
| | | | | | | | | | | |
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**Table 22: HILLMAN 2009 xxxxx (4)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| M. Hillman, C. Torn, M. Landin-Olsson, and DISS study group. The glutamic acid decarboxylase 65 immunoglobulin G subclass profile differs between adult-onset type 1 diabetes and latent autoimmune diabetes in adults (LADA) up to 3 years after clinical onset. Clin.Exp.Immunol. 157 (2):255-260, 2009. | Observational study (prospective case series). Participants recruited from a study in a defined area in southern Sweden. | Total n=83<br><br>TID: n=40<br>LADA: n=43<br><br>Inclusion criteria:<br>LADA:<br>newly diagnosed diabetes.<br>fulfilling the diagnostic criteria for LADA.<br>Age < 30 years<br>Classified phenotypically as type 2 diabetes<br>Positivity for GADA<br>Without insulin treatment for at least 6 months after clinical onset.<br>TID:<br>Adult onset patients (>18 | Adult with:<br>Adult onset type 1 diabetes<br>LADA<br><br>Clinical data of the subject at onset and C-peptide level 3 years after clinical onset. | | | Non-fasting C-peptide.<br>Total GADA<br>GADA IgG subclasses (IgG1, IgG2, IgG3, and IgG4).<br>GADA IgM<br>Cut-offs for positivity<br><br>Non-fasting C-PEPTIDE: Reference interval was 0.25-1.0 nmol/litre and detection limit was 0.13 nmol/litre.<br>Total GADA:<br><br>GADA IgG subclasses (IgG1, IgG2, IgG3, and IgG4).<br><br>GADA IgM | Prospective data obtained (HUNT2 to HUNT3; 10-13 years follow-up) on 44 LADA, 59 type 1 diabetes and 302 type 2 diabetes cases from HUNT2 and 31 LADA and 24 type 1 diabetes incident cases from HUNT3 | IgM and IgG subclasses in type 1 diabetes<br>SS decrease of mean rank in GADA levels (IgG1, IgG2, IgG3 and IgG4 and IgM levels).<br>The decreasing trend was NS in total GADA, even though the pattern was similar to the IgG1 subclass level. | Funding: The Swedish Medical Research Council and funds from Region Skane<br><br>Risk of bias:<br>n/a |
| | | | Median (min-max) | TIDM (n=40) | LADA (n=43) | | | IgM and IgG subclasses in LADA: SS decrease in GADA IgM levels 3 years after clinical onset, but no decrease in mean rank of any GADA IgG subclasses or total GADA. | |
| | | | Gender (male/female) | 26/14 | 23/20 | | | Comparison of levels between the groups:<br>LADA group SS >IgG3 and IgG4 at clinical onset vs. type 1 diabetes. The diff. between the groups increased further with longer duration for the IgG3 subclass, while the IgG4 subclass maintained approximately the same diff. between<br>the groups. A SS diff. in levels of IgG2 was seen after a year and sustained up to 3 years after diagnosis.<br><br>All the GADA IgG subclass levels decreased in the group of type 1 diabetes over time<br>GADA was more sustained in LADA | |
| | | | Age at clinical onset, (years) | 28 (18-65) | 36 (30-79) | | | | |
| | | | BMI at clinical onset (kg/m2) | 20.9 (15.2-25.4) | 25.6 (18.7-46.6) | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| REF ID: HILLMAN 2009 | | years).<br>Initiated on insulin treatment at diagnosis<br>Classified clinically as type 1 diabetes<br><br>Exclusion criteria:<br>None given | | | | patients over time | | |
| | | | | | | C-peptide levels in type 1 diabetes and LADA: C-peptide levels were SS lower in type 1 diabetes vs. LADA at clinical onset and after 3 years. Only LADA showed SS decrease over time. | | |
| | | | | | | Type 1 diabetes | | |
| | | | | | | C-pep (onset); nmol/litre | 0.22 (0.10-0.45) | |
| | | | | | | C-pep (3 years); nmol/litre | 0.12 (0.10-1.10) | |
| | | | | | | LADA | | |
| | | | | | | C-pep (onset); nmol/litre | 0.58 (0.38-2.80) | |
| | | | | | | C-pep (3 years); nmol/litre | 0.44 (0.1-2.90) | |

**Table 23: MCDONALD 2011 xxxxx (85)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| T.McDonald, K. Colclough, R. Brown, B. Shields, M. | Observational: cross-sectional study | Total n=616<br>n=98 type 1 diabetes – but adults | ADULTS<br>DIABETES TYPE:<br>type 1 diabetes<br>MODY | Type 1 diabetes:<br>GAD<br>IA-2 | n/a | Type 1 diabetes | | Funding: None mentioned |
| | | | | | | GAD+ | 24/98 (24.5%) | |
| | | | | | | IA-2+ | 19/98 (94.5%) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Shepherd, P. Bingley, A. Williams, A. Hattersley, and Sian Ellard. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet.Med. 28 (9):1028-1033, 2011.<br><br>REF ID: MCDONALD 2011 | UK study | and adolescents<br>n=508<br>MODY<br><br>Inclusion criteria:<br><br>Clinical history of diabetes<br>HbA1c <6.0%<br>MODY diagnosis by genetic testing<br>type 1 diabetes diagnosis in last 6 months<br><br>Exclusion criteria:<br>None given | | Type 1 diabetes n=98 | MODY n=508 | MODY:<br>GAD<br>IA-2<br><br>Cut-offs for positivity<br>GAD+: 64 WHO units/ml (99th percentile)<br><br>IA-2+: 15 WHO units/ml (99th percentile; lowest calibrator) | | GAD+ and/or IA-2+ | 80/98 (82%) | Risk of bias:<br>n/a |
| | | | | | | | | GAD+ and IA-2+ | 37/98 (37.8%) | |
| | | | Age, years, median (IQR) | 15 (12-25) | 36 (18-50) | | | MODY | | |
| | | | | | | | | GAD+ | 5 (1%) | |
| | | | | | | | | IA-2+ | 0 (0%) | |
| | | | Duration of diabetes, years, median (IQR) | < 6 months | 9 (4-25) | | | GAD+ and/or IA-2+ | 5/508 (1%) | |

**Table 24: SZEPIETOWSKA 2012 xxxxx (18)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| B Szepietowska, A Glebocka, U Puch, M Gorska, and M Szelachowska. Latent autoimmune diabetes in adults in a population-based cohort of Polish patients with newly diagnosed diabetes mellitus. Arch.Med.Sci. 8 (3):491-495, 2012.<br><br>REF ID: SZEPIETOWSKA 2012 | Observational: cross-sectional study<br><br>Polish study | Total n=205<br>n=19 LADA<br>n=186 type 2 diabetes<br><br>Inclusion criteria:<br>Age 20-65 years<br>Primary care physician and diabetologists identified diabetes cases during the study period<br><br>Exclusion criteria:<br>None given | ADULTS<br>DIABETES TYPE:<br>LADA<br>type 2 diabetes | | | LADA:<br>fC-PEPTIDE<br>GAD<br><br>type 2 diabetes:<br>fC-PEPTIDE<br>GAD<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): specificity 88%, sensitivity: 0.01 pmol/ml<br><br>GAD+: >1 U/ml | n/a | LADA | | Funding: Medical University of Bialystok<br><br>Risk of bias:<br>n/a |
| | | | | LADA n=19 | type 2 diabetes n=186 | | | fasting C-PEPTIDE, pmol/litre (SD) | 126.4 (127.9) | |
| | | | Age at diagnosis, years (SD) | 48.5 (9.4) | 54.8 (10.6) | | | GAD+ | 12/19 (63%) | |
| | | | M/F % | 49/51 | 55/45 | | | type 2 diabetes | | |
| | | | HbA1c, % (SD) | 7.9 (3.1) | 7.2 (1.7) | | | fasting C-PEPTIDE, pmol/litre (SD) | 446.3 (592.2) | |
| | | | | | | | | GAD+ | 2/186 (1%) | |

**Table 25: DAVIS 2003 xxxx (91)**

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T. M. E. Davis, Z. Mehta, I. R. Mackay, C. A. Cull, D. G. Bruce, S. Fida, M. J. Rowley, and R. R. Holman. Autoantibodies to the islet cell antigen SOX-13 are associated with duration but not type of diabetes. Diabet.Med. 20 (3):198-204, 2003.<br><br>REF ID: DAVIS 2003 | Observational: cross-sectional study<br><br>patients from 2 studies (FDS and UKPDS)<br><br>Europe (FDS) and UK (UKPDS) | Total n=879<br>FDS study<br>n=119 type 1 diabetes<br>n=427 type 2 diabetes<br>UKPDS study<br>n=333 type 2 diabetes<br><br>Inclusion criteria:<br>FDS study<br>Diabetic patients from one region<br>Taken subset of type 1 diabetes and type 2 diabetes from this.<br>Type 1 diabetes with baseline serum sample available<br>type 2 diabetes random 33% subset<br><br>UKPDS study<br>25-65 years<br>type 2 diabetes without significant vascular complications or other illness<br>Subset: random stratified | ADULTS<br>DIABETES TYPE:<br>type 1 diabetes<br>type 2 diabetes | | | | Type 1 diabetes (FDS):<br>GAD<br>IA-2/ ICA512<br><br>type 2 diabetes (FDS):<br>GAD<br>IA-2/ ICA512<br><br>type 2 diabetes (UKPDS):<br>ICA<br>GAD<br>IA-2/ ICA512<br><br>Cut-offs for positivity<br><br>Not given | n/a | Type 1 diabetes (FDS) | | Funding: Bayer Corp., USA<br><br>Risk of bias:<br>n/a |
| | | | | FDS study | | UKPDS | | | GAD+ | 49/119 (41%) | |
| | | | | Type 1 diabetes n=119 | type 2 diabetes n=427 | type 2 diabetes n=333 | | | IA-2 ( ICA512)+ | 21/119 (18%) | |
| | | | Age, years (SD) | 42.2 (15.6) | 64.5 (11.1) | 47.7 (10.0) | | | type 2 diabetes (FDS) | | |
| | | | M/F % | 43/57 | 57/43 | 56/44 | | | GAD+ | 17/427 (4%) | |
| | | | HbA1c, % median (IQR) | 8.6 (6.8-10.7) | 7.7 (6.2-9.6) | 7.1 (5.5-9.2) | | | IA-2 ( ICA512)+ | 1/427 (0.2%) | |
| | | | Disease duration, years, | 7.4 (1.8-30.4) | 4.3 (1.3-14.7) | 0.26 (0.23-0.31) | | | type 2 diabetes (UKPDS) | | |
| | | | | | | | | | ICA | 88/333 (26%) | |
| | | | | | | | | | GAD+ | 88/333 (26%) | |
| | | | | | | | | | IA-2 ( ICA512)+ | 26/333 (8%) | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | selection to obtain equal no's in the 4 age groups between 25-65, ratio 1:2 for patients GAD+ and/or ICA+ relative to patients Ab negative, and half of all patients requiring insulin treatment within 1st 6 years of diagnosis<br><br>Exclusion criteria: None given | median (IQR) | | | | | | | |

**Table 26: YANG 2008 xxxxx (107)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes (baseline) | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| L. Yang, Z. G. Zhou, S. Z. Tan, G. Huang, P. Jin, X. Yan, X. Li, H. Peng, and W. Hagopian. Carboxypeptidase-H autoantibodies differentiate a more latent subset of autoimmune diabetes from phenotypic type 2 diabetes among Chinese adults. Ann.N.Y.Acad.Sci. 1150:263-266, 2008.<br><br>REF ID: YANG 2008 | Observational: cross-sectional study and prospective<br><br>Chinese study | Total n=1710<br>n=209 type 1 diabetes<br>n=1296 type 2 diabetes<br>n=205 healthy controls<br><br>Inclusion criteria:<br>patients with phenotypic type 2 diabetes and classic type 1 diabetes and health controls<br><br>Exclusion criteria:<br>None given | ADULTS<br>DIABETES TYPE:<br>type 1 diabetes<br>type 2 diabetes | | | Type 1 diabetes:<br>GAD<br><br>type 2 diabetes:<br>fC-PEPTIDE<br>2hrC-PEPTIDE<br>GAD<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): not given<br><br>GAD+: 0.052 (99.5% upper limit) | 3 years but cannot use data<br><br>(in patients with fC-PEPTIDE >250 pmol/litre) | Type 1 diabetes | | Funding: National Natural Science Foundation of China; Eli Lilly Asia, Doctorate Foundation of National Ministry of Education<br><br>Risk of bias:<br>n/a |
| | | | | Type 1 diabetes<br>n=209 | type 2 diabetes<br>n=1296 | | | GAD+ | 11/209 (5.3%) | |
| | | | Age, years (SD) | Adults | Adults | | | type 2 diabetes | | |
| | | | M/F % | Not given | | | | GAD+ | 117/1296 (9%) | |
| | | | HbA1c, % (SD) | Not given | | | | | | |

**Table 27: CERNA 2003 xxxxx (34)**

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M. Cerna, P. Novota, K. Kolostova, P. Cejkova, E. Zdarsky, D. Novakova, P. Kucera, J. Novak, and M. Andel. HLA in Czech adult patients with autoimmune diabetes mellitus: comparison with Czech children with type 1 diabetes and patients with type 2 diabetes. Eur.J.Immunogenet. 30 (6):401-407, 2003.<br><br>REF ID: CERNA 2003 | Observational: cross-sectional study<br><br>Czech republic study<br><br>patients were diagnosed based on the presence of markers and so the useful data for this study is the titres of the markers | Total n=281<br>n=80 type 1 diabetes<br>n=70 LADA<br>n=131 type 2 diabetes<br><br>Inclusion criteria:<br>Diagnosis of diabetes after 35 years of age<br>F-C-PEPTIDE, GAD and IA-2 Abs measured at time of investigation | ADULTS<br>DIABETES TYPE:<br>LADA<br>type 1 diabetes<br>type 2 diabetes | | | | LADA:<br>fC-PEPTIDE<br>GAD<br>IA-2<br><br>type 1 diabetes:<br>fC-PEPTIDE<br>GAD<br>IA-2<br><br>type 2 diabetes:<br>fC-PEPTIDE<br>GAD<br>IA-2<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): ≥200 pmol/litre<br>GAD+: ≥50 ng/mL<br>IA-2+: ≥0.9 U/mL | n/a | Type 1 diabetes | | Funding: Ministry of Education, Youth and Sports of the Czech republic<br><br>Risk of bias: n/a |
| | | | | Type 1 diabetes n=80 | LADA n=70 | type 2 diabetes n=131 | | | fC-PEPTIDE, % and mean (range), pmol/litre | 100%<br>63 (4-197) | |
| | | | | | | | | | GAD, % and mean (range) ng/mL | 50%<br>193 (3-3000) | |
| | | | | | | | | | IA-2, % | 15% | |
| | | | Age, at disease onset, years mean (range) | 43 (36-56) | 52 (35-71) | 53 (35-81) | | | LADA | | |
| | | | | | | | | | fC-PEPTIDE, % and mean (range), pmol/litre | 100%<br>609 (51-2800) | |
| | | | | | | | | | GAD, % and mean (range) ng/mL | 100%<br>379 (210-1753) | |
| | | | M/F % | 39/61 | 43/57 | 42/58 | | | IA-2, % | 11% | |
| | | | | | | | | | type 2 diabetes | | |
| | | | Disease duration, years, mean (range) | 16 (4-27) | 14 (4-29) | 13 (1-22) | | | fC-PEPTIDE, % and mean (range), pmol/litre | 100%<br>772 (1-50) | |
| | | | | | | | | | GAD, % and | 0% | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Exclusion criteria:<br>None given | | | | | | | mean (range) ng/mL | 8 (202-3370) | |
| | | | | | | | | | IA-2, % | Not given | |

**Table 28: YDX STUDY: THANABALASINGHAM 2012 xxxxx (43)**

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| G Thanabalasingham, A Pal, MP. Selwood, C Dudley, K Fisher, PJ. Bingley, S Ellard, AJ. Farmer, MI. McCarthy, and KR. Owen. Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful | Observational: cross-sectional study<br><br>12 centres, UK | Total n=569<br>n= 247 type 1 diabetes<br>n=322 type 2 diabetes<br>(n=14 MODY from the 2 groups above)<br><br>Inclusion criteria:<br>Diagnosis of diabetes up to 45 years of | ADULTS<br>DIABETES TYPE:<br>MODY (taken from the type 1 diabetes and type 2 diabetes groups)<br>Type 1 diabetes<br>type 2 diabetes | | | | MODY:<br>random C-PEPTIDE<br>GAD<br><br>Type 1 diabetes:<br>rC-PEPTIDE<br>GAD<br><br>type 2 diabetes:<br>rC-PEPTIDE<br>GAD<br><br>Cut-offs for positivity | n/a | MODY | | Funding: NIHR, Diabetes UK, European Community and Oxford Hospitals charitable fund.<br><br>Risk of bias: n/a |
| | | | | | | | | | rC-PEPTIDE, % and mean (95% CI), nmol/litre | 100%<br>0.49 (0.17-0.81) | |
| | | | | | | | | | GAD+, N (%) | 3/14 (21%) | |
| | | | | MODY n=14/569 | Type 1 diabetes n=247 | type 2 diabetes n=277 (45 re-classed as LADA) | | | Type 1 diabetes | | |
| | | | Age, at diseas | 25.5 (20.3-30.7) | 23.5 (22.3-24.8) | 36.8 (35.9-37.7) | | | rC-PEPTIDE mean (range), nmol/litre | 0.08 (0.05-0.11) | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| strategy for identifying maturity-onset diabetes of the young. Diabetes Care 35 (6):1206-1212, 2012.<br><br>REF ID: THANABALASINGHAM 2012 | | age<br>Currently aged ≥18 years<br>Clinical diagnosis of type 1 diabetes or type 2 diabetes<br>MODY diagnosis from the type 1 diabetes and type 2 diabetes groups by genetic testing<br><br>Exclusion criteria:<br>None given | e onset, years mean (95% CI) | | | | C-PEPTIDE+ (random): ≥0.2 nmol/litre<br>GAD+: >14 WHO units/mL | | GAD, % | 58.7% | |
| | | | | | | | | | type 2 diabetes | | |
| | | | M/F % | 36/64 | 54/46 | 61/39 | | | rC-PEPTIDE, % and mean (range), nmol/litre | 100%<br>0.76 (0.70-0.83) | |
| | | | Disease duration, years, mean (95% CI) | 18 (9-26.6) | 12.5 (11.9-13.1) | 14.4 (13.1-15.8) | | | GAD, % | n=277 GAD- and n=45 GAD+ (GAD+ re-classified d as LADA) | |

**Table 29: HOSSZU 2003 xxxxx (12)**

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N Hosszufalusi, A Vatay, K Rajczy, Z Prohaszka, E Pozsonyi, L Horvath, A Grosz, L Gero, L Madacsy, L Romics, I Karadi, G Fust, and P Panczel. Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes | Observational: cross-sectional study<br><br>Hungarian study | Total n=301<br>n= 54 LADA<br>n= 57 type 1 diabetes<br>n=190 type 2 diabetes<br><br>Inclusion criteria:<br>LADA, type 1 diabetes or type 2 diabetes<br>Disease onset >25 years of age (adult onset)<br>LADA diagnosis if onset >35 years, any circulating ICA was detected (ICA, GADA or IA-2) and insulin treatment | ADULTS<br>DIABETES TYPE:<br>LADA<br>Type 1 diabetes<br>type 2 diabetes | | | | LADA:<br>fC-PEPTIDE<br>GAD<br>IA-2A<br>ICA<br><br>Type 1 diabetes:<br>fC-PEPTIDE<br>GAD<br>IA-2A<br>ICA<br><br>type 2 diabetes:<br>fC-PEPTIDE<br>GAD<br>IA-2A<br>ICA<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): not given<br>ICA+: >10 JDA units/mL | n/a | LADA | | Funding: Not mentioned |
| | | | | LADA n=54 | Type 1 diabetes n=57 | type 2 diabetes n=190 | | | fC-PEPTIDE at onset, nmol/litre, median (IQR) | 0.53 (0.24-1.40) | |
| | | | Age, years median (IQR) | 59.0 (47.5-67.0) | 44.5 (34.0-53.0) | 63.0 (53.0-72.0) | | | ICA+, % | 33 | |
| | | | M/F % | 46/54 | 53/47 | 54/46 | | | GADA+, % | 26 | |
| | | | Disease duration, years, median (IQR) | 4.0 (1.0-9.5) | 0.1 (0.1-4.5) | 8.0 (3.0-15.5) | | | IA-2A+, % | 0 | |
| | | | | | | | | | ICA+GADA+, % | 22 | Risk of bias: n/a |
| | | | | | | | | | ICA+IA-2+, % | 0 | |
| | | | | | | | | | GADA + IA-2+, % | 2 | |
| | | | | | | | | | ICA+GADA+IA2+, % | 17 | |
| | | | | | | | | | Antibody - , % | 0 | |
| | | | | | | | | | Type 1 diabetes (adult onset) – similar values for child onset | | |
| | | | | | | | | | fC-PEPTIDE at onset, nmol/litre, median (IQR) | 0.46 (0.24-1.05) | |
| | | | | | | | | | ICA+, % | 14 | |
| | | | | | | | | | GADA+, % | 9 | |
| | | | | | | | | | IA-2A+, % | 0 | |
| | | | | | | | | | ICA+GADA+, % | 19 | |
| | | | | | | | | | ICA+IA-2+, % | 2 | |
| | | | | | | | | | GADA + IA-2+, % | 3 | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| with rapid progression. Diabetes Care 26 (2):452-457, 2003.<br><br>REF ID: HOSSZU 2003 | | not indicated in 1st 6 months after diagnosis.<br><br>Exclusion criteria:<br>None given | | | | | GAD+: >1.2 units/mL<br>IA-2+: >1.3 units/mL | | ICA+GADA+IA2+, % | 32 | |
| | | | | | | | | | Antibody - , % | 21 | |
| | | | | | | | | | type 2 diabetes | | |
| | | | | | | | | | fC-PEPTIDE at onset, nmol/litre, median (IQR) | 1.23 (0.70-2.55) | |
| | | | | | | | | | ICA+, % | 3 | |
| | | | | | | | | | GADA+, % | 2 | |
| | | | | | | | | | IA-2A+, % | 0 | |
| | | | | | | | | | ICA+GADA+, % | 0 | |
| | | | | | | | | | ICA+IA-2+, % | 0 | |
| | | | | | | | | | GADA + IA-2+, % | 0 | |
| | | | | | | | | | ICA+GADA+IA2+, % | 0 | |
| | | | | | | | | | Antibody - , % | 95 | |

**Table 30: DAVIES 2008 xxxxx (88)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| H. Davies, S. Brophy, A. Fielding, P. Bingley, M. Chandler, I. Hilldrup, C. Brooks, and R. | Observational: cross-sectional study<br><br>32 centres, UK | Total n=597 (n=387 tested for all markers) | ADULTS<br>DIABETES TYPE:<br>LADA<br>type 2 diabetes | | | LADA:<br>fC-PEPTIDE<br>GADA<br>IA-2<br><br>type 2 diabetes: | n/a | LADA | | Funding: BUPA foundation<br><br>Risk of |
| | | | | | | | | fasting C-PEPTIDE, ng/ml, mean (SD) | 3.4 (2.6) | |
| | | | | | | | | GADA+ | 100% | |
| | | | | LADA | type 2 diabete | | | IA-2, WHO units, mean (SD) | 163.9 (441.2) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Williams. Latent autoimmune diabetes in adults (LADA) in South Wales: incidence and characterization. Diabet.Med. 25 (11):1354-1357, 2008.<br><br>REF ID: DAVIES 2008 | | n=14 LADA<br>n=373 (387-14) type 2 diabetes<br><br>Inclusion criteria:<br>Newly diagnosed type 2 diabetes<br>Age >18 years<br>Free of insulin treatment for at least 1 month from diagnosis<br>General practice patient records<br>LADA defined as GADA+ ≥14 WHO units/mL | | n=14 /387 tested | s n=646 | fC-PEPTIDE<br>GADA<br>IA-2<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): not mentioned<br><br>GADA+: sensitivity 84%, specificity: 92% (≥14 WHO units/mL)??<br><br>IA-2+: sensitivity 58%, spec: 98% | | type 2 diabetes | | bias:<br>n/a |
| | | | Age, years (SD) | 54.1 (17.4) | 60.8 (12.0) | | | fasting C-PEPTIDE, ng/ml, mean (SD) | 4.6 (3.0) | |
| | | | M/F % | 50/50 | 60/40 | | | GADA+ | 0% ??? | |
| | | | | | | | | IA-2, WHO units, mean (SD) | 2.2 (0.83) | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| | | Exclusion criteria:<br>Pregnant<br>Secondary diabetes | | | | | |

**Table 31: HAMAGUCHI 2004 xxxxx (125)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| K Hamaguchi, A Kimura, Y Kusuda, T Yamashita, M Yasunami, M Takahasi, N Abe, and H Yoshimatsu. Clinical and genetic characteristics of GAD-antibody positive patients initially diagnosed as having type 2 diabetes. Diabetes Res.Clin.Pract. 66 (2):163-171, 2004.<br><br>REF ID: HAMAGUCHI 2004 | Observational: cross-sectional study<br><br>Single centre, Japan | Total n=835 type 2 diabetes (screened for GAD+/-)<br><br>n=55 were GAD+ and n=780 were GAD-.<br>n=137 of the GAD- patients were assigned randomly to be the AGD- controls.<br><br>Inclusion criteria:<br>type 2 diabetes<br>Admitted to the clinic<br>Age of onset >30 years<br>Not require insulin treatment for at least 6 months after diagnosis<br><br>Exclusion criteria:<br>None given | ADULTS<br>DIABETES TYPE:<br>type 2 diabetes | | | type 2 diabetes:<br>GADA<br>Urinary C-PEPTIDE<br><br>Cut-offs for positivity<br>GAD+ : >5 Units | n/a | type 2 diabetes GAD+ | | Funding: Grants-in-Aid for Scientific Research and the Japan Society for the Promotion of Science, Japan.<br><br>Risk of bias:<br>n/a |
| | | | | type 2 diabetes | | | | GADA+ | 55/835 (6.6%) | |
| | | | | | | | | GAD titre, U/ml (SD; range) | 2,650 (18730; 5.0-139,000) | |
| | | | | GAD+ n=55 | GAD- n=137 | | | Urinary C-peptide, µg/day (SD) | 47.8 (48.9) | |
| | | | Age, years (SD) | 60.2 (12.3) | 62.9 (13.2) | | | type 2 diabetes GAD- | | |
| | | | M/F, % | 51/49 | 51/49 | | | Urinary C-peptide, µg/day (SD) | 58.1 (49.9) | |
| | | | Age at onset of diabetes, years (SD) | 47.7 (11.4) | 50.0 (12.5) | | | | | |
| | | | Disease duration, years, (SD) | 12.8 (8.6) | 13.3 (7.0) | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |

**Table 32: BOTTAZZO 2005 xxxxx (41)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| G. F. Bottazzo, E. Bosi, C. A. Cull, E. Bonifacio, M. Locatelli, P. Zimmet, I. R. Mackay, and R. R. Holman. IA-2 antibody prevalence and risk assessment of early insulin requirement in subjects presenting with type 2 diabetes (UKPDS 71). Diabetologia 48 (4):703- | Observational: cross-sectional study<br><br>UK study<br><br>UKPDS patients | Total n=4169 type 2 diabetes<br>(n=2556 measured all 3 Abs)<br><br>Inclusion criteria:<br>type 2 diabetes (new diagnosis)<br>Subset of UKPDS study (4169/5102)<br>Caucasians for whom IA2A and IA-2β were avail<br>Age 25-65 years<br>2 x fasting plasma glucose values >6.0 mmol/litre<br><br>Exclusion criteria:<br>Severe vascular disease, renal failure accelerated HT | ADULTS<br>DIABETES TYPE:<br>type 2 diabetes<br><br>type 2 diabetes (n=4169 | | | type 2 diabetes:<br>GADA<br>IA-2A<br>IA-2β<br>ICA<br><br>Cut-offs for positivity<br><br>IA-2A+: 1 Unit<br><br>IA-2 β+: 1 Unit<br><br>GADA+: 20 reference units (JDF)<br><br>ICA+: 5 JDF | n/a | type 2 diabetes All patients (n=4169) | | Funding: UK MRC; British Diabetic Association; British Heart Foundation; UK DH; Italian MoH; National Eye Institute; National Institute of Digestive; Diabetes and Kidney Disease in the NIH (USA); Novo-Nordisk; Bayer; Bristol Myers Squibb; Hoechst; |
| | | | IA-2A status | + n=93 | - n=4076 | | | IA-2A+ | 93 (2.2%) | |
| | | | | | | | | IA-2 β+ | 58 (1.4%) | |
| | | | | | | | | Only IA-2A+ | 42 (1%) | |
| | | | | | | | | Only IA-2 β+ | 7 (0.2%) | |
| | | | | | | | | IA-2A+ and IA-2 β+ | 51 (1.2%) | |
| | | | M/F % | 58/42 | 58/42 | | | type 2 diabetes patients measured for all 3 Abs (n=2556) | | |
| | | | | | | | | GADA+ | 257 (10%) | |
| | | | | | | | | ICA+ | 141 (5.5%) | |
| | | | | | | | | IA-2A+ | 57 (2.2%) | |
| | | | Age, years (SD) | 44 (11) | 53 (9) | | | 2 or 3 Abs + | 96 (3.8%) | |
| | | | | | | | | type 2 diabetes (n=268)<br>Required insulin by 6 years & all 3 Abs measured | | |
| | | | | | | | | IA-2A+ | 42/57 (74%) | |
| | | | | | | | | ICA+ | 75/141 (53%) | |
| | | | | | | | | GADA+ | 125/257 (49%) | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| 708, 2005.<br><br>REF ID: BOTTAZZO 2005 | | proliferative/pre-proliferative retinopathy<br>Other life-threatening disease<br>Illness requiring systemic steroids<br>Job precludes insulin treatment<br>Ketonuria >3 mmol/litre (that is, suggestive of type 1 diabetes) | | units | | IA-2A+/ICA+/GADA+ | 35/43 (81%) | Lilly, Lipha; Farmitalia Carlo Erba.<br><br>Risk of bias: n/a |
| | | | | | | IA-2A+ and ICA+ | 2/2 (100%) | |
| | | | | | | IA-2A+ and GADA+ | 3/6 (50%) | |
| | | | | | | Only IA-2A+ | 2/6 (33%) | |
| | | | | | | ICA+ and GADA+ | 34/45 (76%) | |
| | | | | | | Only ICA+ | 4/51 (8%) | |
| | | | | | | Only GADA+ | 53/163 (33%) | |
| | | | | | | IA-2A &/or ICA &/or GADA | 133/316 (42%) | |
| | | | | | | None+ | 135/2240 (6%) | |

**Table 33: CASTLEDEN 2006 xxxxx (92)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| H. Castleden, B. Shields, P. J. Bingley, A. J. K. Williams, M. Sampson, M. Walker, J. M. Gibson, M. I. McCarthy, G. A. Hitman, J. C. Levy, A. T. | Observational: cross-sectional study<br><br>7 centres, UK<br><br>Recruited through primary | Total n=2059 type 2 diabetes<br><br>Inclusion criteria:<br>type 2 diabetes<br>27-84 years<br>On pharma treatment for diabetes or had | ADULTS<br>DIABETES TYPE:<br>type 2 diabetes | | | type 2 diabetes:<br>GAD<br><br>Cut-offs for positivity<br>GAD+ : 30 WHO Units | n/a | type 2 diabetes | | Funding: Aspects funded by Diabetes UK and UK MRC.<br><br>Risk of bias: |
| | | | | type 2 diabetes | | | | GADA+ % | 136/2059 (7%) | |
| | | | | GAD+ n=136 | GAD- n=1876 | | | No difference in GAD+ titre level by age of diagnosis | | |
| | | | Age, years | 57 | 58 (9.7) | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Hattersley, B. Vaidya, and E. R. Pearson. GAD antibodies in probands and their relatives in a cohort clinically selected for Type 2 diabetes. Diabet.Med. 23 (8):834-838, 2006.<br><br>REF ID: CASTLEDEN 2006 | care or hospital diabetes clinics into the Diabetes UK/MRC familial and case type 2 diabetes genetic resource collection | biochem confirmation of diabetes.<br>To reduce the recruitment of type 1 diabetes, MODY and other subtypes, all subjects were diagnosed at >25 years of age and did not progress to insulin for at least 1 year after diagnosis and had no first degree relatives with type 1 diabetes.<br>All were UK or Irish or European Caucasian origin<br><br>Exclusion criteria:<br>None given | (SD) | (10.2) | | | | | | n/a |
| | | | M/F, % | 54/46 | 60/40 | | | | | |
| | | | Age at onset of diabetes, years (SD) | 47 (9) | 49 (8.6) | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

**Table 34: TRABUCCI 2012 xxxxx (134)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| A Trabucchi, NI. | Observational: | Total n=271 type 2 | ADULTS | type 2 diabetes: | 6 years but | type 2 diabetes | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Faccinetti, LL. Guerra, F M. P, Gustavo D. Frechtel, E Poskus, and SN. Valdez. Detection and characterization of ZnT8 autoantibodies could help to screen latent autoimmune diabetes in adult-onset patients with type 2 phenotype. Autoimmunity 45 (2):137-142, 2012.<br><br>REF ID: TRABUCCI 2012 | cross-sectional study and prospective<br><br>1 Centre, Argentina | diabetes<br><br>Inclusion criteria:<br>type 2 diabetes (Adult onset)<br>Age at diagnosis >30 years<br>Without insulin treatment for the first year of disease<br><br>Exclusion criteria:<br>None given | DIABETES TYPE:<br>type 2 diabetes (adult onset) | | GADA<br>IA-2A<br>ZnT8A<br><br>Cut-offs for positivity<br><br>ZnT8A+: SD score >3<br><br>GADA+: SD score but cut-off not given<br><br>IA-2A+: SD score but cut-off not given | cannot used data<br><br>n=101 patients followed for 6 years for insulin requirement, but measurement of Abs not given. | GADA+ | 21 (7.7%) | Grants from Agency for Science and Technology Promotion, National research Council, and University of Buenos Aires, Argentina.<br><br>Risk of bias:<br>n/a |
| | | | | type 2 diabetes n=271 | | | IA-2A+ | 3 (1.1%) | |
| | | | Age range | 30-84 | | | ZnT8A+ | 19 (7.0%) | |
| | | | Age at diagnosis diabetes, years (SD) | 53.4 (10.9) | | | GADA+/IA2A+ | 2 (0.7%) | |
| | | | M/F % | 62/48 | | | GADA+ /ZnT8A+ | 4 (1.5%) | |
| | | | | | | | IA2A+/ZnT8A+ | 1 (0.4%) | |
| | | | | | | | GADA+/ IA2A+/ZnT8A+ | 3 (1.1%) | |
| | | | | | | | None + | 211 (78%) | |

**Table 35: DESAI 2007 xxxxx (40) from the UKPDS study, follow-up of Davis 2005**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| M. Desai, C. A. Cull, V. A. Horton, M. R. Christie, E. Bonifacio, V. Lampasona, P. J. Bingley, J. C. Levy, I. R. Mackay, P. Zimmet, R. R. Holman, and A. Clark. GAD autoantibodies and epitope reactivities persist after diagnosis in latent autoimmune diabetes in adults but do not predict disease progression: UKPDS 77. Diabetologia 50 (10):2052-2060, 2007.<br><br>REF ID: DESAI 2007 | Observational: prospective case-series<br><br>UK study | Total n=242 LADA<br><br>Inclusion criteria:<br>Subset taken from UKPDS study<br>Subset was LADA patients (all GADA+) and all had plasma samples taken at 0.5, 3 and 6 years after diagnosis, with at least 1 being GADA+.<br><br>Exclusion criteria:<br>None given | ADULTS<br>DIABETES TYPE: LADA | | LADA:<br>GADA<br><br>Cut-offs for positivity<br><br>GADA+: 15 WHO units/ml | 6 years<br><br>Measured at 0.5, 3 and 6 years | LADA<br>GADA+ patients over time, N (%) | | Funding: Diabetes UK<br><br>Risk of bias:<br>n/a |
| | | | | LADA n=242 | | | Baseline | n=242 (100%) | |
| | | | | | | | 0.5 years | n=237 (98%) | |
| | | | | | | | 3 years | n=231 (95%) | |
| | | | | | | | 6 years | n=237 (98%) | |
| | | | Age, years (SD) | 47 (10.8) | | | LADA<br>GADA titre over time, WHO units/ml; median (IQR) | | |
| | | | M/F % | 53/47 | | | Baseline | - | |
| | | | | | | | 0.5 years | 331 (134-674) | |
| | | | | | | | 3 years | 199 (96-318) | |
| | | | | | | | 6 years | 284 (107-518) | |
| | | | | | | | Although the median titre rose at 6 years, patients who had high titres at 0.5 years remained high and those that had low titres remained low at 3 and 6 years. | | |

**Table 36: CHOWTA 2010 xxxxx (2)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| M. N. Chowta, P. M. Adhikari, N. K. Chowta, A. K. Shenoy, and S. D'Souza. Serum C peptide level and renal function in diabetes mellitus. Indian J.Nephrol. 20 (1):25-28, 2010.<br><br>REF ID: CHOWTA 2010 | Observational: cross-sectional<br><br>India study | Total n=168 type 2 diabetes<br><br>Inclusion criteria:<br>type 2 diabetes including newly diagnosed cases<br>Data taken from patients screened for participation in clinical trials on type 2 diabetes<br>>18 years of age<br><br>Exclusion criteria:<br>None given | ADULTS<br>DIABETES TYPE:<br>type 2 diabetes | | type 2 diabetes:<br>fC-PEPTIDE<br><br>Cut-offs for positivity<br><br>C-PEPTIDE (fasting):<br>Not given | Not mentioned | type 2 diabetes<br>C-peptide titre, nmol/litre (SD) | | Funding: None<br><br>Risk of bias:<br>n/a |
| | | | | type 2 diabetes n=168 | | | Baseline | 0.97 (0.05) | |
| | | | Age, years | 57.6 | | | There was a negative correlation between fC-PEPTIDE and duration of diabetes (r= -0.171, p>0.05)<br>Duration of disease was higher in patients with below normal fC-PEPTIDE compared to normal and above normal patients.<br><br>Indicative of progressive beta cell failure. | | |
| | | | M/F % | 46/54 | | | | | |
| | | | Duration of diabetes, years (SD) | 4.3 (0.45) | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

**Table 37: MONGE 2004 xxxxx (115)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| L. Monge, G. Bruno, S. Pinach, G. | Observational: cross-sectional study | Total n=220 type 2 diabetes | ADULTS | LADA:<br>fC-PEPTIDE | n/a | LADA | | Funding: Not mentioned |
| | | | | | | fasting C-PEPTIDE, nmol/ml, mean | 0.53 (0.51) | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| Grassi, G. Maghenzani, F. Dani, and G. Pagano. A clinically orientated approach increases the efficiency of screening for latent autoimmune diabetes in adults (LADA) in a large clinic-based cohort of patients with diabetes onset over 50 years. Diabet.Med. 21 (5):456-459, 2004.<br><br>REF ID: MONGE 2004 | Single centre, Italy | (met inclusion criteria)<br>n=70 LADA (32%)<br>n=150 (220-70) type 2 diabetes<br><br>Inclusion criteria:<br>type 2 diabetes<br>Age of onset >50 years<br>At least one of the following features suggestive of insulin deficiency: i) fasting blood glucose ≥15 mmol/litre and/or HbA1c ≥10% despite adequate compliance to diet and treatment; ii) decreasing body wt ≥10% | DIABETES TYPE:<br>LADA<br>type 2 diabetes | GADA<br>ICA<br><br>type 2 diabetes:<br>fC-PEPTIDE<br>GADA<br>ICA<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): normal values 0.36-1.17 nmol/litre<br><br>GADA65+: >0.9 units/mL<br><br>ICA+: ≥5 JDF units | | (SD)<br>GADA+/ICA+<br><br>Nmol/ml | <br>30/70 (43%)<br>fC-pep = 0.34 (0.28) | Risk of bias:<br>n/a |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| | | in previous 3 months despite constant diet; iii) BMI <25 mg/kg.<br><br>Exclusion criteria:<br>None given | | | | | | |

**Table 38: KIM 2007 xxxxx (14)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| C. S. Kim, M. K. Song, J. S. Park, M. H. Cho, H. J. Kim, J. S. Nam, E. S. Kang, C. W. Ahn, B. S. Cha, E. G. Lee, S. K. Lim, K. R. Kim, H. C. Lee, and K. B. Huh. The clinical and immunogenetic | Observational: cross-sectional study<br><br>Single centre, Korea | Total n=233 type 1 diabetes; patients with adult onset were analysed further (n=128)<br>n=35/128 LADA (32%)<br>n=93/128 type 1 diabetes<br>Acute onset<br><br>Inclusion | ADULTS<br>DIABETES TYPE:<br>LADA<br>Type 1 diabetes acute onset | | | LADA:<br>fC-PEPTIDE<br><br>Type 1 diabetes adult onset:<br>fC-PEPTIDE<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): not given | n/a | All n=233 Type 1 diabetes patients (child-onset, adult-onset)<br>n=105 child onset<br>n=128 adult onset ( n=35 LADA + n=93 acute onset)<br><br>GADA+ in 59.7% of all type 1 diabetes patients<br>GADA+ in 60% of child-onset type 1 diabetes<br>35/128 (27%) of adult onset type 1 diabetes patients were LADA.<br>0/105 (0%) of child onset type 1 diabetes patients were LADA.<br>IA-2A+ in 17.6% of all type 1 diabetes | Funding: Ministry of Health and Welfare, Korea<br><br>Risk of bias:<br>n/a |
| | | | | LADA n=35 | Type 1 diabetes acute n=93 | | | | |
| | | | Age, years (SD) | 46.4 (13.5) | 41.1 (13.8) | | | | |
| | | | Age at onset, years, | 41.3 (13.4) | 33.5 (11.3) | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| characteristics of adult-onset type 1 diabetes mellitus in Korea. Acta Diabetol. 44 (2):45-54, 2007.<br><br>REF ID: KIM 2007 | | criteria:<br>type 1 diabetes<br>Diagnosed as LADA if were GADA+ (>5 U/ml) and age at onset was >35 years, and did not initially (first 6 months) require insulin treatment.<br><br>Exclusion criteria:<br>None given | (SD) | | | GADA+: >1.0 micromole/ml<br><br>IA-2A+: mean+3SD of the control subjects | | IA-2A+ in 19.8% of child onset<br>IA-2A+ in 15.3% of adult onset | | |
| | | | | | | | | LADA | | |
| | | | Duration of diabetes, years (SD) | 5.1 (2.9) | 7.7 (6.1) | | | fasting C-PEPTIDE, micrograms/litre, mean (SD) | 0.83 (0.58) | |
| | | | | | | | | Type 1 diabetes acute | | |
| | | | | | | | | fasting C-PEPTIDE, micrograms /litre, mean (SD) | 0.55 (0.32) | |
| | | | M/F % | 49/51 | 39/61 | | | | | |

**Table 39: AGGARWAL 2010 xxxxx (60)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| S. Aggarwal, A. Goel, and A. Jain. Role of C-peptide in identification of patients suspected of | Observational: cross-sectional study | Total n=100 type 2 diabetes<br>n=34 suspected LADA<br>n=66 classic type 2 diabetes | ADULTS<br>DIABETES TYPE:<br>Suspected LADA<br>type 2 diabetes | | | Suspected LADA:<br>fC-PEPTIDE<br><br>Classic type 2 diabetes:<br>fC-PEPTIDE | 6 months | Suspected LADA<br>fasting C-PEPTIDE, ng/ml | | Funding: Not mentioned<br><br>Risk of |
| | | | | | | | | Baseline (SD)<br>n=66 | 0.39 (0.03) | |
| | | | | | | | | 6 months (SD)<br>n=44 | 0.33 (0.04) | |
| | | | | LADA | type 2 | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| having latent autoimmune diabetes in adults (LADA) in north indian type 2 diabetes mellitus population. Intl.J.Pharma Bio Sci. 1 (3), 2010.<br><br>REF ID: AGGARWAL 2010 | India study | Inclusion criteria:<br>type 2 diabetes<br>Age of diagnosis >25 years<br>Initial 6 months of insulin independence.<br>C-peptide <0.7 ng/ml was used to identify suspected LADA patients<br><br>Exclusion criteria:<br>History of ketoacidosis at time of initial diagnosis<br>Intake of diabetogenic drugs<br>Gestational diabetes<br>Other secondary causes of diabetes | | n=34 | diabetes n=66 | Cut-offs for positivity<br><br>C-PEPTIDE+ (fasting): not given<br>C-peptide <0.7 ng/ml was used to identify suspected LADA patients | | | | bias: n/a |
| | | | Age, years (SD; range) | Not given | | | | | | |
| | | | Age at diagnosis, years, (SD; range) | Not given | | | | Classic type 2 diabetes fasting C-PEPTIDE, ng/ml | | |
| | | | | | | | | Baseline (SD) n=34 | 1.54 (0.09) | |
| | | | | | | | | 6 months (SD) n=29 | 1.43 (0.01) | |
| | | | Duration of diabetes, years (SD; range) | Not given | | | | | | |
| | | | M/F % | 33/67 | 49/51 | | | | | |

**Table 40: ZHANG 2012A xxxxx (98)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| S Zhang, Q Sun, K Feng, Y Fu, O | Observational: cross-sectional study | Total n=102 diabetics<br>n= 11 LADA | ADULTS<br>DIABETES TYPE: | LADA:<br>fC-PEPTIDE | n/a | LADA | | Funding: Not mentioned |
| | | | | | | fC-PEPTIDE at presentation, | 16.3 (4.9) | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wang, F Ping, and Y Li. Clinical, biochemical, and immunological characteristics of newly diagnosed nonobese diabetic patients aged 18-45 years in China. J.Diabetes Complications 26 (1):40-43, 2012.<br><br>REF ID: ZHANG 2012A | Single centre, China | n= 70 type 1 diabetes<br>n=21 type 2 diabetes<br><br>Inclusion criteria:<br>Newly diagnosed diabetes (duration < 3 months)<br>Aged 18-45 years old with BMI <23 kg/m2.<br>Through clinical examination and follow-up they were diagnosed as type 1 diabetes, type 2 diabetes and LADA.<br>LADA diagnosed if: | LADA<br>Type 1 diabetes<br>type 2 diabetes | | | | GADA<br>IA-2A<br>ICA<br><br>Type 1 diabetes:<br>fC-PEPTIDE<br>GADA<br>IA-2A<br>ICA<br><br>type 2 diabetes:<br>fC-PEPTIDE<br>GADA<br>IA-2A<br>ICA<br><br>Cut-offs for positivity<br><br>Not given | | mmol/litre (SD) | | |
| | | | | LADA n=11 | Type 1 diabetes n=70 | type 2 diabetes n=21 | | | fC-PEPTIDE, ng/ml (SD) | 0.4 (0.2) | |
| | | | | | | | | | GADA+, % | 100 | |
| | | | | | | | | | IA-2A+, % | 27.3 | |
| | | | | | | | | | ICA+, % | 36.4 | Risk of bias:<br>n/a |
| | | | | | | | | | Type 1 diabetes | | |
| | | | Age, years mean (SD) | 42 (5.1) | 25 (6.6) | 35 (7.5) | | | fC-PEPTIDE at presentation, mmol/litre (SD) | 20.3 (8.8) | |
| | | | | | | | | | fC-PEPTIDE, ng/ml (SD) | 0.4 (0.3) | |
| | | | | | | | | | GADA+, % | 64.3 | |
| | | | M/F % | 55/45 | 46/54 | 48/52 | | | IA-2A+, % | 30 | |
| | | | | | | | | | ICA+, % | 45.7 | |
| | | | Age range, %<br>- 18-25<br>- 26-35<br>- 36-45 | <br>0<br>9<br>81 | <br>56<br>36<br>9 | <br>19<br>29<br>52 | | | GADA+ only | 14.3 | |
| | | | | | | | | | IA-2A+ only | 4.3 | |
| | | | | | | | | | ICA+ only | 7.1 | |
| | | | | | | | | | GADA+/ICA+ | 20 | |
| | | | | | | | | | GADA+/IA-2+ | 8.6 | |
| | | | | | | | | | ICA+/IA2+ | 4.3 | |
| | | | | | | | | | GADA+/ICA+/IA-2A+ | 4.3 | |
| | | | | | | | | | GADA+ and/or ICA+ | 75.7 | |
| | | | | | | | | | GADA+ and/or IA-2A+ | 74.3 | |
| | | | | | | | | | Antibody - , % | 18.6 | |
| | | | | | | | | | Abs by age-group, years % | | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| | | onset age >30 years, presence of circulating islet autoantibodies, lack of requirement for insulin for at least 6 months after diagnosis.<br><br>Exclusion criteria:<br>None given | | | | 18-25 / 26-35 / 36-45<br>GADA+ 64.1 / 60.0 / 66.4<br>ICA+ 61.5 / 29.2 / 16.7<br>IA-2A+ 38.5 / 20.8 / 16.7<br>type 2 diabetes<br>fC-PEPTIDE at presentation, mmol/litre (SD) 11.5 (4.5)<br>fC-PEPTIDE, ng/ml (SD) 1.4 (0.7)<br>GADA+, % 9.5<br>IA-2A+, % -<br>ICA+, % 4.8 | |

**Table 41: HWANGBO 2012 xxxxx (11)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| Y Hwangbo, J T Kim, E K Kim, A R Khang, T J Oh, | Observational: cross-sectional study | Total n=462 diabetics<br>n= 20 LADA<br>n= 442 type 2 diabetes | ADULTS<br>DIABETES TYPE:<br>LADA<br>type 2 diabetes | LADA:<br>fC-PEPTIDE<br>GADA | n/a | LADA<br>fC-PEPTIDE, ng/ml (SD) 1.2 (0.8)<br>GADA+, % 100 | Funding: Ministry of health and welfare, |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| H C Jang, K S Park, S Y Kim, H K Lee, and Y M Cho. Prevalence and clinical characteristics of recently diagnosed type 2 diabetes patients with positive anti-glutamic Acid decarboxylase antibody. Diabetes Metab. 36 (2):136-143, 2012.<br><br>REF ID: HWANGO 2012 | Single centre, Korea | Inclusion criteria:<br>>20 years of age<br>Diagnosed with diabetes in past 5 years<br><br>Exclusion criteria:<br>Type 1 diabetes<br>Other diabetes who started insulin therapy within 1 year after diabetes diagnosis<br>History of DKA<br>Pregnant<br>Chronic liver disease<br>Acute infection<br>History of organ transplantation<br>Current chemotherapy for malignancy<br>Other conditions that could affect glucose metabolism | | | | type 2 diabetes:<br>fC-PEPTIDE<br>GADA<br><br>Cut-offs for positivity<br><br>GADA+: >1.0 U/mL | | type 2 diabetes | | Republic of Korea.<br><br>Risk of bias:<br>n/a |
| | | | | LADA n=20<br><br>GAD+ | type 2 diabetes n=442<br><br>GAD- | | | fC-PEPTIDE, ng/ml (SD) | 2.0 (1.2) | |
| | | | | | | | | GADA+, % | 0 | |
| | | | Age at study, years mean (SD) | 52.3 (14.1) | 55.3 (11.6) | | | | | |
| | | | Age at onset, years, mean (SD) | 50.0 (14.4) | 53.6 (11.6) | | | | | |
| | | | Duration of diabetes, years, mean (SD) | 2.3 (1.3) | 1.7 (1.6) | | | | | |
| | | | M/F % | 60/40 | 56/44 | | | | | |

**Table 42: MAIOLI 2010 xxxxx (49)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| M. Maioli, G. M. Pes, G. Delitala, L. Puddu, A. Falorni, F. Tolu, R. Lampis, V. Orru, G. Secchi, A. M. Cicalo, et al. Number of autoantibodies and HLA genotype, more than high titres of glutamic acid decarboxylase autoantibodies, predict insulin dependence in latent autoimmune diabetes of adults. European journal of endocrinology 163 (4):541-549, 2010.<br><br>REF ID: MAIOLI 2010 | Observational: cross-sectional study<br><br>Multi-centre, Sardinia | Total n=5568 type 2 diabetes later diagnosed as:<br>n= 251 LADA<br>n= 2510 type 2 diabetes (randomly selected from the total recruited)<br><br>Inclusion criteria:<br>type 2 diabetes<br>35-70 years of age<br>Diagnosed with diabetes in past 5 years<br><br>Exclusion criteria:<br>Severe renal or liver disease | ADULTS<br>DIABETES TYPE:<br>LADA<br>type 2 diabetes | | | LADA:<br>GADA<br>IA-2<br><br>type 2 diabetes:<br>GADA<br><br>Cut-offs for positivity<br><br>GADA+: Not given (but based on health controls)<br><br>IA-2A+: Not given (but based on health controls) | n/a | Total type 2 diabetes recruited (n=5568) | | Funding: Italian Ministry for University and Research and Region of Sardinia grant.<br><br>Risk of bias: n/a |
| | | | | LADA n=251<br>GAD+ | type 2 diabetes n=2510<br>GAD- | | | GADA+ | 4.9% | | |
| | | | | | | | | | | | |
| | | | | | | | | LADA | | | |
| | | | | | | | | GADA+, % | 100 | | |
| | | | | | | | | IA-2+, % | 21 | | |
| | | | | | | | | | | | |
| | | | Age at study, years mean (SD) | 55.2 (11.6) | 58.1 (11.9) | | | type 2 diabetes | | | |
| | | | Age at diagnosis, years, mean (SD) | 54.3 (11.2) | 57.7 (10.1) | | | GADA+, % | 0 | | |
| | | | M/F % | 47/53 | 86/14 | | | | | | |
| | | | Duration of diabetes <8 months to 5 years<br>No evidence of DKA<br>Not had insulin treatment for at least 8 months from diagnosis | | | | | | | | |

**Table 43: VAZIRI 2010 xxxx (131)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| F Vaziri-Sani, S Oak, J Radtke, K Lernmark, K Lynch, CD. Agardh, CM. Cilio, AL. Lethagen, E Ortqvist, M Landin-Olsson, C Torn, and CS. Hampe. ZnT8 autoantibody titres in type 1 diabetes patients decline rapidly after clinical onset. Autoimmunity 43 (8):598-606, 2010.<br><br>REF ID: VAZIRI 2010 | Observational: cross-sectional study<br><br>Single centre, Sweden | Total n=47<br>LADA<br><br>Inclusion criteria:<br>LADA of type 2 diabetes<br>GAD65+<br>Age 30-70 years<br>Taken from those in a clinical trial of GAD65.<br>diagnosis within previous 5 years<br>Controlled blood glucose with diet, oral hypoglycaemic agents, or both, but not with insulin.<br><br>Exclusion criteria:<br>Women of child-bearing potential | ADULTS<br>DIABETES TYPE:<br>LADA | | LADA:<br>ZnT8<br>GADA<br><br>Cut-offs for positivity<br><br>GADA65: index of 0.04<br><br>ZnT8+: 10 and 18 U/ml (for T8R and T8W)<br><br>IA-2A: not given | n/a | LADA | | Funding: NIH; American Diabetes Association; EU framework Programme; Swedish Research Council; Swedish Diabetes Association<br><br>Risk of bias: n/a |
| | | | | LADA n=47 | | | GADA+ | 100% | |
| | | | Age at onset, years, median (range) | 30-70 | | | ZnT8+ (T8R or T8W) | 20/47 (42%) | |
| | | | Duration of diabetes, months (SD; range) | 3 (1-7) | | | | | |
| | | | M/F % | 83/17 | | | | | |

**Table 44: LINDHOLM 2004 xxxxx (135)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| E Lindholm, B Hallengren, and C D Agardh. Gender differences in GAD antibody-positive diabetes mellitus in relation to age at onset, C-peptide and other endocrine autoimmune diseases. Diabetes.Metab.Res.Rev. 20 (2):158-164, 2004.<br><br>REF ID: LINDHOLM 2004 | Observational: cross-sectional study<br><br>Swedish study | Total n=4974 diagnosed as:<br>n= 1078 type 1 diabetes (n=803 adults)<br>n= 3730 type 2 diabetes (n=4956)<br>The rest = other types<br><br>Inclusion criteria:<br>Diabetics from a local diabetes registry<br><br>Exclusion criteria:<br>Gestational diabetes<br>Impaired Glucose tolerance | ADULTS<br>DIABETES TYPE:<br>Type 1 diabetes<br>type 2 diabetes | | | Type 1 diabetes:<br>GADA<br><br>type 2 diabetes:<br>GADA<br><br>Cut-offs for positivity<br><br>GADA+: Not given (but based on health controls) | n/a | Type 1 diabetes | | Funding: Skane County Council R+D foundation; Lundbergs Medical Research Council; Malmo University Hospital Research funds; Swedish Diabetes Foundation |
| | | | | Type 1 diabetes n=1078 | type 2 diabetes n=3730 | | | GADA+ All adults | 407 (51%) | |
| | | | | | | | | GADA+ Age 20-39 years | 270/433 (62%) | |
| | | | | | | | | GADA+ Age 40-59 years | 112/152 (74%) | |
| | | | | | | | | GADA+ Age ≥60 years | 25/30 (83%) | |
| | | | | | | | | type 2 diabetes | | |
| | | | | | | | | GADA+ | 5.8% | |
| | | | Age at study, years mean (SD) | All adult ages | | | | | | Risk of bias: n/a |
| | | | Age at diagnosis, years, mean (SD) | Not given for group as a whole | | | | | | |
| | | | M/F % | Not given for group as a whole | | | | | | |

**Table 45: RADTKE 2009 xxxxx (5)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| MA. Radtke, K Midthjell, T I. L. Nilsen, and V Grill. Heterogeneity of patients with latent autoimmune diabetes in adults: linkage to autoimmunity is apparent only in those with perceived need for insulin treatment: results from the Nord-Trondelag Health (HUNT) study. Diabetes Care 32 (2):245-250, 2009.<br><br>REF ID: RADTKE | Observational: cross-sectional study<br><br>Norwegian study<br><br>HUNT study | Total n=1049 diagnosed as:<br>n= 943 type 2 diabetes<br>n= 106 LADA<br><br>Inclusion criteria:<br>Type 1 diabetes and LADA Diabetics from the HUNT2 study<br>Aged ≥20 years<br>Those who filled out questionnaires and had blood sampling and information on insulin treatment.<br><br>Exclusion | ADULTS<br>DIABETES TYPE:<br>type 2 diabetes<br>LADA | | | Type 1 diabetes:<br>fC-PEPTIDE<br>GADA<br><br>LADA:<br>fC-PEPTIDE<br>GADA<br><br>Cut-offs for positivity<br><br>GADA+: Index ≥0.08 (compared to standard serum) | n/a | type 2 diabetes – with insulin (n=203) | | Funding: Norwegian Diabetes Association; GSK Norway.<br><br>Risk of bias: n/a |
| | | | | | | | | f C-PEPTIDE+ pmol/litre (95% CI) | 377 (343-416) | |
| | | | | | | | | GADA+, units (SD) | 0.01 (0.01) | |
| | | | | | | | | type 2 diabetes – without insulin (n=740) | | |
| | | | | type 2 diabetes n=943 | LADA n=106 | | | f C-PEPTIDE+ pmol/litre (95% CI) | 787 (749-827) | |
| | | | | | | | | GADA+, units (SD) | 0.01 (0.01) | |
| | | | | | | | | LADA with insulin (n=42) | | |
| | | | Age at onset years, mean (SD) | 68 (0.6) | 67 (1.6) | | | f C-PEPTIDE+ pmol/litre (95% CI) | 130 (105-160) | |
| | | | | | | | | GADA+, units (SD) | 0.54 (0.03) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 2009 | | criteria:<br>type 1 diabetes<br>Other forms of diabetes | Diabetes duration, years, mean (SD) | 10.4 (0.4) | 11 (1.0) | | | LADA without insulin (n=64) | | |
| | | | | | | | | f C-PEPTIDE+ pmol/litre (95% CI) | 682 (577-806) | |
| | | | M/F % | 51/49 | 55/45 | | | GADA+, units (SD) | 0.29 (0.02) | |

**Table 46: LEE 2011A xxxxx (89)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| S. A. Lee, W. J. Lee, E. H. Kim, J. H. Yu, C. H. Jung, E. H. Koh, M. S. Kim, J. Y. Park, and K. U. Lee. Progression to insulin deficiency in Korean patients with Type 2 diabetes mellitus positive for anti-GAD | Observational: prospective case-series<br><br>Single centre, South Korea | Total n=174<br>type 2 diabetes<br>n= 87 GAD+<br>n= 87 GAD- (age and sex matched to GADA+)<br><br>Inclusion criteria:<br>type 2 diabetes outpatients<br>≥25 years of age at diagnosis<br>No history of | ADULTS<br>DIABETES TYPE:<br>type 2 diabetes (GAD+ and GAD-)<br><br>patients were recruited specifically for being GADA- and GADA+ | | | type 2 diabetes:<br>C-PEPTIDE<br>GADA<br><br>Cut-offs for positivity<br><br>GADA+: ≥25 WHO units/ml (≥1 IU/ml)<br><br>GADA+ HIGH titre: ≥250 WHO units/ml (≥10 IU/ml) | 6 years | type 2 diabetes GADA+ | | Funding: None mentioned |
| | | | | | | | | fC-PEPTIDE, nmol/litre (SD) | 0.7 (0.1) | |
| | | | | | | | | type 2 diabetes GADA- | | |
| | | | | | | | | f C-PEPTIDE+ pmol/litre (SD) | 0.7 (0.1) | |
| | | | | GADA- n=87 | GADA+ n=87 | | | OVER TIME<br>fC-PEPTIDE concentrations in the GADA+ and GADA- groups were similar at baseline.<br>In GADA- group fC-PEPTIDE did not change significantly over time<br>In GADA+ group fC-PEPTIDE declined over time and became significantly lower than in the | | |
| | | | Age years, mean (SD) | 54 (1.3) | 54 (1.3) | | | | | |
| | | | Age at onset years, mean (SD) | 48 (1.2) | 48 (1.2) | | | | | |
| | | | Diabetes duration, | 5.9 | 6.3 | | | | | Risk of |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| antibody. Diabet.Med. 28 (3):319-324, 2011.<br><br>REF ID: LEE 2011A | | DKA<br>fC-PEPTIDE ≥0.33 nmol/litre<br>Not using insulin<br>87 patient of the whole pool were GADA+<br>Randomly selected 87 age and sex-matched GADA- patients from the same pool of patients.<br><br>Exclusion criteria:<br>None mentioned | years, mean (SD) | (0.8) | (0.8) | | | GADA- group at 1 year and thereafter.<br>F-C-PEPTIDE concentrations were similar at baseline in high and low-titre GADA subgroups (0.6 and 0.7 nmol/litre respectively)<br>After 3 years fC-PEPTIDE became significantly lower in the HIGH titre subgroup tan the low titre group. | bias:<br>n/a |
| | | | GADA (WHO U/mL) | 3.9 (0.4) | 470 (121.0) | | | | |
| | | | GADA (IU/mL) | 0.2 (0.1) | 18.7 (4.8) | | | | |
| | | | M/F % | 57/43 | 57/43 | | | | |

**Table 47: VLAD 2004 xxxxx (113)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| A. Vlad, V. | Observational: | Total n=268 | ADULTS | type 2 diabetes: | n/a | fC-PEPTIDE | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Serban, Alexandra Sima, R. Timar, and Mihaela Rosu. The value of basal C peptide and its relationship with pancreatic autoantibodies in young adults with type 2 diabetes mellitus. Rom.J.Intern.Med. 42 (2):333-341, 2004.<br><br>REF ID: VLAD 2004 | cross-sectional study<br><br>Romanian study | type 2 diabetes<br><br>Inclusion criteria:<br>type 2 diabetes<br>Age of onset between 30 to 50 years<br>Duration of diabetes <5 years<br><br>Exclusion criteria:<br>None mentioned | DIABETES TYPE:<br>type 2 diabetes | | C-PEPTIDE<br>GADA<br><br>Cut-offs for positivity<br><br>fC-PEPTIDE+: normal range between 0.58 and 2.7 ng/ml<br><br>ICA+: 0.61 units of optical density<br><br>GADA+: 2.2 units of optical density | | LOW titre <0.58 ng/ml | n=20 (7.5%) | None mentioned |
| | | | | | | | NORMAL titre 0.58 - 2.7 ng/ml | n=155 (57.8%) | |
| | | | | | | | HIGH titre >2.7 ng/ml | n=93 (34.7%) | |
| | | | | type 2 diabetes n=268 | | | Mean fC-PEPTIDE was higher (2.62 ng/ml) in patients who were both GADA-/ICA- vs. those who were positive for at least one Ab (2.32 ng/ml).<br>However the difference was not SS (p=0.07).<br><br>AUTHORS' NOTE: the n=20 patients in the LOW Titre fC-PEPTIDE group probably represent LADA cases, in act type 1 diabetes.<br>Thus 7.5% of the type 2 diabetes patients may actually have type 1 diabetes. | | Risk of bias:<br>n/a |
| | | | Age at diagnosis, years, mean (SD) | 45 (4.5) | | | | | |
| | | | M/F % | 52/48 | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | fC-PEPTIDE+, nmol/litre (range) | 1.0 (0.5 – 5.1) | |
| | | | | | | | | | |
| | | | | Type 1 diabetes | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n=655 | | | | | |
| | | | Age, years, median (range) | 13.3 (11.1 – 15.7) | | | | | |
| | | | M/F % | 40/60 | | | | | |

### G.1.1.2 Population: Adults and young people (mixed population studies); N≥50

**Table 48: BESSER 2011 (311)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| R. Besser, J. Ludvigsson, A. Jones, T. McDonald, B. Shields, B. Knight, and A. Hattersley. Urine C-peptide creatinine ratio is a noninvasive alternative to | Observational : prospective case-series<br><br>Adults from diabetes clinic, UK; young people from paediatric | Total n=72 type 1 diabetes (mixture of young people and adults)<br><br>Inclusion criteria: Type 1 diabetes Young people (<19 years) and adults (≥18 years) Age of diagnosis: | YOUNG PPLE (n=21) & ADULTS<br>DIABETES TYPE: type 1 diabetes (n=72) | | | patients underwent a standard mixed-meal tolerance test (MMTT)<br><br>type 1 diabetes: C-PEPTIDE (serum, sCP) Urine C-peptide creatinine ratio (UCPCR)<br><br>sCP: collected at 0 and | N/A – immediate testing (up to 120 minutes) | type 1 diabetes (n=75)<br>Association between 90-min sCP (1) and both the MMTT 120-min UCPCR and after the home evening meal<br><br>In the paediatric cohort, correlations were also determined between AUC sCP and 120-min UCPCR. UCPCR cut-offs | Funding: Diabetes UK, Peninsula NIHR Clinical Research Facility, EC program Collaborative European Effort to Develop Diabetes |
| | | | | Young (n=21) | Adults (n=51) | | | | |
| | | | Age, years, median (IQR) | 14 (10.9-16.4) | 18 (13-24) | | | | |
| | | | M/F, % | 33/67 | 51/49 | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| the mixed-meal tolerance test in children and adults with type 1 diabetes. Diabetes Care 34 (3):607-609, 2011.<br><br>REF ID: BESSER 2011 | clinic, Sweden | <30 years<br>on insulin since diagnosis<br><br>Exclusion criteria:<br>known renal impairment (eGFR<60ml/min /1.73m2)<br>severe hypoglycaemic. within last 3 months<br>documented hypoglycaemia unawareness with a blood glucose <3mmol/litre, and HbA1c >10%. | Diabetes duration, years, median (IQR) | 2.6 (0.6-5.0) | 21.4 (2.8-41.0) | 90 min. Additional samples at 30, 60, and 120min in paediatric patients (n=18), allowing area under the curve (AUC) to be calculated. Urine was collected as a fasting second morning void immediately before the start of the MMTT (0 min) and after 120 min.<br>Significant endogenous insulin secretion was defined as 90-min sCP ≥0.2<br>nmol/litre, in accordance with the DCCT<br><br>Urine: collected in boric acid 120 minutes after evening meal following a pre-meal void. Adult patients took further home urine samples 120 min after a standard 60-g CHO breakfast and following the patients' own lunch. Urine | | equivalent to 90-min sCP ≥0.2 nmol/litre<br>were derived using linear regression equations.<br>UCPCR (120 min) following a home evening meal was compared with that after a MMTT.<br><br>RESULTS:<br>MMTT 120-min UCPCR was highly correlated to 90-min sCP (r = 0.97; p< 0.0001). UCPCR ≥0.53 nmol/mmol had 94% sensitivity/100% specificity for significant endogenous<br>insulin secretion (90-min sCP ≥0.2 nmol/litre). The 120-min postprandial evening meal UCPCR was highly correlated to 90-min sCP (r = 0.91; p< 0.0001). UCPCR ≥0.37 nmol/mmol had 84% sensitivity/97% specificity for sCP ≥0.2 | Diagnostics; arndiabetesfonden (The Swedish Child Diabetes Foundation) and the Swedish Research Council.<br><br>Risk of bias: n/a |
| | | | HbA1c, median (IQR), % | 7.2 (6.6-7.9) | 7.8 (6.9-9.0) | | | | |
| | | | To enrich for patients who had endogenous insulin secretion, 43% patients were either within 5 years of diagnosis or known to still secrete C-peptide when previously tested. | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| | | | | samples brought to the research centre within 24h. | | nmol/litre.<br><br>AUTHORS' CONCLUSIONS: UCPCR measured during an MMTT or after a home meal is highly correlated with MMTT sCP. UCPCR testing is a sensitive and specific method for detecting insulin secretion. UCPCR may be a practical alternative to serum C-peptide testing, avoiding the need for inpatient investigation. | |

**Table 49: BORG 2003 xxxx (42)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| H. Borg, H. J. Arnqvist, E. Bjork, J. | Observational: prospective case-series | Total n= 422 type 1 diabetes & | YOUNG PPLE & ADULTS DIABETES TYPE: | type 1 diabetes & type 2 diabetes:<br>ICA | 1 year | type 1 diabetes (n=285) | | Funding: Juvenile diabetes |
| | | | | | | ICA | N (%) = 143 (54) | |

| Reference | Study type | Number of patients | | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Bolinder, J. W. Eriksson, L. Nystrom, J. O. Jeppsson, and G. Sundkvist. Evaluation of the new ADA and WHO criteria for classification of diabetes mellitus in young adult people (15-34 years) in the Diabetes Incidence Study in Sweden (DISS). Diabetologia 46 (2):173-181, 2003. | Registry, Sweden | type 2 diabetes – n=285 type 1 diabetes, n=81 type 2 diabetes (mixture of young people and adults)<br><br>Inclusion criteria:<br>Patients aged 15-34 at diagnosis<br><br>Exclusion criteria:<br>None stated | type 1 diabetes (n=285)<br>type 2 diabetes (n=81)<br>Unclassified (n=85) | | GADA<br>GADA+ index<br>IA-2A<br>IA-2A index<br>Any antibody +<br>3 Ab<br>2 Ab<br>ICA & GADA<br>ICA & IA-2A<br>1 Ab<br>ICA<br>GADA<br>IA-2A<br>C-PEPTIDE<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+: 0.10 nmol/litre<br><br>ICA512/IA-2+: Index* of<br><br>IA-2A: Index* of 1.0<br>GADA+: Index* of 4.6 | | | | foundation-Wallenberg Diabetes research program, Lundstrom foundation, Novo-Nordisk foundation, Research funds of Malmo university hospital, faculty of medicine at Lund university, Albert Pahlson Foundation, Swedish Diabetes association |
| | | | | type 1 diabetes & type 2 diabetes | | | | | |
| | | | Age, years, median (IQR) | 25 (10) | | | IA-2A index | 91 (90) | |
| | | | | | | | Any antibody + | 220 (83) | |
| | | | M/F % | 254 (60%)/168 (40%) | | | 3 Ab | 89 (40) | |
| | | | | | | | 2 Ab | 74 (34) | |
| | | | | | | | ICA & GADA | 47 (21) | |
| | | | | | | | ICA & IA-2A | 6 (3) | |
| | | | | | | | GADA & IA-2A | 21 (10) | Risk of bias: n/a |
| | | | | | | | 1 Ab | 57 (26) | |
| | | | | | | | ICA | 1 (0.5) | |
| | | | | | | | GADA | 49 (22) | |
| | | | | | | | IA-2A | 7 (3) | |

| Reference | Study type | Number of patients | | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: BORG 2003 | | | | | ICA+: >4 JDF units<br><br>*INDEX = sample cpm – negative control cpm /positive control cpm - negative control cpm | | type 2 diabetes (n=81) | | |
| | | | | | | | ICA | 12 (15) | |
| | | | | | | | GADA | 16 (21) | |
| | | | | | | | GADA+ index | 72 (85) | |
| | | | | | | | IA-2A | 12 (15) | |
| | | | | | | | IA-2A index | 94 (101) | |
| | | | | | | | Any antibody + | 18 (23) | |
| | | | | | | | 3 Ab | 7 (39) | |
| | | | | | | | 2 Ab | 8 (44) | |
| | | | | | | | ICA & GADA | 3 (17) | |
| | | | | | | | ICA & IA-2A | 2 (11) | |
| | | | | | | | GADA & IA-2A | 3 (17) | |
| | | | | | | | 1 Ab | 3 (17) | |
| | | | | | | | ICA | 0 | |
| | | | | | | | GADA | 3 (17) | |
| | | | | | | | IA-2A | 0 | |
| | | | | | | | P-C-PEPTIDE: Carried out in patients that were tested for C peptide within 1 week after diagnosis<br>At diagnosis:<br>Undetectable (<0.10 nmol/litre):<br>Ab+: 30/123 (24.4%)<br>Ab-: 1/36 (2.8)<br>Low (<0.25 nmol/litre)<br>Ab+: 72/123 (58.5) | | |

| Reference | Study type | Number of patients | | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Ab-:2/36 (5.6)<br>Follow up:<br>Undetectable (<0.10 nmol/litre):<br>Ab+: 13/123 (10.6)<br>Ab-: 3/36 (8.3)<br>Among all Ab- patients, 13/93 had low fasting P-C Peptide (0.25 nmol/litre) and 12/13 had type 1 diabetes | |

**Table 50: FAN 2013 (301)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| H Fan, QingRong Pan, Pengrui Zhang, Jia Liu, Yuan Xu, and Xinchun Yang. Influence of islet function on typing and prognosis of new-onset diabetes after intensive insulin therapy. Med Sci Monit 19:787-793, 2013.<br><br>REF ID: FAN 2013 | Observational: prospective case-series<br><br>China | n=187 type 2 diabetes subgroup, n=19 type 1 diabetes subgroup (N<50 thus not using results)<br>Total n=206 type 1 diabetes and type 2 diabetes (n=214 originally recruited who were acceptable)<br><br>Inclusion criteria:<br>New onset diabetes (WHO criteria) and ketosis<br>type 2 diabetes patients did not require IIT to control blood glucose after initial honeymoon period (blood glucose controlled by diet and exercise for 2-5 weeks and normalised HbA1c levels <7%)<br><br>Exclusion criteria: | type 2 diabetes adults and young people subgroup<br>DIABETES TYPE:<br>type 2 diabetes | | type 2 diabetes:<br>GAD<br>IAA<br>ICA<br><br>Cut-offs for positivity<br>Not reported | Baseline, and 3 years (follow-up data not given for Abs) | type 2 diabetes adults + young people | | Funding: None mentioned.<br><br>Risk of bias:<br>n/a<br>some missing data at follow-up |
| | | | | type 2 diabetes adults and young people<br>n=187 | | | Baseline GAD+ | 4.8% | |
| | | | | | | | Baseline ICA+ | 3.2% | |
| | | | | | | | Baseline IAA+ | 10.6% | |
| | | | Age mean, (SD, range) | 43.6 years (5.7, 17-58) | | | 36 month follow-up data not given for Abs | | |
| | | | Male | n=107 | | | | | |
| | | | Disease duration, range | 0-12 months | | | | | |
| | | | HbA1c, %, range | 9.71 – 15.20 | | | | | |
| | | | BMI, kg/m2, range | Mean 26.89; range 19.56 – 31.22 | | | | | |
| | | | Drop-outs/missing data: n=8 due to unauthorised medication, withdrawn consent, and lost-to follow-up | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| | | Stress<br>Severe injured liver or kidney function<br>Diseases affecting the glucose metabolism | | | | | | |

**Table 51: LAADHAR 2007 xxxx (30)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| L. Laadhar, M. Zitouni, M. Kallel-Sellami, R. Bouguerra, H. Chaabouni, and S. Makni. Spectrum of autoantibodies in Tunisian adult type 1 diabetes mellitus. Ann.N.Y.Acad.Sci. | Observational: cross-sectional study<br><br>Single centre, Tunisia | Total n=261 type 1 diabetes<br><br>Inclusion criteria:<br>Clinical diagnosis of type 1 diabetes<br><br>Exclusion criteria:<br>None | ADULTS AND YOUNG PEOPLE<br>DIABETES TYPE:<br>type 1 diabetes | | type 1 diabetes:<br>fC-PEPTIDE<br><br>Cut-offs for positivity<br><br>ICA+: not given | n/a | type 1 diabetes (n=261) | | Funding: Not mentioned<br><br>Risk of bias:<br>n/a |
| | | | | | | | ICA+ | 88 (33.7%) | |
| | | | | | | | ICA+ in patients <1yr Diabetes | 47.7% | |
| | | | | | | | | | |
| | | | | type 1 diabetes n=261 | | | | | |
| | | | Age, years, mean (SD; range) | 29.1 (1.9; 16-60) | | | | | |
| | | | Age at diagnosis, years, mean (SD) | 20.3 (10.3) | | | | | |
| | | | M/F % | 48/52 | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 1107:356-362, 2007.<br><br>REFID: LAADHAR 2007 | | mentioned | | | | | | | |

**Table 52: LU 2014 (321)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes (baseline) | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| H Lu, F Hu, Y Zeng, L Zou, S Luo, Y Sun, H Liu, and L Sun. Ketosis onset type 2 diabetes had better islet beta-cell function and more serious insulin resistance. J Diabetes Res 2014:510643, 2014. | Observational: cross-sectional study<br><br>China | n=140<br><br>Inclusion criteria:<br>Newly diagnosed type 2 diabetes<br>Without islet-associated autoantibodies<br>Age 16-68 years<br>Diagnosis: WHO criteria<br>If had Plasma glucose >250 mg/ml and positive urine ketone | ADULTS and YOUNG PPLE<br>DIABETES TYPE:<br>type 2 diabetes | | | type 2 diabetes:<br>Fasting C-PEPTIDE<br><br>Cut-offs for positivity<br>AUC | n/a | type 2 diabetes adults and young people | | Funding: None mentioned<br><br>Risk of bias: n/a |
| | | | | | | | | f-C-PEP, pmol/litre (SD) | Ketosis group: 475.8 (406) | |
| | | | | | | | | | Non-ketotic group: 348.2 (283) | |
| | | | | | | | | | | |
| | | | | Ketosis onset type 2 diabetes | Non-ketotic onset type | | | | | |
| | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes (baseline) | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: LU 2014 | | body = diabetic ketosis diagnosis.<br><br>Exclusion criteria:<br>Evidence of other disease<br>Taking agents known to affect CHO metabolism<br>Obvious precipitating causes for the development of ketosis | | n=62 | 2 diabetes n=78 | | | | | |
| | | | Age, years mean | 44.8 | 47.0 | | | | | |
| | | | M/F % | 66 | 72 | | | | | |
| | | | BMI, mean | 25.0 | 24.4 | | | type 1 diabetes patients vs. LADA:<br>people with type 1 diabetes were younger, lower age of onset.<br>NS difference in number of patients with high GAD titre. | | |
| | | | HbA1c | 11.0% | 11.8 % | | | | | |
| | | | | | | | | | | |
| | | | Drop-outs/missing data: none | | | | | | | |

**Table 53: BRUNOVA 2002 xxxx (28)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| J. Brunova, J. Bruna, M. Koning, M. Meyer, G. Joubert, and W. Mollentze. | Observational: cross-sectional study | Total n=192 (n=55 type 1 diabetes and n=137 | ADULTS AND YOUNG PEOPLE<br>DIABETES TYPE:<br>type 2 diabetes<br>type 1 diabetes | | | type 1 diabetes:<br>GAD65<br><br>type 2 diabetes:<br>fC-PEPTIDE<br>GAD65 | n/a | type 1 diabetes (n=55) | | Funding: Not mentioned |
| | | | | | | | | GAD65+ | 17/55 (30.9%) | |
| | | | | | | | | | | |
| | | | | | | | | type 2 diabetes (n=137) | | |
| | | | | type 1 diabet | type 2 diabet | | | GAD65+ | 9/137 (6.6%) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| GAD65Ab and primary hypothyroidism in type 1 and 2 diabetic subjects. J.Endocrinol. Metab.Diabetes S.Afr. 7 (1):6-8, 2002.<br><br>REFID: BRUNOVA 2002 | Single centre, South Africa | type 2 diabetes)<br><br>Inclusion criteria:<br>Clinical diagnosis of type 1 diabetes and type 2 diabetes<br><br>Exclusion criteria:<br>None mentioned | | es n=55 | es n=137 | Cut-offs for positivity<br><br>fC-PEPTIDE+: not given<br><br>GAD65+: not given | | | | Risk of bias:<br>n/a |
| | | | Age, years, (range) | 13 – 85 years | | | | fC-PEPTIDE in GAD-patients, pmol/litre (SD) | 637.6 (503) | |
| | | | | | | | | fC-PEPTIDE in GAD-patients, pmol/litre (SD) | 1168.1 (732) | |
| | | | M/F % | 50/50 | | | | The presence of GAD65 in type 2 diabetes was associated with lower levels of fC-PEPTIDE | | |

**Table 54: OTA 2005 xxxx (126)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| T Ota, T Takamura, Y Nagai, Y Bando, and R Usuda. Significance of IA-2 antibody in Japanese type 1 diabetes: its association with GAD antibody. Diabetes Res.Clin.Pract. 67 (1):63-69, 2005.<br><br>REF ID: OTA 2005 | Observational: cross-sectional study | Total n=101 type 1 diabetes<br><br>Inclusion criteria:<br>type 1 diabetes classified by American diabetes association<br><br>Exclusion criteria:<br>None mentioned | ADULTS AND YOUNG PEOPLE<br>DIABETES TYPE:<br>type 1 diabetes | | type 1 diabetes:<br>C-PEPTIDE<br>GADA65<br>IA-2A<br><br>Cut-offs for positivity<br><br>ICA512/IA-2: 0.4 U/mL<br><br>GAD65+: 1.3 U/mL | n/a | type 1 diabetes (n=101) | | Funding: Not mentioned |
| | | | | type 1 diabetes n=101 | | | GAD65+ | n=60/101 (59%) | |
| | | | | | | | IA-2+ | 37/101 (37) | |
| | | | | | | | IA-2+/ GAD65- | 10 (10) | |
| | | | | | | | GAD65+/ IA-2+ | 27 (27) | |
| | | | Age, years, mean (range; SD) | 41.3 (14.0-89.0; 15.3) | | | GAD65+/IA-2- | 33 (32) | |
| | | | | | | | | | |
| | | | Duration of diabetes, years, mean (SD) | 10.4 (9.6) | | | | | |
| | | | | | | | Acute onset type 1 diabetes (n=64) | | Risk of bias: n/a |
| | | | | | | | IA-2 Ab+: GAD Ab concentration (U/mL) Mean (SD) | n=19<br>67.7 (97.2 ) | |
| | | | M/F % | 47/54 | | | IA-2 Ab-: GAD Ab concentration (U/mL) | n=45<br>31.1 (132.1) | |
| | | | | | | | GAD+: IA-2 Ab concentration (U/mL) | n=28<br>1.8 (3.0) | |
| | | | | | | | GAD-: IA-2 Ab concentration (U/mL) | n=36<br>1.0 (2.4) | |

**Table 55: RAJALAKSHMI 2014 (322)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| R Rajalakshmi, A Amutha, Harish Ranjani, Mohammed K. Ali, Ranjit Unnikrishnan, Ranjit Mohan Anjana, K. M. V. Narayan, and Viswanathan Mohan. Prevalence and risk factors for diabetic retinopathy in Asian Indians with young onset type 1 and type 2 diabetes. J.Diabetes Complications 28 (3):291-297, 2014.<br><br>REF ID: RAJALAKSHMI 2014 | Observational: cross-sectional study<br><br>India | n=300 type 1 diabetes and type 2 diabetes (n=150 of each)<br><br>Inclusion criteria:<br>Diagnosis between ages 10 and 25 years<br>Duration of diabetes >2 years<br>Diagnosis: FPG ≥126 mg/dl, and/or 2hr post-load glucose level ≥200 mg/dl, or self-reported diabetes treated by a physician or on hypoglycaemic. Medications or insulin.<br>type 1 diabetes diagnosis: accompanied by abrupt onset of symptoms like polyuria, polydipsia, or unexplained wt loss, DKA, absent insulin reserve, requirement of insulin from time of diagnosis for control of hyperglycaemia.<br>type 2 diabetes diagnosis: absence of ketosis, good | ADULTS and YOUNG PPLE<br>DIABETES TYPE:<br>type 1 diabetes<br>type 2 diabetes | | | type 1 diabetes and type 2 diabetes:<br>Fast C-peptide<br>Stimulated C-peptide<br><br>Cut-offs for positivity<br>Not mentioned | n/a | type 1 diabetes adults and young people | | Funding: Global diabetes research centre.<br><br>Risk of bias:<br>n/a<br>no missing data |
| | | | | | | | | Fasting C-peptide, pmol/ml | 0.29 | |
| | | | | | | | | Stimulated C-peptide, pmol/ml | 0.32 | |
| | | | Adults and young people: | | | | | type 2 diabetes adults and young people | | |
| | | | type 1 diabetes (n=150) | | type 2 diabetes (n=150) | | | Fasting C-peptide, pmol/ml | 0.79 | |
| | | | Age | 28 | 33 | | | Stimulated C-peptide, pmol/ml | 1.60 | |
| | | | | | | | | | | |
| | | | Male | 54% | 62% | | | | | |
| | | | Diabetes duration, years | 12 | 12 | | | | | |
| | | | Drop-outs/missing data: none | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | B-cell functional reserve, absence of pancreatic calculi, and good response to oral hypoglycaemic. Agents for >2 years.<br><br>Exclusion criteria:<br>None mentioned. | | | | | | | |

**Table 56: SCHOLIN 2011 xxxxx (93)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A. Scholin, L. Nystrom, H. Arnqvist, J. Bolinder, E. Bjork, C. Berne, F. A. Karlsson, and Diabetes Incidence Study Group. Proinsulin/C | Observational: and prospective case-series<br><br>Swedish study | Total recruited: n=203<br>n=78 type 1 diabetes (had complete data at all the time-points and were confirmed type 1 diabetes) | ADULTS AND YOUNG PEOPLE<br>DIABETES TYPE:<br>type 1 diabetes | | type 1 diabetes:<br>fC-PEPTIDE<br><br>Cut-offs for positivity<br><br>fC-PEPTIDE+: not given | 3 years follow-up post diagnosis. | type 1 diabetes (n=78) | | Funding: Not mentioned<br><br>Risk of bias:<br>n/a |
| | | | | type 1 diabetes n=78 | | | FC-peptide over time: months after diagnosis nmol/litre MEDIAN (min-max) | | |
| | | | | | | | Baseline | 0.24 (0.04-1.4) | |
| | | | | | | | 3 | 0.26 (0.04-1.8) | |
| | | | | | | | 6 | 0.31 (0.04-1.3) | |
| | | | Age, years, mean (SD; range) | 26.2 (6.0) | | | 9 | 0.27 (0-1.9) | |
| | | | | | | | 12 | 0.27 (0-1.6) | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| -peptide ratio, glucagon and remission in new-onset Type 1 diabetes mellitus in young adults. Diabet.Med. 28 (2):156-161, 2011.<br><br>REFID: SCHOLIN 2011 | | Inclusion criteria:<br>type 1 diabetes<br>Age 15-34 years<br>In the nationwide Diabetes Study in Sweden (DISS)<br>type 1 diabetes defined as islet-cell Ab+ and/or need for insulin treatment at diagnosis)<br>Blood samples taken<br><br>Exclusion criteria:<br>Pregnant<br>type 2 diabetes | M/F % | 60/40 | | | 15 | 0.19 (0-1.7) | |
| | | | | | | | 18 | 0.17 (0-1.1) | |
| | | | Islet Ab+, % | 86% | | | 24 | 0.16 (0-1.5) | |
| | | | | | | | 30 | 0.12 (0.04-1.3) | |
| | | | | | | | 36 | 0.19 (0.02-1.8) | |

**Table 57: SCHOLIN 2004A xxxxx (112)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A. Scholin, C. Torn, L. Nystrom, C. Berne, H. Arnqvist, G. Blohme, J. Bolinder, J. W. Eriksson, I. Kockum, M. Landin-Olsson, J. Ostman, F. A. Karlsson, G. Sundkvist, and E. Bjork. Normal weight promotes remission and low number of islet antibodies prolong the duration of remission in Type 1 diabetes. Diabet.Med. 21 (5):447-455, 2004.<br><br>REF ID: SCHOLIN 2004A | Observational: prospective case-series | Total n=362 type 1 diabetes<br><br>Inclusion criteria:<br>People with type 1 diabetes<br>Aged 15-34 years<br>Clinically classified as type 1 diabetes according to WHO criteria<br><br>Exclusion criteria:<br>None mentioned | ADULTS + YOUNG PEOPLE<br>DIABETES TYPE:<br>type 1 diabetes | | type 1 diabetes:<br>C-PEPTIDE<br>GADA<br>ICA<br>IA-2<br>IAA<br><br>Cut-offs for positivity<br><br>C-PEPTIDE+: 0.25 nmol/litre<br>ICA512/IA-2+: Index* of 0.05<br>GAD65+: Index* of 0.07<br>ICA+: >5 JDF units<br>IAA: 0.7%<br><br>*INDEX = sample cpm – negative control cpm /positive control cpm - negative control cpm | n/a | type 1 diabetes - All cases (n=362) | | Funding: Juvenile diabetes foundation-Wallenberg Diabetes research program, Swedish Diabetes association, Swedish society of medicine, Agnes & Mac Rudbergs foundation |
| | | | | type 1 diabetes n=362 | | | P-C-PEPTIDE+ (nmol/litre) Median (range) | 0.27 (0.10, 2.13) | |
| | | | | | | | ICA+ | 213/346 (62%) | |
| | | | | | | | IA-2A+ | 162/345 (47%) | |
| | | | | | | | GADA+ | 229/346 (66%) | |
| | | | Age, years, mean (range; SD) | 24.7 (5.6) | | | IAA+ | 58/248 (23%) | |
| | | | | | | | type 1 diabetes Ab+ (n=307) | | |
| | | | Duration of diabetes, years, mean (SD) | | | | P-C-PEPTIDE+ (nmol/litre) Median (range) | 0.26 (0.10, 2.13) | |
| | | | | | | | ICA+ | 213/295 (72%) | Risk of bias: n/a |
| | | | | | | | IA-2A+ | 162/294 (55%) | |
| | | | M/F % | 242/120 | | | GADA+ | 229/295 (78%) | |
| | | | | | | | IAA+ | 58/215 (27%) | |
| | | | | | | | type 1 diabetes Ab- (n=53) | | |
| | | | | | | | P-C-PEPTIDE+ (nmol/litre) Median (range) | 0.38 (0.10, 1.63) | |

**Table 58: TRIDGELL 2011 xxxxx (46)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| DM. Tridgell, C Spiekerman, Richard S. Wang, and Carla J. Greenbaum. Interaction of onset and duration of diabetes on the percent of gad and ia-2 antibody-positive subjects in the type 1 diabetes genetics consortium database. Diabetes Care 34 (4):988-993, 2011. | Observational: cross-sectional study | Total n= 5,020 type 1 diabetes<br><br>Inclusion criteria:<br>Diagnosed with type 1 diabetes before aged 35 years<br>Treated with insulin within 6 months of diagnosis without subsequent discontinuation of insulin treatment<br>Families with at least 2 non-monozygotic siblings with type 1 diabetes and families where there was a single affected child | ADULTS AND YOUNG PEOPLE<br>DIABETES TYPE:<br>type 1 diabetes | | type 1 diabetes:<br>GADA<br>IA-2A<br>GADA and/or IA-2A<br><br>Cut-offs for positivity<br><br>GAD65+: NR<br><br>ICA+: NR | n/a | type 1 diabetes: onset aged 2-7 (n=1,739)<br>-univariate analyses | | Funding: type 1 diabetes Genetics consortium, National institute of diabetes and digestive and kidney diseases, juvenile diabetes research foundation |
| | | | | type 1 diabetes n=5,020 | | | GADA+ | 35.7% | |
| | | | Age, years, median (range) | 10 (2-52)<br><br>DATA FOR | | | IA-2+ | 43.1% | |
| | | | | | | | type 1 diabetes: onset aged 8-13 years (n=1,767)<br>-univariate analyses | | |
| | | | | | | | GADA+ | 47.6% | |
| | | | | | | | IA-2+ | 53.1% | |
| | | | | | | | type 1 diabetes: onset aged ≥14 years (n=1,514)<br>-univariate analyses | | |
| | | | | | | | GADA+ | 58.9% | |
| | | | | | | | IA-2+ | 40.6% | |
| | | | | | | | type 1 diabetes: duration 0-5 year-<br>univariate analyses | | |
| | | | | | | | GADA+ | 58.6% | |
| | | | | | | | IA-2+ | 60.4% | |
| | | | | | | | type 1 diabetes: duration 6-13 year- | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: TRIDGELL 2011 | | from a population with a low prevalence of type 1 diabetes<br><br>Exclusion criteria:<br>None mentioned | | ADULTS AND YOUNG PPLE HAS BEEN SEPARATED | | | univariate analyses (referent group 0-5 years duration) | | |
| | | | Duration of diabetes, years, median (range) | 8 (0-66) | | | GADA+ | 44.8% | |
| | | | | | | | IA-2+ | 47.2% | Risk of bias: n/a |
| | | | | | | | type 1 diabetes: duration ≥14 year-<br>univariate analyses<br>(referent group 0-5 years duration) | | |
| | | | M/F % | 50.7%/49.3% | | | GADA+ | 35.6% | |
| | | | | | | | IA-2+ | 28.3% | |
| | | | | | | | type 1 diabetes: duration 0-5 year-<br>multivariate analyses | | |
| | | | | | | | GADA+ | 70.5% | |
| | | | | | | | IA-2A+ | 53.4% | |
| | | | | | | | GADA+ and/orIA-2A+ | 82.2% | |
| | | | | | | | type 1 diabetes: duration 6-13 year-<br>multivariate analyses | | |
| | | | | | | | GADA+ | 65.3% | |
| | | | | | | | IA-2A+ | 42.7% | |
| | | | | | | | GADA+ and/orIA-2A+ | 73.8% | |
| | | | | | | | type 1 diabetes: duration ≥14 year- | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | multivariate analyses | | |
| | | | | | | | GADA+ | 42.5% | |
| | | | | | | | IA-2A+ | 26.2% | |
| | | | | | | | GADA+ and/orIA-2A+ | 53.4% | |

**Table 59: SCHOLIN 2004B xxxxx (69)**

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A. Scholin, L. Bjorklund, H. Borg, H. Arnqvist, E. Bjork, G. Blohme, J. Bolinder, JW. Eriksson, S. Gudbjornsdottir, L. Nystrom et al., and Diabetes Inc. Islet antibodies and remaining beta-cell function 8 years after diagnosis of diabetes in young adults: a | Observational: prospective case series | Total n=312 (patients with blood samples at diagnosis and follow up) - n=254 type 1 diabetes, n=30 type 2 diabetes<br><br>Inclusion criteria:<br>Aged 15-34 years<br>Diagnosed* with diabetes | ADULTS AND YOUNG PEOPLE<br>DIABETES TYPE:<br>type 1 diabetes<br>type 2 diabetes | | type 1 diabetes:<br>C-PEPTIDE<br>GADA<br>ICA<br>IA-2<br>ICA & IA-2A<br>ICA & GADA<br>GADA & IA-2A<br><br>Cut-offs for positivity<br><br>P-C-PEPTIDE+: <0.1 nmol/litre | 8 years | type 1 diabetes Baseline (n=312) | | Funding: Juvenile diabetes foundation and Wallenberg diabetes research program, Lundstrom foundation, Novo-nordisk foundation, Albert Palson foundation, Swedish diabetes |
| | | | | type 1 diabetes | | | ICA+ | n=199/312 (64%) | |
| | | | | | | | GADA | 235/311 (76) | |
| | | | | | | | IA-2A+ | 143/311 (46) | |
| | | | Age, years, mean (range; SD) | 24.8 (9.5) | | | type 1 diabetes: follow up (n=312) | | |
| | | | | | | | ICA+ | 73/309 (24%) | |
| | | | | | | | GADA | 200/309 (65%) | |
| | | | M/F % | 182 (58%)/ 130 (42%) | | | IA-2A+ | 106/310 (34%) | |
| | | | | | | | C-peptide at baseline | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| prospective follow-up of the nationwide Diabetes Incidence Study in Sweden. J.Intern.Med. 255 (3):384-391, 2004.<br><br>REF ID: SCHOLIN 2004B | | between 1987-1988<br><br>Exclusion criteria:<br>None mentioned<br><br>*diagnosis based on clinical judgement as reported by diagnosing clinician to DISS registry | type 1 diabetes | 254 (81) | ICA512/IA-2+: Index* of >1<br>GAD65+: Index* of >4.6<br><br>*INDEX = sample cpm – negative control cpm /positive control cpm - negative control cpm | | ≥0.1 nmol/litre: | type 1 diabetes: 25/42 (60%)<br>type 2 diabetes: 8/42 (21%) | association, children's diabetes fund, Swedish medical research council |
| | | | type 2 diabetes | 30 (10) | | | <0.1 nmol/litre: | type 1 diabetes: 204/227 (90%)<br>type 2 diabetes: 10/227 (4%) | |
| | | | Unclassifiable | 27 (9) | | | C peptide at follow up | | |
| | | | Secondary | 1 (0) | | | ≥0.1 nmol/litre: | type 1 diabetes: 31/42 (76)<br>type 2 diabetes: 8/42 (20) | Risk of bias: n/a |
| | | | | | | | <0.1 nmol/litre: | type 1 diabetes: 208/227 (95)<br>type 2 diabetes: 7/227 (3) | |

**Table 60: WENZLAU 2010 xxxxx (55)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| J. M. Wenzlau, M. Walter, T. J. | Observational: prospective case-series | Total n=506<br><br>Inclusion criteria: | ADULTS AND YOUNG PEOPLE<br>DIABETES TYPE:<br>type 1 diabetes | type 1 diabetes:<br>C-PEPTIDE<br>ZnT8<br>GADA<br>IA-2 | Group 1: 2.5 year<br>Group 2: 7 years<br>Group 3: | Group 1: New onset diabetes (n=21)<br>baseline | | Funding: Childhood diabetes foundation, Denver; |
| | | | | | | ZnT8A+ | 85.7% | |
| | | | | | | GADA+ | 95.2% | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gardner, L. M. Frisch, L. Yu, G. S. Eisenbarth, A. G. Ziegler, H. W. Davidson, and J. C. Hutton. Kinetics of the post-onset decline in zinc transporter 8 autoantibodies in type 1 diabetic human subjects. J.Clin.Endocrinol.Metab. 95 (10):4712-4719, 2010. | | New onset patients within 6 weeks of diagnosis type 1 diabetes new onset patients ( 4 years duration)<br>Patients with longstanding diabetes (>20 years)<br><br>Exclusion criteria:<br>None mentioned | | | | | Cut-offs for positivity<br><br>C-PEPTIDE+:.3 pmol/mL<br>ZnT8: index* of 0.015-0.020<br>ICA512/IA-2+: Index* of 0.032<br>GAD65+: Index* of 0.069<br><br>*INDEX = sample cpm – negative control cpm /positive control cpm -negative control cpm | 3-10.9 years | IA-2A+ | 90.5% | university of Colorado health sciences centre diabetes endocrinology research centre (NIH), juvenile diabetes research foundation autoimmunity prevention centre grant |
| | | | | 1 (n=21) | 2 (n=61) | 3 (n=424) | | | C Peptide+ | 100% | |
| | | | Age, years, median (SD; range) | 20.3 (6.2; 12.2-34.6) | 9.8 (5.2; 1.6-36.7) | 11.4 (7.6; 0.5-52.7) | | | Group 1: New onset diabetes (n=21)<br>2.5 years follow up | | |
| | | | | | | | | | ZnT8A+ | 76.2% | |
| | | | | | | | | | GADA+ | 85.7% | |
| | | | Duration of diabetes, years, mean (SD) | | | 26.3 (7.6; 12.0-57.1) | | | IA-2A+ | 90.5% | |
| | | | | | | | | | C Peptide+ | 85.7% | |
| | | | | | | | | | Group 1: new onset diabetes at 12 years follow up (prevalence) | | |
| | | | | | | | | | GAD+ | 11.5% | |
| | | | | | | | | | CWCR | 3.3% | Risk of bias: n/a |
| | | | | | | | | | IA2+ | 4.9% | |
| | | | | | | | | | GAD/CWCR | 4.9% | |
| | | | | | | | | | GAD/ IA2 | 6.6% | |
| | | | | | | | | | IA2/CWCR | 21.3% | |
| | | | | | | | | | GAD/CWCR/IA2 | 41% | |
| | | | | | | | | | Group 2: New onset type 1 diabetes (n=61)<br>Baseline | | |
| | | | | | | | | | ZnT8A+ | 80.3% | |

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|
| REF ID: WENZLAU 2010 | | | | | | GADA+ | 63.0% | |
| | | | | | | IA-2A+ | 73.8% | |
| | | | | | | C Peptide+ | NR | |
| | | | | | | Group 2: New onset type 1 diabetes (n=61) 12 years follow up | | |
| | | | | | | ZnT8A+ | 42.6% | |
| | | | | | | GADA+ | 32.4% | |
| | | | | | | IA-2A+ | 47.5% | |
| | | | | | | C Peptide+ (detected >0.02 pmol/mL) | 27.6% | |
| | | | | | | Group 2: patients with 4 years duration of type 1 diabetes at 12 years follow up (prevalence) | | |
| | | | | | | GAD+ | 10.7% | |
| | | | | | | CWCR | 8.9% | |
| | | | | | | IA2+ | 16.1% | |
| | | | | | | GAD/CWCR | 3.6% | |
| | | | | | | GAD/ IA2 | 10.7% | |
| | | | | | | IA2/CWCR | 19.6% | |
| | | | | | | GAD/CWCR/IA2 | 20% | |
| | | | | | | Group 3: Patients with longstanding diabetes(>20 years) (n=282) 12 year follow up (prevalence) | | |
| | | | | | | GAD+ | 11.0% | |
| | | | | | | CWCR | 1.4% | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | IA2+ | 7.8% | |
| | | | | | | | | | GAD/CWCR | 0.7% | |
| | | | | | | | | | GAD/ IA2 | 7.1% | |
| | | | | | | | | | IA2/CWCR | 2.1% | |
| | | | | | | | | | GAD/CWCR/IA2 | 2.5% | |

**Table 61: MCDONALD 2011 xxxxx (85)**

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| T. McDonald, K. Colclough, R. Brown, B. Shields, M. Shepherd, P. Bingley, A. Williams, A. Hattersley, and Sian Ellard. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet.Med. 28 | Observational: cross-sectional study<br><br>UK study | Total n=616<br>n=98 type 1 diabetes – adults and young people<br>n=508 MODY – but adults only<br><br>Inclusion criteria:<br><br>Clinical | ADULTS & YOUNG PEOPLE<br>DIABETES TYPE:<br>type 1 diabetes<br>MODY | | | type 1 diabetes:<br>GAD<br>IA-2<br><br>MODY:<br>GAD<br>IA-2<br><br>Cut-offs for positivity<br>GAD+: 64 WHO units/ml (99th percentile)<br><br>IA-2+: 15 WHO | n/a | type 1 diabetes | | Funding: None mentioned<br><br>Risk of bias:<br>n/a |
| | | | | type 1 diabetes n=98 | MODY n=508 | | | GAD+ | 24/98 (24.5%) | |
| | | | | | | | | IA-2+ | 19/98 (94.5%) | |
| | | | Age, years, median (IQR) | 15 (12-25) | 36 (18-50) | | | GAD+ and/or IA-2)+ | 80/98 (82%) | |
| | | | | | | | | GAD+ and IA-2+ | 37/98 (37.8%) | |
| | | | | | | | | MODY | | |
| | | | | | | | | GAD+ | 5 (1%) | |
| | | | | | | | | IA-2+ | 0 (0%) | |
| | | | Duration of diabete | < 6 months | 9 (4-25) | | | GAD+ and/or IA-2+ | 5/508 (1%) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| (9):1028-1033, 2011.<br><br>REF ID: MCDONALD 2011 | | history of diabetes<br>HbA1c <6.0%<br>MODY diagnosis by genetic testing<br>type 1 diabetes diagnosis in last 6 months<br><br>Exclusion criteria: None given | s, years, median (IQR) | | | units/ml (99th percentile; lowest calibrator) | | | | |

**Table 62: SCHOLIN 2004 xxxxx (144)**

| Reference | Study type | Number of patients | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| Anna Scholin, Agneta Siegbahn, Lars Lind, | Observational study: prospective case series | Total n= 100 type 1 diabetes . n=3ter excluded as | ADULT (15-34 years)<br>DIABETES TYPE:<br>TID | type 1 diabetes:<br>C-peptide<br>ICA+<br>GADA+ | 12 months | Assays divided into islet antibody positive (ab+) and negative (ab-)<br><br>Ab+ (n=78) | Funding: Supported by Grant from the Swedish |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Christian Berne, Goran Sundkvist, Elisabeth Bjork, F. Anders Karlsson, and Diabetes Incidence Study in Sweden group. CRP and IL-6 concentrations are associated with poor glycemic control despite preserved beta-cell function during the first year after diagnosis of type 1 diabetes. | Diabetic incidence in Sweden study. | pregnant.<br><br>Inclusion criteria:<br>Not pregnant.<br><br>Exclusion criteria:<br>None mentioned | Age of type 1 diabetes patients (n=97) at diagnosis | | IA-2A+<br><br>Cut-offs for positivity<br><br>C-peptide: reference interval for fasting plasma concentration was 0.25 to 0.75 nmol/litre<br><br>GADA index: >4.6 u/ml<br><br>IA-2A index: >1.0<br><br>ICA: Not reported | | C peptide (nmol/litre) | 0.25 (0.04-1.4) | Research Council, the Swedish Heart Lung Foundation, the Swedish Diabetes Association, the family Ernfors Fund, and the Juvenile Diabetes Foundation International and Knut and Alice Wallenberg Foundation. |
| | | | | | | | ICA+ | 58/78 (74%) | |
| | | | | | | | GADA+ | 69/78 (88%) | |
| | | | | | | | IA-2A+ | 55/78 (70%) | |
| | | | | | | | Ab- (n=19 : 19.7%) | | |
| | | | | | | | C peptide (nmol/litre) | 0.34 (0.08-1.41) | |
| | | | | | | | | | |
| | | | | | | | Total population (I have added Ab+ and Ab-) | | |
| | | | | | | | ICA+ | 58/97 (59.8%) | |
| | | | | | | | GADA+ | 69/97 (71.1%) | |
| | | | | | | | IA-2A+ | 55/97 (56.7%) | |
| | | | | All (n = 97) | | | C-peptide – mean of Ab+ and Ab- (nmol/litre) | 0.25 + 0.34 /2 = 0.295 | |
| | | | Age (years) | 28.1 (15.3-34.8) | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Diabetes.Metab.Res.Rev. 20 (3):205-210, 2004.<br><br>REF ID: SCHOLIN 2004 | | | | | | | | | |

**Table 63: VERMEULEN 2011 (250)**

| Reference | Study type | Number of patients | | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| I. Vermeulen, I. Weets, M. Asanghanwa, J. Ruige, Gaal L. Van, C. Mathieu, B. Keymeulen, V. Lampasona, J. M. | Observational: Case-control study<br><br>Registry, Belgium | Total n= 665 type 1 diabetes (n=170 aged 0-9 years; n=223 aged 10-19 years; n=149 aged 20-29 years; n=113 aged 30-39 years)<br><br>Inclusion | YOUNG PPLE & ADULTS (data separated for some age-groups and markers)<br>DIABETES TYPE:<br>type 1 diabetes | | type 1 diabetes<br>IA-2A<br>IA-2βA<br>ZnT8<br>IAA<br>GADA<br>Combinations<br><br>Cut-offs for positivity<br><br>IAA: ≥0.6% tracer | 1 year | type 1 diabetes<br>ADULTS aged 20-29 (n=149) | | Funding: Juvenile diabetes Research F, EU and Belgian fund for Scientific Research |
| | | | | type 1 diabetes | | | MARKER | N (%) | |
| | | | | | | | IA-2βA | 47 (32) | |
| | | | | | | | ZnT8 | 76 (51) | |
| | | | | | | | type 1 diabetes<br>ADULTS aged 30-39 (n=113) | | |
| | | | Age, years, | n=170: 0-9 years<br>n=223: 10-19 years | | | MARKER | N (%) | |
| | | | | | | | IA-2βA | 21 (19) | |

| Reference | Study type | Number of patients | | Patient characteristics | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Wenzlau, J. C. Hutton, D. G. Pipeleers, and F. K. Gorus. Contribution of antibodies against IA-2beta and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. Diabetes Care 34 (8):1760-1765, 2011.<br><br>REF ID: | | criteria:<br>Diagnosed with diabetes before age 40<br>Physician diagnosis of type 1 diabetes on clinical grounds and treated with insulin with 7 days after diagnosis<br>Blood sampled within 7 days after treatment started<br>CONTROLS: sex-matched non-diabetic controls aged 0-39 years. None had relatives with type 1 | | n=149: 20-29 years<br>n=113 30-39 years<br><br>Median: 15 (IQR9-26) years | binding<br><br>IA-2A: ≥0.44% tracer binding<br><br>IA-2βA: ≥0.39% tracer binding<br><br>GADA+: ≥2.6% tracer binding<br><br>ZnT8+:<br>Age 0-14 years = ≥1.28% tracer binding<br>Age15-39 years = ≥1.02% tracer binding | | ZnT8 | 44 (39) | |
| | | | | | | | type 1 diabetes<br>YOUNG PPLE aged 10-19 (n=223) | | |
| | | | M/F | 383 /272 | | | MARKER | N (%) | |
| | | | | | | | IA-2βA | 105 (47) | |
| | | | | | | | ZnT8 | 152 (68) | Risk of bias: n/a |
| | | | | | | | ≥1 Ab+ (GADA, IA-2A or IAA) | 207 (93) | |
| | | | | | | | ≥1 Ab+ (GADA, IA-2A or ZnT8) | 209 (94) | |
| | | | | | | | ≥2 Ab+ (GADA, IA-2A and/or IAA) | 154 (69) | |
| | | | | | | | ≥2 Ab+ (GADA, IA-2A and/or ZnT8) | 162 (73) | |
| | | | | | | | type 1 diabetes<br>ADULTS aged 20-39 (n=262) | | |
| | | | | | | | ≥1 Ab+ (GADA, IA-2A or IAA) | 207 (79) | |
| | | | | | | | ≥1 Ab+ (GADA, IA-2A or ZnT8) | 206 (79) | |
| | | | | | | | ≥2 Ab+ (GADA, | 129 (49) | |

| Reference | Study type | Number of patients | | Patient characteristics | | Diagnostic markers assessed | Length of follow-up | Outcome measure and effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| VERMEULEN 2011 | | diabetes.<br><br>Exclusion criteria:<br>None stated | | | | | | IA-2A and/or IAA) | | |
| | | | | | | | | ≥2 Ab+ (GADA, IA-2A and/or ZnT8) | 139 (53) | |
| | | | | | | | | YOUNG PPLE AND ADULTS:<br>>age 15: | | |
| | | | | | | | | ≥1 Ab+ (IAA, GADA and IA-2A) | 82% | |
| | | | | | | | | ≥2 Ab+ (IAA, GADA or IA-2A) | 51% | |
| | | | | | | | | ≥2 Ab+ (IA-2βA plus one of IAA, GADA or IA-2A) | 56% | |
| | | | | | | | | ≥2 Ab+ (ZnT8 plus one of IAA, GADA or IA-2A) | 63% | |
| | | | | | | | | ≥2 Ab+ (ZnT8 and IA-2βA plus one of IAA, GADA or IA-2A) | 65% | |
| | | | | | | | | The prevalence of IA-2βA and ZnT8 decreased with age at diagnosis (especially after age 20 years). | | |

## G.2 Education programmes and self-care

### G.2.1 Structured education programmes

**Table 64: HERMANNS (PRIMAS education) [62]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N Hermanns, B Kulzer, D Ehrmann, N Bergis-Jurgan, and T Haak. The effect of a diabetes education programme (PRIMAS) for people with type 1 diabetes: results of a randomized trial. Diabetes Res.Clin.Pract. 102 (3):149-157, 2013.<br><br>REF ID: | RCT<br><br>23 centres in Germany | n=160<br><br>Inclusion criteria:<br>type 1 diabetes<br>≥18 and ≤75 years<br>Diabetes duration >1 month<br>BMI >20 and <40 kg/m2<br>HbA1c ≥7 and ≤13<br>German language<br><br>Exclusion criteria:<br>Current psychological or psychiatric disorder | | PRIMAS n=81 | DTTP n=79 | PRIMAS structured education<br><br>ITT: n=81<br>ACA/ reported: 75<br><br>12 lessons of 90 minutes each over 6 weeks<br>Includes carb counting<br>Based on self-management/empowerment approach | DTTP structured education (standard programme in Germany)<br><br>ITT: n=79<br>ACA/reported: 74<br><br>12 lessons of 90 minutes each over 6 weeks<br>Includes carb counting | 6 weeks intervention; 6 months follow-up (post-intervention). | Final HbA1c, % (SD) | PRI: 7.9 (1.0)<br>DTTP: 8.1 (1.0 ) | Funding: Grants from Berlin Chemie AG/Menarini Diagnostics, Germany.<br><br>Risk of bias:<br>Randomisation = good (central, randomisation sequence by computerised system, stratified by centre)<br>Allocation concealment = good (Independent research unit were contacted)<br>Blinding = not mentioned and |
| | | | Severe hypo episodes, per patient/year (SD) | 0.33 (1.4) | 0.29 (0.9) | | | | Change baseline HbA1c, % (SD) | PRI: -0.4 (1.0)<br>DTTP: 0.0 (0.6) | |
| | | | Diabetes, mean years | 19.3 | 19.6 | | | | Severe hypoglycaemic. Episodes/patient/year (SD) | PRI: 0.06 (0.2); change base: -0.2 (0.9)<br>DTTP: 0.01 (0.1); change base: -0.3 (1.5) | |
| | | | Women, % | 38 | 49 | | | | Depression – CES-D (SD) | PRI: 13.0 (9.5); change base: | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HERMANNS 2013 | | (under treatment)<br>Dementia or severe cognitive impairment<br>Severe somatic disease (preventing a regular participation in the training course)<br>pregnancy | | | | | | | | -1.2 (7.9)<br>DTTP: 15.9 (9.5); change base: -0.3 (7.1) | | n/a<br>ITT analysis<br>Powered study (HbA1c)<br>Drop-outs = acceptable (<20% and <10% difference between groups) |
| | | | HbA1c, % (SD) | 8.3 (1.1) | 8.0 (0.9) | | | | Hypo awareness score (SD)<br>Clarke 0-7 (≥4 = impaired) | PRI: 1.3 (1.2); change base:<br>-0.5 (1.4)<br>DTTP: 1.2 (1.3); change base:<br>-0.4 (1.3) | | |
| | | | Age, mean | 45.9 | 45.1 | | | | | | | |
| | | | Depression – CES-D (SD) | 14.2 (9.0) | 16.1 (8.4) | | | | Diabetes knowledge test, (SD)<br>Score 0-11, max 11. | PRI: 7.6 (1.8); change base:<br>0.7 (1.6) | DTTP: 8.0 (1.8); change base:<br>0.6 (1.6) | |
| | | | Diabetes knowledge test (SD) | 7.6 (1.8) | 8.0 (1.8) | | | | | | | |
| | | | Hypo awareness score (SD) | 1.8 (1.7) | 1.5 (1.6) | | | | | | | |
| | | | | | | | | | Adherence (attended | n=1/81 | n=2/79 | |
| | | | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | NS differences between groups for any of the baseline characteristics<br><br>Drop-outs (6 months):<br>n=6 PRIMAS; n=5 DTTP | | | | <half the lessons) | | | |

**Table 65: ROSSI 2013[131]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MC Rossi, A Nicolucci, G Lucisano, F Pellegrini, P Di Bartolo, V Miselli, R Anichini, and G Vespasiani On Behalf Of The Did Study Group. Impact of the "diabetes interactive diary" telemedicine system on | RCT<br><br>12 centres, Italy. | n=127<br><br>Inclusion criteria:<br>type 1 diabetes<br>≥18 years age<br>no previous education on CHO counting<br>HbA1c ≥7.5<br>treatment with basal-bolus regimen with insulin | | DID n=63 | STD EDU n=64 | Standard education<br><br>ITT: n=64<br><br>Standard educational approach used in the centre – no further details given.<br><br>Same insulin scheme as DID group | Diabetes Interactive Diary (DID) – telemedicine system<br><br>ITT: n=63<br><br>Up to 2 week training course given to patients using DID<br>3 prandial injections of glulisine (15-20 minutes before | 6 months | Final HbA1c, % (SE, SD) | DID: 7.9 (0.1, 0.8)<br>STD: 8.1 (0.1, 0.8) | Funding: Sanofi-Aventis, Italy.<br><br>Risk of bias: Randomisation =unclear. stratified by centre, permuted block randomisation<br>Allocation concealment = adequate. Telephone call |
| | | | Age, years (SD) | 38.4 | 34.3 | | | | Change baseline HbA1c, % (SE, SD) | DID: -0.49 (0.11, 0.8)<br>STD: -0.48 (0.11, 0.8) | |
| | | | Women, % | 54 | 33 | | | | Severe hypoglycaemic. Episodes/patient/year<br>INCIDENCE RATE (95% | DID:49.2 (46.7 to 51.9, -10.3)<br>STD: 45.6 (43.2 to 48.1, -9.8)<br>Between groups IRR: | |
| | | | HbA1c, % (SD) | 8.4 (0.1) | 8.5 (0.1) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| metabolic control, risk of hypoglycemia, and quality of life: a randomized clinical trial in type 1 diabetes. Diabetes Technol.Ther. 15 (8):670-679, 2013.<br><br>REF ID: ROSSI 2013 | | analogues<br>practiced self-monitoring of blood glucose at least 3 times/day<br>adequate familiarity in use of mobile phones<br><br>Exclusion criteria:<br>treated with NPH insulin OR soluble regular insulin OR CSII OR other regimens than basal-bolus.<br>eating disorder<br>pregnant<br>unable to send or receive short text messages<br>unable or unwilling to give informed consent<br>any other | | | | | meal), with basal of glargine.<br>DID was used to estimate the CHO content of the meal, and prandial insulin doses were adjusted based on the DID algorithm.<br>DID=software installed into mobile phone:<br>works as a CHO/insulin bolus calculator.<br>Supports patients in CHO counting through a food atlas and in recording SMBG mmts.<br>All recorded info sent to physician every 1-3 weeks via SMS and reviewed on computer of the diabetes clinic. Any new | | CI, SD) | 1.08 (1.0-1.16) | to co-ordinating centre<br>Blinding = none. Open label<br>ITT analysis (LOCF)<br>Powered study (HbA1c)<br>Drop-outs = acceptable (<20%) and <10% difference between groups. |
| | | | Diabetes, mean years (SD) | 16.2 | 15.0 | | | | DSQoL – fear of hypoglycaemia, change from baseline (SE, SD) | DID:2.03 (2.23, 17.7)<br>STD: -3.91 (2.22, 17.8) | |
| | | | Drop-outs (6 months):<br>n=8, 13% (DID)<br>n=7, 11% (STD education) | | | | | | *NOTE: DSQOL Fear score was 11 itels wath score range of 6 points (Likert scale). Higher scores = better QoL or satisfaction. | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | disease or condition that may interfere with compliance or completion of study. | | | behavioural and therapeutic prescription can be then sent from the computer to the patient's mobile phone. | | | | |

**Table 66: DAFNE study[8]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| S. Amiel, S. Beveridge, C. Bradley, C. Gianfrancesco, S. Heller, P. James, N. McKeown, D. Newton, L. Newton, L. Oliver, et al, and DAFNE | RCT<br><br>3 centres in UK | n=169<br><br>(n=84 ID group; n=85 DD group) – final included in analysis – 67 and 72 respectively.<br><br>Inclusion | | ID n=84 | DD n=85 | Immediate DAFNE (ID)<br><br>ITT: n=84<br>ACA/ reported: 67 and 68<br><br>5-day outpatient group training course (6-8 people/centre)<br>Skills to | Delayed DAFNE (DD)/waiting list control<br><br>ITT: n=85<br>ACA/reported: 72<br><br>usual care/waiting list for 6 months, | 6 months after ID group receiving DAFNE (The DD group had not received DAFNE at this point)<br><br>At 12 | HbA1c, % (SD) | ID: 8.4 (1.2)<br>DD: 9.4 (1.3) | Funding: Grants from Diabetes UK.<br><br>Risk of bias: Randomisation = good (computer generated random number list for each centre)<br>Allocation concealment = |
| | | | Hypoglycaemic. (severe, 6 months) | 15/68 (22%) | | | | | Hypoglycaemic. (severe, 6 months) | ID: 12/67<br>DD: 11/72 | |
| | | | Diabetes, mean years | 16 (9.6) | | | | | ADDQoL - average weighted impact (-9 to +9) | ID: -1.6 (1.6)<br>DD: -1.9 (1.4)<br>MD change from baseline 0.4 (-0.1, 0.9); p<0.01 | |
| | | | Women, % | 56 | | | | | DTSQ - total | ID: 31.58 (3.9)<br>DD: 22.82 (6.0) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose adjustment for normal eating (DAFNE) randomised controlled trial. Br.Med.J. 325 (7367):746-749, 2002.<br><br>REF ID 1500 | | criteria:<br>Attendees at hospital diabetes clinics, aged >18 years, clinical feature of type 1 diabetes, moderate or poor glycaemic control (HbA1c 7.5-12%), diabetes duration >2 years without advanced complications<br><br>Exclusion criteria: Inability to understand written and spoken English, | | | | replace insulin by matching with CHO intake on meal by meal basis<br>Principles of adult education with explicit learning objectives<br>Aim to build confidence and appropriate independence, with goal of patient autonomy.<br>patients goal to adjust insulin to suit lifestyle rather than timing and content of meals to be fixed around insulin doses.<br>2- 3 educators taught the course (DSNs and dieticians); | then given DAFNE | months follow-up the DD group had received DAFNE, and this was follow-up 6 months after it. | satisfaction (0-36) | MD 8.75 (7.02, 10.48); p<0.0001 | inadequate (sealed opaque envelopes) [RO: needs to also be sequentially numbered]<br>Blinding = not mentioned and n/a<br>Not ITT analysis<br>Powered study (HbA1c)<br>Drop-outs = acceptable (<20%) |
| | | | HbA1c, % (SD) | 9.4 (1.2) | 9.3 (1.1) | | | | Symptomatic hypoglycaemia - perceived frequency, 0-6 (SD) | ID: 2.16 (1.3)<br>DD: 2.40 (1.3)<br><br>MD: -0.23 (-0.68, 0.21), p=0.31 | |
| | | | Age, mean (SD) | 40 (9) | | | | | | | |
| | | | Retinopathy, % | 15 | | | | | | | |
| | | | Neuropathy, % | 13 | | | | | | | |
| | | | Nephropathy, % | 1.2 | | | | | | | |
| | | | ADDQoL impact of diabetes on QoL | -2.0 (1.6) | -1.9 (1.4) | | | | | | |
| | | | Hypo unawareness - perceived frequency, 0-6 (SD) | 2.04 (1.2) | 2.12 (1.4) | | | | | | |
| | | | NS differences between | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | severe psychiatric illness, pregnancy and complete unawarenes s of hypoglycae mia. | groups for any of the baseline characteristics<br><br>Drop-outs (6 months):<br>ID: n=16 (11 did not start, 3 ineligible, 1 dropped out on 1st day, 1 in hospital)<br>DD: n=13 (12 did not start, 1 ineligible)<br><br>Outcomes:<br>ADDQoL – audit of diabetes-depended QoL questionnaire – impact weighting by importance for 18 domains of life (scores -9 to +9) then averaged. Overall score averages -9 (maximum negative impact of diabetes) to +9 (maximum positive impact of diabetes)<br>DTSQ – diabetes treatment satisfaction questionnaire (8-items; mainly 0-36; higher score = greater satisfaction)<br>W-BQ12 – psychological well-being questionnaire (12-items; 0-36; higher score = greater satisfaction)<br>Hypoglycaemia unawareness | educators given previous training, inspections and peer review given during the course | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | (perceived frequency of hypoglycaemia): measured by the DTSQ. Score of 0-6. Higher scores = greater perceived frequency | | | | | | |

**Table 67: BGAT III study[136]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H Schachinger, K Hegar, N Hermanns, M Straumann, U Keller, G Fehm-Wolfsdorf, W Berger, and D Cox. Randomized controlled clinical trial of blood glucose awareness training (BGAT III) in | RCT<br><br>6 centres in Switzerland and Germany | n=138<br><br>(n=69 BG group; n=69 C group) – included in analysis 56 and 55 respectively<br><br>Inclusion criteria:<br>type 1 diabetes, verified that people were on a 'state of the art' | | BG n=56 | C n=55 | BGAT III (BG)<br><br>ACA/reported: n=56<br><br>BGAT III (German version) psycho-educational programme delivered by a physician-psychologist team<br>groups of 5-12 for 8 x 2 hour | Control (C) - self-help group:<br><br>ACA/reported: n=55<br><br>self-help control group was guided by 1 physician.<br>Sessions lasted 2 hours<br>Focus of sessions: current | 6 months and 12 months | HbA1c, % (SD) – 6 months | BG: 6.93 (1.02)<br>C: 6.95 (0.98) | Funding: Swiss National Diabetes Foundation, Basel Diabetes Foundation, Walter-und Margarethe von Lichtenstein Foundation, Freie Akadamische Gesellschaft Basel, Lilly Inc. Switzerland and Astra Fonds.<br><br>Risk of bias: |
| | | | Age, years (SD) | 45 (14.4) | 47.9 (13.1) | | | | HbA1c, % (SD) – 12 months | BG: 6.93 (0.96)<br>C: 6.94 (0.94) | |
| | | | Women, % | 45 | 38 | | | | Hypoglycaemic. -severe, episodes/6 months at 6 months (SD) | BG:0.13 (0.33)<br>C: 1.07 (2.85) | |
| | | | HbA1c, % (SD) | 6.9 (0.8) | 6.9 (0.9) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Switzerland and Germany. J.Behav.Med. 28 (6):587-594, 2005.<br><br>REF ID: SCHACHINGER 2005 | | intensified insulin regimen, performed 3-5 injections and at least 3 blood glucose mmts/day, had a recent adjustment of insulin dose and dosing schedule (if necessary), and routine determination of HbA1c every 3 months.<br><br>Exclusion criteria: Uncontrolled physical and mental diseases (heart or vascular disease, eating | Hypoglycaemic. -severe, episodes/6 months (SD) | 1.6 (3.5) | 1.8 (3.7) | sessions (1/week)<br>Focus of initial sessions: internal cues (physical symptoms), disruptions in cognitive and motor performance, mood changes. Taught to use all these signals to more accurately recognise when blood glucose is too high or low<br>Focus of later sessions: how to use exogenous cues to better anticipate when blood | problems related to diabetes, stress and diabetes, anatomy and physiology, physical activity, diabetes in the workplace, relationship conflicts, and previous experiences<br>No homework given. | | Hypoglycaemic. -severe, episodes/6 months at 12 months (SD) | BG:0.13 (0.33)<br>C: 1.78 (4.56) | Randomisation = inadequate (matched to controls within each research centre – to reduce known confounders of age and diabetes duration. patients grouped as pairs then a random decision made as to which of the pair was given the main intervention (BGAT III) or control intervention)<br>Allocation concealment = not mentioned<br>Blinding = not mentioned and n/a<br>Not ITT analysis<br>Powering details not |
| | | | Hypoglycaemic. - severe, last 2 years, % | 64 | 47 | | | | Hypoglycaemia Fear Survey – worry: 6 months and 12 months | 6 months: BG:15.2 (12.1)<br>C: 14.6 (12.2)<br>12 months<br>BG:13.2 (9.9)<br>C: 14.7 (12.9) | |
| | | | Diabetes, mean years (SD) | 23.1 (12) | 22.7 (12.2) | | | | Hypoglycaemia Fear Survey – behaviour: 6 months and 12 months | 6 months: BG: 13.7 (8.2)<br>C: 11.6 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | disorder, depression or substance abuse). Somatic comorbidity considered uncontrolled when newly diagnosed or new treatment had to be established within the last 3 months prior to entry. | | | | glucose is likely to rise or fall: previous insulin injections, food consumption, physical exercise<br>Weekly homework and prep. readings were required | | | | (6.4)<br>12 months:<br>BG: 11.6 (6.9)<br>C: 12.2 (8.5) | mentioned<br>Drop-outs = not acceptable (>20%; 25%)<br>Selective outcome reporting: results not given for several outcome measures that were recorded: Well-being questionnaire and Diabetes QoL questionnaire – just says 'there was no overall effect of BGAT on either diabetes specific or general QoL measures. |
| | | | Hypoglycaemic. unawareness (increased recognition of low blood sugar levels) % detection | 52.7 (21.8) | 53.5 (28.0) | | | | Hypoglycaemia unawareness (increased recognition of low blood sugar levels), % detection: 6 months and 12 months | 6 months:<br>BG: 58.2 (24.8)<br>C: 45.8 (28.7)<br>12 months:<br>BG: 65.2 (25.2)<br>C: 48.0 (25.5) | |
| | | | Hypoglycaemia Fear Survey - worry | 16.5 (12.2) | 15.7 (11. | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 7) | | | | | | |
| | | | Hypoglycaemia Fear Survey - behaviour | 14.1 (9) | 11.3 (6.6) | | | | | | |
| | | | NS differences between drop-outs and participating people for any of the baseline characteristics except HbA1c (worse in drop-outs, p=0.05)<br><br>Drop-outs (12 months):<br>Overall: n=27<br>BG: n=13 (6 attended <50% sessions, 7 non-compliant with follow-up examinations)<br>C: n=14 (8 attended <50% sessions, 6 non-compliant with follow-up examinations)<br><br>Outcomes:<br>Severe hypoglycaemia – any hypo episode for which the help of others was required (measured in diaries and questionnaire)<br>HbA1c – from diabetes specialists or family physicians<br>QoL – diabetes specific and general QoL questionnaires: | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Well-being questionnaire and Diabetes QoL questionnaire (results not reported for these in the paper)<br>Hypoglycaemia unawareness (increased recognition of low blood sugar levels): % detection of low blood glucose levels<br>Fear of hypoglycaemia (Hypoglycaemia fear Survey): worry and behaviour domains. Each has multiple items graded on a score of 1-5 (5 indicates very often that is, worse fear-related worry or behaviours). Worry domain has 10 items (total score /50), behaviour domain has 17 items (total score /85).<br>LOW score = better | | | | | | |

**Table 68: BITES study[53]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| J. T. George, A. P. Valdovinos, | RCT | n=114 | | BI n=54 | C n=60 | BITES (BI) | Control (C) – usual care | 3, 6 and 12 month | HbA1c, mean difference (95% CI) – 3 months | 0.01 (-0.23, 0.26); | Funding: Not mentioned. |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I. Russell, P. Dromgoole, S. Lomax, D. J. Torgerson, T. Wells, and J. C. Thow. Clinical effectiveness of a brief educational intervention in type 1 diabetes: Results from the BITES (Brief Intervention in Type 1 diabetes, Education for Self-efficacy) trial. Diabet.Med. 25 (12):1447-1453, 2008. | 1 centre in UK | (n=54 BI group; n=60 C group)<br><br>Inclusion criteria:<br>People with type 1 diabetes attending specialist diabetes service in a hospital setting.<br>type 1 diabetes for >12 months<br>MDI for ≥2 months<br>≥18 years old<br>ability to read and write. | | | | ITT: n=54<br>ACA: n=50 (at 3, 6 and 12 months)<br><br>BITES psycho-educational programme<br>Delivered by a specifically trained DSN and SDD (specialist diabetes dietician)<br>Groups of 8-10 as a 2.5 day course over a 6-week period<br>Used written curriculum (pre-approved education material) and sessions were observed by independent researcher.<br>Interactive | ITT: n=60<br>ACA: n=52, n=53 and n=52 (at 3, 6 and 12 months)<br><br>Controls seen in their usual diabetes clinic in addition to their study patients<br>Had access to DSN and SDD and access to the Clinical Health Psychologist by referral<br>Controls received the full course 12 months later | s | | p=0.92 | Risk of bias:<br>Randomisation = unclear (block randomisation in blocks of 6)<br>Allocation concealment = inadequate (independent evaluator, sealed envelopes in strict ascendant order)<br>Blinding = not mentioned and n/a<br>ITT analysis<br>Powered study (HbA1c)<br>Drop-outs = acceptable (<20%) |
| | | | Age, years (SD) | 41 (10) | 41 (12) | | | | HbA1c, mean difference (95% CI) – 6 months | -0.06 (-0.32, 0.20); p=0.67 | |
| | | | Women, % | 50 | 60 | | | | HbA1c, mean difference (95% CI) – 12 months | 0.01 (-0.30, 0.32); p=0.94 | |
| | | | HbA1c, % (SD) | 8.7 (1.51) | 8.7 (1.13) | | | | Hypoglycaemic. - severe, episodes/12 months at 12 months, mean difference (95% CI) | BI: 0.41 /patient/year<br>C: 0.48 /patient/year<br>MD: -0.05 (-0.61, 0.50); p=0.85 | |
| | | | Diabetes, mean years (SD) | 19.7 (12.7) | 19.4 (11.0) | | | | SF-36 Physical health, 3 months, MD (95% CI) | 1.4 (-1.6,4.3): p=0.35 | |
| | | | | | | | | | SF-36 Physical health, 6 months, MD (95% CI) | 2.2 (-0.7, 5.0); p=0.14 | |
| | | | | | | | | | SF-36 Physical health, 12 months, MD (95% CI) | 1.9 (-0.8, 4.6); p=0.17 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: GEORGE 2008 | | | Hypoglycaemia Fear Survey – worry: | Not given | Not given | sessions with reflection<br>Group-based problem solving exercises; completed a workbook in-between sessions and received feedback from peers & HC professionals at the next session. Also worked with a fictitious individual with type 1 diabetes throughout the course who they mentored throughout and discussed helping them with change. | | | Hypoglycaemia Fear Survey – worry: 6 months and 12 months | 6 months:<br>MD -2.4 (-7.2, 2.4), p=0.33<br>12 months<br>MD -1.4 (-6.2, 3.4), p=0.57 | |
| | | | Hypoglycaemia Fear Survey – behaviour: | Not given | Not given | | | | Hypoglycaemia Fear Survey – behaviour: 6 months and 12 months | 6 months:<br>MD -0.01 (-2.9, 2.9), p=0.99<br>12 months<br>MD -1.2 (-4.2, 1.9), p=0.45 | |
| | | | Groups were comparable at baseline<br><br>Drop-outs (3, 6 and 12 months):<br>BG: n=2 cumulative total at 12 months (all n=2 dropped out at 3 months)<br>C: n=8 cumulative total at 12 months (all n=8 dropped out at 3 months)<br><br>Outcomes: | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Severe hypoglycaemia – a hypo episode for which the patient required assistance with treatment and either documented blood glucose <2.7 mmol/litre or detected clinical signs that require oral CHO administered by a third party, SC glucagon or IV glucose.<br>HbA1c<br>SF-36 (QoL) –<br>DKT (Diabetes knowledge test)<br>DES (Diabetes Empowerment Scale)<br>DTS-Q (Diabetes Treatment Satisfaction Questionnaire)<br>DHP (Diabetes health profile)<br>[RO: These outcomes have data reported, just need to decide which we want]<br>Fear of hypoglycaemia (Hypoglycaemia fear Survey): worry and behaviour domains. Each has multiple items graded on a score of 1-5 (5 | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | indicates very often that is, worse fear-related worry or behaviours). Worry domain has 10 items (total score /50), behaviour domain has 17 items (total score /85). | | | | | | |

**Table 69: HYPOS study[61]**

| Reference | Study type | Number of patients | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| N. Hermanns, B. Kulzer, T. Kubiak, M. Krichbaum, and T. Haak. The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients | RCT<br><br>23 outpatient centres in Germany | n=164<br><br>(n=84 Hypoglycaemic group; n=80 C group) – included in analysis 74 and 72 respectively<br><br>Inclusion criteria:<br>type 1 | HyPOS (HyP) specific training programme to reduce Hypoglycaemic.<br><br>ITT: n=84<br>ACA/reported: n=74<br><br>Bio-psychosocial training/education programme<br>Intensively trained diabetologist and diabetes educators (18 lessons)<br>5 lessons for 90 minutes | Control (C) – standard education:<br><br>ITT: n=80<br>ACA/reported: n=72<br><br>4 lessons of 90 minutes (1/week)<br>Focus of sessions: standards of insulin | 6 months | ADDQoL – impact and importance (-3 to +3) | HyP:1.0 (0.8)<br>C: 1.1 (0.8) | Funding: Berlin-Chemie AG/Menarini Diagnostics.<br><br>Risk of bias:<br>Randomisation = no details mentioned, just 'randomised'<br>Allocation concealment = not mentioned<br>Blinding = not mentioned and n/a<br>Not ITT analysis<br>Powered study (Hypoglycaemic. awareness, |
| | | | | | | HbA1c, % (SD) | HyP:7.2 (0.8)<br>C: 7.1 (0.9) | |
| | | | | | | Hypoglycaemic. -severe, episodes/patient year (SD) | HyP:0.9 (1.9)<br>C: 1.2 (2.0) | |
| | | | | | | Hypoglycaemic. – very severe, episodes/patient year, % | HyP:0.3 (1.1)<br>C: 0.6 (1.2) | |

| Reference | Study type | Number of patients | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| with type 1 diabetes. Diabetes.Metab.Res.Rev. 23 (7):528-538, 2007.<br><br>REF ID: HERMANNS 2007 | | diabetes and hypoglycaemic.<br>MDI or CSII<br>age 18-70 year<br>At least 1 episode of severe hypoglycaemic. in past 12 months (requiring 3rd party assistance) OR high risk of severe hypoglycaemic. (defined as impaired hypo awareness and tight glycaemic control (HbA1c<6.5 %) and disease duration >10 years). | (1/week)<br>Focus of sessions: inform patients about causes and correct treatment of hypoglycaemic. unawareness.<br>learned that frequent hypoglycaemic. episodes reduce window of opportunity for effective treatment and that avoidance of low blood glucose values improves hypoglycaemic. awareness.<br>Learnt symptoms of hypoglycaemic., used diaries and blood glucose estimation to heighten hypoglycaemic. perception, and developed hypo checks to detect early signs of neuroglycopenia<br>Focussed on detection of hypoglycaemic symptoms AND participants' views on causes and consequences of hypoglycaemic. as well as individual glycaemic targets in order to modify dysfunctional treatment goals or health beliefs. | treatment with regard to Hypoglycaemic avoidance were repeated.<br>Adaptation of insulin dosage and relationships between CHOs and insulin demand. | | Hypoglycaemic. unawareness, HAQ | HyP:0.3 (1.1)<br>C: 0.6 (1.2)<br>MD 0.7 (95% CI 0.1, 1.2); p=0.024 (favours Hypoglycaemia) | VAS)<br>Drop-outs = acceptable (<20%) |
| | | | | | | Hypoglycaemic. awareness, VAS | HyP:6.1<br>C: 5.3<br>MD 0.8 (95% CI 0.2, 1.4); p=0.015<br>(favours Hypoglycaemia) | |
| | | | | | | PAID | Hypoglycaemia: 23.3 (11.7)<br>C: 24.0 (11.4) | |
| | | | | | | Depression, CES-D | Hypoglycaemia: 12.6 (7.4)<br>C: 12.1 (7.0) | |
| | | | | | | Anxiety, STAI | Hypoglycaemia: 37.6 (6.5)<br>C: 37.1 (6.1) | |

| Reference | Study type | Number of patients | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | Exclusion criteria: Cancer diagnosis, dementia, pregnancy or diagnosis of current psychiatric disease. | The importance of immediate treatment was stressed, and possible reasons for delayed hypoglycaemic. treatment was analysed.<br>patients analysed their individual insulin treatment with regard to low blood glucose events.<br>Also discussed coping with activities that may pose a risk of hypoglycaemic.; social aspects of hypoglycaemic., and dangers of hypoglycaemic.<br><br>Outcomes:<br>Hypo unawareness (HAQ): Low score is better<br><br>Anxiety (STAI): low score is better<br><br>PAID: low score is better<br><br>Depression (CES-D): lower score = better | | | | | |

| Reference | Study type | Number of patients | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |

**Table 70: Trento 2011**[159]

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M. Trento, A. Trinetta, C. Kucich, G. Grassi, P. Passera, S. Gennari, V. Paganin, S. Tedesco, L. Charrier, F. Cavallo, and M. Porta. Carbohydrate counting improves coping ability and metabolic control in patients with Type 1 diabetes | RCT<br><br>1 centre in Italy | n=56<br><br>(n=27 CCP; n=29 GC)<br><br>Inclusion criteria:<br>type 1 diabetes<br>Diabetes onset before age 30 years<br>start of insulin treatment within 1 year of diagnosis<br>age <70 years<br>All patients on 4-day insulin injections and | | CCP n=27 | GC n=29 | Carbohydrate counting programme (CCP) embedded into the usual group care continuing education programme<br><br>ITT: n=27<br>As for group care group but with CCP added<br>CCP consisted of 8 sessions including: recognition and how to properly manage hypoglycaemic.; recognising effects | Control (GC) – group care continuing education programme<br><br>ITT: n=29<br><br>8 session education (every 3-4 months)<br>Facilitators were a<br>Used principles of adult learning<br>Sessions & group discussions | 30 months | DQoL - change from baseline values (SD) | CCP: -10.7 (1.3)<br>GC: -8.3 (1.47) | Funding: None mentioned.<br><br>Risk of bias:<br>Randomisation = no details mentioned, just 'randomised'<br>Allocation concealment = not mentioned<br>Blinding = not mentioned and n/a<br>ITT analysis (no drop-outs)<br>Powering not mentioned<br>Drop-outs = acceptable |
| | | | Age, years (SD) | 37.3 (12.6) | 36.8 (7.9) | | | | DQoL - final values (SD) | CCP:78.0 (9.9)<br>GC: 80.4 (11.7)<br>MD (final scores): -2.72 (-6.7, 1.2) NS | |
| | | | Women, % | 33 | 59 | | | | Hypoglycaemic. - severe, episodes during study (SD) | CCP: 5<br>GC: 6 | |
| | | | HbA1c, % (SD) | 7.6 (1.3) | 7.7 (1.24) | | | | | | |
| | | | Diabetes, | 22.0 | 21.1 | | | | HbA1c %, | CCP:0.21 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| managed by Group Care. J.Endocrinol. Invest. 34 (2):101-105, 2011.<br><br>REF ID: TRENTO 2011 | | practised self-monitoring of blood glucose<br>None were on lipid lowering agents | mean years (SD) | (10.8) | (9.5) | of insulin on patients own therapy with daily activities: studying, work, physical activities, eating; define effects of various foods on blood glucose and identify foods containing CHO; identify which CHO-rich foods are to be preferred and about sweetening agents and dietetic products;<br><br>All patients did at least 8 group care sessions, whether they were allocated to CCP or not. | were concerned with motivational aspects, acceptance of diabetes, psychosocial problems, & coping strategies.<br>patients are helped to identify & share their problems & successes with other members & report their personal experience.<br>Education programme included cognitive and psychomotor abilities<br>Included a patented educational | | change from baseline values (SD) | (0.18)<br>GC: -0.24 (0.22)<br>MD*: -0.63 (-1.2, -0.03); p<0.05 | (<20%) |
| | | | DQoL | 88.7 (9.2) | 88.7 (12.5) | | | | HbA1c %, final values (SD) | CCP: 7.2 (0.9)<br>GC: 7.9 (1.4) | |
| | | | Knowledge of diabetes, GISED (SD) | 9.3 (1.7) | 10.0 (1.1) | | | | Knowledge of diabetes, GISED, final values | CCP:10.6 (0.6)<br>GC: 10.2 (0.9) | |
| | | | NS differences between groups for any of the baseline characteristics | | | | | | Knowledge of diabetes, GISED, change from baseline | CCP: +1.3 (0.24)<br>GC: +0.17 (0.071) | |
| | | | Drop-outs (30 months):<br>None mentioned<br><br>Outcomes:<br>Severe hypoglycaemic: episodes requiring third | | | | | | *adjusted for gender, age, schooling, duration of diabetes, years of attendance at clinic, and baseline values of the dependent variable. | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | party help (that is, glucagon injection, iv glucose and/or hospital admission.<br>Diabetes QoL questionnaire (DQoL): 4 scales: satisfaction, impact, diabetes worry & social/ vocational worry. 46 core items, each item scores between1 (very satisfied) and 5 (very dissatisfied). Total score thus range: 46 (best QoL) to 230 (worst QoL).<br>CSI (coping)<br>Knowledge of diabetes: 11 item scale questionnaire (GISED) – correct answers = 1 point, incorrect = 0. So total score range 0-11. Higher score = better. | | support kit & operating manual<br>Sessions = structured | | | | |

**Table 71: HAATT (Cox 2004)[31]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D. J. Cox, B. | RCT | n=60 | | HAAT | SMB | SMBG + HAATT | SMBG (self- | 2 | HbA1c, % (6 | HAAT:8.0 | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kovatchev, D. Koev, L. Koeva, S. Dachev, D. Tcharaktchiev, A. Protopopova, L. Gonder-Frederick, and W. Clarke. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. Int.J.Behav. Med. 11 (4):212-218, | 3 centres in Bulgaria | (n=30 in each group)<br><br>Inclusion criteria:<br>type 1 diabetes<br>Adults<br>History of ≥2 episodes of severe hypoglycaemic. in the past year | | n=30 | G n=30 | (Hypoglycaemia, Anticipation, Awareness and Treatment Training) programme to reduce Hypoglycaemic.<br><br>ITT: n=30<br><br>As for SMBG group but with additional HAATT programme.<br>Psycho-educational treatment programme (structured)<br>Group session (10 people) over 7 weeks<br>Daily homework exercises and chapters to go through.<br>Contents included:<br>1. Anticipation and prevention of hypoglycaemic. (risk and | monitoring blood glucose)<br><br>ITT: n=30<br><br>SMBG meter and supplies for 4 months (1 month pre and post-treatment and 2 months of treatment)<br>Educated by physician during the treatment period on the meaning and use of SMBG data.<br><br>In both groups, all participants received routine medical care which involved | months of treatment; follow-up at 6 months post treatment and 13-18 months | months) | SMBG: 8.1 | Grants from the NIH's Fogarty International and from Roche Diagnostics, Germany.<br><br>Risk of bias:<br>Randomisation = no details mentioned, just 'randomised'<br>Allocation concealment = not mentioned<br>Blinding = not mentioned and n/a<br>ITT analysis (no drop-outs)<br>No mention of powering<br>Drop-outs = acceptable (<20%) |
| | | | Age, years (SD) | 37.6 (9.0) | 45.9 (13.3) | | | | Hypoglycaemic. - severe/subject (6 months) | HAAT:0.4<br>SMBG: 1.7 (SS: p=0.03) | |
| | | | Women, % | 47 | 46 | | | | Hypoglycaemic. - severe/subject (18 months) | HAAT:1.76<br>SMBG: 3.65 (SS: p<0.023) | |
| | | | HbA1c, % (SD) | 8.08 (0.74) | 7.98 (0.70) | | | | Hypoglycaemic. unawareness (% detection of low blood glucose) – 6 months | HAATT: 70%<br>SMBG: 55%<br>(SS: p=0.005) | |
| | | | Hypoglycaemic. - severe/subject | 2.0 | 1.8 | | | | | | |
| | | | Diabetes, mean years (SD) | 13.93 (9.33) | 14.0 (7.64) | | | | | | |
| | | | Hypoglycaemic. unawareness (% detection of low blood | 52% | 58% | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 2004.<br><br>REF ID: COX 2004A | | | glucose)<br><br>NS differences between groups for any of the baseline characteristics<br><br>Drop-outs:<br>None mentioned<br><br>Outcomes:<br>Severe hypoglycaemia – inability to treat oneself due to hypoglycaemic stupor or unconsciousness<br>Blood glucose measurements<br>Daily diaries used for recording outcomes | consequences of severe hypoglycaemic. (SH) & personal goals for treatment established; Insulin kinetics & how to anticipate when their insulin action is at its peaks & nadirs; CHO counting & matching intake to insulin action; demands of physical activity & when to optimally perform exercise relative to insulin levels, and how to cover energy expenditure with appropriate CHOs)<br>2. Recognition & treatment of hypoglycaemic. (recognising, interpreting & using neuroglycopenic & neurogenic cues that signal the | monthly physician visits to make adjustments in insulin, food, and exercise routine based on daily SMBG data. | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | presence of hypoglycaemic; using this info to better anticipate, prevent, recognise & treat low blood glucose<br>3. How to use all the info once classes finished. | | | | | |

**Table 72: ROSSI 2010[130]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M. C. Rossi, A. Nicolucci, Bartolo P. Di, D. Bruttomesso, A. Girelli, F. J. Ampudia, D. Kerr, A. Ceriello, Cde L. Mayor, F. Pellegrini, D. | RCT<br><br>Multicentre, Italy, Spain and UK | n=130<br><br>(n=67 DID; n=63 CCP)<br><br>Inclusion criteria:<br>type 1 diabetes<br>≥18 years | | DID n=67 | CCP n=63 | Diabetes Interactive Diary (DID) – telemedicine system<br><br>ITT: n=67<br><br>Software installed into mobile phone: | Carbohydrate counting programme (CCP) standard education<br><br>ITT: n=63<br><br>Standard | 6 months | HbA1c %, 3 month change from baseline values (SD) | DID: -0.5 (0.8)<br>CCP:-0.4 (0.6) | Funding: Me.Te.Da (developer of DID) and Lifescan, Milpitas USA (medical consultant for Me.Te.Da.)<br><br>Risk of bias: |
| | | | Age, years (SD) | 35.4 (9.5) | 36.1 (9.4) | | | | HbA1c %, 6 month change from baseline | DID: -0.4 (0.9)<br>CCP: -0.5 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Horwitz, and G. Vespasiani. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. Diabetes Care 33 (1):109-115, 2010.<br><br>REF ID: ROSSI 2010 | | age<br>no previous education on CHO counting<br>treatment with MDI of short- and long-acting insulin analogues OR with continuous sc insulin infusion<br>practiced self-monitoring of blood glucose at least 3 times/day<br>adequate familiarity in use of mobile phones<br>possession | | | | automatic CHO/insulin bolus calculator, records blood glucose and insulin dose injections in real time<br>patient-physician/dietician communication via short text message<br>Aim to improve metabolic control, reduce education time and increase QoL<br>Allows patients to manage a flexible diet and calculate the matching insulin bolus at each meal<br>Additional calculation of basal insulin dose based on fasting blood glucose values and presence of hypoglycaemic. | educational approach lasting up to 3 months | | values (SD) | (1.0) | Randomisation =unclear. stratified by centre, permuted block randomisation<br>Allocation concealment = adequate. Telephone call to co-ordinating centre<br>Blinding = none. Open label<br>ITT analysis (LOCF)<br>Powered study (HbA1c)<br>Drop-outs = acceptable (<20%) |
| | | | Women, % | 55 | 59 | | | | Hypoglycaemic. - severe, episodes during study (SD) | DID: 0<br>CCP: 0 | |
| | | | HbA1c, % (SD) | 8.2 (0.8) | 8.4 (0.7) | | | | | | |
| | | | Diabetes, mean years (SD) | 17.1 (10.8) | 15.8 (10.7) | | | | SF-36* physical component, 3 month change from baseline values (SD) | DID: 1.3 (6.6)<br>CCP: -1.7 (7.0) | |
| | | | SF-36 physical component(SD) | 50.3 (8.9) | 50.6 (4.9) | | | | SF-36* physical component, 6 month change from baseline values (SD) | DID: 0.6 (7.3)<br>CCP: 1.0 (4.9) | |
| | | | | | | | | | SF-36* mental component, 3 month change from baseline | DID: 2.2 (8.1)<br>CCP: -0.3 (6.8) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | of personal mobile phone card<br><br>Inclusion criteria:<br>treated with NPH insulin OR soluble regular insulin<br>eating disorder<br>pregnant<br>unable to send or receive short text messages<br>unable or unwilling to give informed consent<br>any other disease or condition that may interfere | | | | episodes<br>System suggests daily CHO intake, summing the amount of CHO consumed progressively. patients can decide what to eat during the meal, choosing between all the foods listed in the software; the quantification of the total calories and CHO consumed is facilitated by a list of pictures showing the specific food and amount ingested. The CHO-to-insulin ratio and the glycaemic correction factor, identified and prescribed by the HC professional, together with other info already | | | values (SD) | | |
| | | | | | | | | | SF-36* mental component, 6 month change from baseline values (SD) | DID: 4.2 (12.5)<br>CCP: -0.8 (10.2) | |
| | | | | | | | | | Hospital admissions during study | DID: 0<br>CCP: 0 | |
| | | | NS differences between groups for any of the baseline characteristics<br><br>Drop-outs (6 months):<br>n=9 (DID) – n=1 Lost to follow-up, n=8 discontinued intervention<br>n=2 (CCP)<br><br>Outcomes:<br>Severe hypoglycaemia: episode requiring medical intervention<br>SF-36 scores: Higher score = | | | | | | *NOTE: SF-36 scores were from questionnaires given to a subgroup of patients (n=30 in each group) | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | with compliance or completion of study. | better QoL | filled out in the DID (eg. physical activity, Glycaemic target, insulin dose and specific events), allow it to auto calc. and suggest the most appropriate insulin dose to be injected.<br>DID also provides regular feedback to the patient (periodically sent as text messages and reviewed on the PC of the physician)<br>then any new behavioural prescription can be sent from the computer to the mobile phone, improving the communication between patients and physician.<br><br>Up to 2 week | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | training course given to patients using DID | | | | | |

**Table 73: BGAT study (Snoek 2008)[149]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | [RO: unclear; as says 2 not avail l for analysis and so 86 were left for analysis, Implies 2 more were included at randomisation. This perhaps not ITT either?? UNCLEAR – although abstract says 86 randomised!] | | | | | | | | | | |
| F. J. Snoek, N. C. W. Van Der Ven, J. W. R. Twisk, M. H. E. Hogenelst, A. M. E. Tromp-Wever, H. M. van der Ploeg, and R. J. Heine. Cognitive behavioural therapy | RCT<br><br>Single centre in The Netherlands | n=86<br><br>(n=41 in BGAT; n=45 in CBT)<br><br>Inclusion criteria:<br>type 1 diabetes for at least 1 year<br>Adults<br>HbA1c | | BGAT n=41 | CBT n=45 | BGAT (blood glucose awareness training) programme<br><br>ITT: n=??<br>ACA: n=41<br><br>Programme is standard BGAT aims to help type 1 diabetes | CBT<br><br>ITT: n=??<br>ACA: n=45<br><br>6 weekly group sessions<br>CBT programme specifically designed for type 1 diabetes patients with | 6 weeks intervention;<br><br>3, 6 and 12 months follow-up (post-intervention) | HbA1c, %<br>Between 6 and 12 months | NS change in either group | | Funding: Grant from the Dutch Diabetes Foundation and 3 individuals.<br><br>Risk of bias:<br>Randomisation = no details mentioned, just 'randomised' |
| | | | Age, years (SD) | 37.4 (11.1) | 38.1 (9.7) | | | | HbA1c in depressed patients (baseline, 6 months, 12 months) | BGAT: NS decrease in depressed patients (9.5%, 9.5% and 9.4%) | CBT: SS decrease (9.5%, 8.9%, 8.8%) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic patients: Long-term effects on HbA1c moderated by depression. A randomized controlled trial. Diabet.Med. 25 (11):1337-1342, 2008.<br><br>REF ID: SNOEK 2008 | | ≥8.0% on 2 consecutive occasions prior to the study<br>MDIs (≥2) or continuous sc insulin infusion (CSII)<br><br>Exclusion criteria:<br>pregnancy<br>severe medical co-morbidity<br>current treatment for cancer<br>visually too impaired to read<br>too functionally impaired to attend classes<br>insufficient Dutch | | | | patients prevent and correct in a timely fashion, extreme blood glucose excursions by means of improving symptom discrimination and understanding of the interaction between insulin, food intake and physical activity.<br><br>BGAT and CBT are comparable in format and intensity<br>In both | prolonged self-care difficulties resulting in elevated Glycated Hb and thus at an increased risk for microvascular complications.<br>patients given info sheets and homework assignments.<br>Topics covered: my barriers and goals; how my thoughts impact on my feelings and self-care; coping with stress; worries about complications; diabetes and relationships; being part of | | | | | Allocation concealment = not mentioned<br>Blinding = not mentioned and n/a<br>ITT analysis<br>Powered study (HbA1c)<br>Drop-outs = NOT acceptable (>20% in one group and large difference between groups) |
| | | | | | | | | | PAID, 6 months | 44.4<br>NS<br>p=0.99 | 38.7 | |
| | | | Women, % | 66 | 51 | | | | PAID, 12 months | 45.4<br>NS<br>p=0.68 | 38.3 | |
| | | | HbA1c, % (SD) | 9.1 (1.1) | 8.8 (1.3) | | | | CES-D, 6 months | 15.8<br>NS<br>p=0.74 | 13.5 | |
| | | | Diabetes, mean years (SD) | 18.8 (10.9) | 17.8 (10.1) | | | | CES-D, 12 months | 15.5<br>NS<br>p=0.19 | 15.4 | |
| | | | PAID | 49.0 | 43.4 | | | | | | | |
| | | | CES-D | 16.9 | 15.7 | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | NS differences between groups for any of the baseline characteristics except education level<br><br>Drop-outs (completed <4/6 sessions):<br>During intervention BGAT: | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | reading skills<br>substance abuse<br>learning difficulties<br>history of psychiatric treatment for schizophrenia<br>organic mental disorder or bipolar disorder | 8%; CBT: 27%<br>After 3 months f-up: 2 excluded from analysis due to cancer or pregnancy<br><br>Outcomes:<br>HbA1c<br>SMBG<br>QoL scales: CIDS, PAID and CES-D.<br>CIDS = Confidence in Diabetes Self-care;<br>PAID = Problem areas in Diabetes; measures diabetes emotional stress. 20 items scored from 0-4 (no problem – very serious problem). Transformed total scores to a scale of 0-100, higher scores represent higher levels of distress.<br>CES-D = Centre for Epidemiological studies – depression scale (20-item measure of depressive symptoms in the last week). Total scores 0-60 – higher scores indicate worse depressive symptoms. Scores ≥16 are considered high and | groups: BGAT and CBT delivered by teams of experienced diabetes nurse educators and clinical psychologist | diabetes team.<br>Programme addresses the psychological barriers to improving diabetes self-management helping patients to identify, challenge and reframe their negative beliefs around diabetes and self-care that often result in feelings of frustration and 'letting it all go' rather than keeping up the effort.<br><br>In both groups, during the study patients continued to | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | indicative of clinical depression) | | receive usual care | | | | |

**Table 74: TERENT 1985[151]**

| Reference | Study type | Number of patients | Patient characteristics | | | | | Intervention and Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Terent, O. Hagfall, and U. Cederholm. The effect of education and self-monitoring of blood glucose on glycosylated hemoglobin in type I diabetes. A controlled 18-month trial in a represent | RCT<br><br>Single centre – 1 area of Sweden | n=37<br><br>(n=10 in EDU + SMBG, n=8 in SMBG.=, n=9 in EDU, n=10 in REF)<br><br>Inclusion criteria:<br>T1aD<br>Duration ≤20 years<br>Adults (≥17 years) | | EDU + SMBG (A) n=10 [RO Not using these two separately – at 6 months using all EDU (A+C) … | SMBG (B) n=8 vs. REF (B+D) and at 6 12 and 18 months using EDU (C) and REF (D)] | EDU (C) n=9 | REF (D) n=10 | EDU + SMBG (A)<br>ITT: n=10<br>ACA: n=10<br><br>SMBG (B) EDU (C)<br>ITT: n=8 ITT: n=9<br>ACA: n=8<br>ACA: n=9<br><br>REF (D)<br>ITT: n=10<br>ACA: n=10<br><br>First randomisation: patients randomised to 2 groups : n=19 | 6 months education followed by 6 months SMBG<br><br>6, 12 and 18 months follow-up (18 months = 6 months post-intervention)<br><br>6 months results = EDU (group A+C) vs. | HbA1c, %<br>6 months | A =12.2 (3.2)<br>B= 12.3 (2.5)<br>C= 10.1 (1.7)<br>D= 10.0 (2.0) | Funding: Not mentioned<br><br>Risk of bias:<br>Randomisation = no details mentioned, just 'randomised'<br>Randomisation was done twice: EDUCATION vs. REFERENCE and then each of those were randomised into two: either |
| | | | Age, | 29 (6) | 28 (7) | 26 | 25 (5) | | | HbA1c, % | A =11.0 | |

| Reference | Study type | Number of patients | Patient characteristics | | | | | Intervention and Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ative population. Acta medica Scandinavica 217 (1):47-53, 1985.<br><br>REF ID: TERENT 1985 | | Exclusion criteria: kidney transplantation pregnant alcoholic | years (SD) | | | (5) | | formal education vs. n=18 reference (standard therapy)<br>6 months duration<br><br>Second randomisation:<br>After 6 months<br>Each group randomised into 2 further groups: to additional SMBG education or continuing previous education or reference (standard therapy)<br>Thus 4 groups in total after 2nd randomisation: EDU + SMBG vs. EDU vs. SMBG vs. REF<br>Duration 6 months<br><br>Follow-up:<br>patients followed-up at a further 6 months (18 months total) | CONTROL (group B + D)<br><br>12 and 18 months results = EDU + SMBG (group A) vs. EDU (group C) vs. SMBG (group B) vs. CONTROL (group D) | 12 months | (2.6)<br>B= 10.8 (1.0)<br>C= 9.9 (2.5)<br>D=9.5 (3.2) | additional SMBG or continuing previous education or reference<br>Allocation concealment = not mentioned<br>Blinding = not mentioned<br>ITT analysis (no drop-outs)<br>Powering: not mentioned<br>Drop-outs = acceptable (<20%) |
| | | | Women, % | 40 | 65 | 56 | 20 | | | HbA1c, % 18 months | A =10.2 (1.9)<br>B= 9.8 (3.0)<br>C= 10.2 (2.1)<br>D= 10.4 (2.1) | |
| | | | HbA1c, % (SD) | 12.3 (3.2) | 11.8 (1.4) | 11.2 (2.0) | 11.1 (2.3) | | | Severe hypoglycaemic. – episodes treated in hospital | A+B: n=7<br>C+D: n=14<br>[RO can't use as combined data groups] | |
| | | | Diabetes, mean years (SD) | 12 (6) | 13 (4) | 5 (4) | 13 (5) | | | Ketoacidosis – number patients treated for | A= 2<br>B =0<br>C =3<br>D =0 | |
| | | | BMI, kg/m2 (SD) | 22 (2) | 22 (2) | 21 (2) | 24 (4) | | | Knowledge - % correct test answers | 6 months<br>A =65<br>C =55 [RO: wrong groups – | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention and Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | Education:<br>Individual education<br>6 x 1hr lessons during 1 month<br>Lessons arranged according to Swedish board of Health and Welfare<br>Special model constructed and used by physicians and dietician to explain interplay between food consumption, blood glucose levels, insulin and urinary glucose. excretion.<br>Taught also about hypo- and hyper-glycaemia, foot care, injections, and urine testing techniques.<br>Questions also asked of a social nature<br>Materials given to take away | | | can't use data] | |
| | | | | | | Adherence/compliance - % attending all sessions | A =100%<br>C =100%<br>[RO wrong groups – can't use data] | |
| | | | | | | | | |
| | | | NS differences between groups for any of the baseline characteristics except duration of type 1 diabetes lower in EDU group. | | | | | |
| | | | Drop-outs:<br>None<br><br>Outcomes:<br>Compliance/adherence - measured by number of patients attending all sessions<br>Knowledge of diabetes and management – diabetes, insulin, oral hypoglycaemics, testing and physical exercise. Measured by percentage of correct answers to the test. | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention and Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | Questionnaire at 1 and 6 months after the course<br>Encouraged to test urine for glucose. and ketone bodies.<br><br>SMBG:<br>Method demonstrated of SMBG<br>Finger-pricking and reagent strips<br>Instructed to perform test every day but at least 2 days every fortnight (weekly testers).<br>Tests done before breakfast, 1-2 hours after the 2 main meals and at bedtime.<br>Encouraged to change insulin dose to achieve pre-prandial values <7 mmol/litre and post-prandial <10 mmol/litre.<br>Had to record | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention and Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | hypoglycaemia.<br><br>Standard therapy:<br>patients in group B and D continued their pre0-trial checking habits<br>Fasting Blood glucose and 24h urinary glucose. Values were measured every 3rd month at outpatient dept.<br>Physical examination performed 6-monthly.<br>Patients equipped with devices for monitoring of urinary glucose. | | | | |

**Table 75: TRENTO 2005[158]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures at 3 years – ACA data | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures at 3 years – ACA data | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| M. Trento, P. Passera, E. Borgo, M. Tomalino, M. Bajardi, A. Brescianini, M. Tomelini, S. Giuliano, F. Cavallo, V. Miselli, P. Bondonio, and M. Porta. A 3-year prospective randomized controlled clinical trial of group care in type 1 diabetes. Nutrition, metabolism, and cardiovascular | RCT<br><br>Single centre in Italy | n=62<br><br>(n=31 in EDU; n=31 in Control)<br><br>Inclusion criteria:<br>type 1 diabetes<br>Adults<br>Onset before age 30 and insulin treatment started within 1 year of diagnosis<br>Age <70 and at least 1 year previous attendance in the clinic<br>All patients were on 4-daily insulin | | EDU n=31 | Control (C) n=31 | Structured education programme (group)<br><br>ITT: n=31<br>ACA: n=30<br><br>15 group sessions over 3 years<br>9 education sessions over 18 – 27 months (one session every 2-3 months)<br>6 more visits delivered over the remainder of the 36 months observation<br>Programme developed further based on two rounds of focus group sessions and | Usual care (1:1 consultations) - control (C)<br><br>ITT: n=31<br>ACA: n=28<br><br>Continued to follow habitual 2-3 monthly 1:1 consultations in the diabetes clinic<br>Received individual education sessions from the same psychopaedagogist involved in the group care<br>Also offered 15 individual visits over the 3-year observation period. | 18-27 months intervention;<br><br>3 year follow-up (includes intervention time) | | EDU | C | Funding: Compagnia di San Paolo, Turin, Italy.<br><br>Risk of bias:<br>Randomisation = random number tables<br>Allocation concealment = not mentioned<br>Blinding = single blind (outcome assessors)<br>Not ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%) |
| | | | | | | | | | HbA1c, % (SD) FINAL SCORE | 7.88 (0.20) | 8.79 (1.38) | |
| | | | Age, years median (IQR) | 27 (23-33) | 31 (25-43) | | | | HbA1c % (95% CI) CHANGE FROM BASELINE<br><br>thus SD is 1.21 | -0.38 (- 0.83 to 0.07) | -0.40 (- 0.85 to 0.04)<br>thus SD is -1.15 | |
| | | | Women, % | 39 | 42 | | | | Knowledge of diabetes – GISED (SD) FINAL SCORE | 47.45 (6.03) | 43.34 (6.18) | |
| | | | HbA1c, % (SD) | 8.3 (0.15) | 9.2 (1.64) | | | | Knowledge of diabetes - GISED (95% CI) CHANGE FROM BASELINE<br><br>thus SD is 4.14 | 3.10 (1.56 to 4.65) | 0.24 (- 0.32 to 0.80)<br>thus SD is 1.44 | |
| | | | Diabetes, median years (IQR) | 16 (13 - 19) | 15 (12-19) | | | | DQoL (SD) FINAL SCORE | 70.55 (12.2) | 84.06 (11.35) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures at 3 years – ACA data | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| diseases : NMCD 15 (4):293-301, 2005.<br><br>REF ID: TRENTO 2005 | | injections and practiced SMBG.<br><br>Exclusion criteria:<br>none given | GISED (knowledge of diabetes) | 44.3 (6.97) | 43.10 (6.28) | feedback<br>Programme topics included: differences between type 1 diabetes and type 2 diabetes; principles of nutrition; classification of nutrients; composition of food and food exchanges (personal habits and day-to-day management; how to embed eating patterns into daily life as tastes and habits change over time); physical exercise (adaptation of insulin dosage and daily activity); hypoglycaemia and hyperglycaemia | | | DQoL (95% CI)<br>CHANGE FROM BASELINE | -8.82 (-12.51 to -5.14)<br><br>thus SD is 9.87 | 3.34 (2.38 to 430)<br><br>thus SD is 551.4 | |
| | | | QoL (DQoL score) | 79.4 (13.9) | 80.7 (11.5) | | | | | | | |
| | | | NS differences between groups for any of the baseline characteristics except education level (schooling).<br><br>Concomitant medication:<br>7 patients in each group were on LisPro insulin, none were on hypolipidaemic agents.<br><br>Drop-outs:<br>n=1 (EDU) and n=3 (controls) due to lost-to-follow-up or not | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures at 3 years – ACA data | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | participating in final visit.<br><br>Outcomes:<br>HbA1c<br>QoL scales: DQoL<br>DQoL = 4 primary scales: satisfaction, impact, diabetes worry, and social/vocational worry. 46 core items each item score between 1 (very satisfied) and 5 (very dissatisfied. Total score thus ranges between 46 (higher QoL) and 230 (lower QoL).<br>Knowledge of type 1 diabetes (GISED): 57-item questionnaire. Correct answers scored 1 point, wrong answers 0. Thus total score of 57. | (why they occur, how to recognise and manage them, how to inform relatives and friends); areas of insulin injection and their rotation; retinopathy, neuropathy, microalbinuria and nephropathy (self-care, when and how to screen); hypertension and CV aspects.<br>Also discussed HbA1c and day-to-day problems whenever they felt necessary. | | | | | |

**Table 76: KORHONEN 1983[84]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T. Korhonen, J. K. Huttunen, A. Aro, M. Hentinen, O. Ihalainen, H. Majander, O. Siitonen, M. Uusitupa, and K. Pyorala. A controlled trial on the effects of patient education in the treatment of insulin-dependent diabetes. Diabetes Care 6 (3):256- | RCT<br><br>9 centres in Finland | n=77<br><br>(n=39 in EDU; n=38 in Control)<br><br>Inclusion criteria:<br>Insulin-dependent diabetes<br>Treated with insulin<br>Age 16-57 years<br>Duration of diabetes 1-17 years<br>No symptoms or signs of significant micro- or macro-angiopathy<br>No systematic | | EDU n=39 | Control (C) n=38 | Intensive education programme (group and individual)<br><br>ITT: n=39<br>ACA: n=39<br><br>5 days in-hospital intensive education ( 2 x 30 min sessions plus pre-pre-printed material)<br>Instruction was both individually and in small groups<br>Given by a team of two physicians, a dietician, and two teaching nurses who specialised in the treatment of diabetes. | Traditional education at the hospital - control (C)<br><br>ITT: n=38<br>ACA: n=38<br><br>Received in-hospital traditional 'old-fashioned' education that was given before the organisation of diabetes treatment.<br>Met only the physicians during follow-up visits and not advised to change insulin dose without checking with the doctor. | 5 days intervention<br><br>3 month and 1 year follow-up (post-intervention) | | EDU | C | Funding: Grants from National Research Council for Medical Sciences, Finland; Nordisk Insulinfond; Finnish Cultural Foundation; Foundation for Nutrition Research, Finland.<br><br>Risk of bias:<br>Randomisation = unclear.<br>Stratified according to age, gender and diabetes duration (method not given)<br>Allocation concealment = not mentioned<br>Blinding = not |
| | | | Age, years mean (SD) | 31 (11.5) | 35 (12.3) | | | | Knowledge of diabetes % correct answers (SD) FINAL SCORE | 3mths: 79.5 (1.9)<br><br>1 year: 82.3 (1.8) | 3mths: 72 (2)<br><br>1 year: 73.4 (2) | |
| | | | Women, % | 46 | 45 | | | | | | | |
| | | | Diabetes, mean years (SD) | 7.8 (3.7) | 8 (4) | | | | | | | |
| | | | Knowledge of diabetes % correct answers (SD) | 69.5 (2.5) | 63.2 (2.3) | | | | | | | |
| | | | SS differences between groups for baseline knowledge of diabetes but NS for all other characteristics. | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 261, 1983.<br><br>REF ID: 150 (in old GL) | | education before the start of the study.<br><br>Exclusion criteria:<br>none given | Concomitant medication:<br>Not mentioned<br>Drop-outs:<br>None reported<br><br>Outcomes:<br>Compliance<br>Knowledge<br>Diabetic control (glucose measurements)<br>Compliance: was evaluated in terms of diet history, with a 24 hour recall method at baseline and for every 3 months through to 18 months.<br>Knowledge was assessed at baseline and at 3 and 12 months using a self-administered multiple choice test designed for the study. The questionnaire contained 105 questions covering areas such as diet, insulin administration, urine testing , hypoglycaemia, hyperglycaemia, and foot care<br>Diabetic control: satisfactory metabolic control used abstract criteria with the | Met nurse and physician at all follow-up times (1,3,6,9,12,15,18 month post-intervention)<br>Instructed to adjust their insulin dose during sick days and in other special situations and to call the nurse whenever problems from diabetes were encountered. | | | | | mentioned<br>ITT analysis (no drop-outs)<br>No mention of powering<br>Drop-outs = acceptable (NONE = <20% )<br>Different extra care and advice given to the intervention group |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | following 3 criteria having to be met 1) fasting glucose concentration in morning before visit <7.2mmol/litre 2) urinary glucose excretion on the day preceding the visit <20g/24hrs 3) more than 75% of the urine tests since the previous visit free of glucose | | | | | | |

**Table 77: deWEERDT 1991[35]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures at 6 months | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I de Weerdt, A. P. Visser, G. J. Kok, O. de Weerdt, and E. A. van der Veen. Randomized controlled multicentre evaluation of an education programme for insulin-treated | Cluster RCT<br><br>15 centres in The Netherlands | n=558<br><br>(n=355 in EDU; n=203 in Control)<br><br>Inclusion criteria:<br>Age 18 to 65 years<br>Insulin treatment | | EDU n=355 | Control (C) n=203 | Structured Education programme – professional led or patient led (combined data for the 2 groups)<br><br>ITT: n=355<br>ACA: ?? unclear | Usual care - control (C)<br><br>ITT: n=203<br>ACA: ?? unclear<br><br>Not given any extra education | 4 weeks intervention<br><br>6 months (ie. 5 months post-intervention) | | EDU | C | Funding: Grants from National Research Council for Medical Sciences, Finland; Nordisk Insulinfond<br><br>Risk of bias: Randomisati |
| | | | Age, years mean (SD) | 44 | 47 | | | | HbA1c %, mean (SE) CHANGE FROM BASELINE | -0.25 (0.15); Calculated SD = 2.8 | -0.1 (0.1) Calculated SD = 1.4 | |
| | | | Women, % | Equal distri | Equal distributi | | | | Hypoglycaemia | -0.05 (0.05) | -0.1 (0.0) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures at 6 months | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| diabetic patients: effects on metabolic control, quality of life, and costs of therapy. Diabetic Medicine. 8 (4):338-345, 1991.<br><br>REF ID: 1571 (in old GL) | | over 6 months<br>Able to understand and speak Dutch language<br><br>Exclusion criteria:<br>Pregnant | | butio n of sexes | on of sexes | Highly structured programme was on an out-patient basis<br>4 x weekly group sessions of 3 hours duration<br>A video film, a book, and some practice materials were used as part of the programme.<br>The lessons also had a motivational function.<br>Led by a trained nurse, a dietician or a patient with diabetes. | | | reactions per month - Grade 2<br>CHANGE FROM BASELINE<br>(SE) | Calcul ated SD = 0.9 | Calc ulat ed SD = 0 | on = cluster. Unclear. (method not stated)<br>Allocation concealment = not mentioned<br>Blinding = not mentioned<br>No mention of ITT analysis (drop-outs mentioned but unclear of how analysed or f data imputed or not)<br>No mention of powering<br>Drop-outs = acceptable (<20% ) |
| | | | Diabetes, mean years (SE) | 12 (0.7) | 13.8 (0.7) | | | | | | | |
| | | | HbA1c %, mean (SE) | 9.0 (1.7) | 9.2 (1.6) | | | | | | | |
| | | | Hypoglyc aemia reactions per month - Grade 2 | 0.2 (0.1) | 0.2 (0.0) | | | | COST DATA REPORTED in STUDY | | | |
| | | | NS differences between groups for any baseline characteristics.<br><br>Concomitant medication:<br>Not mentioned; insulin used similar in both groups (NS difference)<br><br>Drop-outs:<br>n=45 (7.5%) | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures at 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Outcomes:<br>HbA1c<br>Hypoglycaemia GRADE 2 – requiring assistance of a second person<br>QoL – REPORTED BUT NOT USING DATA (SCALES ARE NOT COMMON: The Bradburn Affect-Balance scale, a general measure of well-being) | | | | | | |

**Table 78: LENNON 1990[95]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures at 1 year | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| G. M. Lennon, K. G. Taylor, L. Debney, and C. J. Bailey. Knowledge, attitudes, technical competence, and blood | RCT<br><br>1 centre in the UK | n=74<br><br>(n=42 in EDU; n=32 in Control)<br><br>Inclusion criteria: Insulin- | | EDU n=31 | Control (C) n=25 | Structured Education programme (motivational and behavioural features) | Usual care - control (C)<br><br>ITT: n=32<br>ACA: n=25<br><br>received normal clinical care | 1 year intervention<br><br>Additional follow-up at 18 months (but only in intervention group) | | EDU | C | Funding: None mentioned.<br><br>Risk of bias:<br>Randomisation = Unclear. (method not stated)<br>Allocation |
| | | | Age, years mean (SD) | 32 (2.3) | 40 (2.5) | | | | HbA1c, % (SD) – 12 months | 10.5 (0.3) | 11.6 (0.4) | |
| | | | Women, % | 48 | 28 | | | | | | | |
| | | | HbA1c, % (SD) | 11.8 (0.4) | 11.8 (0.5) | | | | Knowledge of diabetes | 1 year: | 1 year: | |
| | | | Diabetes, | 11.7 | 15.8 | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures at 1 year | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| glucose control of Type 1 diabetic patients during and after an education programme. Diabetic Medicine. 7 (9):825-832, 1990.<br>.<br><br>REF ID: 1551 (in old GL) | | treated type 1 diabetes from diagnosis<br>Age <60 years<br>Duration of diabetes >1 year<br>Ideal body weight <130%<br>No serious complications<br>Not pregnant<br>Adequate understanding of English language<br><br>Exclusion criteria:<br>none given | mean years (SD) | (1.2) | (2.3) | ITT: n=42<br>ACA: n=31<br><br>Education programme<br>12 x meetings at monthly intervals<br>Different aspects of diabetes treatment and technical skills were considered.<br>Topics were: diet, insulin, hypoglycaemia, diabetic control, exercise and illness, ketones and hyperglycaemia, the new diet, complications of diabetes, new developments in research, and practical problems in | throughout, in which blood glucose control, diet, and insulin were reviewed at intervals of 3-6 months | | % correct answers (SD)<br>FINAL SCORE | 79.1 (3.5) | 56.3 (5.7) | concealment = not mentioned<br>Blinding = not mentioned<br>Not ITT analysis (completers)<br>No mention of powering<br>Drop-outs = HIGH (>20%) |
| | | | Knowledge of diabetes % correct answers (SD) | 62.7 (3.4) | 60.1 (4.6) | | | | | | | |
| | | | Most baseline variables were similar, but the mean age of the control group was greater than the intervention group ($p < 0.02$)<br><br>Concomitant medication:<br>Not mentioned<br><br>Drop-outs:<br>EDU: n=11 (35%) and C: n=7 (28%)<br><br>Outcomes:<br>HbA1c<br>Knowledge of diabetes (% questions correct):<br>At baseline was DKQ1 (9 item MCQ questionnaire) on the major areas of diabetes management<br>At 12 and 18 months was DKQ2 (16 item MCQ extended questionnaire to facilitate | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures at 1 year | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | discrimination amongst patients with improved knowledge. | self-management.<br>Teaching was by both individual and group format methods. | | | | | |

## G.2.2 Carb counting

**Table 79: BRAZEAU 2013 [19]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| A. S. Brazeau, H. Mircescu, K. Desjardins, C. Leroux, I. Strychar, J. M. Ekoe and R. Rabasa-Lhoret. Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. Diabetes Research and Clinical Practice. 99 (1):19-23, 2013. | Cross-sectional<br><br>Accuracy of patient CHO estimates | n=50<br>Inclusion criteria:<br>Adults aged ≥18 years<br>type 1 diabetes duration >6 months<br>Patients who had worn a CGM for 72 hours and completed concomitant food record assessing carb counting in ≥75% of meals<br><br>Exclusion criteria: | | | Patient estimate of CHO<br><br>Masked CGM placed. Participant taught by a dietician to complete the food diary including their CHO estimates and told to keep food and exercise habits normal. | Dietician assessment of CHO from food diary<br>Food diaries analysed by dietician using Food processor SQL. Mean absolute diff between patient CHO estimate and dietician CHO assessment calc. | 72 hours | HbA1c | Not reported | Funding:<br>Supported by Foundation and research centre of the CHUM, an operating grant, Canadian Institutes of Health Research and FRSQ.<br><br>Other:<br>Main outcome is the accuracy of patient estimates of CHO content and association with BG fluctuations.<br><br>Risk of bias:<br>Observation |
| | | | Age, years, mean (SD) | 42.7 (11.1) | | | | Major hypoglycaemia, | Not reported | |
| | | | Women, % | 48 | | | | Hypoglycaemia, events | Accuracy of patient CHO estimates was not significantly associated with the number of hypoglycaemias over the 72 hours | |
| | | | Diabetes duration, years, mean (SD) | 21.4 (12.7) | | | | Nocturnal Hypoglycaemia, | Not reported | |
| | | | BMI, kg/m2, mean (SD) | 25.1 (3.6) | | | | Hyperglycaemia, duration over 72 hour period | Low accuracy of CHO content estimates by patients was a predictor of longer time of hyperglycaemia (>10mmol/litre) and shorter time of BG between 4-10mmol/litre | |
| | | | HbA1c, %, geometric mean (SD) | 7.6 (1.2) | | | | | | |
| | | | Drop-outs: | | IN BOTH GROUPS:<br>• SCII (n=10) | | | QOL | Not reported | |
| | | | | | | | | Adverse events | Not reported | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: BRAZEAU 2013 | | | Not reported | | • Multiple daily injections with long acting basal analogue injections (n=39)<br>• Intermediate NPH insulin as bedtime insulin (n=1)<br><br>All patients used a short acting insulin analogue as pre-meal insulin | | | | | al study |

**Table 80: BAO 2001** [12]

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| J. Bao, H. R. Gilbertson, R. Gray, D. Munns, G. Howard, P. Petocz, S. Colagiuri and J. C. Brand-Miller. Improving the estimation of mealtime | RCT - crossover<br><br>NIDDA study | n=31<br><br>Inclusion criteria:<br>Adults aged ≥ 18 and ≤70 years<br>type 1 diabetes duration ≥1 year<br>Use of insulin pump therapy (including use of bolus dose | | | CHO counting and the Food Insulin Index (FII) algorithm applied to determine insulin bolus dose<br>Test breakfast using CHO count and FII algorithm (two occasions: meal A had CHO content of 75g CHO; meal B had CHO content of 41g CHO; both had the same energy | CHO counting algorithm applied to determine insulin bolus dose<br>Test breakfast using CHO counting algorithm alone (same CHO content as meal B – 75g) | Monitored for 3 hours after each test meal (3 test breakfasts on consecutive days) | HbA1c | Not reported | Funding:<br>Funding not mentioned. Support provided by the University of Sydney<br><br>Risk of bias:<br>Order of 3 test meal-bolus algorithms randomly assigned |
| | | | Age, years, mean (SD) | 37.8 (14.4) | | | | Severe hypoglycaemia events during 3-hour post-prandial | FII:<br>0 episodes<br>CHO alone:<br>0 episodes | |
| | | | Women | 17/28 | | | | Mild hypoglycaemic events that required treatment | FII:<br>6 episodes<br>CHO alone:<br>1 episode | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| insulin dose in adults with type I diabetes. Diabetes Care. 34:2146-2151, 2011.<br><br>REF ID: BAO 2011 | | calculator for ≥2 months)<br>HbA1c ≤9%<br>Reliably performing SMBG at least 4 times daily.<br><br>Exclusion criteria:<br>Eating disorders<br>Treated with medication known to affect blood glucose. | | | content). Results reported here only for meal B (75g CHO) with comparison.<br>FII takes into account all dietary factors and not just CHO | | | | | using random digit table<br>Allocation concealment - unclear<br>Blinding = not mentioned<br>Not ITT analysis (used ACA, excluding 3 drop-outs)<br>Powered study (BG AUC between CHO count and FII).<br>Drop-outs = acceptable (<20%)<br>ANCOVA analysis for BG level outcomes (best for cross-over studies) |
| | | | Diabetes duration, years, mean (SD) | 19.6 (11.4) | | | | Nocturnal Hypoglycaemia | Not reported | |
| | | | | | | | | Time within normal BG (4-10mmol/litre) in 3 hour post-prandial period, min, mean (SD) | FII: 128 (57)<br>CHO alone: 88 (69)<br>Reported as P=0.025 | |
| | | | HbA1c, %, mean (SD) | 7.8 (0.9) | | | | | | |
| | | | Drop-outs:<br>n=3 | | IN BOTH GROUPS:<br>Both groups: I:CHO ratio calculated before the study.<br>CGM fitted in all participants<br>Insulin treatment: Rapid acting insulin administered before each test meal and meal eaten within 20 minutes. | | | Glucose post-prandial 3 hour AUC, mmol x min/litre, mean (SD) | FII: 197 (220)<br>CHO alone: 409 (373)<br>Reported as P=0.015 | |
| | | | | | | | | Peak blood glucose excursion in 3 hour post-prandial period, mmol/litre, mean (SD) | FII: 2.4 (1.9)<br>CHO alone: 4.1 (3.1)<br>Reported as P=0.009 | |

**Table 81: Dias 2010** [38]

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| V. M. Dias, J. A. Pandini, A. L. M. Sperandei, E. S. Portella, R. A. Cobas and M. Gomes. Effect of the carbohydrates counting method on glycemic control in patients with type 1 diabetes. Diabetology & Metabolic Syndrome. 2:54, 2010.<br>REF ID: DIAS 2010 | Observational before and after study/prospective case-series | n=55<br><br>Inclusion criteria:<br>Aged 10-60 years<br>type 1 diabetes (ADA criteria)<br>Exclusion criteria:<br>Illiteracy<br>Diabetic nephropathy or retinopathy<br>Pregnancy<br>Mobility impairment | Age, years, mean (SD) | 25.3 (1.55) | Carb counting<br><br>Diet prescribed based on the carb counting method.<br>Insulin dose adjusted based on carb content of each meal (1 unit SA human insulin for every 15g CHO).<br>No SMBG during study<br><br>Insulin treatment: All patients used MDI of SA insulin at meals + NPH as basal and at night. | Baseline | 3 month | HbA1c, final value %, mean (SD) | 9.52 (0.32)<br>P=0.0009 as reported vs. baseline | Funding: Not reported<br><br>Risk of bias:<br>Before and after study design<br>Not ITT analysis<br>Drop-outs acceptable (<20%) |
| | | | Women, % | 63 | | | | HbA1c direction of change from baseline (proportion of patients) | Reduction: 38/51<br>Increase: 11/51<br>Same: 2/51 | |
| | | | Diabetes duration, years, mean (SD) | 11.31 (1.09) | | | | Major hypoglycaemia | Not reported | |
| | | | BMI, kg/m2, mean (SD) | 22.87 (0.42) | | | | Hypoglycaemia | Not reported | |
| | | | HbA1c, %, mean (SD) | 10.40 (0.33) | | | | Nocturnal Hypoglycaemia | Not reported | |
| | | | Post-prandial glycaemia (mg/dl) | 256.78 (12.82) | | | | Post-prandial glycaemia (mg/dl) | 3 months: 243.39 (15.92)<br>P=0.46 as reported compared to baseline | |
| | | | Drop-outs:<br>n=4 (excluded because did not attend FU) | | | | | | | |

**Table 82: FRANC 2009** [48]

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| S. Franc, D. Dardari, B. Boucherie, J.-P. Riveline, M. Biedzinski, C. Petit, E. Requeda, P. Leurent, M. Varroud-Vial, G. Hochberg, and G. Charpentier. Real-life application and validation of flexible intensive insulin-therapy algorithms in type 1 diabetes patients. Diabetes & Metabolism. 35 (6):463- | Observational before and after study/prospective case-series | n=35 consecutive patients<br><br>Inclusion criteria:<br>type 1 diabetes duration >1 year<br>Use of the Flexible intensive insulin therapy (FIT) strategy for at least 6 months (CHO counting & algorithms to adjust prandial insulin to achieve post-prandial target of 7.8mmol/litre) and taken 5-day structured inpatient training on | | | Personalised prandial algorithms for Flexible intensive insulin therapy (FIT)<br>Patients taught how to use a personal digital assistant phone (instead of paper logbook).<br>Medical team entered personalised algorithms for FIT onto phone<br>Before each meal, patient entered capillary BG and no. of 20g CHO portions intended to eat.<br>Automatic calculation of | Baseline (patient been using FIT and personalised algorithms for 6 months but only with paper logbook and not calculated from phone) | 4 months (mean 17 weeks, range 5-25 weeks. Median 18 weeks) | HbA1c, final value at end of study, %, mean (SD) | 7.3 (0.6) P=0.003 as reported vs. baseline | Funding:<br>P. Leurent founder, manager, shareholder & CEO of VOLUNTIS (company developed software used).<br>Grant from ALFEDIAM Sanofi-Aventis 2006 and technical support from VOLUNTIS<br>Risk of bias:<br>Before and after study, consecutive patients<br>Drop-outs =acceptable (<20%)<br><br>Additional:<br>Patients |
| | | | Age, years, mean (SD) | 39.1 (10.8) | | | | Major hypoglycaemia, (required assistance) | None reported during study | |
| | | | Diabetes duration, years, | 18.8 (11.1) | | | | Minor hypoglycaemia (BG<3mmol/litre), events/individual/week | Baseline: 1.4<br>Week 12:0.8<br>(R2=0.19, P=0.156 as reported) | |
| | | | Women | 12/35 | | | | Nocturnal Hypoglycaemia | Not reported | |
| | | | BMI, kg/m2, mean (SD) | 25.1 (3.5) | | | | Mean of individual BG excursions (2 hour post-prandial and before) mmol/litre | Breakfast: +0.07<br>Lunch: +0.14<br>Dinner: +0.06 | |
| | | | HbA1c, %, mean | 7.8 (0.9) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 468, 2009.<br>REF ID: FRANC 2009 | | FIT at least 6 months before<br>Treated with SCII or MDI<br>Exclusion criteria: | | | prandial SA insulin dose (reduced by 30-50% if mod to intensive exercise planned).<br>SMBG recommended 6 times daily (including before and 2 hours after each meal).<br>Data transmitted and feedback could be given by caregivers at all times. | | | | | varied CHO content from one day to the next and were shown to enjoy dietary freedom |
| | | | Drop-outs:<br>n=6 (due to technical problems with phone) | | INSULIN TREATMENT IN BOTH GROUPS:<br>CSII (n=14)<br>MDI (n=21) – glargine and lispro, or aspart | | | | | |

**Table 83: KILBRIDE 2011 [75]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| L. Kilbride, J. Charlton, G. Aitken, G. W. Hill, R. C. R. Davison and J. McKnight. Managing blood glucose during and after exercise in type 1 diabetes: reproducibility of glucose response and a trial of a structured algorithm adjusting insulin and carbohydrate intake. JCN. 20 3423-3429, 2011.<br>REF ID: KILBRIDE 2011 | Prospective Cohort study, not randomised | n=14<br>Inclusion criteria:<br>Adults 20-50years<br>type 1 diabetes duration >2years<br>Stable blood glucose control (HbA1c <10%)<br>Experienced in carb counting and insulin adjustment by education<br>Exclusion criteria:<br>Resting BP >165/90 mmHg<br>Diagnosed peripheral vascular disease | | | Algorithm for CHO & insulin adjustment (week 2)<br>Algorithm considered time of exercise in relation to FA insulin, CHO consumption and BG levels.<br>Algorithm reduces usual insulin dose when exercising within 2 hours of eating CHO.<br>CHO prescribed as per algorithm if BG <10mmol/litre prior to exercise (30, 20 and 10g for 4, 6 or 8mmol/litre, respectively). | Self-management (week 1) | 2 weeks (each cross-over period1 week) | HbA1c, final value %, | Not reported | Funding:<br>Supported by an Investigator-initiated Study Program from LifeScan Inc.<br><br>Risk of bias:<br>No randomisation<br>Drop-outs = acceptable (<20%)<br><br>Other:<br>Main outcomes are BG levels during and after exercise (also reports |
| | | | Age, years, mean (SD) | 37.5 (9.5) | | | | Severe hypoglycaemia episodes reported in diary (10 patients completed diary) | No events reported during study period | |
| | | | Women | 6/14 | | | | Mild hypoglycaemia episodes reported in diary, episodes/week (10 patients completed diary) | On exercise days:<br>Algorithm week: 2<br>Self-man week: 18<br>On non-exercise days:<br>Algorithm week: 27<br>Self-man week: 34 | |
| | | | BMI, kg/m2, mean (SD) | 25 (4.5) | | | | Hypoglycaemia (mean duration <4mmol/litre during 40min exercise sessions, CGM) | Algorithm week: 0.3 (0.9) minutes<br>Self-man week: 2.8 (4.5) minutes | |
| | | | HbA1c, | 7.5 | | | | Hypoglycaemia | Algorithm week: | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Orthopaedic problems preventing brisk walking<br>Diagnosed heart disease<br>Proliferative retinopathy<br>Hypoglycaemia unawareness | %, mean (SD) | (0.7) | Post-exercise 30% reduction in next insulin dose<br>Evening exercise (extra 10-20g CHO consumed before bed if <10mmol/litre) | | | (mean duration <4mmol/litre during 6-hour post-exercise period, CGM) | 19.6 (32.4) minutes<br>Self-man week: 24.2 (44.7) minutes | time spent in normal range of 4-9mmol/litre). |
| | | | Drop-outs:<br>n=1 (only completed week 1) | | | | | | | |
| | | | | | IN BOTH GROUPS:<br>2 exercise sessions during each week to assess BG response to exercise during both management strategies (consisting of 40 min treadmill walk with intensity to elicit 50% VO2max)<br>INSULIN TREATMENT: All used basal bolus insulin regime (long-acting basal insulin once-daily and fast-acting insulin boluses at meal times). All participants used analogue insulin (basal – lantus; bolus – Humalog or novorapid) | | | Nocturnal Hypoglycaemia | Not reported | |

**Table 84: KLUPA 2008** [81]

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T. Klupa, T. Benbenek-Klupa, M. Malecki, M. Szalecki and J. Sieradzki. Clinical usefulness of a bolus calculator in maintaining normoglycaemia in active professional patients with type 1 diabetes treated with CSII. J of Int. Medical Res. 36:1112-1116, 2008. REF ID: KLUPA 2008 | Observational retrospective cohort study | n=18<br>Inclusion criteria: type 1 diabetes Treated with CSII for at least 4 years using SA insulin analogues Well trained in food counting (including carb, protein and lipid counting and GI estimation )<br>Exclusion criteria: Using sensor augmented insulin pumps with real- | | BC n=8 | Non-users (n=10) | Bolus calculator Treated with paradigm 712 insulin pump with bolus calculator function for at least 9 months<br>Bolus calculator parameters set by the physician | No bolus calculator (trained in carb counting) Treated with paradigm 712 insulin pump but not using bolus calculator or treated with MiniMed 508 insulin pump without bolus calculator function. | Patients in intervention groups using BC for 9 months | | BC | Non-users | Funding: T. Benbenek employee of Medtronic<br>Risk of bias: No randomisation (observational retrospective cohort study)<br>No ANCOVA |
| | | | Age, years, range | 19-48 | 21-51 | | | | HbA1c, | 6.8% | 7% | |
| | | | Women | 3/8 | 5/10 | | | | 2 hour Post-prandial BG over 7 days, mmol/litre, mean (SD) | 7.6 (2.2) | 8.3 (2.4) *P<0.05 | |
| | | | Diabetes duration, years, range | 6-16 | 11-22 | | | | BG in target range 70-140mg/dl (n=3 in each group CMBG) | 78% | 69% | |
| | | | | | | | | | Hypoglycaemic episodes/day, mean (n=3 in each group CMBG) | 1.4 | 1.6 | |
| | | | | | | | | | Nocturnal Hypoglycaemia | | | |
| | | | Drop-outs: Not reported | | | IN BOTH GROUPS: All treated with CSII (Lispro n=15, Aspart n=3) | | | QOL | Not reported | | |
| | | | | | | | | | Adverse events | Not reported | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | time glucose monitoring. | | | CGMS used by 3 patients in each group<br>SMBG 8 times daily | | | | | |

**Table 85: LAURENZI 2011 [91]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A.Laurenzi, A.M. Bolla, G.Panigoni, V.Doria, A. Uccellatore, E. Peretti, A.Saibene, G. Galimberti, E. Bosi and M. Scavini. Effects of carbohydrate counting on glucose control and quality of life over | RCT<br>GIOCAR trial | n=61 randomised<br>Inclusion criteria:<br>Adults aged 18-65 years<br>type 1 diabetes treated with CSII for >3 months<br>Exclusion criteria:<br>Previous training in CHO counting<br>Serum creatinine >124µmol/litre in women | | CHO counting n=28 analysed | Control n=28 analysed | Carb counting using Insulin:<br>carbohydrate ratio (I:CHO) and sensitivity factor (n=30 randomised)<br>Patients use I:CHO ratio and sensitivity factor to estimate preprandial insulin dose, taking into account preprandial BG and planned CHO.<br>Trained on carb counting | Control (n=31 randomised)<br>No training – continued to estimate pre-meal insulin dose in an empirical way | 24 weeks-training during first 12 weeks. HbA1c measured at 12 and 24 weeks | HbA1c, change score (baseline vs. 24wk) %, mean | ACA (n=28): P=0.252 as reported<br>PP analysis:<br>CHO (n=20): -0.4%<br>Control (n=27): -0.05% (P=0.05 as reported) | Funding:<br>Supported by unrestricted educational grant from GSK.<br>Risk of bias:<br>Randomisation = randomly assigned (computerised random no. generator)<br>Allocation concealment = Yes<br>Blinding = open label.<br>ACA (n=28 per group) |
| | | | Age, mean (SD) | 41.2 (10.0) | 39.8 (9.8) | | | | Major hypoglycaemia requiring assistance | None reported during study | |
| | | | Women, % | 46.4% (13/28) | 67.9% (19/28) | | | | Hypoglycaemia events (BG 2.8mmol/litre) | Freq. reported as similar between 2 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 weeks in adult patients with type 1 diabetes on CSII. Diabetes Care. 34:823-827, 2011. REF ID: LAURENZI 2011 | | and >150µmol/litre in men<br>Celiac disease<br>Pregnancy<br>Severe comorbidities<br>Any disability preventing compliance with study procedures | | | | during first 12 weeks (4-5 individual sessions with dietician and diabetologist). | | | | groups for both ACA and PP analysis | performed for QOL (excluded drop-outs but included those not adhering to protocol) – incorrectly reports this as 'ITT'<br>Per-protocol analysis performed for HbA1c (excluded all drop-outs and those not adhering to protocol)<br>Drop-outs = >20% in intervention group<br>Mixed effects model used for HbA1c levels and hypoglycaemia events |
| | | | Diabetes duration, years mean (SD) | 21.9 (11.0) | 19.8 (11.7) | IN BOTH GROUPS:<br>Same glucose meter for SMBG (OneTouch Ultra2; LifeScan Inc.). Patients asked to SMBG 6 times daily.<br>INSULIN TREATMENT: Patients on Glulisine, Lispro or Aspart.<br>All patients attended a session with the dietician about the recommended diet for patients with diabetes before randomisation. | | | Nocturnal Hypoglycaemia | Not reported | |
| | | | BMI, kg/m2 median (IQR) | 23.7 (21-25.2) | 23.8 (20.8-26.8) | | | | Adverse events | | |
| | | | HbA1c, %, mean (SD) | 7.9 (0.9) | 8.1 (1.5) | | | | | | |
| | | | Drop-outs: n=14 | n=10 (n=6 due to discontinuation of CHO counting (<75% meals); n=2 | n=4 (1 due to shift from CSII to MDI for >7days; 3 drop-outs) | | | | DSQOLS, change from baseline at 24weeks (increase = better QOL), median (IQR). Analysed as ACA (n=28) | Social relations:<br>CHO: 2 (-2.5 to 3.5)<br>Control: 0 (-1.5 to 5);<br>Leisure-time:<br>CHO: -0.5 (-2 to 1),<br>Control: 0 (-1.5 to 5); | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | due to shift from CSII to MDI for >7days; 2 drop-outs) | | | | | Physical complaints: CHO: 2 (0 to 4.5), Control: 2 (-0.5 to 5); Future worries: CHO: 1 (-1 to 4), Control: 0 (-1.5 to 3); Diet restrictions: CHO: 5.5 (0.5 to 8.5), Control: 0 (-2 to 3.5); Daily hassles: CHO: 1.5 (-2.5 to 6), Control: 2 (-1.5 to 3.5); Hypoglycaemia fears: CHO: 0.5 (-2 to 7.5), Control: 1 (-5.5 to 5.5) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Reported as SS for diet restrictions (P=0.008) | |

**Table 86: MAURIZI 2011 [101]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A. R. Maurizi, A. Lauria, D. Maggi, A. Palermo, E. Fioriti, S. Manfrini and P. Pozzilli. A novel insulin unit calculator for the management of type 1 diabetes. Diabetes Technology and Therapeutics. 13 | RCT | n=40<br>Inclusion criteria:<br>Adults aged 18-65 years<br>type 1 diabetes defined according to ADA<br>Diabetes duration >1year<br>Exclusion criteria:<br>Learning disabilities<br>Severe diabetic complicatio | | Calsulin n=20 | Control n=20 | Calsulin n=20<br>Provided with logbook and individual target blood glucose, I:CHO ratio and insulin sensitivity factor (ISF) prior to study<br>Trained on use of the insulin units calculator Calsulin (Thorpe Products Ltd.) to administer insulin dose (enter pre- | Control n=20<br>Provided with logbook and individual target blood glucose, I:CHO ratio and insulin sensitivity factor (ISF) prior to study<br>No Calsulin device provided | 6 months | HbA1c, final value %, mean (SD) at 3 months | Calsulin: 7.3 (0.5)<br>Control: 7.7 (1.0) | Funding: Educational grant from Thorpe Ltd. Thorpe Ltd. Had no role in the study design, management of data or manuscript preparation.<br><br>Risk of bias:<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not |
| | | | Age, years, mean (SD) | 34.5 (15) | 39.3 (13) | | | | HbA1c, change score %, at 6 months | Calsulin: -0.85<br>Control:-0.07<br>Reported as P<0.05 | |
| | | | Women, % | 35% | 35% | | | | Major hypoglycaemia events | Only reported as no significant differences in frequency of hypoglycaemic events between groups | |
| | | | Diabetes duration, years, mean (SD) | 14.4 (10.8) | 13.4 (7.0) | | | | Hypoglycaemia, total events | | |
| | | | BMI, kg/m2, mean (SD) | 23.7 (3.6) | 24.7 (6.1) | | | | Nocturnal Hypoglycaemia | Not reported | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (4):425-428, 2011. REF ID: MAURIZI 2011 | | n Chronic conditions which might influence daily activities (visual or auditory disability, motor impairment for neurological or orthopaedic problems). | HbA1c, %, mean (SD) | 7.9 (1.0) | 7.8 (1.6) | meal BG, I:CHO ratio, CHO content, post-meal exercise). | | | QOL | Not reported | mentioned Blinding = open label Drop-outs and loss to FU not reported Powered study (HbA1c) |
| | | | Drop-outs: Not reported | | | IN BOTH GROUPS: All subjects provided with a logbook and instructed to SMBG, estimate meal CHO content and perform regular exercise. Target blood glucose, I:CHO ratio and insulin sensitivity factor (ISF) determined for all patients (I:CHO ratio calculated by '500 rule'. ISF calculated by '1800 rule'. INSULIN TREATMENT: Not reported (MDI suggested?) All subjects followed up with visits every 3 months | | | Adverse events | Not reported | |

**Table 87: SCAVONE 2010 [135]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| G. Scavone, A. Manto, D. Pitocco, L. | RCT | n=256 | | NEP n= 100 | Control n= 156 | Nutritional educational programme | Control (no education programme) | 9 months (4 weeks training for | HbA1c, final value at 9 | NEP: 7.4 (0.9) Control: 7.5 (1.1) | Funding: Not reported |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gagliardi, S. Caputo, L. Mancini, F. Zaccardi and G. Ghirlanda. Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in type 1 diabetic subjects: a pilot study. Diabetic Medicine. 27:477-479, 2010.<br>REF ID: SCAVONE 2010 | | Inclusion criteria:<br>type 1 diabetes duration >5 years<br>Exclusion criteria:<br>BMI>40 kg/m2<br>Poor glycaemic control (HbA1c>14%)<br>Pregnancy<br>Presence of severe diabetic complications<br><br>No subjects had followed any dietetic/educational programme before the study | | | | (NEP) n=100<br>Phase 1 (4 weeks, 1 session per week): educational training on carb counting & nutrition (including importance of CHO equal to 55-65% of daily calorie intake, and adjustment of insulin to CHO, exercise and pre-meal BG). Based on the guidelines proposed by the EASD.<br>Phase 2: application of NEP (9 months). Patients reassessed every 3 months | n=156<br>No training programme preceded the 9 months | intervention group preceded the 9 months). | months, %, mean (SD) | Reported as significant change from baseline (P<0.01, ACA) | Risk of bias:<br>Randomisation = unclear (as details not given)<br>Allocation concealment = unclear<br>Blinding = none reported<br>Not ITT. Used ACA and excluded patients lost to FU from analysis<br>Drop-outs = acceptable (<20% in total) but, there was a 27% diff in drop-out between groups with all drop-outs in the intervention group.<br>Not done |
| | | | Age, years, mean (SD) | 39 (11) | 39 (11) | | | | Hypoglycaemic events, <3.9 mmol/litre | NEP: 4%<br>Control: 7%<br>Reported as P<0.05 (ACA) | |
| | | | Women, % | 51.0 | 52.6 | | | | Major hypoglycaemia, | Not reported | |
| | | | Diabetes duration, | Only reported as not different between groups at baseline | | | | | Nocturnal Hypoglycaemia, | Not reported | |
| | | | Weight, kg, | Only reported as not different between groups at baseline | | | | | QOL | Not reported | |
| | | | HbA1c, %, mean | 7.8 | 7.5 (0.8) | IN BOTH GROUPS: | | | Adverse events | Not reported | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (SD) | (1.3) | | Patients measured BG 6-times daily (before and 2 hours after breakfast, lunch and dinner).<br>INSULIN TREATMENT: Basal insulin administered at evening meal or bedtime. Rapid acting insulin administered at each meal<br>Logbook kept of daily BG and hypoglycaemic events. | | | | | ANCOVA |
| | | | Drop-outs: n=27 (loss to FU) | n=27 | n=0 | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

**Table 88: SCHMIDT 2012** [138]

| Reference | Study type | No. of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Signe Schmidt, Merete Meldgaard, Nermin Serifovski, Camilla Storm, Tomas Moller Christensen, Birthe | Prospective, randomised, controlled, open label, three-arm parallel, bi-centric study conducted in Denmark | n= 63 (n=8, control; n=21, CarbCount; n=22, CarbCount Automated Bolus Calculato | | ABC (n=22) | CC (n=21) | Control (n=8) | CarbCount Automated Bolus Calculator (CarbCountABC): group received FIIT during a 3-h group teaching, | CarbCount (manual bolus calculation) group received FIIT during a 3-h group teaching, were taught carbohydrat | 16 Weeks | | ABC | CarbCount | Control | Funding: not reported.<br>Risk of bias: Randomisation: "randomisation with a 1:3:3 ratio in blocks of |
| | | | Age (years), mean (SD) | 42 (10) | 41 (10) | 46 (SD 9) | | | | HbA1c (%), mean (SD) | 8.1 (0.4) | 8.4 (0.9) | 8.9 (1.1) | |
| | | | Gend | 10/ | 10/11 | 6/2 | | | | HbA1c (%) within-group difference, (95% CI) | -0.7 (-1.0 to -0.4) | -0.8 (-1.3 to -0.3) | -0.1 (-1 to -0.7) | |
| | | | | | | | | | | Severe | 2 | 2 | 1 | |

| Reference | Study type | No. of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gade-Rasmussen, and Kirsten Norgaard. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. Diabetes Care 35 (5):984-990, 2012. REF ID: SCHMIDT 2012 | | r)<br>Inclusion criteria:<br>Age 18-65 years<br>type 1 diabetes duration ≥12 months<br>Use of multiple daily injections (MDI)<br>Exclusion criteria:<br>Pregnancy<br>Nursing<br>Gastroparesis<br>Present or former practice of | er (m/f) | 12 | | | were taught carbohydrate counting, estimated individual ICRs and ISFs and were also provided with and instructed in the use of the ABC. | e counting, estimated individual ICRs and ISFs<br>Control<br>taught principles of healthy diet but not taught carb counting | | hypoglycaemia, N | | | | 14"<br>Allocation concealment: sealed, opaque envelopes containing the group assignments. The envelopes had been prepared by a person not otherwise involved in the study"<br>Blinding: not applicable – open label trial<br>ITT analysis:<br>Powered study: study was powered.<br>Drop-outs: |
| | | | Diabetes duration (years) | 21 (SD 9) | 19 (SD 10) | 14 (SD 12) | | | | #HFS (0-100 scale) - higher scores indicate more fear, mean (SD) | 22.6 (16.7) | 22.8 (13.8) | 24.5 (18.2) | |
| | | | HbA1c (%) | 8.8 (SD 0.7) | 9.2 (SD 0.6) | 9.1 (SD 0.7) | | | | HFS within-group difference, (95% CI) | -3.4 (-7.2 to 0.3) | -5.2 (-9.8 to -0.6) | -1.9 (-10 to 6.2) | |
| | | | BMI (kg/m2), mean (SD) | 25.8 (SD 3.3) | 27.3 (SD 4.4) | 26.4 (SD 5.6) | | | | &PAID (0-100 scale) - higher scores indicate more problems, mean (SD) | 25.6 (15.3) | 28.0 (19.2) | 27.2 (18.8) | |
| | | | | | | | | | | PAID within-group difference, (95% CI) | -6.9 (-13.5 to -0.4) | -5.8 (-12 to -0.5) | -3.3 (-21 to 14.4) | |
| | | | | | | | | | | ^ADDQoL Total (-9 to | -1.8 | -1.8 (1.6) | -1.4 (0.9) | |

| Reference | Study type | No. of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | carbohydrate counting | | | | | | | 9) - higher scores indicate positive impact, mean (SD) | (1.6) | | | 12 patients (19%) dropped out overall. Drop-outs per group not reported. Relatively small sample size |
| | | | | | | | | | ADDQoL within-group difference, (95% CI) | 0.4 (0.0 to 0.7) | 0.2 (-0.1 to 0.5) | 0.6 (-0.8 to 1.9) | |
| | | | | | | | | | DTSQ Total (0 - 36) - higher scores indicate treatment satisfaction, mean (SD) | 31.5 (3.3) | 26.4 (6.0) | 28.5 (5.1) | |
| | | | | | | | | | DTSQ within-group difference, (95% CI) | 9.1 (6 to 12.2) | 3.0 (0.8 to 5.3) | 2.0 (-0.5 to 4.5) | |
| | | | Drop-outs:<br>12 patients (19%) dropped out overall. Drop-outs per group not reported.<br>Baseline characteristics of the | | | | | | *Comparison of means between Control, CarbCount, and CarbCountABC. Analysis performed using ANOVA. #HFS – Hypoglycaemia Fear Survey. &PAID – Problem Areas In Diabetes. | | | | |

| Reference | Study type | No. of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | randomised patient sample did not differ significantly between the 3 study groups | | | | ^ADDQoL – Audit of Diabetes-Dependent Quality of Life. DTSQ – Diabetes treatment satisfaction questionnaire | | |

**Table 89: ZIEGLER 2013 (ABACUS TRIAL)**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ABACUS trial R Ziegler, DA. Cavan, I Cranston, K Barnard, J Ryder, C Vogel, CG. Parkin et al. Use of an Insulin Bolus Advisor Improves Glycemic Control in Multiple Daily Insulin Injection | RCT (parallel)<br><br>Multicentre (UK and Germany) | n= 218<br>type 1 diabetes and type 2 diabetes (93% type 1 diabetes)<br>n=218<br>Inclusion criteria:<br>type 1 diabetes and type 2 diabetes<br>≥18 years<br>Poorly controlled diabetes (>7.5% | type 1 diabetes and type 2 diabetes patients (92.7% type 1 diabetes) | | | Advanced usual care + integrated bolus calculator BG meter (Accu-Chek Aviva Expert blood glucose meter; Roche)<br><br>patients had to discontinue use of their current BG meter<br>The Aviva Expert includes automated bolus advisor (prandial and | Standard bolus + enhanced usual care<br><br>Standard BG meter and manual bolus calculation<br>----------<br>In both groups: patients received individualised MDI and CHO counting | 26 weeks | | BC n= 105 | Standard bolus n= 113 | Funding: Roche Diagnostics |
| | | | | Standard Bolus n= 113 | BC n= 105 | | | | HbA1c, % change from baseline | -0.7 (SD 0.7) | -0.5 (SD 0.7) | |
| | | | Age (years), mean (SD) | 42 (15) | 43 (14) | | | | Hypoglycaemia (<70mg/dl), number of patients | 43 | 31 | Risk of bias:<br>Randomisation: unclear<br>Allocation concealment: not reported<br>Blinding: not applicable |
| | | | Diabetes duration mean years, | 17 (12) | 18 (11) | | | | Severe hypoglycaemia (<36mg/dl or 3rd party assistance, number of | 11 | 7 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (MDI) Therapy Patients With Suboptimal Glycemic Control: First results from the ABACUS trial. Diabetes Care, 2013.<br><br>REF ID: ZIEGLER 2013 | | HbA1c)<br>MDI-treated for ≥6 months<br>Adjustment of meal doses based on CHO content<br>Completion of CHO training within the past 2 years.<br><br>Exclusion criteria:<br>Treatment with NPH, pre-mixed insulin, noninsulin injectable a-diabetic medication or oral a-diabetic agents (except metformin)<br>Use of fixed | (SD) | | | correction bolus recommendations based on current BG value, planned CHO intake, and individual therapy parameters programmed into the meter<br>Meter auto calculates insulin bolus for the user and stores BG ad meal info in an electronic diary.<br>Investigators entered each patients therapy parameters into their meter and conducted 1hr training sessions regarding its use. | training to address knowledge deficits (as identified at screening) | | patients | | | ITT analysis: adequate<br>Powered study: HbA1c<br>Drop-outs: acceptable <20% |
| | | | Male, % | 53 | 58 | | | | QoL Improvement (Diabetes treatment satisfaction Questionnaire): DTSQ (8 questions each on a 7-point scale) | 11.4 (SD 6.0) | 9.0 (SD 6.3) | |
| | | | HbA1c, % (SD) | 8.9 (1.3) | 8.9 (1.1) | | | | Nocturnal hypoglycaemia | Not reported | | |
| | | | Drop-outs:<br>BOLUS: n=20 (18%) and STD: n=5 (5%) | | | | | | Adverse events | Not reported | | |
| | | | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | dose treatment<br>Use of sliding scale insulin doses determined exclusively by specific BG results. | | | | | | | |

### G.2.3 Glycaemic index diet

**Table 90: Calle-Pascual 1988[23]**

| Reference | Study type | Number of participants | Participant characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Calle-Pascual AL, Gomez V, Leon E, Bordiu E. Foods with a low glycemic index do not improve glycemic control of both type 1 and type 2 diabetic | Non-randomised crossover study | n = 34<br>of which<br>type 1 diabetes = 16<br>type 2 diabetes = 18<br><br>Inclusion criteria:<br>Not strictly inclusion criteria but | All participants underwent both interventions as this was a crossover study. | HFD<br>n = 12<br>(type 1 diabetes only) | LFD<br>n = 12<br>(type 1 diabetes only) | Low GI diet (Diet A)<br><br>This included 5 different foods with GI between 29 and 36: lentils, chickpeas, red kidney beans, haricot | High GI diet (Diet B)<br><br>This included 5 different foods with GI between 50 and 92: rice, potatoes, carrots, spaghetti and | Each diet intervention lasted for 4 weeks (i.e. 8 weeks in total), and HbA1c was measured at the end of each period. | HbA1c, final value at 4 weeks, %, mean (SD) | type 1 diabetes only:<br><br>Low GI = 9.27 (0.45)<br>High GI = 9.02 (0.39) | Funding:<br>Not reported<br><br>Risk of bias:<br>Observational study<br>Participant comparability = Unclear<br>Allocation method = High<br>Blinding = High<br>Treatment |
| | | | Age, years, mean (SD) | type 1 diabetes only:<br>25.6 (4.3) | | | | | Hypoglycaemic events, <3.0 mmol/litre, per patient | Not reported | |

| Reference | Study type | Number of participants | Participant characteristics | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| patients after one month of therapy. Diabetes and Metabolism e. 1988; 14(5):629-633 | | the study states that the participants were chosen from "a group previously educated in self-monitoring of capillary glucose at home" and that they were all "under treatment with 2 daily doses of insulin".<br><br>Exclusion criteria:<br>No pre-enrolment exclusion criteria have been stated, however, the study intended to and did | | | beans and peas. | beetroot. | | per month, mean (SD) | | comparability = Low<br>Follow-up length = Low<br>Outcome availability = Low<br>Outcome definition = High<br>Drop-outs = High<br><br>Overall = VERY HIGH |
| | | | Sex, M:F | Not reported | | | | Major hypoglycaemia | Not reported | |
| | | | Diabetes duration | Not reported | | | | Nocturnal Hypoglycaemia | Not reported | |
| | | | BMI, kg/m2, | type 1 diabetes only: 20.96 (2.21) | | | | Post prandial hyperglycaemia | Not reported | |
| | | | HbA1c, %, mean (SD) | Not reported | IN BOTH GROUPS:<br>The participants were given a diet with a high carbohydrate (60%) and low fat (20%) content. A quarter (25%) of the carbohydrates was supplied at lunch. Each of the food listed above was eaten 5 or 6 times and had to be eaten at lunch. | | | Adherence to treatment (Poor compliance was <45% of total energy +/- fibre consumption >20g/day LFD, <30g day HF diet) | No figures have been given.<br>"Patients had to bring the reagent strips used for determining their capillary glucose the following day and their compliance was confirmed." | |

| Reference | Study type | Number of participants | Participant characteristics | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | exclude participants during the study period if they i) went through any changes in weight >1% of their initial body weight, or ii) changed their insulin doses. | Insulin dose (U/day) | type 1 diabetes only: 39.98 (16.58) | | | | QoL | Not reported | |
| | | | Drop-outs | type 1 diabetes only: n = 4 | | | | Satisfaction with treatment | Not reported | |
| | | | | | | | | Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea) | Not reported | |

**Table 91: Fontvieille 1992**[46,47]

| Reference | Study type | Number of participants | Participant characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fontvieille AM, Rizkalla SW, Penfornis A, Acosta M, Bornet | Crossover RCT | n = 18<br>type 1 diabetes = 12<br>type 2 diabetes = 6 | All participants underwent both interventions as this was a crossover | HFD<br>n = 18 (9 in one peri | LFD<br>n = 18 (9 in one perio d) | Low GI<br>Intake of rice, biscuits, pasta, apples, peas/beans and rye bread was | High GI<br>Intake of bread, potato and bananas was recommended | 5 weeks of each period (10 weeks in total) | No statistically different results were observed for type 1 diabetes and type 2 diabetes patients, thus, results are considered for the whole group. | | Funding:<br>Pierre and Marie Curie University, Paris, France |
| | | | | | | | | | HbA1c, final | Low GI = | |

| Reference | Study type | Number of participants | Participant characteristics | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| FR, Slama G. The use of low glycaemic index foods improves metabolic control of diabetic patients over five weeks. Diabetic Medicine. 1992; 9(5):444-450 | | Inclusion criteria: The study does not list inclusion criteria, however, it provides a description of the participants: "Twelve were classified as having Type I diabetes on the basis of a past clinical history of severe ketosis and weight loss at onset, and low or undetectable plasma C-peptide values at | study. | od) | recommended | | | value at 5 weeks, %, mean (SD) | 8.3 (1.5) High GI = 8.3 (1.4) | Risk of bias: Randomisation = High Allocation concealment = High Blinding = High Drop-outs = Low Outcome assessment not described fully = High Outcome indirect (type 1 diabetes & type 2 diabetes combined) Overall = VERY HIGH |
| | | | Age, years, mean (SD) | 1D only:1D only: 42.7 (10.3) | | | | Hypoglycaemic events, <3.0 mmol/litre, per patient per month, mean (SD) | Not reported | |
| | | | Sex, M:F | type 1 diabetes only: 10:2 | | | | Major hypoglycaemia, | Not reported | |
| | | | Diabetes duration | type 1 diabetes only: 13.4 (5.1) | | | | Nocturnal Hypoglycaemia, | Not reported | |
| | | | BMI, kg/m2, | type 1 diabetes only: 23.7 (2.2) | | | | Post prandial hyperglycaemia | Not reported | |
| | | | HbA1c, %, mean (SD) | Not reported | IN BOTH GROUPS: Each participant entered a run-in period of 15 days to have a homogeneous group. During this period they were asked to follow their usual diet more strictly. Participants were | | | Adherence to treatment (Poor compliance was <45% of total energy +/- fibre consumption | "The diet plans were followed as prescribed." | |

| Reference | Study type | Number of participants | Participant characteristics | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | entry. The other six patients were classified as having Type 2 diabetes and were treated with oral antidiabetic drugs. Before entry into the study, the patients had been seen on a regular basis (at least every 6 months) at our department. ”<br><br>Exclusion criteria:<br>Not reported | | | recommended to consume 55% of their caloric intake as carbohydrate, 15% as protein and 30% as lipid. However, baseline dietary inquiry showed that they actually consumed 45% carbohydrate, 18% protein and 37% lipid. | | | >20g/day LFD, <30g day HF diet) | | |
| | | | Insulin dose (U/day) | 40.9 (12.8) | | | | QoL | Not reported | |
| | | | Drop-outs | n = 0 | | | | Satisfaction with treatment | “Both diets were fond acceptable by the participants.” | |
| | | | | | | | | Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea) | Not reported | |

**Table 92: Lafrance 1998**[89]

| Reference | Study type | Number of participants | Participant characteristics | | | Interventions | Interventions | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lafrance L, Rabasa-Lhoret R, Poisson D, Ducros F, Caisson JL. Effects of different glycaemic index foods and dietary fibre intake on glycaemic control in type 1 diabetic patients on intensive insulin therapy. Diabetic Medicine. 1998; 15(11):972-978 | Crossover RCT | n = 9<br><br>Inclusion criteria:<br>The study does not list inclusion criteria, however, it provides a description of the participants: "The participants had been on intensive insulin therapy for at least 3 months and were accustomed to calculating their pre-meal insulin dose. Gastroparesis was excluded in all patients by gastric | All participants underwent all four interventions as this was a crossover study. | Group A = Low GI = 9<br>Group C = High GI = 9 | Group B = Intermediate GI = 9<br>Group D = High fibre = 9 | Group A<br>Low GI<br>GI < 60 diet | Group B (Control period)<br>Intermediate GI<br>All patients began with this intermediate GI (60 - 90) and low fibre intake diet and were then randomised consecutively without wash-out to Group A, C or D. | 12 days for each intervention (48 days in total) | HbA1c, final value at 12 days, %, mean (SD) | All capillary blood glucose concentrations were comparable between the diets.<br>HbA1c before study for all groups = 5.8% (0.6%)<br>HbA1c after study for all groups = 5.4% (0.6%) | Funding:<br>Pierre and Marie Curie University, Paris, France<br><br>Risk of bias:<br>Randomisation = High<br>Allocation concealment = High<br>Blinding = High<br>Drop-outs = Low<br><br>Overall = VERY HIGH |
| | | | Age, years, mean (SD) | Not reported | | | | | Hypoglycaemic events, <3.0 mmol/litre, per patient per month, mean (SD) | Minor hypoglycaemia (< 4.0 mmol/litre :<br>Low GI = 4.3 (1.3)<br>Interm GI = 3.2 (0.24)<br>High GI = 4.0 (2.8)<br>High fibre = 2.7 (2.8) | |
| | | | Sex, M:F | 7:2 | | Group C<br>High GI | Group D<br>High fibre | | Major hypoglycae | Group A = 0<br>Group B = 0 | |

| Reference | Study type | Number of participants | Participant characteristics | | Interventions | Interventions | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | emptying analysis."<br><br>Exclusion criteria:<br>Not reported | | | GI > 90 diet | Intermediate GI (60 - 90) + high fibre food choices ensuring a daily intake of at least 40g of fibre | | mia, | Group C = 0<br>Group D = 0 | |
| | | | Diabetes duration | 15.0 (7.5) | | | | Nocturnal Hypoglycaemia, | Not reported | |
| | | | BMI, kg/m2, | type 1 diabetes only:<br>23.7 (2.2) | | | | Post prandial hyperglycaemia | Not reported | |
| | | | HbA1c, %, mean (SD) | 5.8 (0.6) | IN ALL GROUPS:<br>For each experimental diet, the subjects were advised to maintain their usual energy intake and distribution: 50 - 55% carbohydrate, 15 - 20% protein and 25 - 30% lipids. They were counselled on keeping dietary records but had no instruction on the GI or fibre content of food. | | | Adherence to treatment (Poor compliance was <45% of total energy +/- fibre consumption >20g/day LFD, <30g day HF diet) | Based on the dietary diaries of the participants, the diets were reported to be identical for energy intake and distribution of carbohydrates, lipids and proteins. The prescribed distribution was closely followed for the 3 daily meals with the | |

| Reference | Study type | Number of participants | Participant characteristics | | | Interventions | Interventions | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | exception of a slightly but significantly lower carbohydrate intake for dinner on the high GI diet (45.5%; p=0.01) | |
| | | | Insulin dose (U/day) | Not reported | | | | | QoL | Not reported | |
| | | | Drop-outs | n = 0 | n = 0 | | | | Satisfaction with treatment | Not reported | |
| | | | | | | | | | Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea) | Not reported | |

**Table 93: McCulloch 1985**[105]

| Reference | Study type | Number of participants | Participant characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| McCulloch DK, Mitchell RD, | RCT | n = 25 randomised | | New diet* | Current diet | *New diet = High carb + | Current diet | Assessment for the | N.B.<br>Final assessment time points: | | Funding: British Diabetic |

| Reference | Study type | Number of participants | Participant characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ambler J, Tattersall RB. A prospective comparison of 'conventional' and high carbohydrate/ high fibre/low fat diets in adults with established type 1 (insulin-dependent) diabetes. Diabetologia. 1985; 28(4):208-212 | | to either of the 2 groups in the 2nd part of this study (this is the part that is relevant to this review)<br><br>Inclusion criteria:<br>type 1 diabetes<br>Completion of the initial run-in period (3 months)<br>Completion of the first intervention (6 months) of either small group teaching using a videotape or practical lunchtime demonstrations<br>Willingness to continue | | (ND) n = 12 (13 initially randomised) | (CD) n = 10 (12 initially randomised) | high fibre + low fat<br><br>In addition to being instructed to maintain a consistent daily carbohydrate profile, participants were told to alter the content of the diet in accordance with the British Diabetic Association's "dietary recommendations for diabetics in the 1980s": most carbohydrate to be eaten as polysaccharides, particularly fibre-rich unprocessed foods, and liberal consumption of | Continuation of current diet | current diet group took place 6 months after enrolment for the 2nd part of the study.<br><br>The new diet group followed their new regimen for 4 months, then they were followed up 6 months after the end of the new diet (i.e. 10 months after enrolment for the 2nd part of the | ND = 10 months<br>CD = 6 months | | Association development project grant<br><br>Risk of bias:<br>Comparability of interventions = High<br>Randomisation = High<br>Allocation concealment = High<br>Blinding = High<br>Drop-outs = High<br>Different follow-up time points = Very high<br><br>Overall = VERY HIGH |
| | | | Age, years, mean (SD) | ND = 39.3 (3.9)<br>CD = 29.8 (2.8) | | | | | HbA1c, final value, %, mean (SD) | ND = 10.0 (0.6)<br>CD = 9.5 (0.4) | |
| | | | Sex, M:F | ND = 7:5<br>CD = 5:5 | | | | | Hypoglycaemic events, <3.0 mmol/litre, per patient per month, mean (SD) | Not reported | |
| | | | Diabetes duration | ND = 14.3 (1.8)<br>CD = 11.6 (1.3) | | | | | Major hypoglycaemia | Not reported | |
| | | | BMI, kg/m2, | ND = 24.3 (0.5)<br>CD = 23.2 (0.8) | | | | | Nocturnal Hypoglycaemia | Not reported | |
| | | | | | | | | | Post prandial hyperglycaemia | Not reported | |

| Reference | Study type | Number of participants | Participant characteristics | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | participating in the study for a further 6 to 10 months<br><br>Exclusion criteria:<br>Not reported | | | vegetables and fruits at both midday and evening meals. | | study) | | | |
| | | | HbA1c, %, mean (SD) | ND = 12.9 (0.5)<br>CD = 12.0 (0.6) | IN BOTH GROUPS:<br>During the last 6 months of the study, the participants were neither seen nor given dietary advice unless they had a specific query. | | | Adherence to treatment<br><br>Definitions used in this study:<br>Coefficient of variation (SD/mean x 100), based on the participants' self-reported food records<br>Comparability of daily fibre intake | ND = 29.8% (SEM=6.7)<br><br>CD = 28.1% (SEM=11.7)<br><br>The daily fibre intake did not differ significantly between the groups.<br><br>Daily fibre intake (g):<br>ND = 31.8 (1.7)<br>CD = 28.5 (3.0) | |

| Reference | Study type | Number of participants | Participant characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Insulin dose (Unit /kg/day) | ND = 0.67 (0.03)<br>CD = 0.88 (0.08) | | | | | QoL | Not reported | |
| | | | Drop-outs | n = 1 | n = 2 | | | | Satisfaction with treatment | No comparative data (degree of enjoyableness only assessed for ND group) | |
| | | | | | | | | | Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea) | Not reported | |

**Table 94: Venhaus 1988[162]**

| Reference | Study type | Number of participants | Participant characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Venhaus A, Chantelau E. Self- | Crossover RCT | n = 10<br><br>Inclusion | All participants underwent | Unrefined carbohydrate diet (URD) | Refined carbohydrate diet (RD) | URD:<br>Low GI (and rich in fibre) | RD:<br>High GI (and fibre-depleted) | 6 weeks for each period (i.e. 12 | HbA1c, final value at 6 weeks, %, mean (SD) | URD = 6.3 (0.8)<br>RD = 5.8 (0.5) | Funding:<br>Peter Klockner Stiftung, |

| Reference | Study type | Number of participants | Participant characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| selected unrefined and refined carbohydrate diets do not affect metabolic control in pump-treated diabetic patients. Diabetologia. 1988; 31(3):153-157 | | criteria:<br>It is unclear whether the given description was inclusion criteria or not. It is stated that the participants were "self-selected (i.e. volunteered) non-obese outpatients with well-controlled Type 1 diabetes who are on subcutaneous insulin infusion therapy.<br><br>Exclusion | both interventions as this was a crossover study. | n = 10 | n = 10 | The participants were instructed to avoid refined fibre-depleted carbohydrates, such as sucrose, white bread, white rice, mashed potatoes and other highly-processed foods, including juices, except for treatment of hypoglycaemia. Whole grain products, leguminous seeds, such as peas, lentils, beans, vegetables and fruits were recommended to the participants. | The participants were instructed to avoid whole grain products, and the intake of vegetables and fruits was limited to one serving of processed vegetables per day and less than five servings of fresh fruit per week. Refined sugar was permitted up to 50g/day. | weeks in total) | | | Duisburg, Germany (West Germany at the time of publication) and the West German Sugar Bureau<br><br>Risk of bias:<br>Randomisation = High<br>Allocation concealment = High<br>Blinding = High<br>Drop-outs = Low<br>Outcome definitions not fully described = High<br><br>Overall = VERY HIGH |
| | | | Age, years, mean (SD) | 27 (9) | | | | | Hypoglycaemic events, <3.0 mmol/litre, per patient per month, mean (SD) | Mild hypoglycaemic episodes (≤ 2.5 mmol/litre per group per month):<br>URD = 9.6 (6.6)<br>RD = 11.4 (8.5) | |
| | | | Sex, M:F | 8:2 | | | | | Major hypoglycaemia, | None | |
| | | | Diabetes duration | 13 (8) | | | | | Nocturnal Hypoglycaemia, | Not reported | |
| | | | BMI, kg/m2, | 22.6 (1.7) | | | | | Post prandial hyperglycaemia | Overall hyperglycaemia episodes:<br>URD = | |

| Reference | Study type | Number of participants | Participant characteristics | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | criteria:<br>Not reported | | | | | | | 18.2 (9.5)<br>RD = 16.7 (7.5) | |
| | | | HbA1c, %, mean (SD) | 6.4 (0.7) | IN BOTH GROUPS:<br>All participants had a 4-week run-in period on their habitual diet prior to randomisation. | | | Adherence to treatment (Poor compliance was <45% of total energy +/- fibre consumption >20g/day LFD, <30g day HF diet) | Not reported in the methods section that compliance to diet prescription was attested at two further diet inquiries taken at the end of each 3-week period, however, no figures have been reported.) | |
| | | | Insulin dose | 41.7 (6.9) | | | | QoL | Not reported | |

| Reference | Study type | Number of participants | Participant characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measure | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (U/day) | | | | | | | | |
| | | | Drop-outs | n = 0 | n = 0 | | | | Satisfaction with treatment | Not reported | |
| | | | | | | | | | Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea) | No ketoacidosis occurred during the study. No other adverse events were reported. | |

## G.3 Blood glucose monitoring

### G.3.1 HbA1c

**Table 95: Araszkiewicz 2006**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A. Araszkiewicz, D. A. Zozulinska, | Case series (prospective) | N = 100 recruited<br>N = 88 completed | Age (years) - mean (SD) | 24.3 (6.2) | All participants were treated with | Mean follow-up = 6.1 ± 1.6 years | After 6 years of follow-up, diabetic retinopathy was found in 18 participants (20%) and positive albuminuria in 17 participants (19%). | | Funding:<br>Poznań University of Medical |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| M. M. Trepinska, and B. Wierusz-Wysocka. Inflammatory markers as risk factors for microangiopathy in type 1 diabetic patients on functional intensive insulin therapy from the onset of the disease. Diabetes Res.Clin.Pract. 74 (2 suppl.):S34-S40, 2006.<br><br>Araszkiewi | Country:<br>Poland | baseline measurements<br><br>Inclusion criteria:<br>Aged < 30 years<br>Newly diagnosed type 1 diabetes<br>Hospitalised due to DKA at a particular diabetes department in Poland between 1994 and 1999.<br>Attendance at a 5-day structured training program during hospitalisation<br><br>Exclusion criteria:<br>Acute or latent inflammatory focuses | Number of M:F | 22:33 | intensive functional insulin therapy from the onset of disease and there was no comparator. | | C-peptide level, ng/ml | W/ retinopathy (n=17)<br>0.17 ± 0.42 | Sciences<br><br>Risk of bias:<br>Appropriate eligibility criteria<br>Appropriate measurement of exposure and outcome<br>Controlled for confounding factors<br>Adequate follow-up |
| | | | type 1 diabetes | 100% | | | | W/out retinopathy (n=69)<br>0.06 ± 0.19 | |
| | | | Mean age at onset of diabetes (SD) | Not reported | | | | Positive low-level (micro) albuminuria (n=18)<br>0.06 ± 0.25 | |
| | | | Mean diabetes duration (SD) | Not reported | | | | Negative low-level (micro) albuminuria (n=70)<br>0.1 ± 0.30 | |
| | | | Mean HbA1c (%) ± SD | 8.1 ± 1.9 | | | High sensitivity C-reactive protein, mg/litre | W/ retinopathy (n=17)<br>2.3 ± 0.6 | |
| | | | Mean BMI (kg/m2) ± SD | 23.5 ± 3.2 | | | | W/out retinopathy (n=69)<br>2.0 ± 0.3 | |
| | | | Missing data: | | | | | Positive low-level (micro) albuminuria (n=18)<br>4.9 ± 1.5 | |
| | | | | | | | | Negative low-level (micro) albuminuria (n=70)<br>1.8 ± 0.2 | |
| | | | | | | | Relationship between development of retinopathy | HbA1c <7.0% vs. >7.0%<br><br>OR = 1.35<br>95% CI 0.21 to 8.52 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| cz 2006 | | Liver dysfunction<br>Connective tissue disease<br>Renal failure and other severe diseases | | | | and HbA1c | p = 1.0<br><br>Patients with retinopathy had higher values of HbA1c (p = 0.04) than those without | |
| | | | | | | Relationship between development of low-level (micro) albuminuria and HbA1c | HbA1c <7.0% vs. >7.0%<br><br>OR = 4.25<br>95% CI 0.50 to 35.50<br>p=0.27<br><br>Patients with low-level (micro) albuminuria had higher values of HbA1c (p = 0.04) than those without | |
| | | | | | | Number of people reaching target HbA1c, n/N (%) | Not reported | |
| | | | | | | Final HbA1c value, % | W/ retinopathy (n=17)<br>8.8 ± 1.3 | |
| | | | | | | | W/out retinopathy (n=69)<br>8.1 ± 1.4 | |
| | | | | | | | Positive low-level (micro) albuminuria (n=18)<br>8.8 ± 1.3 | |
| | | | | | | | Negative low-level (micro) albuminuria (n=70) | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 8.8 ± 1.3 | |
| | | | | | | Incidence of hypoglycaemic episodes | Not reported | |
| | | | | | | Incidence of severe hypoglycaemic episodes | Not reported | |
| | | | | | | Incidence of nocturnal hypoglycaemic episodes | Not reported | |
| | | | | | | Number of adverse events/complications/avoidance | Not reported | |
| | | | | | | Quality of life | Not reported | |

**Table 96: Eeg-Olofsson 2010**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| K Eeg-Olofsson, Jan Cederholm, | Case series (retrospective) | N = 7,454<br><br>Inclusion criteria: | Mean age [95% CI] | All patients 36.9 [10.0 to 0.12]<br>HbA1c 5.0 – | Patients with HbA1c 5.0 – 7.9%<br>vs. | All patients were followed from | Number of adverse events n (events per 1,000 person years) | | Funding: The Swedish Association |
| | | | | | | | All CVD | All patients = 154 (4.7) | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Peter M. Nilsson, Bjorn Zethelius, Ann Marie Svensson, Soffia Gudbjornsdottir, and Bjorn Eliasson. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care 33 (7):1640-1646, 2010. | Country: Sweden | type 1 diabetes patients on the Swedish National Diabetes Register<br>Age range of 20 to 65 years<br>Diabetes duration of 1 to 35 years<br><br>Exclusion criteria:<br>Not reported | | 7.9%<br>36.4 [9.8 – 0.15]<br>HbA1c 8.0 – 11.9%<br>37.4 [10.2 – 0.18]<br>p = < 0.001 | Patients with HbA1c 8.0 – 11.9% | baseline until a cardiovascular event or death or otherwise until censor date 31 December 2007.<br><br>Maximum follow-up = 5 years<br><br>Mean follow-up = 4.95 years | | | of Local Authorities and Regions funds the Swedish National Diabetes register. |
| | | | M:F (overall) | 55.8%:44.2% | | | | | |
| | | | type 1 diabetes | 100% | | | Fatal CVD | All patients = 36<br>HbA1c 5.0 to 7.9% = 17<br>HbA1c 8.0 to 11.9% = 19 | |
| | | | Mean age of diabetes onset ± SD | Not reported | | | All CHD | All patients = 131 (4.0)<br>HbA1c 5.0 to 7.9% = 45 (2.4)<br>HbA1c 8.0 to 11.9% = 86 (6.0)<br>p = < 0.001 | |
| | | | Mean diabetes duration (years) ± SD | All patients<br>19.9 [9.1 to 0.11]<br>HbA1c 5.0 – 7.9%<br>19.1 [9.3 – 0.14]<br>HbA1c 8.0 – 11.9%<br>20.9 [8.9 – 0.15] | | | Fatal CHD | All patients = 34<br>HbA1c 5.0 to 7.9% = 17<br>HbA1c 8.0 to 11.9% = 17 | |
| | | | | | | | All stroke | All patients = 37 (1.1)<br>HbA1c 5.0 to 7.9% = 14 (0.7) | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Eeg-Olofsson 2006 | | | | p = < 0.001 | | | | HbA1c 8.0 – 11.9% = 23 (1.6)<br>p = < 0.05 | |
| | | | Mean HbA1c (%) ± SD | All patients<br>8.0 [1.2 to 0.01] | | | Fatal stroke | All patients = 4<br>HbA1c 5.0 to 7.9% = 0<br>HbA1c 8.0 to 11.9% = 4 | |
| | | | | HbA1c 5.0 – 7.9%<br>7.2 [0.6 to 0.01] | | | All mortality | All patients = 94 (2.8)<br>HbA1c 5.0 – 7.9% = 50 (2.7) | |
| | | | | HbA1c 8.0 – 11.9%<br>9.0 [0.8 to 0.01] | | | | HbA1c 8.0 – 11.9% = 44 (3.0)<br>Non-significant | |
| | | | | p = < 0.001 | | | | | |
| | | | Mean BMI (kg/m2) [95% CI] | All patients<br>25.3 [3.7 to 0.04] | | | Non-CVD mortality | All patients = 58<br>HbA1c 5.0 – 7.9% = 33<br>HbA1c 8.0 – 11.9% = 25 | |
| | | | | HbA1c 5.0 – 7.9%<br>25.1 [3.5 to 0.06] | | | Incidence and hazard ratios of adverse events with baseline or updated mean HbA1c as predictor<br>n/N (%); HR [95% CI]<br>i) Model 1: adjusted for age, sex, diabetes duration, systolic BP, total cholesterol<br>ii) Model 2: Model 1 + adjusted for albuminuria (>20µg/min) | | |
| | | | | HbA1c 8.0 – 11.9%<br>25.5 [3.8 to 0.07] | | | | | |
| | | | | p = < 0.001 | | | | | |
| | | | Missing data: | | | | All CVD | 154/7454 (2.07%)<br>Baseline HbA1c as predictor: | |

| Reference | Study type | Number of patients | Patient characteristics | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | i) 1.26 [1.09 to 1.45]<br>ii) 1.22 [1.06 to 1.40]<br>Updated mean HbA1c as predictor:<br>i) 1.32 [1.14 to 1.54]<br>ii) 1.27 [1.09 to 1.80] | |
| | | | | | | All CHD | 131/7454 (1.76%)<br>Baseline HbA1c as predictor:<br>i) 1.31 [1.12 to 1.52]<br>ii) 1.28 [1.09 to 1.49]<br>Updated mean HbA1c as predictor:<br>i) 1.34 [1.14 to 1.58]<br>ii) 1.30 [1.10 to 1.53] | |
| | | | | | | All stroke | 37/7454 (0.50%)<br>Baseline HbA1c as predictor:<br>i) 1.12 [0.83 to 1.51]<br>ii) 1.08 [0.80 to 1.47]<br>Updated mean HbA1c as predictor:<br>i) 1.24 [0.89 to 1.72]<br>ii) 1.19 [0.86 to 1.66] | |
| | | | | | | All mortality | 94/7454 (1.26%)<br>Baseline HbA1c as predictor:<br>i) 0.97 [0.80 to 1.17]<br>ii) 0.92 [0.76 to 1.11]<br>Updated mean HbA1c as predictor: | |

| Reference | Study type | Number of patients | Patient characteristics | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | i) 1.04 [0.85 to 1.28]<br>ii) 0.98 [0.80 to 1.20] | |
| | | | | | | Incidence and hazard ratios for adverse events with baseline HbA1c as predictor, by mean baseline HbA1c categories<br>n/N (%); HR [95% CI]<br>i) Model 1 adjustment (details as above)<br>ii) Model 2 adjustment (details as above) | | |
| | | | | | | All CVD | HbA1c 5.0 to 7.9%:<br>n/N (%) = 55/4186 (1.31%)<br>i) HR = 1<br>ii) HR = 1<br>HbA1c 8.0 to 11.9%:<br>n/N (%) = 99/3268 (3.03%)<br>i) HR = 1.70 [1.21 to 2.38]<br>ii) HR = 1.59 [1.13 to 2.24] | |
| | | | | | | All CHD | HbA1c 5.0 to 7.9%:<br>n/N (%) = 45/4186 (1.08%)<br>i) HR = 1<br>ii) HR = 1<br>HbA1c 8.0 to 11.9%:<br>n/N (%) = 86/3268 (2.63%)<br>i) HR = 1.80 [1.24 to 2.60]<br>ii) HR = 1.71 [1.18 to 2.48] | |
| | | | | | | All stroke | HbA1c 5.0 to 7.9%:<br>n/N (%) = 14/4186 (0.33%)<br>i) HR = 1<br>ii) HR = 1 | |

| Reference | Study type | Number of patients | Patient characteristics | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | HbA1c 8.0 to 11.9%:<br>n/N (%) = 23/3268 (0.70%)<br>i) HR = 1.51 [0.76 to 2.98]<br>ii) HR = 1.40 [0.70 to 2.79] | |
| | | | | | | Incidence of any hypoglycaemic episodes | Not reported | |
| | | | | | | Quality of life | Not reported | |

**Table 97: Forrest 2000**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| K. Y. Forrest, D. J. Becker, L. H. Kuller, S. K. Wolfson, and T. J. Orchard. Are predictors of coronary | Case series (prospective)<br><br>Country: USA | N = 658 met eligibility criteria<br><br>Inclusion criteria:<br>Diagnosed or seen within a year of diagnosis at a particular hospital | Mean age | 28 | Not applicable | 6 years | Incidence of coronary heart disease (CHD) | No CHD = 566 (86.0%) | Funding: National Institutes of Health, USA |
| | | | M:F | 332:326 | | | | CHD morbidity = 46 (7.0%) | |
| | | | type 1 diabetes | 100% | | | | CHD mortality = 18 (2.7%) | |
| | | | Mean age of diabetes onset ± SD | Not reported | | | | Total CHD = 64* (9.7%) | |
| | | | Mean diabetes duration (years) ± | No CHD<br>18.4 ± 7.2 | | | The subjects who developed either macrovascular outcome were found to be older and to have a longer duration of type 1 diabetes.<br>The prevalence of hypertension and blood pressure levels were higher at baseline for | | |
| | | | | CHD morbidity<br>25.7 ± 6.6 | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. Atherosclerosis 148 (1):159-169, 2000.<br><br>Forrest 2000 | | between 1950 and 1980<br>Diagnosed at an age of <17 years<br>On insulin therapy at discharge<br><br>Exclusion criteria:<br>Not reported | SD, by CHD status | CHD mortality 25.9 ± 7.1<br>Total CHD 25.7 ± 6.6 | | | those who subsequently developed CHD or LEAD.<br>Diastolic blood pressure showed no relationship to subsequent LEAD.<br>HbA1c levels did not differ significantly between subjects whether or not they subsequently developed CHD or LEAD.<br>Insulin dose was significantly lower in those with subsequent CHD, especially CHD morbidity, but showed no association with LEAD.<br>The independent predictors of CHD mortality were hypertension, type 1 diabetes duration, Beck Depression Inventory scores, and white blood cell counts.<br>The independent predictors of total CHD were hypertension, type 1 diabetes duration, Beck Depression Inventory scores, high density lipoprotein level and overt nephropathy.<br>The independent predictors of LEAD were type 1 diabetes duration, HbA1c, low density lipoprotein level and smoking. | | |
| | | | Mean HbA1c (%) ± SD, by CHD status | No CHD 10.4 ± 1.9<br>CHD morbidity 10.2 ± 2.0<br>CHD mortality 10.7 ± 1.8<br>Total CHD 10.2 ± 1.9 | | | | | |
| | | | Mean BMI (kg/m2) ± SD, by CHD status | No CHD 23.5 ± 3.3<br>CHD morbidity 24.3 ± 3.3<br>CHD mortality 23.3 ± 2.8<br>Total CHD 24.1 ± 3.3 | | | | | |
| | | | Missing data:<br>623/658 (94.7%) provided follow-up data for coronary heart disease (CHD) incidence<br>567/658 (86.2%) provided follow-up data for lower- | | | | Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported. | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | extremity arterial disease (LEAD) incidence | | | | | |

**Table 98: Guerci 1999**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| B. Guerci, L. Meyer, S. Sommer, J. L. George, O. Ziegler, P. Drouin, and K. Angioi-Duprez. Severity of diabetic retinopathy is linked to lipoprotein (a) in type 1 diabetic patients. Diabetes & Metabolism 25 (5):412- | Cross-sectional study<br><br>Country:<br>France | N = 341<br><br>Inclusion criteria:<br>type 1 diabetes patients of an outpatient clinic, diagnosed according to WHO criteria<br>C-peptide negative<br>On a weight-maintaining diet<br>Treated by intensive conventional insulin therapy (split and mixed insulin regimens)<br><br>Exclusion criteria:<br>Recent onset of diabetes | Mean age | NR = 43.9 ± 15.7 | Group 1 (NR):<br>No retinopathy<br><br>Group 2 (N-PDR):<br>Non-proliferative diabetic retinopathy<br><br>Group 3 (PDR):<br>Proliferative diabetic retinopathy | N/A | Number of people in each group | NR = 123<br>N-PDR = 188<br>PDR = 30 | Funding:<br>Ministère de la Santé et de la Solidarité Nationale: Projet Hospitalier de Recherche Clinique 1994 |
| | | | | N-PDR = 48.7 ± 13.3 | | | Number of people who had been diabetic for ≥20 years in each group | NR = 30<br>N-PDR = 108<br>PDR = 24 | |
| | | | | PDR = 49.9 ± 10.3 | | | Independent variables that significantly predicted retinal status in all subjects | Diabetes duration<br>Prevalence of microproteinuria<br>Hypertension<br>HbA1c | |
| | | | | p < 0.01 | | | Independent variables that significantly predicted retinal status in those who had had | Prevalence of microproteinuria<br>HbA1c<br>Lipoprotein (a) | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 418, 1999.<br><br>Guerci 1999 | | An episode of DKA, thyroid or liver disease, non-diabetic renal disease, pregnancy, acute/chronic inflammatory syndrome, alcoholism/malnutrition<br>On diuretics, beta blockers, hypolipaemic agents, or any other drug or hormone known to influence lipid or lipoprotein metabolism | | | | | diabetes for ≥20 years | | |
| | | | M:F | 199:142 | | | Hypoglycaemic episodes, adverse events, quality of life and other protocol-specified outcomes were not reported. | | |
| | | | type 1 diabetes | 100% | | | | | |
| | | | Mean age of diabetes onset ± SD | Not reported | | | | | |
| | | | Mean diabetes duration (years) ± SD | NR = 15.4 ± 8.8 | | | | | |
| | | | | N-PDR = 21.1 ± 7.8 | | | | | |
| | | | | PDR = 25.8 ± 3.5 | | | | | |
| | | | | p < 0.0001 | | | | | |
| | | | Mean HbA1c (%) ± SD | NR = 7.25 ± 0.97 | | | | | |
| | | | | N-PDR = 7.44 ± 1.14 | | | | | |
| | | | | PDR = 8.01 ±1.32 | | | | | |
| | | | | p < 0.01 | | | | | |
| | | | Mean BMI (kg/m2) ± SD | NR = 7.25 ± 0.97 | | | | | |
| | | | | N-PDR = 7.44 ± 1.14 | | | | | |
| | | | | PDR = 8.01 ± 1.32 | | | | | |
| | | | | p < 0.01 | | | | | |

**Table 99: Hietala 2013**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| K. Hietala, J. Waden, C. Forsblom, V. Harjutsalo, J. Kyto, P. Summanen, P. H. Groop, and FinnDiane Study Group. HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Diabetologia 56 (4):737-745, 2013.<br><br>Hietala 2013 | Case series (Prospective)<br><br>Country:<br>Finland | N = 2,019<br><br>Inclusion criteria:<br>Adult patients with type 1 diabetes<br>C-peptide negative<br>Age of onset <40 years<br>Insulin treatment initiated within 1 year of diagnosis<br><br>Exclusion criteria:<br>Not reported | Mean age ± SD | 35.0 ± 11.4 | HbA1c variability quartiles:<br><br>First quartile = 361<br>Second quartile = 365<br>Third quartile = 365<br>Fourth quartile = 368<br><br>In total, 1,459 patients were prospectively followed as a sub-cohort. | First follow-up: Mean ± SD = 5.2 ± 2.2 years | Number of people who had their first laser treatment during the follow-up period | 175 | Funding:<br>Folkhälsan Research Foundation<br>Wilhelm and Else Stockmann Foundation<br>Finnish Eye Foundation<br>European Commission<br>Medicinska Understödsföreningen Liv och Hälsa<br>Signe and Ane Gyllenberg Foundation<br>Waldemar von Frenckell Foundation<br>An EVO governmental grant |
| | | | M:F | 995:1024 | | | Estimated 5-year cumulative incidence of laser treatment (%) | 1st Q = 10%<br>2nd Q = 9%<br>3rd Q = 12%<br>4th Q = 19%<br>p < 0.001 | |
| | | | TID | 100% | | | Mean HbA1c (%) at the first follow-up visit (N = 1,459) | 1st Q = 8.1 ± 1.1<br>2nd Q = 8.3 ± 1.1<br>3rd Q = 8.4 ±1.1<br>4th Q = 8.6 ± 1.4<br>p < 0.001 | |
| | | | Mean age of diabetes onset ± SD | 15.3 ± 9.2 | | | Patients with nephropathy (N = 1,459) | 1st Q = 4%<br>2nd Q = 4%<br>3rd Q = 6%<br>4th Q = 10%<br>p = 0.001 | |
| | | | Mean | 22.9 ± | | | Mortality | 1st Q = 1% | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | diabetes duration (years) ± SD | 11.9 | | | (N = 1,459) | 2nd Q = 2%<br>3rd Q = 2%<br>4th Q = 2%<br>p < 0.001 | | | |
| | | | Mean HbA1c (%) ± SD | 8.4 ± 1.2 | | | | | | | |
| | | | Mean BMI (kg/m2) ± SD | 25.0 ± 3.4 | | | HbA1c variability by retinopathy status | | | | |
| | | | | | | | | No retinopathy (n = 311) | Non-proliferative retinopathy (n = 601) | Proliferative retinopathy (n=434) | |
| | | | | | | | Mean HbA1c (%) ± SD (p < 0.001) | 8.2 ± 1.2 | 8.5 ± 1.2 | 8.7 ± 1.3 | |
| | | | | | | | HbA1c variability (p = 0.03) | 0.082 ± 0.050 | 0.081 ± 0.042 | 0.088 ± 0.042 | |
| | | | | | | | Risk of proliferative retinopathy by HbA1c quartile: HR [95% | 1st Q: HR = 1; p = 0.003<br>2nd Q: HR = 1.3 [0.97 to 1.8]; p = 0.07<br>3rd Q: HR = 1.5 [1.1 to 2.0]; p < 0.001<br>4th Q: HR = 1.7 [1.3 to 2.2]<br><br>Mean HbA1c: | | | |

| Reference | Study type | Number of patients | Patient characteristics | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | CI]; p-value | HR = 1.2 [1.1 to 13]; p < 0.001 | |
| | | | | | | Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported. | | |

**Table 100: Kullberg 1994**

| Reference | Study type | Number of patients | Patient characteristics | | Interventions Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| C. E. Kullberg, K. Finnstrom, and H. J. Arnqvist. Severity of background retinopathy in type 1 diabetes increases with the level of long-term glycated haemoglobin. Acta Ophthalmol (Oxf) 72 (2):181-188, 1994.<br><br>Kullberg 1994 | Case series (Retrospective)<br><br>Country:<br>Sweden | N = 90<br><br>Inclusion criteria:<br>Adult type 1 diabetes patients that regularly attended an outpatient diabetes clinic during 1988 to 1991<br>Age at diagnosis ≤30 years<br>Duration of diabetes ≤25 years<br>Glycated haemoglobin followed for | Mean age ± SD | 35.2 ± 7.7 | Not applicable | This was a retrospective data analyses of patients who were attending the clinic between 1988 and 1991. Their glycated haemoglobin had been determined on average for 9.2 years before the examination of retinopathy. | Mean HbA1c for whole measurement period (%) ± SD | 7.2 ± 1.0 | Funding:<br>The Swedish Medical Research Council, the Swedish Diabetes Association, and the County Council of Östergötland |
| | | | M:F | 50:40 | | | Relative risks (RR) of background retinopathy for patients with HbA1c > 8% (n=22) vs. HbA1c ≤ 7% (n=41) | Patients with mean HbA1c > 8% had higher RRs for all kinds of background retinopathy compared to patients with HbA1c ≤ 7% | |
| | | | TID | 100% | | | | | |
| | | | Mean age of diabetes onset ± SD | Not reported | | | | | |
| | | | Mean diabetes duration (years) ± SD | 19.3 ± 4.2 | | | Multiple regression analyses:<br>Dependent variables were scores for retinopathy: higher score = worse state | Mean HbA1c for the preceding year did not contribute further to any regression model. | |
| | | | Mean | 7.2 ± 1.3 | | | | The impact of | |

| Reference | Study type | Number of patients | Patient characteristics | | Interventions Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | ≥5 years<br>Having background retinopathy at the latest regular retinopathy screening during 1988 to 1991<br><br>Exclusion criteria:<br>Not reported | HbA1c (%) ± SD previous year | | | | Independent variables were long and short term HbA1c diabetes duration, age, sex, BMI, insulin dose per kg of body weight, hypertension, smoking | long-term HbA1c concentration was significant for all sets of retinopathy scores. | |
| | | | Mean BMI (kg/m2) ± SD | 24.8 ± 3.2 | | | | Short and long term HbA1c measures were correlated (Pearson's r = 0.749, p < 0.001) | |
| | | | | | | | Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported. | | |

**Table 101: LeCaire 2013**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| TJ. Lecaire, Mari Palta, Ronald Klein, Barbara E. K. Klein, | Case series (prospective) | N = 888<br><br>[Wisconsin Diabetes Registry | Mean age ± SD at exam | WDRS = 30.9 ± 7.0<br>WESDR = 33.4 ± 7.4 | WDRS population was compared with WESDR | 20 years of diabetes duration was applied | Presence of any diabetic retinopathy (DR) | WDRS = 281 (92.1%)<br>WESDR = 567 (97.2%) | Funding:<br><br>WDRS was supported by the National |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| and Karen J. Cruickshanks. Assessing progress in retinopathy outcomes in type 1 diabetes: comparing findings from the Wisconsin Diabetes Registry Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care 36 (3):631-637, 2013.<br><br>LeCaire | Country:<br>US | Study (WDRS) = 305<br>Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) = 583]<br><br>Inclusion criteria:<br><br>WDRS<br>All residents ≤30 years old in 28 counties of central and southern Wisconsin newly diagnosed with type 1 diabetes during May 1987 through to April 1992 | M:F | WDRS = 150:155<br>WESDR = 292:291 | population | for data analyses | Proliferative DR or treated DR (DR grade ≥60 = very severe) | WDRS = 32 (10.5%)<br>WESDR = 208 (35.7%) | | | Institute of Diabetes and Digestive and Kidney Diseases.<br><br>WESDR was supported by the National Eye Institute, National Institutes of Health, Bethesda, MD. |
| | | | TID | 100% | | | DR category and HbA1c trend | | | | |
| | | | Mean age of diabetes onset ± SD | WDRS = 11.2 ± 7.0<br>WESDR = 14.1 ± 7.3 | | | Registry | WDRS | | | |
| | | | Mean diabetes duration (years) ± SD | WDRS = 19.7 ± 1.2<br>WESDR = 19.2 ± 1.4 | | | DR severity | None to minimal | Mild to moderate | Vision threatening | |
| | | | | | | | n (%) | n = 104 (34.1%) | n = 146 (47.9%) | n = 55 (18.0%) | |
| | | | | | | | Mean HbA1c (%) | 7.6 ± 1.3 | 8.0 ± 1.4 | 8.8 ± 1.7 | |
| | | | | | | | HbA1c < 7% | 34.0% | 18.5% | 18.2% | |
| | | | Mean HbA1c (%) ± SD | WDRS = 8.0 ± 1.5<br>WESDR = 9.3 ± 1.7 | | | | | | | |
| | | | | | | | Registry | WESDR | | | |
| | | | Number of patients with | WDRS = 72 (23.7%) | | | DR severity | None to minimal | Mild to moderate | Vision threatening | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2013 | | WESDR<br>type 1 diabetes patients from 11 counties of central and southern Wisconsin during 1979 to 1980 who were diagnosed at <30 years old, all of whom were using insulin<br><br>Exclusion criteria:<br>Not reported | HbA1c <7% | WESDR = 40 (7.4%) | | | n (%) | n = 94 (16.1%) | n = 239 (40.5%) | n = 253 (43.4 %) | |
| | | | | | | | Mean HbA1c (%) | 8.7 ± 1.7 | 9.1 ± 1.6 | 9.7 ± 1.7 | |
| | | | Mean BMI (kg/m2) ± SD | WDRS = 28.3 ± 5.9<br>WESDR = 26.1 ± 4.6 | | | HbA1c < 7% | 11.1% | 9.5% | 4.2% | |
| | | | Number of patients on intensive insulin management (MDI or CSII) | WDRS = 285 (93.4%)<br>WESDR = 124 (21.3%) | | | Odds ratios [95% Wald CI] from ordinal logistic regression analysis modelling the odds of DR severity by HbA1c (per 1%) | Adjusted for WESDR study cohort, age, sex, diabetes duration, education, and HbA1c:<br>OR = 1.34 [1.23 to 1.47] | | | |
| | | | | | | | | Adjusted for BPs in addition to the above adjustments:<br>OR = 1.31 [1.20 to 1.43] | | | |
| | | | | | | | Ordinal logistic regression models for the three DR severity categories confirmed higher, unadjusted average odds of more severe retinopathy in the WESDR era than in the WDRS era (OR 3.3 [95% CI 2.5 | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | to 4.3]). With adjustment for age, sex, diabetes duration and education, the OR was reduced to 3.0 [95% CI 2.2 to 4.0]. The inclusion of 20-year HbA1c in the model further reduced the OR for WESDR vs. WDRS to 2.2 [95% CI 1.6 to 3.0]. | | |
| | | | | | | Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported. | | |

**Table 102: Nordwall 2009**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M Nordwall, Hans J. Arnqvist, Mats Bojestig, and Johnny Ludvigsson. Good glycemic control remains crucial in prevention of late diabetic complicati | Case-series with prospective and retrospective elements<br><br>Country:<br>Sweden | N = 269<br><br>Inclusion criteria:<br>type 1 diabetes patients diagnosed <15 years old during 1961 to 1985 in the catchment area of a paediatric clinic in | Mean age | Not reported | The study population was divided into 5 groups, according to the period of type 1 diabetes onset:<br>G1) 1961 - 1965<br>G2) 1966 - 1970<br>G3) 1971 - 1975<br>G4) 1976 - | The study patients diagnosed with type 1 diabetes during 1961 to 1985 were followed up until the end of the 1990s.<br><br>HbA1c was measured regularly at the clinical | HbA1c as a risk factor for diabetic retinopathy (DR)<br>p < 0.001 | No DR<br>(n = 64) | Background DR<br>(n = 131) | Severe laser-treated DR<br>(n = 69) | Funding:<br>The Juvenile Diabetes Research Foundation International (JDRF)-Wallenberg, the Swedish Research Council, and the Swedish Child Diabetes |
| | | | M:F | Not reported | | | Long-term HbA1c ± SD (%) | 7.8 ± 0.8<br>(n = 62) | 8.5 ± 0.8<br>(n = 130) | 9.0 ± 1.0<br>(n = 52) | |
| | | | TID | 100% | | | In a multivariable model, only diabetes duration (OR 1.2 [95% CI 1.1 to 1.3]; p < 0.001) and HbA1c (OR 4.1 [95% CI 1.8 to 9.2]; p = 0.001) showed a significant correlation to any retinopathy. | | | | |
| | | | Mean age of diabetes onset ± SD | 8.6 ± 3.8 | | | HbA1c as a risk factor for nephropath | No DN<br>(n = 210) | Low-level (micro) albuminuria | Overt DN<br>(n = 36) | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ons--the Linkoping Diabetes Complications Study. Pediatr.Diabetes 10 (3):168-176, 2009.<br><br>Nordwall 2009 | | Sweden<br><br>Exclusion criteria:<br>Not reported | | | 1980<br>G5) 1981 - 1985 | visits 3 to 4 times per year. | y (DN)<br>p < 0.001 | | (n = 20) | | Foundation |
| | | | Mean diabetes duration (years) ± SD at last follow-up of retinopathy | 25.2 ± 7.6 | | | Long-term HbA1c ± SD (%) | 8.3 ± 0.9 (n = 206) | 8.7 ± 0.9 (n = 19) | 9.7 ± 1.1 (n = 19) | |
| | | | | | | | As with retinopathy, the significant correlation to nephropathy was shown only by diabetes duration (OR 1.1 [95% CI 1.0 to 1.2]; p = 0.016) and HbA1c (OR 2.6 [95% CI 1.3 to 5.1]; p = 0.007) | | | | |
| | | | Mean diabetes duration (years) ± SD at last follow-up of nephropathy | 25.5 ± 7.6 | | | The influence of possible risk factors on the occurrence of overt nephropathy and severe retinopathy was analysed with Cox regression models. When the significant variables in the univariate analysis were entered in the model, the only significant variable for occurrence of retinopathy was HbA1c (HR 2.1 [95% CI 1.2 to 3.4]; p = 0.005), and for development of nephropathy, it was also HbA1c (HR 5.3 [95% CI 2.3 to 12.4]; p < 0.001) only. Other models with other combination of variables yielded the same result with HbA1c as the only significant variable. | | | | |
| | | | Mean HbA1c (%) ± SD by period of onset | G1: 8.6 ± 0.9<br>G2: 8.5 ± 0.8<br>G3: 8.5 ± 0.9<br>G4: 8.4 ± 1.1<br>G5: 8.2 ± 0.9 | | | Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported. | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | p = 0.19 | | | | | |
| | | | Mean BMI (kg/m2) ± SD by period of onset | G1: 25.7 ± 3.5<br>G2: 25.5 ± 3.4<br>G3: 26.0 ± 4.2<br>G4: 25.6 ± 3.3<br>G5: 24.9 ± 3.6<br>p=0.63 | | | | | |
| | | | Number of patients with severe retinopathy | 69 (26.1%) | | | | | |
| | | | Number of patients with low-level (micro) albuminuria | 20 (7.5%) | | | | | |
| | | | Number of patients with overt nephropathy | 36 (13.5%) | | | | | |

**Table 103: Rossing 1996**

| Reference | Study type | Number of patients | Patient characteristics | | | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P. Rossing, P. Hougaard, K. Borch-Johnsen, and H. H. Parving. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ (Online) 313 (7060):779-784, 1996.<br><br>Rossing 1996 | Prospective or retrospective cohort study?<br><br>Country: Denmark | N = 939<br><br>Inclusion criteria:<br>Insulin-dependent diabetes<br>≥18 years old<br>Had diabetes for ≥ 5 years<br>Onset of diabetes at ≤40 years old<br><br>Exclusion criteria:<br>Patients who had been referred by the study group were excluded. | Nephropathy status | Normoalbuminuria (n = 593) | Low-level (micro) albuminuria (n = 181) | Overt nephropathy (n = 165) | Not applicable | 10 years | All-cause mortality, n (%) | Overall = 207/939 (22% of the study population died during the follow-up period)<br>w/ normoalbuminuria = 90/207 (43.5%)<br>w/ low-level (micro) albuminuria = 45/207 (21.7%)<br>w/ overt nephropathy = 72/207 (34.8%) | Funding: None |
| | | | Mean age ± SD (not significant) | 40 ± 12 | 38 ± 14 | 40 ± 13 | | | | | |
| | | | M:F (not significant) | 302:291 | 96:85 | 95:70 | | | Cardiovascular (CV) mortality, n (%) | Overall = 74/207 (35.7% of the deaths were due to CV causes)<br>w/ normoalbumi | |
| | | | Mean diabetes duration (years) | 17 [5 to 60] | 21 [5 to 56] | 22 [6 to 54] | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | [range] (p < 0.001) | | | | | | | nuria = 33/74 (44.6%) w/ low-level (micro) albuminuria = 18/74 (24.3%) w/ overt nephropathy = 23/74 (31.1%) | |
| | | | Mean HbA1c (%) ± SD (p < 0.05) | 8.8 ± 1.7 | 9.2 ± 2.0 | 9.5 ± 1.8 | | | Significant predictors of all-cause mortality (Cox multiple regression analysis) | Male sex; age; eight; smoking; social class; presence of albuminuria; hypertension; log10 serum creatinine concentration; HbA1c (RR 1.11 [95% CI 1.03 to 1.20]; p < 0.02) | |
| | | | Number of people with retinopathy (p < 0.001) | 107 (69%) | 157 (87%) | 162 (98%) | | | | | |
| | | | Mean age of diabetes onset ± SD | Not reported | | | | | Significant predictors of CV mortality (Cox multiple regression analysis) | Age; smoking; presence of low-level (micro) albuminuria; presence of overt nephropathy; | |
| | | | Mean BMI (kg/m2) | Not reported | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | ± SD | | | | | hypertension | |
| | | | type 1 diabetes | 100% | | | Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported. | | |
| | | | Missing data: | | | | | | |

**Table 104: Weinstock 2013**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R S. Weinstock, Dongyuan Xing, David M. Maahs, Aaron Michels, Michael R. Rickels, Anne L. Peters, Richard M. Bergenstal, Breanne Harris, Stephanie N. DuBose, Kellee M. Miller, Roy W. Beck, and D. Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis in | Cross-sectional study<br><br>Country: US | N = 7012<br><br>Inclusion criteria:<br>Patients on the type 1 diabetes Exchange Clinic Network database (registered by US-based paediatric and adult endocrinology practices)<br>≥ 26 years old | type 1 diabetes | 100% | Not applicable | There was no follow-up period as such as this was a cross-sectional study, however, information on the occurrence of severe hypoglycaemia (SH) and diabetic ketoacidosis (DKA) in the 12 months | Data available | SH data from 4973 participants<br>DKA data from 6797 participants | | | | Funding:<br><br>The type 1 diabetes Exchange Clinic Network is funded through a grant provided by the Leona M. an Harry B. Helmsley Charitable Trust. Some of the authors of |
| | | | Age range | 26 to 93 years old (mean age not reported) | | | Incidence of SH | ≥ 1 SH events = 587/4973 (11.8%) | | | | |
| | | | | | | | Incidence of DKA | ≥ 1 DKA events = 326/6796 (4.8%) | | | | |
| | | | Age categories: taken from those who provided DKA data | 26 to 49 years old = 4108/6796 (60.4%) | | | HbA1c and frequency of SH event | | | | | |
| | | | | | | | Mean HbA1c (%) | n | % with ≥ 1 SH events | Initial multivariate model*, OR [95% CI] (p < 0.001) | Final multivariate model **, OR [95% CI] (p < | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| adults with type 1 diabetes: results from the type 1 diabetes Exchange clinic registry. J.Clin.Endocrinol. Metab. 98 (8):3411-3419, 2013.<br><br>Weinstock 2013 | | Duration of type 1 diabetes ≥ 2 years<br><br>Exclusion criteria:<br>Not reported | | | | prior to enrolment was obtained from the participants. | | | | | 0.001) | the study have received funding from industry. |
| | | | | 50 to 64 years old = 2010/6796 (29.6%) | | | < 6.5 | 582 | 13.9 | 1.88 [1.34 to 2.62] | 1.95 [1.40 to 2.72] | |
| | | | | | | | 6.5 - 6.9 | 672 | 12.5 | 1.59 [1.15 to 2.21] | 1.64 [1.18 to 2.72] | |
| | | | | 65 years old and above = 678/6796 (9.98%) | | | 7.0 - 7.4 | 1002 | 8.3 | 1.0 | 1.0 | |
| | | | | | | | 7.5 - 7.9 | 907 | 12.4 | 1.46 [1.07 to 1.98] | 1.47 [1.09 to 2.00] | |
| | | | M:F | 3078 (45%) : 3717 (55%) | | | 8.0 - 8.9 | 1058 | 13.7 | 1.59 [1.19 to 2.13] | 1.62 [1.21 to 2.17] | |
| | | | Ethnicity | 91% non-Hispanic White | | | 9.0 - 9.9 | 393 | 9.4 | 0.96 [0.63 to 1.46] | 1.01 [0.66 to 1.52] | |
| | | | Mean diabetes duration (years) [IQR] | 24 [15 to 34] | | | ≥ 10.0 | 264 | 12.1 | 1.19 [1.76 to 1.89] | 1.25 [0.80 to 1.97] | |
| | | | | | | | *The initial multivariate model includes variables having p-value of < 0.10. **The final multivariate model was conducted by using | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | backward selection, keeping those variables with p value<0.01 and variables of clinical interest. | | | | | |
| | | | | | | | HbA1c and frequency of DKA event | | | | | |
| | | | | | | | Mean HbA1c (%) | n | % with ≥ 1 SH events | Initial multivariate model*, OR [95% CI] (p < 0.001) | Final multivariate model **, OR [95% CI] (p < 0.001) | |
| | | | Mean age of diabetes onset ± SD | Not reported | | | < 6.5 | 854 | 1.6 | 0.77 [0.40 to 1.45] | 0.80 [0.42 to 1.51] | |
| | | | | | | | 6.5 - 6.9 | 983 | 2.7 | 1.24 [0.74 to 2.09] | 1.26 [0.75 to 2.13] | |
| | | | | | | | 7.0 - 7.4 | 1413 | 2.3 | 1.0 | 1.0 | |
| | | | Mean HbA1c (%) ± SD | 7.7 ± 1.2 | | | 7.5 - 7.9 | 1218 | 4.2 | 1.68 [1.07 to 2.64] | 1.67 [1.06 to 2.61] | |
| | | | | | | | 8.0 - 8.9 | 1363 | 5.5 | 1.93 [1.26 to 2.95] | 1.98 [1.30 to 3.02] | |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 9.0 - 9.9 | 503 | 10.3 | 3.16 [1.98 to 5.04] | 3.41 [2.15 to 5.40] | |
| | | | BMI categories (mean BMI not reported): taken from those who provided DKA data | Underweight or Normal = 1697/4969 (34.2%) | | | ≥ 10.0 | 334 | 21.0 | 5.22 [3.28 to 8.31] | 6.26 [3.99 to 9.83] | |
| | | | | Overweight = 1938/4969 (39.0%) | | | Quality of life and other protocol-specified outcomes were not reported. | | | | | |
| | | | | Obese = 1334/4969 (26.8%) | | | | | | | | |
| | | | Missing data: | | | | | | | | | |

**Table 105: Aiello 2014**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| LP Aiello and | Prospective | N = 1441 for the | type 1 | DCCT: | After original | DCCT: 6.5 | | At end of DCCT | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| DCCT/EDIC Research Group. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 37 (1):17-23, 2014.<br><br>AIELLO 2014 | Case-series (DCCT data as well as 10-year follow-up of original DCCT RCT = EDIC)<br><br>NOTE: data linking HbA1c and retinopathy during the 10-year follow-up is not reported in this paper.<br><br>Country:<br>USA | DCCT<br><br>Inclusion criteria:<br>DCCT patients follow-up 17 years (ie. 10 years EDIC)<br>Original RCT: n=1441 (n=711 randomly assigned to intensive treatment, and n=730 to conventional treatment).<br><br>Exclusion criteria:<br>Not reported | diabetes | n=1441<br><br>NOT REPORTED | DCCT (RCT) all patients who volunteered entered into a follow-up trial (EDIC) and were put on intensive therapy | years | | (6.5 years)<br><br>Retinopathy: Higher values of HbA1c were all associated with higher rate of retinopathy progression<br>For each 10% decrease in HbA1c –eg. 9.0-8.1): 44% decreased risk of progression). | A number of research grants from National Institutes and academic bodies. |

**Table 106: Jacobsen 2013**

| Reference | Study type | Number of patients | Patient characteristics | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| JACOBSEN 2013<br>AM. Jacobson, BH. Braffett, PA. Cleary, RA. Gubitosi-Klug, ME. Larkin, and DCCT/EDIC Research Group. The long-term effects of type 1 diabetes treatment and complications on health-related quality of life: a 23-year follow-up of the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications cohort. Diabetes Care 36 (10):3131-3138, 2013. | Prospective<br>Case-series (23-year follow-up of original DCCT RCT)<br><br>Country:<br>USA | N = 1177 (91%) completers of the 1287 EDIC patients<br><br>Inclusion criteria:<br>DCCT patients follow-up 23 years (ie. 17 years EDIC)<br>Original RCT: n=1441 (n=711 randomly assigned to intensive treatment, and n=730 to conventional treatment).<br>Completed DQoL survey at end of follow-up<br><br>Exclusion criteria:<br>Not reported | type 1 diabetes | DCCT 23 years/EDIC 17years: n=1175 | After original DCCT (RCT) all patients who volunteered entered into a follow-up trial (EDIC) and were put on intensive therapy | 23 years (DCCT) and 17 years (EDIC) | | At 23 years follow-up | Funding:<br><br>A number of research grants from National Institutes and academic bodies. |
| | | | Age mean | 51 | | | DQOL: Higher values of HbA1c were all associated with a sustained drop of ≥5 points in DQOL score (multivariate: HR 1.12, 95% CI 1.06 – 1.19; p<0.01).<br><br>DQOL = 46 items; scale of 0-100. 100 = highest QoL. | | |
| | | | Duration of diabetes, mean years | 29.5 | | | | | |
| | | | HbA1c, mean (SD) | 7.9 (1.2) | | | | | |
| | | | Retinopathy | 92% | | | | | |
| | | | DQOL, total score, mean | 74.5 | | | Retinopathy: Higher values of HbA1c were all associated with a sustained drop of ≥5 points in DQOL score (multivariate: HR 1.12, 95% CI 1.06 – 1.19; p<0.01). | | |

**Table 107: LIND 2011**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| LIND 2011<br><br>M Lind, I Bounias, M Olsson, S Gudbjornsdottir, AM Svensson, and A Rosengren. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet 378 (9786):140-146, 2011. | Prospective Case-series<br><br>Country: Sweden | N = 20,985 (n=635, 3% admitted to hospital for HF).<br><br>Inclusion criteria:<br>Age ≥18 years<br>type 1 diabetes<br>No known Heart Failure<br>patients from Swedish National Diabetes registry (NDR)<br>treatment with insulin only<br>Age of onset ≤30 years<br><br>Exclusion criteria:<br>Not reported | type 1 diabetes | n=20,985 | Followed until hospital admission for heart failure, death, or end of follow-up (Dec 2009) | Median follow-up 9.0 years (IQR 7.3-11.0) | | At Follow-up | Funding:<br><br>AstraZeneca, NovoNordisk, Swedish Heart and Lung Foundation, Swedish Research Council. |
| | | | Age mean<br><br>Female | 38.6<br><br>45% | | | Heart failure: Incidence increased monotonically with HbA1c, with a range of 1.42 - 5.20 per 1000 patient-years in the lowest (<6.5%) and highest (≥10.5%) categories of HbA1c.<br><br>Risk of HF per 1% increase in HbA1c: HR 1.30 (95% CI 1.21 – 1.40; p<0.0001). | | |
| | | | Duration of diabetes, mean years | 23.1 | | | | | |
| | | | HbA1c, mean (SD) | 8.8 (1.34) | | | Risk of HF at intervals of HbA1c (multivariate*): | | |
| | | | BMI | 25.0 | | | <6.5% (reference) | 1.0 | |
| | | | | | | | 6.5 to <7.5% | HR 1.26 (0.76 – 2.07) | |
| | | | | | | | 7.5 to <8.5% | HR 1.47 (0.91 – 2.38) | |
| | | | | | | | 8.5 to <9.5% | HR 1.75 (1.07 – 2.85) | |
| | | | | | | | 9.5 to <10.5% | HR 2.58 (1.54 – 4.34) | |
| | | | | | | | ≥10.5% | HR 3.98 (2.23 – 7.14) | |
| | | | | | | | *adjusted for age, sex, duration of diabetes, smoking, BMI, blood pressure, comorbidities. | | |

**Table 108: ZOFFMANN 2014**

| Reference | Study type | Number of patients | Patient characteristics | | Study groups | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| ZOFFMANN 2014<br>V. Zoffmann, D. Vistisen, and M. Due-Christensen. A cross-sectional study of glycaemic control, complications and psychosocial functioning among 18- to 35-year-old adults with Type 1 diabetes. Diabet.Med. 31 (4):493-499, 2014. | Cross-sectional study<br><br>Country: Norway | N = 710 (completers, n=406, 57.2%)<br><br>Inclusion criteria:<br>Age 18-35 years<br>type 1 diabetes<br>From a referral centre<br><br>Exclusion criteria:<br>Not reported | type 1 diabetes | n=406 completers | Patient questionnaire<br><br>PAID score (max 100): High levels of diabetes distress = PAID ≥30 | N/A | | | Funding:<br><br>Steno Diabetes Centre. |
| | | | Age mean | 27.1 | | | PAID score: SS higher prevalence of diabetes distress (PAID ≥30) among patients with HbA1c ≥8% (Score 48.3, 95% CI 41.4-55.3) vs. those with lower HbA1c (score 35.7, 95% CI 29.0 – 42.9), p<0.01.<br><br>HbA1c was positively correlated with: lack of motivation, and the PAID score (both p<0.001).<br><br>HbA1c was negatively correlated with: perceived competence, self-esteem, well-being, and autonomy index (all p<0.001). | | |
| | | | Duration of diabetes, mean years | 13.5 | | | | | |
| | | | HbA1c, mean (SD) | 8.2 (1.5) | | | | | |
| | | | BMI | 24.8 | | | | | |
| | | | CSII<br><br>No. of SMBG mmts/week<br><br>PAID score, max 100 (SD) | 13.3%<br><br>28.9<br><br>29.1 (21.1) | | | | | |

**Table 109: Agardh 1997[7]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow- | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | up | | | |
| Agardh 1997 [7] | Prospective case series<br>Sweden | n=442<br><br>Inclusion criteria: type 1 diabetes, at least one HbA1c measurement per patient per observation year or at least two measurements in case of death (34 patients did not fulfil these criteria and were excluded from further analysis)<br><br>Exclusion criteria: none listed | Age, years (mean±SD) | 35±11 | Case series; glucose control treatment not reported | 5 years | Retinopathy<br>Severe retinopathy (clinically significant macular oedema, severe non-proliferative or proliferative retinopathy)<br>Urinary albumin concentration (UAC) change<br>Death<br>MI<br>CV disease | Any retinopathy (n=64); HbA1c; 8.2±1.1%<br>No retinopathy (n=57); HbA1c; 7.5±1.1%, p<0.01 | Funding:<br>Crafoord Fndn, Lund, the Royal Physiographic Society, Lund, Crown Princess Margareta's Cittee for the Blind, the Medical Faculty, University of Lund, Tore Nilsson Fndn, the Swedish Society of Medicine, the Novo Nordisk Research Fndn Swedish Diabetes Federation<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes, although limited inclusion criteria |
| | | | Women, % | 47 | Concomitant therapy: some patients on antihypertensives | | | Cumulative frequency retinopathy;<br>50% patients who still had no signs of retinopathy at 5 years, the mean HbA1c levels were <7.5% during the observation period<br><br>50% patients who developed any type of retinopathy, the mean HbA1c levels were >8.3% (P <0.0002 for all comparisons). | |
| | | | TIDM, % | 100 | | | | In 50% patients who progressed to severe retinopathy mean HbA1c levels were >8.9%, (P <0.001) compared with patients without retinopathy at follow-up or those who developed any type of retinopathy | |
| | | | Age at onset of diabetes, years (mean±SD) | 15±8 | | | | UAC; logistic regression analysis;<br>increase UAC associated mean HbA1c levels (p<0.01) | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Diabetes duration, years (mean±SD) | 20±12 | | | | MI<br>CV disease, death not associated with mean HbA1c levels | Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =unclear as no details of logistic regression modelling and unclear adjustments<br>Adequate follow-up=yes 5 years |
| | | | HbA1c, % (mean±SD) | 8.5±1.6 | | | | 5 year period; the meanHbA1c value for the entire patient group was 8.4±1.3%. HbA1c values were measured 16±5 times. The mean HbA1c values correlated with the levels at entry (r = 0.72, P <0.001) and at follow up (r = 0.73, P <0.001) | |
| | | | Weight or BMI | NR | | | | | |
| | | | Missing data:<br>34 patients | | | | | | |

**Table 110: Brinchmann-Hansen 1992[20]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention<br>Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Brinhmann-Hansen 1992[20] | Prospective case-series of patients originally enrolled in Oslo 1985 RCT[34]<br>Norway | n=45<br><br>Inclusion criteria: type 1 diabetes history diabetes for more than seven years | Age, years mean (range) | 26(18-36) | Cohort at 7 years:<br>10 patients used insulin pumps<br>29 used multiple injections (regular insulin before meals and isophane insulin at bedtime) delivered by an | 7 years | Retinopathy | Mean ±SD number of microaneurysms and haemorrhages according to mean HbA1:<br><br><9.0% (n=20)<br>Baseline; 11.8(14.8)<br>7 years; 25.5(43.1) | Funding<br>Norwegian Council for Science & Humanities, Norwegian Diabetes Association, Norwegian |

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|---|---|---|---|---|---|---|---|---|---|
| | | Initially randomised to 3 different treatments: continuous subcutaneous insulin infusion, multiple insulin injections, or continued conventional treatment with two daily injections of mixed insulin<br><br>Exclusion criteria: none listed | | | insulin pen<br>6 patients used conventional treatment (regular insulin and isophane insulin twice daily)<br><br>Glycaemic control estimated every second month by concentration of "stable" HbA1c | | | Change; 13.8(39.5)<br><br>9.1 to 10.0%<br>(n=13)<br>Baseline; 24.7(40.8)<br>7 years; 41.1(58.7)<br>Change; 16.4(56.6)<br><br>>10.1%<br>(n=12)<br>Baseline; 17.6(16.2)<br>7 years; 80.5(66.7)<br>Change; 62.8(65.8)*<br><br>*p= 0.014 compared with patients with HbA1 <10.0%<br>No definitive thresholds were observed giving definite increase in progression or below which the subject protected, but in the 15 (34%) patients with a seven year mean HbA1 >8.7% there was no severe progression of retinopathy<br>Multivariate regression analysis (to identify independent variables) severity of retinopathy not correlated to age, BP, or | Council on CV Diseases, University of Oslo, Ander Jahres Medial Fndn, Novo-Nordisk<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes, although limited inclusion criteria<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors(multivariate regression model)=yes<br>Adequate follow-up=yes 7 years |
| | | | Women, % | 53 | Concomitant therapy: NR | | | | |
| | | | TIDM, % | 100 | | | | | |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years mean (range) | 28(6-23) | | | | | |
| | | | HbA1, % (mean±SD) | 11.2±2.2 | | | | | |
| | | | Weight or BMI | NR | | | | | |
| | | | Severity of retinopathy: counts of micro-aneurysms, | 17(0-154) | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| | | | haemorrhages(both eyes), mean(range) | | | | | kidney function, patients with retinopathy at baseline were more likely to have more severe retinopathy at 7 years (r = 0.41; p=0.005)<br>independent variables; baseline HbA1, change Hb1A1, duration diabetes, baseline retinopathy<br>regression coefficient(95%CI); baseline HbA1 r=0.36(0.06 to 0.66) p=0.027, change Hb1A r=-0.35(-0.068 to -0.02) p=0.041 duration diabetes r=0.009(0 to 0.018)p=0.44, baseline retinopathy r=0.35(0.02 to 0.68) p=0.046<br><br>Initial treatment code did not contribute (p>0.05) outcome of retinopathy at 7 years<br>At 7 years retinopathy not correlated with baseline HbA1 value (r-0.22, p=0.14) | |
| | | | Missing data:<br>none | | | | | | |

**Table 111: DCCT 1993[152], DCCT 1995[1], DCCT 1996[2], DCCT 1997[3]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| DCCT 1993[152]<br>DCCT 1995[1]<br>DCCT 1996[2]<br>DCCT 1997[3] | RCT<br>Diabetes Control and Complications Trial (DCCT)<br><br>USA | n=1441<br>Primary cohort; n=726<br><br>Secondary cohort; n=715<br><br>Inclusion criteria: DCCT type 1 diabetes insulin dependent, HbA1c <6.5%, age of 13 to 39 years; and the absence of hypertension, hypercholesterolemia, and severe diabetic complications or medical conditions<br><br>Primary prevention cohort; IDDM for 1-5 years, no retinopathy, UAE of < 40 mg/24 hours<br>Secondary intervention cohort, IDDM for 1-15 years, very-mild-to-moderate non-proliferative retinopathy, UAE < 200 mg/24 hours | Age, years (range) | Intensive therapy(n=711); 27±7<br>Conventional therapy (n=730); 27±7 | Intensive therapy ≥ 3 insulin injections or external<br>insulin pump use; dose adjustments based on at least four≥ 4 SMGM/day, daily glucose target; 70 to 120 mg/dl (3.9 to 6.7 mmol/litre) before meals<br><br>Conventional therapy had no<br>glucose target (prevent<br>symptoms of hyperglycaemia and hypoglycaemia only), 1-2 daily insulin injections | 6.5 years | Progression to retinopathy; three steps or more on fundus photography that was sustained over a 6-month period<br>Macular oedema<br>Severe non-proliferative or proliferative retinopathy<br>Nephropathy;<br>UAE (mg/24 hours)<br>≥40<br>≥300<br>Clinical neuropathy at 5 years; abnormal neurologic examination consistent | Progression of retinopathy;<br>Primary prevention cohort; intensive vs. conventional RR (95%CI) 0.73 (0.62 to 0.85)<br>Secondary prevention cohort; intensive vs. conventional RR (95%CI) 0.54 (0.39 to 0.66) | Funding:<br>Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases and by the National Heart, Lung, and Blood Institute, the National Eye Institute, the National Center for Research Resources, and various corporate sponsors<br><br>Risk of bias:<br>Randomisation : adequate |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Exclusion criteria: excluded patients with a history of cardiovascular disease or with hypertension (defined by a blood pressure of 140/90 mm Hg or more) or hypercholesterolemia (defined by a serum cholesterol level obtained after an overnight fast that was at least 3 SD above age- and sex-specific means | Women, % | Intensive therapy; 49<br>Conventional therapy; 46 | Percentage of patients on intensive therapy at EDIC start (1993);<br>Intensive group; 98%<br>Conventional group; 2%<br><br>Percentage of patients on intensive therapy at year 11 EDIC follow-up;<br>Intensive group; 97%<br>Conventional group; 94%<br><br>Concomitant therapy: NR | | with presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least 2 peripheral nerves or unequivocally abnormal autonomic-nerve testing<br>Mortality<br>Hypoglycaemia | Absolute rate reduction per 100 patient-years (95%CI)<br>Progression of retinopathy<br>Primary cohort<br>Conventional; 4.7<br>Intensive; 1.2<br>Risk reduction 76 (95%CI 62 to 85)<br>Secondary cohort<br>Conventional; 7.6<br>Intensive; 3.7<br>Risk reduction 54 (95%CI 39 to 66) | Allocation concealment: adequate<br>Blinding: adequate<br>ITT analysis: yes<br>Powered study: yes |
| | | | TIDM, % | 100 | | | | Macular oedema<br>Secondary cohort<br>Conventional; 3.0 | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Intensive; 2.0<br>Risk reduction 54 (95%CI -13 to 48)<br>Severe non-proliferative or proliferative retinopathy<br>Secondary cohort<br>Conventional; 2.4<br>Intensive; 1.1<br>Risk reduction 47 (95%CI 14 to 68) | |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | UAE ≥40 mg/24 hours<br>Primary cohort<br>Conventional; 3.4<br>Intensive; 2.2<br>Risk reduction 34 (95%CI 2 to 56)<br>Secondary cohort<br>Conventional; | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 5.7<br>Intensive; 3.6<br>Risk reduction 43 (95%CI 21 to 58) | |
| | | | Diabetes duration, years (mean±SD)<br>13.8±1.0 | Intensive therapy; 6±4<br>Conventional therapy; 5±4 | | | | UAE ≥300 mg/24 hours<br>Primary cohort<br>Conventional; 0.3<br>Intensive; 0.2<br>Risk reduction 44 (95%CI -124 to 86)<br>Secondary cohort<br>Conventional; 1.4<br>Intensive; 0.6<br>Risk reduction 56 (95%CI 18 to 76) | |
| | | | HbA1c, % (mean±SD), | Primary cohort<br>Intensive therapy; 8.8±1.6<br>Conventional therapy; | | | | Clinical neuropathy at 5 years<br>Primary cohort<br>Conventional; 9.8 | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 8.8±1.7<br>Secondary cohort<br>Intensive therapy; 8.9±3.8<br>Conventional therapy; 8.6±3.7 | | | | Intensive; 3.1<br>Risk reduction 34 (95%CI 2 to 56)<br>Secondary cohort<br>Conventional; 16.1<br>Intensive; 7.0<br>Risk reduction 57 (95%CI 29 to 73)<br><br>Mortality; conventional 7 patients died vs. intensive 4 patients died<br><br>Regression model estimates of the effect of 10% higher mean HbA1c on the change in risk of other outcome<br>Retinopathy; ≥3 | |
| | | | BMI or weight | NR | | | | | |
| | | | Missing data:<br>8 patients | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | microaneurysms (primary cohort only)<br>Conventional therapy<br>%change in risk; 56, 95%CI 39 to 74<br>Intensive therapy<br>%change in risk; 66, 95%CI 39 to 96<br><br>Neuropathy at 5 years; confirmed<br>Conventional therapy<br>%change in risk; 41, 95%CI 19 to 66<br>Intensive therapy<br>%change in risk; 43, 95%CI 9 to 87<br><br>Nephropathy; AER≥300 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mg/24 hours<br><br>Conventional therapy<br>%change in risk; 71, 95%CI 32 to 121<br>Intensive therapy<br>%change in risk; 57, 95%CI 7 to 133<br><br>Hypoglycaemia requiring assistance<br>HbA1c at eligibility screening subgroups; intensive versus conventional therapy<br><7.825%; intensive n=189, conventional n=171<br>RR(95%CI) | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 2.098 (1.37 to 3.19)<br>7.825-8.819%; intensive n=185, conventional n=175 RR(95%CI) 3.12(2.15 to 4.51)<br>8.820-10.099%; intensive n=166, conventional n=192 RR(95%CI) 4.13(2.79 to 6.13)<br>>10.100%; intensive n=190, conventional n=173 RR(95%CI) 4.89 (3.05 to 7.83)<br>Relative risk reductions associated with a 10% lower | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | mean HbA1c among HbA1c values ≤8 vs. values >8% estimated from a segmented (change point) model<br>Sustained retinopathy progression, %risk reduction (95%CI)<br>Intensive<br>≤8%; 49 (27 to 65) vs. >8%; 37 (17 to 53), p=0.46<br>Conventional<br>≤8%; 69 (29 to 87) vs. >8%; 37 (26 to 41), p=0.055<br>Sustained low-level (micro) albuminuria, %risk reduction (95%CI)<br>Intensive<br>≤8%; 43 (2 to | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 67) vs. >8%; 44 (17 to 62), p=0.97<br>Conventional<br>≤8%; 58 (-50 to 87) vs. >8%; 33 (17 to 45), p=0.47<br>Confirmed clinical neuropathy, %risk reduction (95%CI)<br>Intensive<br>≤8%; 30 (-19 to 58) vs. >8%; 35 (-17 to 64), p=0.87<br>Conventional<br>≤8%; 32 (-70 to 56) vs. >8% ; 29 (13 to 42), p=0.90 | |

**Table 112: DCCT/EDIC 2005[116,117], DCCT/EDIC 2008[166,167]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| DCCT/EDIC 2005[116,117]<br>DCCT/EDIC 2008[166,167] | Prospective case series study;<br>Epidemiology of Diabetes Interventions and Complications (EDIC) of patients originally enrolled in RCT (Diabetes Control and Complications Trial (DCCT)<br><br>USA | n=1441<br><br>Inclusion criteria: DCCT type 1 diabetes insulin dependent, age of 13 to 39 years; and the absence of hypertension, hypercholesterolemia, and severe diabetic complications or medical conditions<br><br>Exclusion criteria: excluded patients with a history of cardiovascular disease or with hypertension (defined by a | Age, years (range) | DCCT at Baseline (1983–1989);<br>Intensive therapy(n=711); 27±7<br>Conventional therapy (n=730); 27±7<br><br>End of DCCT (1993);<br>Intensive therapy (n=698); 34±7<br>Conventional therapy (n=723); 33±7<br><br>Year 11 of EDIC (2004);<br>Intensive therapy (n=593); 45±7<br>Conventional therapy (n=589); 45±7 | Intensive therapy ≥ 3 insulin injections or external insulin pump use; dose adjustments based on at least four≥ 4 SMGM/day, daily glucose goals; 70 to 120 mg/dl (3.9 to 6.7 mmol/litre) before meals<br><br>Conventional therapy had no glucose target (prevent symptoms of hyperglycaemia and hypoglycaemia only), 1-2 daily insulin injections | 17 years | CVD events; non-fatal MI, stroke; CVD death; angina<br>Retinopathy | End DCCT;<br>HbA1c; 9.1±1.5% intensive group vs.7.4±1% conventional group, p<0.01<br>End 11 year EDIC;<br>Absolute difference in the HbA1c between groups; 0.1%<br><br>CVD event at 17 years;<br>144 events in 83 patients<br>Intensive therapy; 46 in 31 patients, 0.38 events/100 patient years<br>Conventional therapy; 98 in 52 patients, 0.80 events/100 patient-years (p=0.007 vs. intensive therapy)<br><br>Progression to retinopathy from DCCT closeout to EDIC at 10 years (n=1211)<br>Risk reduction (95%CI) with intensive vs. conventional therapy;<br>53% (43% to 61%), | Funding:<br>Not reported<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =yes proportional hazard model adjustment appropriate<br>Adequate follow-up=yes 17 years |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | blood pressure of 140/90 mm Hg or more) or hypercholesterolemia (defined by a serum cholesterol level obtained after an overnight fast that was at least 3 SD above age- and sex-specific means | | | | | | p<0.001<br>HbA1c intensive vs. conventional therapy; 87.07% vs. 7.98% p=ns | |
| | | | Women, % | DCCT at Baseline (1983–1989); Intensive therapy; 49<br>Conventional therapy; 46<br><br>End of DCCT (1993); Intensive therapy; 49<br>Conventional therapy; 46<br><br>Year 11 of EDIC (2004); Intensive therapy; 48<br>Conventional therapy; 46 | Percentage of patients on intensive therapy at EDIC start (1993); Intensive group; 98%<br>Conventional group; 2%<br><br>Percentage of patients on intensive therapy at year 11 EDIC follow-up; Intensive group; 97%<br>Conventional group; 94%<br><br>Concomitant therapy: NR | | | Cumulative incidence 1st CVD event<br>Intensive vs. conventional therapy vs. ; RR (95%CI) 0.59 (0.9 to 0.63), p=0.02<br>Cumulative incidence 1st non-fatal MI, stroke or CVD death<br>Intensive vs. conventional therapy; RR (95%CI) 0.57 (0.12 to 0.79), p=0.02<br>HbA1c; per 10% increase (adjusted for HbA1c, age, cholesterol, smoking status at baseline);<br>HR (95%CI) 1.25 (1.10 to 1.43)<br>HbA1c; per 10% decrease (adjusted for HbA1c, age, cholesterol, smoking status at baseline);<br>HR (95%CI) 0.8 (0.70 to 0.91) | |
| | | | TIDM, % | 100 | | | | Higher HbA1c levels (9.5% vs. 9.0%), at DCCT | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | baseline associated with occurrence of the CV events independent of treatment assignment (p=0.014) | |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years (mean±SD)<br>13.8±1.0 | DCCT at Baseline (1983–1989);<br>Intensive therapy; 6±4<br>Conventional therapy; 5±4<br><br>End of DCCT (1993);<br>Intensive therapy; 12±5<br>Conventional therapy; 12±5<br><br>Year 11 of EDIC (2004);<br>Intensive therapy; 24±5 | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Conventional therapy; 23±5 | | | | | |
| | | | HbA1c, % (mean±SD), | DCCT at Baseline (1983–1989); Intensive therapy; 9.1±1.6 Conventional therapy; 9.1±1.6<br><br>End of DCCT (1993); Intensive therapy; 7.4±1.1 Conventional therapy; 9.1±1.5<br><br>Year 11 of EDIC (2004); Intensive therapy; 7.9±1.3 Conventional therapy; 7.8±1.3 | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | BMI or weight | NR | | | | | |
| | | | Missing data: None | | | | | | |

**Table 113: Diamante 1997[37]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcomes | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Diamante 1997[37] | Cross-sectional study<br><br>Spain; 18 centres | n=1822<br>2 subgroups;<br>type 1 diabetes <5 years<br>type 1 diabetes >30 years<br><br>Inclusion criteria: type 1 diabetes, all patients visited over 3 month period, > 18 years, insulin dependent, disease detected prior | Age, years (mean±SD) | 30.5±9.7 | Insulin treatment (%)<br>1 dose; 1.1<br>2 doses; 35.7<br>3 doses; 46.3<br>4 doses; 16.4 | 4 years | Nephropathy<br>Normal; UAE (at least 3) < 20 µg/min (minimum of one determination being within last 6 months)<br>Micro-albuminuria or macro-albuminuria; UAE 20-200 µg/min or >200 µg/min respectively, detected in 2 | Logistic regression analysis<br>HbA1c correlated with ESRF vs. no ESRF (p<0.00005)<br>HbA1c correlated with low-level (micro) albuminuria vs. normoalbuminuria (p<0.00005)<br>Low-level (micro) albuminuria vs. CVD; HbA1c no influence | Funding:<br>Not stated<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes, although limited inclusion criteria<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for |
| | | | Women, % | 49 | Concomitant therapy; NR | | | HbA1c (all patients)<br>Normoalbuminuria; 7.3±1.6%<br>Low-level (micro) albuminuria; 8.0±1.6% | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | age 30 years and required insulin treatment within 6 months<br>Exclusion criteria: none listed | | | | | out of 3 consecutive tests (in the absence of urinary infection)<br>ESRF; plasma creatinine > 1.4 mg/dl (2 occasions) | Macroalbuminuria + ESRF; 7.7±1.9% | confounding factors =unclear description limited<br>Adequate follow-up=NA cross-sectional study |
| | | | TIDM, % | 100 | | | | HbA1c (diabetes <5 years evolution)<br>Normoalbuminuria; 7.3±1.6%<br>Low-level (micro) albuminuria; 8.0±1.6%<br>Macroalbuminuria + ESRF; 7.7±1.9% | |
| | | | Age at onset of diabetes, years (mean±SD) | 15±8 | | | | | |
| | | | Diabetes duration, years (mean±SD) | NR | | | | | |
| | | | HbA1c, % (mean±SD) | 7.5±1.6 | | | | | |
| | | | | ±3.2 | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 114: Eid Fares 2010[44]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Eid Fares 2010[44] | Retrospective case series | n=117 | Age, years (range) | 9–33 | Glycaemic control; NR | 5 years | Fluctuations in HbA1c defined | Nephropathy<br>18/117 (15.4%) developed | Funding:<br>Not listed |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | UK | Inclusion criteria: type 1 diabetes, within 18 months of diagnosis<br>Exclusion criteria: duration of diabetes <5 years, wolfram syndrome, thalassemia or other haemoglobinopathy | | | | | as an; increase in HbA1c > 2% between 2 consecutive measurements (3 months interval±2 weeks) or an increase in HbA1c >1% at 2 points in time (from estimated between-individual difference in HbA1c > 2% more than doubles risk of developing microvascular complications | nephropathy<br>HbA1c in patients with;<br>Neuropathy;<br>9.4±1.6%<br>No neuropathy; 8.5±1.1%<br>Overall; 8.6± 1.2% | Risk of bias:<br>Appropriate eligibility criteria=some patients <18 years (proportion not given)<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =regression analysis adequately adjustments<br>Adequate follow-up=yes 5 years |
| | | | Women, % | 55 | Concomitant therapy: NR | | | Fluctuations in HbA1c;<br>Present with nephropathy; 15/18(83%)<br>Present without nephropathy; 54/117(54%)<br>Absent with nephropathy; 3/18(17%)<br>Absent without nephropathy; 45/117(45%) | |
| | | | TIDM, % | 100 | | | | Multivariate analysis;<br>prediction of diabetic nephropathy | |
| | | | Age at onset of diabetes, years (mean±SD) | Neuropathy (n=18), 10.94±4.5<br>No neuropathy( n=99); 10.12±3.9 | | | Neuropathy; rate of albumin excretion between 20-200 micro-g/min (or between 30-300 mg/24 h) | Average mean of HbA1c; OR(95%CI) 1.66 (1.03 to 2.68) [Model 1], 1.55 (1.01; 2.38) [Model 2], 1.75 (1.18; 2.59) [Model 3]<br>Fluctuations in HbA1c; OR(95%CI) 1.89 (0.42 to 8.41) [Model 1], 2.34 (0.56 to 9.77) [Model 2], 4.17 (1.13 to 15.31) [Model 4]<br>Gender; OR(95%CI) 0.85 (0.27 to 2.63) [Model 1] | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Family history; OR(95%CI) 1.32 (0.42 to 4.13) [Model 1]<br>Age at onset; OR(95%CI) 1.06 (0.88 to 1.26) [Model 1]<br>Time between onset of diabetes till admission to diabetes clinic; OR(95%CI) 0.93 (0.80 to 1.08) [Model 1]<br>Baseline BMI; OR(95%CI) 0.93 (0.75 to 1.14) [Model 1]<br>Model 1; all risk covariates (average mean of HbA1c, Fluctuations in HbA1c, gender, family history, age at onset, time between diabetes onset to clinic admission, baseline BMI)<br>Model 2; mean and fluctuations HbA1c<br>Model 3; mean HbA1c<br>Model 4; fluctuations HbA1c | |
| | | | Time period from onset of diabetes to admission to Chronic Care Center for children and young adults, | Neuropathy; 3.96±4.2<br>No neuropathy; 3.72±4.2 | | | | Fluctuations on incidence of nephropathy in 77 patients HbA1c≤8%;<br>With nephropathy, fluctuations present; 15(26%)<br>With nephropathy, fluctuations absent; 5(1%) | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | years (mean±SD) | | | | | Without nephropathy; fluctuations present; 42(74%)<br>Without nephropathy, fluctuations absent 19(95%) | |
| | | | HbA1c, % (mean±SD)<br>Result at each visit | Neuropathy; 9.4±1.6<br>No neuropathy; 8.5±1.1<br>Overall; 8.6± 1.2 | | | | | |
| | | | BMI, (kg/m2) (mean±SD) | Neuropathy; 19.84±5.2<br>No neuropathy; 19.04±3.4 | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 115: Hislop 2008[65]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Hislop 2008[65] | Prospective case series | n=108<br>Inclusion criteria: type 1 | Age, years (mean±SD) | 21.6±2.8 | On continuous subcutaneous insulin fusion; 17 patients | 6 months | Quality of life<br>Centre for Epidemiological Studies- | Patients with abnormal CES-D score (≥16) poorer glycaemic higher HbA1c compared with those with normal CES-D (9.4% vs. | Funding:<br>Australian Diabetes Society Servier |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Australia | diabetes for at least 12 months<br>Exclusion criteria: type 2 diabetes | | | | | Depression Scale (CES-D); 20 items about the individual's behaviour, higher scores indicate greater distress, scores <16 were classified as 'normal', ≥16 'depressive symptoms', scores > 23 'severe depressive symptoms' | 8.4%, p=0.01) | Research Award, NovoNordisk Australia, Regional Diabetes Support Scheme<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome= yes<br>Controlled for confounding factors =unclear<br>Adequate follow-up=yes 10 years |
| | | | Women, % | 50 | Concomitant therapy: NR | | | No correlation between HbA1c and CES-D in total cohort (r=0.2, p=0.14) | |
| | | | TIDM, % | 100 | | | | Controlling for CSII use, CES-D and HbA1c correlated (r = 0.3, p=0.02) | |
| | | | Age at onset of diabetes, years (mean±SD) | 12.2±5.9 | | | | Patients on CSII vs. patients not; lower HbA1c (7.9 vs. 8.9%, p=0.03) | |
| | | | Diabetes duration, years (mean±SD) | 9.3±5.4 | | | | No difference in glycaemic control between patients with normal ASR-T scores (≤ 59) and psychologically distressed ASR-T scores (≥ 60) | |
| | | | HbA1c, % (mean±SD) | 8.7±1.8 | | | Adult-Self-Report Scale (ASR); ASR subdivided into Internalising and Externalising. Anxious/Depressed, Withdrawn, Somatic Complaints, Thought Problems, | | |
| | | | BMI, (kg/m2), (mean±SD) | NR | | | | | |
| | | | Missing data:<br>None | | | | | | |

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|---|---|---|---|---|---|---|---|---|
| | | | | | | Attention Problems, Aggressive Behaviour, Rule-Breaking behaviour, and Intrusive. Higher scores indicate higher distress. Total Problem Score (ASR-T), Internalising (ASR-I) and Externalising scores, (ASR-E).<br>For each scale, recommended cut-off scores were used (<60 = normal, 60-63 = borderline, >63 = clinical distress, with those scoring ≥60 being considered 'psychologically distressed'. | | |

**Table 116: Larsen 1990[90]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Larsen 1990[90] | RCT<br><br>On the basis of the 1st measurement of HbA1c, age and sex, patients were matched and randomly assigned to one of two comparable groups<br><br>HbA1c measured every 3 months<br><br>Denmark | n=240, consecutive patients<br><br>Inclusion criteria: type 1 diabetes, symptoms before 30 years, IDDM, propensity to ketosis, > 60 years,<br>Exclusion criteria:<br>None listed | Age, years (mean (range))<br><br>Control group<br>Men<br>Women<br>Monitored group<br>Men<br>Women | | Monitored group; HbA1c levels available to staff, used with blood or urine glucose values to adjust treatment, target NFBG <9mmol/(162 mg /dl) | 1 year intervention, year 2 post intervention | | Visited the clinic ≥ 4 times 1st year;<br>Monitored group; n=117<br>Control group; n=107<br>Mean number of visits during the year was 4.2 (range 4 to 8) in the control group and 4.5 (range 4 to 7) in the monitored group<br><br>Mean(±)HbA1c in monitored (n=98) vs. control group (n=99)<br>Baseline; monitored group 10.1±1.9% vs. control 9.9±1.8%<br>3 months; monitored group 9.9±1.9% vs. control; 10.1±1.6%<br>6 months; monitored group 9.8±1.7% vs. control; 10.2±1.7%<br>9 months; monitored group 9.9±1.6% vs. control; 10.2±1.7%<br>12 months; monitored | Funding:<br>Not listed<br><br>Risk of bias:<br>Risk of bias:<br>Randomisation : unclear<br>Allocation concealment: unclear<br>Blinding: single blind<br>ITT analysis: no<br>Powered study: unclear |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | group 9.4±1.4% vs. control; 10.0±1.7%, p<0.02<br>18 months; monitored group 9.6±1.4% vs. control; 10.1±1.5%<br>24 months; monitored group 9.3±1.2% vs. control; 10.1±1.5% | |
| | | | Women, % | 43 | Control group; HbA1c levels (including the randomisation values) not entered into the patients' records during study period, staff treated patients on blood or urine glucose values, target NFBG <9mmol/(162 mg /dl) | | | Mean(±)HbA1c in monitored (n=98) vs. control group (n=99)<br>Baseline; monitored group 10.1±1.9% vs. control 9.9±1.8%<br>3 months; monitored group 9.9±1.9% vs. control; 10.1±1.6%<br>6 months; monitored group 9.8±1.7% vs. control; 10.2±1.7%<br>9 months; monitored group 9.9±1.6% vs. control; 10.2±1.7%<br>12 months; monitored group 9.4±1.4% vs. control; 10.0±1.7%, p<0.02<br>18 months; monitored group 9.6±1.4% vs. control; 10.1±1.5% | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 24 months; monitored group 9.3±1.2% vs. control; 10.1±1.5% | |
| | | | TIDM, % | 100 | At 1 year, all HbA1c values controls entered into their records, HbA1c measurement was then routine, both groups followed 2nd year (compared HbA1c in 2 groups after another 6 and 12 months (18 and 24 months after randomisation ) | | | | |
| | | | Age at onset of diabetes, years (mean±SD) | Neuropathy (n=18), 10.94±4.5<br>No neuropathy( n=99); 10.12±3.9 | | | | | |
| | | | Time period from onset of diabetes to admission to Chronic Care Center for children and young adults, years (mean±SD) | Neuropathy ; 3.96±4.2<br>No neuropathy; 3.72±4.2 | | | | Treatment changes during 1 year<br>Group/regimen<br>Control group (n=107)<br>1 daily injection; at entry 14.0% vs. 11.2% at 12 months<br>2 daily injections; at entry 80.4% vs. 67.7% at 12 months<br>3 or 4 daily injections; at entry 5.6% vs. 27.1% at 12 months<br>Monitored group (n=115)<br>1 daily injection; at entry 10.4% vs4.3% at 12 months<br>2 daily injections; at | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | entry 80.0% vs. 55.7% at 12 months<br>3 or 4 daily injections; at entry 9.6% vs. 40.0% at 12 months ($p<0.05$ for comparison between groups) | |
| | | | HbA1c, % (mean±SD)<br>Result at each visit | Monitored 9.9±1.8<br>Control; 10.1±1.9 | | | | | |
| | | | BMI, (kg/m2) (mean±SD) | Neuropathy; 19.84±5.2<br>No neuropathy; 19.04±3.4 | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 117: Lehto 1999[93]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Lehto 1999[93] | Prospective case series<br><br>Finland | n=177<br><br>Inclusion criteria: type 1 diabetes, age from 45-64 years, diabetes diagnosed at the age of 30 years or later<br><br>Exclusion criteria: none listed | Age, years (mean±SD) | Men without CHD (n=70)<br>53.5±0.5<br>Men with (n=17) CHD<br>58.6 ±1.4<br>Women without CHD (n=79)<br>56.1 ±1.8<br>Women with (n=11) CHD<br>56.4 ±1.8 | Glycaemic control; NR<br><br>Concomitant therapy: NR | 7 years | CHD death<br><br>CHD event; death from CHD or non-fatal MI | Univariate Cox regression model;<br>HbA1 associated with risk of CHD death (p<0.001) and all CHD events (p<0.01)<br>poor Glycaemic control (10.4% versus ≤10.4%) was associated with the incidence of CHD death (p<0.05)<br>high HbA1 (>10.4) associated with all CHD events | Funding:<br>Academy of Finland, the Finnish Heart Research Fndn, Aarne and Aili Turunen Fndn<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =yes multivariate analysis adjustment appropriate<br>Adequate follow-up=yes 7 years |
| | | | Women, % | 50 | | | | Multivariate analysis (adjustment CV factors; age, sex, area of residence, previous MI, smoking, BMI, hypertension, total cholesterol, total triglycerides, and HDL cholesterol);<br>high HbA1 (>10.4%, HR 5.4 [1.4 to 20.4]) associated with the incidence of CHD death (p=0.013)<br>high HbA1 (>10.4%, HR 2.8 [1.2 to 6.9]) associated | |

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| | | | | | | | | with the incidence of all CHD events (p=0.021) | |
| | | | TIDM, % | 100 | | | | | |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years (mean±SD)<br>13.8±1.0 | Men without CHD<br>13.8±1.0Men with CHD<br>15.7±1.6Women without CHD<br>13.0 ±0.8<br>Women with CHD<br>56.4 ±1.8 | | | | | |
| | | | HbA1, % (mean±SD) | Men without CHD 9.5±0.21<br>Men with CHD<br>10.5±0.4<br>Women without CHD<br>10.1 ±0.2<br>Women with CHD<br>11.1±0.4 | | | | | |
| | | | BMI, (kg/m2), (mean±SD) | Men without CHD<br>25.1±0.Men with CHD<br>24.4±0.8 | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | Women without CHD<br>25.5±0.5<br>Women with CHD 26.1 ±1.4 | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 118: Lustman 2005 [100]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Lustman 2005 [100] | Cross sectional observational study<br><br>USA | n=118<br><br>Inclusion criteria: type 1 diabetes Exclusion criteria: none listed | Age, years (mean±SD) | 40.7±12.7 | Use of insulin pump; 55/188(29%)<br>Total daily insulin dose, units mean(±SD); 37.2±20.9 | NA | Quality of life<br>Symptom Checklist-90 (SCL-90) and the Summary of Diabetes Self-Care Activities (SDSCA)<br><br>SCL-90; Measures psychological symptom patterns both psychiatric and medical patients | SDSA;<br>HbA1c levels positively correlated with depression symptoms on SDSA (t=0.44, p<0.02) | Funding:<br>National Institutes of Health<br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome= yes<br>Controlled for confounding factors =yes<br>Adequate |
| | | | Women, % | 50 | Concomitant therapy: NR | | | SDSA;<br>HbA1c levels were higher in the depressed than in the non-depressed patients (covariate-adjusted means±standard error of mean=8.8%± 0.3% vs. 7.6%±0.1%, F=10.1, p<0.0001) | |
| | | | TIDM, % | 100 | | | | SDSCA composite score; | |

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| | | | | | | | (validated in both populations). Each item rated on a five-point distress scale (0–4) ranging from “not at all” at one pole to “extremely” at the other. The SCL-90 is scored and interpreted in terms of 9 primary dimensions or subscales, one of which assesses depression, 20 items that comprise this subscale used to assess the severity of depression symptom | Addition of SDSCA composite score to regression analysis, the parameter estimate for depression effect on HbA1c level was attenuated minimally (parameter estimate 0.50, t =3.3, p<0.001), SDSCA score had no effect within the model (p=0 .40) | follow-up=NA |
| | | | Age at onset of diabetes, years (mean±SD) | 21.7±13.2 | | | | SCL-90;<br>Scores on SCL-90 depression subscale were 2.3±0.4 in the depressed group compared with 0.6± 0.4 in the non-depressed group | |
| | | | Diabetes duration, years (mean±SD) | NR | | | | SCL-90;<br>HbA1c levels correlated to severity depression symptoms within depressed group (p<0 .02, across subgroups) | |
| | | | HbA1c, % (mean±SD) | 7.7±1.3 | | | SDSCA assesses diabetes self-care were assessed; 12-item self- | | |
| | | | Weight (lbs), (mean±SD) | 169.3±34.0 | | | | | |
| | | | Missing data: | | | | | | |

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| | | | None | | | report questionnaire that measures levels of self-care behaviour and degree of adherence with physician-recommended activities including diet amount, exercise, and adherence to glucose monitoring<br><br>Raw scores for each converted to z scores and averaged to form composite z score for the SDSCA, higher score indicates greater attention to self-care | | |

**Table 119: Pirez Mendez 2007[124]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Pirez Mendez 2007[124] | Prospective case series<br><br>Spain | n=59<br><br>Inclusion criteria: type 1 diabetes and bad metabolic control (glycosylate haemoglobin HbA1c values equal to or higher than 9% in the previous year)<br><br>Exclusion criteria: unwilling to transfer from conventional to Multiple Dose Insulin regime | Age, years mean (range) | 31.9(15-47) | Cohort<br>Patients offered change of insulin regimen from a conventional to Multiple Dose Insulin; 2 or 3 daily injection of NPH insulin with short-acting analogue lispro as a pre-meal bolus (59/73 changed from conventional therapy and were included in study)<br>HbA1c measured every 3 months and frequency of hypoglycaemia episodes<br>The goal of HbA1cvalues was <6.2% | 7 years | Target HbA1c values of <6.2%<br><br>Frequency of severe hypo-glycaemia (coma or neuroglycopenia requiring 3rd party, with /without need for intra-muscular glucagons or intravenous glucose or emergency hospitalisation)<br><br>Frequency of mild hypo-glycaemia<br>(any self-treated episode without need for assistance from 3rd party) | Mean values of HbA1c: 7.5±1.5%, 7.2±1.8%, 7.6±1.6%, 7.1±1.7%, 7±1.4±6.6 1.6% and 6.8±1.4% for first, second, third, fourth, fifth, sixth and seventh year of follow-up respectively<br><br>Percentage of patients reaching target HbA1c < 6.2% for the first, second, third, fourth, fifth, sixth and seventh year of follow-up: 16%, 27.5%, 15.7%, 33.3%, 28.6%, 42% and 33% | Funding<br>None stated<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes, although limited inclusion criteria<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors=no<br>Adequate follow-up=yes 7 years |
| | | | Women, % | 41 | Concomitant therapy: NR | | | | |
| | | | TIDM, % | 100 | | | | | |
| | | | Age at onset of diabetes, | NR | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| | | | years (mean±SD) | | | | | Severe hypoglycaemic episodes (episodes/patient-year)<br>year before study; 0.32±0.2<br>during study; 0.28±0.1 (ns compared with before study)<br>Mild/moderate hypoglycaemia episodes (episodes/patient-month)<br>year before study started; 17.7±6<br>during study; 16.5±4 to 21.7±5 (ns compared with before study value)<br>(mean±SD) insulin (IU); 43±23.1, 36.7±22.5, 50.8±21.1, 53.9±16.3, 52±16.4, 54.4±17.2, 52.8±19.8 for | |
| | | | Diabetes duration, years mean (range) | 9.9±8.4 | | | | | |
| | | | HbA1c, % (mean±SD) | NR | | | | | |
| | | | BMI, (kg/m2), (mean±SD) | 23.2±3.1 | | | | | |
| | | | Missing data:<br>2 patients dropped out | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | first, second, third, fourth, fifth, sixth and seventh years of follow-up respectively | |
| | | Dropout rate: not reported | | | | | | |

**Table 120: Pittsburgh EDC 2002[121]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Pittsburgh EDC 2002[121] | Prospective case series<br><br>Analysis of cohort from Pittsburgh Epidemiology of Diabetes Complications (EDC) study (type 1 diabetes children < 17 years, 10 year study, follow- | n=586<br><br>Inclusion criteria: type 1 diabetes diagnosed before age of 17 years<br><br>Exclusion criteria: patients with LEAD in original | Age, years (range) | Without LEAD; 26.5±7.6<br>With LEAD; 31.3±7.1 | Glycaemic control; NR | 10 years | Lower extremity arterial disease(LEAD); claudication (Rose questionnaire), foot ulceration or lower extremity amputation | LEAD events in 70/586 patients (11% men, 13% of women)<br>Total of 40 first events were claudication, 13 amputation, 10 ulcer, and 7 combined, with no gender differences in type of first event | Funding: National Institutes of Health Grant<br><br>Risk of bias: Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes |
| | | | Women, % | Without LEAD; 48<br>With LEAD; 53 | Concomitant therapy: NR | | | HR(95%CI) for 10 year incident LEAD (men and women); 1.53(1.22 to 1.92), p<0.001 | |
| | | | TIDM, % | 100 | | | | HR(95%CI) for 10 year incident LEAD (men); | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | up 1996-1998) USA | cohort at baseline were excluded | | | | | | 1.70(1.27 to 2.29), p<0.001 | Controlled for confounding factors =yes multivariate analysis adjustment appropriate<br>Adequate follow-up=yes 10 years |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years (mean±SD) 13.8±1.0 | Without LEAD; 18.1±7.2<br>With LEAD 23.4±7.1 | | | | | |
| | | | HbA1, % (mean±SD) | Without LEAD 10.3±1.8<br>With LEAD 10.9±1.9 | | | | | |
| | | | BMI or weight | NR | | | | | |
| | | | Missing data: None | | | | | | |

**Table 121: Pittsburgh EDC 2003[122]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Pittsburgh EDC 2003[122] | Prospective case series<br><br>Analysis of | n=603<br><br>Inclusion criteria: | Age, years (range) | Without CAD; 25.9±7.3<br>With CAD; 33.0±6.8 | Case Series<br>Insulin dose/kg BW; Patients | 10 years | CAD death, Non-fatal MI, ECG ischaemia<br>Revascularisation | CAD death; 5/606 patients<br>Non-fatal MI; 25/606<br>ECG ischaemia; | Funding: National Institutes of Health Grant |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | cohort from Pittsburgh Epidemiology of Diabetes Complications (EDC) study (type 1 diabetes children < 17 years, 10 year study, follow-up 1996-1998) USA | type 1 diabetes diagnosed before age of 17 years<br><br>Exclusion criteria: CAD at baseline | | | without CAD; 0.81±0.25<br>Patients with CAD; 0.75±0.31 | | Angina | 17/606<br>Angina; 49/606<br>Revascularisation 12/606 | Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =yes multivariate analysis adjustment appropriate<br>Adequate follow-up=yes 10 years |
| | | | | | | | | | |
| | | | Women, % | Without CAD; 50<br>With CAD; 42 | Concomitant therapy: NR | | | HbA1 no association with subsequent CAD events | |
| | | | TIDM, % | 100 | | | | RR (95% CI) for HbA1 (per 1–percentage point increase) and incident coronary heart disease CAD death, non-fatal MI, ECG ischaemia, revascularisation, angina);<br>0.97 (0.86 to 1.09) | |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years (mean±SD) | Without CAD; 17.6±6.9<br>With CAD<br>24.9±6.9 | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | 13.8±1.0 | | | | | | |
| | | | HbA1, % (mean±SD) | Without CAD 10.4±1.8<br>With CAD 10.3±1.8 | | | | | |
| | | | BMI or weight | NR | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 122: SDIS 1995[127-129]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| SDIS 1995[127-129] | RCT/ Prospective cohort study<br>Sweden | n=89<br><br>Inclusion criteria: non proliferative retinopathy, normal s-creatinine, inadequate blood glucose | | ICT Therapy; n=42 | ST n=47 | Intensified conventional insulin treatment (ICT); insulin with education to ensure constant monitoring and treatment<br>Standard | 94 months /10 years | Retinopathy; on scale of 0 (no retinopathy) over 1 (only micro-aneurysms) to 6 (proliferative changes)<br>Mean retinopathy | Cumulative frequency of serious retinopathy;<br>increased with higher HbA1c levels only in patients with mild retinopathy at baseline, no increase in patients with moderate retinopathy<br>(shown graphically)<br><br>Patients with mild | Funding:<br>Swedish Division of NOVO-Nordisk Inc, Boehringer Mannheim Scand Inc<br><br>Risk of bias:<br>Appropriate |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | control<br>Exclusion criteria: albuminuria | | | | therapy (ST); 2 to 3 insulin injections/day | | level of ≥ 2.5 = mild, levels 3-5 = moderate (still non proliferative)<br>Serious retinopathy = sight-threatening retinal changes with immediate need for focal or scatter photocoagulation due to macular oedema or proliferations<br><br>Relationship between mean HbA1c during the 1st 5 years and serious retinopathy after 94 months analysed separately for patients with mild (n=53) and moderate (n=47) retinopathy at | retinopathy with mean HbA1c below 7% did not develop serious retinopathy | eligibility criteria=yes, although limited inclusion criteria<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =unclear as not controlled for ICT vs. ST<br>Adequate follow-up=yes,94 months |
| | | | Age, years (mean± SD) | 30±8 | 32±7 | Concomitant therapy: NR | | | Visual acuity seldom deteriorated in patients with initial mild retinopathy if HbA1c <8% | |
| | | | Women, % | 50 | 53 | | | | No deterioration in visual acuity in patients with mean HbA1c <7% | |
| | | | type 1 diabetes | 100 | 100 | | | | Patients with moderate retinopathy at baseline;<br>visual acuity sometimes deteriorated even if the HbA1c <7%<br>for mean HbA1c <8% patients had less visual deterioration compared patients with mild retinopathy (p= 0.01) | |
| | | | Age at onset of diabetes, years (mean± SD) | NR | NR | | | | Analysis of variance (nonparametric) showed a significant difference between proportions of patients with serious retinopathy between the various HbA1c levels when initial retinopathy was mild (p<0.01)<br><br>Development of serious retinopathy at any time during follow-up; | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | study entry<br><br>Nephropathy; albumin excretion of > 20 µg/min normal, 20-200 µg/min = low-level (micro) albuminuria, and > 200 µg/min = diagnostic of manifest nephropathy<br><br>Neuropathy; combination of symptoms of peripheral neuropathy in legs and nerve conduction velocity of at least 1 nerve of leg below the lower normal limit (41 m/sec)<br><br>Relationship between mean HbA1c during the 1st | Related to HbA1c at baseline [OR(95%CI) 1.70(1.0 to 2.8)] and during first 6 to 60 months of follow-up [OR(95%CI) 2.4(1.4 to 4.3)], not after 60 months<br>OR for HbA1c during the study<br>Serious retinopathy; 2.70(1.55 to 4.69)<br>Nephropathy; 3.33(1.66 to 7.56)<br>Neuropathy; 3.13 (1.56 to 6.28) | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 5 years and serious retinopathy after 94 months analysed separately for patients with mild (n=53) and moderate (n=47) retinopathy at study entry<br><br>Renal function<br>Neuropathy | | |
| | | | Diabetes duration, years (mean± SD) | 18±7 | 16±5 | | | HbA1c analysed at entry, after 6 months, and then every 4 months | Nephropathy;<br>patients with a mean HbA1c > 9% did not develop nephropathy<br>5/10 patients with a mean HbA1c ≥ 9% developed nephropathy<br>0/12 patients with mild initial retinopathy and mean HbA1c ≥ 9% during the study had nephropathy<br>Urinary albumin excretion (microgram/min);<br>HbA1c <7%; 87±40 | |
| | | | HbA1c, % (mean± SD) | 9.5±1.3 | 9.4±1.4 | | | | | |
| | | | BMI, (kg/m2), (mean± SD) | 22.5± 1.9 | 22.8.± 27 | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Missing data:<br>None | | | | HbA1c 7%-7.99%; 21±5<br>HbA1c 8%-8.99%; 55±19<br>HbA1c ≥9% 308±123<br>HbA1c ; 266±150<br>Neuropathy<br>Neuropathy (patients without neuropathy at baseline)<br>HbA1c <7% (6.5±0.1%); 2/20 patients<br>HbA1c 7%-7.99% (7.5±0.1%); 8/24 patients<br>HbA1c 8%-8.99% (8.4±0.1%); 7/18 patients<br>HbA1c ≥9% (9.6±0.2%); 3/7 patients<br>OR for HbA1c<br>Serious retinopathy; 2.70 (1.55 to 4.69)<br>Nephropathy; 3.33(1.66 to 7.56)<br>Peripheral neuropathy; 3.13 (1.56 to 6.28) | |

**Table 123: Shaban 2006[143]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Shaban 2006[143] | Cross sectional | n=273 | Age, years (mean±SD) | 38.7±11.4 | Glycaemic control; NR | NA | The Hospital Anxiety and | HbA1c positively correlated with HADS | Funding: |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | observational study<br><br>UK | Inclusion criteria: type 1 diabetes (defined by clinical parameters suggestive of absolute insulin deficiency e.g. low body mass index and ketonuria) aged 16-60 years, duration at least 1 year<br>Exclusion criteria: aged >60 years | | | | | Depression Scale (HADS);<br>2 subscales assess symptoms anxiety and depression separately, each subscale consists 7 questions with maximum score of 21<br><br>Scores interpreted to indicate symptomatology that is either mild (between 8 and 10), or moderate to severe (between 11 and 21) | scores (anxiety r=0.2, p=0.001, depression r=0.14, p=0.02) | British Diabetic Association Grant<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome= yes<br>Controlled for confounding factors =unclear<br>Adequate follow-up=NA |
| | | | Women, % | 45 | Concomitant therapy: NR | | | Patients 'moderate to severe levels' of anxiety demonstrated poorer glycaemic control than those reporting 'none to mild';<br>Anxiety ≥ 11: HbA1c 9.4%; anxiety < 8, HbA1c 8.5%, p= 0.001) | |
| | | | TIDM, % | 100 | | | | No difference in HbA1c for patients reporting different symptom severity for depression (depression ≥ 11: HbA1c 8.7%; depression < 8, HbA1c 8.9% p=0.5) | |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years (mean±SD) | 17.2±12.0 | | | | | |
| | | | HbA1c, % (mean±SD) | 8.8±1.5 | | | | | |
| | | | BMI, (kg/m2), (mean±SD) | NR | | | | | |
| | | | Missing data:<br>1 patient did not return | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | questionnaire (excluded from analysis) | | | | | |

**Table 124: Tabaei 2004[150]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Tabaei 2004[150] | Cross-sectional study<br><br>USA | n=634<br><br>Inclusion criteria: type 1 diabetes(onset before 30 year and IDDM)<br><br>Exclusion criteria: none listed | Age, years median (min.-max.) | 33(18-78) | Glycaemic control; NR | NR | Quality of life<br>Quality of Well-Being Self-Administered (QWB-SA); symptoms (acute and chronic) and functioning (self-care, mobility, physical activity and social activity) to provide a health-utility score as a summary measure of quality of life<br>Subgroups:<br>subjects (younger onset), with diabetes diagnosis < 30 years (IDDM) | Linear regression<br>HbA1c not associated with QWB-SA derived utility score | Funding:<br>Not reported<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes validated scale<br>Controlled for confounding factors =yes<br>Adequate follow-up=NA |
| | | | Women, % | 54 | Concomitant therapy: NR | | | Multivariable regression analysis (adjustments; hypoglycaemia, gender, complications)<br>HbA1c not associated with QWB-SA derived utility score (partial R2 = -0.05, p= 0.25) | |
| | | | TIDM, % | 100 | | | | Suggested lack of association explained in part by the generally good Glycaemic control and narrow range of HbA1c levels observed (fewer than 10% of patients with diabetes had HbA1c levels >11%) | |
| | | | Age at onset of diabetes, | NR | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | years (mean±SD) | | | | | | |
| | | | Diabetes duration, median (min.-max.) | 19(0-77) | | | | | |
| | | | HbA1c, % median (min.-max.) | 8.3(4.7-14.1) | | | | | |
| | | | BMI, (kg/m2), median (min.-max.) | 25(15-70) | | | | | |
| | | | Missing data: NR | | | | | | |

**Table 125: Van Tilburg 2001[161]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Van Tilburg 2001[161] | Cross sectional observational study | n=30<br><br>Inclusion criteria: type 1 diabetes and type 2 diabetes | Age, years (mean±SD) | 40.7±14.7 | Insulin pump; 9/30(30%)<br>Insulin 1–2 injections/day ; 5/30 (17%)<br>Insulin ≥3 injections/day | NA | Quality of life<br>Beck Depression Inventory (BDI); scores 16 indicate depression in | Linear regression<br>HbA1c levels positively correlated with BDI scores with (r=0 .44, p<0.02) | Funding:<br>Not reported<br><br>Risk of bias:<br>Appropriate eligibility |

| | | | | | | | | | |
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| | USA | patients presenting to routine clinic appointment (type 1 diabetes analyses separately) Exclusion criteria: documented history of psychiatric diagnosis, history of stroke, brain surgery, or closed head injury, mild dementia, pregnancy, or recent infection or illness that could have affected glucose control, inability to independently complete the BDI questionnaire | | | ; 16/30(53%) | | population | | criteria=yes Appropriate measurement of exposure and outcome= yes Controlled for confounding factors =unclear Adequate follow-up=NA |
| | | | Women, % | 70 | Concomitant therapy: NR | | | Age, duration of illness, BMI, and gender not associated with either BDI or HbA1c | |
| | | | TIDM, % | 100 | | | | | |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years (mean±SD) | 19.3± 12.5 | | | | | |
| | | | HbA1c, % (mean±SD) | 8.3±1.2 | | | | | |
| | | | BMI, (kg/m2), (mean±SD) | 24.6±4.8 | | | | | |
| | | | Missing data: None | | | | | | |

**Table 126: WESDR 1998a [79,80]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| WESDR 1998a [79,80] | Prospective case series | n=634<br><br>Inclusion criteria: type 1 diabetes, IDDM, Physician diagnosis; primary care of physician during the study period<br><br>Exclusion criteria: none listed | Age, years (mean±SD) | 26.8±11.2 | Glycaemic control; NR | 14 years | Retinopathy; macular oedema defined as thickening of the retina with or without partial loss of transparency within one disc diameter from the centre of the macula, estimated from all patients without macular oedema and had not been previously treated with photocoagulation at baseline (n=688 for younger onset | Retinopathy<br>After controlling for baseline retinopathy, duration of diabetes and gender, each percentage point of lower glycosylated haemoglobin at baseline was associated with increased odds of improvement of retinopathy (odds ratio 1.41; 95% CI 1.19, 1.67) | Funding:<br>National Institutes of Health Grant,<br>Research to Prevent Blindness<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =regression analysis adequately adjustments<br>Adequate follow-up=yes 10 years |
| | | | Women, % | 51 | Concomitant therapy: NR | | | Progression to retinopathy<br>HbA1 5.1-9.4% (n=187); 75.4%, RR 1.00<br>HbA1 9.5 to 10.5% (n=153); 79.5%, RR (95%CI) 1.37 (1.12 to 1.68)<br>HbA1 10.6 to 12.0%(n=174); 95.2%, RR (95%CI) 1.99 (1.67 to 2.38)<br>HbA1 12.1 to 19.5% (n=168); 95.0%, RR (95%CI) 2.64 (2.18 to 3.20)<br>Incidence of macular oedema<br>HbA1 5.1-9.4% (n=187); | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | patients, 329 for older onset patients)<br><br>Nephropathy proteinuria estimated from patients with < 0.30 g/litre urine protein concentration at baseline (n=666 for younger onset patients, 376 for older onset patients taking insulin) (proteinuria was defined protein concentration ≥ 0.30 g/litre)<br>Neuropathy<br>Loss of tactile sensation or loss of temperature sensitivity was defined as reporting a history of these | 12.7%, RR 1.00<br>HbA1 9.5 to 10.5% (n=153); 22.6%, RR (95%CI) 1.90 (1.12 to 3.25)<br>HbA1 10.6 to 12.0% (n=174); 33.9%, RR (95%CI) 3.11 (1.95 to 4.95)<br>HbA1 12.1 to 19.5% (n=168); 36.8%, RR (95%CI) 3.37 (2.12 to 5.34) | |
| | | | TIDM, % | 100 | | | | | |
| | | | Age at onset of diabetes, years (mean±SD) | 14.2±7.4 | | | | | |
| | | | Diabetes duration, years (mean±SD) | 12.6±9.0 | | | | | |

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| | | | | | | | complications patients who did not have them at the baseline (n=444 for younger onset patients, 148 for older onset patients) | | |
| | | | HbA1, % (mean±SD) | 10.6±2.0 | | | | | |
| | | | BMI, (kg/m2) (mean±SD) | NA | | | | | |
| | | | Missing data:75(18%) patients from 10 year follow-up; 765 patients participated at 10 year follow-up | | | | | | |

**Table 127: WESDR 1994[111,113]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| WESDR 1994[111,113] | Prospective case series | n=2990<br><br>Inclusion criteria: | Age, years (range) | Younger onset; 19.1±13.3<br>Older onset; 11.6±8.1 | Glycaemic control; NR | 10 years | Ischaemic heart disease mortality | Younger onset;<br>HR (95% CI) for ischaemic heart disease mortality for a 1–percentage point increase in GHb; 1.18 (1.00 | Funding: National Institutes of Health Grant |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | type 1 diabetes diagnosed before age of 17 years<br><br>Exclusion criteria: LEAD | | | | | | to 1.40) | |
| | | | Women, % | Younger onset; 49<br>Older onset; 54 | Concomitant therapy: NR | | | Older onset;<br>HR (95% CI) for ischaemic heart disease mortality for a 1–percentage point increase in GHb; 1.18 (1.04 to 1.17) | Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =yes multivariate analysis adjustment appropriate (18 factors for proportional hazards model in addition to age and sex for younger onset, 28 factors proportional hazards model in addition to age and sex for older onset)<br>Adequate follow-up=yes 10 years |
| | | | TIDM, % | 100 | | | | | |
| | | | Age at onset of diabetes, years (mean±SD) | Younger onset; 14.5±7.5<br>Older onset; 55.0±12.4 | | | | | |
| | | | Diabetes duration, years (mean±SD)<br>13.8±1.0 | Younger onset; 14.6±10.5<br>Older onset; 11.6±8.1 | | | | | |
| | | | GHb, % (mean±SD) | Younger onset; 12.6±2.6<br>Older onset; 11.1±2.4 | | | | | |
| | | | BMI, (kg/m2) | Younger onset; 23.6±4.3<br>Older onset; 28.8±5.7 | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 128: WESDR 1999[111,112]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| WESDR 1999[111,112] | Prospective case series<br><br>USA | n=1890<br><br>Inclusion criteria: type 1 diabetes, IDDM, Physician diagnosis; primary care of physician during the study period (1 July 1979 to 30 June 1980, and 3) were alive and resided within the 11-county area during | Age, years (mean±SD) | Younger onset (n=906); 14.4±7.5<br>Older onset (n=984); 53.5±12.3 | Glycaemic control; NR<br><br>Concomitant therapy: NR | 14 years | Lower extremity amputations (LEA); (amputations of toes, feet, or legs, traumatic amputations and unrelated to diabetes excluded) | Univariate analysis<br>LEA<br>Younger onset;<br>GHb 5.6-9.4% (n=223); incidence=2.5%, RR 1.00<br>GHb 9.5-10.5% (n=206); incidence= 6.7%, RR(95%CI)2.93 (1.10 to 7.83)<br>GHb 10.6-12.0% (n=220); incidence=7.6%, RR(95%CI) 3.21 (1.24 to 8.33)<br>GHb 12.1-19.5% (n=216); incidence=13.4%, RR(95%CI) 5.64 (2.43 to 13.10) | Funding:<br>National Institutes of Health<br>Research to Prevent Blindness<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =unclear no description confounders<br>Adequate follow-up=yes 14 years |
| | | | Women, % | Younger onset; 50<br>Older onset; 56 | | | | Univariate analysis<br>LEA<br>Older onset<br>GHb 5.4-8.1% (n=244); incidence= 4.4%, RR 1.00<br>GHb 8.2-9.4% (n=218); incidence=8.5%, RR (95%CI) 1.98 (0.78 to 4.99)<br>GHb 9.5-10.8% (n=223); | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | the same period<br><br>Exclusion criteria: none listed | | | | | | incidence=12.6%, RR(95%CI) 2.68 (1.15 to 6.24)<br>GHb 10.9-20.8% (n=225); incidence=14.6%, RR(95%CI) 3.79 (1.72 to 8.35) | |
| | | | TIDM, % | Younger onset; 100<br>Older onset; 100 | | | | Multivariable analyses (linear logistic model)<br>Younger onset<br>GHb associated with a higher incidence of amputations; OR 1.39 (1.21-1.59), p<0.0001<br>Older onset<br>GHb associated with a higher incidence of amputations; OR 1.25 (1.09-1.43), p<0.005 | |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years (mean±SD)<br>13.8±1.0 | Younger onset; 13.5±9.6<br>Older onset; 10.9±7.8 | | | | | |
| | | | GHb, % (mean±SD) | Younger onset; 10.8±2.1<br>Older onset; 9.6±2.0 | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | BMI, (kg/m2) | Younger onset; 23.4±4.2<br>Older onset; 29.2±5.7 | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 129: WESDR 1998[76,80]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| WESDR 1998[76,80] | Retrospective cohort study | n=987<br><br>Inclusion criteria: type 1 diabetes, IDDM, Physician diagnosis; primary care of physician during the study period (1 July 1979 to 30 June 1980, and 3) were alive and | Age, years (mean±SD) | Younger onset (n=654); 23.9 ±11.0<br>Older onset (n=333); 58.4 ±11.2 | Glycaemic control; NR<br><br>Concomitant therapy: NR | 14 years | Quality of life measured using SF-36<br><br>Scales; general health (GH), physical functioning (PF), physical role (RP)<br><br>Subgroups: subjects (younger onset), with diabetes diagnosis < 30 years (IDDM)<br><br>subjects | Multiple linear regression<br>Younger onset subgroup; GHb variable for negatively associated general health coefficient (r= -1.6, p<0.005), no association with physical functioning or physical role<br>Older onset subgroup; GHb variable no association with general health, physical functioning or physical role | Funding:<br>National Institutes of Health Grant<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =unclear no description of analysis<br>Adequate |
| | | | Women, % | Younger onset; 49<br>Older onset; 50 | | | | | |
| | | | TIDM, % | Younger onset; 100<br>Older onset; | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | resided within the 11-county area during the same period<br><br>Exclusion criteria: none listed | | 100 | | | (older onset), with diabetes diagnosis ≥30 years (IDDM) | | follow-up=yes 14 years |
| | | | Age at onset of diabetes, years (mean±SD) | NR | | | | | |
| | | | Diabetes duration, years (mean±SD)<br>13.8±1.0 | Younger onset; 11.6 ±9.0<br>Older onset; 8.9±6.7 | | | | | |
| | | | GHb, % (mean±SD) | Younger onset; 10.9±2.1<br>Older onset; 9.6±2.6 | | | | | |
| | | | BMI, (kg/m2), (mean±SD) | Younger onset; 22.8±3.8<br>Older onset; 29.6±5.5) | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 130: WESDR 1995[77,78]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| WESDR 1995[77,78] | Prospective case series<br><br>USA | n=2990<br><br>Inclusion criteria: type 1 diabetes, IDDM,<br>Physician diagnosis;<br>primary care of physician<br>during the study period<br><br>Exclusion criteria: none listed | Age, years (mean±SD) | Younger onset (n=1210); 29.3<br>Older onset (n=824); 652 | Glycaemic control; NR | 10 years | Retinopathy;<br>proliferative retinopathy for patients free of this complication at the baseline (n=112 for younger onset patients, 417 for older onset )<br>macular oedema defined as thickening of the retina with or without partial loss of transparency within one disc diameter from the centre of the macula, estimated | Retinopathy<br>Younger onset patients;<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of progression to proliferative retinopathy; 0.58 (0.48 to 0.72)<br><br>Older onset patients<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of progression to proliferative retinopathy; 0.69 (0.47 to 1.04)<br><br>Younger onset patients;<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of macular oedema; 0.53 (0.43 to 0.66) | Funding:<br>National Institutes of Health Grant,<br>Research to Prevent Blindness<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors =regression analysis adequately adjustments<br>Adequate follow-up=yes 10 years |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | from all patients without macular oedema and had not been previously treated with photocoagulation at baseline (n=688 for younger onset patients, 329 for older-onset patients)<br><br>Nephropathy proteinuria estimated from patients with < 0.30 g/litre urine protein concentration at baseline (n=666 for younger onset patients, 376 for older onset patients | Older onset patients<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of macular oedema; 1.06 (0.67 to 1.69) | |
| | | | Women, % | NA | Concomitant therapy: NR | | | Nephropathy<br><br>Younger onset patients;<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of gross proteinuria; 0.71 (0.59 to 0.86)<br><br>Older onset patients<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of gross proteinuria; 0.81 (0.61 to 1.09)<br><br>2% difference GHb from baseline to 4 years estimated to lead to 29% decrease in 10-year | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | taking insulin) (proteinuria was defined protein concentration ≥ 0.30 g/litre) | incidence of gross proteinuria in younger-onset patients, and 19% decrease in older onset patients | |
| | | | TIDM, % | Younger onset; almost all<br>Older onset; 100 | | | Neuropathy<br>Loss of tactile sensation or loss of temperature sensitivity was defined as reporting a history of these complications patients who did not have them at the baseline (n=444 for younger onset patients, 148 for older onset patients) | Neuropathy<br>Younger onset patients;<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of tactile sensation; 0.81 (0.67 to 0.98)<br><br>Older onset patients;<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of tactile sensation; 0.77 (0.54 to 1.06)<br><br>Younger onset patients;<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | self-reported loss of self-reported loss of temperature sensitivity; 0.84 (0.67 to 1.04)<br><br>Older onset patients;<br>OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of self-reported loss of temperature sensitivity; 0.84 (0.61 to 1.16)<br><br>2% difference GHb from baseline to 4 years estimated to lead to 19% decrease in 10-year incidence of loss of tactile sensation in younger onset patients, and 23% decrease in older onset patients<br>2% difference GHb from baseline to 4 years estimated to lead to 16% decrease in incidence of self-reported loss of temperature sensitivity in younger and older onset | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | patients | |
| | | | Age at onset of diabetes, years (mean±SD) | NA | | | | Younger-onset; any retinopathy<br>GHb 5.6-9.4% (n=52), incidence; 82.1%, RR 1.0<br>GHb 9.5-10.5% (n=61), incidence 86.4%, RR(95%CI) 1.1 (0.8 to 1.4)<br>GHb 10.6-12.0% (n=71) incidence 93.1%, RR(95%CI) 1.3 (1.0 to 1.7)<br>GHb 12.1-19.5% (n=64) incidence 96.9%, RR(95%CI) 1.6 (1.3 to 2.1)<br>Younger-onset; progression to proliferative retinopathy<br>GHb 5.6-9.4% (n=52), incidence; 6.2%, RR 1.0<br>GHb 9.5-10.5% (n=61), incidence 11.6%, RR(95%CI) 1.9 (0.8 to 4.5)<br>GHb 10.6-12.0% (n=71) incidence 34.4, RR(95%CI) 5.9 (3.0 to 11.6)<br>GHb 12.1-19.5% (n=64) incidence 96.9, RR(95%CI) 9.9 (5.4 to 18.0)<br>older onset; any | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | retinopathy<br>GHb 5.6-9.4% (n=40), incidence; 65.9%, RR 1.0<br>GHb 9.5-10.5% (n=40), incidence 85.0%, RR(95%CI) 1.1 (0.9 to 2.1)<br>GHb 10.6-12.0% (n=32) incidence 78.8%, RR(95%CI) 1.2 (0.7 to 1.9)<br>GHb 12.1-19.5% (n=23) incidence 100.0%, RR(95%CI) 2.1 (1.4 to 3.2)<br><br>older onset; progression to proliferative retinopathy<br>GHb 5.6-9.4% (n=40), incidence; 10.7 %, RR 1.0<br>GHb 9.5-10.5% (n=40), incidence 13.1%, RR(95%CI) 1.1 (0.4 to 2.8)<br>GHb 10.6-12.0% (n=32) incidence 27.6%, RR(95%CI) 1.3 (1.2 to 5.5)<br>GHb 12.1-19.5% (n=23) incidence 37.9%, RR(95%CI) 1.6 (1.6 to 7.3) | |
| | | | Diabetes | Younger onset; | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | duration, years (mean±SD) | 14.7<br>Older onset; 15.0 | | | | | |
| | | | GHb, % (mean±SD) | Younger onset; 10.8<br>Older onset; 10.2 | | | | | |
| | | | BMI, (kg/m2) | NA | | | | | |
| | | | Missing data:<br>None | | | | | | |

**Table 131: Wikblad 1996[168,169]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Wikblad 1996[168,169] | Retrospective case series<br><br>Sweden | n=108<br><br>Inclusion criteria: type 1 diabetes born between 1939 to 1959, duration of diabetes at least 5 years | Age, years (mean±SD) | 43±5.7 | Glycaemic control; NR | 10 years | Quality of life<br>SWEDQUAL, a questionnaire (61 items) measures 7 dimensions of quality of life; physical functioning, role functioning, | Patients grouped according to metabolic control; good acceptable, unsatisfactory, unacceptable | Funding:<br>Not reported<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and |
| | | | Women, % | 49 | Concomitant therapy: NR | | | Mean values for HbA1c (during 1 year); | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | (onset of diabetes in 1975 or earlier), currently treated with ≥ 20 U insulin daily<br>Exclusion criteria: none listed | | | | | pain, sleep, emotional well-being, family functioning and general health perceptions)<br><br>Items are scored (0-100); high score indicates better health/more favourable health state<br><br>Hypoglycaemia | Good;HbA1c ≤ 7.0, n=35<br>Acceptable; HbA1c = 7.1–8.0%, n=23<br>Unsatisfactory; HbA1c = 8.1 – 9.0%, n=24 | outcome=yes<br>Controlled for confounding factors =unclear<br>Adequate follow-up=yes<br>10 years |
| | | | TIDM, % | 100 | | | | Physical functioning;<br>Good; 88.1±2.9<br>Acceptable; 91.0±2.4<br>Unsatisfactory; 78.2±5.5 | |
| | | | Age at onset of diabetes, years (mean±SD) | 14.1±8.3 | | | | Satisfaction with physical health;<br>Good; 71.5±4.8<br>Acceptable; 72.8±5.8<br>Unsatisfactory; 61.6±6.1 | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Diabetes duration, years (mean±SD) | 28.7±9.5 | | | | Role limitation due to emotional health;<br>Good; 92.2±3.0<br>Acceptable; 89.4±5.8<br>Unsatisfactory; 85.9±4.6 | |
| | | | | | | | | Groups comparable for;<br>Satisfaction with family life<br>Marital functioning<br>Sexual functioning<br>General health<br>Positive feelings<br>Negative feelings<br>Pain<br>Mobility | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparisons | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | HbA1c, % (mean±SD) | 7.7±1.0 | | | | Patients who reported episodes of hypoglycaemia had significantly lower HbA1c mean values when compared with patients without severe hypoglycaemia (6.9%±1.0 vs. 7.9%±1.2; F= 5.7, p=0.01) | |
| | | | BMI, (kg/m2), (mean±SD) | NR | | | | | |
| | | | Missing data: Of original cohort; 36 patients moved out of the area and 18 died, of the remaining 131 patients, 108 answered the quality of life questionnaire | | | | | Patients with hypoglycaemic episodes rated their general health as being poorer compared with those without hypoglycaemia (57.7±9.2 vs. 74.9±3.2; F= 4.2, p=0.04 | |

**Table 132: Wikblad 1991[169]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparisons | Length of follow- | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **up** | | | |
| Wikblad 1991[169] | Prospective /retrospective case series<br>Sweden | n=185<br><br>Inclusion criteria: type 1 diabetes born between 1939 to 1959, duration of diabetes at least 5 years (onset of diabetes in 1975 or earlier), currently treated with ≥ 20 U insulin daily<br>Exclusion criteria: none listed | Age, years range | 26-46 | Glycaemic control; NR | 9 years | Retinopathy<br>Nephropathy (negative proteinuria test) | Patients without retinopathy changes<br>HbA1c ≥7.5%; 53%<br>HbA1c 7.6-8.4%; 28%<br>HbA1c 8.5-9.4%; 30%<br>HbA1c ≥9.5%; 29% | Funding:<br>Not reported<br><br>Risk of bias:<br>Appropriate eligibility criteria=yes<br>Appropriate measurement of exposure and outcome= unclear description outcomes<br>Controlled for confounding factors =unclear<br>Adequate follow-up=yes 9 years |
| | | | Women, % | 44 | Concomitant therapy: NR | | | Patients without proteinuria;<br>HbA1c ≥7.5%; 88%<br>HbA1c 7.6-8.4%; 77%<br>HbA1c 8.5-9.4%; 58%<br>HbA1c ≥9.5%; 47% | |
| | | | TIDM, % | 100 | | | | | |
| | | | Age at onset of diabetes, years (mean±SD) | Men 15.5±7.7<br>Women 12.3±7.9 | | | | | |
| | | | Diabetes duration, years (mean±SD) | 22.1±8.5 | | | | | |
| | | | HbA1c, % (mean±SD) | 8.7±1.3 | | | | | |
| | | | BMI, (kg/m2), (mean±SD) | 25(15-70) | | | | | |
| | | | Missing data:<br>NR | | | | | | |

## G.3.2 SMBG – frequency and timing

**Table 133: ABDELGADIR 2006 [4]**

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| M. Abdelgadir, M. Elbagir, M. Eltom, and C. Berne. The influence of glucose self-monitoring on glycaemic control in patients with diabetes mellitus in Sudan. Diabetes Res.Clin.Pract. 74 (1):90-94, 2006.<br><br>REF ID: ABDELGADIR 2006 | Cross-sectional study<br><br>carried out in an out-patient clinic in Sudan | n=193 consecutive type 2 diabetes (n=143 (74%)) and type 1 diabetes (n=50 (26%))<br>Inclusion criteria:<br>Age ≥20 years<br>Duration of diabetes ≥1 year<br>Exclusion criteria: not reported | | | Fasting blood glucose using portable glucose meters Accutrend sensor | | Frequency distribution of SMBG for type 1 diabetes (26%) and type 2 diabetes (74%) | | | Funding: Supported by grants from In-develop Uppsala and the Swedish Diabetes Association.<br><br>Risk of bias: No NICE checklist<br><br>"The study from an urban population in Sudan shows that the frequency of self-monitoring of glucose was positively associated to good glycaemic control in type 1 diabetes but not in type 2 diabetes patients. Education level |
| | | | | Patient characteristics (n=193) | | | Self-monitoring technique | SMBG<br>Blood glucose (mmol/litre) | | |
| | | | | | | | Once a day (n=4), mean (SD) | 6.2 (SD 1.8) | | |
| | | | Age (years), mean (SD) | 50.0 (SD 13.4) | | | Once a week (n=48) | 9.4 (SD 3.5) | | |
| | | | Gender (m/f) | 95/98 | | | None (n=141), mean (SD) | 13.1 (SD 4.5) | | |
| | | | Duration of diabetes (years), mean (SD) | 10.1 (SD 7.9) | | | | | | |
| | | | HbA1c (%) | Not reported | | | Random blood glucose values for type 1 diabetes (n=50) | | | |
| | | | BMI (kg/m2), mean (SD) | 22.9 (SD 4.9) | | | | Never monitored blood glucose | Monitored blood glucose | |

| Reference | Study type | Number of patients | Patient characteristics | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | of the participants was neither associated to frequency of self-monitoring nor to level of glycaemic control" |
| | | | | | | Random blood glucose (mmol/litre), mean (SD) | 17.2 (SD 4.5) | 7.2 (SD 1.8) | |
| | | | Drop-outs:<br>None reported | | | HbA1c (%), mean (SD) | 9.4 (SD 2.1) | 5.6 (SD 1.5) | |

**Table 134: BOTT 1994** [16]

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| U. Bott, V. Jorgens, M. Grusser, R. Bender, I. Muhlhauser, and M. Berger. Predictors of glycaemic | Prospective case series<br><br>Non-randomised multi-centre study | n=697 type 1 diabetes patients.<br>Inclusion criteria:<br>type 1 diabetes patients, age 15-40 years<br>Free of | type 1 diabetes taking part in an in-patient treatment and teaching programme (TTP) for intensified insulin treatment (IIT) | SMBG (n=697)<br>Baseline | Patients were advised to measure blood glucose before main meals and | 3 years | No. of blood glucose measurement/day | Patients, n (%) | A1c (3-year follow-up) | Funding:<br>Financed through a grant by the Bundesminister fur Forschung und Technologie |
| | | | | | | | 0 | 73 (10) | 10.4 (SD 2.2) | |
| | | | | | | | 0 - 1 | 40 (6) | 9.5 | |

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| control in type 1 diabetic patients after participation in an intensified treatment and teaching programme. Diabet.Med. 11 (4):362-371, 1994.<br><br>REF ID: BOTT 1994 | Germany | advanced diabetic late complications<br>Exclusion criteria: not reported | | | at bed time and to inject NPH-insulin in the morning and at bedtime and regular insulin before meals | | | | (SD 1.8) | Risk of bias: No NICE checklist<br><br>One way analysis of variance revealed a significant linear association between the frequency of daily home blood glucose monitoring and HbA1c |
| | | | Age (years), mean (SD) | 26 (SD 7) | | | 1 - 2 | 115 (17) | 9.3 (SD 1.6) | |
| | | | Duration of diabetes, mean (SD) | 8 (SD 7) | | | > 2 | 469 (67) | 8.9 (SD 1.5b) | |
| | | | HbA1c (%), mean (SD) | 10 (SD 2.2) | | | | | | |
| | | | Incidence of severe hypoglycaemia | 0.28 | | | | | bP<0.001 | |
| | | | | | | | | Incidence of severe hypoglycaemia (3-year follow-up) | 0.13 b | |
| | | | | | | | | bP<0.005 | | |
| | | | Only patients with diabetes duration of more than 1 year at baseline (n=547)<br><br>Drop-outs:<br>None reported | | | | One way analysis of variance revealed a significant linear association between the frequency of daily home blood glucose monitoring and HbA1c | | | |

**Table 135: BRAGD 2003** [17]

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: BRAGD2003 | Prospective case series survey of a cohort at two different time points | n= 178<br><br>Inclusion criteria: type 1 diabetes registered at outpatient clinic in 1984 to be repeated in 1998<br><br>Exclusion criteria: none listed | | 1984 n=178 | 1998 n=178 | ITT: n=178. Same cohort followed up 14 years later | 14 years. But cross-sectional data collected | Predictors of hypoglycaemia.<br>Variable:<br>Self-monitoring of blood glucose | Stepwise logistic regression analysis showed SMBG was not a predictor of severe hypoglycaemia<br>1984<br>x2=1.9, r2=0.22<br>p=0.19<br><br>1998<br>x2=0.48<br>r2=0.09<br>p=0.49 | Funding: None listed.<br><br>Risk of bias:<br>Appropriate eligibility criteria = yes all type 1 diabetes but little detail on inclusion/exclusion criteria<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors = yes, used stepwise logistic regression analysis. Adjusts for other variables<br>Adequate follow-up = |
| | | | Age, years (SD) | 35±9.8 | 49±9.8 | | | | | |
| | | | Women, % | 54 | 54 | Concomitant medication: none listed | | | | |
| | | | % TID | 100 | 100 | | | | | |
| | | | Diabetes duration, years (SD) | 17.9±10.9 | 32.3±10.9 | | | | | |
| | | | Weight or BMI | NA | NA | | | | | |
| | | | HbA1c/GHb, % (SD) | 7.6±1.3 | 7.4±1.1 | | | Change in SMBG+ severe hypoglycaemia | No significant association | |
| | | | Difference between groups: yes for age, duration of DM, HbA1c, SMBG daily, severe hypoglycaemia<br><br>Drop-outs:<br>none | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | yes, 14 years |

**Table 136: COX 2007** [30,32]

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: COX2007 | Prospective case series | n=90<br><br>Inclusion criteria: type 1 diabetes taking insulin. Diagnosed for at least 2 years.<br><br>Exclusion criteria: age >65 years, mental retardation, psychosis, active substance abuse, or significant depression. | | n=90 | ITT: n=90<br><br>One Touch Ultra meter were used to store the SMBG readings.<br><br>Severe hypoglycaemia episodes were captured in questionnaires | 4 months | Prediction of upcoming SH episodes | Min. number of SHBG readings in the 24 h preceding SH episode + % predicted SH episodes.<br>n=3 = 57%<br>n=4 =60%<br>n=5 =63%<br><br>There is a trend for a higher number of SMBG levels and the prediction of severe hypoglycaemia. | Funding: Grant from National Institutes of Health Grants and LifeScan.<br><br>Risk of bias:<br>Appropriate eligibility criteria = yes, although limited inclusion criteria<br>Appropriate measurement of exposure and outcome=yes<br>Controlled for confounding factors = |
| | | | Age, years (SD) | 40.7±11.2 | | | | | |
| | | | Women, % | 57 | | | | | |
| | | | % TID | 100 | | | | | |
| | | | Diabetes duration, years (SD) | 20±10.7 | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Weight or BMI | 25.3±4.4 | | | | | unclear. Used an undefined algorithm to find patterns in SMBG data shown to precede severe hypoglycaemic episodes.<br>Adequate follow-up = short-term. 4 months |
| | | | HbA1c/GHb, % (SD) | 7.6±1.2 | | | | | |
| | | | Difference between groups: not relevant<br><br>Drop-outs:<br>Unclear, none stated | | Concomitant medication: None listed | | | | |

**Table 137: EVANS1999** [41]

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: EVANS1999 | Retrospective case-series<br><br>Non-RCT Diabetes database | n=807<br><br>Inclusion criteria: diagnosed with T1 diabetes before Jan1993 to Dec 1995 | n=807 TID | | ITT: n=807 | 2 years | Predictor of haemoglobin A1c concentration | Total number of reagent strips dispensed (+180) r=-0.613, p<0.01. A decrease in haemoglobin A1c concentration for every 180 test strips dispensed (equivalent | Funding: Grant from Wellcome trust training fellowship in Health Services Research |
| | | | Age, years (SD) | Range; 0 to >65 years of age | | | | | |
| | | | Women, % | Men and women, unclear ratio | Concomitant medication: | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Exclusion criteria: none listed | % TID | 100 | | | | to one a day) of 0.7% | Risk of bias: Appropriate eligibility criteria = no, included <18 year olds. Also provided very little detail<br>Appropriate measurement of exposure and outcome=yes but only in 258 patients with haemoglobin A1c outcome available.<br>Controlled for confounding factors = no, linear regression analysis only.<br>Adequate follow-up = yes, 2 years |
| | | | Diabetes duration, years (SD) | Range 0 to >20 years | | | | | |
| | | | Weight or BMI | NA | | | | | |
| | | | HbA1c/GHb, % (SD) | NA | | | | | |
| | | | Difference between groups: not relevant<br><br>Drop-outs:<br>Not relevant for registry data | | | | | | |

**Table 138: GORDON1991 [57]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: GORDEN1991 | RCT.<br>Cross-over study.<br><br>UK | n=25<br><br>Inclusion criteria: Insulin dependent patients were recruited from the hospital outpatient clinic. Either sex and aged 18-50 years; have TID for 12 months or longer; taking at least two insulin injections per day; already be performing SMBG for longer than 6 m.<br><br>Exclusion criteria: pregnant or planning pregnancy. Significant intercurrent illness (hepatic, | n=25 | | ITT: n=25<br>Patients undertook in random order, one of three different protocols:<br>A 4-point profile on any two non-consecutive days per week.<br>One 4-point on any day of the week<br>Two blood glucose measurements on each day for 7 days per week<br>Four-point profiles measured blood glucose before the three main meals of the day and at 22h.<br>Two-point profiles involved measurements at any two of these times but varying from day to day. | 3x12 week periods | There was no significant relationship between frequency at which a patient altered insulin dosage and their metabolic control as estimated by mean glycosylated haemoglobin.<br><br>Patient preference:<br>n=9 preferred 2dx4 tests/week,<br>n=6 preferred 1dx4 tests/week;<br>n=3 preferred 7dx2 tests/wk. | | Funding: Grant from CP Pharmaceuticals.<br><br>Risk of bias:<br>Appropriate eligibility criteria = yes<br>Appropriate measurement of exposure and outcome=yes measured blood glucose, glycosylated Hb, and fructosamine<br>Controlled for confounding factors = no. no discussion on confounders or did they account for |
| | | | Age, years (SD) | 31±10 | | | | | |
| | | | Women, % | 36% | Concomitant medication: none listed. | | | | |
| | | | % TID/type 2 diabetes | 100% TID | | | | | |
| | | | Diabetes | 10.9±7.7 | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | renal or life threatening disease or other systemic illness) or hospitalization for diabetic ketoacidosis in previous 12 months. | duration, years (SD) | | | | | | them in the analysis. Also cross-over trials have a risk of carry-over effects. Adequate follow-up = yes, 12 weeks for each trial |
| | | | Weight or BMI | NA | | | | | |
| | | | HbA1c/GHb, % (SD) | NA | | | | | |
| | | | Drop-outs: n=4 (no reason) | | | | | | |

**Table 139: HILLMAN 2004[64]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: HILLMAN2004 | Retrospective case-series<br><br>SPAIN | n=146<br><br>Inclusion criteria: consecutive home blood glucose records from 71 C-peptide-negative Type 1 | n=146 | | ITT: n=146<br><br>Blood glucose values obtained before and 2 h after breakfast, lunch and dinner during a period of 8 weeks.<br><br>Target dose of 3.9-6.7 mmol/litre before meals or during fasting periods and 5.6-7.8 mmol/12 h | 8 weeks | Stepwise multiple regression to assess predictors of HbA1c: Constant β = 3.487 | | Funding: None listed.<br><br>Risk of bias: Appropriate eligibility criteria = yes<br>Appropriate measurement of exposure and outcome= yes |
| | | | Age, years (SD) | NA | | | Pre-dinner glycaemia | β=0.0118<br>R2=0.347<br>P<0.0001 | |
| | | | Women, % | NA | | | Pre-breakfast glycaemia | β=0.0063<br>R2=0.462<br>p<0.0001 | |
| | | | % TID/type 2 | 100% TID | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | diabetic patients undertaking intensive diabetes therapy.<br><br>Exclusion criteria: None. | diabetes | | after meals. | | | | Controlled for confounding factors = yes, performed stepwise multiple linear regression. Results were weighted to account for variation in number of records per patient. However, no other potential confounders were discussed.<br>Adequate follow-up = yes, 8 weeks |
| | | | Diabetes duration, years (SD) | 10.2±7.2 | | | | | |
| | | | Weight or BMI | NA | | | Post-breakfast glycaemia | β=0.0046<br>R2=0.478<br>p=0.020 | |
| | | | Drop-outs:<br>None. | | Concomitant medication: All patients received individualized meal plans to ensure an adequate energy intake and to achieve glycaemic goals, with carbohydrate and monounsaturated fat providing 60-70% of energy intake.<br>None others listed. | | Mean pre-breakfast and mean post-breakfast glycaemia correlated significantly and independently with HbA1c. The model accounted for 47.8% of the variance in HbA1c. | | |

**Table 140: KARTER2001** [71]

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention<br>Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: KARTER2001 | Retrospective case-series<br><br>Observational – registry cohort<br><br>USA | n=1159<br><br>Inclusion criteria: >19 years of age with continuous membership to database from Jan1, 1996 to Dec 31 1997, full pharmacy benefits and HbA1c level that was measured during follow-up were included.<br><br>Exclusion criteria: | n=1159<br>Adherers = monitored at least 3xday | | | ITT: n=1159<br><br>Monitoring<br>≥ 3xday, if average utilization was >2.5 strips/day, n=395<br>1-<3x/day, if utilization was <2.5 to >0.75 strips/day, n=385<br><1 daily if <0.75 but >0 strips/day, n=189<br>No practicing self-monitoring if no record of strip utilization, n=190 | 1 year | Adherence was associated with significantly greater glycaemic control (lower HbA1c levels), after adjusting for demographic, socioeconomic, behavioural, and clinical variables<br>Adherent = 7.7 (7.6,7.9)<br>Non-A = 8.7 (8.6, 8.9) | | Funding: Grant from American Diabetes Association, NIH and Kaiser Research Foundation Institute.<br><br>Risk of bias:<br>Appropriate eligibility criteria = yes.<br>Appropriate measurement of exposure and outcome= yes, self-monitoring levels were based on average daily strip utilization.<br>Controlled for confounding |
| | | | | Adherent n=395 | Non-Adherent, n=764 | | | As monitoring frequency increased, adjusted HbA1c levels declined.<br><br>No utilization=9.1%<br>< 1 daily = 8.9%<br>Daily = 8.5%<br>≥ 3xday = 7.7% | | |
| | | | Age, years (SD) | 43.2 12.9 | 40.4 12.6 | | | In pharmacologically treated patients, the largest improvement in HbA1c levels was in | | |
| | | | Women, % | 59% | 49% | Concomitant medication: | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | non-listed | % TID | 100% | 100% | use of diet and exercise as therapy, 43% and 48% respectively. | | those with monitoring at the recommended frequency (<3 x daily) whereas lesser frequencies conferred little benefit | | factors = yes, adjusted for variables in analysis.<br>Adequate follow-up = yes 12 months |
| | | | Diabetes duration, 0-9 years<br>≥10years | 14%<br>86% | 18%<br>83% | | | | | |
| | | | Weight or BMI | NA | NA | | | | | |
| | | | HbA1c/GHb, % (SD) | 7.6±1. 4 | 8.8±1.9 | | | | | |
| | | | Difference between groups:<br>Differences were detected for HbA1c, age, female sex, ethnicity, occupation, years since diagnosis, injections per day, use of diet, smoking.<br>Drop-outs:<br>Missing data n=100 from large study 24,312. | | | | | | | |

**Table 141: KLEIN 1992** [80]

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| R. Klein, S. E. Moss, and B. E. Klein. Change in glycemia in a four-year | Prospective case-series<br>Non-randomised study conducted | n=1210 eligible patients with IDDM. n=996 participated in the | Patients attending out-patient clinic, who had been on IIT for at least a year | | 33% of the population was practicing self-monitoring of blood glucose at least once a day or more<br>64% of the population was using two or more | Participants followed up over 4 years | Frequency of blood glucose self-testing/week | Change in glycosylated haemoglobin (%)a | Funding: study was supported by grant to the primary author from the National Eye Institute. |
| | | | | SMBG (n=996) | | | Never test (n=254) | -0.6 | |
| | | | | | | | < 6 (n=212) | -0.6 | |

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| interval in younger-onset insulin-dependent diabetes. Ann Epidemiol 2 (3):283-294, 1992.<br>REF ID: KLEIN 1992 | in 11 county area in southern Wisconsin | baseline examination . n=891 participated in the follow-up examination .<br>Inclusion criteria:<br>Having diabetes before 30 years old<br>Patients taking insulin<br>Exclusion criteria: not reported | Age | Diagnosed at 30 years or older | insulin injections per day<br>68% was using a combination of intermediate and short acting insulin | | 7 – 13 (n=71) | -1.0 | Risk of bias: No NICE checklist |
| | | | | | | | 14 – 20 (n=83) | -1.3 | |
| | | | | | | | ≥ 21 (n=77) | -1.1 | |
| | | | | | | | a Test of trend P <0.01 | | |
| | | | | | | | Hypoglycaemia | Not reported | |
| | | | Drop-outs:<br>26% of the participants. | | | | | | |

**Table 142: MINDER 2013**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| AE. Minder, D. Albrecht, J. Schafer, and H. | Cross-sectional study | n=150<br><br>Inclusion | n=150<br><br>All patients were treated with principles of flexible intensified insulin therapy, | Monitoring<br>SMBG measurements<br>HbA1c | n/a | Mean HbA1c declined with increasing number of SMBGs per day<br>Decline continued up to at least 4 SMBGs/day before flattening | | Funding: Grant from Santesuisse and Gottfried and Julia |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Zulewski. Frequency of blood glucose testing in well educated patients with diabetes mellitus type 1: How often is enough? Diabetes Res.Clin.Pract. 101 (1):57-61, 2013.<br><br>REF ID: MINDER 2013 | Switzerland | criteria:<br>type 1 diabetes adults (well-educated)<br>Availability of at least one HbA1c mmt and concomitant data set of directly preceding SMBG data<br><br>Exclusion criteria: none listed | and patients were encouraged to SMBG at least 4 times/day. | | measurements | | Differences in HbA1c corresponding to an 1 measurement increase in no. of SMBGs/day were as follows (adjusted model):<br>No. of SMBGs/day per 1 mmt increase and difference in HbA1c (95% CI)<br>≤4 SMBGs = -0.19% (-0.42,0.05)<br>>4 SMBGs = -0.02 (-0.10, 0.06)<br><br>Study concludes to measure SMBG at least 4 times/day | | Bangerter-Rhyner-Foundation.<br><br>Risk of bias:<br>No NICE checklist for this study type |
| | | | Age, years median | 46 | | | | | |
| | | | Women, % | 44 | | | | | |
| | | | Diabetes duration, median | 21 | | | | | |
| | | | Median BMI | 24 | | | | | |
| | | | SH within past 5 years | 31% | | | | | |
| | | | Median most recent HbA1c (IQR) | 7.1 (6.6-7.8) | | | | | |
| | | | Drop-outs:<br>N/A. | | | | | | |

**Table 143: NATHAN1996[117]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Length of follow-up | Outcome measures<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: NATHAN1996 | Prospective case-series data we are using, but main study design is prospective cohort<br><br>Registry data. Cohort analysis. | n= 183<br><br>Inclusion criteria: Consecutive outpatients who had a haemoglobin A1c assay performed in during March 1985 and 1993.<br><br>Exclusion criteria: did not carry the diagnosis for at least 1 year. Patients enrolled in diabetes research studies. | Group recruited | 1984-5<br>n=94 | 1992-3<br>n=89 | ITT: n=183<br>Usual care | 12 months (unclear) | Multiple linear regression models of mean HbA1c in the combined 1985 and 1993 IDDM groups showed that frequency of insulin injections and of self-monitoring of blood glucose were independently and significantly associated with HbA1c, R2 = 0.15, p<0.001<br>Frequency:<br>Visits β=0.16, p=0.12<br>Self-monitoring β=-0.30, p=0.010<br>HbA1c measurement β=-0.29, p=0.065<br>Insulin injection = β=-0.47, p=0.034 | Funding: Grant from Earle. P Charlton Jr. Charitable Foundation and Mallinckrodt General Clinical Research Centre.<br><br>Risk of bias:<br>Appropriate eligibility criteria = yes<br>Appropriate measurement of exposure and outcome= yes, good spread of patients representing different no. of injections per day<br>Controlled for confounding |
| | | | Age, years (SD) | 27±17 | 31±18 | | | | |
| | | | Women, % | 48 | 54 | Concomitant medication: none listed | | | |
| | | | % TID | 100 | 100 | | | | |
| | | | Diabetes duration, years (SD) | 11±10 | 13±12 | | | | |
| | | | Weight or BMI | NA | NA | | | | |
| | | | HbA1c/% (SD) | 9.47±2.1 | 8.77±1.7 | | | | |
| | | | Difference between groups: HbA1c<br>Drop-outs:<br>Registry data, so not relevant | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | | factors = yes, multiple linear regression analysis was performed.<br>Adequate follow-up = 1 year, unclear what the mean was for patients |

**Table 144: PICKUP 2006[125]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: PICKUP2006 | Prospective case series | n=30<br><br>Inclusion criteria: consecutive patients in a hospital based programme of intensification of diabetic control, where subjects were offered a | | On MDI n=30 | On CSII n=30 | All subjects were receiving multiple daily injections (MDI) as part of their routine therapy at entry into the study, be we made a renewed attempt to achieve | 5 months (3-9 months) on MDI and 16mo on CSII | Multivariate correlates of HbA1c | During MDI<br>Within-day blood glucose variability<br>β=0.62 SE=0.22 p=0.01<br>Blood glucose <3.5mmol/litre β =-0.10, SE=0.02, p=0.001 | Funding: Grant from Medtronic Ltd.<br><br>Risk of bias:<br>Appropriate eligibility criteria = yes<br>Appropriate measurement |
| | | | Age, years (SD) | 41.6±11.0 | - | | | | | |
| | | | Women, | 66% | - | | | Multivariate | During CSII | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | trial of CSII if they failed to achieve good control on MDI. Twenty of the subjects had been included in a previous study.<br><br>Exclusion criteria: 5 were excluded because of incomplete blood glucose self-monitoring data and one because she became pregnant | % | | | optimum control on MDI over 5 months.<br><br>At the end of the period on MDI all patients switched to DSII and reviewed at 2, 6, 11, 16 months after the start of therapy.<br><br>ITT: n=30<br><br>CSII – continuous s.c. insulin infusion. | | predictor of HbA1c on CSII | Only MDI on HbA1c<br>β=0.70 SE=0.18<br>p=0.001 | of exposure and outcome= cross-over trial, risk of carry over effect. In fact, correlate of HbA1c on CSII was HbA1c on MDI<br>Controlled for confounding factors = yes, multivariate analysis but unclear which variables included<br>Adequate follow-up = yes, 5 m and 16m |
| | | | % TID | 100 | - | | | Hypoglycaemia frequency was negatively correlated with HbA1c during MDI.<br><br>Within day BG variability was correlated with HbA1c on MDI.<br><br>Hypoglycaemia frequency and within-day blood glucose variability were only significant at the p=0.09 level.<br><br>Hypoglycaemia (BG <3.5 mmol/litre) was reduced from a median of 9.5% during MDI to 3.8% during pump therapy (p=0.01).<br><br>Within day and between day blood glucose variability were also significantly reduced on CSII compared with MDI | | |
| | | | Diabetes duration, years (SD) | 23.4±11.3 | - | | | | | |
| | | | BMI | 25.6±3.6 | 25.9±4.3 | | | | | |
| | | | HbA1c % (SD) | 8.5±1.4 | 7.3±0.9 | | | | | |
| | | | SMBG test/day | 4.2±1 3 | 4.6±0.7 | | | | | |
| | | | Difference between groups: HbA1c and hypoglycaemia<br><br>Drop-outs:<br>none | | | Concomitant medication: none listed | | | | |

**Table 145: SCHIFFRIN 1992[137] 1982**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| REF ID: SCHIFFRIN 1992 | Cross-over design | n=21<br><br>Inclusion criteria: Insulin dependent diabetes aged 15-36 years participated in the study. All patients had fasting C-peptide levels below 0.08pmol/ml and responded to i.v. glucogen with C-peptide levels below 0.2 pmol/ml. Patients followed a diet which consisted of 30-40% fat, 15-20% | No patient characteristics provided<br><br>Difference between groups:<br>None provided<br><br>Drop-outs:<br>Unclear | CSII= continuous subcutaneous insulin infusion<br>MSI = multiple subcutaneous insulin injections<br>CBG = capillary self-blood glucose<br><br>Cross-over trial.<br>Initiation: 0-12m<br>0-6m n=14 on CSII + MSI, 5-7 x/d CBG.<br>6-12m n=7 on CSII<br>6-12m n=7 on MSI<br>0-12m n=7 on CSIII+MSI<br><br>Phase 1: 12-18m<br>Group A – CSII 4x/d CBG<br>Group B – CSII 2x/d CBG<br>Group C – MSI 4x/d CBG<br>Group D – MSI 2x/d CBG<br><br>Phase 2: 18-21m<br>Group A – CSII 2x/day CBG<br>Group B – CSII 4x/day CBG<br>Group C – MSI 2x/day CBG<br>Group D – MSI 4x/day CBG<br><br>Phase 3: >21 m | 21 months | Group A | HgbA1%<br>Initiation: 8.1±0.5<br>Phase I: 7.9±0.4<br>Phase II: 10.3±0.5<br>Phase III: 8.0±0.1 | Funding: Grant from Montreal Children's Hospital Research Institute and Diabetic Children's Foundation, Canada<br><br>Risk of bias:<br>Appropriate eligibility criteria = unclear. Patients aged 15-36 and no details on their characteristics provided.<br>Appropriate measurement of exposure and outcome= cross-over trial, so risk of carry-over effect from |
| | | | | | | Group B | HgbA1%<br>Initiation:7.9±0.4<br>Phase I: 10.2±0.5<br>Phase II: 8.2±0.4<br>Phase III: 8.1±0.2 | |
| | | | | | | Group C | HgbA1%<br>Initiation:8.3±0.6<br>Phase I: 8.1±0.4<br>Phase II: 10.0±0.9<br>Phase III: 8.0±0.6 | |
| | | | | | | Group D | HgbA1%<br>Initiation:8.2<br>Phase I:10<br>Phase II:8.6<br>Phase III:8.7 | |
| | | | | | | | Conclusion:<br>Diabetic control was significantly better during periods of frequent self-monitoring<br>Frequent SMBG is critical for the long- | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | protein, and 40-45% carbohydrate given as 3 meals and a bedtime snack.<br><br>Exclusion criteria: none listed | | All 4x/day CBG | | | term maintenance of glycaemic control. | one phase to the next<br>Controlled for confounding factors = no.<br>Adequate follow-up = yes, each phase min 6 months. |
| | | | | Concomitant medication: controlled diet | | | | |

**Table 146: SCHUTT 2006** [139]

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| M. Schutt, W. Kern, U. Krause, P. Busch, A. Dapp, R. Grziwotz, I. Mayer, J. Rosenbauer, C. Wagner, A. Zimmermann, W. Kerner, R. W. Holl, and | Prospective case series<br><br>Standardised, prospective, multicentre, computer-based documentation of diabetes care and outcome from 191 centres in | n=24500 participants with 19491(80%) type 1 diabetes (type 1 diabetes). For each patient the most recent complete year of diabetes care was evaluated.<br>Inclusion criteria: | Patients with type 1 diabetes | | SMBG:<br>Intensified conventional (≥4 daily injections) or continuous subcutaneous insulin infusion therapy (CSIIT)<br>conventional (1-3 daily injections) therapy (CT) | At least 6 months | | CSIIT | CT | Funding:<br>Financial support for the development of the DPV software was provided by the Bundesministerium fur Gesundheit and NovoNordisk Germany. |
| | | | | SMBG (n=19491) | | | HbA1c (%) - reduction for one additional measurement /day | 0.3% reduction | 0.16 % reduction | |
| | | | Age (years), mean (SD) | | | | | | | |
| | | | Gender (m/f) | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| D. P. V. Initiative. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. Exp.Clin.Endocrinol.Diabetes 114 (7):384-388, 2006.<br><br>REF ID: SCHUTT 2006 | Germany and Austria | Patients on intensive conventional insulin therapy for at least 6 months<br>Performing SMBG for at least 6 months using the dextrostix-glucometer system<br>Previous instruction on the use of SMBG during a 5-day inpatient educational session<br>Exclusion criteria: not reported | Duration of diabetes, mean | 5.8 years | On average patients with type 1 diabetes performed 4.4 blood glucose measurements per day. This number increased continuously during the last 10 years (1995: 3.1 values/day and 2004: 4.9 values/day; p<0.0001).<br><br>SMBG frequency was significantly associated with better metabolic control (p<0.0001). One additional daily blood glucose measurement improved the HbA1c level by 0.26%. | | | | | Risk of bias: No NICE checklist |
| | | | HbA1c (%), mean | 8.5% | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| | | | Data were adjusted for age, diabetes duration, gender, BMI, treatment centre and year of therapy.<br>Drop-outs:<br>None reported | | | | | | | |

**Table 147: SERVICE 2007** [141,142]

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| F. John Service and Peter C. O'Brien. Influence of glycemic variables on hemoglobin | Prospective case series from the Diabetes Control and Complications Trial database (DCCT) | n=565 volunteers.<br>n=296 assigned to conventional therapy; n=269 assigned to | | | Intensive therapy – no details | Conventional therapy – no details | >4 years | Correlation between various components of the 7-point capillary glucose profile and haemoglobin AIC* | | | Funding:<br>Not reported<br><br>Risk of bias: No NICE checklist<br>Drop-outs = none reported |
| | | | | | | | | Glucose variable | R2 | P value | |
| | | | | | | | | Overall mean | 0.443 | <0.001 | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A1c. Endocr Pract 13 (4):350-354, 2007.<br><br>REF ID SERVICE 2007 | | intensive therapy<br>Inclusion criteria:<br>Volunteers whose 7-point capillary profiles collected pre-prandial and 90 minutes postprandial for each of the major meals and at bedtime were complete in 80% or more of quarterly collections who were in the study for 4 years or longer<br><br>Exclusion criteria: | | | | | | **Mean digestive | 0.406 | <0.0001 | In the multivariate analysis, the primary predictor of A1C was Mean Blood Glucose (MBG). All other glucose variables added nothing further to the models.<br><br>Conclusion: "within the limitations of correlating 7-point glucose profiles obtained quarterly (over several years) with A1C, the strongest influence is from overall mean glycaemia. Furthermore |
| | | | Age (years) | Not reported | | | | Mean postprandial | 0.399 | <0.01 | |
| | | | Type of diabetes | Not reported | | | | ***Mean inter-digestive | 0.316 | <0.01 | |
| | | | | | | | | Mean after supper | 0.256 | <0.01 | |
| | | | | | | | | Mean after lunch | 0.255 | <0.01 | |
| | | | | | | | | Mean bedtime | 0.231 | <0.01 | |
| | | | | | | | | Mean before supper | 0.224 | <0.01 | |
| | | | | | | | | Mean after breakfast | 0.201 | <0.01 | |
| | | | | | | | | Mean fasting | 0.170 | <0.01 | |
| | | | | | | | | Mean before lunch | 0.168 | <0.01 | |
| | | | Drop-outs:<br>None reported | | | | | *R2 = multivariate coefficient of determination.<br>**Mean of after breakfast, before and after lunch, and before and after supper.<br>***mean of bedtime and fasting. | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | "women in the conventional treatment group who became pregnant" | | | | | | | there seem to be unidentified influences on this relationship not attributable to variability of glycaemia". |

**Table 148: SHIMIZU 2008** [145]

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hiroyuki Shimizu, Yutaka Uehara, Shuichi Okada, and Masatomo Mori. Contribution of fasting and postprandial hyperglyce | Non-randomised cross-sectional outpatient study conducted in Japan | n=57 type 1 diabetes and type 2 diabetes participants. n=24 (type 1 diabetes; 1, type 2 diabetes; 23) treated with insulin twice a day n=33 ((type 1 | | | | Intensively treated group (IIT) | Twice daily | | | IIT | Twice daily | Funding: not reported<br><br>Risk of bias: No NICE checklist |
| | | | | Twice daily | IIT | | | | HbA1c levels and fasting glucose (FG) correlation | In the intensely treated group, a significant correlation between HbA1c levels and FG levels was found before lunch and at 2hr | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| mia to hemoglobin A1c in insulin-treated Japanese diabetic patients. Endocr.J. 55 (4):753-756, 2008.<br><br>REF ID: SHMIZU 2008 | | diabetes; 14, type 2 diabetes; 19) intensively treated (IIT)<br>Inclusion criteria:<br>Diagnosis of diabetes for at least 12 months<br><br>Exclusion criteria: not reported | | | | | | | | after breakfast and dinner. | | |
| | | | Age (years), mean (SD) | 60.7 (SD 3.3) | 46.4 (SD 2.9) | | | | HbA1c levels and fasting glucose (FG) correlation | In all subjects, only FG levels before lunch correlated significantly with HbA1c levels although post prandial glucose (PPG) levels were significantly correlated with HbA1c at all points | | |
| | | | M/F | 7/17 | 6/27 | | | | | | | |
| | | | HbA1c (%), mean (SD) | 7.71 (SD 0.38) | 7.92 (SD 0.26) | | | | | | | |
| | | | BMI (kg/m2), mean (SD) | 24 (SD 0.8) | 25.2 (SD 1) | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | Drop-outs: | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Dropout rate: not reported | | | | | | |

**Table 149: SKEIE 2009 [148] (randomised study)**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Svein Skeie, Gunn B. B. Kristensen, Siri Carlsen, and Sverre Sandberg. Self-monitoring of blood glucose in type 1 diabetes patients with insufficient metabolic control: | Parallel RCT.<br><br>Single centre trial carried out at the diabetes outpatient clinic at Stavanger University Hospital, Norway | n= 134 adults with type 1 diabetes.<br>n=65, control group ; n=69, intervention<br><br>Inclusion criteria:<br>Glycated haemoglobin (A1C) ≥8%<br>Treatment with | Patients 18-70 years with type 1 diabetes and A1C levels of ≥8%. | | | Focussed, structured 9-month SMBG:<br>Six visits scheduled over 9 months<br>Participants introduced to HemoCue Monitor<br>Consultation performed by a diabetes nurse and a biomedical laboratory | Regular care: Daily SMBG performance, weekly eight-point SMBG profiles, and an A1C goal of <7.0-7.5%.<br>All patients performed a number of additional measurements for | 9 months | | Intervention group | | Funding: research was supported by grants from the Juvenile Diabetes Research Foundation.<br><br>Risk of bias:<br>Randomisation: "recruited and randomised consecutively"<br><br>Allocation |
| | | | | Intervention group (n=59) | Control group (n=64) | | | | A1C (%), at study end | 10% had reached A1C<7%, 24% had A1C<7.5%, and 39% had A1C <8% | | |
| | | | Age (years) , mean (SD) | 39 (SD 12) | 38 (SD 9) | | | | | Control group | | |
| | | | Diabetes duration | 20 (SD | 19 (SD | | | | A1C (%), at study end | No patient obtained A1C<7.5%, and 13% had A1C<8% | | |
| | | | | | | | | | | Interventio | Control | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| focused self-monitoring of blood glucose intervention can lower glycated hemoglobin A1C. J Diabetes Sci Technol 3 (1):83-88, 2009.<br><br>REF ID: SKEIE 2009 | | multiple insulin injections or continuous subcutaneous insulin infusion pump (CSII)<br>18-70 years and a SMBG user<br>Exclusion criteria:<br>Unstable condition with more than 5KG weight variation<br>More than 1.5% variation in A1C within past 12 months<br>Hypoglycaemia unawareness<br>Mental instability | (years), mean (SD) | 11) | 12) | scientist<br>Enhance focus on BG self-management<br>Participants received and brought a BG diary for BG profiles at every visit, a "fasting BG map", and a hypoglycaemia registration | monitoring hypoglycaemia | | | n group | group | concealment: not reported<br>Blinding: not reported<br>ITT analysis: "analysis was based on ITT principle"<br>Powered study: pre-study power calculations reported<br>In the control group, 22.5% of patients were insulin pump users at study start, 25% at study end. |
| | | | | | | | | | A1C (%), at study end | Comparing the 2 groups, A1C was approximately 0.6% lower in the intervention group | | |
| | | | Body mass index (kg/m2) | 25 (SD 3) | 26 (SD 5) | | | | Hypoglycaemia | No increase in major or minor hypoglycaemia in both groups during the study period | | |
| | | | Women (%) | 57.4 | 52.4 | | | | | | | |
| | | | CSII users (%) | 20.4 | 22.5 | | | | | | | |
| | | | Mean A1C at inclusion (%) | 8.65 (SD 0.1) | 8.61 (SD 0.09) | | | | | | | |
| | | | In the control group, 2 additional patients started pump therapy during the study period. All patients had a long-standing experience in performing<br>Drop-outs:<br>Dropout rate: 23% dropped out of the intervention group and | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Any condition limiting the patient's ability to follow the study protocol | 2% dropped out of the control group | | | | | | |

**Table 150: TILDESLEY 2004** [156]

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| H. D. Tildesley and K. W. Johns. Long-term treatment of type 1 diabetes in the outpatient setting: Results of 934 patients during up to 10 years' | Prospective case series<br><br>Observational study conducted at a diabetic teaching and training centre in Canada. Retrospective cohort study | 1447 patients attended the 4-day diabetes education program, of which 934 (64.5%) returned for at least 1 follow-up visit and 513 (35.5%) were lost to follow-up. | n=934 TID using insulin therapy | SMBG (n=934) | The number of insulin injections per day increased during the 10-year observation period.<br>The majority of patients included in the study used 2 injections of insulin per day, with a treatment goal of A1C<8.0% (normal range: 4.0% to 6.0%) | 10 year observation period with an average of 4.7 visits | HbA1c (%), mean (SD) | A1C values were negatively correlated with the frequency of SMBG at baseline ($p<0.001$) and 5 years ($p<0.008$). At year 10, this correlation was not significant. A correlation between all quartiles and | | Funding: Not reported<br><br>Risk of bias: No NICE checklist |

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| follow-up. Can.J.Diabetes 28 (3):190-195, 2004.<br><br>REF ID: TILDESLEY 2004 | | n=934 TID using insulin therapy<br><br>Inclusion criteria:<br>Age at onset of diabetes <30 years<br>History of proven diabetic ketoacidosis<br>Negative C Peptide challenge<br>Exclusion criteria: not reported | | | | | | frequency of SMBG was observed at baseline (p<0.0001) but was not maintained at 5 years (p=0.057). | |
| | | | | | | | Hypoglycaemia | At 5 and 10 years, there was a trend toward a reduction in the number of hypoglycaemic episodes, but was not significant (p<0.055) | |
| | | | Age (years), mean (SD) | 44 (SD 13.2) | | | | | |
| | | | Male (%) | 55.5 | | | | | |
| | | | Duration of diabetes, mean (SD) | 21.1 (SD 12.2) | | | | | |
| | | | HbA1c (%), mean | 6.9 (SD 1.4) | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (SD) | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | Drop-outs:<br>None reported | | | | | | | | |

**Table 151: WEITGASSER 1994** [165]

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| R. Weitgasser, F. Schnoll, I. Pretsch, and U. Gruber. Evaluation of self-monitoring of blood glucose after five years of intensive insulin therapy | Prospective case-series<br><br>Observational study carried out in an out-patient clinic in<br><br>Austria | n=57; on intensive insulin therapy (IIT) requiring SMBG<br><br>Inclusion criteria:<br>Patients attending out-patient clinic<br>Intensive insulin therapy (IIT) for at least a year<br>Exclusion criteria: not reported | Patients attending out-patient clinic, who had been on IIT for at least a year | | At baseline (year one) and five years SMBG was done ≤2 per day by 51% versus 12%, >2 but <4/day in 20% versus 21%, and ≥4/day by 29% versus 67% of the patients.<br><br>Authors observed an increase in daily SMBG from median of 2.5 in year one to 4.5 in year five when the sum of all blood glucose measurements of all | 5 years | | Year 1 (base line)<br>n=57 | Year 5<br>n=57 | Funding:<br>Not reported<br><br>Risk of bias: No NICE checklist |
| | | | | | | | HbA1c (%), mean (SD) | 7.2 (SD 1.2) | 6.4 (SD 1.1) | |
| | | | | | | | Severe hypoglycaemia (events per patient years) | 0.24 | 0.26 | |
| | | | | SMBG (n=57) | | | Retinopathy | 19*/ 8+ | 24*/ 11+ | |
| | | | Age | 34 (SD 9) | | | Neuropathy | 11 | 15 | |

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| following a basal bolus regimen. Diabetol.Croat. 23 (1):13-17, 1994.<br><br>REF ID: WEITGASSER 1994 | | | (years), mean (SD) | | patients (n=57) was analysed. | | | | | |
| | | | Gender (m/f) | 18/39 | | | | | | |
| | | | Duration of diabetes, mean (SD) | 18 (SD 8) | Type of insulin administered:<br>Short acting insulin<br>Intermediate<br>Long acting insulin<br>External pump treatment | | Subgroup of patients who increased frequency of SMBG from <4 to ≥4/day (n=21) | | | |
| | | | | | | | HbA1c (%), mean (SD) | 7.2 (SD 1.6) | 6.2 (SD 1.4) | |
| | | | | | | | | | | |
| | | | Drop-outs:<br>None reported | | | | *Background retinopathy<br>+Proliferative retinopathy | | | |

**Table 152: WILLEY 1993[170]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| K. A. Willey, S. M. Twigg, M. I. Constantino, D. K. Yue, and J. R. Turtle. Home blood glucose monitoring: How often? Pract.Diabetes 10 (1):22-25, 1993.<br><br>REF ID: WILLEY 1993 | Prospective case-series<br><br>Observational study | n=12 insulin dependent diabetes mellitus (IDDM) participants treated three to four times daily were asked by their clinicians to perform Home Blood Glucose Monitoring (HBGM)<br>Inclusion criteria: not reported<br><br>Exclusion criteria: not reported | Twelve insulin dependent diabetes mellitus (IDDM) | SMBG | Once daily HBGM at a variable time each day (Var1/day), derived by extracting one blood glucose reading from consecutive time zones. | Four times daily (4/Day) HBGM.<br>Blood glucose readings divided into the following time zones:<br>Pre-breakfast<br>Pre-lunch<br>Pre-dinner<br>Pre-bed<br><br>Participants tested their blood glucose levels for four weeks using the Ames Glucometer M. | 4 weeks | | Var1/day | 4/day | Funding: one of the authors (Stephen Twigg) is a recipient of a Juvenile Diabetes Foundation International Summer Student Scholarship.<br><br>Risk of bias: No NICE checklist<br>Risk of bias:<br>Outcome assessors were not informed that there were two profiles from each patient's HBGM data (one from 4/day and one from Var1/day HBGM), nor were they given any |
| | | | | | | | | Mean blood glucose | No significant difference in the mean blood glucose values.<br>Comparison of 4/day with 1/day HBGM taken at a set time of the day did show a significant difference ($p<0.05$) in three of the 12 patients | | |
| | | | Age (years), mean (SD) | 32 (SD 12); range = 21-69 years | | | | Hypoglycaemia not reported | | | |
| | | | Duration of diabetes, mean (SD) | 7.4 (SD 3.5); range = 2-13 years | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | details about the frequency of testing used to derive each profile.<br><br>“this study showed that 1/day HBGM at a variable time gave similar information to 4/day HBGM for glycaemic control (mean blood glucose levels), whereas 1/day HBGM at a set time each day was found to produce different results on some occasions” |
| | | | Drop-outs:<br>Dropout rate: not reported | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |

**Table 153: ZIEGLER 1993** [172,173]

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| O. Ziegler, M. Kolopp, J. Louis, J. P. Musse, A. Patris, G. Debry, and P. Drouin. Self-monitoring of blood glucose and insulin dose alteration in type 1 diabetes mellitus. Diabetes Res.Clin.Pract. 21 (1):51-59, 1993.<br><br>REF ID: ZIEGLER | Cross-sectional study | n=80 insulin dependent diabetic patients chosen at random among diabetic patients treated by intensive insulin therapy (IIT)<br>Inclusion criteria:<br>Patients on intensive conventional insulin therapy for at least 6 months<br>Performing SMBG for at | Patients attending out-patient clinic, who had been on IIT for at least a year | | Blood glucose measured 4 times a day (1 + 1 + 2 in a 3-injection regimen, 2 + 2 in a 2-injection-split and mixed regimen) before each meal and at bed-time.<br><br>Fewer than 2 daily blood glucose determination was considered as incompatible with proper use of SMBG | Intensive conventional insulin therapy for at least 6 months | | Good compliance n=59 | Poor compliance n=21 | Funding:<br>Not reported<br>Risk of bias: No NICE checklist<br><br>"this limited cross-sectional study seems to indicate that SMBG can lead to an improvement in metabolic control but only if it is coupled with a regular alteration of insulin dosage" |
| | | | | SMBG (n=80) | | | HbA1c (%), mean (SD) | 6.7 (SD 1.1) | 7.5 (SD 1.9) | |
| | | | | | | | Hypoglycaemia not reported | | | |
| | | | Age (years), mean (SD) | 34 (SD 14) | | | | | | |
| | | | Gender (m/f) | 43/37 | | | | | | |
| | | | Duration of diabetes, mean (SD) | 12 (SD 8) | | | | | | |
| | | | HbA1c (%), | 6.9 (SD 1.4) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1993 | | least 6 months using the dextrostix-glucometer system<br>Previous instruction on the use of SMBG during a 5-day inpatient educational session<br>Exclusion criteria: not reported | mean (SD) | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | Drop-outs:<br>None reported | | | | | | | | |

**Table 154: Summary table of papers that were not fully extracted.**

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| ANON 1993[152] | n=1441 | 6.5 years<br><br>RCT | IDDM | Intensive ≤4xday | Conventional 1xday | ≤4 vs. 1 times a day | Insulin injections<br>Intensive ≤3xday<br><br>Conventional 1-2xday | NS difference in mortality<br>Intensive n=7 vs. conventional n=4<br>Hypoglycaemic episodes per 100 patient-years<br>Intensive 62 vs. conventional 19 |

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Diabetic ketoacidosis per 100 patient-years<br>Intensive 2 vs. 1.8 conventional<br>Quality of life no difference (no numbers provided) |
| ARASZKIEWICZ 2008 [9,10] | n=86 | 7.1±1.5 years<br><br>Prospective case series | Type 1 diabetic patients | No intervention. Only logistic regression model was used to estimate RR for diabetic retinopathy and low-level (micro) albuminuria events. | | 3.6 to 4.1xday | Multiple daily injections with adapting short-acting insulin for before meals<br>After 7 years<br>Retinopathy<br>Yes<br>Self-control n/day=3.9±1.7<br>Hypoglycaemic episodes/m = 5.8±7.1<br>No<br>Self-control n/day=3.8±1.4<br>Hypoglycaemic episodes/m = 6.0±5.7<br><br>Low-level (micro) albuminuria<br>Yes<br>Self-control n/day=3.6±1.6<br>Hypoglycaemic | Subjects who developed retinopathy had higher HbA1c.<br>Risk of retinopathy was associated with infrequent monitoring of blood glucose RR=5.5 (2-15.11)<br>Risk of low-level (micro) albuminuria was associated with bad self-monitoring of glucose (RR=2.86 (1.1-7.24) |

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | episodes/m = 5.3±6.0<br><br>No<br>Self-control n/day=4.1±1.3<br>Hypoglycaemic episodes/m = 6.2±6.3 | |
| BELL 1994 [14,15] | n=211 | Questionnaire 3 months<br><br>Prospective case series | Insulin dependent diabetes | No intervention. Only interviewed over 3 months. Comparisons were made between those with and without a history of severe hypoglycaemia. | | 2.3 to 2.5xday | History of SH<br>N injections/day = 2.72<br>N glucose tests/day = 2.26<br>No history of SH<br>N injections/day = 3.06<br>N glucose tests/day = 2.49 | Patients with severe hypoglycaemia took a greater number of insulin injections per day. Also more likely to be using animal insulin and perform home glucose monitoring tests more frequently |
| BELL [15]1984 | n=36 | Prospective case series, 3-4 months | Diabetic patients | No intervention. | | 1xday 24%<br>2-3xday 36%<br>4xday 10%<br><3xweek 23% | n=30 insulin 1xday<br>n=54 insulin 2xday | Frequent testing was not more prevalent in those whose haemoglobin A1 improved. |
| BRUTTOMESSO 1992 [22] | n=17 | Retrospective case-series mean 23.6 months (3-83mo) | Type 1 diabetes | No intervention. Correlation analysis. | | 1.6 times a day | Analysis of blood glucose levels. Mean readings/day/patient =1.6 (0.5-5) | A weak correlation was found between number of blood glucose readings/day and daily blood glucose level, r=0.44, and serum HbA1c r=0.45, both p<0.05 |

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| CHAN 2009 [24,25] | n=1898 | Prospective case-series<br><br>5 years, this includes 2 week cross-sectional and a 9-month longitudinal survey. | Type 1 diabetes | No intervention. Logistic univariate regression analysis was used to identify factors for achieving A1C<7% | | Regular | 73% regularly self-monitors blood glucose. No other details. | SMBG vs. not was associated with two to three fold increased odds of reaching the A1C goal of <7%.<br>Patient self-adjusted insulin was not predictive of reaching the goal of A1C. |
| BRINCHMANN-HANSEN 1992 [20] | n=45 | Prospective case series<br>7 years | Insulin dependent diabetic patients | Insulin pumps (continuous s.c. insulin infusion) | Multiple injections (4-6 x day) and conventional insulin (2xday) | Unclear | See intervention | Intensified insulin treatment and home blood glucose monitoring improved concentrations of HbA1c from 11.2% to 9.5% |
| GONDER 1988 [56] | n=30 | 2 weeks Prospective case series | Adults with insulin dependent diabetes of at least 1 year | Use of memory meters | Record test results in diaries | 0.21 to 4.43 x day | Fast and intermediate-acting insulin, except one who used multiple injections of regular insulin | Self-report of SMBG frequency correlated with HbA1 (r=-0.39)<br><br>Majority of patients were self-reporting as often or more often than they had been instructed. |
| HARTEMANN2001 [60] | n=122 | Cross-sectional | Adults with Type 1 DM | Good glycaemic control. HbA <7.5% | Poor glycaemic control HbA >8.5% | 2.7 to 3.6 x day | Daily injections 3.1± 0.9<br>Number of daily blood glucose tests<br>Good = 3.6 ± 1.7<br>Poor = 2.7 ± 1.7 | Well controlled group carried out more home blood glucose tests and fewer complications (physical complaints, psychological distress, leisure restrictions, conscious experience and |

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | management of hypoglycaemia, diet, difficulties at work) |
| LLOYD 1993 [98] | n=592 | Cross-sectional | Adults with insulin dependent diabetes | No intervention. Multiple regression analysis to assess which factors are independent correlates of glycaemic control (as measured by GHb). | | NA | NA | The number of blood and urine tests performed daily were all significant predictors of glycaemic control.<br>Number of daily injections r=-0.15, p=0.0253<br>Number of tests performed daily r=-0.12 p=0.0146<br>Injecting at recommended times r=-0.15 p=0.19<br><br>STRATA. Correlates of glycaemic control<br>Proliferative retinopathy<br>Number of tests performed, r=-0.25 p=0.0013<br><br>Neuropathy<br>Injecting at recommended times, r=-0.32 p=0.0003<br>Number of daily injections r=-0.23 p=0.0041 |

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| MERIMEE 1984 [106] | n=15 adults | 6 months<br>Prospective case series | Diabetic patients (unclear if T1 or T2 DM) with normal IGF-I and IGF-II values | Glucose monitored initially daily, later 2xweek | | 1xday then 2xweek | Min 2x/day injections of insulin with supplementary insulin given on the basis of monitoring blood glucose 4x/day | HbA1c<br>Baseline: 14.8±0.95%<br>3 months: 10.7±0.82%<br>6 months: 10.3±0.80%<br><br>HbA1c decreased significantly. |
| MCCLEAN 2005 [104] | n=290 | Cross-sectional | Type 1 and Type 2 diabetes | No intervention. Logistic regression analysis was used to identify characteristics associated with the presence of complications. | | Microvascular complications<br>Daily blood monitoring<br>46.8% daily testing<br>53.2% no daily testing<br><br>No microvascular complications<br>Daily blood monitoring<br>34.4% daily testing<br>65.6% no daily testing | NA | When controlling for other predictors, patients at risk of developing retinopathy/neuropathy were those who had a HbA1c of 8% or more<br><br>Blood glucose monitoring was not associated with patients at risk of developing retinopathy/neuropathy |
| MILLER 2013 [109,110] | n=8914 | Cross-sectional registry study | Type 1 diabetes (adult data only) | No intervention. General linear relationship between HbA1c levels and SMBG | | SMBG Mean±SD Age group<br>18 to <26 | NA | A higher number of SMBG measurements per day was strongly associated with a lower |

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | =4.4±2.3 per day<br>26 to <50=5.2±2.6 per day<br>50 to <65 =5.5±2.5 per day<br>>65 = 5.6±2.2 per day | | HbA1c in all groups. |
| NAYAK 2011[118]<br>ABSTRACT | n=127 | Cross-sectional study | Type 1 diabetes 61.4% | No Intervention. Regression analysis was used to determine factors that predicted HbA1c. | | NA | NA | Blood glucose variability explained 39% of variance of HbA1c.<br>HbA1c is a weak reflection of glycaemic attainment<br>HbA1c is more closely related to variability of blood glucose than the central or median attainment |
| SJOBERG 1988 [147] | n=44 | Cross sectional analysis | Insulin dependent diabetes. Excretors of C-peptide vs. non-excretors | No intervention. Pearson correlation analysis. | | 4x month (range 0 -120) | n=34 insulin 2xday, n=8 3xday, n=1 4xday.<br><br>82% were receiving a combination of intermediate or long-acting insulin and soluble insulin. The other 8 patients were receiving single injections of | In the group with residual insulin secretion a correlation was found between low HbA1c and frequency of SMBG (r=-0.62, p<0.01) |

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | intermediate or long-acting insulin. | |
| VANTILBURG 2001[161] | n=30 | Cross sectional analysis | Type 1 diabetes | No intervention. Linear regression analysis. | | 25.5±09.9x week | 53% ≥3 injections/day<br>30% insulin pump<br>17% 1-2 injections/day | Self-reported SMBG frequency correlated with HbA1c (r=-0.47, p<0.01) |
| WOO 2011 [171] ABSTRACT | n=325 type 1 diabetes<br>n=293 type 2 diabetes | Cross sectional study | Type 1 diabetes (and type 2 but results presented separately) | No intervention. Assess relationship between the frequency of home glucose monitoring and HbA1c in people with T1 and T2 diabetes | | < 2 to > 3 times a day | NA | HbA1c values for type 1 diabetes<br><2 checks/day = 8.65%<br>2-3 checks/day = 8.58%<br>>3 checks/day = 8.22%<br>NS different |
| ZIEGLER [172]1989 | n=14 | 21 days Prospective case series | Type 1 diabetes mellitus | Memory-reflectance meters | Log book | ≥3x day | NA | The number of SMBG measurements recorded in the memory reflectance meter was negatively correlated with HbA1c (r=-0.85, p<0.001).<br><br>Over-reporting was positively correlated with HbA1c r=0.76, p<0.01. |
| ZIEGLER 2012 [172,174] ABSTRACT | n=202 TIDM<br>n=17 type 2 diabetes | Cross sectional analysis from RCT | Type 1 and Type 2 diabetes | Data extracted from an RCT. Correlation between clinical outcomes and SMBG frequency. | | 4.34±1.51 times a day<br>Frequency of SMBG x/day<br>Type 1<br>4.34 (1.51) | | SBMG frequency correlated with HbA1c (r=-0.30) More frequent SMBG is associated with lower HbA1c independent on the type of diabetes |

| Reference | Sample size | Duration | Patients | Intervention | Comparison | SMBG | Insulin regimen | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Type 2<br>3.76 (1.35)<br>NS different. | | |

### G.3.3 SMBG – glucose targets

**Table 155: COX1994** [29,32]

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| D. J. Cox, B. P. Kovatchev, D. M. Julian, L. A. Gonder-Frederick, W. H. Polonsky, D. G. Schlundt, and W. L. Clarke. Frequency of severe hypoglycemia in insulin-dependent diabetes mellitus can be predicted from self-monitoring | Prospective case series<br><br>Non-randomised multicentre study carried out in the USA | n=78 Insulin Dependent Diabetic Mellitus (IDDM)<br>Inclusion criteria:<br>IDDM for at least 2 years<br>Insulin usage since time of diagnosis<br>Routine SMBG of twice daily or more<br>No diagnosable depression of substance abuse<br><br>Exclusion criteria: not reported | | | 50 SMBG readings over a 2 to 3 week period with a hand held computer. | Data collected during a 6 month baseline period. | Results | | Funding:<br>Not reported<br>Risk of bias: No NICE checklist<br>The Predictor variables were not linearly related to the number of severe hypoglycaemic episodes.<br>Participants demonstrating a smaller low BG index and less BG variance were more likely to have to have no severe hypoglycaemic |
| | | | | Patient characteristics (n=78) | | | Blood glucose (BG) is associated with a greater low BG index, a greater SMBG and a lower glycosylated HbA1c.<br><br>Participants with a BG index less than 2.75 had an average of 5.2 hypoglycaemic episodes, whereas participants with a low BG index of 2.75 or more had 13.6 episodes. | | |
| | | | | | | | Participants with SMBG below 4.6 had an average of 6.5 hypoglycaemic episodes, whereas subjects with a SMBG of 4.6 or greater had 12.3 such episodes | | |
| | | | Age (years), mean (SD) | 38.2 (SD 9.05) | | | Low glycosylated Hb was no significantly associated with the number of severe hypoglycaemic episodes. | | |

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| blood glucose data. J.Clin.Endocrinol.Metab. 79 (6):1659-1662, 1994.<br><br>REF ID: COX 1994 | | | Gender (m/f) | 28/50 | | | | | | episodes. |
| | | | Duration of diabetes, mean (SD) | 19.3 (SD 10.04) | | | | | | |
| | | | HbA1c (%), mean (SD) | 10.25 (SD 2.13) | | | | | | |
| | | | Insulin dose (U/day)+, mean (SD) | 38.6 (SD 16.04) | | | | | | |
| | | | Drop-outs:<br>None reported | | | | | | | |

**Table 156: KOVATCHEV2000** [85]

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| B. P. Kovatchev, D. J. Cox, M. Straume, and L. S. Farhy. | Prospective case series<br><br>Non- | n=608 participants with Insulin Dependent Diabetes | Patients characteristics not reported | SMBG: all participants were instructed to use blood glucose (BG) memory meters for 4-6 months and to measure their BG two to | | 6 months | HbA1c within categories identified by average SMBG | | | Funding:<br>Supported by the National Institutes of Health grant, |
| | | | | | | | SMBG categories | Mean HbA1 | SEM | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Association of self-monitoring blood glucose profiles with glycosylated hemoglobin in patients with insulin-dependent diabetes. Methods Enzymol. 321:410-417, 2000.<br><br>REF ID KOVATCHEV 2000C | randomised study conducted by Amylin Pharmaceuticals | Mellitus (IDDM)<br>Data for n=608 participants were completed with SMBG and HbA1c records<br>Inclusion criteria: not reported<br><br>Exclusion criteria: not reported | | | | four times a day. During the same period of time 5 to 8 HbA1c assays were performed for each subject. | | | | c (%) | | by Amylin Pharmaceuticals, San Diego, CA and by Lifescan Inc., Milpitas, CA.<br><br>Risk of bias: No NICE checklist<br><br>"The SMBG records were considered accurate according to an automated rejection criterion"<br><br>"Only subjects who had SMBG records and HbA1c assays were selected for analysis". |
| | | | | | | | | | Below 8.6 mM (n=118) | 8.29 | 0.06 | |
| | | | | | | | | | 8.6-9.7 mM (n=124) | 8.70 | 0.06 | |
| | | | | | | | | | 9.7-10.6 mM (n=119) | 9.14 | 0.08 | |
| | | | Age (years), | - | - | | | | 10.6-12 mM (n=126) | 9.50 | 0.07 | |
| | | | Male/female | - | - | | | | Above 12 mM (n=121) | 121 | 0.12 | |
| | | | Duration diabetes (months) | - | - | | | | | | | |
| | | | | | | | | | Average SMBG within categories identified by HbA1c | | | |
| | | | HbA1c (%) | | | | | HbA1c (%) category | Mean SMBG | SEM | | |
| | | | | | | | | Below 8.3 (n=125) | | 8.58 | 0.1 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 1 | |
| | | | | | | 8.3-8.8 (n=123) | 9.54 | 0.11 | |
| | | | | | | 8.8-9.4 (n=118) | 10.28 | 0.13 | |
| | | | | | | 9.4-10 (n=116) | 11.01 | 0.15 | |
| | | | | | | Above 10 (n=126) | 12.74 | 0.22 | |
| | | | Drop-outs:<br>Seven hundred participants recruited for study and data available for 608 (87%) participants. | | | | | | |

**Table 157: MUHLHAUSER1998** [114,115]

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| I. | Prospective | n=669 with | | A self-administered | | 19 | | | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Muhlhauser, H. Overmann, R. Bender, U. Bott, and M. Berger. Risk factors of severe hypoglycaemia in adult patients with Type I diabetes--a prospective population based study. Diabetologia 41 (11):1274-1282, 1998.<br><br>REF ID MUHLHAUSER 1998 | case series population based study from a random sample of 630 family physician practices in the district of<br><br>Northrhine | type 1 diabetes<br>Inclusion criteria:<br>Age 18 years or older<br>Initiation of insulin therapy before 31 years of age<br>Exclusion criteria: not reported | | | questionnaire was used in order to assess patients' treatment goals.<br>The instrument consisted of 10 items which were rated on a 6-point Likert scale (1 = very important; 6 = totally unimportant). For this study, five questions possibly relevant for the prediction of severe hypoglycaemia (SH) were used. | | months follow up | Number of blood glucose values <3.3 mmol/litre | Baseline: n (%) | SH during 19 months follow-up (events per patients | Not reported<br><br>Risk of bias: No NICE checklist<br><br>Blood glucose self-monitoring - score 0: patients who report to measure at least twice daily; score 1: patients who measure less often. |
| | | | | n=669 | | | | 0 | 256 (38) | 0.22 | |
| | | | | | | | | 1-2 | 211 (32) | 0.34 | |
| | | | Age (years), mean (SD) | 36 (11); range: 18-77 | | | | >2 | 202 (30) | 0.39 | |
| | | | Male/women | 392/277 | | | | Trend to show number of BG values <3.3 mmol/litre, the higher the number of episodes of severe hypoglycaemia. | | | |
| | | | Diabetes duration, mean (SD) | 18 (SD 11) | | | | | | | |
| | | | BMI (kg/m2), mean (SD) | 24.6 (SD 3.4) | | | | | | | |
| | | | HbA1c (%), mean (SD) | 8 (SD 1.5) | | | | | | | |
| | | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | Drop-outs:<br>None reported | | | | | | |

**Table 158: SERVICE 2001** [140,141]

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| F. John Service and Peter C. O'Brien. Influence of glycemic variables on hemoglobin A1c. Endocr Pract 13 (4):350-354, | Prospective case series from the Diabetes Control and Complications Trial database (DCCT) | n=565 volunteers.<br>n=296 assigned to conventional therapy; n=269 assigned to intensive therapy | Each participant was expected to collect at quarterly intervals, a 7-point set of capillary specimens preprandially and 90min | Intensive therapy: administration of insulin at least 3 times a day by injection pump, with doses adjusted based on | Conventional therapy: one or two daily insulin injections | ?1-15 years | Glycaemic parameters for study cohort during DCCT | | | Funding:<br>Not reported<br><br>Risk of bias: No NICE checklist<br>Drop-outs = none reported |
| | | | | | | | Glucose variable | Intensive a | Conventional | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 2007.<br><br>REF ID SERVICE 2001 | | Inclusion criteria:<br>Volunteers whose 7-point capillary profiles collected pre-prandial and 90 minutes postprandial for each of the major meals and at bedtime were complete in 80% or more of quarterly collections who were in the study for 4 years or longer<br><br>Exclusion criteria:<br>"women in the | postprandially for each of the 3 major meals and before bedtime snack | self-blood glucose monitoring and with the goal of normoglycaemia. | | | | | | Risk of retinopathy:<br>In the multivariate analysis, the primary determinants for risk of a 3-step change in retinopathy were updated mean blood glucose (MBG) p< 0.001 and baseline mean amplitude of glycaemic excursion (MAGE) p< 0.005.<br>The association between updated MBG and risk for retinopathy |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | conventional treatment group who became pregnant" | | | | | | | | was non-linear.<br>No association with updated MBG was observed for values below 8.3 mmol/litre. Beyond 8.3 mmol/litre the risk increased with increasing updated MBG with approximately a 15-fold increase in risk at updated MBG of 16.6 mmol/litre relative to updated MBG at 8.3mmol/litre. |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Results show that an increase in updated MBG from 8.3 mmol/litre to 11.1 mmol/litre increases the risk by approximately fourfold. |
| | | | | Intensive therapy | Conventional therapy | | | HbA1c (%), mean (SD) | 7 (SD 0.7) | 9 (SD 1.3) | |
| | | | | | | | | Mean blood glucose (mmol/litre), mean (SD) | 8.4 (SD 1.2) | 13 (SD 2.5) | |
| | | | | | | | | Mean postprandial (mmol/litre), mean | 9.4 (SD 1.4) | 14.4 (SD 2.7) | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (SD) | | | |
| | | | Age (years), mean (SD) | 29 (SD 7) | 27 (SD 7) | | | Mean prepran dial (mmol/li tre), mean (SD) | 7.7 (SD 1.3) | 11.7 (SD 2.4) | |
| | | | Adolescent (%): 13-18years | 22 (8) | 47 (16) | | | Before breakfas t blood glucose (mmol/li tre), mean (SD) | 8.3 (SD 1.6) | 11.4 (SD 2.5) | |
| | | | Male/female | 122/147 | 138/158 | | | | | | |
| | | | Duration of type 1 diabetes (months) | 76 | 69 | | | 90min after breakfast blood glucose (mmol/litr e), mean (SD) | 10.8 (SD 2.1) | 15.5 (SD 3.1) | |
| | | | HbA1c (%) | 8.7 | 8.7 | | | Before lunch blood glucose (mmol/litr e), mean | 7 (SD 1.5) | 11 (SD 2.9) | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (SD) | | | |
| | | | Mean blood glucose (mmol/litre) | 12.1 | 13 | | | 90min after lunch blood glucose (mmol/litre), mean (SD) | 8.6 (SD 1.6) | 13.8 (SD 2.8) | |
| | | | | | | | | Before supper blood glucose (mmol/litre), mean (SD) | 7.7 (SD 1.7) | 12.6 (SD 3.1) | |
| | | | | | | | | 90min after supper blood glucose (mmol/litre), mean (SD) | 8.8 (SD 1.6) | 13.9 (SD 3.4) | |
| | | | | | | | | Bedtime blood glucose (mmol/litre), mean (SD) | 8 (SD 1.6) | 12.6 (SD 3.4) | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Drop-outs:<br>None reported | | | | p≤ 0.001 comparing intensive and conventional therapies for each glucose variable.<br>The intensive treatment group had significantly lower values of each glycaemic parameter and HbA1c than the conventional treatment group during the total period of the study. | | |

**Table 159: VERVOORT 1996** [163]

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| G. Vervoort, H. M. Goldschmidt, and L. G. van Doorn. Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple (> or = 4) daily insulin injection regimens. Diabet.Med | Prospective case-series<br><br>Non-randomised study conducted in the Netherlands | n=31 type 1 diabetes randomly selected from the population of a diabetes outpatient clinic.<br>Inclusion criteria:<br>Stable patients for more than I year on multiple daily injection therapy | | Patient characteristics (n=31) | All treated with short acting insulin at least three times a day and intermediate-acting insulin at night. | Participants observed overnight. | Results<br>Two separate intervals of hypoglycaemia were observed during the night:<br>Early night from 23.00 to 01.00 h<br>Early morning from 04.00 to 07.30 h<br>There were 5 participants with hypoglycaemic episodes in the early night and 6 with episodes in the early morning; 2 experienced an 'early night' as well as an 'early morning' hypoglycaemia.<br>A fasting glucose of ≥5.5mmol/litre was never preceded by 'early morning' | | Funding:<br>Novo Nordisk The Netherlands for financial support.<br><br>Risk of bias: No NICE checklist<br><br>"The study shows a high frequency (29%) of nocturnal hypoglycaemia, defined as a blood glucose |

| Reference | Study type | Number of patients | Patient characteristics | | SMBG | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| . 13 (9):794-799, 1996.<br><br>REF ID: VERVOORT 1996 | | Exclusion criteria: not reported<br><br>"all patients received intensive education including the use of simple algorithms to correct their blood glucose levels" | | | | | hypoglycaemia.<br>A fasting blood glucose level at 07.30 h of <5.5mmol/litre was associated with 'early morning' hypoglycaemia in 6 of 12 patient-nights; in 4 cases a fasting glucose <3mmol/litre at 07.30 h was measured. | | | level <3.0 mmol/litre, in type 1 diabetes patients on multiple insulin injections regimens". |
| | | | Age (years) | 40.4 (19-67) | | | 'Early night' hypoglycaemia was already apparent at 23.00 h in 4 of 5 cases. | | | |
| | | | Gender (m/f) | 20/11 | | | | | | |
| | | | Duration of diabetes (years) | 17.6 (2-57) | | | | | | |
| | | | HbA1c (%) | 8.6 (6.1-11.6) | | | | | | |
| | | | Total Insulin dose (IU/kg), mean (SD) | 0.68 (SD 0.15) | | | | | | |
| | | | Drop-outs:<br>None reported | | | | | | | |

**Table 160: WHITE1982** [167]

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N. H. White, S. R. Waltman, T. Krupin, and J. V. Santiago. Reversal of abnormalities in ocular fluorophotometry in insulin-dependent diabetes after five to nine months of improved metabolic control. Diabetes 31 (1):80-85, 1982.<br><br>REF ID WHITE 1982 | Prospective case series non-randomised cohort study | n=36 participants with Insulin Dependent Diabetes Mellitus (IDDM). 5.5% (2) of the population <18 years of age.<br><br>n=25 assigned to conventional therapy; n=11 non-obese assigned to intensive therapy<br>Inclusion criteria: | | | | Intensive therapy: home blood glucose monitoring and either multiple daily insulin injections or a portable insulin infusion pump.<br>All participants were taught home blood glucose monitoring using Dextrostix and reflectance meter | Conventional therapy: conventional methods employing urine glucose monitoring and one or two injections of mixtures of insulin daily. | 4-6 months | | | | Funding:<br>Supported in part by grants from the Diabetic Children's Welfare Association, American Diabetes Association St. Louis Affiliate, and NIH grants<br><br>Risk of bias: No NICE checklist<br><br>Participants choosing treatment with multiple injections did so because they thought that the |
| | | | | Intensive therapy (n=11) | Conventional therapy (n=25) | | | | HbA1c (%), mean (SD) | 7.5 (0.2) | 11.0 (SD 0.4) | |
| | | | | | | | | | Retinopathy | 1 | 0 | |
| | | | Age (years) | Range 13-33 | Mean 25.3 (SD 8.4) | | | | | | | |
| | | | Male/female | 5/6 | - | | | | | | | |
| | | | Duration of diabetes (years) | Range 3-22 | Mean 9.8 (SD 4.9) | | | | | | | |
| | | | HbA1c (%), mean (SD) | 10.4 (SD 0.7) | 10.2 (SD 0.5) | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Initial abnormal vitreous fluorophotometry measurement<br>Willingness to participate in a research study involving home blood glucose monitoring and either multiple daily insulin injections or a portable insulin infusion pump<br>Exclusion criteria: not | | | | | | | | | | insulin infusion pump would be more cumbersome, complicated, or unnecessary. They were given regular insulin 15-60 min before each meal depending on preprandial blood glucose measurements, and either long-acting insulin in the morning and evening or intermediate-acting insulin at bedtime.<br><br>Participants were also trained in the operation of insulin pump |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | Drop-outs:<br>None reported | | | | | | All participants in the intensively treated group achieved excellent glycaemic control with preprandial blood glucose values mostly under 200mg/dl and complete absence of glycosuria. | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | reported. | | | | | | | and taught to adjust the insulin dose on the basis of measured capillary blood glucose |

**Table161: WEI 2014**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| N Wei, Hui Zheng, and David M. Nathan. Empirically Establishing Blood Glucose Targets to Achieve HbA1c Goals. Diabetes Care 37 | Prospective case-series<br><br>People from the ADAG study (Nathan 2006) | n=387<br>(237 type 1 diabetes and 141 type 2 diabetes)<br><br>Data from type 1 diabetes reported only.<br><br>Inclusion criteria: | No further details given | SMBG monitored over an average of 11 days per person during the 12 week study period<br><br>8-point SMBG: Fasting blood glucose, pre-meal, post-meal and bedtime SMBG | 12 weeks | type 1 diabetes subgroup only: mean (95% CI) blood glucose values for specified HbA1c levels | Fasting blood glucose values for:<br>HbA1c of 5.5-6.49 = 122 mg/dL (113-132)<br>HbA1c of 6.5-6.99 = 144 mg/dL (134-154)<br>HbA1c of 7.0-7.49 = 155 mg/dL (143-168)<br>HbA1c of 7.5-7.99 = 170 mg/dL (159-181)<br>HbA1c of 8.0-8.49 = 178 mg/dL (161-194)<br><br>Preprandial blood glucose values for:<br>HbA1c of 5.5-6.49 = 119 mg/dL (115-124) | Funding:<br>National Institute of Diabetes and Digestive and Kidney Diseases training grant.<br><br>Risk of bias: No NICE checklist<br>Drop-outs = none reported |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| (4):1048-1051, 2014.<br><br>REF ID WEI 2014 | | Adults with diabetes from the ADAG study participants who had HbA1c values at 3 months between 5.5 and 8.5%<br>Blood glucose values (SMBG) monitored over 12 weeks<br>ns<br><br>Exclusion criteria:<br>"women in the conventional treatment group who became pregnant" | | HbA1c was measured monthly | | HbA1c of 6.5-6.99 = 140 mg/dL (134-147)<br>HbA1c of 7.0-7.49 = 156 mg/dL (150-163)<br>HbA1c of 7.5-7.99 = 159 mg/dL (151-166)<br>HbA1c of 8.0-8.49 = 175 mg/dL (162-188)<br><br>Postprandial blood glucose values for:<br>HbA1c of 5.5-6.49 = 139 mg/dL (133-145)<br>HbA1c of 6.5-6.99 = 161 mg/dL (155-168<br>HbA1c of 7.0-7.49 = 175 mg/dL (167-183)<br>HbA1c of 7.5-7.99 = 190 mg/dL (180-199)<br>HbA1c of 8.0-8.49 = 197 mg/dL (188-205)<br><br>Bedtime blood glucose values for:<br>HbA1c of 5.5-6.49 = 140 mg/dL (132-148)<br>HbA1c of 6.5-6.99 = 154 mg/dL (144-164)<br>HbA1c of 7.0-7.49 = 180 mg/dL (164-195)<br>HbA1c of 7.5-7.99 = 179 mg/dL (166-193)<br>HbA1c of 8.0-8.49 = 214 mg/dL (189-240) | | |

### G.3.4 SMBG technologies

**Table 162: GROSS 2003**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Todd M. Gross, David Kayne, Allen King, Carla Rother, and Suzanne Juth. A bolus calculator is an effective means of controlling postprandial glycemia in patients on insulin pump therapy. Diabetes Technol.Ther. 5 (3):365-369, 2003.<br><br>REF ID: GROSS 2003 | RCT<br><br>A two-period cross-over repeater-measure randomised design from two clinical sites. | n= 49 participants with TID and on Continuous Subcutaneous Insulin Infusion (CSII)<br><br>Inclusion criteria:<br>type 1 diabetes<br>On CSII therapy for a minimum of 3 months<br>Exclusion criteria: not reported | Participants with type 1 diabetes, and on CSII therapy using Medtronic MiniMed insulin pumps. | | Bolus calculator software implemented on a PDA platform.<br><br>Participants were required to enter their pre-meal blood glucose value (obtained from their home blood glucose meter) and the total CHO (g) in the meal into the bolus calculator in order to obtain a pre-meal bolus insulin dose.<br>After 7 days, participants | Standard bolus period | 7 days then cross-over for 7 days | | Bolus calculator | Standard bolus | Funding: not reported<br>Risk of bias:<br>Randomisation: unclear<br>Allocation concealment: not reported<br>Blinding: not applicable<br>ITT analysis: not reported<br>Powered study: not reported<br>Drop-outs: not reported<br>Wash-out period: not reported<br>"no adverse events were reported in either period"<br>"the target blood |
| | | | | n=49 | | | | *Hypoglycaemia events/week, mean (SD) | 3.1 (SD 2.9) | 3.4 (SD 3.1) | |
| | | | Age (years), mean (SD) | 43 (SD 15) | | | | Adverse events | 0 | 0 | |
| | | | Diabetes duration (years), mean (SD) | 22 (SD 16) | | | | | | | |
| | | | Male/female (%) | 43/57 | | | | HbA1c not reported | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | crossed over to the alternate treatment period.<br>The software setup required each participants to input his or her<br>Target blood glucose<br>Insulin sensitivity factors (ISF)<br>Carbohydrate to insulin ratios (CIR) | | | | | | glucose, ISF, and CIR were determined for all subjects, individually, by the physician using subjects' logbooks at the start of their BC period in the study" |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | Participants were asked to test their blood glucose using their home | | | | | *Hypoglycaemia was defined as blood glucose >250mg/dL | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | meters.<br>Drop-outs:<br>Dropout rate: not reported | | | | | | |

**Table 163: SCHMIDT 2012**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Signe Schmidt, Merete Meldgaard, Nermin Serifovski, Camilla Storm, Tomas Moller Christensen, Birthe Gade-Rasmussen, and Kirsten | RCT<br><br>Prospective, randomised, controlled, open label, three-arm parallel, bi-centric study conducted in Denmark | n= 51 with type 1 diabetes (n=8, control; n=21, CarbCount; n=22, CarbCount Automated Bolus Calculator)<br><br>Inclusion | Patients' ≥ 18 years with type 1 diabetes | | | CarbCount Automated Bolus Calculator (CarbCountABC): group received FIIT during a 3-h group teaching, were taught carbohydrate counting, estimated individual | Control arm: not trained in estimating the carbohydrate content of food but received FIIT during a 3-h group teaching. | 16 Weeks | | *Carb Count ABC | *Control | Funding: not reported.<br><br>Risk of bias:<br>Randomisation: "randomisation with a 1:3:3 ratio in blocks of 14"<br>Allocation concealment: sealed, opaque |
| | | | | CarbCountABC (n=22) | Control (n=8) | | | | HbA1c (%), mean (SD) | 8.1 (SD 0.4) | 8.9 (SD 1.1) | |
| | | | Age (years), mean (SD) | 42 (SD 10) | 46 (SD 9) | | | | HbA1c (%) within-group difference, (95% CI) | -0.7 (-1.0 to -0.4) | -0.1 (-1.0 to 0.7) | |
| | | | Gender (m/f) | 10/12 | 6/2 | | | | | | | |
| | | | Diabetes duration | 21 (SD 9) | 14 (SD 12) | | | | #HFS (0-100 scale) | 22.6 (SD | 24.5 (SD | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Norgaard. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. Diabetes Care 35 (5):984-990, 2012. REF ID: SCHMIDT 2012 | | criteria: Age 18-65 years type 1 diabetes duration ≥12 months Use of multiple daily injections (MDI) Exclusion criteria: Pregnancy Nursing Gastroparesis Present or former practice of carbohydrate counting | (years) | | | ICRs and ISFs and were also provided with and instructed in the use of the ABC. | | | - higher scores indicate more fear, mean (SD) | 16.7) | 18.2) | envelopes containing the group assignments. The envelopes had been prepared by a person not otherwise involved in the study" Blinding: not applicable – open label trial ITT analysis: Powered study: study was powered. Drop-outs: 12 patients (19%) dropped out overall. Drop-outs per group not reported. Relatively small sample |
| | | | HbA1c (%) | 8.8 (SD 0.7) | 9.1 (SD 0.7) | | | | HFS within-group difference, (95% CI) | -3.4 (-7.2 to 0.3) | -1.92 (-10 to 6.2) | |
| | | | BMI (kg/m2), mean (SD) | 25.8 (SD 3.3) | 26.4 (SD 5.6) | | | | &PAID (0-100 scale) - higher scores indicate more problems, mean (SD) | 25.6 (SD 15.3) | 27.2 (SD 18.8) | |
| | | | | | | | | | PAID within-group difference, (95% CI) | -6.9 (-13.5 to -0.4) | -3.3 (-21 to 14.4) | |
| | | | | | | | | | ^ADDQoL Total (-9 to 9) - higher scores indicate positive impact, | -1.8 (SD 1.6) | -1.4 (SD 0.9) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | mean (SD) | | | size |
| | | | | | | | | | ADDQoL within-group difference, (95% CI) | 0.4 (0.0 to 0.7) | 0.6 (0.8 to 1.9) | |
| | | | Drop-outs:<br>12 patients (19%) dropped out overall. Drop-outs per group not reported.<br>Baseline characteristics of the randomised patient sample did not differ significantly between the 3 study groups | | | | | | *Comparison of means between Control, CarbCount, and CarbCountABC. Analysis performed using ANOVA. #HFS – Hypoglycaemia Fear Survey. &PAID – Problem Areas In Diabetes. ^ADDQoL – Audit of Diabetes-Dependent Quality of Life. | | | |

### G.3.5 SMBG versus CGM

**Table 164: LITTLE 2014**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S. A. Little, L. Leelarathna, E. Walkinshaw, H. K. Tan, O. Chapple, A. Lubina-Solomon, T. J. Chadwick, S. Barendse, D. D. Stocken, C. Brennand, S. M. Marshall, R. Wood, J. Speight, D. Kerr, D. Flanagan, S. R. Heller, M. L. Evans, and J. A. Shaw. Recovery of Hypoglycemia Awareness in Long-Standing | RCT | N = 96<br><br>Inclusion criteria:<br>Age 18 - 74 years<br>C-peptide negative type 1 diabetes<br>Impaired awareness of hypoglycaemia confirmed by Gold score ≥4<br><br>Exclusion criteria:<br>Not reported | | RT-CGM (n = 48) | SMBG (n = 48) | All participants were given an insulin pump enabling benefit from direct transmission of SMBG levels to bolus calculator. | | Every 4 weeks for 24 weeks | | RT-CGM (n=48) | SMBG (n=48) | Funding:<br>Peer review grant from Diabetes UK, the National Institute for Health Research, and the Cambridge National Institute for Health Research Biomedical Research Centre<br><br>Risk of bias:<br>Randomisation: Low<br>Allocation concealment: Low |
| | | | | | | RT-CGM:<br>Real-time continuous glucose monitoring (Medtronic)<br><br>The participants were trained on sensor insertion, calibration, and use of monitor including trend analysis and hypo/hyperglycaemia alerts. Continuous real-time use was encouraged but not mandatory. | SMBG:<br>Self-monitoring of blood glucose<br><br>As described above for all participants and no access to RT-CGM. | | HbA1c (%) at 24 weeks | 8.2 (1.1) | 8.1 (0.9) | |
| | | | | | | | | | HbA1c final value mean difference - calculated (95% CI; SE) | 0.10 (-0.30 to 0.50; -0.2) p=0.63 | | |
| | | | Age (years), mean (SD) | 50.1 (12.6) | 47.1 (11.8) | | | | Severe hypoglycaemia, annualized rate (patient-year), mean (SD) | 0.8 (1.8) | 0.9 (2.1) | |
| | | | Gender, male (%) | 15/48 (31.3 %) | 20/48 (41.7 %) | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Type 1 Diabetes: A Multicenter 2 x 2 Factorial Randomized Controlled Trial Comparing Insulin Pump With Multiple Daily Injections and Continuous With Conventional Glucose Self-Monitoring (HypoCOMPass). LID - DC_140030 [pii]. Diabetes Care (1935-5548 (Electronic)), 2014.<br><br>LITTLE 2014 | | | Diabetes duration (years), mean (SD) | 31.0 (12.2) | 26.7 (12.1) | All participants recorded severe hypoglycaemia episodes prospectively and were recalled every 4 weeks up to 24 weeks.<br><br>Each study visit was preceded by a 7-day retrospective CGM profile, with participants and investigators blinded to data until study completion.<br><br>All participants were telephoned weekly to reinforce insulin titration guidelines and maintain focus on hypoglycaemia avoidance. | | | Quality of life | Not reported | | Blinding: Not possible<br>ITT analysis carried out<br>Drop-out = 12/96 (12.5%) in total - acceptable (<20%). Difference in drop-out rate was 12.5%. |
| | | | HbA1c (%), mean (SD) | 8.2 (1.1) | 8.3 (1.3) | | | | Adverse events (No. of DKA episodes) - There were no hospital admissions or insulin delivery/monitoring-related infections. | 0 | 3 | |
| | | | BMI (kg/m2), mean (SD) | 26.9 (4.7) | 26.1 (4.3) | | | | Adherence | Not reported | | |
| | | | Drop-outs | 3/48 (6.3%) | 9/48 (18.8 %) | | | | | | | |

**Table 165: SEQUEIRA 2013**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PA. Sequeira, L Montoya, V Ruelas, D Xing, V Chen, R Beck, and AL. Peters. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. Diabetes Technol.Ther. 15 (10):855-858, 2013.<br><br>SEQUEIRA 2013 | Crossover RCT | N = 39<br><br>Inclusion criteria:<br>Diagnosis of diabetes ≥6 months prior to enrolment<br>Subject self-report of SMBG ≥3 times/day<br>On multiple daily insulin injections<br>Age ≥18 years<br><br>Exclusion criteria:<br>Not reported | All the participants were economically challenged type 1 diabetes patients, primarily of Latino ethnicity with minimal prior education on intensive diabetes management. | | Participants were provided with education on CHO counting and insulin dose adjustments using developed educational materials. | | Aspirationally, up to 28 weeks per period, however, the length of participation varied greatly amongst the participants. | | Group A (CGM then SMBG) | Group B (SMBG then CGM) | Funding:<br>JDRF Artificial Pancreas grant<br><br>Risk of bias:<br>Randomisation: Unclear<br>Allocation concealment: Unclear<br>Blinding: Not possible<br>Insufficient and unclear description given for study methods<br>ACA<br>Drop-out rate significantly high<br>Population is very specific |
| | | | | | Group A = RT-CGM first:<br><br>Before starting CGM use, all had 1 week of a CGM blind period where participants were not able to see the glucose values recorded in the receiver. There onwards, it is presumed that the participants were able to see the recorded values. | Group B = SMBG first:<br><br>In the absence of clear description for the comparator group, it is assumed that normal self-monitoring of blood glucose was performed by the participants. | | HbA1c | Baseline = 8.3%<br>End of Period 1 = 8.0%<br>End of Period 2 = 8.5% | Baseline = 8.3%<br>End of Period 1 = 7.8%<br>End of Period 2 = 8.3% | |
| | | | Age (years), mean (SD) | patients who completed study only: 40 (13) | | | | Severe hypoglycaemia, annualized rate (patient-year), mean (SD) | Not reported | | |
| | | | Gender, male (%) | patients who completed study only: 13/25 (52%) | | | | | | | |
| | | | Diabetes duration | patients who completed study only: 13 (10 - 21) | | | | Quality of life | Not reported | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | (years), median (IQR) | | At each routine clinic visit, the participants brought in their meter for downloading in the clinic providing the researcher with access to the patient CGM downloads and CHO counting logs. | | | | | |
| | | | HbA1c (%), mean (SD) | patients who completed study only: 8.5 (1.7) | | | | Adverse events | Not reported | |
| | | | BMI (kg/m2), mean (SD) | patients who completed study only: Not reported | | | | Adherence | Not reported | |
| | | | Drop-outs | Overall = 14/39 (35.9%) | | | | | | |

**Table 166: BATTELINO 2012**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T. Battelino, I. Conget, B. Olsen, I. Schutz-Fuhrmann, E. Hommel, R. Hoogma, | Cross-over RCT.<br><br>6 month treatment periods with 4 | n=153; 53% adults and 47% children.<br>(n=77 CGM sensor on first; n=76 CGM sensor | | | | CGM sensor on (MiniMed Medtronic)<br>Patients were all fitted with insulin pump system with | CGM sensor off Self-monitoring blood glucose (SMBG): Approximately 8 daily SMBG readings. | 6 months | | CGM sensor on | CGM sensor off | Funding: Medtronic International<br>Risk of bias: Randomisation : electronically |
| | | | | CGM on first (n=77) | CGM off first (n=76 | | | | HbA1c (%) mean difference in adults | Mean difference (-0.41 (95% CI -0.28%, -0.53%; p<0.001)) | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| U. Schierloh, N. Sulli, and J. Bolinder. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomised controlled trial. Diabetologia 55 (12):3155-3162, 2012.<br><br>REF ID: BATTELINO 2012 | month wash-out<br><br>Multicentre- four adult and four paediatric sites in Europe | off first )<br><br>Inclusion criteria:<br>Age 6-70 years<br>type 1 diabetes for >1 year<br>HbA1c 7.5-9.5%<br>Using CSII for >6 months<br>Naïve to CGM<br>Exclusion criteria:<br>≥3 incidents of severe hypoglycaemia in the last 12 months<br>History of hypoglycaemic unawareness<br>Concomitant chronic disease affecting diabetes | | | ) | CGM. During 1 month run-in phase sensors were off and patients advised to use SMBG.<br><br>Each treatment period was 6 months long, with a 4 month washout phase between two periods. | | | population at 6 months | | | generated sequence. Stratified randomisation, paediatric and adult groups. Allocation concealment: randomisation implemented by statistician.<br>Blinding: not possible due to nature of intervention. No blinding to HbA1c results<br>Baseline values not reported<br>ITT analysis carried out<br>Drop-outs = 15 (10%) total<br>n=8 in on/off sequence group<br>n=7 in off/on sequence group |
| | | | Age (years), mean (SD) | 28 (SD 16) | 28 (SD 17) | | | | Severe hypoglycaemic events (per 100 patient years) | 5.7 per 100 patient years | 2.83 per 100 patient years | |
| | | | Gender (m/f) | 42/34 | 37/40 | | | | | | | |
| | | | Diabetes duration (years), mean (SD) | 16 (SD 12) | 14 (SD 12) | | | | | | | |
| | | | HbA1c (%), mean (SD) | 8.3 (SD 0.7) | 8.5 (SD 0.6) | | | | | | | |
| | | | | | | | | | | | | |
| | | | Drop-outs:<br>15 (10%) total<br>n=8 in on/off sequence group | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | control<br>Pharmacological treatment that might modify glycaemic values | n=7 in off/on sequence group | | | | | | |

**Table 167: BECK 2010 –JUVENILE 2010 study**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R. W. Beck, J. M. Lawrence, L. Laffel, T. Wysocki, D. Xing, E. S. Huang, B. Ives, C. Kollman, J. Lee, K. J. Ruedy, and W. V. Tamborlane. Quality-of-life | Parallel RCT.<br><br>Multicentre trial carried out in 10 centres in the USA. | n= 451 adults and children (stratified into two groups according to age: ≥ 18 years, and < 18 years) with type 1 diabetes.<br>Adult (≥ 18 years) = 228 (> 50% of total | Patients ≥ 18 years with type 1 diabetes and initial A1C levels of <7%. | | | CGM: Participants were instructed to use the CGM daily if possible. | Standard glucose monitoring (SMBG): instructed to perform BGM ≥4 times per day. | 26 weeks | | CGM | SMBG | Funding: research was supported by grants from the Juvenile Diabetes Research Foundation.<br><br>Risk of bias: Randomisation: reported but insufficient information given. |
| | | | | CGM (n=122) | SMBG (n=106) | | | | QoL: SF12 Physical component, scale 0-100 (high is better), mean (SD) at 26 weeks | 55.5 (SD 4.9) | 54.1 (SD 6.9) | |
| | | | Baseline QoL (SF-12): Physical compon | 54.1 (SD 5.9 | 54.1 (SD 7.2) | | | | SF12 Mental component, scale 0-100 (high is better), mean (SD) at 26 | 48.4 (SD 10.1) | 48.7 (SD 9.6) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. Diabetes Care 33 (10):2175-2177, 2010. W. V.<br><br>REF ID: BECK 2010 | | population)<br>Sub-group analysis based on baseline A1c (≥7.0% versus <7.0%) carried out for ≥ 18 years population.<br><br>For the ≥ 18 years population (n=122, continuous glucose monitoring [CGM] ; n=106, self-monitoring blood glucose (SMBG)<br><br>Inclusion criteria:<br>type 1 diabetes at least 1 year.<br>Use of either an insulin | ent , mean (SD) | | | | | | weeks | | | Allocation concealment: not reported<br>Blinding: not reported<br>ITT analysis: not reported<br>Powered study: not reported<br>Drop-outs: not reported |
| | | | Baseline Mental component, mean (SD) | 49.5 (SD 8.4) | 48.2 (SD 10.0) | | | | | | | |
| | | | | | | | | | Hypoglycaemia Fear Survey (HFS), total score (scale 0-100, high = worse); mean (SD) | 33.3 (SD 11.5) | 36 (SD 13.6) | |
| | | | | | | | | | Problem Areas in Diabetes (PAID), (scale 0-100, high = worse) mean (SD) | 18.1 (SD 14.1) | 18.2 (SD 14.6) | |
| | | | | | | | | | HbA1c not reported | | | |
| | | | | | | | | | Hypoglycaemia not reported | | | |
| | | | *Social Functioning Health Survey (SF-12) version 2.<br>Drop-outs: | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | pump or at least 3 daily insulin injections.<br>HbA1c level of <7%<br>Exclusion criteria: not reported | Dropout rate: not reported | | | | | | |

**Table 168: CHICO 2003**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients | Parallel RCT.<br>Single centre trial carried out in Spain. | n= 105 diabetic patients (75 with type 1 diabetes, 30 with type 2 diabetes) were included in the study.<br>For the | Patients' ≥ 25 years with type 1 diabetes and initial A1C levels of 7 to 10%. | | | CGM: CSII; Disetronic, MiniMed.<br>CGM group monitored three days using the CGM and the information obtained was used to modify treatment. | Standard glucose monitoring (SMBG): frequent capillary glucose measurement:<br>At least 8 measurements per day for 3 days: before each | 3 months | | CGM | SMBG | Funding: not reported.<br>Risk of bias:<br>Randomisation: unclear<br>Allocation concealment: not reported<br>Blinding: not reported<br>ITT analysis: not reported |
| | | | | CGM (n=40) | SMBG (n=35) | | | | HbA1c (%), mean (SD) at 3 months | 7.5 (SD 1.2) | 7.5 (SD 0.8) | |
| | | | Age (years), mean (SD) | 36.5 (SD 12) | 41 (SD 10) | | | | hypoglycaemia not reported | | | |
| | | | Gender (m/f) | 18/22 | 17/18 | | | | | | | |
| | | | Diabetes | 17 (SD | 21 | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care 2003;4:1153–7.<br>REF ID: CHICO 2003 | | type 1 diabetes population (n=40, continuous glucose monitoring [CGM] ; n=35, self-monitoring blood glucose (SMBG)<br><br>Inclusion criteria:<br>Inadequate metabolic control<br><br>Exclusion criteria:<br>n.a. | duration (years) | 12) | (SD 10) | They were instructed to enter glucose meter values (at least four a day). | meal, 2h after meals, at bedtime, and at 4:00 A.M | | | | | Powered study: study was adequately powered.<br>Drop-outs: None reported. |
| | | | HbA1c (%) | 8.3 (SD 1.6) | 8.0 (SD 1.4) | | | | | | | |
| | | | | | | | | | | | | |
| | | | Drop-outs:<br>All patients completed follow-up | | | | | | | | | |

**Table 169: DEISS 2006**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D. Deiss, J. Bolinder, J. P. Riveline, T. Battelino, E. Bosi, N. Tubiana-Rufi, D. Kerr, and M. Phillip. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 29 (12):2730-2732, 2006.<br>REF ID: DEISS 2006 | Parallel RCT.<br><br>Multicentre trial carried out in 8 centres in Europe and Israel. | n= 162 adults and children.<br>81 (50%) children (median age 14.4 years [range 8.0-18.9]) and 81 (50%) adults (age 39.1 years [19-59.5]) with stable type 1 diabetes.<br>(n= 54 continuous glucose monitoring [CGM] ; n=54, self-monitoring blood glucose (SMBG)<br><br>Adults = 50% 0f the population. | Patients with type 1 diabetes and also used an insulin pump (48%) | | | CGM: Guardian RT continuously (arm 1) or biweekly for 3 day periods every 2 weeks (arm 2). | Standard glucose monitoring (SMBG) | 3 months | | CGM | SMBG | Funding: study was sponsored by Medtronic Europe sarl, Tolochenaz, Switzerland.<br><br>Risk of bias:<br>Randomisation: unclear<br>Allocation concealment: not reported<br>Blinding: not reported.<br>ITT analysis: Data analysed by ITT approach using last value carried forward for missing end points and adjusted for age-group as participants were randomised within age groups.<br>Powered study: |
| | | | | CGM (*n=54) | SMBG (*n=54) | | | | Change (from baseline) in HbA1c (%), mean (SD) at 3 months. | -1.0 (SD 1.1) | -0.4 (SD 1.0) | |
| | | | Age (years), mean (SD) | 26.2 (13.4) | 27.4 (16.5) | | | | Hypoglycaemia not reported | | | |
| | | | HbA1c (%); mean (SD) | 9.5 (1.1) | 9.7 (1.3) | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | *n = 54 is an assumption based on 1:1:1 randomisation assigned to participants.<br><br>Drop-outs:<br>Dropout rate: one discontinued before the start of the intervention. | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Inclusion criteria:<br>type 1 diabetes before randomisation.<br>Use an insulin pump or received at least 3 daily insulin injections.<br>HbA1c level > 8.1% despite intensive insulin treatment<br>Exclusion criteria:<br>Hearing or vision impairment or other chronic illnesses. | Four (7%) discontinued arm 1 and one (2%) discontinued arm 2 due to difficulties with continuous sensor use and/or alarms. | | | | | | not reported<br>Drop-outs = one discontinued before the start of the intervention. Four (7%) discontinued arm 1 and one (2%) discontinued arm 2 due to difficulties with continuous sensor use and/or alarms.<br>Authors reported that "severe hypoglycaemia occurred once in arms 1 and 2. The patient in arm 2 was not wearing the device at the time" |

**Table 170: GARG 2006**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S. Garg, H. Zisser, S. Schwartz, T. Bailey, R. Kaplan, S. Ellis, and L. Jovanovic. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care 29 (1):44-50, 2006.<br><br>REF ID: GARG2006 | Parallel RCT. | n= 91<br><br>(n= 47 continuous glucose monitoring [CGM] ; n=44, self-monitoring blood glucose (SMBG)<br><br>(75 of 91 patients [82%] type 1 diabetes)<br><br>Inclusion criteria:<br>Age ≥ 18 years old<br>type 1 diabetes or type 2 diabetes requiring | | | | CGM sensor on (STS DexCom System) for three 72 hour periods. Patients were fitted with STS Dexcom System (CGM) and all assigned two SMBG meters, one to calibrate CGM and for comparison/confirmation of alerts. Patients were instructed to use SMBG values to guide major therapeutic decisions in diabetes management | CGM sensor off with self-monitoring blood glucose (SMBG):<br>Patients were fitted with STS Dexcom System (CGM) but continuous glucose data was not displayed. Control group was also asked to calibrate CGM twice daily with SMBG meters and to use SMBG values to guide treatment. | 10 days | | CGM | SMBG | Funding:<br>Devices provided by DexCom<br>Risk of bias:<br>Randomisation : computer generated stratified randomisation patients with type 1 diabetes and type 2 diabetes.<br>Allocation concealment: not described.<br>Blinding: not blinded due to nature of intervention<br>ITT analysis : not reported<br>Drop-outs: none reported |
| | | | Age (years) | 44 (SD 13) | | | | | Severe hypoglycaemic events (requiring assistance) | 0 | 2 | |
| | | | Gender (m/f) | 53/38 | | | | | HbA1c not reported | | | |
| | | | Diabetes duration (years), mean (SD) | 21 (SD 12) | | | | | | | | |
| | | | | CGM (n=44) | SMBG (n=47) | | | | | | | |
| | | | CSII | 27 | 24 | | | | | | | |
| | | | HbA1c (%), mean (SD) | 8.0 (SD 1.5) | 7.6 (SD 1.1) | | | | | | | |
| | | | Drop-outs:<br>None reported | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | insulin therapy<br>Exclusion criteria: n/a | | | | | | | |

**Table 171: HIRSCH (STAR-1) 2008**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I. B. Hirsch, J. Abelseth, B. W. Bode, J. S. Fischer, F. R. Kaufman, J. Mastrototaro, C. G. Parkin, H. A. Wolpert, and B. A. Buckingham. Sensor-augmented insulin pump therapy: | Parallel RCT.<br><br>Multicentre treat-to-target trial carried out in 7 centres in the USA. | n= 146 participants between 12 and 72 years with type 1 diabetes.<br>Adult (18-80 years) = 98 (67% of total population)<br>Sub-group analysis carried | Patients with type 1 diabetes and initial A1C levels of ≥ 7.5%. | | | CGM: CSII therapy, augmented with real-time CGM (Medtronic).<br>Participants used the real-time glucose sensor features of their pumps in addition to advanced insulin pump features, which were made available to | Insulin pump with standard glucose monitoring (SMBG) | 26 weeks | | CGM | SMBG | Funding: research was supported by a grant from Medtronic, inc.<br><br>Risk of bias:<br>Randomisation: "subjects were randomised". Insufficient information.<br>Allocation concealment: not reported |
| | | | | CGM (n=49) | SMBG (n=49) | | | | Change in HbA1c (%), mean at 26 weeks. | -0.69 (SD 0.73) | -0.64 (SD 0.57) | |
| | | | Age categories (years) (n[%]): 18-80 | 49 | 49 | | | | Hypoglycaemia/severe hypoglycaemia not reported for type 1 diabetes. | | | |
| | | | Gender (m/f) | 28/44 | 32/34 | | | | | | | |
| | | | Diabete | 16.7 | 20.8 ± | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| results of the first randomized treat-to-target study. Diabetes Technol.Ther. 10 (5):377-383, 2008.<br><br>REF ID: HIRSCH 2008 | | out for adult population.<br><br>For the adult population (n=49, continuous glucose monitoring [CGM] ; n=49, self-monitoring blood glucose (SMBG)<br><br>Inclusion criteria:<br>Diagnosed with type 1 diabetes > 1 year prior to entering the study.<br>Continuous subcutane | s duration (years), mean (SD) | (SD 10.49) | 12.41 | both groups. | | | | | | Blinding = "all CGM data were blinded to the subjects"<br>ITT analysis not reported<br>Powered study: not reported<br>Drop-outs: 8% dropout in the CGM group and 3% dropout in the SMBG group.<br>Severe hypoglycaemic event not related to device |
| | | | HbA1c (%), mean (SD) | 8.3 (SD 0.54) | 8.37 (SD 0.6) | | | | | | | |
| | | | | | | | | | | | | |
| | | | Drop-outs:<br>Dropout rate: 8% dropout in the CGM group and 3% dropout in the SMBG group. | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | ous insulin infusion (CSII) for at least 6 months.<br>Age 12-72 years<br>HbA1c levels ≥ 7.5%<br>Exclusion criteria: n.a. | | | | | | | |

**Table 172: NEWMAN 2009**

| | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S. P. Newman, D. Cooke, A. Casbard, S. Walker, S. Meredith, A. Nunn, L. Steed, A. Manca, M. | RCT (parallel trial)<br>RCT<br>Multicentre trial with | n= 106 adults with type 1 diabetes<br>(n=53, continuous glucose | Participants aged over 18 years with insulin-treated DM for at least 6 months receiving two or more injections of insulin daily. | | | CGMS (MiniMed): Participants were requested to wear it for 72 hrs. In addition | Standard care using an OneTouch Ultra meter. They were asked to monitor capillary blood glucose | 18 months | | CGMS | Attention control | Funding: funded by the National Institute of Health Research, Health Technology Assessment |
| | | | | CGMS (n=53) | Attention control | | | | Percentage Change in HbA1c (%), mean | -5.7 (SD 9.4) | -3.1 (SD 14.8) | |

| | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sculpher, M. Barnard, D. Kerr, J. Weaver, J. Ahlquist, and S. J. Hurel. A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technol.Assess. 13 (28):iii-194, | participants recruited from care diabetes clinics in four hospitals in England.<br>Stratified by age, centre and type of diabetes | monitoring [CGM]; n=53, standard treatment (One Touch Ultra meter) reflecting common practice in the UK.<br><br>Inclusion criteria:<br>Individual with insulin-treated DM receiving two or more injections daily<br>Age over 18 years.<br>Duration of diabetes | | | (n=52) | to wearing the CGMS participants were asked to continue to perform capillary blood glucose monitoring as desired. | at their normal frequency. | | at 18 months follow-up, mean (SD) | | | Programme.<br><br>Risk of bias:<br>Randomisation was site specific and ensured balanced allocation in terms of centre, age and type of diabetes by use of the minimisation method.<br>Allocation concealment =adequate (Central randomisation)<br>Blinding = not reported<br>ITT analysis carried out<br>Study was powered.<br>Drop-outs (overall) = acceptable |
| | | | Age (years), median (IQR) | 53 (42-63) | 51 (42-59) | | | | Hypoglycaemia not reported | | | |
| | | | Diabetes duration (years), median (IQR) | 15 (9-26) | 14 (9-24) | | | | | | | |
| | | | Years on insulin, median (IQR) | 11 (5-25) | 12.5 (5.5-22) | | | | | | | |
| | | | Baseline HbA1c (%), mean (SD) | 9 (SD 1.1) | 9.4 (SD 1.3) | | | | | | | |

| | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 2009.<br><br>REF ID: NEWMAN 2009 | | over 6 months.<br>HbA1c results:<br>Two HbA1c levels greater than or equal to 7.5%, one in the last 3 months and another within the previous 15 months.<br>Fluent in English, Bengali, Cantonese or Turkish.<br>Exclusion criteria:<br>Previous inability to use a capillary glucose | | | | | | | (<20%) |

| | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | meter<br>Previous use of the CGMS sensor.<br>Presence of elevated levels of Hbf or HbS (abnormal haemoglobin)<br>Pregnancy or planned pregnancy.<br>Skin conditions, e.g. eczema, psoriasis or other skin irritation, at the sites of monitor use.<br>Receiving dialysis | | | | | | | |

| | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Visual or physical impairment limiting ability to use monitors.<br>Planned major surgery.<br>Participation in any other on-going trial. | | | | | | | |

**Table 173: O'CONNELL 2009**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| M. A. O'Connell, S. Donath, D. N. O'Neal, P. G. Colman, G. R. Ambler, T. | Open parallel RCT.<br><br>Multicentre trial carried out in 5 outpatients | n= 62 adults and children (stratified into two groups according to age: 13- | Patients with type 1 diabetes. Insulin pump users = 100%. | | | CGM: Paradigm (Metronic Minimed). | Standard glucose monitoring (SMBG). | 3 months. | | CGM | SMBG | Funding: Investigator initiated study was supported by Medtronic Australasia.<br><br>Risk of bias: |
| | | | | CGM (n=31) | SMBG (n=31) | | | | HbA1c (%), mean (SD) at 3 months | 7.1 (SD 0.8) | 7.8 (SD 0.9) | |
| | | | Age | 23.4 | 23.0 | | | | Mean HbA1c | 0.43 (-0.19 to | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| W. Jones, E. A. Davis, and F. J. Cameron. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia 52 (7):1250-1257, 2009. REF ID: O'CONNELL 2009. | centres in Australia. | 19 years and >19-40 years but no subgroup analysis done) with type 1 diabetes. (n=31, continuous glucose monitoring [CGM] ; n=31, self-monitoring blood glucose (SMBG)<br><br>Inclusion criteria:<br>Age 13-40 years.<br>type 1 diabetes >1 year.<br>Use of insulin pump therapy including proficiency with use of a bolus- | (years), mean (SD) | (SD 8.6) | (SD 8.1) | | | | adjusted for baseline values | -0.75); p = 0.009 | | Randomisation : "computer generated schedule which randomly assigned each of the pair to one of two study groups."<br>Allocation concealment: not clear<br>Blinding: "baseline and end of study investigations for all participants comprised 6 days of blinded continuous glucose monitoring using the CGMS Gold (Medtronic) and HbA1c measurement.<br>ITT analysis: reported.<br>Powered study: study was adequately powered.<br>Drop-outs = |
| | | | Gender (m/f) | 9/22 | 9/22 | | | | | | |
| | | | Diabetes duration (years), mean (SD) | 11.1 (SD 7.6) | 9.2 (SD 7.2) | | | | Severe hypoglycaemia | 0 | 0 |
| | | | HbA1c (%) | 7.3 (SD 0.6) | 7.5 (SD 0.7) | | | | | | |
| | | | | | | | | | | | |
| | | | Drop-outs:<br>Dropout rate: 5/31 (16%) and 2/31 (6%) withdrew from intervention and control groups, respectively. | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | dose calculator for >3 months.<br>HbA1c ≤8.5%.<br>Reliably performing self-monitoring of blood glucose (SMBG) at least 4 times daily.<br>Internet access and willingness to use the subcutaneous sensor component of the system for at least 70% of the total 3 month study period.<br>Exclusion criteria:<br>Co-existent | | | | | | | 5/31 (16%) and 2/31 (6%) withdrew from intervention and control groups, respectively.<br>Results for adults and children were combined. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | medical problems that would interfere with their ability to use the system (e.g impaired vision), co-existent illness that otherwise predisposes to hypoglycaemia (e.g. adrenal insufficiency) or a history of severe hypoglycaemia while using insulin pump therapy. | | | | | | | |

**Table 174: RACCAH 2009**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D. Raccah, V. Sulmont, Y. Reznik, B. Guerci, E. Renard, H. Hanaire, N. Jeandidier, and M. Nicolino. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. Diabetes | Parallel RCT.<br><br>Multicentre trial carried out in 8 outpatients centres in France. | n= 132 (81 adults and 51 children) with uncontrolled type 1 diabetes. Adult population = 61%.<br>(n=55, continuous glucose monitoring [CGM] ; n=60, self-monitoring blood glucose (SMBG)<br><br>Inclusion criteria:<br>Age between 2 and 65 years. | Patients with type 1 diabetes. Insulin pump users = 0%. | | | CGM: Paradigm (Metronic Minimed).<br><br>All patients continued to perform fingerpick measurements for glucose self-monitoring as they did before the study. | Standard glucose monitoring (SMBG) plus insulin pump. | 6 months. | | CGM | SMBG | Funding: study was funded by Medtronic France. The study was designed and approved by the sponsor.<br><br>Risk of bias:<br>Randomisation: not clear<br>Allocation concealment: not clear<br>Blinding: open label study. "physicians and patients were blinded to centralised A1c data from baseline to completion of study"<br>ITT analysis: |
| | | | | CGM (n=55) | SMBG (n=60) | | | | Change in HbA1c (%), mean (SD) at 6 months – full analysis set population | -0.81 (SD 1.09) | -0.57 (SD 0.94) | |
| | | | Age (years), mean (SD) | 28.1 (SD 5.1) | 28.8 (SD 16.7) | | | | Hypoglycaemia (episodes/day) – full analysis set population | 0.1 (SD 0.9) | 0.1 (SD 0.7) | |
| | | | Gender (m/f) | 30/25 | 34/26 | | | | | | | |
| | | | Diabetes duration (years), mean (SD) | 11.2 (SD 9.0) | 12.3 (SD 8.8) | | | | SAEs | 3/55 | 7/60 | |
| | | | Baseline HbA1c (%), mean (SD) | 9.11 (SD 1.28) | 9.28 (SD 1.19) | | | | | | | |
| | | | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Care 32 (12):2245-2250, 2009.<br>REF ID: RACCAH 2009. | | type 1 diabetes >1 year.<br>Follow up by the respective investigator for at least 3 months<br>HbA1c ≥8%.<br>Treatment with basal/bolus MDI with rapid insulin analogues at mealtimes.<br>Exclusion criteria: not reported. | Drop-outs:<br>Dropout rate: 14 (25%) from the CGM group (6 (10%) children and 8 (15%) adults) and 6 (10%) from the SMBG group. | | | | | | primary covariance analysis was based on the comparison of HbA1c changes between the groups using last observation carried forward (LOCF) method on the full analysis set (FAS) of patients. Analysis on the FAS population was ITT. Analyses were adjusted for age as patients were randomly assigned within age groups.<br>Powered study: not reported.<br>Drop-outs = 14 (25%) from the CGM group (6 (10%) children |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | and 8 (15%) adults) and 6 (10%) from the SMBG group.<br>Results for adults and children were combined. No subgroup analysis. |

**Table 175: RADERMECKER 2010**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| R. P. Radermecker, A. Saint Remy, A. J. Scheen, J. Bringer, and E. Renard. Continuous glucose monitoring reduces both hypoglycaemia and HbA1c | RCT (cross-over after 12 weeks)<br><br>1 centre (clinic) in Belgium | n=13<br><br>(n=7 started with CGM by Continuous Subcutaneous Insulin Infusion (CSII) plus SMBG ; n=6 started with | | | Permanent use of a CGM device (Guardian Medtronic) which displays estimated blood glucose levels at 5-min | Self-Monitoring Blood Glucose (SMBG) | 24 weeks | | CGM | SMBG | Funding: financially supported in part by the Leon Fredericq Foundation at the University of Liege, Belgium.<br><br>Risk of bias: Randomisation |
| | | | Diabetes duration, mean (SD) years | 25 (SD 15) years | | | | HbA1c (change scores), mean (SD) | -0.53 (SD 0.66) | 0.09 (SD 0.50) | |
| | | | CSII, mean (SD) years | 5.5 (SD 7) years | | | | DQOL total score (change scores), scale 0-100 (high = better), | -2.3 (SD 5.3) | 0.7 (SD 4.1) | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. Diabetes Metab. 36 (5):409-413, 2010.<br><br>REF ID: RADERMECKER 2010 | | SMBG only)<br><br>Inclusion criteria:<br>type 1 diabetes<br>More than six recorded capillary blood glucose (CBG) values <60mg/dL<br><br>Exclusion criteria:<br>Not reported | | | intervals plus SMBG | | | mean (SD) | | | = unclear (as details not given)<br>Allocation concealment not reported<br>Blinding not reported<br>ITT analysis not reported<br>Powered study: unclear<br>Drop-outs >20% (about 31%) NS significant differences in baseline characteristics between the nine who completed the study and the 13 who were initially randomised. |
| | | | | | | | | Number of hypoglycaemic episodes – events per 14 days (change scores), mean (SD) | 6.2 (SD 5.2) | 0.67 (SD 6.9) | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | NS differences between groups for any of the baseline characteristics<br><br>Drop-outs:<br>Four patients withdrew from the study within the first 2 weeks. And results reported for the 9 completers | | | | | | | | |

**Table 176: TAMBORLANE 2008 – JUVENILE 2008 STUDY**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| W. V. Tamborlane, R. W. Beck, B. W. Bode, B. Buckingham, H. P. Chase, R. Clemons, R. Fiallo-Scharer, L. A. Fox, L. K. Gilliam, I. B. Hirsch, E. S. Huang, C. Kollman, A. J. Kowalski, L. Laffel, J. M. Lawrence, J. Lee, N. Mauras, M. O'Grady, K. J. Ruedy, M. Tansey, E. Tsalikian, S. Weinzimer, | Parallel RCT.<br><br>Multicentre trial carried out in 10 centres in the USA. | n= 322 adults and children (stratified into three groups according to age: ≥ 25 years, 15 to 24 years, and 8 to 14 years) with type 1 diabetes.<br>≥ 25 years = 98 (30% of total population); 15-24 years = 110 (34% of total population)<br>Sub-group analysis carried out | Patients' ≥ 25 years with type 1 diabetes and initial A1C levels of 7 to 10%., either used an insulin pump or received at least 3 daily insulin. | | | CGM: patients were instructed to use the device on a daily basis and to verify the accuracy of the glucose measurement with a home blood glucose meter (provided by the study)<br>Dexcom Seven,<br>Paradigm Real-Time Insulin Pump<br>CGMS (Medtronic)<br>FreeStyle Navigator (Abbot Diabetes | Standard glucose monitoring (SMBG): home monitoring with a blood glucose meter.<br>Patients were given blood glucose meters and test strips and asked to perform home blood glucose monitoring at least 4 times daily. | 26 weeks | | CGM | SMBG | Funding: research was supported by grants from the Juvenile Diabetes Research Foundation.<br><br>Risk of bias:<br>Randomisation: "patients meeting these criteria were randomly assigned with the use of a permuted block design".<br>Allocation concealment: not reported<br>Blinding: control group had blinded CGM at 13 and |
| | | | | CGM (n=52) | SMBG (n=46) | | | | Change in HbA1c (%) ≥25 years, mean (SD) at 26 weeks | -0.50 (SD 0.56) | -0.02 (SD 0.45) | |
| | | | | | | | | | Change in HbA1c (%) 15-24 years, mean (SD) at 26 weeks | -0.18 (SD 0.65) | -0.21 (SD 0.61) | |
| | | | Age: ≥25 years, mean (SD) | 41.2 (SD 1.2) | 44.6 (SD 12.3) | | | | Severe hypoglycaemia ≥25 years: no. of patients (%) | 5/52 (10) | 4/46 (9) | |
| | | | Age: 15-24 years, mean (SD) | 18.8 (SD 3) | 18.2 (SD 2.7) | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D. M. Wilson, H. Wolpert, T. Wysocki, and D. Xing. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N.Engl.J.Med. 359 (14):1464-1476, 2008.<br>REF ID: TAMBORLANE 2008 | | for ≥25 years population and 15-24 years<br><br>For the ≥ 25 years population (n=52, continuous glucose monitoring [CGM] ; n=46, self-monitoring blood glucose (SMBG)<br><br>For the 15-24 years population (n=57, continuous glucose monitoring [CGM] ; n=53, self-monitoring | Gender (m/f): ≥25 years | 21/31 | 20/26 | Care). | | | | | | 26 weeks<br>ITT analysis: not sufficient information.<br>Powered study: study was adequately powered.<br>Drop-outs = acceptable (<20%). |
| | | | Gender (m/f): 15-24 | 22/29 | 15/38 | | | | Severe hypoglycaemia 15-24 years: no. of patients (%) | 3/57 | 5/53 | |
| | | | Diabetes duration ≥25 years, mean (SD) | 23.6 (SD 10.6) | 21.8 (SD 10.4) | | | | Adverse events: no. of patients | 0 | 0 | |
| | | | Diabetes duration 15-24 years, mean (SD) | 9.5 (SD 4.8) | 8.8 (SD 4) | | | | | | | |
| | | | HbA1c (%): ≥25 years, mean (SD) | 7.6 (SD 0.5) | 7.6 (SD 0.5) | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | blood glucose (SMBG)<br><br>Inclusion criteria:<br>type 1 diabetes at least 1 year before randomisation.<br>Use an insulin pump or received at least 3 daily insulin injections.<br>HbA1c level of 7 to 10%<br>Exclusion criteria:<br>Use of CGM at home in the 6 months leading up to the trial. | HbA1c (%): 15-24 years, mean (SD) | 8 (SD 0.7) | 7.9 (SD 0.8) | | | | | | |
| | | | Drop-outs:<br>Dropout rate: < 5% | | | | | | | | |

**Table 177: TANENBERG 2004**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R. Tanenberg, B. Bode, W. Lane, C. Levetan, J. Mestman, A. P. Harmel, J. Tobian, T. Gross, and J. Mastrototaro. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. Mayo | Parallel RCT.<br><br>Multicentre trial carried out in 7 centres in the USA. | n= 128 participants between 19 and 76 years with insulin treated diabetes (76% (97) being type 1 diabetes)<br><br>(n=62, continuous glucose monitoring [CGM] ; n=66, self-monitoring blood glucose (SMBG)<br><br>Inclusion criteria:<br>Insulin | Patients with insulin treated diabetes ≥ 19years. insulin pump users: 46% | | | CGM (Medtronic MiniMed) for 2 periods of 3 days (week 1 and week 3).<br>The CGM glucose values are reported retrospectively in the range of 40 to 400 mg/dl. | Self-monitoring blood glucose (SMBG):<br>At least 4 times each day (before meals and at bed time) and in response to symptoms of hypoglycaemia for the duration of the study. | 3 months | | CGM | SMBG | Funding: study was sponsored by Medtronic Minimed.<br><br>Risk of bias:<br>Randomisation by random number list, computer generated by Medtronic Minimed with SAS statistical software was used.<br>Allocation concealment: random assignments to the treatment or control group were provided to the study centres in sealed |
| | | | | CGM (n=51) | SMB (n=58) | | | | Change from baseline HbA1c (%), mean at 3 months | -0.74 (SD 0.95) | -0.73 (SD 1.17) | |
| | | | Age (years), mean (SD) | 44 (SD 10.2) | 44.5 (SD 12.6) | | | | Severe hypoglycaemia events at 3 months. | 1/51 | 1/58 | |
| | | | Gender (m/f) | 19/32 | 25/33 | | | | | | | |
| | | | Diabetes duration (years), mean (SD) | 20.4 (SD 10.7) | 19.5 (SD 11.9) | | | | | | | |
| | | | HbA1c (%), mean (SD) | 9.1 (SD 1.1) | 9 (SD 1) | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Clin Proc 79 (12):1521-1526, 2004.<br><br>REF ID: TANENBERG 2004 | | treated diabetes<br>Age 17-76 years<br>HbA1c levels ≥ 7.9%<br>Exclusion criteria: n.a. | Drop-outs:<br>Dropout rate 18% (11/62) in CGM versus 12% (8/66) in control group | | | | | | envelopes.<br>Blinding = not reported<br>ITT analysis not reported<br>Powered study: study was powered according to the result of a 5-week pilot study.<br>Drop-outs = 18% (11/62) in CGM versus 12% (8/66) in control group |

# G.4 Insulin therapy

## G.4.1 Rapid-acting insulin

### G.4.1.1 Lispro (+NPH) versus human insulin (+NPH)

**Table 178: Pfutzner 1996 (ID 1053) – In old GL xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Pfutzner A, Kustner E, Forst T, Schulze-Schleppinghoff, Trautmann ME, Haslbeck, Schatz H, Beyer J 1996 Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. Experimental & Clinical Endocrinology & Diabetes 104:25-30<br><br>REF ID: PFUTZNER | RCT - crossover<br><br>Multicentre, Germany | n=107<br><br>Inclusion criteria:<br>type 1 diabetes (WHO)<br>Insulin treatment at least 2 months<br><br>Exclusion criteria:<br>Known allergy to insulin<br>CV or CeV symptoms of atherosclerosis<br>Cancer<br>Renal or hepatic failure<br>Signs of drug abuse<br>Life threatening disease<br>Pregnant or lactating women or those planning pregnancy | | All patients n=107 | Lispro + NPH<br><br>Lispro<br>NPH basal<br><br>Timing and regimen not stated in paper | Regular human + NPH<br><br>Regular human<br>NPH basal<br><br>Timing and regimen not stated in paper | 3 months treatment (each cross-over period) | HbA1c, final value, % (SD) | LI: 7.42 (0.12)<br><br>HI: 7.47 (0.12)<br>NS diff | Funding: Drugs from Eli Lilly<br><br>Risk of bias:<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = open label to allow optimal time administration.<br>Not ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA |
| | | | Age, years (SD) | 32 ± 9.7 range 18-65 years | | | | | | |
| | | | Women, % | 50.5% | | | | Hypoglycaemia, episodes/month (SEM) | LI: 8.57 (0.70)<br><br>HI: 9.61 (0.72)<br>P=0.008 | |
| | | | Diabetes, mean years (SD) | 9.55 ± 7.74 | | | | Treatment satisfaction | Significant improvement in LISPRO vs. Human group | |
| | | | HbA1c, % (SD) | | | | | | | |
| | | | Drop-outs:<br>n=10 | | BOTH GROUPS: --- | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 1996 (ID 1053) | | | | | | | | | analysis (best for cross-over studies). |

**Table 179: Annuzzi 2001 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| G. Annuzzi, Prato S. Del, R. Arcari, Damato A. Bellomo, L. Benzi, D. Bruttomesso, M. C. Calderini, C. Coscelli, D. Fedele, A. Galluzzo, M. Giordano, R. Giorgino, A. Lapolla, P. Orsini, G. Pagano, D. | RCT - crossover<br><br>8 centres, Italy | n=85<br><br>Inclusion criteria:<br>type 1 diabetes (WHO)<br>diagnosis before age 35 and interval between treatment and diagnosis of <1 year<br>Age 18-50<br>Diabetes duration >2 years<br>At least 3 daily | | All patients n=85 | Lispro + NPH + ISOCALORIC DIET<br><br>Lispro NPH once/day (added before breakfast or lunch according to needs)<br><br>Lispro taken 0-5 minutes | Regular human + NPH + ISOCALORIC DIET<br><br>Regular human NPH c once/day (added before breakfast or lunch according to needs) | 3 months treatment (each cross-over period) | HbA1c, final value, % (SD) | LI: 8.12 (0.85)<br><br>HI: 8.27 (0.79)<br>P<0.05 | Funding: Drugs from Eli Lilly<br><br>Risk of bias:<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = |
| | | | Age, years (SD) | 31.4 ± 7.6 range 18-65 years | | | | | | |
| | | | Women, % | 56% | | | | Hypoglycaemia, episodes/month/patient | LI: 256<br><br>HI: 204<br>NS | |
| | | | Weight, kg (SD) | 65.9 (9.9) | | | | | | |
| | | | Diabetes, mean years (SD) | 12.1 ± 7.6 | | | | Severe hypoglycaemia, episodes/month/patient | LI: 0.7<br><br>HI: 1.0<br>NS | |
| | | | HbA1c, % (SD) | 8.67 (0.72) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Santoro, and G. Riccardi. Preprandial combination of lispro and NPH insulin improves overall blood glucose control in type 1 diabetic patients: a multicenter randomized crossover trial. Nutrition, metabolism, and cardiovascular diseases: NMCD 11 (3):168-175, 2001.<br><br>REF ID: ANNUZZI 2001 | | Insulin injections for >2 months<br>Insulin dose >0.3 U/Kg<br>HbA1c 7.5-10.0%.<br><br>Exclusion criteria:<br>History of cancer<br>CeV or symptomatic peripheral vascular disease<br>Heart failure<br>Liver or renal disease<br>Visual impairment<br>Pregnant or lactating women<br>Clinically significant hypoglycaemia. unawareness | Drop-outs:<br>n=5 | before meals | Human insulin taken 30-45 minutes before meals | | Weight, kg (SD) | LI: 66.7 (10.3)<br><br>HI: 66.4 (10.5) | open label<br>Not mention ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | | BOTH GROUPS:<br>NPH could be given 3 times/day before each meal | | | DTSQ | Preference for Lispro (p<0.001) | |

**Table 180: VIGNATI 1997 (275) xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| L. Vignati, J. H. Anderson, Jr., and P. W. Iversen. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. Clin.Ther. 19:1408-1421, 1997.<br><br>REF ID: VIGNATI 1997 (275) | RCT - crossover<br><br>16 countries, 75 centres | n=379 type 1 diabetes<br>(707 total of type 1 diabetes and type 2 diabetes); type 1 diabetes subgroup analysis done so results are for type 1 diabetes only.<br><br>Inclusion criteria:<br>IDDM or NIDDM (WHO)<br>Regular human + NPH insulin twice/day for at least 2 months<br>18-70 years<br><br>Exclusion criteria:<br>Severe concomitant disease<br>Use of oral hypoglycaemia. | | All patients n=379 | Lispro + NPH<br><br>Lispro = Humalog<br>NPH = Humulin N<br>Twice/day (morning and eve meals)<br><br>Lispro taken immediately before meals | Regular human + NPH<br><br>Regular human = Humulin R<br>NPH = Humulin N<br>Twice/day (morning and eve meals)<br><br>Human insulin taken as had done before enrolment | 2 months treatment<br>(each cross-over period) | HbA1c, final value, % (SD) | LI: 7.8 (1.4)<br><br>HI: 7.9 (1.5)<br>P=0.660 | Funding: Drugs and main authors from Eli Lilly<br><br>Risk of bias:<br>Randomisation = Adequate (computer generated)<br>Allocation concealment = adequate (sequence assignment from central location)<br>No wash-out period<br>Blinding = open label<br>ITT analysis<br>Powered study (Blood glucose.)<br>Drop-outs = acceptable (<20%) |
| | | | Age, years (range) | 39.1 (18-70) | | | | Hypoglycaemia, episodes/month (SD) | LI: 4.6 (5.5) n=365<br><br>HI: 4.5 (5.0) P=0.677 n=363 | |
| | | | Women, % | 44% | | | | | | |
| | | | BMI, kg/m2 (range) | 24.8 (17.7-50.5) | | | | | | |
| | | | Diabetes, mean years (range) | 13.1 (0.2-48.2) | | | | | | |
| | | | HbA1c, % (SD) | 7.9 (1.5) | | | | | | |
| | | | Drop-outs:<br>Overall 4.1% | | BOTH GROUPS:<br>patients were allowed to use premix or self-mixed insulin during treatment with regular human insulin<br>Allowed only self-mixed | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | agents or other factor that would preclude patients participation or completion of the study. | | insulin during treatment<br>Dose adjustment could be done monthly | insulin Lispro | | | | Unclear if done ANCOVA analysis (best for cross-over studies). |

**Table 181: GALE 2000 (1060) xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| E. A. Gale. A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with Type 1 diabetes on intensified insulin therapy. The UK Trial | RCT - crossover<br><br>10 sites in UK | n=93<br><br>Inclusion criteria:<br>type 1 diabetes before age 40 years<br>Diabetes >1 year<br>No evidence of major complications<br>Good to moderate control (HbA1c <1.5x upper limit of non-diabetic | | All patients n=93 | Lispro + NPH<br><br>Lispro (before meals)<br>NPH = Humulin I (bedtime) | Regular human + NPH<br><br>Regular human = Humulin S (before meals)<br>NPH = Humulin I (bedtime) | 12 weeks (each cross-over period) | HbA1c, final value, % (SD) | LI: 7.5 (1.1)<br><br>HI: 7.4 (1.1)<br>P=0.807 | Funding: Eli Lilly<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = double blind<br>ITT analysis |
| | | | Age, years median (range) | 35 (18-63) | | | | | | |
| | | | Women, % | 47% | | | | Hypoglycaemia, episodes/month (SD) | LI: 2.6 (3.0)<br><br>HI: 3.1 (4.4)<br>P=0.96 | |
| | | | BMI, kg/m2, median (range) | 25.2 (20-33.7) | | | | | | |
| | | | Diabetes, median years | 13.1 (1-51) | | | | Nocturnal hypoglycaemia, | LI: 0.7 (1.6) | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Group. Diabet.Med. 17:209-214, 2000.<br><br>REF ID: GALE 2000 (1060) | | range)<br>4 daily insulin injections<br>Injections within 15 minutes of meals on >50% of occasions<br><br>Exclusion criteria:<br>None given | (range) | | | | | episodes/month (SD) | HI: 1.8 (3.1)<br>P<0.001 | Powered study (HbA1c)<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | HbA1c, % (SD) | Not given | | | | Severe hypoglycaemia, no. of patients | LI: 2/92<br><br>HI: 6/89 | |
| | | | Drop-outs:<br>Overall n=6 | | | | | | | |
| | | | | | BOTH GROUPS:<br>Insulin supplied double blind as pens<br>Doses adjusted according to target Blood glucose values | | | Severe hypoglycaemia, episodes (SD) | LI: 3<br><br>HI: 10<br>P=0.135 | |

**Table 182: FERGUSON 2001 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| S. C. Ferguson, M. W. Strachan, J. M. Janes, and B. M. Frier. Severe hypoglycaemi | RCT - crossover<br><br>1 centre in UK | n=40<br><br>Inclusion criteria:<br>type 1 diabetes<br>19-65 years | | All patients n=40 | Lispro + NPH | Regular human + NPH | 12 weeks (each cross-over period) | HbA1c, final value, % (SD) | LI: 9.1 (0.83)<br><br>HI: 9.3 (1.0) | Funding: Eli Lilly<br><br>Risk of bias:<br>Randomisation = unclear (no details given) |
| | | | Age, years mean (SD; range) | 46 (11; 19-65) | BOTH GROUPS:<br>The regimen could be | | | Hypoglycaemia, episodes | LI: 1156<br><br>HI: 1115 | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| a in patients with type 1 diabetes and impaired awareness of hypoglycaemia: a comparative study of insulin lispro and regular human insulin. Diabetes.Metab.Res.Rev. 17 (4):285-291, 2001.<br><br>REF ID: FERGUSON 2001 | | Reduction in their warning symptoms of hypoglycaemia in last 2 years<br>Experienced 2 or more episodes of hypoglycaemia in past 2 years (ie. impaired awareness of hypoglycaemia)<br>HbA1c (5.0-6.5%)<br><br>Exclusion criteria:<br>Systemic, renal or hepatic disease<br>Pregnancy | | | either:<br>a) twice/day (ie. SA insulin and NPH mixed and given before breakfast and main evening meal), or<br>b) MDI (ie. SA insulin before meals and NPH before bed)<br>Doses adjusted according to target Blood glucose values | | | | P=NS | Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = open label<br>ITT analysis (no drop-outs)<br>No mention of powering<br>Drop-outs = none mentioned<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | Women, % | 46% | | | | Nocturnal hypoglycaemia, episodes | LI: 25<br><br>HI: 47<br>p=0.01 | |
| | | | BMI, kg/m2, mean (SD) | 25.4 (2.6) | | | | Severe hypoglycaemia, no. of patients | LI: 18/33<br><br>HI: 18/33 | |
| | | | Diabetes, mean years (SD) | 25.8 (9.8) | | | | Severe hypoglycaemia, episodes | LI: 55<br><br>HI: 84<br>P=0.087 | |
| | | | HbA1c, % (SD) | 9.0 (1.1) | | | | | | |
| | | | Drop-outs:<br>Overall: none mentioned | | | | | DTSQ – QoL questionnaire | NS difference between groups | |
| | | | | | | | | HFS (Hypo Fear survey) – QoL questionnaire | NS difference between groups | |

**Table 183: HOLLEMAN 1997 (1051) xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| F. Holleman, H. Schmitt, R. Rottiers, A. Rees, S. Symanowski, J. H. Anderson, P. Van Crombrugge, F. Fery, L. F. Van Gaal, R. Rottiers, G. Somers et al. Reduced frequency of severe hypoglycemia and coma well-controlled IDDM patients treated with insulin lispro. Diabetes Care 20 (12):1827-1832, 1997.<br><br>REF ID: HOLLEMAN 1997 (1051) | RCT - crossover<br><br>19 centres in UK, Belgium and Netherlands | n=199<br><br>Inclusion criteria:<br>IDDM (WHO criteria)<br>Age 16-65 years<br>Insulin treatment for at least 1 year<br>MIT using regular insulin for past 3 months<br>HbA1c <1.5x upper limit of normal range of local lab).<br><br>Exclusion criteria:<br>History of hypoglycaemia unawareness<br>More than 2 | | All patients n=199 | Lispro + NPH<br><br>Lispro = Humalog (before meals)<br>NPH = Humulin (once/day) | Regular human + NPH<br><br>Regular human = Actrapid (before meals)<br>NPH = Insulatard or Protaphane (once/day) | 12 weeks (each cross-over period) | HbA1c, final value, % (SD) | LI: 7.6 (1.3)<br><br>HI: 7.5 (1.2)<br>p=0.697 | Funding: Eli Lilly<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = open label<br>ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | Age, years mean (SD) | 35.4 (9.6) | | | | Hypoglycaemia, episodes | LI: 2249<br><br>HI: 2344<br>p=NS | |
| | | | Women, % | 37% | | | | | | |
| | | | BMI, kg/m2, mean (SD) | 25.0 (3.1) | | | | Nocturnal hypoglycaemia, episodes | LI: 176<br><br>HI: 312<br>p<0.001 | |
| | | | Diabetes, mean years (SD) | 13.1 (9.1) | | | | | | |
| | | | HbA1c, % (SD) | 7.3 (1.1) | | | | Severe hypoglycaemia, episodes | LI: 36<br><br>HI: 58<br>p=0.037 | |
| | | | Body weight, kg (SD) | 75.0 (12.7) | | | | | | |
| | | | Drop-outs:<br>Overall n=10 | | BOTH GROUPS:<br>Regular insulin to be taken 30 minutes before meals, and Lispro immediately before meals<br>Doses adjusted according to target Blood glucose values | | | Body weight, kg (SD) | LI: 75.3 (13.1)<br><br>HI: 75.8 (13.0)<br>p=0.03 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | hospitalisations for hypoglycaemia in the past year. | | | | | | | |

**Table 184: CHAN 2004 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| WB Chan, CC Chow, VTF Yeung, JCN Chan, WY So, and CS Cockram. Effect of insulin lispro on glycaemic control in Chinese diabetic patients receiving twice-daily | RCT - crossover<br><br>Chinese study | n=12 type 1 diabetes (30 total of type 1 diabetes and type 2 diabetes); type 1 diabetes subgroup analysis done so results are for type 1 diabetes only.<br><br>Inclusion criteria:<br>type 1 diabetes or type 2 diabetes<br>18-70 years<br>Receiving twice/day insulin injections | | All patients n=30 | Lispro + NPH<br><br>Lispro<br>NPH = Humulin (twice/day)<br><br>Lispro taken immediately before meals | Regular human + NPH<br><br>Regular human = Humulin R<br>NPH = Humulin N (twice/day)<br><br>Human insulin taken as had done before enrolment | 12 weeks treatment (each cross-over period) | HbA1c, final value, % | LI: 6.8)<br><br>HI: 6.6 | Funding: Not mentioned<br><br>Risk of bias:<br>Randomisation = Unclear (details not given)<br>Allocation concealment Unclear (details not given)<br>No wash-out period<br>Blinding = open label |
| | | | Age, years (range) | 42.2 (20-67) | | | | | | |
| | | | Women, % | 47% | | | | - | - | |
| | | | BMI, kg/m2 (range) | 25.0 (4.3) | | | | | | |
| | | | Diabetes, mean years (range) | 7.8 (2.7) | | | | - | - | |
| | | | HbA1c, % (SD) | 9.0 (2.2) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| regimens of insulin. Chin.Med.J .(Engl). 117 (9):1404-1407, 2004.<br><br>REF ID: CHAN 2004 | | Exclusion criteria:<br>Weakened liver function<br>Impaired renal function<br>CV events in previous 6 months<br>History of peripheral vascular disease<br>Pregnant, lactating or planning pregnancy.<br>Unlikely to complete study due to non-compliance, inability to self-inject<br>History of allergies to insulin | Drop-outs:<br>None mentioned | BOTH GROUPS:<br>Dose adjustment based on HMBG values | | | - | - | ITT analysis (no drop-outs)<br>Not mention powering<br>Drop-outs = none<br>Not done ANCOVA analysis (ANC best for cross-over studies). |

**Table 185: HELLER 1999 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures<br>PERIOD 1 | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| S. R. Heller, S. A. Amiel, and P. Mansell. Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. U.K. Lispro Study Group. Diabetes Care 22 (10):1607-1611, 1999.<br><br>REF ID: HELLER 1999 | RCT - crossover<br><br>11 centres in UK | n=165<br><br>Inclusion criteria:<br>type 1 diabetes for at least 2 years<br>Using basal-bolus regimen for at least 3 months<br>HbA1c <8%<br>Desire to achieve tight glucose control<br><br>Exclusion criteria:<br>Active proliferative retinopathy<br>Symptomatic peripheral neuropathy<br>Serum creatinine >250 micromole/litre<br>Hospitalisation >3 times with severe hypoglycaemia. in past 12mths. | | Lispro n=68 | RHI n=67 | Lispro + NPH<br><br>Lispro = Humalog (before meals)<br>NPH = Humulin (once/day) | Regular human + NPH<br><br>Regular human = Actrapid (before meals)<br>NPH = Insulatard or Protaphane (once/day) | 12 weeks (each cross-over period) | HbA1c, final value, % (SD) | LI: 6.0 (0.9)<br><br>HI: 6.2 (0.8) | Funding: Eli Lilly<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = open label<br>ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | Age, years mean (SD) | 37 (11) | 39 (11) | | | | | | |
| | | | Women, % | 49% | 46% | | | | Hypoglycaemia, episodes | LI: 775<br><br>HI: 1156<br>p=0.04 | |
| | | | BMI, kg/m2, mean (SD) | 25.2 (2.6) | 25.4 (2.9) | | | | Nocturnal hypoglycaemia, episodes | LI: 52<br><br>HI: 181<br>P=0.001 | |
| | | | Diabetes, mean years (SD) | 16.4 (9.6) | 16.7 (8.8) | | | | Severe hypoglycaemia, no. of patients | LI: 2<br>HI: 6 | |
| | | | HbA1c, % (SD) | 6.2 (1.1) | 6.4 (0.9) | BOTH GROUPS:<br>Regular insulin to be taken 30 minutes before meals, and Lispro immediately before meals<br>Doses adjusted according to target Blood glucose values | | | Severe hypoglycaemia, episodes | LI: 8<br><br>HI: 12<br>p=NS | |
| | | | Body weight, kg (SD) | 74.8 (11.4) | 73.5 (10.1) | | | | Body weight, kg (SD) | LI: 74.7 (11.7)<br><br>HI: 75.7 (10.2) | |
| | | | Drop-outs:<br>Overall n=10 | | | | | | | | |

**Table 186: ANDERSON 1997 (1062) xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| J. H. Anderson, Jr., R. L. Brunelle, V. A. Koivisto, A. Pfutzner, M. E. Trautmann, L. Vignati, and R. DiMarchi. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. Diabetes 46:265-270, 1997.<br><br>REF ID: ANDERSON 1997 (1062) | RCT - crossover<br><br>102 centres in 17 countries | n=11,008<br>Mainly adults as high mean and small SD<br><br>Inclusion criteria:<br>IDDM (WHO criteria)<br>Age 12-70 years<br>Insulin treatment for at least 2 months.<br><br>Exclusion criteria:<br>Presence of other severe disease<br>Pregnancy<br>BMI >35 kg/m2<br>Daily insulin dose >2.0 U/kg<br>History of clinically | | All patients n=11008 | Lispro + NPH or Ultralente<br><br>Lispro = Humalog (before meals)<br>NPH = Humulin N<br>Ultralente = Humulin U<br><br>Basal insulin once or twice/day – 54% once/day | Regular human + NPH<br><br>Regular human = Humulin R (before meals)<br>NPH = Humulin N<br>Ultralente = Humulin U<br><br>Basal insulin once or twice/day – 56% once/day | 3 months (each cross-over period) | HbA1c, final value, % (SE) | LI: 8.2 (0.1)<br><br>HI: 8.2 (0.1) | Funding: Eli Lilly<br><br>Risk of bias:<br>Randomisation = not mentioned<br>Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = open label<br>ITT analysis (LOCF)<br>Not mention powering but huge study<br>Drop-outs = no details<br>ANCOVA analysis for hypoglycaemia. rate (best |
| | | | Age, years mean (SD) | 33.2 (0.4) | | | | Hypoglycaemia, episodes | LI: 11906<br><br>HI: 21522 | |
| | | | Women, % | 42% | | | | | | |
| | | | BMI, kg/m2, mean (SD) | 24.2 (0.1) | | | | Hypoglycaemia, episodes/ 30 days (SE) | LI: 6.4 (0.2)<br><br>HI: 7.2 (0.3)<br><br>p<0.001 | |
| | | | Diabetes, mean years (SD) | 12.0 (0.3) | | | | | | |
| | | | HbA1c, % (SD) | 8.5 (0.1) | | | | | | |
| | | | Body weight, kg (SD) | 71.2 (0.4) | BOTH GROUPS:<br>Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals<br>patients allowed to mix pre-meal and basal insulin in the syringe at time of injection<br>Doses adjusted according to target Blood glucose values | | | Severe hypoglycaemia, no. of patients | LI: 24<br><br>HI: 36 | |
| | | | Drop-outs:<br>Overall not mentioned | | | | | Severe hypoglycaemia, episodes | LI: 30<br><br>HI: 42 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | significant hypoglycaemia. unawareness. | | | | | | | for cross-over studies). |

**Table 187: LALLI 1999 (1066) xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C. Lalli, M. Ciofetta, P. Del Sindaco, E. Torlone, S. Pampanelli, P. Compagnucci, M. G. Cartechini, L. Bartocci, P. Brunetti, and G. B. Bolli. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. Diabetes Care 22 (3):468-477, 1999.<br><br>REF ID: LALLI 1999 (1066) | RCT<br><br>1 centre in Italy | n=56<br><br>Inclusion criteria:<br>type 1 diabetes<br>In long-term near-normoglycaemia (HbA1c6.0-7.5%) during intensive treatment<br>Treated with intensive insulin therapy<br>C-peptide negative<br>Free of any detectable microangiopathic complications<br>Negative for autonomic neuropathy<br><br>Exclusion criteria:<br>None given | | Lispro n=28 | RHI n=28 | Lispro + NPH<br><br>Lispro (at meals)<br>NPH (bedtime + with meals if needed – most patients did 3 or 4 times/day)<br><br>64% mixed Lispro with NPH in syringes– rest used separate insulin pens | Regular human + NPH<br><br>Regular human = Hum-R (at meal)<br>NPH (bedtime – most patients did twice/day)<br><br>71% mixed RHI with NPH in syringes – rest used separate insulin pens | 1 year | HbA1c, final value, % (SD) | LI: 6.34 (0.1)<br><br>HI: 6.71 (0.11) | Funding: None mentioned<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = not mentioned<br>Blinding = open label<br>ITT analysis (no drop-outs)<br>No mention of powering<br>Drop-outs = none |
| | | | Age, years mean (SD) | 35 (2.2) | 33 (3) | | | | Hypoglycaemia, episodes (SD) | LI: 7.4 (0.5)<br><br>HI: 11.5 (1.2) | |
| | | | Women, % | 46% | 43% | | | | Severe hypoglycaemia, no. of patients | LI: 0<br>HI: 0 | |
| | | | BMI, kg/m2, mean (SD) | 22.6 (1) | 22.5 (0.9) | | | | | | |
| | | | Diabetes, mean years (SD) | 13.6 (2.8) | 16 (2.6) | | | | | | |
| | | | HbA1c, % (SD) | 6.6 (0.23) | 6.7 (0.2) | | | | | | |
| | | | Drop-outs:<br>None mentioned | | | BOTH GROUPS:<br>Regular insulin to be taken 10-40 minutes before meals, and Lispro 0-5 minutes before meals<br>Doses adjusted according to target Blood glucose values | | | | | |

**Table 188: CIOFETTA 1999 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| M. Ciofetta, C. Lalli, P. Del Sindaco, E. Torlone, S. Pampanelli, L. Mauro, D. L. Chiara, P. Brunetti, and G. B. Bolli. Contribution of postprandial versus interprandial blood glucose to HbA1c in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. Diabetes Care 22 (5):795-800, 1999.<br><br>REF ID: CIOFETTA 1999 | RCT - Parallel<br><br>10 centres in Europe and South Africa | n=24<br><br>Inclusion criteria:<br>type 1 diabetes<br><br>Exclusion criteria: None given<br><br>patients were free of detectable microangiographic complication<br>patients having treatment with intensive insulin therapy (regular insulin at each meal, NPH at bedtime) | | HI + NPH once n=8 | Lisp + NPH once n=8 | MIX Lisp + NPH bed n=8 | Hum R (+ NPH bedtime)<br>Pre-meal human regular insulin.<br>NPH at bedtime.<br><br>----------<br><br>Lispro + NPH<br>Pre-meal insulin lispro.<br>NPH at bedtime.<br><br>Lispro given 0-5mins, and Hum R at 10-40 minutes before meals | SELF-MIX: Lispro + NPH (+ NPH bedtime)<br><br>Pre-meal Mixed insulin (Lispro + NPH).<br>NPH at bedtime.<br><br>Pre-meal Lispro given in separate injection to pre-meal NPH | 3 months treatment | HbA1c, final value, % (SEM) | HI: 6.84 (0.2)<br>Lisp: 6.96 (0.2)<br>MIX: 6.41 (0.12) | Funding: BB and sons<br><br>Risk of bias:<br>Randomisation = unclear (details not given)<br>Allocation concealment = not mentioned<br>Blinding = not mentioned.<br>ITT analysis (no drop-outs)<br>Powering not mentioned.<br>Drop-outs = None |
| | | | Age, years (SEM) | 33 (4) thus likely to be all adults - small SE | | | | | | | | |
| | | | Women, % | 29 | | | | | | Severe hypoglycaemia., no. of patients | HI: 0<br>Lisp: 0<br>MIX: 0 | |
| | | | Diabetes, mean years (SEM) | 13 (2.1) | | | | | | | | |
| | | | HbA1c, % (SEM) | Overall 6.84 (0.20) | | | | | | Mild hypoglycaemia, episodes/ patient/month (SEM) | HI: 4.0 (0.5)<br>Lisp: 8.1 (0.8)<br>MIX: 5.2 (1.2) | |
| | | | HbA1c, % (SEM) | 6.79 (0.17) | 6.89 (0.16) | 6.83 (0.18) | | | | | | |
| | | | Drop-outs (6 months):<br>None mentioned | | | | BOTH GROUPS:<br>Injections by pen HumaPen, Eli Lilly). | | | Unclear if done | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Doses adjusted to specific treatment goals of blood glucose. | | | ANCOVA analysis (best for cross-over studies). | | |

**Table 189: LILLY 1994 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAA(b). LY275585 vs. Humulin R: pre-meal therapy in type 1 diabetes. Anonymous. Anonymous. 1994.<br><br>REF ID: LILLY 1994 | RCT<br><br>14 centres in 6 countries | n=167 – most are adults as mean age is 31.5 years<br><br>Inclusion criteria:<br>type 1 diabetes (WHO)<br>Ages 12-70<br>On human insulin for at least 2 months | | Lispro n=81 | RHI n=86 | Lispro + NPH<br><br>Lispro (before meals)<br>NPH = Humulin U (once or twice/day) | Regular human + NPH<br><br>Regular human =Humulin R (before meals)<br>NPH = Humulin U (once or twice/day) | 1 year | HbA1c, final value, % (SD) | LI: 8.14 (1.3)<br><br>HI: 8.38 (1.37) | Funding: Eli Lilly: registered trial data (not published in a journal)<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = not mentioned<br>Blinding = open label<br>ITT analysis<br>No mention of |
| | | | Age, years mean (SD) | 29.1 | 32 | | | | | | |
| | | | Women, % | 49% | 54% | | | | Hypoglycaemia, no. of patients | LI: 69/75<br>HI: 70/80 | |
| | | | BMI, kg/m2, mean (SD) | 24.2 | 24.5 | | | | Hypoglycaemia, episodes/patient/30 days (SD) | LI: 5.41 (6.74) n=81<br><br>HI: 5.4 (6.36) n=86 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eli Lilly registered trial data (not published in a journal. | | prior to study<br><br>Exclusion criteria:<br>None given | Diabetes, mean years (SD) | 12.3 | 13.3 | | | | Body weight, kg (SD) – change from baseline | LI: 1.43 (3.56) n=81<br><br>HI: 1.04 (2.62) n=86 | powering<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | HbA1c, % (SD) | 8.17 (1.41) | 8.32 (1.67) | BOTH GROUPS:<br>Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals<br>Doses adjusted according to target Blood glucose values | | | | | |
| | | | Body weight, kg (SD) | 71.97 (12.73) | 70.56 (11.28) | | | | Body weight, kg (SD) – final value | LI: 73.4 (13.27) n=81<br><br>HI: 71.6 (11.13) n=86 | |
| | | | Drop-outs:<br>LI: n=7<br>HI: n=7 | | | | | | | | |

**Table 190: LILLY 1995A xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAC(b). LY275585 vs. Humulin R: pre-meal | RCT<br><br>17 centres in 8 countries | n=169 – most are adults as mean age is 33.5 years<br><br>Inclusion criteria:<br>type 1 diabetes (WHO) | | Lispro n=81 | RHI n=88 | Lispro + NPH<br><br>Lispro (before meals)<br>NPH = Humulin N (frequency | Regular human + NPH<br><br>Regular human =Humulin R (before meals) | 12 months treatment | HbA1c, final value, % (SD) | LI: 8.08 (1.43)<br><br>HI: 8.22 (1.44) | Funding: Eli Lilly: registered trial data<br><br>Risk of bias:<br>Randomisation = unclear (no details |
| | | | Age, years mean | 35.2 | 32.0 | | | | | | |
| | | | Women, % | 49.4% | 47.7% | | | | Hypoglycaemia, no. of patients | LI:62 n=76<br><br>HI: 64 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| therapy in type 1 diabetes. Anonymous. Anonymous. 1995.<br><br>REF ID: LILLY 1995A<br><br>Eli Lilly registered trial data (not published in a journal. | | Ages 12-70<br>On human insulin for at least 2 months prior to study<br><br>Exclusion criteria:<br>None given | | | | not mentioned) | NPH = Humulin N (frequency not mentioned) | | | n=84 | given)<br>Allocation concealment = none<br>Blinding = open label<br>ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | BMI, kg/m2, mean | 24.0 | 24.3 | | | | Hypoglycaemia, episodes/patient/30 days (SD) | LI: 3.48 (4.91) n=76<br><br>HI: 3.69 (4.19) n=84 | |
| | | | Diabetes, mean years | 13.0 | 10.9 | | | | Body weight, kg (SD) – change from baseline | LI: 0.92 (3.61) n=76<br><br>HI: 2.41 (8.32) n=84 | |
| | | | HbA1c, % (SD) | 8.28 (1.58) | 8.14 (1.62) | BOTH GROUPS:<br>Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals<br>Doses adjusted according to target Blood glucose values | | | | | |
| | | | | | | | | | Body weight, kg (SD) – final value | LI: 72.16 (11.57) n=76<br><br>HI: 74.51 (13.05) n=84 | |
| | | | Drop-outs:<br>LI: n=6<br>RHI: n=5 | | | | | | | | |

**Table 191: LILLY 1995B xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAE. LY275585 vs. Humulin R: premeal therapy in new patients with type 1 diabetes. Anonymous. Anonymous. 1995.<br><br>REF ID: LILLY 1995B<br><br>Eli Lilly registered trial data (not published in a journal. | RCT<br><br>19 centres in 6 countries | n=98 – most are adults as mean age is 25 years<br><br>Inclusion criteria:<br>type 1 diabetes (WHO)<br>Ages 12-70<br>On human insulin for at least 2 months prior to study (NEW PTS WITH type 1 diabetes)<br><br>Exclusion criteria:<br>None given | | Lispro n=50 | RHI n=48 | Lispro + NPH<br><br>Lispro (before meals)<br>NPH = Humulin N or U (once/day – before evening meal or bedtime) | Regular human + NPH<br><br>Regular human =Humulin R (before meals)<br>NPH = Humulin N or U (once/day – before evening meal or bedtime) | 12 months treatment | HbA1c, final value, % (SD) | LI: 7.77 (2.24)<br><br>HI: 7.84 (2.35) | Funding: Eli Lilly: registered trial data<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = none<br>Blinding = open label<br>ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | Age, years mean | 24.1 | 24.6 | | | | Hypoglycaemia, no. of patients | LI: 30 n=45<br><br>HI: 35 n=43 | |
| | | | Women, % | 44% | 33.3% | | | | Hypoglycaemia, episodes/patient/30 days (SD) | LI: 3.28 (4.36) n=45<br><br>HI: 3.74 (5.13) n=43 | |
| | | | BMI, kg/m2, mean | 23.3 | 23.1 | | | | Body weight, kg (SD) – change from baseline | LI: 4.02 (8.73) n=45<br><br>HI: 4.61 (4.75) n=43 | |
| | | | Diabetes, mean years | 0.17 | 0.19 | | | | | | |
| | | | HbA1c, % (SD) | Not given | Not given | BOTH GROUPS:<br>Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals<br>Doses adjusted according to | | | | | |
| | | | | | | | | | Body weight, kg (SD) – final | LI: 72.88 (15.52) | |
| | | | Drop-outs: | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | LI: n=5<br>RHI: n=5 | target Blood glucose values | | | value | n=45<br><br>HI:71.02 (16.08) n=43 | |

**Table 192: LILLY 1995C xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAG. LY275585 vs. Humulin R: premeal therapy in type 1 diabetes. Anonymous. Anonymous. 1995.<br><br>REF ID: LILLY | RCT - cross-over<br><br>101 centres in 17 countries | n=1008 – most are adults as mean age is 33 years<br><br>Inclusion criteria: type 1 diabetes (WHO)<br>Ages 12-70<br>On human insulin for at least 2 months | | Lispro n=508 | RHI n=500 | Lispro + NPH<br><br>Lispro (before meals)<br>NPH = Humulin U or N (once or twice/day) | Regular human + NPH<br><br>Regular human =Humulin R (before meals)<br>NPH = Humulin U or N (once or twice/day) | 3 months treatment (each cross-over period) | HbA1c, final value, % (SD) | LI: 8.24 (1.49)<br><br>HI: 8.17 (1.46) | Funding: Eli Lilly: registered trial data<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = not mentioned<br>Blinding = open label<br>No wash-out period<br>ITT analysis |
| | | | Age, years mean (SD) | 33.3 | 33.16 | | | | | | |
| | | | Women, % | 42% | 42% | | | | - | - | |
| | | | BMI, kg/m2, mean (SD) | 24.2 | 24.3 | | | | Hypoglycaemia, episodes/patient /30 days (SD) | LI: 6.44 (7.63)<br><br>HI: 7.19 (8.08) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1995C<br><br>Eli Lilly registered trial data (not published in a journal. | | prior to study<br><br>Exclusion criteria:<br>None given | Diabetes, mean years (SD) | 12.18 | 11.77 | | | | Body weight, kg (SD) – change from baseline | LI: 0.3 (2.5)<br><br>HI: 0.6 (3.5) | No mention of powering<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |
| | | | HbA1c, % (SD) | 8.45 (1.71) | 8.45 (1.71) | BOTH GROUPS:<br>Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals<br>Doses adjusted according to target Blood glucose values | | | | | |
| | | | Drop-outs:<br>Overall: 48 | | | | | | Body weight, kg (SD) – final value | LI: 71.5 (12.3)<br>HI: 71.8 (12.5) | |

### G.4.1.2 Lispro (+glargine) versus human insulin (+glargine)

**Table 193: BRUNETTI 2010 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P. Brunetti, M. Muggeo, L. Cattin, A. Arcangeli, P. Pozzilli, V. Provenzano, A. Francesconi, P. Calatola, | RCT<br><br>47 centres in Italy | n=395<br><br>Inclusion criteria:<br>type 1 diabetes for at least 3 years<br>Age 18-60 | | Lispro n=202 | RHI n=193 | Lispro + Glargine<br><br>Lispro (at meals)<br>Glargine (dinner time) | Regular human + Glargine<br><br>Regular human (at meals)<br>Glargine (dinner | 16 weeks treatment, 2 weeks follow-up | HbA1c, final value, % (SD) | LI: 6.95 (0.78)<br><br>HI: 7.1 (0.83) | Funding: Sanofi-Aventis<br><br>Risk of bias:<br>Randomisation = adequate??? sequence generated by biometrician |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| and F. Santeusanio. Incidence of severe nocturnal hypoglycemia in patients with type 1 diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargine. Nutr Metab Cardiovasc Dis 20 (7):519-526, 2010.<br><br>REF ID: BRUNETTI 2010 | | years<br>Using MDI basal-bolus regimen (with NPH or glargine as basal)<br>HbA1c ≤9%<br>fC-peptide ≤0.1 nmol/litre with fBG >6.9 mmol/litre<br>BMI <30 kg/m2<br>Ability and willingness to perform SMBG<br>Adequate contraception<br><br>Exclusion criteria:<br>Diabetes other than type 1 diabetes | | | | | time) | | | | but no other details given<br>Allocation concealment = not concealed<br>Blinding = open label<br>Not true ITT analysis<br>Underpowered<br>Drop-outs = acceptable (<20%)<br>Unclear if done ANCOVA analysis (best for cross-over studies). |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total insulin dose ≥1U/kg/day<br>Serum creatinine >1.5 mg/dl<br>History of renal transplantation<br>Current renal dialysis<br>Congestive heart failure<br>Hypoglycaemia unawareness<br>Concomitant used of β-blockers, thiazides or systemic corticosteroids<br>>1 episode of severe hypoglycaemia. with seizure or coma during | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | past year. | | | | | | | | | |

### G.4.1.3 Lispro (+ glargine) versus glulisine (+ glargine)

**Table 194: DREYER 2005A xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M. Dreyer, R. Prager, A. Robinson, K. Busch, G. Ellis, E. Souhami, and R. Leendert. Efficacy and safety of insulin glulisine in patients with type 1 diabetes. Hormone and metabolic research = Hormon- und Stoffwechselforschung = | RCT<br><br>62 centres in 14 countries | n=683<br><br>Inclusion criteria:<br>type 1 diabetes Requiring continuous insulin treatment since diagnosis and >1 year before study<br>Ages ≥18 years<br>Age of onset <40 years<br>BMI <35 kg/m2<br>HbA1c 6-11% | | Lispro n=341 | Glucose n=342 | Lispro + GLARGINE<br><br>Lispro (before meals)<br>GLARGINE (once/day) | Glulisine + GLARGINE<br><br>Glulisine (before meals)<br>GLARGINE (once/day) | 26 weeks treatment | HbA1c, final value, % (SD) | LI: 7.45 (0.92)<br><br>GL: 7.46 (0.91) | Funding: Aventis Pharma<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = none<br>Blinding = open label<br>ITT analysis<br>No mention of powering<br>Drop-outs = |
| | | | Age, years mean (SD) | 37.9 (12.4) | 39.1 (12.1) | | | | | | |
| | | | Women, % | 43% | 42% | | | | Hypoglycaemia, episodes/patient-months (SD) | LI: 3.48 (4.38)<br><br>GL: 3.64 (4.49) | |
| | | | BMI, kg/m2, mean | 25.1 | 24.9 | | | | Severe hypoglycaemia, episodes/patient-months (SD) | LI: 0.02 (0.11)<br><br>GL: 0.03 (0.12) | |
| | | | Diabetes, | 15.6 | 17.4 | | | | Nocturnal | LI: 0.53 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hormones et métabolisme 37 (11):702-707, 2005.<br><br>REF ID: DREYER 2005A | | Exclusion criteria:<br>Active proliferative/unstable retinopathy in 6 months before study<br>Impaired hepatic or renal function<br>History of seizures or hypersensitivity to insulin or excipients in glulisine formulation. | mean years | (10.3) | (10.9) | | | | hypoglycaemia, episodes/patient-months (SD) | (0.84)<br>GL: 0.55 (0.94) | acceptable (<20%) |
| | | | HbA1c, % (SD) | 7.58 (0.89) | 7.60 (0.96) | BOTH GROUPS:<br>SA insulin to be taken 0-15 minutes before meals<br>Dose adjustment not mentioned | | | Injection site reactions, no. of patients | LI: 14<br>GL: 11 | |
| | | | Drop-outs:<br>LI: n=21 (6%); GL: n=13 (4%) | | | | | | | | |

**Table 195: KAWAMORI 2009 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| R. Kawamori, T. Kadowaki, H. Ishii, M. | RCT<br><br>24 centres | n=267<br><br>Inclusion criteria: | | Glucose n=132 | Lispro n=135 | Glulisine + GLARGINE (+ intensive diet and | LISPRO + GLARGINE GLARGINE (+ intensive | 28 weeks | HbA1c, final value, % (SD) | GL: 7.54 (0.97)<br><br>LI: 7.54 | Funding: Sanofi-Aventis. |
| | | | Age, years | 38.9 (14.3) | 38.8 (12.9) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Iwasaki, and Y. Iwamoto. Efficacy and safety of insulin glulisine in Japanese patients with type 1 diabetes mellitus. Diabetes Obes.Metab. 11 (9):891-899, 2009.<br><br>REF ID: KAWAMORI 2009 | in Japan | ≥18 years<br>type 1 diabetes<br>At least 1 year continuous insulin treatment<br>treatment with bolus every meal and basal once or twice/day for at least 12 weeks before study<br>BMI <35 kg/m2<br>HbA1c ≥6.0-11.0%<br><br>Exclusion criteria:<br>Receiving treatment or have diseases considered to interfere with the conduct of the study | mean (SD) | | | exercise)<br><br>Glulis (0-15 minutes before meals)<br>GLARGINE = (once/day - bedtime) | diet and exercise)<br><br>Lispro (0-15 minutes before meals)<br>GLARGINE = (once/day - bedtime) | | | (0.98) | Risk of bias:<br>Randomisation = unclear (only says minimisation method)<br>Allocation concealment = unclear (no details given)<br>Blinding = open label<br>ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>ANCOVA analysis done |
| | | | Women, % | 62% | 62% | | | | Symptomatic hypoglycaemia, events/patient-month | GL: 3.93<br><br>LI: 3.86<br><br>p=0.164 | |
| | | | BMI, kg/m2, mean | 23.11 | 22.8 | | | | Severe hypoglycaemia, events/patient-month | GL: 0.02<br><br>LI: 0.02<br><br>p=0.658 | |
| | | | Diabetes, mean years (SD) | 12.8 (9.5) | 11.1 (7.1) | | | | DTSQ, change from baseline, median (range) | GL: 0.0 (-15 to 13)<br><br>LI: 0.0 (-16 to 11) | |
| | | | HbA1c, % (SE) | 7.44 (0.93) | 7.50 (0.96) | BOTH GROUPS:<br>Dose adjustment to meet targets for blood glucose control<br>To perform intensive diet and exercise therapies (details not given) | | | treatment satisfaction | NS difference, p=0.313 | |
| | | | Drop-outs:<br>Glucose: n=3; HI: n=9 | | | | | | Body weight, kg | NS change in either group | |

### G.4.1.4 Aspart (+NPH) versus human insulin (+NPH)

**Table 196: HOME 1998 (ID 1021)xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| P. D. Home, A. Lindholm, B. Hylleberg, and P. Round. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. UK Insulin Aspart Study Group. Diabetes Care 21 (11):1904-1909, 1998.<br><br>REF ID: HOME 1998 (ID 1021) | RCT - crossover<br><br>11 centres in the UK. | n=104 type 1 diabetes<br><br>Inclusion criteria:<br>type 1 diabetes<br>Men only (as pending reproductive drug toxicology for aspart).<br>18-60 years<br>BMI <29.0 kg/m2<br>HbA1c <9.0%<br>Using unmodified pre-meal insulin + NPH at bedtime for at least 1 month before study<br><br>Exclusion criteria:<br>Active proliferative retinopathy or nephropathy<br>Recurrent severe hypoglycaemia<br>Insulin resistance<br>Other systemic diseases | | All patients n=104 | Aspart + NPH<br><br>Aspart at meals<br>NPH = Insulatard (once/day bedtime)<br><br>Lispro taken immediately before meals | Regular human + NPH<br><br>Regular human = Actrapid at meals<br>NPH = Insulatard (once/day bedtime)<br><br>Human insulin taken immediately before meals | 4 weeks (each cross-over period) | Hypoglycaemia, no. of patients | AS: 16<br><br>HI: 24 | Funding: NovoNordisk<br><br>Risk of bias:<br>Randomisation = Unclear (details not given)<br>Allocation concealment Unclear (details not given)<br>No wash-out period<br>Double blind<br>ITT analysis<br>Powered study (fructosamine)<br>Drop-outs = acceptable (<20%)<br>Not done ANCOVA analysis (ANC best for cross-over studies). |
| | | | Age, years (SD) | 34.3 (8.6) | | | | Hypoglycaemia, episodes | AS: 20<br><br>HI: 44 | |
| | | | Women, % | 0% | | | | - | - | |
| | | | BMI, kg/m2 (SD) | 25.3 (2.3) | | | | - | - | |
| | | | Diabetes, mean years (SD) | 14.8 (8.7) | | | | | | |
| | | | HbA1c, % (SD) | 7.1 (1.0) | | | | | | |
| | | | Drop-outs:<br>n=14 | | BOTH GROUPS:<br>Doses adjusted according to target Blood glucose values | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Drug abuse | | | | | | | |

**Table 197: TAMAS 2001 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gy Tamas, M. Marre, R. Astorga, I. Dedov, J. Jacobsen, and A. Lindholm. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. | RCT<br><br>48 centres in 11 countries across Europe and Israel | n=423<br><br>Inclusion criteria:<br>18-70 years<br>type 1 diabetes (WHO criteria) for at least 2 years<br>treatment by intensified meal-time + Basal insulin regimen<br>BMI ≤35 kg/m2<br>HbA1c 7-10%<br><br>Exclusion criteria:<br>Requirement of >1.4 U/kg/day insulin<br>Active | | Aspart n=213 | HI=213 | Aspart + NPH<br><br>Aspart = Novorapid (before meals)<br>NPH = Insulatard (twice or 3 times/day)<br><br>Aspart to be injected within 0-5 minutes before meals | Human Insulin + NPH<br><br>Human insulin = Actrapid (before meals)<br>NPH = Insulatard (twice or 3 times/day)<br><br>HI to be injected within 30 minutes before | 12 weeks data collected (but 64 weeks of treatment – final 64 week results nor given) | HbA1c, final value, % (SE) | AS: 8.02 (0.05)<br><br>HI: 8.18 (0.05) | Funding: Not mentioned<br><br>Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = adequate ( central telephone voice response system)<br>Blinding = open label<br>ITT analysis (LOCF)<br>No mention of powering |
| | | | Age, years mean (SD) | 35.6 (11.4) | 36.1 (11.7) | | | | | | |
| | | | Women, % | 42% | 45% | | | | Major hypoglycaemia, episodes | AS: 32<br><br>HI: 31 | |
| | | | BMI, kg/m2, mean | 24.2 | 24.0 | | | | Major hypoglycaemia, no. of patients | AS: 15<br><br>HI: 17 | |
| | | | Body weight, kg (SD) | 71.2 (12.3) | 69.9 (11.3) | | | | DTSQ (score 0-6) | MD: -0.33 (95% CI -0.56 to -0.10; p=0.005 | |
| | | | Diabetes, mean | 14.0 (9.1) | 14.2 (9.2) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes Res.Clin.Pract. 54 (2):105-114, 2001.<br><br>REF ID: TAMAS 2001 | | proliferative retinopathy or nephropathy<br>Recurrent severe hypoglycaemia or hypo unawareness<br>Significant CV or hepatic disease<br>Systemic corticosteroid treatment<br>Pregnant<br>Abusing drugs | years (SD) | | | | meals | | | Aspart SS lower – ie. Asp perceived high blood glucose levels to be less marked than people on HI. | Drop-outs = acceptable (<20%) |
| | | | HbA1c, % (SE) | 8.36 (0.05) | 8.29 (0.05) | | | | | | |
| | | | Drop-outs:<br>AS: n=5; HI: n=11 | | | BOTH GROUPS:<br>Dose adjustment algorithm; targets for blood glucose control | | | Treatment satisfaction | NS difference between groups | |

**Table 198: NIELSEN 1995 (ID 1034) xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| F. S. Nielsen, L. N. Jorgensen, M. Ipsen, A. I. Voldsgaard, and H. H. Parving. Long-term | RCT - crossover<br><br>Single centre, Denmark | n=21 type 1 diabetes<br><br>Inclusion criteria:<br>IDDM<br>Men only<br>18-40 years | | All patients n=21 | Aspart + NPH<br><br>Aspart at meals | Regular human + NPH<br><br>Regular human = Actrapid at | 8 weeks treatment (each cross-over | HbA1c, final value (SD) | AS: 7.7 (0.9)<br><br>HI: 7.8 (0.6) | Funding: NovoNordisk<br><br>Risk of bias:<br>Randomisation = Unclear (details |
| | | | Age, years median (range) | 28 (23-33) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| comparison of human insulin analogue B10Asp and soluble human insulin in IDDM patients on a basal/bolus insulin regimen. Diabetologia 38 (5):592-598, 1995.<br><br>NIELSEN 1995 (ID 1034) | | Duration >1 year<br>Treated with MDI >6 months<br>BMI <27.0 kg/m2<br>HbA1c <10.0%<br>Stable metabolic control (HbA1c varying <1% for previous 6 months)<br><br>Exclusion criteria:<br>History of hypo. Unawareness<br>Local lipodystrophy<br>Urinary albumin excretion >400mg/24h<br>Proliferative retinopathy<br>Other medication<br>Concurrent disease | Women, % | 0% | NPH = Protaphane (once/day bedtime)<br><br>Aspart taken <5 minutes before meals | meals<br>NPH = Protaphane (once/day bedtime)<br><br>Human insulin taken <5 minutes before meals | period) | Severe hypoglycaemia, episodes | AS: 0<br><br>HI: 3<br><br>p=NS | not given)<br>Allocation concealment Unclear (details not given)<br>No wash-out period<br>Double blind<br>ITT analysis<br>Powered study (HbA1c)<br>Drop-outs = none<br>Not done ANCOVA analysis (ANC best for cross-over studies). |
| | | | BMI, kg/m2 (SD) | 23.6 (1.8) | | | | - | - | |
| | | | Diabetes, median years (range) | 111 (2-28) | | | | | | |
| | | | HbA1c, % (SD) | 8.0 (1.2) | | | | - | - | |
| | | | Drop-outs:<br>None | | BOTH GROUPS:<br>Doses adjusted according to target Blood glucose values | | | | | |

**Table 199: BROCK 2011 (xxxxxxx)**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Jacobsen Brock, I, B. F. Vind, L. Korsholm, A. | RCT - crossover | n=16 type 1 diabetes | | All patients n=16 | Aspart + NPH | Regular human + NPH | 8 weeks treatm | HbA1c, final value (SD) | AS: 7.0 (1.2) | Funding: NovoNordisk |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Flyvbjerg, J. Frystyk, J. J. Holst, H. Beck-Nielsen, and J. E. Henriksen. Counter-regulatory hormone responses to spontaneous hypoglycaemia during treatment with insulin aspart or human soluble insulin: a double-blinded randomized cross-over study. Acta Physiol. 202 (3):337-347, 2011.<br><br>REF ID: BROCK 2011 | Single centre in Denmark. | Inclusion criteria:<br>type 1 diabetes<br>18-60 years<br>Duration >1 year<br>Treated with MDI >6 months<br>BMI 18-27.5 kg/m2<br>Use of soluble human insulin before all meals and NPH at bedtime for at least 3 months prior to study<br><br>Exclusion criteria:<br>Pregnancy<br>Impaired vision<br>Impaired renal or hepatic function<br>Cardiac diseases<br>Uncontrolled hypertension<br>Hypoglycaemia unawareness | Age, years mean (SD) | 44.4 (8.2) | Aspart = NovoRapida t meals<br>NPH = twice/day (split dose between morning and eve) | Regular human = Actrapid at meals<br>NPH = twice/day (split dose between morning and eve) | ent (each cross-over period) | | HI: 7.0 (1.2) | Risk of bias:<br>Randomisation = Unclear (details not given)<br>Allocation concealment Unclear (details not given)<br>No wash-out period<br>Double blind<br>No mention of ITT analysis<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>Not done ANCOVA analysis (ANC best for cross-over studies). |
| | | | Women, % | 18.8% | | | | Hypoglycaemia, events | AS: 214<br><br>HI: 297 | |
| | | | BMI, kg/m2 (SD) | 24.6 (1.3) | | | | | | |
| | | | Diabetes, mean years (SD) | 19 (10) | | | | Hypoglycaemia, events/patient/week | AS: 0.9 (0.1)<br><br>HI: 1.1 (0.2) | |
| | | | HbA1c, % (SD) | 7.8 (1.1) | | | | | | |
| | | | Drop-outs:<br>n=2 | | | | | Nocturnal Hypoglycaemia, events | AS: 3<br><br>HI: 5 | |
| | | | | | BOTH GROUPS:<br>Doses adjusted according to algorithm target Blood glucose values | | | treatment satisfaction, VAS 0-6 (6=very satisfied) | NS difference | |

**Table 200: RASKIN 2000A xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P. Raskin, R. A. Guthrie, L. Leiter, A. Riis, and L. Jovanovic. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care 23 (5):583-588, 2000.<br><br>REF ID: RASKIN 2000A | RCT<br><br>59 centres in USA and Canada | n=882<br><br>Inclusion criteria:<br>18-75 years<br>type 1 diabetes for at least 18 months<br>BMI ≤35 kg/m2<br>HbA1c ≤11%<br><br>Exclusion criteria:<br>Impaired hepatic, renal or cardiac function<br>Recurrent major hypoglycaemia<br>Active proliferative retinopathy<br>Total daily | | Aspart n=596 | HI=286 | Aspart + NPH<br><br>Aspart = (before meals)<br>NPH = Novolin N (once/day - bedtime)<br><br>Aspart to be injected immediately before meals | Human Insulin + NPH<br><br>Human insulin = Novolin R (before meals)<br>NPH = Novolin N (once/day - bedtime)<br><br>HI to be injected within 30 minutes before meals | 6 months<br><br>(extra 6 months extension in n=714 patients) | HbA1c, final value, % (SE) | AS: 7.78 (0.03)<br><br>HI: 7.93 (0.05) | Funding: Authors supported by NovoNordisk.<br><br>Risk of bias:<br>Randomisation = unclear (only says random in 2:1 ratio)<br>Allocation concealment = unclear (no details given)<br>Blinding = open label<br>ITT analysis (LOCF)<br>No mention of powering<br>Drop-outs = acceptable (<20%)<br>ANCOVA analysis done |
| | | | Age, years mean (SD) | 38.9 (10.5) | 39.9 (12.2) | | | | | | |
| | | | Women, % | 49% | 47% | | | | Major hypoglycaemia, episodes/patient year | AS: 0.91<br><br>HI: 1.13 | |
| | | | BMI, kg/m2, mean | 25.6 | 25.7 | | | | Major nocturnal hypoglycaemia, % of patients | AS: 4%<br><br>HI: 8% | |
| | | | Diabetes, mean years (SD) | 15.7 (9.7) | 15.8 (9.3) | | | | | | |
| | | | HbA1c, % (SE) | 7.90 (1.13) | 7.95 (1.25) | BOTH GROUPS:<br>Dose adjustment to meet targets for blood glucose control<br><4% patients were treated with twice/day NPH | | | | | |
| | | | Drop-outs:<br>AS: n=44 (7%); HI: n=23 (8%) | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | insulin dose ≥1.4 IU/kg<br>Pregnant, breastfeeding or not practicing contraception | | | | | | | |

**Table 201: HELLER 2004 (xxxxxxx)**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| S. R. Heller, S. Colagiuri, S. Vaaler, B. H. Wolffenbuttel, K. Koelendorf, H. H. Friberg, K. Windfeld, and A. Lindholm. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with | RCT - crossover<br><br>19 centres in Europe and Australia | n=155 type 1 diabetes<br><br>Inclusion criteria:<br>type 1 diabetes<br>18-65 years<br>Duration >2 years<br>BMI ≤35 kg/m2<br>HbA1c ≤9.0%<br>On human insulin (at meals) and NPH once/day or twice/day for 3 | | All patients n=155 | Aspart + NPH<br><br>Aspart = NovoRapidat meals<br>NPH = Insulatard (once or twice/day) | Regular human + NPH<br><br>Regular human = Actrapid at meals<br>NPH = Insulatard (once or twice/day) | 16 weeks treatment (each cross-over period) | HbA1c, final value (SD) | AS: 7.7 (0.8)<br><br>HI: 7.7 (0.9) | Funding: NovoNordisk<br><br>Risk of bias:<br>Randomisation = good (computer generated)<br>Allocation concealment = good (central telephone)<br>No wash-out period |
| | | | Age, years mean (SD) | 35.7 (9.4) | | | | | | |
| | | | Women, % | - | | | | Major hypoglycaemia, episodes | AS: 38<br><br>HI: 51 | |
| | | | BMI, kg/m2 (SD) | 24.0 (2.6) | | | | | | |
| | | | Diabetes, mean | - | | | | Major hypoglycaemia, | AS: | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Type 1 diabetes. Diabet.Med. 21 (7):769-775, 2004.<br><br>REF ID: HELLER 2004 | | months before trial.<br><br>Exclusion criteria:<br>Impaired renal or hepatic function<br>Cardiac problems<br>Uncontrolled hypertension<br>Presence of progressed late-diabetic complications<br>Drug or alcohol abuse<br>Concurrent treatment with systemic corticosteroids | years (SD) | | Aspart injected 0-5 minutes before meals | Aspart injected 0-5 minutes before meals | | events/patient/ year | 0.85<br><br>HI: 1.11 | Double blind<br>Not ITT analysis<br>Powered study (hypoglycaemia)<br>Drop-outs = acceptable (<20%)<br>Not done ANCOVA analysis (ANC best for cross-over studies). |
| | | | HbA1c, % (SD) | 8.6 (1.1) | | | | Major nocturnal Hypoglycaemia, events | AS: 9<br><br>HI: 31 | |
| | | | Drop-outs:<br>n=16 | | | | | | | |
| | | | | | BOTH GROUPS:<br>Doses adjusted according to algorithm target Blood glucose values | | | | | |

**Table 202: HOME 2000 and BOTT 2003 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P. D. Home, A. Lindholm, and | RCT | n=1070 | | Aspart n=707 | HI n=3 | Aspart + NPH | Soluble human | 6 month | HbA1c, final value, % (SE) | ASP: 7.88 (0.03) | Funding: NovoNordisk. |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Riis. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: A randomized controlled trial. Diabet.Med. 17 (11):762-770, 2000.<br><br>REF ID: HOME 2000<br><br>U. Bott, S. Ebrahim, S. Hirschberger, and S. E. Skovlund. Effect of the rapid-acting insulin | 88 centres in Europe | Inclusion criteria:<br>Adults<br>type 1 diabetes (WHO)<br>Diabetes duration ≥2 years<br>Insulin treatment 1 year<br>BMI <35 kg/m2<br>HbA1c ≤11.0%<br><br>Exclusion criteria:<br>Active proliferative retinopathy<br>Nephropathy<br>Recurrent severe hypoglycaemia.<br>Significant CV | | | 58 | Aspart = NovoRapid (immediately before meals)<br>NPH = Insulatard (once or twice/day) | insulin + NPH<br><br>Human = Actrapid (30 minutes before meals)<br>NPH = Insulatard (once or twice/day) | s treatment | | HI: 8.0 (0.04) | Risk of bias:<br>Randomisation = unclear (only says randomised)<br>Allocation concealment = unclear (no details given)<br>Blinding = open label<br>ITT analysis<br>Sample size calculation met (HbA1c)<br>Drop-outs = acceptable (<20%) |
| | | | Age, years mean (SD) | 38 (11) | 38 (12) | | | | Minor hypoglycaemia, no. of patients | ASP: 563/707<br><br>HI: 270/358 | |
| | | | Women, % | 45% | 44% | | | | Minor hypoglycaemia, episodes | ASP: 10113<br><br>HI: 4322 | |
| | | | BMI, kg/m2, mean (SD) | 25.1 (3.1) | 24.9 (3.9) | | | | Minor hypoglycaemia, episodes/patient-year | ASP: 7.64<br><br>HI: 7.542 | |
| | | | Diabetes, mean years (SD) | 15 (10) | 15 (10) | BOTH GROUPS:<br>Dose adjustment to meet targets for blood glucose control | | | Major hypoglycaemia, no. of patients | ASP: 111/707<br><br>HI: 65/358 | |
| | | | HbA1c, % (SD) | 7.96 (1.16) | 7.98 (1.17) | % of patients on once or twice/day NPH at end of trial was not reported in the paper. At baseline 40% were on >1/day. | | | Major hypoglycaemia, episodes | ASP: 314<br><br>HI: 152 | |
| | | | Drop-outs:<br>Aspart: 4%; HI: 6% | | | NOTE: QoL was only measured in a subset of patients. ASP: n=271, | | | Major hypoglycaemia, | ASP: 0.81 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| analogue insulin aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. Diabet.Med. 20 (8):626-634, 2003.<br><br>REF ID: BOTT 2003 | | disease<br>Systemic corticosteroid treatment<br>Requiring >1.4 U/kg/day insulin<br>Pregnant<br>Drug abuse | | HI: n=148.<br><br>DSQoL and DTSQ: HIGHER SCORE = better QoL for both | | | episodes/patient-year | HI: 0.97 | |
| | | | | | | | DTSQ total, points (SE)<br>Max score=36 | ASP: 32 (0.3), n=271<br>HI: 29.7 (0.4), n=148 | |
| | | | | | | | DSQoL total, change from baseline, between group differences | ASP: SS greater improvement compared to HI (p<0.0001) | |
| | | | | | | | | | |
| | | | | | | | | | |

**Table 203: HOME 2006 (TRIAL EXTENSION OF HOME 2000) xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PD. Home, P. Hallgren, | RCT extension (OF Home | n=753<br><br>Inclusion | | Asp n=567 | HI n=186 | Aspart + NPH | Soluble human insulin + | 30 months treatment extension | HbA1c, final value, % (SE) | ASP: 8.09 (0.04) | Funding: NovoNordisk. |
| | | | Age, | 38 (11) | 40 (12) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| KH. Usadel, T. Sane, J. Faber, V. Grill, and HH. Friberg. Pre-meal insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. Diabetes Res.Clin.Pract. 71 (2):131-139, 2006.<br><br>REF ID: HOME 2006 | 2000 study)<br><br>Completers from Germany, Switzerland, Austria and the UK | criteria:<br>Adults<br>type 1 diabetes (WHO)<br>Diabetes duration ≥2 years<br>Insulin treatment 1 year<br>BMI <35 kg/m2<br>HbA1c ≤11.0%<br><br>Exclusion criteria:<br>Active proliferative retinopathy<br>Nephropathy<br>Recurrent severe hypoglycaemia.<br>Significant CV disease<br>Systemic corticosteroid | year mean (SD) | | | Aspart = NovoRapid (immediately before meals)<br>NPH = Insulatard (once or twice/day) | NPH<br><br>Human = Actrapid (30 minutes before meals)<br>NPH = Insulatard (once or twice/day) | (ie. 36 months total treatment); however data used was for 30 months total treatment because Aspart became commercially available in the respective countries at various times between 30 and 36 months. | | HI: 8.25 (0.07) | Risk of bias:<br>Randomisation = unclear (no details)<br>Allocation concealment = unclear (no details given)<br>Blinding = open label<br>ITT analysis<br>Sample size calculation met (HbA1c)<br>Drop-outs = unacceptable (fine for longer trial duration, but differential between two arms is >10%; due to ineffective treatment in HI arm). |
| | | | Women, % | 73% | 69% | | | | Minor hypoglycaemia, no. of patients | ASP: 488/567<br><br>HI: 153/186 | |
| | | | BMI, kg/m2, mean (SD) | 25.1 (3.1) | 24.8 (2.9) | | | | Minor hypoglycaemia, episodes | ASP: 25253<br><br>HI: 6543 | |
| | | | Diabetes, mean years (SD) | 14.8 (10.2) | 15.6 (11.0) | BOTH GROUPS:<br>Dose adjustment to meet targets for blood glucose control<br>% of patients on once or twice/day NPH at end of trial was not reported in the paper. At baseline 40% were on >1/day. | | | Minor hypoglycaemia, episodes/month | ASP: 2.46<br><br>HI: 2.03 | |
| | | | HbA1c, % (SD) | Values from end of the previous trial (6 months) | | | | | Major hypoglycaemia, no. of patients | ASP: 162/567<br><br>HI: 58/186 | |
| | | | Drop-outs:<br>Aspart: 17%; HI: 32%; main reason for difference was due to ineffective therapy in the HI group. | | | | | | Major hypoglycaemia, episodes | ASP: 820<br><br>HI: 261 | |
| | | | | | | | | | Major hypoglycaemia., episodes/mon | ASP: 0.08<br><br>HI: 0.08 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | treatment<br>Requiring >1.4 U/kg/day insulin<br>Pregnant<br>Drug abuse | | | | | th | | |

### G.4.1.5 Glulisine (+glargine) versus human insulin (+glargine)

**Table 204: GARG 2005 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S. K. Garg, J. Rosenstock, and K. Ways. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine | RCT<br><br>Multicentres in USA, Canada and Australia | n=860<br><br>Inclusion criteria:<br>≥18 years<br>type 1 diabetes<br>Required continuous insulin | | GLU (pre) n=286 | GLU (post) n=296 | HI n= 278 | Glulisine (pre-meal) + GLARGINE<br><br>Glulis = (0-15 minutes before meals)<br>GLARGINE = Lantus (once/day - | Human Insulin + GLARGINE<br><br>Regular human insulin (30-45 minutes before meals) | 12 weeks treatment | HbA1c, change from baseline (98.8% CI) | GPre: -0.26 (-0.02 to -0.29)<br><br>GPost: -0.11 (-0.11 to -0.16) | Funding: Sanofi-Aventis.<br><br>Risk of bias:<br>Randomisation = unclear (only says random in 1:1:1 ratio)<br>Allocation concealment = |
| | | | Age, years mean (SD) | 40.8 (11.9) | 39.8 (11.8) | 40.2 (11.4) | | | | | | |
| | | | Women | 44% | 47% | 50% | | | | | | |
| | | | BMI, | 27.0 | 27.3 | 27.0 | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| versus regular human insulin in combination with Basal insulin glargine. Endocr Pract 11 (1):11-17, 2005.<br><br>REF ID: GARG 2005 | | treatment from diagnosis<br>BMI ≤35 kg/m2<br>HbA1c 6.0-11%<br><br>Exclusion criteria:<br>Active proliferative retinopathy<br>History of seizure disorders<br>Hypersensitivity to insulin or analogues<br>Impaired renal or hepatic function<br>Pancreatectomy or islet | kg/m2, mean | | | | bedtime) | GLARGINE = Lantus (once/day - bedtime) | | | HI: -0.13 (-0.26 to -0.01) | unclear (no details given)<br>Blinding = open label<br>ITT analysis<br>Sample size calculation<br>Drop-outs = acceptable (<20%) |
| | | | Diabetes, mean years (SD) | 20.0 (11.4) | 20.2 (11.5) | 19.4 (11.2) | Glulisine (post-meal) + GLARGINE<br><br>Glulis = (20 minutes after starting or immediately after meals; whichever came first)<br>GLARGINE = Lantus (once/day - bedtime) | | | Body weight, kg change | GPre: +0.3<br>GPost: -0.3<br>HI: +0.3 | |
| | | | HbA1c, % (SE) | 7.7 (0.056) | 7.7 (0.055) | 7.6 (0.057) | | | | Symptomatic hypoglycaemia, no. of patients | GPre: 234<br>GPost: 248<br>HI: 228 | |
| | | | Drop-outs:<br>Overall: n=69 | | | | | | | Symptomatic hypoglycaemia, rate/patient/month (SD) | GPre: 3.46 (4.11)<br>GPost: 3.71 (4.97)<br>HI: 3.49 (4.16) | |
| | | | | | | | | | | Severe hypoglycaemia, no. of patients | GPre: 24<br>GPost: 25<br>HI: 28 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures – 6 months | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | cell transplant<br>History of alcohol or drug abuse<br>Any other clinically relevant physical or psychological medical condition | | | | | Severe hypoglycaemia, rate/patient/month (SD) | GPre:0.05 (0.24)<br>GPost: 0.05 (0.23)<br>HI: 0.13 (0.96) | |
| | | | | BOTH GROUPS:<br>Dose adjustment to meet targets for blood glucose | | | Nocturnal hypoglycaemia., no. of patients | GPre: 161<br>GPost: 156<br>HI: 151 | |
| | | | | | | | Nocturnal hypoglycaemia., rate/patient/month (SD) | GPre: 0.64 (0.99)<br>GPost: 0.71 (1.19)<br>HI: 0.71 (1.086) | |

## G.4.2 Long-acting insulin

### G.4.2.1 Glargine versus NPH

**Table 205: Rosenstock 2000 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: ROSENSTOCK 2000 | RCT<br><br>USA study | n=256<br><br>Inclusion criteria:<br>type 1 diabetes<br>18-70 years old<br>BMI 18-28<br>HbA1c <10%<br>Post-prandial serum C-peptide <0.2 pmol/ml<br>Been on basal bolus MDI for at least 2 months<br><br>Exclusion criteria:<br>None given | | Glarg 30 n=82 | Glarg 80 n=86 | NPH n=88 | Glargine 30 (ZnCl 30 micrograms/ml)<br><br>ITT: n=81<br>ACA: n=81<br><br>Contained the recombinant human insulin analogue equimolar to 100 U/ml human insulin<br>SD abdominal injection once/day at bedtime<br>Initial dose was to be equal to the total daily dose of NPH insulin the patient was using at the time | NPH<br><br>ITT: n=88<br>ACA: n=87<br><br>SD abdominal injection once/day at bedtime OR twice/day (before breakfast and at bedtime) – based on the patient's pre-study regimen.<br>NPH contained 100 U/ml recombinant human insulin. | 4 weeks treatment | Hypoglycaemic episodes | Glarg30 : 97.6%<br><br>Glarg80 : 100%<br><br>NPH: 93.2% | Funding: None mentioned but authors have grants from Pharma<br><br>Risk of bias:<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not mentioned<br>Blinding = n/a for NPH vs. Glarg but double for glargine vs. glargine. NPH was not possible to |
| | | | Age, years (SD) | 37.5 (11.7) | 37 (11.5) | 37.9 (12.5) | | | | | | |
| | | | Women, % | 49 | 49 | 47 | | | | HbA1c, change from baseline, % (SD) | Glarg30 : -0.4 (0.48)<br><br>Glarg80 : -0.4 (0.49)<br><br>NPH: -0.4 (0.48) | |
| | | | Diabetes, mean years (SD) | 16.7 (11.3) | 15.8 (10) | 16.3 (10.8) | | | | | | |
| | | | HbA1c, % (SD) | 7.8 (1.1) | 7.9 (1.2) | 8.0 (1.2) | | | | | | |
| | | | NS differences between groups for any of the baseline characteristics<br><br>Drop-outs (6 months): | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | n=2 (n=1 in each group) | of randomisation to treatment.<br>---<br>Glargine 80 (ZnCl 80 micrograms/ml)<br>ITT: n=86<br>ACA: n=85<br>As for glargine 30 | | | | | blind as drug is cloudy.<br>ITT analysis (patients with pre-treatment and during treatment value)<br>Sample size calculation based on FPG<br>Drop-outs = acceptable (<20%) |
| | | | | BOTH GROUPS: Injections of regular insulin were administered before meals according to patient's usual practice.<br>Basal insulin doses were adjusted during titration phase to maintain FBG between 4-7 mmol/litre (72-126 mg/dl)<br>Dose was increased (or reduced) if higher (or lower) FPG values were obtained over a 2-4 day | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | period in the absence (or presence) of nocturnal hypoglycaemia. Dose of regular insulin was adjusted every 2–4 days if needed to achieve target ranges (basis of 1–4 U per meal). Premeal and bedtime target blood glucose were 4–7 mmol/litre (72–126 mg/dl) and 6–8 mmol/litre (100–144 mg/dl). | | | | | |

**Table 206: PIEBER 2000 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: PIEBER 2000 | RCT<br><br>Austria /France study | n=333<br><br>(n=110 Glarg 30, n=113 Glarg 80 and n=110 NPH)<br><br>Inclusion criteria:<br>type 1 diabetes | | Glarg 30 n=110 | Glarg 80 n=113 | NPH n=110 | Glargine (30 micrograms of zinc) Once daily (bedtime)<br><br>ITT: n=110 | NPH Once daily (bedtime) or twice daily (morning and bedtime)<br><br>ITT: n=110 | 4 weeks treatment | Severe hypoglycaemia., N<br><br>At 4 weeks treatment | G30: 7/110<br><br>G80: 5/113<br><br>NPH: 5/110 | Funding: None mentioned but authors have grants from Pharma<br><br>Risk of bias: Randomisati |
| | | | Age, years | 35.6 | 37.5 | 35.7 | Glargine (80 micrograms of | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Been receiving insulin therapy for 1 year<br>A basal-bolus regimen of NPH insulin once daily at bedtime (n = 177) or twice daily in the morning and at bedtime (n = 156) plus regular human insulin before meals was used for at least 2 months<br><br>Exclusion criteria:<br>presence of known proliferative diabetic retinopathy<br>impaired hepatic or renal function<br>history of hypoglycaemia | (SD) | | | | zinc)<br>Once daily (bedtime)<br><br>ITT: n=113 | (47.3% on twice/day – thus counted as once/day as most started on once/day) | | | | on = unclear (as details not given)<br>Allocation concealment = not mentioned<br>Blinding = not possible for NPH vs. glargine as NPH cloudy. Double blind for glargine vs. glargine<br>Unclear if ITT analysis (seems like some missing data but not mentioned)<br>Powering not mentioned<br>Drop-outs = acceptable (<20%) |
| | | | Women, % | 44 | 34 | 38 | | | | HbA1c, % (SE) | G30: 7.85 ± 0.10 (n=110)<br><br>G80: 7.80 ± 0.10 (n=112)<br><br>NPH: 7.79 ± 0.09 (n=109) | |
| | | | Diabetes, median years (range) | 11.0 (1.0–36.0) | 8.0 (1.0–48.0) | 11.0 (2.0–48.0) | IN ALL 3 GROUPS:<br>Bedtime insulin was injected into the abdomen between 2100 and 2300, and injection time was kept as stable as possible throughout the study. The first 3 weeks of the treatment phase were used to adjust the daily basal insulin dose according a titration scheme (FBG from 4 to 7 mmol/litre without nocturnal hypoglycaemia); basal insulin then was maintained during the final week of treatment. The dose of regular insulin was adjusted according the patients' habits, the premeal blood glucose concentration, and the | | | | | |
| | | | HbA1c, % (SE) | 8.09 ± 0.11 | 7.96 ± 0.11 | 7.85 ± 0.11 | | | | HbA1c, % (SE)<br><br>Change from baseline | G30: 0.25 ± 0.05 (n=110)<br><br>G80: 0.15 ± 0.05 (n=112)<br><br>NPH: 0.03 ± 0.05 (n=109) | |
| | | | Drop-outs (6 months):<br>None mentioned | | | | | | | | | |
| | | | | | | | | | | AEs, N during 4 weeks treatment (injection site | G30: 3<br>G80: 10<br>NPH: 3 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | unawareness | | carbohydrate content of the meal.<br><br>Concomitant medication:<br>In all groups patients received regular human insulin before meals | | | reactions) | | |

**Table 207: RATNER 2000 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: RATNER 2000 | RCT<br><br>Multicentre, USA. | n=534<br><br>Inclusion criteria:<br>type 1 diabetes<br>18–80 years old<br>Postprandial C-peptide levels of ≤0.5 nmol/litre<br>Duration at least 1 year | | Glarg n=264 | NPH n=270 | Glargine (once/day before bedtime)<br><br>ITT: n=264 | NPH (once or twice daily<br><br>ITT: n=270 | 28 weeks treatment (6 months) | Severe hypo, at least 1 episode, % | Glarg: 1.9%<br>NPH: 5.6%<br>p=0.0117 | Funding: Grant from Hoechst Marion Roussel<br><br>Risk of bias:<br>Randomisation = unclear (just says randomised)<br>Allocation concealment |
| | | | Age, years (SD) | 38.2 (12.2) | 38.9 (11.9) | | | | HbA1c/GHb, % (SEM) change from baseline | Glarg: -0.16 (0.05)/n=256<br>NPH: -0.21 (0.05)/n=262 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GHb ≤12.0%.<br><br>Exclusion criteria:<br>treatment with antidiabetic drugs other than insulin within 1month of study entry<br>pregnancy<br>impaired hepatic or renal function | Women, % | 47 | 52 | In both groups: dose titration of both basal insulins was based on capillary fasting blood glucose (FBG) levels. Goal was premeal blood glucose conc. 4.4–6.7 mmol/litre (80–120 mg/dl). Dose increases were made if morning capillary FBG levels consistently >6.7 mmol/litre with no symptomatic nocturnal hypoglycaemia. Dose decreases were made if morning capillary FBG levels were <4.4 mmol/litre or if symptomatic nocturnal hypoglycaemia. was evident | | | Injection site reactions, % | Glarg: 15.2%<br>NPH: 10.4% | = not mentioned<br>Blinding = not possible as NPH cloudy)<br>ITT analysis<br>Powered study (GHb)<br>Drop-outs = acceptable (<20%) |
| | | | Diabetes duration, years (SD) | 17.9 (11.7) | 16.9 (10) | | | | | | |
| | | | HbA1c/GHb, % (SD) | 7.6 (1.19) | 7.7 (1.2) | | | | Injection site pain, N | Glarg: 10/264<br>NPH: 3/270<br>All pain was rated as mild | |
| | | | There was NS difference between groups for all of the baseline characteristics<br><br>Drop-outs:<br>Discontinued drug - Glarg: 11.7%, NPH: 8.1% | | | Concomitant medication: Both gps used regular insulin approx. 30 min before meals to meet prandial insulin requirements. | | | Withdrawals due to AEs, % | Glarg: 8/264<br>NPH: 3/270 | |

**Table 208: RASKIN 2000 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: RASKIN 2000 | RCT<br><br>60 centres, USA. | n=619<br><br>Inclusion criteria:<br>type 1 diabetes<br>18–80 years old<br>Been receiving NPH at least 1 year and premeal insulin lispro at least 3 months<br>Serum C-peptide levels of ≤0.5 nmol/litre in presence of glucose ≥99.0 mg/dl (5.5 mmol/litre)<br>GHb ≤12.0%.<br><br>Exclusion criteria:<br>Treatment with antidiabetic drugs other than insulin within 1mth of study<br>pregnancy<br>impaired hepatic or renal function | | Glarg n=310 | NPH n=309 | Glargine (once/day before bedtime)<br><br>ITT: n=310 | NPH (once or twice daily<br><br>ITT: n=309 | 16 weeks treatment (4 months) | Severe hypo, n | Glarg: 20/310<br>NPH: 60/309 | Funding: Grant from Hoechst Marion Roussel<br><br>Risk of bias:<br>Randomisation = unclear, telephone<br>Allocation concealment = unclear, telephone<br>Blinding = not possible as NPH cloudy)<br>ITT analysis = yes. Not mentioned but all numbers included in calculation<br>Powering not mentioned<br>Drop-outs = acceptable (<20%) |
| | | | HbA1c/GHb, % (SD) | 7.7 (1.2) | 7.7 (1.1) | | | | HbA1c/GHb, % (SD) final value | Glarg: 7.5 (1.19)<br>NPH: 7.60 (1.14) | |
| | | | Age, years (SD) | 38.9 (12.2) | 39.5 (12.2) | In both groups: Starting dosages of glargine and NPH were based on prior NPH insulin dosage on a unit-for-unit basis but were left to the discretion of the investigator. Investigators were informed of results of phase II comparative studies, which suggested a 10% decrease in the insulin glargine dose compared with total dosage in patients receiving NPH insulin twice a day. Thereafter, glargine and NPH doses were to be individually titrated to obtain a target fasting blood glucose <120.6 mg/dl (6.7 mmol/litre). | | | AEs – Cancer (but not study drug related) | Glarg: 1/310<br>NPH: 0/309 | |
| | | | Diabetes duration, years (SD) | 18.7 (11.5) | 18.4 (11.8) | | | | | | |
| | | | Women, % | 49.4 | 47.6 | | | | Injection site pain, % | Glarg: 6.1%<br>NPH: 0.3% | |
| | | | BMI, kg/m2 | 25.5 (3.4) | 25.7 (3.9) | | | | | | |
| | | | There was NS difference between groups for all of the baseline characteristics except once daily insulin use before study was SS higher in glargine group<br><br>Drop-outs: | | | | | | Body weight, change from baseline, kg | Glarg: +0.12<br>NPH: +0.54; p=0.034 | |
| | | | | | | Concomitant medication: Both gps continued to | | | Withdrawals due to | Glarg: 0/310 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Glarg: n=15 (4.8%)<br>NPH: n=16 (5.2%) | administer individually titrated insulin lispro before meals. | | | AEs, N | NPH: 2/309 | |

**Table 209: HOME 2005 xxxxxx**

| Reference | Study type | Number of patients | Patient | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: HOME 2005 | RCT<br><br>63 centres, across Europe. | n=602 randomised; n=585 treated.<br><br>Inclusion criteria:<br>type 1 diabetes<br>17-77 years old<br>Treated with insulin for at least 1 year<br>Serum post-prandial C-peptide levels of <0.5 nmol/litre in presence of blood glucose | | Glarg n=292 | NPH n=293 | Glargine (once/day before bedtime)<br><br>ITT: 301<br>ACA: n=292<br><br>Dose determined on 1st treatment day by the total basal dose the day before. Protocol of dose titration by ≥1% according to SMBG (FBG) | NPH (once or twice daily<br><br>ITT: 301<br>ACA: n=293<br><br>Once or twice daily injection according to person's previous treatment regimen. Starting evening doses were same as those on the | 28 weeks treatment (6 months) | HbA1c, % (SD) change from baseline | Glarg: 0.21 (0.05)<br>NPH: 0.10 (0.05) | Funding: Aventis Pharma<br><br>Risk of bias:<br>Randomisation = unclear; just says randomised.<br>Allocation concealment = telephone central randomisation, independent agency<br>Blinding = not possible as NPH cloudy) |
| | | | Age, years (SD) | 39 (12) | 39 (12) | | | | AEs – Severe hypoglycaemia: at least 1 episode, N (%) | Glarg: 31 (10.6)<br>NPH: 44 (15) | |
| | | | Diabetes duration, years (SD) | 16 (12) | 15 (9) | | | | | | |
| | | | Women, % | 45 | 43 | | | | Injection site reaction, n (%) | Glarg: 3 (1)<br>NPH: 6 (2) | |
| | | | Weight, kg (SD) | 73.2 (11.8) | 74.8 (12.5) | | | | | | |

| Reference | Study type | Number of patients | Patient | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ≥100 mg/dl (5.5 mmol/litre)<br><br>Exclusion criteria:<br>None given | HbA1c, % (SD) | 7.9 (1.2) | 8.0 (1.2) | levels. Nominal target of 80-120 mg/dL averaged over at least 2-4 days and absence of nocturnal hypoglycaemia. All adjustments at investigator and diabetic's discretion. | previous day, with subsequent adjustment as described for insulin glargine group. Morning insulin was adjusted as required. | | | | Not mention ITT analysis.<br>Powering not mentioned<br>Drop-outs = acceptable (<20%) |
| | | | The groups were similar for all of the baseline characteristics.<br><br>Drop-outs:<br>Glarg: n=16 (5%)<br>NPH: n=21 (7%)<br>Main reason was they did not wish to continue. | | | | | | Withdrawals due to AEs, n/N | Glarg: 2/292<br>NPH: 2/293 | |
| | | | | | | Concomitant medication: Both gps used unmodified human insulin before meals, according to their individual habit. | | | | | |

**Table 210: BOLLI 2009 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: BOLLI 2009 | RCT<br><br>21 centres, Italy | n=175<br><br>Inclusion criteria:<br>type 1 diabetes<br>18–60 years old<br>>3 years duration<br>Been receiving intensive insulin treatment: NPH twice or more daily, and lispro or regular human insulin at mealtimes.<br>Fasting plasma C-peptide levels of <0.1 nmol/litre<br>HbA1c 7-9%.<br>BMI 18-26 kg/m2.<br><br>Exclusion criteria:<br>Micro or macro-angiographic complications | | Glarg n=85 | NPH n=90 | Glargine (once/day before bedtime) using pen<br><br>ITT: n=85<br>ACA: n=78 | NPH (twice or more daily) using pen<br><br>ITT: n=90<br>ACA: n=74 | 24 weeks treatment (5 months) | HbA1c, final value, % (SD) | Glarg: 7.26 (0.74)<br>NPH: 7.26 (0.98) | Funding: Sanofi-Aventis<br><br>Risk of bias:<br>Randomisation = unclear. Just says randomised.<br>Allocation concealment = not mentioned.<br>Blinding = not possible as NPH cloudy)<br>Not ITT analysis = not true ITT (had to have at least one baseline visit and one dose of study drug).<br>Under powered (for FBG) |
| | | | Age, years (SD) | 35.5 (10.6) | 37.0 (9.4) | In both groups: Dinnertime glargine and bedtime NPH were titrated to achieve FBG target value of 90-120 mg/dL, but avoiding nocturnal hypoglycaemia. Lunchtime dose of NPH was adjusted to a target pre-dinner BG 90-120 mg/dl. | | | Serious (not severe) hypoglycaemia. Episodes/patient/month, mean (SD) final value | Glarg: 1.01 (1.07)<br>NPH: 0.88 (1.04) | |
| | | | Diabetes duration, years (SD) | 12.9 (8.3) | 14.8 (9.6) | | | | | | |
| | | | Women, % | 44 | 46 | | | | QoL: WED, median (IQR) : Impact, Satisfaction, general worries, Diabetes-related worries | NS difference between groups for any of the scores except diabetes worries was SS better in the glargine group. | |
| | | | Weight, kg (SD) | 67.5 (9.4) | 68.4 (10.4) | Concomitant medication: Both groups took insulin lispro. Dose of lispro was adjusted to a target post-prandial BG of <140 mg/dL. Additional doses of lispro (1 or 2 U) were also used to correct unexpected hyperglycaemia. | | | | | |
| | | | HbA1c, % (SD) | 7.8 (0.7) | 7.8 (0.6) | | | | | | |
| | | | There was NS difference between groups for any of the baseline characteristics<br><br>Drop-outs:<br>Glarg: n=7 (8%) | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | NPH: n=12 (13%) plus additional n=4 withdrew consent and did not participate (thus n=16 did not complete = 18%)<br><br>Outcomes:<br>WED questionnaire – quality of life Well-Being Enquiry for Diabetics. 50 item questionnaire on symptoms, discomfort, serenity and impact. Low score = better | | | | Withdrawals due to AEs, N | Glarg: 0/85<br>NPH: 0/90 | Drop-outs = acceptable (<20%) |

**Table 211: FULCHER 2006 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: FULCHER 2006 | RCT<br><br>9 centres, Australia | n=125<br><br>Inclusion criteria:<br>type 1 diabetes<br>18–80 years old<br>At least 1 year of insulin treatment<br>Inadequate glycaemic control (HbA1c ≥8%). | | Glarg n=65 | NPH n=63 | Glargine (once/day before bedtime) using pen<br><br>ITT: n=65<br>ACA: ? | NPH (once/day before bedtime) using pen<br><br>ITT: n=63<br>ACA: ? | 30 weeks treatment (7 months) | HbA1c, change from baseline, % | Glarg: -0.89<br>NPH: -0.67 | Funding: Aventis<br><br>Risk of bias: Randomisation = unclear. Just says randomised. Allocation concealment |
| | | | | | | | | | HbA1c, final value, % | Glarg: 8.3<br>NPH: 9.1 | |
| | | | Age, years (SD) | 41.6 (12.9) | 39.3 (13.9) | In both groups: targets were FBG 5.5 mmol/litre, pre-prandial BG 3.9-6.7 | | | Severe hypoglycaemia. | Glarg: 0.87<br>NPH: | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Exclusion criteria:<br>Nightshift workers<br>Impaired hepatic function<br>Sensitivity to study drugs or related drugs<br>Clinically relevant physiological or psychological medical conditions.<br>Use of systemic corticosteroids and BG lowering drugs was not permitted. | | | | mmol/litre, 2h post-prandial BG <8 mmol/litre and 3am BG >3.6 mmol/litre. Basal insulin dose adjustments were made twice/week during titration phase, and fortnightly in the treatment follow-up phase, based on FBG measurements.<br>Concomitant medication: Both groups took preprandial insulin lispro three times/day. | | | Events/100 patient days | 0.99 | = not mentioned.<br>Blinding = Single. Double blinding not possible as NPH cloudy.<br>Not ITT analysis = not true ITT (had to have at least one dose of study medication). But unclear if ITT as some outcomes it is out of the total.<br>Powering not mentioned<br>Drop-outs = not acceptable (>20% in NPH and large differential between groups) |
| | | | Diabetes duration, years (SD) | 17.9 (10.5) | 17.1 (9.7) | | | | | | |
| | | | Women, % | 61 | 60 | | | | At least 1 symptomatic hypoglycaemia episode, n/N | Glarg: 65/65<br>NPH: 59/63 | |
| | | | BMI, kg/m2 (SD) | 27.0 (3.6) | 26.0 (3.9) | | | | | | |
| | | | HbA1c, % (SD) | 9.2 (1.1) | 9.7 (1.3) | | | | Injection site reactions, n/N | Glarg: 5<br>NPH: 7/ | |
| | | | There was NS difference between groups for any of the baseline characteristics except HbA1c was SS higher in the NPH group.<br><br>Drop-outs:<br>Glarg: n=4 (6.4%)<br>NPH: n=14 (22%)<br>None were due to AEs | | | | | | Body weight, change from baseline, kg | Glarg: +1.97<br>NPH: +2.34 | |
| | | | | | | | | | Withdrawals due to AEs, N | Glarg: 0/65<br>NPH: 0/63 | |

**Table 212: CHATTERJEE 2007 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| CHATTERJEE 2007 | RCT<br><br>UK study | n=58 randomised, n=60 recruited.<br>Initially n=25 glargine, and n=33 NPH then crossed over.<br><br>Inclusion criteria:<br>type 1 diabetes<br>18–75 years old<br>At least 6 months diabetes<br>Previously using twice/day or MDI inulin.<br>BMI <45<br>Baseline HbA1c 6-11%<br>Ability and willingness to perform SMBG.<br><br>Exclusion criteria:<br>None given. | | n=60 | Glargine (once/day, bedtime) using pen | NPH (twice/day, 30 minutes before breakfast and evening meal) using pen | 16 weeks treatment (4 months) | HbA1c, final value, % | Glarg: 8.07<br>NPH: 8.26<br>MD: -0.19, 95% CI -0.36 to -0.01. p=0.04 | Funding: Novo Nordisk and Aventis<br><br>Risk of bias:<br>Randomisation = unclear. Just says randomised.<br>Allocation concealment = poor - consecutively numbered sealed envelopes.<br>Open. Double blinding not possible as NPH cloudy.<br>4-week run-in period but no mention of washout between |
| | | | Age, years (SD) | 42.9 (12.5) | | | | | | |
| | | | Women, % | 42 | In both groups: when switching from glargine to NPH dose was increased by 20% to compensate for switching from a once/day to twice/day regimen. When switching from NPF to glargine, dose was decreased by 20% to compensate for switching from a twice/day to once/day regimen. Dose was adjusted according to local algorithm. Targets were pre-prandial 4-6.7 mmol/litre, and 2h post-prandial and bedtime <8 mmol/litre. | | | Severe hypoglycaemia. N | Glarg: 1/58<br>NPH: 1/58 | |
| | | | Diabetes duration, years (SD) | 18.2 (11.8) | | | | DTSQ | NS difference between groups for perception of hyper or hypo - glycaemia. Greater satisfaction with glargine (4 points difference) vs. NPH. | |
| | | | Weight, kg (SD) | 81.0 (14.0) | | | | | | |
| | | | HbA1c, % (SD) | 8.5 (1.2) | Concomitant medication: Both groups took insulin aspart as the rapid-acting | | | | | |
| | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Drop-outs:<br>Glarg: n=4 (16%)<br>NPH: n=2 (6%)<br>None were due to AEs | insulin. | | | ADDQoL | NS difference between groups. P=0.08 | crossing over<br>Not ITT analysis.<br>Powered study (HbA1c)<br>Drop-outs = acceptable (<20%) |
| | | | | | | | Body weight, kg | Glarg: 81.86<br>NPH: 81.92.<br><br>MD -0.24, 95% CI -0.87 to 0.39. p=0.45 | |

**Table 213: PORCELATTI 2004 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: PORCELLATTI 2004 | RCT<br><br>1 centre in Italy | n=121<br><br>Inclusion criteria: type 1 diabetes<br>Fasting plasma C-peptide <0.15nmol/litre<br>On 4 times daily NPH insulin plus mealtime insulin lispro for at least 2 years | | Glarg n=61 | NPH n=60 | Glargine (once/day: dinner time)<br><br>Titrated to blood glucose 6.4-7.2mmol/litre (fasting, before meals and at bedtime) and 8.0-9.2 | Continue NPH (4/day)<br><br>Titrated to same as Glargine group | 1 year | HbA1c, final % | Glargine: 6.7 (0.1) at 4 months vs. NPH: 7.1 (0.1) at 12 months | Funding: National Ministry of Scientific Research and University of Perugia (no pharmaceutical sponsorship)<br><br>Risk of bias: Randomisation |
| | | | Age, years (SD) | 36 (1.0) | 34 (1.0) | | | | | | |
| | | | Women, % | 44.3 | 45.0 | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | after meals. | | | | | = adequate (computer generated)<br>Allocation concealment = adequate (independent person; locked unreadable computer file)<br>Blinding = no (open study)<br>ITT analysis = yes<br>Sample size: powered for HbA1c<br>Drop-outs = acceptable (none) |
| | | Exclusion criteria:<br>Detectable microangiopathic complication<br>Autonomic neuropathy | Diabetes duration, years (SD) | 13 (0.3) | 15 (0.3) | Concomitant medication: Both groups took insulin lispro as the rapid-acting insulin. | | | Severe hypoglycaemia | None | |
| | | | Weight, BMI (SD) | 22.9 (0.14) | 23.2 (0.15) | | | | Mild hypoglycaemia, episodes/patient-month | Glargine: 7.2 (0.5)<br>NPH: 13.2 (0.6) | |
| | | | HbA1c, % (SD) | 7.1 (0.1) | 7.1 (0.2) | | | | Body weight | No change with either treatment | |

### G.4.2.2 Degludec versus glargine

**Table 214 MATHIEU 2013**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C Mathieu, | RCT | n=493 randomised | | Degludec | Glargine | Degludec | Glargine | 26 weeks | | Deg | Glarg | Funding: NovoNordisk |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P Hollander, B Miranda-Palma, J Cooper, E Franek, D Russell-Jones, J Larsen, SC Tamer, SC. Bain, and Flex T. BEGIN. Efficacy and safety of insulin degludec in a flexible dosing regimen vs. insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target | Multinational | (3 arm trial but only using the 2 relevant arms)<br><br>Inclusion criteria:<br>type 1 diabetes<br>Adults ≥18 years<br>On basal-bolus therapy<br>HbA1c ≤ 10%<br>BMI ≤35kg/m2<br>Basal insulin allowed at screening: Glargine, detemir, or NPH (as 1 or 2 daily injections)<br>Bolus insulin allowed at screening: 3 or more | Mean (SD) age (year)<br><br>Female (%)<br><br>Duration of diabetes (year)<br><br>HbA1c (%) | n=165<br><br>44.5 (13.1)<br><br>43%<br><br>20.0 (12.5)<br><br>7.7 (0.9) | n=164<br><br>44.1 (12.6)<br><br>48%<br><br>18.2 (11.9)<br><br>7.7 (0.9) | Once/day, titrated to fasting blood glucose targets.<br><br>Degludec – Forced-flex regimen Given Mon, Wed, Fri mornings, and Tues, Thurs, Sat and Sun evenings.<br><br>ALL GROUPS: mealtime insulin bolus Aspart. | Once/day, titrated to fasting blood glucose targets. | + extension (extension data not using here as mixed randomised groups) | HbA1c, % (SD) change from baseline | -0.41 (0.71) | -0.58 (0.72) | Risk of bias:<br>Randomisation = unclear (no details given)<br>Allocation concealment = adequate (central activated voice response)<br>Blinding = no (open study)<br>ITT analysis = yes<br>Powered study for HbA1c.<br>Drop-outs = acceptable (<20% in each arm, and <10% differential between groups) |
| | | | | | | | | | Weight, kg (SD) change from baseline | 0.8 (2.5) | 1.6 (3.7) | |
| | | | | | | | | | Severe hypo, no. of patients | 21/165 | 16/161 | |
| | | | | | | | | | Hypo, no. of patients | 164/165 | 156/161 | |
| | | | | | | | | | Nocturnal hypo, no. of patients. | 121/165 | 117/161 | |
| | | | | | | | | | AEs, events per 100-pt years of exposure | 550 | 527 | |
| | | | | | | | | | SAEs, % of patients | 4.2% (n= approx. 7/165) | 5.0% (n= approx. 8/161) | |
| | | | | | | | | | Injection | 3/16 | 4/161 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| trial with a 26-week extension. J.Clin.Endocrinol.Metab. 98 (3):1154-1162, 2013.<br><br>REF ID: MATTHIEU 2013 | | daily injections of (aspart, lispro, glulisine, or human)<br><br>Exclusion criteria:<br>Any other antidiabetes glucose lowering drug within past 3 months<br>Initiation or change in any systemic treatment which could interfere with glucose metabolism<br>CVD within past 6 months<br>Uncontrolled severe Hypertension<br>Impaired liver or renal | | | | | | | site reactions, no. of patients | 5 | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | function<br>Recurrent SH or hypo unawareness<br>Proliferative retinopathy or maculopathy requiring treatment<br>Pregnancy, breastfeeding or planning pregnant<br>Cancer and history of cancer<br>Clinically significant disease or disorder which could interfere with trial results. | | | | | | | | | | |

**Table 215: BIRKELAND 2011 and HOME 2012 (same study) xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| K. I Birkeland, P. D. Home, U Wendisch, et al. Insulin degludec in type 1 diabetes. Diabetes Care 34:661-665, 2011.<br><br>REF ID: BIRKELAND 2011<br><br>and<br><br>Home PD, Meneghini L, Wendisch U, et al. Improved health status with insulin degludec | RCT<br><br>28 centre in 5 countries: Australia, Germany, Norway, Sweden and the US | n=178<br><br>(n=59 IDeg(A) group; n=60 IDeg (B) group; n=59 IGlar group)<br><br>Inclusion criteria:<br>Age 18-75 years<br>type 1 diabetes for at least 12 months<br>Treated continuously with insulin<br>HbA1c 7.0 to 11.0%<br><br>Exclusion criteria:<br>Clinically | | IDeg(A) n=59 | IDeg (B) n=60 | IGlar n=59 | IDeg(A) (600µmol/litre; 1 unit = 6nmol; once daily in the evening)<br>ITT: n=59<br><br>IDeg(B) (900µmol/litre; 1 unit = 9nmol; once daily in the evening)<br>ITT: n=60<br><br>Basal insulin doses adjusted once a week aiming for fasting plasma glucose 4-6mmol/litre<br><br>Concomitant medication: | IGlar (100 units/mL once daily in the evening)<br><br>ITT: n=59<br><br>Basal insulin doses adjusted once a week aiming for fasting plasma glucose 4-6mmol/litre | 16 weeks treatment | Decrease in HbA1c, mean (SD) % | 0.57 (0.76) IDeg(A); 0.54 (0.78) IDeg (B); 0.62 (0.68) IGlar | Funding: Novo Nordisk A/s<br><br>Risk of bias:<br>Randomisation = unclear (not stated)<br>Allocation concealment = adequate (remote voice response system)<br>Blinding = no (open label)<br>ITT analysis (LOCF)<br>Powered for treatment difference not superiority/ non-inferiority |
| | | | Age, years (SD) | 44.5 (12.7); 45.6 (12.5); 47.2 (13.5) | | | | | | Final mean (SD) HbA1c | 7.8 (0.8) IDeg(A); 8.0 (1.0) IDeg (B); 7.6 (0.8) IGlar | |
| | | | Women, % | 37%; 38%; 46% | | | | | | Decrease in fasting plasma glucose mean (SD) | 1.60 (4.66) IDeg(A); 2.06 (5.17) IDeg (B); 0.54 (4.36) IGlar | |
| | | | Diabetes, mean years (SD) | 22.7 (14.6); 20.8 (10.6); 19.1 (10.8) | | | | | | Final fasting plasma glucose mean (SD) | 8.3 (4.0) IDeg(A); 8.3 (2.8) IDeg (B); 8.9 (3.5) IGlar | |
| | | | White<br>Black/African<br>Asian<br>Other | 98%; 98%; 97%<br>2%; 0%; 0%<br><br>0%; 2%; 2%<br>0%; 0%; 2% | | | | | | | | |
| | | | Baseline HbA1c | 8.4 (0.9)%; 8.5 (1.0)%; 8.3 (0.8)% | | | | | | Confirmed hypoglycaemia (events/ patient-year) | 47.9 IDeg(A) (RR 0.72 vs. IGlar, 95% CI 0.52 to 1.00); 59.5 IDeg (B) (RR 0.90 vs. IGlar, 95% CI 0.65 to 1.24); 66.2 IGlar | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| compared with insulin glargine in people with Type 1 diabetes. Diabet Med 29: 716-720, 2012<br><br>REF ID: HOME 2012 | | significant concomitant illness<br>Impaired renal and hepatic function<br>history of recurrent major hypoglycaemia or hypoglycaemia unawareness<br>pregnant or breastfeeding | Pre-trial insulin: basal (once daily) + mealtime<br>basal (twice daily) + mealtime<br>Other | 51%; 50%; 56%<br><br>42%; 43%; 42%<br><br>7%; 7%; 2% | In both groups, patients received IAsp at mealtimes (100 units/mL) titrated weekly to 2-hour post-prandial target of 4-8mmol/litre | | | Confirmed nocturnal hypoglycaemia (events/ patient-year) | 5.1 IDeg(A) (RR 0.42 vs. IGlar, 95% CI 0.25 to 0.69); 8.8 IDeg (B) (RR 0.71, 95% CI 0.44 to 1.16); 12.3 IGlar | (HbA1c)<br>Drop-outs = acceptable (<20%) |
| | | | Basal insulin dose at baseline | 29 (12) units; 28 (13) units; 23 (11) units (described as "small difference" between degludec and glargine groups | | | | AE | 8.7 IDeg(A); 6.5 IDeg (B); 9.1 IGlar events/ patient-year; most mild or moderate; unlikely relation to study insulins | |
| | | | No major differences between groups for any other baseline characteristics; minor differences adjusted in analysis<br><br>Drop-outs (16 weeks): | | | | | Serious AE | Abdominal distension IDeg(A); hypoglycaemic unconsciousness IDeg(A); | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | 7 (12%; 2 AE, 2 non-compliance; 1 ineffective; 2 other reasons) IDeg (A) group; 5 (8%; 0 AE; 1 non-compliance; 2 ineffective; 2 other reasons) IDeg (B) group; 7 (12%; 1 AE, 1 non-compliance; 0 ineffective; 5 other reasons) IGlar group | | | | | hypoglycaemia IDeg (B); diabetic ketoacidosis IGlar | |
| | | | | | | | Body weight change mean (SD) | +0.1 (2.7) kg IDeg(A); +1.0 (2.5) kg IDeg (B); +0.7 (1.6) kg IGlar | |
| | | | | | | | SF36 Change in physical component score (Mean (SE)) | 0.26 (1.08) IDeg vs. -0.41 (1.07) IGlar | |
| | | | | | | | Change in mental component score (Mean (SE)) | 1.88 (0.98) IDeg vs. -1.13 (0.97) IGlar | |

**Table 216: HELLER 2012 and BODE 2013 – BEGIN trial xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority | RCT<br><br>79 centres in 6 countries. | n=629 (52 weeks);<br>n=469 (extension)<br><br>Degludec group:<br>n=472<br><br>Glargine group:<br>n=157<br><br>Inclusion criteria:<br>Age ≥18 years<br>type 1 diabetes for at least 12 months<br>Treated with basal bolus | 1 year (n=629) patients baseline data | Degludec:<br>n=472 | Glargine:<br>n=157 | Degludec: 100U/mL, titrated to before-breakfast glucose of 3.9mmol/litre to less than 5mmol/litre<br><br>n=472<br><br>Concomitant medication:<br>Insulin aspart at mealtimes, titrated to 3.9mmol/litre to less than 5mmol/litre before next meal | Glargine: 100U/mL, titrated to before-breakfast glucose of 3.9mmol/litre to less than 5mmol/litre<br><br>n=157 | 52 weeks and 104 weeks (extension trial of additional 52 weeks) | 52 weeks data (Heller 2012) | | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation adequate (computer generated using blocks)<br>Allocation concealment = adequate (interactive voice response system)<br>Blinding = open label<br>ITT analysis (LOCF)<br>Powered study (to detect non-inferiority) |
| | | | Age, mean (SD) years | 42.8 (13.7) | 43.7 (13.3) | | | | Decrease in HbA1c, Mean (SE) % | 0.40 (0.03) % IDeg vs. 0.39 (0.07) IGlar | |
| | | | Women, % | 41 | 43 | | | | Final HbA1c <7% | 188/472 (40%) IDeg vs. 67/157 (43%) IGlar | |
| | | | | | | | | | Confirmed hypo. (no. patients) | 451 (96%) IDeg vs. 147 (95%) IGlar | |
| | | | HbA1c ≥10%, % | 7.7 (0.9) | 7.7 (1.0) | | | | Confirmed nocturnal hypo. (no. patients) | 341 (72%) IDeg vs. 114 (74%) IGlar | |
| | | | BMI kg/m2 (SD) | 26.3 (3.7) | 26.4 (4.2) | | | | Severe hypo. (no. patients) | 58 (12%) IDeg vs. 16 (10%) IGlar | |
| | | | Diabetes duration, years | 19.1 (12.2) | 18.2 (11.4) | | | | AE, no. of patients at | 397 (84%) IDeg vs. 128 (83%) IGlar | |
| | | | Comparable between groups for all of the baseline characteristics | | | | | | SAE, no. of patients | 49 IDeg<br>17 IGlar | |
| | | | | | | | | | Body weight change mean (SE) | +1.8 (0.2)kg IDeg<br>+1.6 (0.3)kg IGlar | |
| | | | | | | | | | 104 week data (extension; Bode 2013) | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| trial. Lancet 379: 1489-97, 2012.<br><br>REF ID: HELLER 2012 | | insulin injections ≥12 months<br>HbA1c ≤10.0%<br>BMI 35kg/m2<br><br>Exclusion criteria:<br>not stated (but in appendix) | Drop-outs at 1 year:<br>IDeg 14% (3% AE; 2% non-compliance; <1% ineffective; 3% withdrawal criteria for lack of effect; 6% other); IGlar 11% (<1% professional reason; 1% AE; 2% non-compliance; 2% withdrawal criteria for lack of effect; 6% other)<br>Drop-outs at 2 years (extension):<br>IDeg 6% of those entering extension (330/351) and 30% from baseline.<br>IGlar 4% of those entering extension (113/118) and 28% from baseline. | | | | HbA1c (final values) | Deg: 7.3%<br>Glarg: 7.5% | Drop-outs = 1 year acceptable (<20% and <10% differential between groups)<br>Drop-outs = 2 years acceptable (30% and <10% differential between groups) |
| | | | | | | | HbA1c (change) | Deg: -0.31%<br>Glarg: -0.24%;<br>MD -0.04% (95% CI -0.17 to 0.09) | |
| | | | | | | | Confirmed Hypoglycaemia. (episodes/patient-year) | MD: 0.98 (95% CI 0.80 to 1.20); NS | |
| | | | | | | | Confirmed Nocturnal hypoglycaemia. (episodes/patient-year) | MD: 0.75 [95% CI 0.59–0.95);<br>p=0.02<br>Favours degludec | |
| | | | | | | | Severe hypoglycaemia (episodes/patient-year) | Deg: 0.17<br>Glarg: 0.15<br>(NS between groups) | |
| | | | | | | | AEs, no. of patients | Deg: 413/472<br>Glarg: 137/154 | |
| | | | | | | | SAEs, no. of patients | Deg: 71/472<br>Glarg: 29/154 | |
| | | | | | | | Body weight increase, kg | Deg: 2.1, Glarg: 2.0 (NS between groups) | |
| | | | | | | | Injection site reactions, no. | Deg: 14/475<br>Glarg: 9/154 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | of patients | | |

### G.4.2.3 Degludec versus detemir

**Table 217: IWAMOTO 2013**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Y. Iwamoto, P. Clauson, T. Nishida, and K. Kaku. Insulin degludec in Japanese patients with type 1 diabetes mellitus: A randomized controlled trial. J.Diabetes Invest. 4 (1):62-68, 2013.<br>REF ID: | RCT<br><br>8 centres, Japan | n=65<br>Degludec: n=33<br>Detemir: n=32<br><br>Inclusion criteria:<br>Age ≥20 years<br>type 1 diabetes for at least 12 months<br>HbA1c <10.4%<br>BMI <30 kg/m2<br>Treated for at least 12 weeks with basal-bolus insulin of glargine or NPH, and aspart. | | Deg: n=33 | Det: n=32 | Degludec: once daily (bedtime) titrated aiming for fasting blood glucose values.<br><br>Concomitant medication:<br>Mealtime insulin aspart | Detemir: once daily (bedtime) titrated aiming for fasting blood glucose values.<br><br>Concomitant medication:<br>Mealtime insulin aspart | 6 weeks treatment | HbA1c | Not reported | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation = unclear (just says randomised 1:1)<br>Allocation concealment = adequate (external registration centre)<br>Blinding = no (open |
| | | | | | | | | | Severe hypo, no of patients: | Deg: 0<br>Det: 0 | |
| | | | | | | | | | AEs and SAEs | Deg: 0<br>Det: 0 | |
| | | | Age, mean years | 45.5 | 43.2 | | | | Reports nocturnal hypo | | |
| | | | Women, % | 27 | 40 | | | | | | |
| | | | Diabetes duration, mean years | 13.2 | 11.8 | | | | | | |
| | | | HbA1c mean % (SD) | 7.79 (0.86) | 7.72 (0.86) | | | | | | |
| | | | BMI (SD) | 22.9 | 22.9 | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IWAMOTO 2013 | | Exclusion criteria:<br>Clinically significant concomitant disease<br>Impaired renal or hepatic function<br>Non-stabilised proliferative retinopathy or maculopathy<br>History of Recurrent severe hypoglycaemia or hypo unawareness.<br>pregnant or breastfeeding | kg/m2 | (2.49) | (2.5) | | | | | | label)<br>ITT analysis<br>Not calculated powering/sample size<br>Drop-outs = acceptable (<20%) |
| | | | | | | | | | | | |
| | | | Drop-outs:<br>n=0 in each group | | | | | | | | |

### G.4.2.4 Detemir versus glargine

**Table 218: HELLER 2009xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiorit | RCT<br><br>Multinational | n=443<br><br>Detemir group:<br>n=300<br><br>Glargine group:<br>n=147<br><br>Inclusion criteria:<br>Age ≥18 years<br>type 1 diabetes for at least 12 months<br>Treated with basal bolus insulin injections ≥3 months<br>HbA1c ≤11.0% | | Detemir: n=300 | Glargine: n=147 | Detemir: once daily (evening), or twice daily (if achieving target at breakfast but not dinner, a second dose - initially 4U administered in the morning was added)<br><br>66% ended up on twice/day detemir.<br><br>Concomitant medication:<br>Insulin aspart at mealtimes, adjusted to 90-minute post-prandial | Glargine: once daily (evening) no second dose added.<br><br>In both groups the dose was titrated to specific target blood glucose values. | 52 weeks | OVERALL: Final HbA1c (SE)<br><br>HbA1c ≤7%<br><br>HbA1c ≤7% without hypoglycaemia | Det: 7.57 (0.05); n=283<br>Glarg: 7.56 (0.06); n=134<br><br>87/263 det. 37/122 glarg<br><br>84/263 det 35/122 glarg | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation = unclear (just says randomised)<br>Allocation concealment = adequate (telephone system)<br>Blinding = open label<br>ITT analysis (LOCF)<br>Power = adequate (435 patients enough to give 95% power to demonstrate |
| | | | Age, mean (SD) years | 42 (13) | 41 (12) | | | | | | |
| | | | Diabetes duration | 17.2 (11.7) | 17.3 (10.7) | | | | HbA1c, change from baseline (SE) | Det: -0.53 (0.05); n=283<br>Glarg:-0.54 (0.06); n=134 | |
| | | | | | | | | | HbA1c: detemir once/day | 90 patients<br>-0.49% change; final 7.59% | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| y trial. Clinical Therapeutics 31(10): 2086-2097, 2009.<br><br>REF ID: HELLER 2009 | | Exclusion criteria:<br>Proliferative retinopathy or maculopathy requiring acute treatment within 6 months before study<br>history of recurrent major hypoglycaemia<br>anticipated change in any medication affecting glucose metabolism<br>impaired renal or hepatic function<br>cardiac problems or uncontrolled | BMI kg/m2 | 26.5 (4.0) | 26.3 (3.9) | target ≤9mmol/litre | | | HbA1c: detemir twice/day | 173 patients -0.58% change; final 7.60% | non-inferiority based on a 1-sided p=0.025; SD 1.0% and dropout rate of 15%; margin 0.4%<br>Drop-outs = acceptable (<20%) |
| | | | Women, % | 44.1 | 43.8 | | | | Hypoglycaemic episodes/patient-year | 53.6 det vs. 57.3 glar | |
| | | | HbA1c % | 8.1 (1.1) | 8.1 (1.2) | | | | Final fasting plasma glucose | 8.58 det vs. 8.81 glarg | |
| | | | Comparable between groups for all of the baseline characteristics<br><br>Drop-outs:<br>Detemir: 37/300 (6 AE; 6 ineffective therapy; 15 non-compliance; 10 other); Glargine: 25/147 (4 AE; 5 ineffective therapy; 4 non-compliance; 12 other) | | | | | | Body weight change | +0.36kg det vs. +0.42kg glarg | |
| | | | | | | | | | Major hypoglycaemic episodes/patient-year | 0.5 detemir vs. 0.4 glargine | |
| | | | | | | | | | Nocturnal hypoglycaemic episodes/pt-year | 9.9 detemir vs. 8.9 glargine | |
| | | | | | | | | | Hypoglycaemic episodes classified as | <0.1 detemir vs. <0.1 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | hypertension believed to affect study participation | | | | | SAE/ pt-year | glargine | |
| | | | | | | | AE (no. patients) | 277/299 det vs. 129/144 glarg | |
| | | | | | | | Serious AE (no. patients) | 35 (11.7%) vs. 7 (4.9%) | |
| | | | | | | | Injection site reactions | 24 (8%) det vs. 2 (1.4%) glarg | |

**Table 219: RENARD 2011xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Renard E, Dubois-Laforgue D, Guerci B, et al. Non-inferiority of insulin glargine versus insulin detemir on | RCT<br><br>25 centres in France. | n=88<br><br>Detemir first group: n=38<br><br>Glargine first group: n=50 | | Detemir first: n=34 (PP population) | Glargine first: n=44 (PP population) | Detemir: once daily evening injection, titrated on fasting blood glucose (5mmol/litre to ≤7.2mmol/litre), but | Glargine: once daily evening injection, titrated on fasting blood glucose (5mmol/litre to ≤7.2mmol/li | 16 weeks each treatment period; no washout | Coefficient of variation of fasting blood glucose (%) | 39.9 (10.9) detemir vs. 41.1 (12.0) glargine | Funding: Sanofi-Aventis<br><br>Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = unclear (just |
| | | | Age, mean (SD) years | 46.4 (14.1) | 48.3 (13.6) | | | | Decrease in HbA1c, mean (SD) % | 0.20 (0.55) first detemir period; 0.14 (0.38) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| blood glucose variability in type 1 diabetes patients: a multicenter, randomized, crossover study. Diabetes Technology and Therapeutics 13 (12): 1213-1218, 2011<br><br>REF ID: RENARD 2011 | | Inclusion criteria:<br>type 1 diabetes for at least 3 years<br>Intensive insulin therapy at least 6 months using basal bolus regimen with glargine as evening basal insulin<br>HbA1c ≤8.5%<br>>50% of pre-dinner blood glucose ≤8.3 mmol/litre in last 3 weeks of run-in period using glulisine as prandial insulin | Women, % | 44.1 | 34.1 | second dose could be added if patients failed to reach pre-dinner target<br><br>Concomitant medication:<br>Glulisine as the mealtime insulin, titrated using 1-2 hour post-meal blood glucose <9.9mmol/litre | tre) | | | second detemir period; 0.19 (0.34) first glargine period; 0.10 (0.52) second glargine period; | says randomised)<br>Blinding = no<br>ITT analysis = no (per protocol)<br>Power = adequate (86 patients required for power of 95% at p=0.025 for a true difference of 1.05 SD 0.2, margin 1.25, drop out 15%<br>Drop-outs = acceptable (<20%) |
| | | | Diabetes duration (years) | 18.5 (10.1) | 17.1 (8.4) | | | | Body weight change | Decreased 0.2kg on detemir and unchanged on glargine | |
| | | | HbA1c % | 7.16 (0.71) | 7.06 (0.69) | | | | AE (n, % of patients) | 32/88 (36.0%) on detemir vs. 29/88 (32.9%) on glargine | |
| | | | BMI kg/m2 | 25.3 (3.5) | 24.6 (3.5) | | | | | | |
| | | | | | | | | | Serious AE (no. patients) | 4 detemir vs. 4 glargine | |
| | | | Comparable between groups for all of the baseline characteristics<br><br>Drop-outs: | | | | | | Severe hypoglycaemia reported as serious AE | 1 in glargine group | |
| | | | | | | | | | Median monthly rate | 2.16 detemir vs. | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Exclusion criteria:<br>not stated | Ten patients excluded from analysis due to protocol violations (crossover period duration <3 months (8) or number of fasting blood glucose measurements <42 per period (2) | | | | symptomatic hypoglycaemia | 2.32 glargine | |
| | | | | | | | Severe symptomatic hypoglycaemia | 4/88 on detemir vs. 10/88 on glargine | |

### G.4.2.5 Detemir versus NPH

**Table 220: GOLEN 2013**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures – all n=28 patients | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| L. W. Golen, R. G. Ijzerman, M. C. Huisman, J. F. Hensbergen, ET AL. Cerebral blood flow and glucose metabolism in appetite-related brain regions in | RCT (cross-over)<br><br>Multicentre, The Netherlands. | n=28<br><br>Detemir: n=28 (started as 13)<br>NPH: n=28 (started as 15)<br><br>Inclusion criteria:<br>Age 18-65 years<br>type 1 | | All patients: n=28 | Detemir: once daily (evening); dose titrated where needed for fasting glucose of <7.<br><br>Concomitant medication: Mealtime | NPH: 100U/mL once daily (evening) titrated as for detemir group<br><br>Concomitant medication: Mealtime insulin aspart | 12 weeks treatment (each cross-over period)<br><br>Had 4-week run-in period to optimise current insulin therapy, | Final HbA1c Mean (SD) % | Det: 7.4 (0.6)<br>NPH: 7.4 (0.6) | Funding: Novo Nordisk<br><br>Risk of bias: Randomisation = adequate (randomised block design by the trial pharmacy)<br>Allocation concealment = |
| | | | | | | | | Final weight Mean (SD) kg | Det: 82.4 (12.4)<br>NPH: 83.4 (13.0) | |
| | | | Age, mean years | 36.9 | | | | | | |
| | | | Diabetes duration, mean years | 12.8 | | | | DTSQ – perceived hypo and hyper-glycaemia | NS diff between groups (details not reported) | |
| | | | HbA1c mean % (SD) | 7.5 (0.6)<br>Det: 7.4 | | | | Patient satisfaction | SS greater for detemir vs. NPH (p=0.003) | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures – all n=28 patients | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| type 1 diabetic patients after treatment with insulin detemir and NPH insulin: A randomized controlled crossover trial. Diabetes Care 36 (12):4050-4056, 2013.<br><br>REF ID: GOLEN 2013 | | diabetes<br>BMI 18-35 kg/m2<br><br>Exclusion criteria:<br>Duration <1 year<br>HbA1c >8.5%<br>Proliferative retinopathy<br>History of recurrent SH<br>History of hypo unawareness<br>History of CV, renal, liver or severe head trauma, neurological or psychiatric disorder.<br>Endocrine diseases not well controlled in last 3 months<br>Substance abuse | | (0.6); NPH: 7.3 (0.6) | insulin aspart | | before randomisation. | | | inadequate (the author enrolled and assigned them, by envelopes)<br>Blinding = no (open label)<br>ITT analysis<br>Powered study (for glucose mmts)<br>Drop-outs = acceptable (<20%) |
| | | | BMI kg/m2 | 24.9 (SD 2.7) | | | | | | |
| | | | Body weight, kg (SD) | Det: 83.1 (12.6)<br>NPH:82.7 (12.6) | | | | | | |
| | | | Drop-outs:<br>Up to 18 patients (<20% drop-outs) were included for some outcomes, but ITT analysis done on all n=28. Unclear numbers of drop-outs for each outcome. | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures – all n=28 patients | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Use of anticoagulants, oral steroids or any centrally acting agent | | | | | | | |

**Table 221: BARTLEY 2008xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bartley PC, Bogoev M, Larsen J, et al. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients | RCT<br><br>33 centres in 10 countries. | n=497<br><br>Detemir group: n=331<br><br>NPH group: n=166<br><br>Inclusion criteria: Age ≥18 years | | Detemir: n=331 | NPH: n=164 (2 withdrew before treatment) | Detemir: once daily (evening) or twice/day (add at breakfast) if not achieve targets<br><br>MOST PTS (63% FINISHED THE TRIAL ON TWICE/DAY | NPH: once daily (evening) or twice/day (add at breakfast) if not achieve targets<br><br>MOST PTS (55% FINISHED THE TRIAL ON TWICE/DAY | 24 months | Reduction in HbA1c | 0.94% detemir vs. 0.72% NPH | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation = unclear (just says randomised)<br>Allocation concealment = adequate (telephone randomisation system)<br>Blinding = no (open label) |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 25: 442-449, 2008.<br><br>REF ID: BARTLEY 2008 | | type 1 diabetes for at least 12 months<br>Treated with basal-bolus insulin regimen ≥3 months<br>HbA1c ≤11.0%<br>BMI ≤35kg/m2<br>Able and willing to self-measure plasma glucose<br><br>Exclusion criteria:<br>Proliferative retinopathy or maculopathy<br>Other | | | | BASAL)<br><br>Concomitant medication:<br>Mealtime insulin aspart | BASAL)<br><br>In both groups, insulin doses were titrated to achieve specific target blood glucose values | | | | ITT analysis<br>Powered study (HbA1c)<br>Drop-outs = acceptable (<20%) |
| | | | | | | | | | Final HbA1c Mean (SE) % | 7.36 (0.06) n=320 detemir vs. 7.58 (0.08) n=159 NPH | |
| | | | | | | | | | HbA1c ≤7.0% without confirmed hypoglycaemia in last month of treatment | 73/331 (22%) detemir vs. 21/164 (13%) NPH | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | significant medical disorders<br>Recurrent major hypoglycaemia<br>Allergy to insulin<br>pregnant or breastfeeding | | | | | | | | | |
| | | | Age, mean (range) years | 35 (18-75) | 35 (18-70) | | | | Reduction in fasting plasma glucose mmol/litre | 3.01 detemir vs. 1.93 NPH | |
| | | | Women, % | 44.4 | 47.0 | | | | | | |
| | | | Diabetes duration, mean (range) years | 12.7 (1.0-50.4) | 13.5 (1.1-49.4) | | | | Final fasting plasma glucose Mean (SE) mmol/litre | 8.35 (0.27) n=318 detemir vs. 9.43 (0.38) n=158 NPH | |
| | | | HbA1c mean (range) % | 8.3 (5.0-11.6) | 8.4 (5.3-11.4) | | | | | | |
| | | | BMI kg/m2 | 24.7 (15.4 - 34.6) | 24.7 (16.9 - 34.7) | | | | Weight gain kg | 1.7 detemir vs. 2.7 NPH | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Final weight Mean (SE) kg | 72.92 (0.26) n=320 detemir vs. 73.91 (0.37) n=159 NPH | |
| | | | | | | | Major hypoglycaemia (no. patients) | 49/331 (14.8%) detemir vs. 42/164 (25.6%) NPH | |
| | | | Comparable between groups for all of the baseline characteristics<br><br>Drop-outs:<br>52 (15.7%) discontinued detemir (13 AE, 2 ineffective therapy, 8 non-compliance, 31 other reasons); 22 (13.3%) discontinued NPH (1 AE, 2 ineffective therapy, 6 non-compliance, 13 other reasons) | | | | Nocturnal major hypoglycaemia | 18/331 (5.4%) detemir vs. 25/164 (15.2%) NPH | |
| | | | | | | | Hypoglycaemia reported as serious AE (no. patients) | 14 detemir vs. 12 NPH | |
| | | | | | | | AE possibly/ probably related to trial drug | 36/331 (10.9%) detemir vs. 28/164 (17.1%) NPH | |
| | | | | | | | Serious AE possibly/ probably related to | 14/331 (4.2%) detemir vs. | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | trial drug | 11/164 (6.7%) NPH | |
| | | | | | | | | | |

**Table 222: HERMANSEN 2001xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| K. Hermansen, S. Madsbad, H. Perrild, A. Kristensen, and M. Axelsen. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: A randomized open crossover | RCT (cross-over)<br><br>7 centres in Denmark | n=59<br><br>Inclusion criteria:<br>Age 18-55 years<br>type 1 diabetes for at least 2 years<br>Had received once/day (evening) NPH plus meal-time human soluble insulin for at least 6 months<br>HbA1c ≤8.7%<br>Glucagon-stimulated C-peptide ≤0.1 nmol/litre or fC-pep ≤0.04 nmol/litre<br>NPH dose <40 IU/day<br>BMI <27.5 kg/m2 | | All: n=56 | Detemir + Human insulin<br><br>Det: Once/day (evening)<br><br>HI: = Actrapid (30 minutes before meals)<br><br>Dose of detemir was titrated to reach target blood glucose. levels | NPH + Human insulin<br><br>NPH: Once/day (evening)<br><br>HI: = Actrapid (30 minutes before meals)<br><br>Dose of NPH was titrated to reach | 6 weeks (each cross-over period) | HbA1c | NO DATA | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation = adequate?? (symmetrically in blocks of 4 to a treatment sequence)<br>Allocation concealment = unclear (just says randomised)<br>Blinding = no (open label)<br>Not ITT analysis<br>Powered study |
| | | | Age, mean (range) years | 34.5 (19-52) | | | | Hypoglycaemia, no. of patients | Det: 54/57<br>NPH: 51/56 | |
| | | | Women, % | 17.9 | | | | Hypoglycaemia, episodes | Det: 432<br>NPH: 577 | |
| | | | Diabetes, mean (range) duration years | 14.8 (2.6-47.8) | | | | Major hypoglycaemia, no. of patients | Det: 4/57<br>NPH: 7/56 | |
| | | | HbA1c % (range) | 7.9 (5.7-8.7) | | | | Major hypoglycaemia, episodes | Det: 4<br>NPH: 11 | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes Care 24 (2):296-301, 2001.<br><br>REF ID: HERMANSEN 2001/ID 1045 | | Exclusion criteria:<br>Proliferative retinopathy<br>Impaired renal or hepatic function<br>Decompensated heart failure<br>Unstable angina pectoris<br>MI within the past year<br>Hypertension<br>Hypoglycaemia unawareness<br>Recurrent major hypoglycaemia<br>Allergy to insulin or any component<br>Drug or alcohol abuse<br>Use of systemic corticosteroids, BBs or hormones within past month<br>Pregnant, breast-feeding or inadequate contraception | Weight (SD) kg/m2 | 23.8 (2.0)<br><br>Drop-outs:<br>n=3 at beginning of trial | | target blood glucose. levels | | AEs<br>Numbers have been reported in the paper if we need to get data for HEc | | (serum glucose).<br>Drop-outs = acceptable (<20%) |

**Table 223: HERMANSEN 2004xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 47: 622-629, 2004 | RCT<br><br>64 centres in Europe. | n=595<br><br>Detemir group: n=298<br><br>NPH group: n=297<br><br>Inclusion criteria:<br>Age ≥18 years<br>type 1 diabetes for at least 12 months<br>Current treatment any basal-bolus insulin regimen or biphasic insulin treatment at least 6 months<br>Total daily insulin <1.4 U/kg<br>HbA1c ≤12.0% | | Detemir: n=298 | NPH: n=297 | Detemir: 100U/mL morning and bedtime titrated to pre-breakfast and pre-dinner 5.7-7.3 mmol/litre<br><br>Concomitant medication:<br>Mealtime insulin aspart 100U/mL immediately before meals, titrated to 8.5-10.1mmol/litre 90 minutes after a meal | NPH: 100U/mL morning and bedtime titrated to pre-breakfast and pre-dinner 5.7-7.3 mmol/litre<br><br>Concomitant medication:<br>Mealtime regular human insulin 100U/mL 30 minutes before meals titrated to 8.5-10.1mmol/litre 90 minutes after a meal | 18 weeks (6 week titration and 12 week maintenance) | Change in HbA1c | -0.50% detemir vs. -0.28% NPH | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation = unclear (just says randomised)<br>Allocation concealment = unclear (just says randomised)<br>Blinding = no (open label)<br>ITT analysis<br>Power education study (HbA1c).<br>Drop-outs = acceptable |
| | | | Age, mean (SD) years | 38.8 (13.5) | 39.3 (12.9) | | | | Final HbA1c mean (SE) % | 7.88 (0.05) n=298 detemir vs. 8.11 (0.05) NPH n=297 | |
| | | | Women, % | 38.6 | 35.0 | | | | Final fasting plasma glucose mean (SE) mmol/litre | 7.58 (0.19) n=298 detemir vs. 8.10 (0.20) NPH n=297 | |
| | | | Diabetes, mean (SD) duration years | 15.4 (10.1) | 15.1 (10.4) | | | | Change in weight mean (SE) kg | -0.95 (0.14) n=298 detemir vs. +0.07 (0.14) NPH n=297 | |
| | | | HbA1c % (SD) | 8.48 (1.12) | 8.29 (1.19) | | | | Final weight mean (SE) kg | 73.0 (0.14) detemir vs. 74.1 (0.14) NPH | |
| | | | BMI mean | 24.8 (3.0) | 24.9 (3.2) | | | | Coefficient of variation | 36.9% detemir vs. | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: HERMANSEN 2004 | | BMI ≤35kg/m2<br><br>Exclusion criteria:<br>Proliferative retinopathy requiring acute treatment<br>Impaired renal or hepatic function<br>Severe cardiac problems<br>Uncontrolled hypertension<br>Recurrent major hypoglycaemia<br>Allergy to insulin<br>History of drug or alcohol dependence<br>pregnant or breast-feeding | (SD) kg/m2 | | | | | | within person in overall plasma glucose (%) | 39.6% NPH | (<20%) |
| | | | Comparable between groups for all of the baseline characteristics except slightly higher HbA1c and slightly lower fasting plasma glucose level in detemir group<br><br>Drop-outs:<br>9 withdrew from detemir group (5 AE, 2 non-compliance, 2 other reasons); 14 from NPH group (1 AE, 4 ineffective therapy, 3 non-compliance, 6 other reasons) | | | | | | Major hypoglycaemia (no. patients) | 19/298 (6.5%) detemir vs. 18/297 (6.3%) | |
| | | | | | | | | | Major nocturnal hypoglycaemia (no. patients) | 3/298 (1.0%) detemir vs. 12/297 (4.2%) | |
| | | | | | | | | | AE | 141/298 (47.3%) detemir vs. 139/297 (46.8%) NPH | |
| | | | | | | | | | Serious AE | 12/298 detemir vs. 7/297 NPH | |
| | | | | | | | | | Withdrawal due to serious AE considered to be | 3/298 detemir vs. 0/297 NPH | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | related to trial product | | |

**Table 224: HOME 2004xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycaemic control compared with NPH insulin in people with type 1 diabetes. Diabetes Care 27: 1081-1087, 2004 | RCT<br><br>52 centres in Australasia and Europe. | n=408<br><br>Detemir 12 hour group: n=137<br><br>Detemir Morn + bed group: n=139<br><br>NPH group: n=132<br><br>Inclusion criteria: Age >18 years type 1 diabetes for at least 12 | | Detemir 12h: n= 137 | Detemir Morn + bed: n= 139 | NPH: n= 132 | Detemir:<br><br>100U/mL either before breakfast and at bedtime (morn + bed) or at 12 hour intervals (12-hour),<br><br>titrated to pre-breakfast/night 4.0-7.0mmol/litre and post-prandial ≤10mmol/litre | NPH: (twice/day)<br><br>before breakfast and at bedtime<br><br>titrated to pre-breakfast/ night 4.0-7.0mmol/litre and post-prandial ≤10mmol/litre | 16 weeks | Decrease in HbA1c mean (SE) | Detemir 12h: 0.85 (0.07)%; Detemir Morn + bed: 0.82 (0.07)%; NPH: 0.65 (0.07)% | Funding: Novo Nordisk<br><br>Risk of bias: Randomisation = unclear (just says randomised)<br>Allocation concealment = adequate (remote telephone randomisation)<br>Blinding = no (open label)<br>ITT analysis (missing data interpolated)<br>Powered |
| | | | Age, mean (SD) years, | 40.9 (13.0) | 41.3 (11.4) | 38.3 (12.4) | | | | Final HbA1c mean (SE) | Detemir 12h: 7.75 (0.07); Detemir Morn + bed: 7.78 (0.07); NPH: 7.94 (0.07) | |
| | | | Women, % | 48 | 43 % | 47 | | | | Final fasting plasma glucose (mean (SE) | Detemir 12h: 9.75 (0.37); Detemir | |
| | | | BMI | 25.1 | 25.2 | 25.2 | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: HOME 2004 | | months<br>Using mealtime + basal regimen >2 months<br>Daily basal insulin <100 U/day<br>HbA1c ≤12.0%<br>BMI ≤35.5kg/m2<br><br>Exclusion criteria:<br>Significant medical problems (including proliferative retinopathy, recurrent major hypoglycaemia, impaired hepatic or renal function, uncontrolled cardiovascula | kg/m 2 | (3.3) | (3.6) | (3.7) | Concomitant medication:<br>Insulin aspart at mealtimes | | | mmol/litre) | Morn + bed: 8.94 (0.37); NPH: 11.24 (0.38) | study<br>Drop-outs = acceptable (<20%) |
| | | | Diab etes, years | 17.1 (10.6) | 17.6 (10.7) | 15.1 (10.6 ) | | | | Mean (SE) change in body weight (kg) | Detemir 12h: 0.02 (0.22); Detemir Morn + bed: 0.24 (0.22); NPH: 0.86 (0.23) | |
| | | | HbA1 c % | 8.55 (1.20) | 8.74 (1.20) | 8.52 (1.19 ) | | | | Major hypoglycae mia (no. patients) | Detemir 12h: 6/137 (4%); Detemir Morn + bed: 11/139 (8%); NPH: 10/132 (8%) | |
| | | | Comparable between groups for all of the baseline characteristics<br><br>Drop-outs:<br>17 withdrew (5 IDet 12 h; 4 IDet morn + bed; 8 NPH): 2AE, 3 ineffective therapy, 9 non-compliance, 3 other (fear of | | | | | | | Major nocturnal hypoglycae mia (no. patients) | Detemir 12h: 3/137 (2%); Detemir Morn + bed: 5/139 (4%); NPH: 4/132 (3%) | |
| | | | | | | | | | | SAE | Combined detemir | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | r problems<br>using medication know to interfere with glucose metabolism<br>pregnant or breastfeeding | hypoglycaemic event, withdrawal of consent, pregnancy) | | | | | group: 14/276 (5%) vs. NPH group: 4/132 (3%) | |

**Table 225: KOLENDORF 2006xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kølendorf K, Ross GP, Pavlik-Renart I, et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma | RCT (crossover)<br><br>11 centres in Australia, Europe and South Africa. | n=130 (crossover; periods pooled apart from weight)<br><br>Detemir first: n=66<br><br>NPH first: n=64 | | Detemir first: n=66 | NPH first: n=64 | Detemir: 100 U/mL twice daily, (before breakfast and at bedtime); bedtime dose titrated by pre-breakfast glucose (increase dose if >7mmol/litre), pre-breakfast | NPH: 100IU/mL twice daily (before breakfast and at bedtime); bedtime dose titrated by pre-breakfast glucose (increase | 16 weeks each treatment | Decrease in HbA1c | Detemir: 0.3%; NPH 0.3% | Funding: Novo Nordisk<br><br>Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = unclear (just says randomised) |
| | | | | | | | | | Final HbA1c mean (SE) | 7.6 (0.06)% detemir; 7.6 (0.06)% NPH | |
| | | | Age, mean (SD) years | 38.5 (12.3) | 39.9 (12.4) | | | | Pre-breakfast plasma glucose ≤6.0% | 30/125 (24%) detemir; 19/127 (15%) NPH | |
| | | | White (%) | 92.4 | 95.3 | | | | Pre-evening meal plasma | 16/125 (13%) detemir; | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| glucose levels compared with NPH insulin in type 1 diabetes. Diabet Med 23: 729-735, 2006.<br><br>REF ID: KØLENDORF 2006 | | Inclusion criteria:<br>Age ≥18 years<br>type 1 diabetes for at least 12 months<br>Treated with basal bolus insulin injections ≥4 months<br>Able and willing to perform SMPG<br>HbA1c ≤9.0%<br>BMI ≤35kg/m2<br>C-peptide negative<br>Total daily insulin dose ≤1.4 IU/kg/day<br>Basal insulin requirement ≥30% of total daily dose | | | | dose titrated by pre-evening meal glucose (increase dose if >7mmol/litre)<br><br>Concomitant medication:<br>Pre-meal insulin aspart immediately before each main meal, titrated to ≤8.0mmol/litre 90 minutes post-prandially | dose if >7mmol/litre), pre-breakfast dose titrated by pre-evening meal glucose (increase dose if >7mmol/litre) | | glucose ≤6.0% | 27/127 (21%) NPH | Blinding = no (open label)<br>ITT analysis<br>Power education study (hypoglycaemia)<br>Drop-outs = acceptable (<20%) |
| | | | Women, % | 48.5 | 43.8 | | | | Coefficient of variation of SMPG | 38.4% detemir vs. 41.1% NPH | |
| | | | Diabetes duration mean (SD) years | 16.5 (10.0) | 16.6 (10.6) | | | | Change in body weight | Period 1: detemir -0.3kg vs. NPH -1.0kg<br>Period 2: -0.2kg detemir vs. +1.3kg NPH | |
| | | | BMI mean (SD) kg/m2 | 25.1 (3.4) | 25.6 (3.5) | | | | | | |
| | | | HbA1c mean (SD) % | 7.9 (0.7) | 7.9 (0.8) | | | | Hypoglycaemia (PG <3.1mmol/litre with symptoms) | 97/125 (77.6%) detemir vs. 104/128 (81.3%) NPH | |
| | | | | | | | | | Nocturnal hypoglycaemia (PG <3.1mmol/litre with symptoms) | 46/125 (36.8%) detemir vs. 63/128 (49.2%) NPH | |
| | | | Comparable between groups for all of the baseline characteristics<br><br>Drop-outs: | | | | | | Severe hypoglycaemia (episodes not patients) | 19 episodes detemir vs. 33 episodes NPH | |
| | | | | | | | | | Hypoglycaemic coma reported | 0 detemir vs. | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Exclusion criteria:<br>Significant medical disorders<br>recurrent major hypoglycaemia or hypoglycaemia unawareness<br>allergy to insulin<br>pregnant or breastfeeding | 7 withdrawn (3 AE, 2 personal reasons, 1 ineffective therapy (2nd period on NPH) and 1 non-compliance) | | | | as SAE | 2 NPH | |

**Table 226: LEEUW 2005xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Leeuw ID, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in | RCT<br><br>42 centres in Europe. | n=428 initially randomised; 316 of 425 eligible at 6 months accepting extension phase; NS difference between accepters and decliners | | Detemir: n=216 | NPH: n=99 | Detemir: 1200nmol/mL; twice daily before breakfast and at bedtime, titrated to 4- | NPH: 100IU/mL twice daily before breakfast and at bedtime | 12 months (initial 6 months trial then 6 month extension phase) | Decrease in HbA1c | 0.64% detemir vs. 0.56% NPH | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation = unclear |
| | | | Age, mean (SD) years | 40.1 (12.8) | 40.8 (13.2) | | | | Final mean (SE) HbA1c | 7.53 (0.10)% detemir vs. 7.59 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes, Obesity and Metabolism 7: 73-82, 2005<br><br>REF ID: LEEUW 2005 | | Detemir group:<br>n=216<br><br>NPH group:<br>n=99<br><br>Inclusion criteria:<br>Caucasian<br>Age ≥18 years<br>type 1 diabetes for at least 12 months<br>Treated with basal bolus insulin injections ≥2 months<br>Total daily basal insulin requirement ≤100IU/day<br>HbA1c ≤12.0%<br>BMI ≤35kg/m2<br><br>Exclusion criteria:<br>Proliferative retinopathy<br>Impaired hepatic or renal function<br>severe cardiac problems<br>uncontrolled | | | | 7mmol/litre for fasting blood glucose<br><br>Concomitant medication:<br>Mealtime insulin aspart, titrated to 90 minute post-prandial target <10.0mmol/litre | | | | (0.13)% NPH | (just says randomised)<br>Allocation concealment = unclear (just says randomised)<br>Blinding = no (open label)<br>ITT analysis<br>Powered study (non-inferiority)<br>Drop-outs = acceptable (<20%) |
| | | | Women, % | 46.3 | 47.5 | | | | Decrease in fasting plasma glucose (mmol/litre) | 0.58 detemir vs. 0.42 NPH | |
| | | | Diabetes duration mean (SD) years | 17.8 (9.7) | 16.6 (10.2) | | | | Final fasting plasma glucose (mmol/litre) | 10.7 detemir vs. 10.8 NPH | |
| | | | HbA1c % (SD) | 8.18 (1.14) | 8.03 (1.11) | | | | | | |
| | | | BMI mean (SD) kg/m2 | 24.4 (2.9) | 24.6 (3.5) | | | | Major hypoglycaemia | 30/216 (14%) detemir vs. 21/99 (21%) NPH | |
| | | | | | | | | | Weight change (kg) | -0.1 detemir vs. +1.2kg NPH | |
| | | | Comparable between groups for all of the baseline characteristics<br><br>Drop-outs:<br>1 detemir patient lost to follow up before treatment; 5 withdrew (1 non-compliance, 2 AE, 2 other); 3 withdrew from | | | | | | Final weight mean (SD) kg | 71.2 (11.4) detemir vs. 72.7 (13.1) NPH | |
| | | | | | | | | | Severe AE possibly/ probably related to study drug | 2/216 detemir vs. 2/99 NPH | |
| | | | | | | | | | Serious AE (no. | 12/216 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | hypertension<br>recurrent major hypoglycaemia<br>allergy to insulin<br>pregnant or breastfeeding | NPH group (ineffective therapy, non-compliance and other) | | | | patients)<br><br>Injection site reactions | detemir vs. 7/99 NPH<br><br>4/216 (1.9%) detemir vs. 1/99 (1.0%) NPH | |

**Table 227: RUSSELL-JONES 2004xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Russell-Jones D, Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or Neutral Protein Hagedorn on blood glucose control in patients | RCT<br><br>92 centres in Europe and Australia | n=747<br><br>Detemir group: n=491<br><br>NPH group: n=256<br><br>Inclusion criteria:<br>Age ≥18 years type 1 | | Detemir n=491 | NPH: n=256 | Detemir: 100U/mL at bedtime, titrated to pre-breakfast/ night 4.0-7.0mmol/litre and 90 minutes post-prandial ≤10.0mmol/litre<br><br>Concomitant medication: Regular human insulin 100IU/mL | NPH: 100U/mL at bedtime | 6 months | AE possibly/ probably related to treatment | 1/491 detemir vs. 1/256 NPH | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation = adequate (computer randomisation)<br>Allocation concealment = unclear (just says randomised)<br>Blinding = no |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| with type 1 diabetes mellitus using a basal-bolus regimen. Clinical Therapeutics 26: 724-736, 2004<br><br>Ref ID: RUSSELL-JONES 2004 | | diabetes for at least 12 months<br>Treated with basal bolus insulin injections ≥2 months<br>Total daily basal insulin requirement ≤100IU/day<br>HbA1c ≤12.0%<br><br>Exclusion criteria:<br>Proliferative retinopathy<br>Impaired hepatic or renal function<br>severe cardiac problems<br>uncontrolled hypertension<br>recurrent major hypoglycaemia<br>concomitant | | | | with main meals | | | | | (open label)<br>ITT analysis<br>Powered study (HbA1c).<br>Drop-outs = acceptable (<20%) |
| | | | | | | | | | | | |
| | | | | | | | | | Change in HbA1c mean (SD) % | -0.06 (0.92) detemir vs. +0.06 (1.05) NPH | |
| | | | | | | | | | Final HbA1c | 8.30 (1.08) detemir vs. 8.41 (1.32) NPH | |
| | | | | | | | | | Change in fasting plasma glucose mean (SD) mmol/litre | -1.61 (5.98) detemir vs. -0.15 (6.24) NPH | |
| | | | Women (%) | 34.4 | 38.7 | | | | Final fasting | 10.27 (3.95) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | medications known to interfere with glucose metabolism pregnant or breastfeeding | Mean (SD) | | | | | | plasma glucose mean (SD) mmol/litre | detemir vs. 11.40 (5.13) NPH | |
| | | | Age (year) Mean (SD) | 40.9 (12.4) | 39.8 (12.3) | | | | Coefficient of variability SMPG (%) | 37.4 detemir vs. 43.0 NPH | |
| | | | BMI kg/m2 | 25.1 (3.4) | 25.4 (3.4) | | | | Change in body weight mean (SD) kg | -0.23 (2.83) detemir vs. +0.31 (2.93) NPH | |
| | | | Mean (SD) duration diabetes (year) | 17.1 (11.3) | 16.4 (9.5) | | | | Final body weight mean (SD) kg | 76.3 (12.4) detemir vs. 76.5 (12.3) NPH | |
| | | | HbA1c | 8.35 (1.20) | 8.35 (1.21) | | | | Major hypo-glycaemia | 31/491 detemir vs. 22/256 NPH | |
| | | | Drop-outs: | | | | | | Major nocturnal | 14/491 detemir | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | AE<br>Ineffective therapy<br>Non-compliance<br>Other<br>Completed | 26<br>5<br>3<br>2<br>17<br>465 | 21<br>2<br>0<br>5<br>15<br>235 | | | | hypo-glycaemia | vs. 10/256 NPH | |
| | | | | | | | | | Serious AE possibly/ probably related to study drug | <2% both detemir and NPH | |
| | | | Comparable between groups for all of the baseline characteristics | | | | | | | | |

**Table 228: STANDL 2004xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Standl E, Lang H, Roberts A. The 12-month efficacy and | RCT<br><br>47 centres in Europe, | n=461 initially enrolled, 421 completed initial 6 month period; 289 entered extension | | Detemir n=154 | NPH: n=135 | Detemir: 100U/mL twice daily<br><br>, titrated to | NPH:<br><br>100U/mL twice daily, | Initial 6 months, then 6 months extension = 12 | Final mean (SE) HbA1c | 7.88 (0.082) detemir vs. 7.78 (0.088) | Funding: Novo Nordisk<br><br>Risk of bias: Randomisatio |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technology and Therapeutics 6(5): 579-588, 2004<br><br>Ref ID: STANDL 2004 | Australia and New Zealand | Detemir group:<br>n=154<br><br>NPH group:<br>n=135<br><br>Inclusion criteria:<br>Age 18-74 years<br>type 1 diabetes for at least 12 months<br>Treated with twice daily basal insulin plus mealtime bolus injections ≥2 months<br>Total daily basal insulin requirement ≤100IU/day<br>HbA1c ≤12.0%<br>BMI ≤35kg/m2<br><br>Exclusion criteria:<br>Proliferative retinopathy<br>Impaired hepatic or renal function<br>severe cardiac | | | | fasting 4.0-7.0mmol/litre and 90 minutes post-prandial ≤10.0mmol/litre | titrated to fasting 4.0-7.0mmol/litre and 90 minutes post-prandial ≤10.0mmol/litre | month results | | NPH | n = unclear (just says randomised)<br>Allocation concealment = unclear (just says randomised)<br>Blinding = no (open label)<br>ITT analysis<br>Power not stated<br>Drop-outs = acceptable (<20%) |
| | | | Women (%) | 34.4 | 38.7 | | | | Final fasting plasma glucose mean (SE) mmol/litre | 10.1 (0.45) detemir vs. 9.84 (0.48) NPH | |
| | | | Age (year), mean (SD) | 40.7 (13.4) | 42.5 (12.3) | | | | Major hypo-glycaemia (no. patients | 18/154 detemir vs. 14/135 NPH | |
| | | | BMI kg/m2 Mean (SD) | 25.2 (3.0) | 25.6 (3.3) | | | | | | |
| | | | Duration diabetes (year), Mean (SD) | 16.1 (9.1) | 16.0 (10.6) | | | | Major nocturnal hypo-glycaemia | 5/154 detemir vs. 5/135 NPH | |
| | | | HbA1c % (SD) | 7.72 (1.26) | 7.66 (1.19) | | | | | | |
| | | | Drop-outs:<br>Protocol | 20<br>1 | 17<br>1 | Concomitant medication: Human soluble | | | Mean weight change | -0.3kg detemir vs. | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | problems<br>uncontrolled hypertension<br>recurrent major hypoglycaemia<br>insulin allergy<br>pregnant or breastfeeding | violation<br>AE<br>Ineffective therapy<br>Non-compliance<br>Other<br>Completed | 2<br><br>6<br>6<br>6<br>134 | 0<br><br>8<br>2<br>7<br>118 | insulin with main meals | | | | +1.4kg NPH | |
| | | | | | | | | | AE possibly/ probably related to study drug | 17/154 (11%) detemir vs. 8/135 (6%) NPH | |
| | | | Comparable between groups for all of the baseline characteristics | | | | | | Serious hypo-glycaemia recorded as AE (episodes) | 4 detemir vs. 3 NPH | |
| | | | | | | | | | Injection site reaction | 1 detemir vs. 0 NPH | |

**Table 229: VAGUE 2003xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P. Vague, J. | RCT | n=448 | | Detemir | NPH: | Detemir: | NPH: | 26 weeks | | | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| L. Selam, S. Skeie, I. Leeuw, J. W. Elte, H. Haahr, A. Kristensen, and E. Draeger. Insulin detemir is associated with more predictable glycaemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care 26 | 46 centres in 5 countries in Europe. | Detemir group: n=301<br><br>NPH group: n=146<br><br>Inclusion criteria:<br>type 1 diabetes for at least 1 year<br>Treated with basal-bolus insulin regimen ≥2 months<br>HbA1c ≤12.0%<br>BMI ≤35kg/m2<br><br>Exclusion criteria:<br>Proliferative retinopathy<br>Impaired hepatic or renal function<br>Severe cardiac problems<br>Uncontrolled | | : n=301 | n=146 | 1200nmol/mL twice/day (morning and evening) titrated aiming for fasting/pre-prandial 4-& mmol/litre; post-prandial <10 mmol/litre; from 0200 to 0400, 4-7 mmol/litre<br><br>Concomitant medication:<br>Mealtime insulin aspart | 600nmol/mL twice/day (morning and evening) titrated aiming for same targets as Detemir group | treatment | Final HbA1c Mean (SE) % | 7.60 (0.09) n=280 detemir vs. 7.64 (0.10) n=139 NPH | Novo Nordisk<br><br>Risk of bias:<br>Randomisation = unclear. 2:1 ratio telephone randomisation system (Interactive voice response system).<br>Allocation concealment = adequate (telephone randomisation system)<br>Blinding = not mentioned<br>Not true ITT analysis (patients exposed)<br>Powering not mentioned |
| | | | | | | | | | Final weight Mean (SE) kg | 70.9 (0.28) n=282 detemir vs. 71.8 (0.33) n=138 NPH | |
| | | | Age, mean (SD) years | 8.9 (13.3) | 41.8 (14.2) | | | | Major hypoglycaemia (no. patients) | 24 detemir vs. 21 NPH | |
| | | | Women, % | 46.2 | 49.3 | | | | | | |
| | | | Diabetes duration, mean (SD) years | 17.1 (9.9) | 17.4 (11.0) | | | | No AEs thought to be related to study drug | | |
| | | | HbA1c mean (SD) % | 8.18 (1.14) | 8.11 (1.12) | | | | | | |
| | | | Weight, kg (SD) | 71.5 (11.9) | 71.2 (11.5) | | | | | | |
| | | | Comparable between groups for all of the baseline characteristics | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| (3):590-596, 2003.<br><br>REF ID: VAGUE 2003 | | HT<br>Recurrent major hypoglycaemia<br>Allergy to insulin<br>Pregnant or breast-feeding women | Drop-outs:<br>5.6% (Detemir)<br>3.4% (NPH) | | | | | | Drop-outs = acceptable (<20%) |

**Table 230: ZACHARIAH 2011xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Zachariah S, Sheldon B, Shojaee-Moradie F, et al. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes | RCT (crossover)<br><br>1 centre in the UK | n=23<br><br>Inclusion criteria:<br>Age >18 years<br>type 1 diabetes for at least 12 months<br>Treated with basal insulin plus mealtime bolus injections >3 months<br>HbA1c 7.0-11.0%<br>BMI <40kg/m2<br><br>Exclusion criteria: | Women: 39.1%<br><br>Mean (SE) age: 38.8 (2.17) year<br><br>Mean (SE) BMI: 28 (3.6) kg/m2<br><br>Mean (SE) duration diabetes: 19.95 (2.09) year | Detemir: once or twice daily,<br><br>titrated to pre-breakfast and pre-dinner <6.0mmol/litre without hypoglycaemia<br><br>Concomitant medication: Insulin aspart with main | NPH: once or twice daily,<br><br>titrated to pre-breakfast and pre-dinner <6.0mmol/litre without hypoglycaemia | 16 weeks each treatment | Weight change mean (SE) kg<br><br>Final mean (SE) HbA1c<br><br>Major hypo-glycaemia (no. patients) | -0.69 (0.39) detemir vs. +1.7 (0.52) NPH<br><br>7.8 (0.23) detemir vs. 7.5 (0.26) NPH<br><br>none in either group | Funding: Novo Nordisk<br><br>Risk of bias:<br>Randomisation = unclear (just says randomised)<br>Allocation concealment = unclear (just says randomised)<br>Blinding = |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Care 34: 1487-1491, 2011<br><br>Ref ID: ZACHARIAH 2011 | | Anticipated change in medication known to affect glucose metabolism<br>Proliferative retinopathy<br>Impaired hepatic or renal function<br>uncontrolled hypertension<br>recurrent major hypoglycaemia or hypoglycaemia unawareness<br>pregnant | HbA1c mean (SE) 8.2 (0.22)%<br><br>Drop-outs:<br>1 dropped out for personal reasons | meals | | | | | no (open label)<br>ITT analysis = not stated<br>Power not stated<br>Drop-outs = acceptable (<20%) |

## G.4.3 Mixed insulin

### G.4.3.1 Basal-bolus (mixed insulin) versus basal (NPH)-bolus (HI)

**Table 231: CIOFETTA 1999 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| M. Ciofetta, C. Lalli, P. Del | RCT - | n=24 | | HI + NPH | Lisp + NPH | MIX Lisp + | Hum R (+ NPH | SELF-MIX: Lispro + NPH | 3 month | HbA1c, final value, | HI: 6.84 | Funding: BB |

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sindaco, E. Torlone, S. Pampanelli, L. Mauro, D. L. Chiara, P. Brunetti, and G. B. Bolli. Contribution of postprandial versus interprandial blood glucose to HbA1c in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. Diabetes Care 22 (5):795-800, 1999.<br><br>REF ID: CIOFETTA 1999 | Parallel<br><br>10 centres in Europe and South Africa | Inclusion criteria:<br>type 1 diabetes<br><br>Exclusion criteria: None given<br><br>patients were free of detectable microangiographic complication<br>patients having treatment with intensive insulin therapy (regular insulin at each meal, NPH at bedtime) | | once n=8 | once n=8 | NPH bed n=8 | bedtime)<br>Pre-meal human regular insulin.<br>NPH at bedtime.<br><br>----------<br><br>Lispro + NPH<br>Pre-meal insulin lispro.<br>NPH at bedtime.<br><br>Lispro given 0-5mins, and Hum R at 10-40 minutes before meals | (+ NPH bedtime)<br><br>Pre-meal Mixed insulin (Lispro + NPH).<br>NPH at bedtime.<br><br>Pre-meal Lispro given in separate injection to pre-meal NPH | s treatment | % (SEM) | (0.2)<br>Lisp: 6.96 (0.2)<br>MIX: 6.41 (0.12) | and sons<br><br>Risk of bias:<br>Randomisation = unclear (details not given)<br>Allocation concealment = not mentioned<br>Blinding = not mentioned.<br>ITT analysis (no drop-outs)<br>Powering not mentioned.<br>Drop-outs = None |
| | | | Age, years (SEM) | 33 (4) thus likely to be all adults - small SE | | | | | | | | |
| | | | Women, % | 29 | | | | | | Severe hypoglycaemia., no. of patients | HI: 0<br>Lisp: 0<br>MIX: 0 | |
| | | | Diabetes, mean years (SEM) | 13 (2.1) | | | | | | | | |
| | | | HbA1c, % (SEM) | Overall 6.84 (0.20) | | | | | | Mild hypoglycaemia, episodes/patient/month (SEM) | HI: 4.0 (0.5)<br>Lisp: 8.1 (0.8)<br>MIX: 5.2 (1.2) | |
| | | | HbA1c, % (SEM) | 6.79 (0.17) | 6.89 (0.16) | 6.83 (0.18) | | | | | | |
| | | | Drop-outs (6 months):<br>None mentioned | | | | BOTH GROUPS:<br>Injections by pen HumaPen, Eli Lilly).<br>Doses adjusted to specific treatment goals of blood glucose. | | | Unclear if done ANCOVA analysis (best for cross-over studies). | | |

**Table 232: Herz 2002 xxxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M. Herz, V. Arora, B. Sun, S. C. Ferguson, G. B. Bolli, and B. M. Frier. Basal-bolus insulin therapy in Type 1 diabetes: Comparative study of pre-meal administration of a fixed mixture of insulin lispro (50%) and neutral protamine lispro (50%) with human soluble | RCT - crossover<br><br>10 centres in Europe and South Africa | n=109<br><br>Inclusion criteria:<br>type 1 diabetes<br>22-43 years old<br>type 1 diabetes > 2 years duration<br>In good health<br>HbA1c <1.75 x upper limit of non-diabetic range<br>SMBG<br>Using basal-bolus regimen with pre-meal human soluble insulin or Lispro, supplemented by NPH at bedtime, for at least 3 months.<br>Regular meals at least 3/day | | Mix50/ HI<br>n=53 | HI/Mix 50<br>n=56 | Humalog Mix50 + NPH<br><br>Pre-meal insulin lispro mixture (Humalog Mix50).<br>NPH at bedtime.<br><br>Lispro given 0-5mins before meals | Human soluble Insulin + NPH<br><br>Pre-meal Human Soluble Insulin.<br>NPH at bedtime.<br><br>Human insulin given 30mins before meals | 12 weeks treatment (each cross-over period) | HbA1c, final value, % (SD) | Mix: 8.1 (1.3)<br><br>HI: 8.2 (1.2)<br>NS diff | Funding: Eli Lilly<br><br>Risk of bias:<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = open label as different appearances of drugs.<br>ITT analysis (LOCF)<br>Powered study (Blood glucose.).<br>Drop-outs = acceptable (<20%)<br>Not done |
| | | | Age, years (SD) | 34.4 (9.8) | 31.4 (8.9) | | | | Hypoglycaemia, episode/patient (SD) | Mix: 4.8 (5.1)<br><br>HI: 5.1 (5.3)<br><br>NS diff | |
| | | | Women, % | 56 | 46 | | | | Nocturnal hypoglycaemia, No. patients | Mix: 69<br><br>HI: 71<br><br>NS diff | |
| | | | Diabetes, mean years (SD) | 11.2 (7.2) | 11.0 (7.3) | | | | Severe hypoglycaemia, No. patients | Mix: 6<br><br>HI: 10<br><br>NS diff | |
| | | | HbA1c, % (SD) | 8.1 (1.2) | 7.9 (1.5) | | | | Weight, change from baseline, kg (SD) | Mix: 0.3 (2.2) | |
| | | | Both groups similar for all baseline characteristics | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| insulin. Diabet.Med. 19 (11):917-923, 2002.<br><br>REF ID: HERZ 2002 | | Exclusion criteria:<br>2 or more episodes of severe hypoglycaemia. (requiring external assistance within the previous 3 months) | Drop-outs (6 months):<br>n=9 (Mixed) and n=10 (HI) | | | | | HI: 1.0 (2.2) | ANCOVA analysis (best for cross-over studies). |
| | | | | BOTH GROUPS:<br>Injections given using a pen device (HumaPen, Eli Lilly).<br><br>Doses adjusted to specific treatment goals of blood glucose. | | | | | |

### G.4.3.2 Basal (some patients)-bolus (mixed insulin) versus basal (NPH)-bolus (HI)

**Table 233: CHEN 2006 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| J. W. Chen, T. Lauritzen, A. Bojesen, and J. S. Christiansen. Multiple mealtime | RCT - crossover<br><br>Denmark study | n=27<br><br>Inclusion criteria:<br>Adults aged ≥18 years | | All completers (n=23) | Biphasic Insulin Aspart (BIAsp 30) + NPH (in n=48% patients)<br><br>Pre-meal | Human short-acting (SA) soluble Insulin + NPH<br><br>Pre-meal | 12 weeks treatment (each cross-over | HbA1c, final value %, geometric mean (range) | MIX: 8.3 (6.7-9.8)<br>HI: 8.6 (7.4-11.4) | Funding: Novo Nodisk<br><br>Risk of bias:<br>Randomisation = unclear (as details not |
| | | | Age, years, median | 44.8 (20.6 – | | | | patient preference for | n=19 (83%) | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| administration of biphasic insulin aspart 30 versus traditional basal-bolus human insulin treatment in patients with type 1 diabetes. Diabetes Obes.Metab. 8 (6):682-689, 2006.<br><br>REF ID: CHEN 2006 | | Insulin-treated type 1 diabetes (ADA criteria)<br>Diabetes duration >12 months<br>Treated with soluble human insulin (Actrapid) 3x/day plus bedtime NPH (Insulatard) during last 6 months – total daily insulin dose <1.8 IU/kg<br>BMI <35 kg.<br>Mean HbA1c ≥8% in last 6 months<br><br>Exclusion criteria:<br>Diabetic complications requiring acute treatment<br>Uncontrolled hypertension<br>History of drug and alcohol abuse | (range) | 62.5) | BIAsp30 (NovoMix30 FlexPen).<br>NPH at bedtime (in some patients).<br><br>BIAsp30 given immediately before meals | Human SA soluble insulin (ActRapid Pen).<br>NPH (Insulatard FlexPen) at bedtime.<br><br>Human insulin given between 0-10 minutes before meals. | period) | MDI MIX vs. Basal-bolus HI | | given)<br>Allocation concealment = not mentioned<br>No wash-out period<br>Blinding = open label.<br>Not ITT analysis (for blood glucose, unclear otherwise)<br>Powered study (HbA1c).<br>Drop-outs = acceptable (<20%)<br>Not done ANCOVA analysis (best for cross-over studies). |
| | | | Women, % | 35 | | | | Major hypoglycaemia, no patients | MIX: 2<br>HI: 1 | |
| | | | Diabetes duration, years, median (range) | 19.35 (1.6 – 44.6) | | | | Hypoglycaemia, total events/patient /week, median (range) | MIX: 1.2 (0.1-3.1)<br><br>HI: 0.7 (0 0-3.3) | |
| | | | Weight, kg, mean (SD) | 77.6 (10.9) | | | | Nocturnal Hypoglycaemia, total events/patient /week, median (range) | MIX: 0.2 (0.1-0.7)<br><br>HI: 0.2 (0.1-0.7) | |
| | | | HbA1c, %, geometric mean (range) | 9.2 (8.1-12.3) | | | | | | |
| | | | Drop-outs:<br>n=4 | | IN BOTH GROUPS:<br>Dose adjustments made by patients according to Blood glucose. Targets and results of SMBG and advice of diabetes nurse. | | | IN PTS WHO TOOK MIX + NPH:<br>Hypoglycaemia, total events/patient /week, median (range) | MIX + NPH: 1.2 (0.1-3.1) | |
| | | | | | | | | IN PTS WHO TOOK MIX ONLY: | MIX ONLY: 1.1 (0.3-1.9) | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Treated with other drugs known to affect blood glucose. | | | | | Hypoglycaemia, total events/patient/week, median (range) | | |

### G.4.3.3 Basal-bolus (mixed insulin) versus basal (HI)- (bolus optional)

**Table 234: KHACHADURIAN 1989 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A. K. Khachaduri an, J. A. Davidson, S. Braunstein , G. Redmond, M. Greenfield, A. A. Lauritano, and P. Haycock. | RCT<br><br>5 centre s, USA | n=78 (n=72 analysed) type 1 diabetes + type 2 diabetes but >70% type 1 diabetes<br><br>Inclusion criteria:<br>Adults<br>Diabetes (type 1 diabetes and type 2 diabetes)<br>Treated with MDI | | MIX (n=29) | HI (n=43) | MIXED fixed dose: 30% regular human/70% NPH<br><br>30% Semisynthei c regular human insulin (Novolin R) and 70% | Human (LA) semi-synthetic insulin + optional bolus<br><br>Human semi-synthetic insulin NPH (Novolin N) | 12 weeks treat ment | HbA1c, final value %, mean | MIX: 8.4<br>HI: 8.6 | Funding: Not mentioned<br><br>Risk of bias:<br>Randomisati on = unclear (as details not given)<br>Allocation concealment = not mentioned<br>Blinding = |
| | | | Age, years, mean (SE) | 44.0 (2.9) | 42.9 (2.3) | | | | Ketoacidosis, no. of patients | MIX: 1<br>HI: 0 | |
| | | | Women, % | 52 | 58 | | | | Hypoglycaemia, events/week, mean | MIX: 0.8<br>HI: 1.4<br><br>NS diff between groups or change | |
| | | | Diabetes duration, years, mean (SE) | 15.1 (1.5) | 15.0 (1.4) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Comparison of fixed-ratio versus variable-ratio regular and NPH semisynthetic human insulin in insulin-requiring diabetic patients. Clin.Ther. 11 (4):485-494, 1989.<br><br>REF ID: KHACHADURIAN 1989 | | of animal NPH insulin with or without supplemental regular insulin.<br><br>Exclusion criteria:<br>Significant hypertension or CV, renal, hepatic or neurological disease<br>Life expectancy <3 years<br>Cancer<br>Alcoholism<br>Pregnancy or risk of conception<br>Hypersensitivity or allergy or resistance to insulin<br>Significant abnormalities in laboratory values<br>Use within preceding 3 months of any insulin formulations other than animal NPH insulin. | | | | NPH semisynthetic human insulin isophane suspension (Novolin N)<br>Given BID (ie. twice/day)<br>patients mixed the insulins in the syringe (as no pre-mix available at the time).<br><br>Insulin injection administered immediately after mixing. | Varying dose supplements of regular semisynthetic human insulin (Novolin R) could be added to the NPH (Novolin N) if necessary. | | | | |
| | | | Weight, kg, mean (SE) | 76.8 (2.7) | 72.9 (2.3) | | | | | | |
| | | | HbA1c, %, mean | 8.3 | 8.2 | | | | | | |
| | | | Type of diabetes:<br>type 1 diabetes<br>type 2 diabetes | 20 (69%)<br>9 (31%) | 32 (74%)<br>11 (26%) | | | | | | |
| | | | NS for all baseline characteristics except for Mean FSG SS higher in the mixed vs. control group.<br><br>Drop-outs:<br>n=6<br>Additionally n=5 patients were mis-randomised from fixed ratio group into the control group. | | | | | | | | |
| | | | | | | | | | Injection site reactions, no of patients | MIX: 2<br>HI: 3 | not mentioned.<br>Not ITT analysis for efficacy but ITT for safety<br>Powering not mentioned.<br>Drop-outs = acceptable (<20%) |

### G.4.3.4 Basal (mixed)-bolus (aspart) versus basal (detemir)-bolus (aspart)

**Table 235: HIRSCH 2012B xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I B. Hirsch, B Bode, JP Courreges, P Dykiel, E Franek, K Hermansen, A King, H Mersebach, and M Davies. Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal-bolus | RCT<br><br>79 sites in 9 countries around the world | n=548<br><br>Inclusion criteria:<br>Adults aged ≥18 years<br>type 1 diabetes<br>Diabetes duration ≥12 months<br>Currently treated with insulin (basal-bolus, pre-mixed or self-mixed regimens for at least 12 months.<br>BMI ≤35 kg.<br>Mean HbA1c 7-10%<br><br>Exclusion criteria:<br>Insulin regimen other than above, within 3 months of trial | | IDeg/Asp (n=366) | IDet (n=182) | IDegAspart + IAsp (n=366)<br><br>Once/day with main meal IDegAsp (70% LA degludec/30% SA aspart; 3ml Flexpen). 100U/ml<br>Aspart given at the remaining meals (100U/ml, 3ml FlexPen).<br><br>IDegAsp could be moved to another main meal, at | IDet + IAsp (n=182)<br><br>IDet (detemir; 3ml Flexpen) once/day at evening meal or bedtime. 100U/ml<br>Aspart given at all meals (100U/ml, 3ml FlexPen).<br><br>A second dose of detemir could be added in the morning, if | 26 weeks treatment | HbA1c, final value %, | MIX: 7.6<br>DET: 7.6 | Funding: Novo Nodisk<br><br>Risk of bias: Randomisation = unclear (2:1, stratified based on previous insulin treatment regimen but other details not given)<br>Allocation concealment = not mentioned<br>Blinding = open label, as the drugs required different |
| | | | Age, years, mean (SD) | 40.7 (12.8) | 42.6 (13.8) | | | | HbA1c, change from baseline and MD, %<br><br>NS difference, thus non-inferior | MIX: -0.75%<br>DET: -0.70%<br><br>Overall MD: -0.05% (95% CI -0.18 to 0.08) | |
| | | | Women, % | 48 | 55 | | | | | | |
| | | | Diabetes duration, years, mean (SD) | 17.2 (11.3) | 17.9 (12.3) | | | | % patients reaching target <7.0% | MIX: 24.6<br>DET: 20.3<br><br>NS diff | |
| | | | Weight, kg, mean (SD) | 76.7 (14.6) | 76.0 (14.0) | | | | Severe hypoglycaemia, n | MIX: 35/362<br>DET: 22/180 | |
| | | | HbA1c, %, mean | 8.3 (0.8) | 8.36 (0.7) | | | | Confirmed hypoglycae | MIX: 341/362 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| regimen in patients with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. Diabetes Care 35 (11):2174-2181, 2012.<br><br>HIRSCH 2012B | | Basal-bolus regimen with basal insulin injected twice/day (BID).<br>Anticipated change in concomitant medications known to interfere with glucose metabolism<br>Recurrent severe hypoglycaemia or hypoglycaemia unawareness<br>Proliferative retinopathy or maculopathy requiring treatment<br>Pregnancy or breast-feeding<br>Renal or hepatic dysfunction<br>Significant CV disease<br>Cancer<br>Other conditions likely to interfere with trial results. | (SD) | | | physician's discretion | inadequate Glycaemic control (investigator's discretion) | | mia, n | DET: 168/180 | number and timing of injection.<br>ITT analysis (LOCF)<br>Non-inferiority study (HbA1c).<br>Drop-outs = acceptable (<20%) |
| | | | Previous treatment, % on basal-bolus | 91.3 | 88.5 | | | | Nocturnal hypoglycaemia, n | MIX: 192/362<br>DET: 125/180 | |
| | | | patients well matched for all baseline characteristics.<br><br>Drop-outs:<br>MIX: n=46 (12.6%)<br>DET: n=27 (14.3%) | | | IN BOTH GROUPS:<br>Aspart given immediately before the meals<br>Dose adjustments once/week according to protocol-specified titration guidelines (details are given in paper).<br>Treat to target approach (details are given in paper).<br>Adjustments based on mean SMBG from preceding 3 days. | | | SF-36 physical, change from baseline: MIX – DET | 0.3 (95%CI -0.6 to 1.3)<br><br>NS diff | |
| | | | | | | | | | SF-36 mental, change from baseline: MIX – DET | -0.1 (95%CI -1.6 to 1.3)<br><br>NS diff | |
| | | | | | | | | | AEs, n | MIX: 239/362<br>DET: 114/180 | |
| | | | | | | | | | SAEs, probably related to trial treatment, n | MIX: 15/362<br>DET: 5/180 | |

### G.4.3.5 Basal/bolus (self-mixed insulin) versus basal (NPH) plus bolus (human regular)

**Table 236: JANSSEN 2000 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M. M. Janssen, F. J. Snoek, N. Masurel, R. P. Hoogma, W. L. Deville, C. Popp-Snijders, and R. J. Heine. Optimized basal-bolus therapy using a fixed mixture of 75% lispro and 25% NPL insulin in type 1 diabetes patients: no favorable effects on | RCT<br><br>Netherlands study | n=35 (mainly adults)<br><br>Inclusion criteria:<br>Diabetes (type 1 diabetes)<br>Reasonable glycaemic control (HbA1c <8.3%)<br>Using MIT (multiple injection therapy) with human regular insulin before meals and NPH at bedtime.<br><br>Exclusion criteria:<br>None given. | | MIX (n=17) | HI (n=18) | MIXED fixed dose: Lispro high mixture (HM) and NPL<br><br>75% Lispro/25% NPL<br>Given BID (ie. twice/day)<br>patients self-mixed the insulins in the syringe (as no pre-mix available at the time).<br><br>Insulin HM taken immediately before meals | Human (SA) regular insulin + NPH (LA)<br><br>Human semi-synthetic insulin NPH (Novolin N)<br>Varying dose supplements of regular semisynthetic human insulin<br><br>Regular Insulin to be taken 30 minutes before meals | 12-14 weeks treatment | HbA1c, final value %, mean (SD) | MIX: 7.2 (0.7)<br>HI: 6.7 (0.6) | Funding: Eli Lilly<br><br>Risk of bias:<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not mentioned<br>Blinding = open label.<br>ITT analysis (no drop-outs mentioned)<br>Powering not mentioned.<br>Drop-outs = not mentioned |
| | | | Age, years, mean (SD) | 33.0 (8.5) | 29.4 (8.7) | | | | Severe hypoglycaemia. n/N | MIX: 1/17<br>HI: 1/18 | |
| | | | Women, % | 35 | 39 | | | | DTSQ Treatment satisfaction – 6 item Likert scale 0-6 | No different between groups (data not given) | |
| | | | Diabetes duration, years, mean (SD) | 15.7 (7.7) | 11.9 (8.5) | | | | | | |
| | | | BMI, kg/m2, (SD) | 24.9 (3.1) | 23.0 (2.3) | | | | WBQ (well-being questionnaire) – 3 item Likert scale 0-3 | No difference between groups (data not given) | |
| | | | HbA1c, %, mean , SD | 7.5 (0.5) | 7.0 (0.7) | | | | | | |
| | | | All baseline characteristics were similar for both groups, except for mean HbA1c levels in the Mixed vs. Regular group. | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| glycemic control, physiological responses to hypoglycemia, well-being, or treatment satisfaction. Diabetes Care 23 (5):629-633, 2000.<br><br>REF ID: JANSSEN 2000 | | | Drop-outs:<br>Not mentioned | IN BOTH GROUPS: dose of insulin if necessary were adjust by increments of 2U every 3 days to attain glucose targets. patients kept SMBG diaries. | | | | | |

### G.4.3.6 Basal/bolus (mixed insulin: aspart) versus basal/bolus (mixed insulin: human)

**Table 237: BOEHM 2002 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| B. O. Boehm, P. D. Home, C. Behrend, N. M. Kamp, and A. Lindholm. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients. Diabet.Med. 19 (5):393-399, 2002.<br><br>REF ID: BOEHM 2002 | RCT<br><br>36 centres in Europe | n=294 type 1 diabetes and type 2 diabetes<br>(only n=104/36% type 1 diabetes) – but type 1 diabetes subgroup analysis was presented for outcome of major hypoglycaemia<br><br>Inclusion criteria:<br>Adults<br>Diabetes (type 1 diabetes and type 2 diabetes)<br>BMI <35.0<br>HbA1c ≤11.0%<br>Already using twice/day insulin regimens.<br><br>Exclusion criteria:<br>None given. | type 1 diabetes subgroup | BIAsp (n=55) | BHI (n=49) | MIXED: BIAsp 30<br><br>BIPHASIC ASPART 30 /70 (pre-mix of30% free IAsp and 70% protamine-bound IAsp)<br>Given twice/day, before breakfast and dinner)<br><br>BiAsp30 to be injected within 10 minutes before meals | MIXED: BHI 30<br><br>BIPHASIC HUMAN INSULIN 30/70 (Pre-mix equivalent of BiAsp)<br>Given twice/day, before breakfast and dinner)<br><br>BHI to be injected approx. 30 minutes before meals | 12 weeks treatment | Major hypoglycaemia, no. of episodes in type 1 diabetes patients | BIAsp : 14<br>BHI: 30 | Funding: Part of Novo Nordisk programme<br><br>Risk of bias:<br>Randomisation = unclear. Blocks of 8, stratified within each centre; but details of generation method not given<br>Allocation concealment = good. Electronic drug request/voice response system<br>Blinding = open label.<br>Not true ITT |
| | | | Age, years, mean (SD) | 43.2 (13.4) | 46.3 (12.8) | | | | | | |
| | | | Women, % | 36 | 31 | | | | | | |
| | | | Diabetes duration, years, mean (SD) | 14.9 (11.0) | 17.0 (13.0) | | | | | | |
| | | | Weight, kg (SD) | 76.1 (14.2) | 79.7 (14.5) | | | | | | |
| | | | HbA1c, %, mean , SD | 8.37 (1.24) | 8.38 (1.14) | | | | | | |
| | | | All baseline characteristics were similar for both groups.<br><br>Drop-outs:<br>Unclear for type 1 diabetes subgroup. However overall trial population was only 10% drop-outs in BIAsp group and 4% in the BHI group. In the BIAsp group some drop-outs were due to personal reasons, and so the two groups have almost exactly the | | | IN BOTH GROUPS: | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | same % drop-outs for all other /study-related reasons. | Dose of both biphasic insulins were initially 100U/litre and contained in a 1.5ml Penfill cartridges (Novo Nordisk), administered using NovoPen 1.5 device.<br>Doses adjusted according to SMBG measurements. | | | | | analysis<br>Powered study (HbA1c)<br>Drop-outs = <20% overall, type 1 diabetes not mentioned. |

### G.4.3.7 Basal/bolus (mixed insulin: Humalog25 or Novolog30) versus basal-bolus (glargine plus glulisine)

**Table 238: TESTA 2012A xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MA. Testa, J Gill, M Su, RR. Turner, L Blonde, and DC. Simonson. Comparative Effectiveness of Basal-Bolus | RCT – crossover<br>52 centres in USA | n=388 type 1 diabetes and type 2 diabetes (only n=82 /21% type 1 diabetes) – but type 1 diabetes subgroup analysis was | type 1 diabetes + type 2 diabetes | GLARG (n=192) | MIX (n=196) | GLARGINE + GLULISINE<br>Glargine once/day<br>Glulisine | MIXED BIPHASIC ANALOGUE: HUMALOG25 or NOVOLOG 30<br>Pre-mixed | 12 weeks treatment | treatment satisfaction, type 1 diabetes patients mean (SE)<br>Data from | GLARG: 56.2 (2.6)<br>MIX: 28.5 (2.6) | Funding: Part of Novo Nordisk programme<br>Risk of bias: Randomisation = unclear |
| | | | Age, years, mean (SD); range | 53.7 (10.7); 22-76 | 53.4 (11.5); 23-76 | | | | | | |
| | | | Women, % | 20.3 | 21.9 | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Versus Premix Analog Insulin on Glycemic Variability and Patient-Centered Outcomes during Insulin Intensification in Type 1 and Type 2 Diabetes: A Randomized, Controlled, Crossover Trial. J.Clin.Endocrinol.Metab. 97 (10):3504-3514, 2012.<br><br>REF ID: TESTA 2012A | | presented for outcome of QoL<br><br>Inclusion criteria:<br>Adults age 21-70 years<br>Diabetes (type 1 diabetes and type 2 diabetes) for at least 6 months<br>Stable on premix 75/25 or 70/30 insulin, NPH or insulin glargine with SA insulin consisting of 2 injections/day, with or without concomitant oral medications (metformin, thiazolidione, and/or α-glucosidase inhibitor) for 3 months before screening.<br>HbA1c between 7.0% and 9.0%<br>Employed, unpaid work or active | | | | before meals | insulins<br>Humalog 25 = 25% Lispro/75% Lispro-protamine<br>Novolog 30 = 30% aspart/70% aspart-protamine<br>Mix taken twice/day | | both periods combined | | (no details provided).<br>Allocation concealment = unclear (not mentioned)<br>Blinding = not mentioned.<br>No wash-out period<br>ITT analysis<br>No details of powering,<br>Drop-outs = approx.. 20% overall, type 1 diabetes not mentioned.<br>Not done ANCOVA analysis (best for cross-over studies). |
| | | | Diabetes duration, years, mean (SD) | 15.5 (9.3) | 16.6 (9.7) | | | | Regimen acceptance, type 1 diabetes patients mean (SE)<br><br>Data from both periods combined | GLARG: 64.6 (1.3)<br><br>MIX: 60.6 (1.3) | |
| | | | BMI, kg/m2 (SD) | 34.7 (7.9) | 33.9 (7.74) | | | | | | |
| | | | HbA1c, %, mean , SD | 7.8 (0.7) | 7.8 (0.7) | | | | | | |
| | | | treatment satisfaction (type 1 diabetes patients), mean | 44.8 | | IN BOTH GROUPS:<br>Doses adjusted according to pre-specified algorithm to achieve target blood glucose. Values.<br>Clinic staff phone patients each week to provide insulin-dosing recommendations.<br>patients adjusted dose according to diet and exercise requirements (but not given a specific CHO counting algorithm).<br><br>OUTCOME MEASURES: QoL<br><br>1. Treatment satisfaction: 71- | | | | | |
| | | | Regimen acceptance (type 1 diabetes patients), mean | 63.5 | | | | | | | |
| | | | No difference between groups for any of the baseline characteristics.<br><br>Drop-outs: | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | lifestyle.<br><br>Exclusion criteria:<br>Significant cardiac disease<br>Cancer<br>Laboratory abnormalities<br>Insulin pump or concomitant oral diabetes medications not listed above<br>Inability to complete a 72 hour CGM session after 3 attempts during the lead-in period before randomisation. | Unclear for type 1 diabetes subgroup. However overall trial population was only 10% drop-outs in each group after period 1; and after period 2 was 3.5% and 13.9% (Glarg vs. MIX groups respectively). In the MIX group some drop-outs were due to personal reasons, and so the two groups have almost exactly the same % drop-outs for all other /study-related reasons. | item Treatment Satisfaction module – actual score range not given.<br>2. Regimen acceptance: 12-item Comparative Treatment Preference module – actual score range not given.<br><br>HIGHER SCORES= more favourable response | | | | | |

### G.4.3.8 Basal/bolus (mixed insulin: Lispro25 and 50) versus basal/bolus (mixed human 50 and 30)

**Table 239: ROACH 1999 (ID 1029) xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P. Roach, M. Trautmann, V. Arora, B. Sun, and J. H. Anderson, Jr. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. Clin.Ther. 21 (3):523-534, 1999.<br><br>REF ID: ROACH 1999 | RCT – crossover<br><br>20 centres in Europe | n=100 type 1 diabetes and type 2 diabetes<br>(only n=37 /37% type 1 diabetes) – but type 1 diabetes subgroup analysis was presented for HbA1c and all hypoglycaemia. Outcomes.<br><br>Inclusion criteria:<br>Adults age 18-70 years<br>Diabetes (type 1 diabetes and type 2 diabetes) (WHO criteria)<br>Treated with commercially avail human insulin twice/day for at least 120 days prior to study<br><br>Exclusion criteria:<br>HbA1c >9.2% | type 1 diabetes | LISPRO MIX (n=19) | HI MIX (n=18) | LISPRO MIX25 and MIX50<br><br>AM Before breakfast: Pre-mix lispro Mix50 (50% lispro/50% NPL)<br>PM Before dinner: Mix25<br><br>Lispro mixes given immediately before the meals | HUMAN INSULIN MIX 50/50 and MIX 30/70<br><br>AM Before breakfast: Pre-mix human insulin 50/50 (50% regular/50% NPH)<br>PM Before dinner: mix 30/70<br><br>Human mixes given 30-40 minutes before the meals. | 3 months each treatment period | HbA1c, final value, %<br>(for type 1 diabetes subgroup) | LISP: 7.69<br><br>HI: 7.40<br><br>P=0.44 | Funding: Not mentioned specifically, but main authors work for Eli Lilly and drugs provided by Eli Lilly.<br><br>Risk of bias:<br>Randomisation = unclear (no details provided).<br>Allocation concealment = unclear (not mentioned)<br>Blinding = open label.<br>No wash-out period<br>ITT analysis – LOCF; all dropouts had 1 month data |
| | | | Age, years, mean | 42.2 | 36.5 | | | | Severe hypoglycaemia., number of episodes<br>(for type 1 diabetes subgroup) | LISP: 2<br><br>HI: 4<br><br>P=NS | |
| | | | Women, % | 37 | 28 | | | | Hypoglycaemia, % patients<br>(for type 1 diabetes subgroup) | LISP: 71%<br>HI: 68%<br><br>p=NS | |
| | | | Diabetes duration, years, mean | 14.3 | 11.4 | | | | | | |
| | | | BMI, kg/m2 | 25.1 | 24.5 | | | | | | |
| | | | HbA1c, %, mean , | Not given | | | | | Nocturnal hypoglycaemia, mean (SD) episodes/patient | LISP: 1.5 (2.3)<br><br>HI: 2.9 | |
| | | | Both groups similar for all baseline characteristics. | | | IN BOTH GROUPS:<br>Doses adjusted by investigators to reach specific treatment goals of blood glucose. | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| (ID 1029) | | Significant renal, hepatic or cardiac disease<br>Cancer<br>History of drug or alcohol abuse<br>Insulin allergy<br>Recurrent severe hypoglycaemia<br>Anaemia or haemoglobinopathy<br>Treated with oral antidiabetic agents, systemic glucocorticoids<br>Insulin doses >2.0U/kg/day. | Drop-outs:<br>n=3 (8.1%) for type 1 diabetes subgroup; between the two treatment groups. | | | | (for type 1 diabetes subgroup) | (5.1)<br>P=0.13 | No details of powering,<br>Drop-outs = <20%.<br>Unclear if done ANCOVA analysis (best for cross-over studies). |

### G.4.3.9 Basal/bolus (mixed insulin: Lispro) versus basal/bolus (mixed Human)

**Table 240: ROACH 2001 (ID 1043) xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P. Roach, T. | RCT | n=166 type 1 | type 1 | LP/NPL | HR/NP | LP/NPL MIX | HR/NPH MIX | 12 | Hypoglycaemia, | LP/NPL | Funding: Not |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Strack, V. Arora, and Z. Zhao. Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin lispro protamine suspension in patients with types 1 and 2 diabetes. Int.J.Clin.Pract. 55 (3):177-182, 2001.<br><br>REF ID: ROACH 2001 (ID 1043) | 5 centres world wide | diabetes and type 2 diabetes (n=100 /60% type 1 diabetes) – but type 1 diabetes subgroup analysis was presented for hypoglycaemia outcomes.<br><br>Inclusion criteria:<br>Adults age 18-75 years<br>Diabetes (type 1 diabetes and type 2 diabetes) (WHO criteria)<br>Treated with mixed insulin SA or RA ( regular human or Lispro) and IA or LA insulin twice/day (self-mixed or pre-mixed) for at least 120 days before study<br><br>Exclusion criteria:<br>HbA1c >9.2%<br>Significant renal, | diabetes and type 2 diabetes | MIX (n=86) | H MIX (n=80) | LP = Lispro<br>NPL = Lispro-protamine<br>Self-mixed Twice/day (morning and evening, 0-15 minutes before the two meals) | HR = human regular insulin (humulin R)<br>NPH = Human NPH (Humulin N)<br>Self-mixed<br>Twice/day (morning and evening, 30-45 minutes before the two meals) | months treatment | median rate (episodes/patient/30 days)<br><br>(for type 1 diabetes subgroup) | : 1.61<br><br>HR/NPH: 1.65 | mentioned specifically, but main authors work for Eli Lilly and drugs provided by Eli Lilly.<br><br>Risk of bias:<br>Randomisation = unclear (no details provided).<br>Allocation concealment = unclear (not mentioned)<br>Blinding = open label.<br>ITT analysis – LOCF<br>No details of powering,<br>Drop-outs =not mentioned. |
| | | | Age, years, mean | 47.0 | 47.0 | | | | | | |
| | | | Women, % | 31.4 | 33.8 | | | | | | |
| | | | Diabetes duration, years, mean | 14.0 | 14.9 | | | | | | |
| | | | BMI, kg/m2 | 25.6 | 26.1 | | | | | | |
| | | | HbA1c, %, mean , | Not given | | | | | | | |
| | | | NS differences between groups for all baseline characteristics except SS lower post-prandial blood glucose. In the LP/NPL group.<br><br>Drop-outs:<br>Not mentioned. | | | IN BOTH GROUPS:<br>Doses adjusted to meet blood glucose. Targets<br>After 3 month visit, investigators and patients allowed to alter treatment regimen based on SMBG. | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | hepatic or cardiac disease<br>Cancer<br>History of drug or alcohol abuse<br>Insulin allergy<br>Recurrent severe hypoglycaemia<br>Anaemia or haemoglobinopathy<br>Proliferative retinopathy<br>BMI >35 kg/m2<br>Lactating, pregnant or intending to become pregnant<br>Treated with oral antidiabetic agents, systemic glucocorticoids<br>Insulin doses >2.0U/kg/day. | | | | | | | |

### G.4.3.10 Basal/bolus (mixed insulin: Penmix) versus basal/bolus (usual human mix)

**Table 241: DUNBAR 1999 (ID 1054) xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| J. M. Dunbar, P. M. Madden, D. T. Gleeson, T. M. Fiad, and T. J. McKenna. Premixed insulin preparations in pen syringes maintain glycemic control and are preferred by patients. Diabetes Care 17 (8):874-878, 1994.<br><br>REF ID: DUNBAR 1999 (ID 1054) | RCT – cross-over<br><br>Single centre, Ireland | n=32 Outpatients<br><br>Inclusion criteria:<br>Adults aged >18 years<br>type 1 diabetes at least 1 year before study<br>Receiving Human Actrapid & Human Monotard (IA-insulin) as appropriate to clinical requirements.<br>Been on stable insulin regimens for ≥ 2 months<br>Exclusion criteria:<br>None given | | All completers (n=27) | PEN MIX<br><br>patients transferred to a SA/LA preparation closest to their previous treatment ratios: Penmix (Novo Nordisk) 10/90%, 20/80%, 30/70%, 40/60% and 50/50%<br><br>Delivered by Novopen II<br>patients may use different mixtures in morn & eve | PT MIX<br><br>Continue usual/previous treatment (Human Actrapid and Human Monotard (IA-insulin)<br><br>IN BOTH GROUPS:<br>Doses adjusted by patients or physicians to meet blood glucose. Targets | 2 months treatment | HbA1c, % (SD)<br><br>After both cross-over periods, data combined for all patients | PEN MIX: 11.3 (2.0)<br><br>PT MIX: 11.2 (2.0) | Funding: Not mentioned specifically, but insulins were Novo Nordisk.<br><br>Risk of bias:<br>Randomisation = unclear (no details provided).<br>Allocation concealment = unclear (not mentioned)<br>Blinding = open label.<br>No mention of wash-out period<br>Not ITT analysis<br>No details of powering, |
| | | | Age, years, mean (SD) | 34.77 (12.9): range 18-63 | | | | | | |
| | | | Women, % | Not given | | | | Hypoglycaemia grade 3* or 4**, no of patients | PEN MIX: 5<br>PT MIX: 4 | |
| | | | Diabetes duration, years, mean (SD) | 10.61 (8.1) – range 9 months – 29 years | | | | | | |
| | | | BMI, kg/m2 | Not given | | | | Hypoglycaemia grade 3* or 4**, no. of episodes | PEN MIX: 8<br>PT MIX: 22 | |
| | | | HbA1c, %, mean, | PEN MIX: 11.3 (2.2)<br>PT MIX: 11.8 (1.8)<br>ALL: 11.6 (1.9) | | | | patient preference: 83% Pre-mix<br>Pre-mix easier to use: 86%<br>Continue using pre-mix: 83% | | |
| | | | Drop-outs: | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | n=5 (16%) other details not mentioned. | | | | *GRADE 3: assistance required (but not parenteral treatment)<br>**GRADE 4: Parenteral treatment or treatment by physician required. | | Drop-outs <20%.<br>Unclear if done ANCOVA analysis, mentions that used analysis of variance suitable for cross-overs (ANCOVA best for cross-over studies). |

### G.4.3.11 Basal-bolus (bolus normal but mixed basal in evening) versus basal-bolus

**Table 242: FANELLI 2002 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| C. G. Fanelli, S. Pampanelli, F. Porcellati, P. Rossetti, P. Brunetti, and G. B. Bolli. Administration of neutral protamine | RCT - crossover<br><br>1 centre, Italy | n=22<br><br>Inclusion criteria: type 1 diabetes patients receiving long-term intensive insulin treatment (Multiple injections | | All patients | BASAL-BOLUS using MIXED evening treatment<br><br>Regular insulin (RI) at breakfast and lunch, with MIXED INSULIN | BASAL-BOLUS/split treatment (BB)<br><br>4/day INSULIN: (RI) before all 3 meals and | 4 months treatment | HbA1c, final value %, mean (SE) | MIX: 7.5 (0.15)<br>BB: 7.0 (0.11) | Funding: JDRF International<br><br>Risk of bias: Randomisation = unclear (as details |
| | | | Age, years, mean (SD) | 29 (3) | | | | Frequency of self-treatment nocturnal hypoglycaemia. n/patient-day | MIX: 0.28 (0.04)<br>BB: 0.1 (0.02) | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Hagedorn insulin at bedtime versus with dinner in type 1 diabetes mellitus to avoid nocturnal hypoglycemia and improve control. A randomized, controlled trial. Ann.Intern.Med. 136 (137):504-514, 2002.<br><br>REF ID: FANELLI 2002 (ID 1019) | | with regular HI before meals and NPH at bedtime)<br><br>Exclusion criteria:<br>Hypoglycaemia unawareness<br>History of severe hypoglycaemia<br><br>patients had no detectable microangiographic complications, autonomic neuropathy, peripheral neuropathy, or microalbinuria<br>patients had no history or clinical evidence of HT and were taking no other medications other than insulin. | | | (regular + NPH) at dinner (evening mixed treatment) | NPH bedtime) | | (SE) | | not given)<br>Allocation concealment = not mentioned<br>Blinding = not mentioned.<br>No mention of wash-out period<br>ITT analysis (no drop-outs)<br>Powered study.<br>Drop-outs = none<br>Unclear if have done ANCOVA analysis – mentions used 2-period cross-over analysis of variance (ANCOVA best for cross-over |
| | | | Women, % | 45 | | | | Symptomatic nocturnal hypoglycaemia, episodes/patient-day (SE) | MIX: 0.045 (0.005)<br><br>BB: 0.027 (0.003) | |
| | | | Diabetes duration, years, mean (SD) | 14 (2) | | | | | | |
| | | | BMI, kg/m2, (SD) | 23 (1) | IN BOTH GROUPS:<br>Doses of meal-time (SA) insulins and NPH insulin were titrated to attain glucose targets.<br>To prevent nocturnal hypoglycaemia, patients were suggested to consume a snack containing 20g CHO when blood glucose. Reached particular levels at bedtime or at night. If hypoglycaemia. Symptoms were not relieved after 10 minutes, then they were to try another similar snack | | | Severe hypoglycaemia | MIX: 0<br>BB: 0 | |
| | | | HbA1c, %, mean , SD | 6.7 (0.4) | | | | 40% and 50% of hypoglycaemia. episodes (MIX and BB respectively), were corrected by consuming 20g CHO; 60%/43% corrected by 40g CHO. | | |
| | | | Drop-outs:<br>None | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | studies). |

### G.4.3.12 Basal/bolus (mixed 3/7) versus basal/bolus (mixed 2/8 – 4/6)

**Table 243: CUCINOTTA 1991 xxxxxx**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| D. Cucinotta, D. Mannino, A. Lasco, E. Di Cesare, C. Musolino, and R. Alessi. Premixed insulin at ratio 3/7 and regular + isophane insulins at mixing ratios from 2/8 to 4/6 achieve the same metabolic control. Diabetes Metab 17 (1):49-54, | RCT - crossover<br><br>Single centre, Italy | n=20<br><br>Inclusion criteria:<br>type 1 diabetes (IDDM)<br>Insulin treated for at least 1 year<br>Stable insulin dose at last 3 months<br>Constant fasting glucose <200mg/dl during the last 2 months<br>BMI between 20-30 kg/m2 | | All patients | HUMAN PRE-MIX 3/7 (Actraphane HM)<br><br>Actraphane = Human + NPH<br><br>Timing not mentioned – but assuming same as for comparison group | REGULAR MIX (Human + NPH 2/8 to 4/6)<br><br>2/day before breakfast and dinner | 4 months treatment | Hypoglycaemia, episodes/week/patient | MIX 3/7: 0.03<br>R + NPH: 0.03 | Funding: Not mentioned<br><br>Risk of bias:<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not mentioned<br>Blinding = not mentioned.<br>No mention of wash-out period<br>ITT analysis (no |
| | | | Age, years, mean (range) | 41.5 (19-72) | | | | Hypoglycaemia, no. of patients | MIX 3/7: 2<br>R + NPH: 2 | |
| | | | Women, % | 45 | | | | | | |
| | | | Diabetes duration, years, mean (range) | 21.4 (4-31) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 1991.<br><br>REF ID: CUCINOTTA 1991 | | Exclusion criteria:<br>None mentioned<br><br>patients had treatment with regular + NPH human insulin at mixing ratios ranging from 2/8 to 4/6 injected before breakfast and dinner. | Drop-outs:<br>None | | | | *GRADE3: requires assistance of another person | | drop-outs)<br>Powering not mentioned.<br>Drop-outs = none<br>Unclear if done ANCOVA analysis (best for cross-over studies). |

## G.4.4 Adjuncts

**Table 244: PITOCCO 2013**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D. Pitocco, F. Zaccardi, P. Tarzia, M. Milo, G. Scavone, P. Rizzo, et al. Metformin improves endothelial | RCT<br><br>Single centre, Italy | n=42<br><br>Inclusion criteria:<br>type 1 diabetes<br>Age >18 years<br>Diabetes duration ≥5 years | | Metf (n=21) | Plac (n=21) | Metformin (+ insulin as already on insulin)<br><br>titrated up to 850mg TDS (after 2 | Placebo (+ insulin as already on insulin) | 6 months | | Metfor | Placebo | Funding: None mentioned<br><br>Risk of bias:<br>Randomisation: unclear |
| | | | | | | | | | HbA1c (95% CI), SE | Between group difference:<br>0.17 (-0.36, 0.72), -0.27 | | |
| | | | Age<br>Mean (SD) | 46 (8) | 41 (10) | | | | Total daily insulin (95% CI), | Between group difference:<br>-0.027 (-0.10, | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| function in type 1 diabetic subjects: a pilot, placebo-controlled randomized study. Diabetes Obes.Metab. 15 (5):427-431, 2013.<br><br>REF ID: PITOCCO 2013 | | Exclusion criteria:<br>Baseline HbA1c ≥10%<br>Plasma creatinine >1.6 mg/dl<br>Plasma AST elevated > 2x above normal upper limit<br>Co-morbidities<br>Pregnancy<br>Current or former smoking or alcohol abuse<br>treatment other than insulin at baseline and during study. | Disease duration, years | 9.2 | 8.8 | weeks) | | | SE | 0.51), -0.22 | | – no details given just says 'randomised'<br>Allocation concealment: unclear – no details given<br>Blinding: double<br>ITT analysis: yes as no drop-outs<br>Drop-outs: none |
| | | | | | | | | | Weight, kg (95% CI), SE | Between group difference:<br>-2.27 (-3.99, -0.54), -0.85 | | |
| | | | M/F | 9/12 | 9/12 | | | | Severe hypo episodes | 0 | 0 | |
| | | | HbA1c % (SD) | 7.24 (0.90) | 7.73 (0.42) | | | | Adverse events:<br>Gastrointestinal side-effects | Not reported | | |
| | | | BMI | 28.7 | 27.3 | | | | | | | |
| | | | Weight (SD) | 83 (12) | 77 (11) | | | | | | | |
| | | | Drop outs: none | | | | | | | | | |

**Table 245: BURCHARDT 2013**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P Burchardt, A Zawada, P Tabaczewski, | RCT | n=68 randomised, n=52 completers | | Metf + insulin (n=33) | Insulin (n=19) | Metformin (+ insulin as already on | Remained on usual insulin | 6 months | | Met | Insulin | Funding: Grant from Ponzan |
| | | | | | | | | | HbA1c, | 7.7 | 8.1 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D Naskret, et al. Metformin added to intensive insulin therapy reduces plasma levels of glycated but not oxidized low-density lipoprotein in young patients with type 1 diabetes and obesity in comparison with insulin alone: a pilot study. Pol.Arch.Med .Wewn. 123 (10):526-532, 2013.<br><br>REF ID: BURCHARDT 2013 | Poland | Inclusion criteria:<br>type 1 diabetes<br>Age 18-60 years<br>Duration >5 years<br>Lack of metabolic control (HbA1c >7.5% despite education and intensive insulin treatment)<br>Obese patients<br><br>Exclusion criteria:<br>Metabolically decompensate diabetes with acetonuria<br>Suspected lack of compliance as well as glucose and ketone self-monitoring<br>Hypo unawareness or recurrent SH in past 3 months<br>Recurret DKA<br>Pregnancy or lack of contraception<br>Renal impairment<br>Liver disease | | | | insulin)<br><br>Doses adjusted to body fat content of individuals. Overweight followed regime of 500-1500 mg/d; Obese took 1000-2550 mg/d according to drug tolerance<br><br>Metformin taken with meals to minimise GI side-effects | treatment<br><br>BOTH GROUPS: before randomised treatment started, both groups wre hospitalised for 1 week to o[ptimise insulin treatment. | | final (SDI) | (1.2) | (1.4) | University of Medical Sciences<br><br>Risk of bias:<br>Randomisation: unclear – no details given just says ‘randomised and 1:1’<br>Allocation concealment: no details given<br>Blinding: open label<br>ITT analysis: no<br>Drop-outs: >20% overall and >10% diff btwn arms |
| | | | Age Mean | 35.3 | 30.5 | | | | | | | |
| | | | Disease duration, years | 15.9 | 15.9 | | | | | | | |
| | | | M/F | 27 women (total 52 patients) | | | | | NOTE: patients in metformin group had a SS higher BMI to start with | | | |
| | | | HbA1c % (SD) | 9.0 (1.9) | 8.3 (1.0) | | | | | | | |
| | | | BMI (SD) | 29.5 (3.2) | 27.1 (2.4) | | | | | | | |
| | | | Drop outs:<br>n=2 (metformin) – 6%<br>n=14 (control) – 41% | | | | | | | | | |

**Table 246: SARKAR 2014**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| G. Sarkar, M. Alattar, R. J. Brown, M. J. Quon, D. M. Harlan, and K. I. Rother. Exenatide treatment for 6 months improves insulin sensitivity in adults with type 1 diabetes. Diabetes Care 37 (3):666-670, 2014.<br><br>REF ID: SARKAR 2014 | RCT (cross-over)<br><br>USA | n=16 randomised, n=13 completers<br><br>Inclusion criteria:<br>Long-standing type 1 diabetes (duration mean 21 years)<br><br>Exclusion criteria:<br>None reported | | Baseline (end of run-in period) n=13 | Exenatide (+ insulin as already on insulin) +/- daclizumab<br><br>NOTE: analysis done about effects of daclizumab and shown to make no difference to results if patients had dac or not.<br><br>Exenatide dose: administered sc at starting dose of 2.5ug 2x/day and increased gradually to 10 micrograms 4 times a day.<br><br>Prandial insulin doses were reduced by 50% at initiation of exenatide treatment then | Remained on usual insulin treatment<br><br>BOTH GROUPS: before randomised treatment started, both groups had a 2-4 month optimisation period (insulin doses and carb counting adjusted and improved). This was followed by a run-in period in which no further insulin dose changes were made. | 6 months treatment (each cross-over period) | | Exen | Insulin | Funding: Grant from NIDDK and NIH Clinical Centre, USA.<br><br>Risk of bias:<br>Randomisation: unclear – no details given just says 'randomised'<br>Allocation concealment: unclear – no details given<br>Blinding: open label<br>No wash-out period<br>ITT analysis: no<br>Drop-outs: <20%; approx. 10% difference between |
| | | | Age Mean | 37.3 (10.7) | | | | HbA1c - final (SDI) | 6.6 (0.5) | 6.7 (0.6) | |
| | | | Disease duration, years (SD) | 21.3 (10.7) | | | | Weight, kg (SD) | 72.7 (11.8) | 76.9 (11.3) | |
| | | | M/F | n=9 male | | | | | | | |
| | | | HbA1c % (SD) | 6.4 (0.7) | | | | Insulin, units/kg/day | 0.47 (0.1) | 0.54 (0.13) | |
| | | | BMI (SD) | - | | | | | | | |
| | | | Weight, kg (SD) | 77.7 (11.0) | | | | | | | |
| | | | Drop outs:<br>n=2 (no exenatide)<br>n=1 (exenatide) | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | gradually increased to reach blood glucose targets. | | | | | | arms |

**Table 247: Edelman 2006[39]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Edelman S, Garg S, Frias J, Maggs D, Wang Y, Zhang B et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care. 2006; 29(10):2189- | Parallel RCT | n=296<br>n=148 Pramlintide<br>n=147 Placebo<br>Inclusion criteria: Age ≥18 years, insulin use >1 year, HbA1c 7.5-9.0%, no severe hypo-glycaemia for 6 months before screening.<br>Exclusion criteria: Clinically | Adults with type 1 diabetes treated with multiple daily injections (MDI) OR continuous subcutaneous insulin infusion (CSII) | | | Pramlintide 15-60 µg/meal | Placebo | 29 weeks | | Pram | Placebo | Funding: Unclear. Authors affiliated with Amylin pharmaceuticals<br>Risk of bias: Randomisation method unclear<br>Allocation concealment: not reported<br>Blinding: said to be "double blind"<br>ITT analysis: last value carried forward<br>Drop-outs: acceptable <20% |
| | | | | Pram | Placebo | | | | HbA1c (SD) | -0.5% ±0.87 | -0.5% ±0.87 | |
| | | | Age Mean (SD) | 41 ±14 | 41 ±12 | | | | Hypo-glycaemia (symptoms of) | 136/ 148 | 134/ 147 | |
| | | | M/F | 60/87 | 72/76 | | | | Dose of insulin (SD not reported) | -12IU | +1IU | |
| | | | | | | | | | Weight Change | -1.3 ±3.65 | +1.2 ±2.9 | |
| | | | | | | | | | Quality of Life (Likert Scale 1-6) | 3.74 | 2.74 | |
| | | | | | | | | | Adverse events: | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2195<br><br>REF ID: EDELMAN2006 | | significant comorbid condition including gastroparesis, using medications affecting gastrointestinal motility, using oral anti-diabetic or antiobesity agents | Hb A1c | 8.1 ±0.8 | 8.1 ±0.8 | | | | Nausea<br><br>Vomiting<br><br>Reduced appetite | 93/148<br><br>20/148<br><br>13/148 | 53/147<br><br>9/147<br><br>3/147 | |
| | | | | | | | | | | | | |
| | | | Drop outs: Pramlintide 12.2%; Placebo 7.5% | | | | | | | | | |

**Table 248: Khan 2006**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Khan AS, McLoughney CR, Ahmed AB. The effect of metformin on blood glucose control in | Cross-over RCT | n=15<br><br>Inclusion criteria: C-peptide <0.18 nmol/litre at a time when blood | Overweight patients (BMI >27) with type 1 diabetes > 1 year. C-peptide negative | | Metformin 850mg TDS | Placebo | 16 weeks<br><br>(4 week washout) | | Metfor | Placebo | Funding: Equipment/drugs provided by industry<br>Risk of bias:<br>Randomisation: computer generated<br>Allocation concealment: adequate |
| | | | | Crossover | | | | HbA1c ±SD<br>baseline<br>final | 8.5±1.4<br>7.8±1.1 | 8.7±1.1<br>8.5±1.4 | |
| | | | Age<br>Mean (SD) | 48 ± 12 | | | | Insulin<br>baseline<br>final | 60 ±14<br>50 ±13 | 60 ±13<br>58 ±12 | |
| | | | | | | | | Weight | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| overweight patients with Type 1 diabetes. Diabetic Medicine. 2006; 23(10):1079-1084 [72,73]<br>REF ID: KHAN 2006 | | glucose level as >5.0,type 1 diabetes for >1 year, BMI>27 stable on insulin therapy, baseline HbA1c >6.1%, no late diabetic complications<br><br>Exclusion criteria: Not reported | | | | | | baseline final | 91 ±12<br>89 ±11 | 91 ±12<br>90 ±12 | Blinding: patients and investigators blinded<br>ITT analysis: true ITT<br>Drop-outs: none |
| | | | M/F | 8/7 | | | | Hypos (per pt. per month) | 12 ±7 | 11 ±6 | |
| | | | Hb A1c | 8.6% ±1.4 | | | | Adverse events:<br>Gastrointestinal side-effects | 3 | 1 | |
| | | | BMI | 31.3 ± 2.6 | | | | | | | |
| | | | Insulin Regimen | Basal bolus: 12<br>Twice daily: 3 | | | | | | | |
| | | | Drop outs: none | | | | | | | | |

**Table 249: Levetan 2003**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Levetan C, Want LL, Weyer C, Strobel SA, Crean J, Wang Y et al. Impact of pramlintide on glucose fluctuations | Parallel RCT | n=24<br>Pramlintide= 18;<br>Placebo n=6<br>Inclusion criteria: type 1 diabetes >1 year, not changed total daily | Patients with type 1 diabetes >1 year CSII basal-bolus regimen for at least 6 months | | Pramlintide 30 µg/ meal TDS | Placebo | 4 weeks | | Pramlin | Placebo | Funding: Authors employed by Amylin pharmaceuticals<br>Risk of bias:<br>Randomisation:3:1 block randomisation<br>Allocation |
| | | | | Baseline characteristic given for Pramlintide group only | | | | Change in Insulin dose IU (mean mealtime) | -1.2 IU | | |
| | | | Age | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| and postprandial glucose, glucagon, and triglyceride excursions among patients with type 1 diabetes intensively treated with insulin pumps. Diabetes Care. 2003; 26(1):1-8<br><br>REF ID: LEVETAN 2003 [96] | | insulin dosage by more than ±10% for 2 months before study, no severe hyper/hypo-glycaemia for >4 weeks<br>Exclusion criteria: significant history of cardiac disease, poorly controlled HTN, GI hepatic renal or CNS disorders, acute illness, history of drug or alcohol abuse, treatment with drugs known to affect GI motility or glucose metabolism | Mean (SD) | 44 ± 11 | | | | | | concealment: unclear<br>Blinding: subjects blinded, other blinding unclear<br>ITT analysis: ACA<br>Drop-outs: acceptable ( 2/24 8%) |
| | | | M/F | 8/10 | | | | | | |
| | | | HbA1c | 8.2% ± 1.3 | | | | | | |
| | | | BMI | 25 ± 10 | | | | | | |
| | | | Insulin Regimen | Lispro 16<br>Regular 2 | | | | | | |
| | | | Drop outs: 2 | | | | | | | |

**Table 250: Ratner 2004**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Ratner RE, Dickey R, Fineman M, Maggs DG, Shen L, Strobel SA et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. | Parallel RCT | n=304<br>Safety Data n=651<br><br>Inclusion criteria: type 1 diabetes >1 year (C-peptide <1ng/ml/DKA/islet cell Abs), HbA1c >8% at screening, stable weight ±2.5kg and stable daily insulin ±10% for >2 months, no severe hypo/hyper-glycaemia for>2 weeks, females post-menopausal, | Patients aged 16-76 with type 1 diabetes >1year<br><br>Placebo: M/F 53/47; HbA 9.0 ±1.1<br>Pramlintide 60 µg TDS: M/F 52/48; HbA 8.9 ±1.1<br>Pramlintide 60 µg QD: M/F 52/48; HbA 8.9 ±1.0<br>Pramlintide 90 µg TDS: M/F 47/53; HbA 8.9 ±0.9 | Pramlintide 60 µg - 90 µg TDS and QDS | Placebo | 1 year | HbA1c no SD (p<0.05)<br>Insulin dose (no SDs)<br>Safety data: 90 µg group included<br>Severe Hypos (per 100 patient | Pramlintide: HbA1c -0.316; Insulin dose TDS -3% QDS -6%; Safety data: 90 µg group included<br>Placebo: HbA1c -0.04; Insulin dose ±0%<br>Pramlintide 60 TDS / 60 QD / 90 TDS; Plac | Funding: Authors employed by Amylin pharmaceuticals<br><br>Risk of bias: Randomisation : method unclear<br>Allocation concealment: unclear<br>Blinding: double blinded<br><br>ITT analysis: ITT stated but missing data (not true ITT)<br>Drop-outs: High (pramlintide 42% placebo 33%) |

| Reference | Study type | Number of patients | Patient characteristics | | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetic Medicine. 2004; 21(11):1204-1212<br>REF ID: RATNER 2004 | | sterilized or using adequate contraception<br>Exclusion criteria: Clinically significant cardiovascular, respiratory, CNS, GI, renal or haematological disorders, drug or alcohol abuse, acute febrile illness, drugs that affect GI motility or glucose metabolism | 1c | | | | | | | | years) | | | | | |
| | | | BMI | 26.5 ±4.9 | 26.4 ±4.5 | 26.8 ±4.4 | 26.3 ±4.1 | | | | Incidence (%)<br>Nausea<br>Vomiting<br>Anorexia | 47<br>9.8<br>18 | 47<br>11<br>11 | 59<br>12<br>16 | 12<br>6.5<br>2.6 | |
| | | | Age ±SD | 41.3 ±13.6 | 39.2 ± 13.1 | 41.9 ±13.1 | 41.0 ±12.8 | | | | | | | | | |
| | | | Drop outs:<br>Placebo = 51/154 (33%)<br>Pramlintide = 210/497 (42%) | | | | | | | | | | | | | |

**Table 251: Meyer 2002**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Meyer L, Bohme | Parallel | n=62 | Outpatients with type | Metformin | Placebo | 6 months | | Metfor | Placeb | Funding: |

<table>
<tr>
<td>P, Delbachian I, Lehert P, Cugnardey N, Drouin P et al. The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. Diabetes Care. 2002; 25(12):2153-2158<br>REF ID: Meyer 2002 [107,108]</td>
<td>RCT</td>
<td>n= 31 Metformin<br>n=31 Placebo<br>Inclusion criteria: type 1 diabetes>1 year, C-peptide <0.3 after IV 1g glucagon, Treated with CSII > 1 year, HbA1c<9%, hypo-glycaemic unawareness<br>Exclusion criteria: any endocrine/ infectious/ inflammatory disease that modifies blood glucose, cardiac/renal/hepatic dysfunction, unstable retinopathy</td>
<td>1 diabetes >1 year. Treated with CSII >1 year (HbA1c<9%)
<table>
<tr><td></td><td>Plac</td><td>Met</td></tr>
<tr><td>Age Mean (SD)</td><td>41.1 ±9.8</td><td>39.9 ±12.9</td></tr>
<tr><td>M/F</td><td>20/ 11</td><td>17/ 14</td></tr>
<tr><td>Hb A1c</td><td>7.57 % ±0.76</td><td>7.58 % ±0.84</td></tr>
<tr><td>BMI</td><td>25.8 ±3.6</td><td>26.4 ±4.6</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
Drop outs: None reported</td>
<td>850mg BD</td>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td></td><td>o</td></tr>
<tr><td>HbA1c ±SD</td><td>7.45% ±0.78</td><td>7.46 ±0.6</td></tr>
<tr><td>Insulin Dose</td><td>-4.3 ±9.9</td><td>-1.7 ±8.3</td></tr>
<tr><td>Weight</td><td colspan="2">Full data not reported</td></tr>
<tr><td>Severe Hypo-glycaemia</td><td>3</td><td>5</td></tr>
<tr><td>Hypo-glycaemia (events/patient/month)</td><td>7.8 ±4.5</td><td>7.5 ±3.9</td></tr>
<tr><td>Adverse events:<br>Gastrointestinal side-effects</td><td>8</td><td>2</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
</td>
<td>Unclear. Supported by LIPHA pharmaceuticals<br>Risk of bias:<br>Randomisation method unclear<br>Allocation concealment: unclear<br>Blinding: double blinded<br>ITT analysis: true ITT<br>Drop-outs: None reported</td>
</tr>
</table>

**Table 252: Whitehouse 2002**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Whitehouse F, Kruger DF, Fineman M, Shen L, Ruggles JA, Maggs DG et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care. 2002; 25(4):724-730<br>REF ID: Whitehouse 2002 | Multi-centre Parallel RCT | n=480<br><br>Inclusion criteria: Aged 16 to 70 years, type 1 diabetes >1 year, C-peptide<1ng/ml, baseline HbA1c 7-13%, no hyper/hypo-glycaemia >2 weeks, not adjusted insulin dose >±10% 1 week<br>Exclusion criteria: Clinically significant IHD, HTN, GI disease, renal disease, unstable diabetic retinopathy, treatment | Patients with type 1 diabetes>1 year | | | Pramlintide 30-60 µg QDS | Placebo | 1 year | | Pram | Placebo | Funding: Unclear. Authors affiliated with amylin pharmaceuticals<br>Risk of bias: Randomisation method unclear<br>Allocation concealment: initial randomisation – unclear. Re-randomisation – third party randomisation<br>Blinding: double blinded<br>ITT analysis: ITT stated but missing data (not true ITT)<br>Drop-outs: Pramlintide 28.4%<br>Placebo 29.1% |
| | | | | Plac | Pram | | | | HbA1c ±SD | -0.39 ±0.824 | -0.12 ±0.824 | |
| | | | Age Mean (SD) | 40.4 ±12.1 | 40.3 ±11.6 | | | | Insulin | +2.3% ±27.7 | +10.3% ±27.7 | |
| | | | M/F | 55%/ 45% | 55%/ 45% | | | | Weight | | | |
| | | | Hb A1c | 8.9% ±1.5 | 8.7% ±1.3 | | | | | | | |
| | | | BMI | 25.8 ±3.5 | 25.2 ±3.3 | | | | Adverse events: (Incidence)<br>Nausea<br>Anorexia<br>Vomiting | <br>46.5%<br>17.7%<br>11.5% | <br>21.9%<br>2.1%<br>8% | |
| | | | | | | | | | | | | |
| | | | Drop outs: Pramlintide 28.4%. Placebo 29.1% | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | with drugs known to affect GI motility or glucose metabolism | | | | | | | | |

**Table 253: Jacobsen 2009[69]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Jacobsen IB, Henriksen JE, Beck-Nielsen H. The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. Basic and Clinical Pharmacology and Toxicology. 2009; 105(3):145- | Parallel RCT<br><br>Setting: Odense University Hospital Denmark | N =24 n=12 Metformin n=12 Placebo<br>Inclusion criteria: Aged 18-60 years, diagnosed with type 1 diabetes for at least 1 year (plasma C-peptide <5), BMI ≥ 25 kg/m²,<br><br>Exclusion criteria: | Adults with type 1 diabetes and BMI ≥ 25 kg/m²<br><br>Met / Placebo<br>Age: 43.5 ±13.1 / 37.3 ±9.6<br>BMI: 29.5 ±2.7 / 29.2 ±2.8<br>Male:Female 14:10<br><br>Drop outs: None | Metformin 1g BD | Placebo | 24 weeks | | Met | Placebo | Funding: Grant from Sehested Masden Foundation. Equipment/drugs provided by industry<br>Risk of bias: Randomisation: method unclear. Number of patients entering run-in period not reported<br>Allocation concealment: not reported<br>Blinding: |
| | | | | | | | Hb A1c | -0.48% ±0.9 | -0.17% ±0.6 | |
| | | | | | | | Dose of insulin | -5.9 IU ±7.6 | -2.9 IU ±5.6 | |
| | | | | | | | Weight Change | -3.0 ±3.5 | +0.8 ±1.1 | |
| | | | | | | | Adverse Events:<br>Vomiting<br>Gastro discomfort | <br>1/12<br>2/12 | <br>0/11<br>0/11 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 149<br><br>REF ID: JACOBSEN2009 | | Pregnancy, impaired vision, impaired renal or hepatic function, cardiac diseases, uncontrolled hypertension, hypo-glycaemic unawareness. | reported | | | | | | | "double blind" no description<br>ITT analysis: Unclear<br>Drop-outs: None reported |

**Table 254: Kielgast 2011**[74]

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Kielgast U, Krarup T, Holst JJ, Madsbad S. Four weeks of treatment with liraglutide reduces insulin dose | Parallel RCT | n=19<br>n=9 Liraglutide<br>n=10 Placebo<br>Inclusion criteria: Aged 18-50 years, BMI 18-27 kg/m², | Adults with type 1 diabetes<br>C-peptide negative | Liraglutide 0.6-1.2 mg/day | Usual Care | 4 weeks | | Liraglut | Placebo | Funding: Academic grant<br>Risk of bias: Randomisation: adequate, computer generated<br>Allocation concealment: adequate |
| | | | | | | | HbA1c | -0.47% ±0.45 | -0.2% ±0.32 | |
| | | | | | | | Dose of insulin | -0.13 IU/kg ±0.12 | +0.017 IU/kg ±0.06 | |
| | | | | | | | Weight Change | -1.8 ±1.8 | +0.2 ±0.95 | |
| | | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| without loss of glycemic control in type 1 diabetic patients with and without residual beta-cell function. Diabetes Care. 2011; 34(7):1463-1468<br><br>REF ID: KIELGAST2011 | | diagnosed between ages of 5 and 40 years, remission period assumed to be ended, no known late diabetes complications (except low-level (micro) albuminuria), no symptoms of autonomic neuropathy, no use of medication known to affect glucose metabolism<br>Exclusion criteria:<br>Late diabetes complications, autonomic neuropathy, | | Liraglutide | Placebo | | | | | | | Blinding: no blinding<br>ITT analysis: unclear<br>Drop-outs: Not reported |
| | | | Age | 35.7 ±2.2 | 32.9 ±1.7 | | | | | | | |
| | | | M/F | 9/0 | 9/1 | | | | | | | |
| | | | Drop outs: Not reported | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | anaemia, HbA1c >8.5%. | | | | | | | | |

**Table 255: Kolterman 1996[82,83]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Kolterman OG, Schwartz S, Corder C, Levy B, Klaff L, Peterson J et al. Effect of 14 days' subcutaneous administration of the human amylin analogue, pramlintide (AC137), on an intravenous insulin challenge and response to a standard | Multi-centre Parallel RCT | n=63<br>n=41Pramlintide (30µg n=18 100µg n=23)<br>n=22 Placebo<br>Inclusion criteria: Aged between 18 and 51 years, IDDM for at least 2 years with fasting plasma C-peptide <1 ng/ml, BMI <27, not needed to vary insulin dose by | Adults with type 1 diabetes> 2 years<br>C-peptide negative<br>Pram: 30 µg / 100 µg; Placebo<br>Age: 36± 8.5 / 34± 9.6 / 37 ±9.4<br>Hb A1c: 8.3± 1.87 / 8.8± 1.4 / 8.9 ±1.87<br>M/F: 11/ 7 / 19/ 4 / 14/8<br>Drop outs:<br>Pramlintide 30µg – 1/18<br>Pramlintide 100µg – 1/23<br>Placebo – 1/22<br>Total: 3/63 | Pramlintide 30µg/meal 100µg/meal (300µg/meal not included for this review)<br>three times daily | Placebo | 4 weeks | Adverse Events:<br>Gastro-intestinal Symptoms (including nausea, vomiting and anorexia) | Pram: 21/41<br>Placebo: 4/22 | | Funding: Unclear. Authors affiliated with Amylin pharmaceuticals<br>Risk of bias: Randomisation unclear<br>Allocation concealment: not reported<br>Blinding: "double blinded"<br>ITT analysis: adverse event data, per-protocol analysis<br>Drop-outs: majority drop-outs due to |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| liquid meal in patients with IDDM. Diabetologia. 1996; 39(4):492-499<br><br>REF ID: KOLTERMAN 1996 | | more than ±10% during the prior week, no severe hypo/ hyper -glycaemia during the 2 weeks prior to the study<br><br>Exclusion criteria: Not reported | | | | | | | | adverse events (outcome) therefore not a significant source of risk of bias |

**Table 256: Lund 2008**[99]

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC et al. Effect of adjunct metformin | Parallel RCT | n=100<br>n=49 Metformin<br>n=51 Placebo<br>Inclusion criteria: type 1 diabetes ≥ 5 years, age ≥ | Adults with type 1 diabetes ≥5 years<br>Caucasian. | Metformin 1g BD | Placebo | 1 year | | Metformin | Placebo | Funding: Equipment/drugs provided by industry<br><br>Risk of bias: Randomisation adequate, computer |
| | | | | | | | HbA1c | -0.1% ±0.78 | -0.23% ±0.79 | |
| | | | | | | | Hypo-glycaemia:<br>Minor<br><br>Severe | <br>48/49<br><br>15/49 | <br>49/50<br><br>10/50 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study. PloS One. 2008; 3(10):e3363<br><br>REF ID: LUND2008 | | 18 years, mean HbA1c ≥ 8.5% at enrolment and in all available measurements during one year before enrolment.<br>Exclusion criteria: HbA1c <8.0% at baseline, hypo-glycaemic unawareness, clinical signs of heart failure, plasma creatinine above normal upper limit, plasma AST >3 times above the normal upper limit, factors II, VII and X decreased <0.7, serious co-morbidities, | | | | | | | | | | generated<br>Allocation concealment: adequate<br>Blinding: double blinded<br>ITT analysis: last value carried forward<br>Drop-outs: Low rate, similar missing in both groups |
| | | | | | | | | | Dose of insulin | -3.5 ±7.07 | +2.5 ±7.03 | |
| | | | | | | | | | Weight change | -1.21 ±3.87 | 0.53 ±4.07 | |
| | | | | | | | | | Gastro-intestinal Symptoms | 43/49 | 39/50 | |
| | | | | Metformin | Placebo | | | | | | | |
| | | | Age | 46.1 ±11.6 | 44.9 ±10.8 | | | | | | | |
| | | | M/F | 33/16 | 31/20 | | | | | | | |
| | | | Drop outs:<br><br>Metformin 1/49 (2%)<br>Placebo 1/51 (2%) | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | pregnancy, history of drug or alcohol abuse | | | | | | | | |

**Table 257: Nyholm 1999[119,120]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nyholm B, Orskov L, Hove KY, Gravholt CH, Møller N, Alberti KG et al. The amylin analog pramlintide improves glycemic control and reduces postprandial glucagon concentrations in patients with type 1 diabetes mellitus. Metabolism: Clinical and Experimenta | Cross-over RCT | n=14<br><br>Inclusion criteria: Not reported<br><br>Exclusion criteria: Not reported | Adults with type 1 diabetes | | Pramlintide 30 µg QDS | Placebo | 4 weeks per intervention with 3-5 week washout period | | Pram | Placebo | Funding: Not reported<br>Risk of bias:<br>Randomisation: unclear<br>Allocation concealment: not reported<br>Blinding: "double blinded"<br>ITT analysis: Unclear. No drop-outs. Switching not reported<br>Drop-outs: None |
| | | | | Crossover | | | | HbA1c | 7.9% ±1.12 | 8.2% ±1.12 | |
| | | | Age (range) | 36.6 (24-53) | | | | Hypo-glycaemia | 11/14 | 7/14 | |
| | | | M/F | 14/0 | | | | Weight change | -2.3 ±1.12 | -1.3 ±1.45 | |
| | | | HbA1c (range) | 8.6% (7.3-9.9) | | | | | | | |
| | | | Drop outs: None | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| l. 1999; 48(7):935-941<br><br>REF ID: NYHOLM1999 | | | | | | | | | | |

**Table 258: Thompson 1997[154]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Thompson RG, Pearson L, Kolterman OG. Effects of 4 weeks' administration of pramlintide, a human amylin analogue, on glycaemia control in patients with IDDM: effects on plasma glucose profiles and serum fructosamin | Parallel RCT<br><br>Setting: Outpatient clinic in USA | n=215<br>n=173 Pramlintide<br>n=42 Placebo<br><br>Inclusion criteria: Aged 18 to 66 years, IDDM, a basal C-peptide concentration less than 1.0ng/ml and/or a history of diabetic ketoacidosis, and negative results for serum | Adults with type 1 diabetes<br><br>Pramlintide 6/173 (3.5%)<br>Due to adverse events<br>Placebo 0/42 | Pramlintide 30-60 µg<br><br>in four different dosing regimens: | Placebo | 4 weeks | Hypo-glycaemia: Severe<br>Adverse Events | Pram<br>3/173 | Placebo<br>1/42 | Funding: Not reported. Authors employed by Amylin pharmaceuticals<br>Risk of bias: Randomisation method unclear<br>Allocation concealment: not reported<br>Blinding: double blinded<br>ITT analysis: safety data used per-protocol analysis<br>Drop-outs: differential rate |

| | Pram | Placebo |
|---|---|---|
| Age | 35.3 | 35.6 |
| HbA 1c | 8.9% | 9.3% |
| BMI | 25.0 | 25.2 |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| e concentrations. Diabetologia. 1997; 40(11):1278-1285<br><br>THOMPSON 1997 | | hepatitis B surface antigen<br>Exclusion criteria:<br>Not reported | | | | | | | | acceptable (<10%) |

**Table 259: Thompson 1997[154,155]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Thompson RG, Peterson J, Gottlieb A, Mullane J. Effects of pramlintide, an analog of human amylin, on plasma glucose profiles in patients with IDDM: results of a multicenter trial. Diabetes. | Parallel Multicentre RCT | n=168<br>n=126 Pramlintide<br>n=42 Placebo<br><br>Inclusion criteria: Aged 18-60 years, IDDM, HbA1c level <13%, negative for hepatitis B surface antigen (HBsAg) and stable body | Adults with type 1 diabetes | | | Pramlintide 10µg QDS<br>30µg QDS<br>100µg QDS | Placebo | 2 weeks | | Pram | Placebo | Funding:<br>Authors employed by Amylin Pharmaceuticals<br>Risk of bias:<br>Randomisation: unclear<br>Allocation concealment: not reported<br>Blinding: "double blind"<br>ITT analysis: Not reported<br>Drop-outs: Acceptable |
| | | | | Pram | Placebo | | | | Hypo-glycaemia: Mild | 103/126 | 34/42 | |
| | | | Age | 36.8 | 35.3 | | | | Adverse Events: | | | |
| | | | M/F | 92/34 | 35/7 | | | | Nausea | 27/126 | 1/42 | |
| | | | Drop outs: 3/168 | | | | | | Anorexia | 5/126 | 0/42 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 1997; 46(4):632-636<br><br>REF ID: THOMPSON 1997A | | weight prior to admission to trial<br>Exclusion criteria:<br>Not reported | | | | | | | | (<10%) |

## G.4.5 Needle length, site and rotation

**Table 260: HIRSCH 2012**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| L. J. Hirsch, M. A. Gibney, J. Albanese, S. Qu, K. Kassler-Taub, L. J. Klaff, and T. S. Bailey. Comparative glycemic control, safety and patient | Cross-over RCT.<br><br>Multicentre trial (four clinical centres) in the United states | n= 173 participants (37% type 1 diabetes)<br><br>(n= 85: 4mm x 32G vs. 5mm x 31G pen needles (PN); n= 83: 4mm x 32G vs. 8mm x 31G PN)<br>Inclusion criteria:<br>Using insulin pen at least once per day for two months or | Patients with type 1 diabetes and type 2 diabetes. Participants were either 'low dose' or 'regular dose' users (highest single insulin dose ≤20 units and 21 – 40 units, respectively). | | | 4 mm x 32G pen needles | 5 mm x 31G pen needles and 8 mm x 31G pen needles | 3 weeks | | 4mm vs. 5mm (n=68) | 4mm vs. 8mm (n=69) | Funding: BD (Beckton, Dickinson and company) provided funding for this study and manufactures all pen needles tested.<br><br>Risk of bias: Randomisatio |
| | | | | 4mm/5mm (n=83) | 4mm/8mm (n=81) | | | | VAS scores for pain; mean diff (SD) (SE) | -11.9 (SD 46.3) (5.6) | -23.3 (SD 35.3) (4.2) | |
| | | | Age (years), | 54.4 (SD 14) | 50.8 (SD | | | | HbA1c (not reported) | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ratings for a new 4 mm x 32G insulin pen needle in adults with diabetes. Curr.Med.Res.Opin. 26 (6):1531-1541, 2010.<br><br>REF ID: HIRSH 2010 | | more<br>BMI 18-50 kg/m2<br>HbA1c 5.5-9.5%<br>Able to monitor blood glucose at least 4 times per day<br>Exclusion criteria:<br>Physical conditions which would make them unable to perform study procedures<br>Recent history of unstable diabetes including ketoacidosis or hypoglycaemic unawareness, bleeding disorders, or hypoglycaemic unawareness<br>Bleeding disorders<br>Pregnancy | mean (SD) | | 16.8) | | | | Pre- and post-prandial blood glucose (not reported) | | | n "using an investor site and dose-group specific computer-generated list of sequential numbers developed by BD biostatistics.<br>Allocation concealment: unclear<br>Blinding: not reported<br>ITT analysis: unclear - not enough info<br>Powered study.<br>Drop-outs: acceptable (<20%) and acceptable differential between groups<br>Both type 1 diabetes |
| | | | Male; number (%) | 46 (55%) | 46 (57%) | | | | | | | |
| | | | BMI (kg/m2); mean (SD) | 31 (SD 6) | 30.1 (SD 6.3) | | | | | 4mm (n= 173) | 5mm (n= 89) | |
| | | | HbA1c (%); mean (SD) | 7.6 (SD 1) | 7.4 (SD 1) | | | | Hypoglycaemia; number (%) | 36 (20.8) | 21 (23.6) | |
| | | | Drop-outs:<br>Dropout rate: four (4) participants in the (4/5 mm) group and 1 participant in the 4/8 mm group. Nine participants in total (5%) | | | | | | Injection site pain; number (%) | 27 (15.6) | 11 (12.4) | |
| | | | | | | | | | | 4mm (n= 173) | 8mm (n=84) | |
| | | | | | | | | | Hypoglycaemia; number (%) | 36 (20.8) | 22 (26.2) | |
| | | | | | | | | | Injection site pain; | 27 (15. | 11 (13.1) | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | number (%) | 6) | | (37%) and type 2 diabetes were included in the trial with no sub-group analysis or data reported separately for the type 1 diabetes group. |

**Table 261: IGNAUT 2012**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D. A. Ignaut and H. Fu. Comparison of insulin diluent leakage post injection using two different needle lengths and injection | RCT ( crossover)<br><br>Conducted at two outpatient centres in the USA. | n= 56<br>(n=13 /23% type 1 diabetes and n=43/77% type 2 diabetes).<br><br>Inclusion criteria:<br>≥18 years of age with type 1 diabetes or type 2 diabetes. | type 1 diabetes and type 2 diabetes | | 5mm needles using the HumanPen Memoir insulin pen injector to deliver both 20 U and 60 U equivalent volume injections of preserved | 8mm needles using the HumanPen Memoir insulin pen injector to deliver both 20 U and 60 U equivalent volume injections of | Not reported | | 20 U equivalent volume | 60 U equivalent volume | Funding: Eli Lilly and Company.<br><br>Risk of bias:<br>Randomisation: "randomly assigned to 1 of 8 sequence groups in |
| | | | | Total (N = 56) | | | | *VAS Pain scores, mean (SD) difference (5mm minus 8mm) | 0.14 (SD 2.56) | 0.74 (SD 2.49) | |
| | | | Age (years), mean (SD) | 55.75 (SD 9.77) | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| volumes in obese patients with type 1 or type 2 diabetes mellitus. J Diabetes Sci Technol 6 (2):389-393, 2012.<br><br>REF ID: IGNAUT 2012 | | BMI ≥30.0 kg/m2<br>injecting insulin at least once/day for 6 months before screening<br>Exclusion criteria:<br>>2 abdominal surgical scars >2 inches within the provided injection grid area<br>Self-perceived dullness or loss of sensation on either side of abdomen<br>Known hypersensitivity or allergy to preserved sterile insulin diluent or insulin<br>Taking anticoagulant or antiplatelet medications other than aspirin<br>diagnosis or past history of significant bleeding disorder<br>Significant wt | M/Fe<br>BMI (kg/m2), mean (SD)<br>type 1 diabetes / type 2 diabetes<br><br>Drop-outs:<br>No drop-outs - "All patients completed the study" | 30/26<br>35.6 (SD 5.5)<br>13/43 | sterile insulin diluent. | preserved sterile insulin diluent. | | *VAS Pain scores, mean (SD) – reported narratively.<br>Adverse events<br>HbA1c (not reported)<br>Hypoglycaemia (not reported)<br>Pre- and post-prandial blood glucose (not reported) | No SAEs reported (NS difference) | | order to reduce bias during study execution"<br>Allocation concealment : unclear<br>Blinding: Single (patients).<br>ITT analysis: not reported<br>Powered study: not reported<br>Wash out period: not reported.<br>Drop-outs: None. |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | change (±10% body wt) within 6 weeks of screening. | | | | | | | |

**Table 262: KREUGEL 2011**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| G. Kreugel, J. C. Keers, M. N. Kerstens, and B. H. Wolffenbuttel. Randomized trial on the influence of the length of two insulin pen needles on glycemic control and patient preference in obese | RCT ( crossover)<br><br>5 centres in The Netherlands | n= 130 (n=4 /5% type 1 diabetes)<br><br>Inclusion criteria:<br>≥18 years of age with type 1 diabetes or type 2 diabetes.<br>BMI ≥30.0 kg/m2<br>injecting insulin with pen device at least 1 year<br>Exclusion criteria: | Adults<br>type 1 diabetes and type 2 diabetes<br>Obese | | | 5mm x 31G pen needles.<br><br>(Used at 90° angle, no skin fold) | 8mm x 31G pen needles<br><br>(Injected into a lifted skin fold) | 3 months each needle | HbA1c, % (SD) FINAL VALUE | 5mm: 7.47 (0.9)<br>8mm: 7.59 (1.0)<br>SS difference (p=0.02) | Funding: Beckton Dickinson.<br><br>Risk of bias: Randomisation : method not reported.<br>Allocation concealment: not reported<br>Blinding: none (open label).<br>ITT analysis: no – ACA used.<br>Powered study: to HbA1c and patient |
| | | | | Group A (n=64) | Group B (n=62) | Both groups<br>used BD microfine Mini and short insulin pen needles<br>Thigh and abdomen recommended sites of injection for LA and SA insulin respectively<br>injections rotated within specific body area.<br>Insulin volume 50 IU per injection (if >50, patients advised to split the dose | | | VAS Pain perception scores, median (IQR) | 5mm: 7 (0-22)<br>8mm: 9 (0-23)<br>NS difference | |
| | | | Age, years, mean (SD) | 60 (11) | 61 (11) | | | | | | |
| | | | M/Fe | 34/30 | 36/26 | | | | | | |
| | | | BMI (kg/m2), mean (SD) | 36.7 (5.5) | 36.1 (5.8) | | | | Hypoglycaemia (self-reported) | NS difference, p=0.337 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| patients with diabetes. Diabetes Technol.Ther. 13 (7):737-741, 2011.<br><br>REF ID: KREUGEL 2011 | | Self-adjustments of insulin dose incompletely recorded<br>HbA1c >15% variation in past year<br>Hypo unawareness<br>Pregnancy or intention to become pregnant<br>Haemoglobin-opathies<br>Presence of lipodystrophy | type 1 diabetes/ type 2 diabetes | 3/61 | 2/60 | and give 2 injections into same specific body area). | | | Bleeding | SS less for 5mm vs. 8 mm (p=0.04) | preference<br>Wash out period: not reported and N/A.<br>Drop-outs: acceptable (<20%). |
| | | | HbA1c, % (SD) | 7.7 (1.1) | 7.6 (0.9) | | | | Insulin backflow | SS less for 5mm vs. 8 mm (p=0.01) | |
| | | | Drop-outs:<br>n=4 did not complete study | | | | | | Bruising | NS difference | |
| | | | | | | | | | patient preference | NS difference (46% 5mm vs. 41% 8 mm; p-value not given) | |
| | | | | | | | | | Pre- and post-prandial blood glucose (not reported) | | |

**Table 263: MCKAY 2009**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| M. Mckay, G. Compion, and L. Lytzen. A | RCT ( crossover ) | n= 119<br>(n=26 /22% type 1 diabetes) | Adults<br>type 1 diabetes and type 2 diabetes | 6mm x 32G pen needles. | 8mm x 30G pen needles | 1-2 weeks each | VAS Pain perception scores | SS less pain with 6mm/32- | Funding: NovoNordisk . |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| comparison of insulin injection needles on patients' perceptions of pain, handling, and acceptability: a randomized, open-label, crossover study in subjects with diabetes. Diabetes Technol.Ther. 11 (3):195-201, 2009.<br><br>REF ID: MCKAY 2009 | 10 centres, UK | Inclusion criteria:<br>Adults with type 1 diabetes or type 2 diabetes.<br><br>No further details given<br><br>Exclusion criteria:<br>Not reported | | | (no further details given) | (no further details given) | needle | | Gauge vs. 8mm 30G (p<0.001) | Risk of bias:<br>Randomisation : block design (blocks of 4).<br>Allocation concealment: not reported<br>Blinding: none (open label).<br>ITT analysis: yes.<br>Powered study: patient preference<br>Wash out period: not reported and N/A.<br>Drop-outs: acceptable - none. |
| | | | | Group A (n=119) | Both groups used NovoNordisk Novofine needles with the Flexpen<br>Usual insulin of patients was used using usual regimen. | | | AEs: Bleeding or bruising, number of events | less for 6mm/32-Gauge vs. 8mm 30G (n=1 vs. n=3) | |
| | | | Age, years, mean (SD) | 58 (12) | | | | | | |
| | | | M/Fe | 62/57 | | | | | | |
| | | | BMI (kg/m2), mean (SD) | 31 (5.7) range: 20-48.7 | | | | patient preference | SS favouring 6mm/32-Gauge vs. 8mm 30G (58% vs. 27% - p<0.001) | |
| | | | type 1 diabetes/ type 2 diabetes | 26 (22%)/93 (78%) | | | | Pre- and post-prandial blood glucose (not reported) | | |
| | | | HbA1c, % (SD) | Not reported | | | | | | |
| | | | Drop-outs:<br>None | | | | | | | |

**Table 264: MIWA 2012**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T. Miwa, R. Itoh, T. Kobayashi, T. Tanabe, J. Shikuma, T. Takahashi, and M. Odawara. Comparison of the effects of a new 32-Gaugex4-mm pen needle and a 32-Gaugex6-mm pen needle on glycemic control, safety, and patient ratings in Japanese adults with diabetes. Diabetes Technol.Ther. 14 (12):1084-1090, 2012.<br><br>REF ID: MIWA 2012 | RCT (cross over).<br><br>Conducted at two outpatient centre in Japan. | n= 41 type 1 diabetes (n=5 (12%)) or type 2 diabetes (n =36 (88%)).<br><br>Inclusion criteria:<br>Age ≥20 years with type 1 diabetes or type 2 diabetes<br>BMI <35 kg/m2<br>Using insulin pen device ≥1 year, and current users of NovoFine 32G X 6mm tapered needles<br>injecting insulin 2+ times/ day<br>HbA1c level in range 5.9-8.9%.<br>Exclusion criteria:<br>Any physical condition that may hinder adherence to study procedures<br>Any neurological | Participants with type 1 (n = 5) or type 2 (n =36) diabetes. | | Group 1:<br>32G x 4mm needle<br><br>during the first month of the study then cross-over. | Group 2:<br>32G X 6mm needle<br><br>during the first month of the study then cross-over. | 2 months (1 month each needle) | | Group 1 | Group 2 | Funding: "the materials used in this study were provided by Nippon Becton Dickinson Company Ltd."<br><br>Risk of bias:<br>Randomisation: not clear.<br>Allocation concealment: not reported<br>Blinding: Open label<br>ITT analysis: not reported<br>Powered study: reported<br>Wash out period: not reported.<br>Drop-outs: n=2 (10%) Group 1 and n=1 (5%) Group 2. |
| | | | | Total (N = 41) | | | | Average VAS score for comparative pain – validated 150-mm VAS | -16.6 mm (-26.0 mm, -7.3 mm) | | |
| | | | Age (years), mean (SD) | 64.3 (SD 11.1) | | | | | | | |
| | | | Male/female | 28/13 | | | | Adverse events | None | | |
| | | | BMI (kg/m2), mean (SD) | 23.2 (SD 3.2) | | | | HbA1c (not reported)<br>Hypoglycaemia (not reported)<br>Pre- and post-prandial blood glucose (not reported) | | | |
| | | | | | | | | | | | |
| | | | Drop-outs:<br>n=3 (7%) excluded from end-point analyses due to protocol deviations. n=2 (10%) from Group 1, n=1 (5%) Group 2). | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | diseases<br>Nephrotic syndrome<br>Pregnancy or lactation. | | | | | | | |

## G.5 Pancreas transplant and islet cell transplantation

None

## G.6 Hypoglycaemia

### G.6.1 Identification and quantification of impaired awareness of hypoglycaemia

**Table 265: HENDRIECKX 2014**

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| C. Hendrieckx, J. A. Halliday, J. P. Bowden, P. G. Colman, N. Cohen, A. Jenkins, and J. Speight. Severe hypoglycae | Retrospective case-series<br><br>Country: Australia (3 centres) | n=502 (n=422 completers)<br><br>Inclusion:<br>Age >18 years<br>Type 1 diabetes for >6 months<br>Able to complete | Adults with type 1 diabetes<br>Invited participants<br>Age: mean 37.5 years<br>Female: 54%<br>Diabetes duration: mean 18.4 years<br>HbA1c: mean 7.8% | Questionnaire given – covered:<br>1. Hypoglycaemia (recall of events, impaired awareness, and fear of hypo)<br>2. Psychological well-being and clinical questions. | - | IAH (Gold ≥4): = 20.5%<br>Intact awareness (Gold = 1): 27%<br>Most patients (52.4%) had Gold score 2 or 3.<br>SH: 18.5% at least one event in past 6 months (mean 0.5; ie. 1 event/year)<br><br>46% of patients who reported SH episode in past 6 months also | Not reported |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| mia and its association with psychological well-being in Australian adults with type 1 diabetes attending specialist tertiary clinics. Diabetes Res.Clin.Pract. 103 (3):430-436, 2014.<br><br>HENDRIECKX 2014 | | survey in English without assistance.<br><br>Exclusion:<br>None stated | SH recollection in past 6 months: mean 0.5 (range 0-20)<br>IAH (Gold score ≥4): n=86 (21%)<br>SMBG ≥4 times/day: n=285 (67.9%)<br>Most patients on MDI therapy (26% on CSII) | SCORE TO RATE IAH:<br>GOLD score (cut-off ≥4)<br>HypoCOMPASS questionnaire (HypoA-Q) about severe hypo events. | | reported IAH; only 7% had intact awareness.<br><br>Patients with SH were more likely to have IAH, experienced fewer symptoms of hypo, and relied more often on others to recognise a hypo event.<br>Multivariate analyses:<br>Greater IAH was SS associated with occurrence of SH<br>IAH was SS associated with more frequent SH. | |

**Table 266: HOPKINS 2012**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| D. Hopkins, I. Lawrence, P. Mansell, G. Thompson, S. Amiel, M. | Retrospective case-series (data from DAFNE audit) | n=639 available data (501 for frequency of SH; 539 for IAH) | Baseline (pre-DAFNE)<br><br>HbA1c: mean 8.5% | Data collected in audit:<br>subjects<br>were asked to rate their perceived | 1 year (mean 380 +/- 62 days) | Baseline data (before DAFNE so not showing intervention effect)<br>IAH: 40%<br>Hypo aware: 60%<br>SH: 25% at least one event in past 1 year; 16% | NIHR (UK) |

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| Campbell, and S. Heller. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 35 (8):1638-1642, 2012.<br><br>HOPKINS 2012 | Country: UK | Inclusion:<br>all participants who attended DAFNE courses in one 12-month period<br>DAFNE used adults with type 1 diabetes.<br><br>Exclusion:<br>None stated | IAH: 40%<br>Hypo aware: 60%<br>SH at least 1 event in past year: 25% | awareness of hypoglycaemia by stating whether they usually recognized that they were hypoglycaemic at a blood glucose concentration ≥3 mmol/litre, <3 mmol/litre, or not at all. And self-reported frequency of SH.<br><br>SCORE TO RATE IAH:<br>IAH = those reporting symptom onset <3 mmol/litre or not at all<br>Hypo aware = those recognizing hypo symptoms at a glucose of ≥3mmol/litre | | more than one episode in past year.<br><br>Baseline data (after DAFNE so showing intervention effect)<br>62% of those who had experienced SH remained free of further episodes at follow-up<br>10% of those who had been free of SH in the preceding year experienced one or more episodes.<br>The overall mean SH rate for the cohort fell from 1.93 (range 0–99) to 0.61 (0–70) episodes/person/year after DAFNE (difference 1.15 [95% CI 0.73–1.57]; P < 0.001)<br><br>At follow-up, 43% of those with IAH at enrolment reported restoration of the ability to detect hypoglycaemia at a blood glucose >3 mmol/litre.<br>The rate of SH fell significantly in both groups.<br><br>Shows in subgroup of patients who had IAH, 43% reported restored awareness (ability to detect hypo when blood glucose was >3 mmol/litre, 1 year after DAFNE. Rate of SH also fell significantly. | |

**Table 267: CHOUDHARY 2010A**

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| P. Choudhary, J. Geddes, J. V. Freeman, C. J. Emery ET AL. Frequency of biochemical hypoglycaemia in adults with Type 1 diabetes with and without impaired awareness of hypoglycaemia: no identifiable differences using continuous glucose monitoring. Diabet.Med. 27 (6):666-672, 2010.<br><br>CHOUDHARY 2010A | Prospective case-series<br><br>Country: UK<br><br>Data from the UK Hypoglycaemia Group study | n=95<br><br>Adults with type 1 diabetes<br>n=74 normal awareness, n=21 impaired hypo awareness (IAH)<br><br>Inclusion:<br>Type 1 diabetes (WHO criteria)<br><br>Exclusion:<br>HbA1c >9%<br>Pregnancy<br>Advanced complications of diabetes<br>Severe systemic disease or malignancy<br>History of seizures unrelated to hypo<br>Inability to give informed consent | xxxxxxx | Weekly 4-point capillary home blood glucose monitoring (HBGM), 5 days of CGM and prospective reporting of severe hypoglycaemia<br><br>SCORE TO RATE IAH:<br>GOLD score<br>Cut-off ≥4 | 9-12 months | Patients with IAH vs. normal awareness:<br>3 x higher incidence of severe hypoglycaemia<br>1.6 x higher incidence of hypoglycaemia on weekly HBGM<br>NS differences observed with CGM | Funding: Part of another larger study funded by the Department of Transport, UK, not reported |

**Table 268: CLARKE 1995**

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| W. L. Clarke, D. J. Cox, L. A. Gonder-Frederick, D. Julian, D. Schlundt, and W. Polonsky. Reduced awareness of hypoglycaemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 18 (4):517-522, 1995.<br><br>CLARKE 1995 | Prospective case-series<br><br>Country: UK | n=78<br><br>Adults with type 1 diabetes<br>n=39 IAH<br><br>Inclusion:<br>IDDM for at least 2 years<br>Between 21 and 55 years old<br>Were routinely performing SMBG<br><br>Particular efforts were made to recruit and include subjects with extreme degrees of hypoglycaemic awareness.<br><br>Exclusion: None mentioned. | Mean age 38.3 ± 9.2 years;<br>Duration of diabetes 19.3 ± 10.4 years. | 2 assessments<br>separated by 6 months. Each assessment<br>included a battery of questionnaires<br>and a BG symptom rating/ estimation trial. During the intervening 6 months, subjects completed diaries of hypo events. HbA1c was determined before the initial assessment and after 2nd assessment.<br><br>SCORE TO RATE IAH:<br>CLARKE score (8 questions)<br>Cut-off ≥4 answers as 'R' = reduced awareness, ≤2 = aware.<br><br>Compared scores with answers to question: "to what extent can you tell<br>by your symptoms that your sugar is low? (never, sometimes, often, always)." | 6 months | n=39 with IAH<br>Patients with IAH vs. normal awareness had/were:<br>NS difference for age, disease duration, insulin dose, or HbA1c<br>SS less accurate in detecting BG <3.9 mmol/1 (33.2 ± 47 vs. 47.6 ± 50% detection, P = 0.001)<br>SS fewer autonomic (0.41 ± 0.82 vs.1.08 ± 1.22, P = 0.006) and neuroglycopenic (0.44 ± 0.85 vs. 1.18 ± 1.32, P = 0.004) symptoms per subject.<br><br>Prospective diary records revealed that reduced-awareness subjects experienced more moderate (351 vs. 238, P = 0.026) and severe (50 vs. 17, P = 0.0062) hypoglycaemic<br>events. The second assessment results were similar to the first and verified the reliability of the data.<br><br>Authors' conclusions: IDDM subjects who believe they have reduced awareness of<br>hypoglycaemia are generally correct. They have a history of more moderate and severe<br>hypo, are less accurate at detecting BG <3.9 mmol/1, and prospectively experience more moderate and severe | Funding: Not stated |

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | hypo than do aware subjects. Neither disease duration nor level of glucose control explains their reduced awareness of hypo. Reduced-awareness individuals may benefit from interventions designed to teach them to recognize all of their potential early warning symptoms | |

**Table 269: GEDDES 2007**

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| J Geddes, RJ. Wright, NN. Zammitt, IJ. Deary, and BM. Frier. An evaluation of methods of assessing impaired awareness of hypoglycaemia in type 1 diabetes. Diabetes Care 30 (7):1868-1870, 2007. | Prospective case-series<br><br>Country: UK | n=140 (n=80 completers)<br><br>Inclusion:<br>None stated<br><br>Exclusion:<br>None stated | Xxxxx<br><br>Adults with type 1 diabetes<br>Randomly selected cohort | 4 times a day HBGM for 4 weeks. Recorded when any value was <3 mmol/litre<br><br>Also filled out Edinburgh Hypoglycaemia Score (rates the nature and intensity of hypo symptoms experienced).<br><br>SCORE TO RATE IAH:<br>GOLD score (cut-off ≥4)<br>CLARKE score (cut- | 4 weeks | IAH: GOLD = 24%, CLARKE = 26%, PEDERSEN = 63%<br>Strong association between Gold and Clarke methods for IAH (p=0.001)<br>If Pederson used 'occasionally and never' as IAH, the % fell to 15.4% - still a poor correlation between this method and Gold or Clarke methods (rs = 0.5 for both)<br>Patients with IAH vs. normal awareness had/were:<br>SS older (using Gold and Clarke scores). NS difference for Pedersen score.<br>SS longer duration of diabetes (using all 3 methods)<br>NS difference in HbA1c (using all 3 methods) | Not reported |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| GEDDES 2007 | | | | off ≥4)<br>PEDERSEN-BJERGAARD score (cut-off: always) | | SS more episodes of biochemical hypo over the 4 weeks (using Gold and Clarke scores). NS difference for Pedersen score.<br>Lower autonomic symptoms reported during biochemical hypo (using Gold and Clarke scores). NS difference for Pedersen score.<br>NS difference in self-reported neuroglycopenic symptoms (using all 3 methods).<br>SS incidence of severe hypos in previous year (using all 3 methods). | |

**Table 270: GEDDES 2008**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| J. Geddes, J. E. Schopman, N. N. Zammitt, and B. M. Frier. Prevalence of impaired awareness of | Cross-sectional study<br><br>Country: UK | n=518<br><br>Inclusion:<br>Type 1 diabetes >2 years duration<br>Aged >16 years<br><br>Exclusion:<br>Pregnancy, | Adults with type 1 diabetes<br>Randomly selected cohort<br><br>n=242 male<br>HbA1c: mean 8.4% (SD 1.4%)<br>Age: median 39 years<br>Duration of diabetes: median 16 years | Retrospective recall of severe hypo over previous year also assessed.<br><br>SCORE TO RATE IAH:<br>GOLD score (cut-off ≥4) | 4 weeks | IAH: 101 (19.5%)<br>Patients with IAH vs. normal awareness had/were:<br>SS older (p<0.001)<br>SS longer duration of diabetes (p<0.001)<br>6 x higher number of episodes of severe hypo (per person) in preceding year p<0.001)<br>SS lower intensity of autonomic | Not reported |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| hypoglycaemia in adults with Type 1 diabetes. Diabet.Med. 25 (4):501-504, 2008.<br><br>GEDDES 2008 | | advanced renal failure<br>Inability to understand or complete the questionnaire | 74% on insulin analogues<br>18% on mix of analogue and human<br>8% human alone<br>Basal-bolus: 82% and 18% on twice/day mixed insulin. | | | symptoms during episodes of self-treated hypo (p=0.004).<br>NS difference in intensity of neuroglycopaenic symptoms<br>NS difference for HbA1c<br>Moderate and SS association between IAH and duration of diabetes (rs = 0.21, p<0.001) and rate of SH (rs = 0.34, p<0.001). | |

**Table 271: GIMENEZ 2009**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| M Gimenez, M Lara, A Jimenez, and I Conget. Glycaemic profile characteristics and frequency of impaired awareness of hypoglycaemia in subjects | Prospective case-series<br><br>Country: Spain | n=20<br><br>Inclusion:<br>Type 1 diabetes >5 years duration<br>Aged >18 years<br>Conventional insulin MDI<br>NS hypo >4/week (for 8 weeks)<br>SH hypo >2 (for 3 years) | Adults with type 1 diabetes<br><br>n=11 male<br>HbA1c: mean 6.9% (SD 1.0%)<br>Age: mean 35 years<br>Duration of diabetes: mean 16 years<br>100% on MDI. | Compares 2 methods of IAH detection during an acute induction of hypoglycaemia with regular insulin.<br><br>Hypo symptoms score questionnaire answered after 30 minutes of euglycaemia, and after 30 minutes of hypoglycaemia. | 72 hours | IAH: GOLD = 100%, CLARKE = 95%.<br>Clarke test score was SS negatively correlated with HbA1c values (ie. lower HbA1c = higher Clarke score, thus IAH).<br>Percentage of increase in symptoms during induction of hypo:<br>Clarke's: sensitivity 100%, specificity 25%, Kappa index 0.35<br>CGM from the whole group revealed 18% of measurements <70 mg/dl; this was correlated with Clarke's test score and with increase in % of signs/symptoms | Ministerio de Sanidad y Consumo of Spain; and Medtronic Iberica. |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| with type 1 diabetes and repeated hypoglycaemic events. Acta Diabetol. 46 (4):291-293, 2009.<br><br>GIMINEZ 2009 | | Exclusion:<br>None mentioned | | Also measured CGM for 72hrs<br><br>SCORE TO RATE IAH:<br>GOLD score (cut-off ≥4)<br>CLARKE score (cut-off ≥4) | | during induced hypo.<br>In patients with abnormal response of symptoms during hypo, CGM % of values <70 mg/dl was higher (23% vs. 8%) than in those with a normal response (10%; p<0.028). | |

**Table 272: GOLD 1994**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A. E. Gold, K. M. MacLeod, and B. M. Frier. Frequency of severe hypoglycaemia in patients with type I diabetes with impaired | Prospective case-control study<br><br>Country: UK | n=60<br><br>Adults with type 1 diabetes<br>n=31 normal awareness<br>n=29 impaired hypo awareness (IAH)<br><br>Inclusion:<br>Type 1 diabetes<br>2 groups | | Normal (n=31) | IAH (n=29) | Monitored blood glucose<br><br>Hypo episodes documented<br><br>Assessed every 3 months and insulin adjusted accordingly<br><br>Fear of Hypo questionnaire | 12 months | IAH vs. normal awareness:<br>• SS more patients had 1 or more episodes of SH (66% vs. 26%)<br>• SS higher incidence of SH episodes/patients/year (2.8 vs. 0.5)<br>• SS more patients had greater worry/fear of hypoglycaemia, but did not modify their behaviour accordingly. | Funding: Not stated. |
| | | | Age | 44 (11) | 48 (12) | | | | |
| | | | HbA1c % | 10 (1.2) | 10 (1.5) | | | | |
| | | | Duration of diabetes, years | 19 | 21 | | | | |
| | | | Insulin: | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| awareness of hypoglycaemia. Diabetes Care 17 (7):697-703, 1994.<br><br>GOLD 1994 | | recruited simultaneously based on their self-reported awareness of hypoglycaemia (normal vs. impaired awareness).<br>'Matched for age, duration of diabetes, age at onset and glycaemic control at start of the survey.<br><br>Exclusion:<br>Taking any medication that may have impaired awareness of hypo (eg. BBs) | >70% in both groups taking twice/day regimen. | given.<br><br>SCORE TO RATE IAH:<br>GOLD score<br>Cut-off ≥4 | | | |

**Table 273: HOIHANSEN 2010**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| T. Hoi-Hansen, U. Pedersen- | Cross-sectional study | n=372 responders (n=470 recruited) | Adults with type 1 diabetes | Compares 3 methods of IAH | n/a | Normal awareness: 75%, 51% and41%<br>Impaired awareness/unawareness | None stated. |

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| Bjergaard, and B. Thorsteinsson. Reproducibility and reliability of hypoglycaemic episodes recorded with Continuous Glucose Monitoring System (CGMS) in daily life. Diabet.Med. 22 (7):858-862, 2005.<br><br>HOIHANSEN 2010 | Country: Denmark | Inclusion:<br>None mentioned.<br><br>Exclusion:<br>None mentioned | 57% male<br>HbA1c: mean 8.2% (SD 1.0%)<br>Age: mean 51 years<br>Duration of diabetes: mean 24 years<br>81% on MDI (≥4/day). | Also answered questions on severe hypo in the past and symptoms of hypo.<br><br>SCORE TO RATE IAH:<br>GOLD score (cut-off ≥4)<br>CLARKE score (cut-off ≥4)<br>PEDERSEN score (cut-off: always) | | (C): 25%, 28% and 13%<br>46% belonged to intermediate group of impaired awareness (C) and 21% not classifiable (B)<br>Higher rates of severe hypo in patients with impaired awareness (A,B)/unawareness (C) vs. aware patients<br>Patients with impaired awareness (C) had more severe hypo than aware patients, and less severe than unaware patients.<br>Lower rate of hypo in method C vs. method A<br>Fractions of patients with normal awareness without an event of severe hypo were 0.81, 0.86, 0.91<br><br>All 3 methods of hypo unawareness are feasible in clinical practice since degree of awareness is associated with risk of severe hypo. Method C (trisected method) identifies and intermediate group with impaired awareness and with a risk of severe hypo that is SS different from those of aware and unaware patients. | |

**Table 274: JANSSEN 2000A**

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| M. M. Janssen, F. J. Snoek, and R. J. Heine. Assessing impaired awareness of hypoglycaemia in type 1 diabetes: agreement of self-report but not of field study data with the autonomic symptom threshold during experimental hypoglycaemia. Diabetes Care 23 (4):529-532, 2000.<br><br>JANSSEN | Prospective case-series (taken during 10-week lead in to a clinical trial)<br><br>Country: The Netherlands | n=19<br><br>Inclusion:<br>Type 1 diabetes<br>Reasonable glycaemic control (HbA1c ≤8.3%)<br>Basal-bolus treatment regular insulin before meals and NPH bedtime.<br><br>Exclusion:<br>None mentioned. | Adults with type 1 diabetes<br><br>n=15 male<br>HbA1c: mean 7.2% (SD 0.6%)<br>Age: mean 30 years<br>Duration of diabetes: mean 13 years<br>100% basal-bolus with regular and NPH insulin. | Hand held computer to assess their recognition of hypo episodes occurring during 2-4 weeks<br>Underwent stepped hypoglycaemic clamp, so could study response to standardised hypo. diagnosis of IAH was based on the self-report questions, a composite self-report score and 3 different cut-off levels for the % of accurately recognised hypo episodes during the field study. Agreement with the hypo clamp measure was tested by kappa, sensitivity and spec.<br><br>SCORE TO RATE | 2-4 weeks | The composite self-report score agreed reasonably well with the hypo clamp measure (kappa 0.49, sensitivity 66.7, spec 85.7%) and showed a better agreement than the separate self-report questions.<br>The HHC criterion of IAH did not agree with the hypo clamp criterion at any of the cut-off levels tested. | None stated. |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| 2000A | | | | IAH:<br>CLARKE score (cut-off ≥4) | | | |

**Table 275: PEDERSEN 2003**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| U Pedersen-Bjergaard, S Pramming, and B Thorsteinsson. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes.Metab.Res.Rev. 19 (3):232-240, 2003.<br><br>PEDERSEN | Prospective case-series<br><br>Country: Denmark | n=230<br><br>Inclusion:<br>type 1 diabetes<br>Insulin treatment from time of diagnosis<br>Unstimulated C-peptide <300pmol/litre or stimulated C-peptide <600pmol/litre.<br><br>Exclusion:<br>Haemodialysis<br>Concomitant malignant disease<br>Pregnancy | Adults with type 1 diabetes<br><br>60% male<br>HbA1c: mean 8.5% (SD 1.0%)<br>Age: mean 46 years<br>Duration of diabetes: mean 21 years<br>84% on ≥4 injections/day | Questionnaire based on Pramming and Deary studies for occurrence of hypo, aspects of hypo unawareness and sections on demographic issues and lifestyle.<br><br>Hypo/SH in previous year was also recorded, and mild hypos in previous week.<br><br>SCORE TO RATE IAH:<br>PEDERSEN-BJERGAARD score (questionnaire | 1 year | Almost 90% patients correctly recalled whether they had had SH over the previous year. Those with high recorded numbers of episodes had incomplete recall, resulting in 15% underestimation of overall rate.<br><br>Qu: do you recognise symptoms when you have a hypo? 40% normal awareness, 47% impaired awareness and 13% unawareness.<br><br>Groups with IAH had 5.1 and 9.6 x higher rates of SH vs. normal awareness groups (p<0.001). | Several Foundations in Denmark. |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| 2003 | | | | based on Pramming and Deary studies)<br>cut-off: usually = IAH, occasionally or never = severe IAH (unawareness). | | | |

**Table 276: RYAN 2004**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Ryan,E.A.; Shandro,T.; Green,K.; Paty,B.W.; Senior,P.A.; Bigam,D.; Shapiro,A.M.; Vantyghem, M.C.<br>Assessment of the severity of hypoglycaemia and glycemic lability in type 1 diabetic | Prospective case-series<br><br>Country: USA | n=151<br>n=100 type 1 diabetes (random selection; completers of the questionnaire – 877 were originally recruited – data used for these n=100 only)<br>n=51 islet transplantation patients)<br><br>Inclusion:<br>Adults with type 1 diabetes<br>had attended our | | Type 1 diabetes (n=100) | Islet transplant (n=51) | Prospective monitoring of blood glucose ≥2x/day for 4 weeks.<br><br>Frequency of SH over preceding year also estimated.<br><br>Composite score comprising: glucose readings collected from patients over a 4 week period; details of each hypoglycaemic event (glucose <3.0 | 4 weeks | In the n=100 type 1 diabetes patients<br>IAH patients vs. normal awareness:<br>median 8.0 vs. 2.0 episodes of hypoglycaemia per patient in previous 4 weeks (p<0.001),<br>0.4 vs. 0.0 SH episodes per patient in previous 4 weeks (p-value not reported). | Juvenile Diabetes Foundation International. |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| subjects undergoing islet transplantation. Diabetes 53 (4): 955-962.<br><br>RYAN 2004 | | diabetes educational program at least once and were cared for by either community physicians or our diabetes clinic staff<br><br>Exclusion:<br>None stated. | | | | mmol/litre); no. of occurrences of hypoglycaemia; questionnaire about the frequency and severity of hypoglycaemia episodes over the previous year<br><br>SCORE TO RATE IAH:<br>HYPO score<br>Cut-off: Score of ≥433* is representative of problematic hypoglycaemia, ≥1,047* is indicative of very serious problems with hypoglycaemia. Patients with IAH had a median score of ≥850 (IQR 485 – 1228), and those with intact awareness had a score of 91 (IQR 23-203).<br>*NOTE: These cut- | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | off points were based on calculating the median and various percentiles of the distribution of patients in the study itself. | | | |

**Table 277: SCHOPMAN 2011**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| J. E. Schopman, J. Geddes, and B. M. Frier. Frequency of symptomatic and asymptomatic hypoglycaemia in Type 1 diabetes: effect of impaired awareness of | Prospective case-control study<br><br>Country: UK | n=38<br><br>Adults with type 1 diabetes<br>n=19 normal awareness<br>n=19 impaired hypo awareness (IAH)<br><br>Inclusion:<br>Type 1 diabetes<br>2 groups recruited based on their self-reported awareness of | | Normal (n=19) | IAH (n=19) | Prospective monitoring of blood glucose 4x/day for 4 weeks.<br><br>Frequency of SH over preceding year also estimated.<br><br>SCORE TO RATE IAH:<br>GOLD score<br>Cut-off ≥4 | 4 weeks | IAH patients vs. normal awareness:<br>2 x frequency of all episode of hypo over 4-week monitoring period (SS; p=0.003)<br>NS difference in total no of symptomatic hypo episodes.<br>7 x higher incidence of symptomatic hypo (SS, p=0.001) – comprised 47% of all glucose values <3.0 mmol/litre vs. 14% in normal group.<br>Higher annual prevalence of SH: 53% vs. 5%<br>SS higher incidence of severe events (p=0.001). | Funding: Not stated. |
| | | | Age , median | 50 | 54 | | | | |
| | | | HbA1c % | 8.3 | 7.8 | | | | |
| | | | Duration of diabetes, years | 23 | 25 | | | | |
| | | | Insulin:<br>100% on Basal-bolus (rapid before meals, and once/day long acting) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| hypoglycaemia. Diabet.Med. 28 (3):352-355, 2011.<br><br>SCHOPMAN 2011 | | hypoglycaemia (normal vs. impaired awareness by GOLD score).<br>Matched for age, sex, duration of diabetes, and glycaemic control (HbA1c).<br>Basal-bolus insulin regimen (rapid before meals, and once/day long acting)<br><br>Exclusion:<br>None stated. | | | | | |

**Table 278: STREJA 2005**

| Reference | Study type | Number of patients | Patient characteristics | Intervention Comparison | Length of follow-up | Outcome measures and Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| D Streja. Can continuous glucose monitoring provide objective documentation of | Prospective case-series<br><br>Country: USA | n=60<br><br>Inclusion:<br>Type 1 diabetes<br>Age >18 years<br>Diabetes duration >5 years | Adults with type 1 diabetes<br><br>n=27 male<br>HbA1c: mean 7.5% (SD 0.11%)<br>Age: mean 50 years | SMBG and clinical data collected<br>72hr CGMS<br><br>IAH Questionnaire<br><br>SCORE TO RATE | 2-4 weeks | HUN by Questionnaire: 42%<br>Best predictor of HUN was maximal duration of hypo, as determined by CGMS (p=0.001)<br>Detection of hypo episodes with duration >90 minutes identified patients with HUN (sensitivity 75%, spec 885) | None stated. |

| Reference | Study type | Number of patients | Patient characteristics | Intervention<br>Comparison | Length of follow-up | Outcome measures and<br>Effect sizes | Comments |
|---|---|---|---|---|---|---|---|
| hypoglycaemia unawareness? Endocr Pract 11 (2):83-90, 2005.<br><br>STREJA 2005 | | fC-peptide <0.6 ng/ml<br>HbA1c <9.0%<br>Use of CSII or MDI and preprandial and post-prandial SMPG at least 4x/day.<br><br>Exclusion:<br>Pregnant or breast feeding<br>Serum creatinine >2.0 mg/dl<br>Unstable CVD<br>History of recent substance abuse<br>Poor cognitive function at time of consent<br>Diagnosis of a major comorbid condition other than long-term diabetes complications. | Duration of diabetes: mean 24 years<br>n=17 CSII, rest = MDI. | IAH:<br>Adapted Janssen questionnaire (cut-off: 3/5 questions answered yes = HUN) | | HUN was SS associated with used of ACEs or ARBs (p=0.003), and longer duration of diabetes (p=0.008) | |

**Table 279: Summary of additional studies – including conference abstracts USED FOR ADDITIONAL GDG INFORMATION ONLY (not fully included in the review)**

| Study | Intervention/comparison | Population | Outcomes |
|---|---|---|---|

| Study | Intervention/comparison | Population | Outcomes |
|---|---|---|---|
| ACAMPO 2012 | Conference abstract<br><br>Cross-sectional study<br><br>Dutch translation of the Clarke questionnaire: score ≥3 out of 5 was assumed to indicate HU. SH was assessed on the basis of the same questionnaire. | n=486<br>Type 1 diabetes adults?? | HUN: n=158 patients (33%) and n=103 patients (21%) recalled SH in the year prior to the Clarke questionnaire.<br>HUN was associated with male sex, lower HbA1c, duration of diabetes, autonomic neuropathy and estimated GFR < 60ml/min/1.73 $m^2$ (all P < 0.05).<br>After adjustments, duration of diabetes, estimated GFR < 60ml/min/1.73 $m^2$ and lower HbA1c were still SS associated with HUN.<br>SH was independently associated with the presence of autonomic neuropathy (3.62; 1.65-7.94) and the use of benzodiazepines (4.59; 1.80-11.73), but not with HbA1c or diabetes duration.<br>No association with SH or HUN: use of insulin analogues, insulin pump therapy, ACE inhibitors or beta-blockers<br><br>Conclusion: HUN is still highly prevalent in type 1 diabetes patients despite advances in insulin therapy. Diabetes duration, lower HbA1c level and kidney dysfunction were independent risk factors for HU. Autonomic neuropathy and use of benzodiazepines were risk factors for SH. Clinicians treating patients with type 1 diabetes should be aware of the still high prevalence of HUN and its risk factors. (Table presented). |
| CZYEWSKA 2012 | Conference abstract | n=238<br>Type 1 diabetes adults and young people | HUN was assessed by Clarke and Gold.<br>HUN: CLARKE = 58 patients (24.4%), GOLD = 68 patients (28.5%).<br>Patient split into 3 groups:<br>Group I- patients with Hypo awareness confirmed by both tests (n = 142)<br>Group II- patients with HUN confirmed by one test (n = 66)<br>Group III- patients with HUN confirmed by both tests (n = 30).<br>Patients with HUN vs. awareness patients:<br>were older (P = 0.040)<br>had longer diabetes duration (P = 0.014)<br>NS difference in lipid level, waist circumference, creatinine level, BMI, arterial pressure and HbA1c.<br>had more glycaemia level below 55 mg/dl (P = 0.016).<br>Performed measurements of glycaemia more frequently (P = 0.049).<br><br>Conclusion: Hypoglycaemia unawareness was observed in 40% type 1 diabetic patients. The severity |

| Study | Intervention/comparison | Population | Outcomes |
|---|---|---|---|
| | | | of hypoglycaemia unawareness was associated with longer diabetes duration. The patients with hypoglycaemia unawareness had more frequent low glycaemia level |
| GANDHI 2013 | Conference abstract | n=100<br>Type 1 diabetes (age not given) | HUN assessed by Clarke, Gold and Pederson and the Edinburgh Hypoglycaemic Score, questions on causes and worry for hypoglycaemia scored on a seven-point Likert scale.<br>Clarke score was used to assess HUN.<br>HUN: Clarke = 18%, Gold = 19% and Pederson = 7%.<br>HUN:<br>were SS older (p = 0.0018)<br>Had SS longer duration of diabetes (p = 0.0015)<br>Had SS increased prior severe hypoglycaemic episodes (p = 0.024)<br>Giving the insulin dose twice was increased (p = 0.011)<br>Were SS more worried about night-time hypoglycaemia (p = 0.041)<br>Felt significantly less empowered to avoid future hypoglycaemic episodes (p = 0.047).<br><br>There was very poor correlation between the Pederson questionnaire and the other two methods used to assess HU.<br>There was moderate agreement between the Clarke and Gold scores (kappa = 0.503).<br><br>Conclusion: This report demonstrates lower prevalence of HU compared with the literature and may reflect recent improvements in Type 1 diabetes management, most notably education. It highlights opportunities to improve education to avoid hypoglycaemia. The findings of this study are in keeping with a previous report suggesting that Clark and Gold questionnaires are better discriminators for HU than Pederson |
| KANC 2010 | Conference abstract | n=114<br>Type 1 diabetes (n=53) and type 2 diabetes insulin treated | Hypoglycaemia awareness status by Clarke's questionnaire<br>Confirmed high internal consistency reliability of the translated questionnaires (Cronbach's alphas were 0.93, 0.94, and 0.49 for HFS, PAID, and Clarke's questionnaire, respectively).<br>SS correlation found between HFS score and Clarke's score in general (r = 0.20, p = 0.030), type 2 diabetes (r = 0.27, p = 0.036), type 1 diabetes (r = 0.17, p = 0.217), meaning that patients with type 2 diabetes experience an increase in FoH as their awareness decreases (but NS for type 1 diabetes).<br>SS association of HbA1c with HFS score (r = 0.23, p = 0.015) and PAID score (r = 0.47, p < 0.001), indicating worse glucose control with increasing FoH and diabetes problems. On the contrary, four |

| Study | Intervention/comparison | Population | Outcomes |
|---|---|---|---|
| | | | patients had very high PAID and HFS score and low HbA1c.<br><br>Conclusion: In particular MDI-treated women with type 1 diabetes, bad glycaemic regulation and lower awareness of hypoglycaemia need clinical attention, focused on hypoglycaemia. Patients with excellent glycaemic control, combined with great FoH and pronounced diabetes-related problems however, should not be overlooked |
| MOHEET 2012<br>Additional info | Conference abstract | n=18<br>Type 1 diabetes adults with IAH (Clarke score) | History of severe HG and high total score on CQ (Clarke questionnaire/ Clarke score) is significantly related to reduced CR response to HG in patients with type 1 diabetes. Therefore, such responses on the CQ may indicate those patients with the most profound IAH, which can be of value in both the research and the clinical setting |
| SPEIGHT 2011 | Conference abstract<br><br>Patient, physician and psychologist discussions drafting new items to the Clarke Score. | n=14 type 1 diabetes adults tested the new items of score<br>Score = The Hypo Awareness Questionnaire | Patient input identified the need for separate questions about:<br>• hypoglycaemia when awake and asleep<br>• ways to improve specificity/acceptability.<br>• 18 items assess recall of hypoglycaemic events, blood glucose thresholds at which symptoms occur, awareness of symptoms, altered awareness, and frequency of checking blood glucose when 'feeling low'.<br>Completion time: average 7 min (range 5-15), shorter following each revision.<br>Authors' Conclusion: A comprehensive, collaborative and iterative design process has generated a detailed measure of IAH with good face and content validity. The Hypo Awareness Questionnaire is likely to be useful in clinical trials and enable improved recognition of IAH together with more accurate evaluation of medical fitness for activities including driving |
| TAN 2012A | Conference abstract | n=30<br>type 1 diabetes | Clarke and Gold scores for IAH<br>IAH: GOLD = 8patients (27%)<br>IAH vs. aware patients<br>NS difference in HbA1c<br>SS longer mean duration diabetes<br>Discussed IAH during their consultation with a specialist (88% vs. 64%).<br><br>Conclusion: The prevalence of IAH was higher in this study than in previous work suggesting that the problem may still be underestimated. It was appropriately recognised, and treatment strategies |

| Study | Intervention/comparison | Population | Outcomes |
|---|---|---|---|
| | | | documented for the majority, on attendance at specialist clinics |

## G.6.2 Recovering hypoglycaemia awareness

**Table 280: BROOKS 2013[21]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| Brooks et al., 2013. Attainment of Metabolic Goals in the Integrated UK Islet Transplant Program With Locally Isolated and Transported Preparations. American Journal of Transplantation 2013; 13: 3236–3243<br><br>REF ID: BROOKS2013 | Retrospective observational case series<br><br>UK<br><br>Recipients of a first islet transplant between April 2008 and March 2011 at all NHS-funded centres | n=20<br>Inclusion:<br>• C-peptide-negative type 1 diabetes<br>• recurrent severe hypoglycaemia ≥1 event over the preceding 12 months requiring assistance to actively administer carbohydrate, glucagon or other resuscitative actions despite optimized conventional management.<br>Exclusion:<br>Insulin resistance<br>Contraindications to immunosuppression therapy<br>Body weight >80kg | Male, %<br>25%<br><br>Age, median (IQR)<br>49 (44-54)<br><br>Duration of diabetes median (IQR)<br>30 (17-39)<br><br>n=16 islet transplant alone, n=4 islet after kidney | Islet transplant | 12 months and 24 months (13.5-36 months) | Severe Hypoglycaemia, number of patients | Baseline 12 months: 20/20 (100%)<br>During 24 month follow-up: 8/20 (40%) | Funding: UK islet transplant program funded by the NHS National Commissioning group. UK Islet Transplant Consortium supported by Diabetes UK, Diabetes Research and Wellness Foundation, Diabetes Foundation and Juvenile Diabetes Research Foundation. Current study funded by a Diabetes UK Grant. |

**Table 281: CHOUDHARY 2013[26]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Choudhary et al. 2013. Real-time continuous glucose monitoring significantly reduces severe hypoglycaemia in hypoglycaemia-unaware patients with type 1 diabetes. Diabetes Care: 36: 4160-4162<br><br>REF ID: CHOUDHARY2013 | Prospective observational case series<br><br>UK | n=35<br>Adults<br>Inclusion:<br>• Type 1 diabetes<br>• Ongoing problematic hypoglycaemia leasing to limitation of daily activities and Gold score >4 despite structured education with or without CSII<br>• Use of CGM in addition to CSII or MDIs for at least 12 months | Age, mean (SD) 43.2 (12.4)<br><br>Type 1 diabetes duration 29.6 (13.6)<br><br>Male:Female 11:24<br><br>33 used CSII; 1 converted to CSII; 1 used MDI | CGM 12months<br><br>CGM in addition to either MDIs or CSII<br><br>23 patients used the Medtonic Paradigm Veo system; 7 patients used the Medtonic Paradigm RT system; 3 patients used Dexcom G4 sensors in combination with an Anamas Vibe pump; 1 patient used MDI; 1 patient used a CGM system. | none | 1 year | Severe hypoglycaemia rate, episodes/year, mean (SD) | Before intervention: 8.1 (13)<br>After intervention: 0.6 (1.2)<br>Reported as P=0.005 | Funding: authors received fees or honoraria from Madtronic, Animas, Roche, Abbott. Authors received funding for clinical trials from Medtronic |
| | | | | | | | HbA1c, %, mean (SD) | Before intervention: 8.1 (1.2)<br>After intervention: 7.8 (1.0)<br>Reported as P=0.007 | |
| | | | | | | | IAH, Gold score (n=19), range 1-7, mean (SD) | Before intervention: 5.0 (1.5)<br>After intervention: 5.0 (1.9)<br>Reported as P=0.67 | |

**Table 282: COX 2004[31,32]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cox et | RCT | n=60 | | HAATT | Control | SMBG + | SMBG (provided | 1-18 | Severe | HAATT: before | Patients |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| al., 2004. Hypoglycaemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycaemia among adults with type 1 diabetes mellitus. International Journal of Behavioral Medicine: 11: 212-218<br><br>REF ID: | Country: Bulgaria (HAATT developed in US). Standard care in Bulgaria at the time did not routinely employ SMBG) | Inclusion:<br>• Type 1 diabetes<br>• History of ≥2 episodes of SH (inability to treat oneself due to hypoglycaemic stupor or unconsciousness) in the past year.<br>•<br>Exclusion: | | (n=30) | (n=30) | HAATT (also received SMBG supplies along with a 7 week structured group psycho-educational treatment programme designed to reduce occurrences of low BG, and increase awareness and improve treatment of low BG) | with SMBG Accucheck Easy Meter 1 month pre-treatment and 1 month post-treatment). 2 month treatment phase – educated by their physician on SMBG data | months post-treatment<br><br>2 months treatment | hypoglycaemia/subject | 2.0; after 0.4<br><br>SMBG: before 1.8; after 1.7<br><br>(F value 5.0; p value 0.03) | matched on baseline hypo occurrence and randomised.<br>Physician change routine based on SMBG data?<br><br>As an incentive to participate, participants were given an Accucheck Easy Meter (Roche Diagnostics), 4 months worth of supplies and $20. |
| | | | Age | 37.6 (9.0) | 38.6 (9.8) | Both groups:<br>6 months before treatment participants recorded moderate and SH<br>1 month before treatment participants provided with SMBG equipment and diaries<br>4-times daily participants estimated whether their BG was hypoglycaemic, euglycaemic or hyperglycaemia; whether they were having hypo symptoms; and record their actual BG. | | | Nocturnal hypoglycaemia/subject | HAATT: before 1.1; after 0.8<br><br>SMBG: before 0.6; after 1.6<br><br>(F value 3.9; p value 0.055) | |
| | | | HbA1c | 8.1 (0.7) | 8.0 (0.7) | | | | HbA1c | Only reported as estimated HbA1c | |
| | | | Male % | 53 | 54 | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| COX2004 | | | Duration of diabetes | 13.9 (9.3) | 14.0 (7.6) | Monthly physician visits to make adjustments to insulin, food and exercise routine based on SMBG data | | | % low BG accompanied by symptoms | HAATT: before 60%; after 70%<br><br>SMBG: before 56%; after 58%<br><br>(F value 0.4; p value NS) | |
| | | | | | | | | | % detection of low BG | HAATT: before 52%; after 70%<br><br>SMBG: before 58%; after 55%<br><br>(F value 8.4; p value 0.005) | |

**Table 283: CRANSTON 1994[33]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| Cranston | Prosp | n=12 | Male: 12/12 | Hypoglycaemia avoidance | Mean | HbA1c | Group A: before 6.5 | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| et al., 1994. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet: 344: 283-287<br><br>REF ID: CRANSTON 1994 | ective observational case series<br><br>UK | Inclusion:<br>• IDDM (duration >10years)<br>• History of hypoglycaemia without warning<br>• At least three BG <3mmol/litre per 2 weeks in the month prior to the study<br>•<br>Exclusion: | IDDM duration range: 11-32 years<br><br>Two groups:<br>Group A (n=6): Good control HbA1c <7% (mean 6.5±0.2)<br>Group B (n=6): Poor control – swung from one extreme of glycaemia to the other (mean HbA1c 8.2±0.3)<br><br>2 patients on thyroxine and 2 patients on ACEi. 1 patient in group A had peripheral neuropathy | (treatment programme designed to achieve 3 weeks without BG<3.5 mmol/litre – achieved by diet review, advice about exercise, redistribution of insulin) | period to achieve 3 weeks absence of hypo was 4.1 (1.1) months | | (0.2); after 6.9 (0.3) (p=0.32)<br><br>Group B: before 8.2 (0.2); after 8.7 (0.3) (p=0.26) | British Diabetic Association Grant |
| | | | | | | Hypoglycaemia (<3mmol/litre). Frequency/month for 3 week period | Group A: before 21; after 0<br><br>Group B: before 14; after 0 | |
| | | | | • Symptom scores recorded to controlled hypoglycaemia during clamp study<br>• 1 month before treatment – continued usual treatment but recorded 4-daily SMBG (3-pre meal and 1 pre-bed)<br>• 3 patients in group B converted from twice daily mixed insulin to pre-meal soluble and overnight intermediate acting insulin. | | Total autonomic symptom scores during clamp | Both groups had higher scores after the intervention (displayed graphically only) | |
| | | | | | | Hospital admissions | 1 (group B) | |

**Table 284: DE ZOYSA 2014[36]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| De Zoysa et al., 2014. A Psychoeducational Program to Restore Hypoglycaemia Awareness: The DAFNE-HART Pilot Study. Diabetes Care. 2014 Mar;37(3): 863-6. doi: 10.2337/dc13-1245. Epub 2013 Dec 6.<br><br>REF ID: DEZOYSA2014 | Prospective case series | n=24<br><br>Inclusion:<br>• Type 1 diabetes<br>• Using DAFNE principles for insulin self-adjustment<br>• Persistent impaired awareness of hypoglycaemia assessed clinically and Gold score ≥4.<br>Exclusion: | Male, %<br>50%<br><br>Age, mean (SD)<br>54.4 (7.9)<br><br>Duration of diabetes, mean (SD)<br>30.7 (11.9)<br><br>n=15 using twice daily background and pre-meal insulin, n=8 using pumps | DAFNE-Hypoglycaemia Restoration Awareness Training (DAFNE-HART).<br>Relevant sections from DAFNE and interventions targeting problematic hypoglycaemia. 6 week intervention using motivational interviewing and cognitive behavioural techniques | 12 months | Self-reported severe hypoglycaemia (<3.5mmol/litre requiring assistance), events/patient-year, median (range) | Before: 3.0 (0-104)<br>After: 0 (0-3) | Funding: NIHR Programme Grants for Applied Research Theme<br><br>1 drop out to follow-up |
| | | | | | | HbA1c, % | Before: 7.8 (1.2)<br>After: 7.8 (1.1) | |
| | | | | | | Gold score, range 1-7, ≥4 = impaired awareness | Before: 5.6 (1.4)<br>After: 4.5 (1.9) | |
| | | | | | | Clarke score, ≥4 = impaired awareness | Before: 5.4 (1.2)<br>After: 3.8 (1.8) | |
| | | | | | | Ryan score, hypoglycaemia burden (<423 considered to indicate hypoglycaemia not a major clinical concern) | Before: 948 (831)<br>After: 372 (466) | |
| | | | | | | Anxiety, hospital anxiety and depression score, (score >8 indicates clinically relevant psychological distress) | Before: 5.9 (5.0)<br>After: 6.0 (5.7) | |
| | | | | | | Depression, hospital anxiety and depression score, (score >8 indicates clinically relevant psychological distress) | Before: 5.2 (4.6)<br>After: 5.1 (4.7) | |
| | | | | | | PAID, score ≥40 indicates clinically relevant psychological distress | Before: 30.7 (22.6)<br>After: 24.7 (20.5) | |

**Table 285: Fanelli 1993[43]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Fanelli et al., 1993. Meticulous prevention of hypoglycaemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycaemia in intensively treated patients with short-term IDDM. Diabetes: 42: 1683- | Prospective case series observational before and after study<br><br>Italy | n=8 (plus n=12 controls)<br><br>Inclusion:<br>• IDDM (duration ≤7years)<br>• Treatment with intensive insulin therapy<br>• Consistent history of frequent hypoglycaemia (BG<3mM) in the absence of autonomic warning symptoms for at least 6 months before the study<br>• Absence of clinically overt autonomic neuropathy<br>Exclusion:<br>• Diabetic complications, other diseases or other drugs apart from insulin | Male:Female<br>4:4<br><br>Age, years mean (SE)<br>26 (2)<br><br>Duration of diabetes, years mean (SE)<br>5.0 (0.6)<br><br>HbA1c, % mean (SE)<br>5.8 (0.3)<br><br>Estimated duration of unawareness, years, mean (SE)<br>1.2 (0.3)<br><br>All were on 3-4 daily injections | Hypoglycaemia avoidance by change in regime and counselling. To prevent hypoglycaemia, insulin doses aimed at fasting, preprandial and bedtime BG of ~7.2-8.3mM.<br><br>Regular insulin at meal times and intermediate acting NPH at 2300-2330. Diet changed to 3 meals with no snacks. Daily telephone counselling. SMBG 4 times daily. | None | 2 weeks and 3 months | Severe hypoglycaemia (coma, seizure or 3rd party assistance), number of patients | Year before study: 2/8<br><br>During 3 months: 0/8 | Funding: Juvenile Diabetes foundation Grant and Aging Grant. |
| | | | | | | | HbA1c, %, mean (SE) | Before: 5.8 (0.3)<br>After: 6.9 (0.2)<br>Reported as P<0.05 | |
| | | | | | | | Autonomic symptom score during hypoglycaemia clamp, mean (SE), scored zero-5 (none-severe) for six autonomic symptoms | Before: 2.2 (0.9)<br>2 week: 4.7 (1.7)*<br>3 month: 5.8 (0.6)*<br>*Reported as P<0.05 from baseline | |
| | | | | | | | Neuroglycopenic symptom score during hypoglycaemia clamp, mean (SE), scored zero-5 (none-severe) for five neuroglycopenic | Before: 5.4 (1.5)<br>2 week: 7.4 (1.7)*<br>3 month: 9.4 (1.1)*<br>*Reported as P<0.05 from baseline | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 1689<br><br>REF ID: FANELLI1993 | | | | | | | symptoms | | |

**Table 286: Fanelli 1994[42]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fanelli et al., 1994. Long-term recovery from unawareness, deficient counter regulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, | Prospective observational cohort study<br><br>Italy | n=21 (plus n=20 healthy participants)<br><br>Inclusion:<br>• IDDM<br>• Consistent history of frequent hypoglycaemia (BG<3mmol/litre) in the absence of autonomic warning symptoms for at least | | Int n=16 | Comp n=5 | Hypoglycaemia avoidance by change in regime and counselling. To prevent hypoglycaemia, insulin doses aimed at fasting, preprandial and bedtime BG of ~7.2-8.3mM.<br><br>Insulin changed to 4-daily injections, regular insulin at meal times and intermediate acting NPH at supper. In n=9 patients who | Continued therapeutic regime they followed at entry | 2 weeks,<br>3 months and<br>1 year | Severe hypoglycaemia | Not reported for each group separately | Funding: Juvenile Diabetes foundation Grant and Aging Grant.<br><br>All patients reported to be different to those recruited in FANELLI 1993<br><br>Control group changed to |
| | | | M:F | 8:8 | 3:2 | | | | | | |
| | | | Age, years mean (SE) | 32 (2.7) | 33 (2.7) | | | | HbA1c, %, mean (SE), only reported before and after for intervention group, no group comparison. | Before: 5.8 (0.2)<br>After: 6.9 (0.1) | |
| | | | HbA1c, % mean (SE) | 5.8 (0.2) | 5.8 (0.2) | | | | Autonomic symptom score during hypoglycaemia clamp, final | 2 week<br>Intervention: 6.9 (1.0)<br>Control: 1.9 (0.2) | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| intensive insulin therapy in IDDM. Diabetologia: 37: 1265-1276<br><br>REF ID: FANELLI1994 | | 6 months before the study<br>• Absence of clinically overt autonomic neuropathy<br>Exclusion:<br>• Other diseases or other drugs apart from insulin | | | | had late dinner, NPH was added to regular insulin at lunchtime. Diet changed to 3 meals with no snacks. Daily telephone counselling. | | | score, mean (SE), scored zero-5 (none-severe) for six autonomic symptoms | Reported to have normalised at 3 months and 1 year in intervention group | same insulin regime as intervention group at 3 months due to ethical reasons |
| | | | Duration of diabetes, years mean (SE) | 12 (2) | 9.2 (3.4) | | | | Neuroglycopenic symptom score during hypoglycaemia clamp, final values, mean (SE), scored zero-5 (none-severe) for five neuroglycopenic symptoms | 2 week<br>Intervention: 9.7 (1.1)<br>Control: 6.1 (0.6)<br><br>Reported to have normalised at 3 months and 1 year in intervention group | |
| | | | 13 on 2-daily injections of mixed regular and NPH insulin, 8 on 3-daily injections at meal times and NPH at supper. | | | | | | | | |

**Table 287: Ferguson 2001[45]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Ferguson et al., 2001. Severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia: a comparative study of insulin lispro and regular human insulin. Diabetes/ Metabolism Research and Reviews: 17: 285-291<br><br>REF ID: | Open label randomised crossover study<br><br>Outpatient clinic<br><br>UK | n=40<br>Adults<br>Inclusion:<br>• Type 1 diabetes > 5years<br>• Aged 19-65 years<br>• Reported a reduction in their warning symptoms for hypoglycaemia for at least 2 years; had ≥2 episodes of SH in the 2 years preceding and self-scored on Likert scale<br>• HbA1c less than double the non-diabetic reference range of 5-6.5%<br>Exclusion:<br>• Systematic, renal or | Age, mean (SD): not reported<br><br>Type 1 diabetes duration: not reported<br><br>Male:Female 19:21 | Insulin Lispro and human NPH insulin for 6 months<br><br>4 week run-in period: all treated with regular human insulin in combination with NPH<br><br>SMBG as per normal routine | Regular human insulin and human NPH insulin for 6 months | 1 year | Severe hypoglycaemia during treatment, no. of patients | Lispro: 18/33<br>Regular: 18/33<br>Reported as NS | Funding: Research grant from Eli Lilly<br><br>Drop-outs 7 ACA n=33<br><br>Powered for incidence of SH<br><br>Open-label, randomised, crossover<br><br>Not ANCOVA<br><br>Questionnaire data using ANCOVA |
| | | | | | | | BG level at which hypoglycaemia initiated the perception of symptoms, mmol/litre | Lispro: 2.5<br>Regular: 2.6<br>Reported as NS | |
| | | | | | | | HbA1c %, end of each treatment period, mean (SD) | Lispro: 9.1 (0.8)<br>Regular: 9.3 (1.0)<br>Reported as P=0.14 | |
| | | | | | | | QOL (DTSQ and HFS) | Reported as NS difference for both DTSQ and HFS | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| FERGUSON 2001 | | hepatic disease<br>• Pregnancy | | | | | | | |

**Table 288: Fritsche 2001[51]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Fritsche et al., 2001. Avoidance of hypoglycaemia restores hypoglycaemia awareness by increasing beta-adrenergic sensitivity in type 1 diabetes. Annals of Internal Medicine: 134: 729-736 | Prospective observational before and after study (prospective case-series)<br><br>Germany | n=10 (plus 10 controls and 10 aware type 1 diabetes)<br>Adults<br>Inclusion:<br>• Type 1 diabetes receiving an intensive insulin regime<br>• Self-reported IAH and a history of SH as defined by DCCT (SH resulting | Male:Female<br>10:0<br><br>Age, mean (SD)<br>46 (16)<br><br>Duration of diabetes, mean (SD)<br>20 (10)<br><br>HbA1c, %, mean (SD)<br>6.8 (0.9)<br><br>All were receiving intensive insulin regimes (LA insulin in the | Avoidance of hypoglycaemia<br><br>Target pre-prandial BG levels increased from<br>5.6 mmol/litre to<br>8.3 mmol/litre and at bedtime from<br>5.6 mmol/litre to<br>10 mmol/litre. to achieve this, long-acting insulin dose reduced. Daily RA insulin reduced and adjusted for carbs and BG | None | 4 months | HbA1c, %, mean (SD) | Before: 6.8 (0.9)<br>After 7.7 (0.9)<br>Reported as P<0.05 | Funding: Grants from the National Institute of Health, Division of Research Resources, General Clinical Research Centre and Deutsche Forschungsgemeinschaft. |
| | | | | | | | Autonomic symptom score during hypoglycaemia clamp, mean (SE), scored zero-7 (none-severe) for nine autonomic symptoms | Before: 1.8 (0.6)<br>After 3.3 (0.7)<br>Reported as P=0.004 | |
| | | | | | | | Neuroglycopenic symptom score during hypoglycaemia clamp, mean (SE), scored zero-7 (none-severe) for ten neuroglycopenic symptoms | Before: 2.2 (0.7)<br>After 3.7 (0.7)<br>Reported as P=0.01 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: FRITSCHE2001 | | in coma or seizure, requiring assistance from another person and treatment with glucagon or IV glucose<br>Exclusion:<br>• Autonomic neuropathy | morning and at bedtime and RA insulin before meals – usually 3 times daily) | level. SMBG 5 times daily. Participants contacted twice weekly for adjustments of insulin dose to avoid BG levels below 3.9mmol/litre. | | | Severe hypoglycaemia (requiring 3rd party assistance and glucagon or IV glucose), episodes per patient, mean (SE) | 4 months before: 2.0 (0.5)<br>During study: 0.0 (0.0) | |

**Table 289: GIMENEZ 2010[55]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Gimenez et al., 2010. Sustained efficacy of continuous subcutane | Prospective observational before and after study (prospective case-series) | n=20 (plus 20 aware type 1 diabetes)<br>Inclusion:<br>• Type 1 diabetes | Male:Female<br>8:12<br><br>Age, years, mean (SD)<br>34 (7.5) | CSII<br><br>All received education programme for patients beginning | None | 6 months, 12 months and 24 months | SH (require 3rd party assistance), episodes per subject year, mean (SD) | Before: 1.3 (0.4)<br>24 months: 0.1 (0.2)<br>Reported as P<0.001 | Funding: Part sponsored by Medtronic Iberica.<br>Grant from the Ministerio de Sanidad y |
| | | | | | | | Clarke score, number of patients with HU | Before: 19/20<br>24 months: | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| ous insulin infusion in type 1 diabetes subjects with recurrent non-severe and severe hypoglycaemia and hypoglycaemia unawareness: a pilot study. Diabetes technology and therapeutics: 12: 517-521<br><br>REF ID: GIMENEZ2010 | Spain | duration >5 years<br>• >18 years old<br>• Conventional insulin treatment using MDI of RA (lispro or aspart) and glargine as basal insulin<br>• Presenting more than 4 mild hypoglycaemia events per week (in the last 8 weeks) and more than 2 SH events | Duration of diabetes, years, mean (SD)<br>16.2 (6.6)<br><br>HbA1c %, mean (SD)<br>6.7 (1.1)<br><br>Conventional insulin treatment using MDI of RA (lispro or aspart) and glargine as basal insulin | CSII. Patients also seen every 2-3months after the education programme up to 24 months. Patients were encouraged to avoid BG values below 70mg/dl | | | (score≥4)<br><br>Clarke score, mean (SD) | 3/20<br><br>Before: 5.5 (1.2)<br>6 months: 3.7 (1.7)<br>12 months: 2.7 (1.1)<br>24 months: 1.6 (2.0) Reported as P<0.001 for baseline vs. 24 months) | Consumo of Spain |
| | | | | | | | Hypoglycaemia symptom score questionnaire during hypoglycaemia clamp study, mean (SD) | Before: 31.6 (16.4)<br>24 month: 62.3 (23.6)<br>Reported as P<0.001 | |
| | | | | | | | HbA1c %, mean (SD) | Before: 6.6 (1.1)<br>6 months: 6.7 (0.9)<br>12 months: 6.7 (0.8)<br>24 months: 6.3 (0.9)<br>Reported as NS | |
| | | | | | | | DQoL, 46-item instrument with a 5-point Likert scale and 4 subscales (1-5, lower scores indicate | Satisfaction<br>Before: 36.0 (6.4)<br>24 month: 28.8 (5.5) | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | (in the last 2 years)<br>Exclusion:<br>• Micro or macro-vascular complications<br>• Low-level (micro) albuminuria<br>• Contradictions for CSII | | | | | better QOL) | Reported as P<0.001<br>Impact of treatment<br>Before: 33.6 (7.5)<br>24 month: 27.4 (6.0)<br>Reported as P<0.002<br>Social worry<br>Before: 13.3 (4.1)<br>24 month: 11.5 (3.8)<br>Reported as P<0.05<br>Diabetes related issues<br>Before: 10.1 (2.6)<br>24 month: 8.0 (1.9)<br>Reported as P<0.01 | |
| | | | | | | | SF-12 health survey questionnaire, mean (SD) | Before: 34.1 (3.9)<br>24 month: 37.0 (2.9)<br>Reported as P<0.01 | |

**Table 290: HERMANNS 2007[61]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Hermanns et al., 2007. The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients with type 1 diabetes. Diabetes/ metabolism research and reviews: 23: 528-538.<br><br>REF ID: HERMANNS2007 | RCT<br><br>23 outpatient centres<br><br>Germany | n=164<br>Adults<br>Inclusion:<br>• Type 1 diabetes >10years<br>• MDI or CSII<br>• Aged 18-70 years<br>• At least one episode of SH in the past 12 months (requiring 3rd party assistance) or impaired awareness of hypoglycaemia and tight glycaemic control (HbA1c <6.5%)<br>Exclusion: | Age, mean (SD)<br>HyPOS: 46.0 (11.7)<br>Control: 45.9 (13.3)<br><br>Male, %<br>HyPOS: 50<br>Control: 50<br><br>Disease duration:<br>HyPOS: 20.2 (10.8)<br>Control: 22.1 (10.9)<br><br>% patients with reduced awareness (HAQ Clarke score)<br>HyPOS: 87.8<br>Control: 83.3<br><br>HbA1c, %:<br>HyPOS: 7.2 (0.9) | Avoidance of hypoglycaemia (n=84):<br><br>HyPOS training programme focusing on avoiding low BG values, causes of HU, improving detection and recognition of warning symptoms and need for treatment of low BG values. 5-weekly lessons (each 90mins) | Control (n=80)<br><br>Education programme aimed at optimising intensive insulin therapy without regard to hypoglycaemia problems. 4-weekly lessons (each 90mins) | 6 months | Hypoglycaemia awareness questionnaire (HAQ; Clarke score), 8 items about freq. of SH and MH, detection of these episodes and glycaemic thresholds for detection of low BG. Each item scored 0 or 1 (total range 0-7, maximal awareness – maximal unawareness) | Mean difference: 0.7 (95% CI 0.1-1.2)<br>Treatment effect reported as P=0.024<br><br>Improvement greater in HyPOS group | Funding: Berlin-Chemie AG funded the development of HyPOS and supported the evaluation study.<br><br>Power analysis done on awareness measured using a VAS<br><br>Cont. outcomes using ANCOVA<br><br>18 drop-outs (11%) (control 13%, Hypos 9%) |
| | | | | | | | Gold score, modified VAS, range 0-10 (minimal awareness – maximal awareness) | Mean difference: 0.8 (95% CI 0.2-1.4)<br>Treatment effect reported as P=0.015<br><br>Improvement greater in HyPOS group | |
| | | | | | | | Severe hypoglycaemia (requiring 3rd party assistance) , no. of episodes/patient-year | Mean difference: 0.3 (95% CI -0.4-1.0)<br>Treatment effect reported as P=0.4 | |
| | | | | | | | BG level for detection | Mean | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | • Cancer diagnosis, dementia, pregnancy or diagnosis of psychiatric disease | Control: 7.4 (1.1) | | | | of low BG, mmol/litre | difference: -0.2 (95% CI -0.03-0.4) Treatment effect reported as P=0.02<br><br>Improvement greater in HyPOS group | ACA |
| | | | | | | | HbA1c, %, final values | HyPOS: 7.2 (0.8)<br>Control: 7.1 (0.9) | |
| | | | | | | | QOL, Problem Areas in Diabetes scale (PAID), 5-point Likert scale 0-4 (no problem-serious problem). PAID scores transformed onto a 0-100 scale (higher scores = more serious problems) | Mean difference: -0.7 (95% CI -4.6-3.2) Treatment effect reported as P=0.7 | |
| | | | | | | | QOL, Audit of Diabetes Dependent QOL (ADDQoL), 7-point scale (-3 to +3) | Mean difference: 0.1 (95% CI -0.1-0.4) Treatment effect reported as P=0.4 | |

**Table 291: HERNANDEZ 2008[63]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Hernandez et al., 2008. Evaluation of a self-awareness intervention for adults with type 1 diabetes and hypoglycaemia unawareness. Canadian journal of nursing research: 40: 38-56<br><br>REF ID: | Prospective observational case-series<br><br>Canada | n=23<br><br>Inclusion:<br>• Type 1 diabetes for >5 years<br>• >21years old<br>• Currently SMBG<br>• Previously diagnosed with HU by an endocrinologist and verified with the Clarke score<br>Exclusion:<br>• Cancer diagnosis, dementia, pregnancy or diagnosis of psychiatric disease | Male:Female 12:11<br><br>Age, median (range)<br>54 (29-75)<br><br>Duration of diabetes, mean (range)<br>26.5 (10-47) | Self-awareness educational intervention<br><br>Eight 3-hour sessions held biweekly. Aimed at promoting increased awareness of body cues associated with differing levels of glycaemia and enhancing the well-being of patients with HU | None | 18 months | Number of symptoms of hypoglycaemia, mean (SD) | Baseline: 3.4 (1.9)<br>6 months: 3.4 (2.0)<br>12 months: 2.7 (2.3)<br>18 months: 3.3 (2.6)<br><br>RM_ANOVA reported as F[3,19]=4.4 P<0.05. | Funding: Canadian Diabetes Association<br><br>6 drop-outs |
| | | | | | | | Severe hypoglycaemia requiring treatment, number of events | Baseline: 13.3 (17.4)<br>6 months: 9.4 (14.8)<br>12 months: 6.9 (11.0)<br>18 months: 7.1 (11.6)<br><br>RM_ANOVA reported as F=0.86 P=0.5 | |
| | | | | | | | HbA1c (units not reported), mean (SD) | Baseline: 0.088 (0.015)<br>6 months: 0.085 (0.014)<br>12 months: 0.084 (0.017)<br>18 months: 0.080 (0.015)<br><br>RM_ANOVA reported as F=7.54 P=0.002 | |
| | | | | | | | The Diabetes Questionnaire (TDQ), 15 item instrument with 6-point Lekert scale (1-6, strongly disagree-strongly agree) | Baseline: 75.3 (7.8)<br>6 months: 76.5 (8.7)<br>12 months: 79.3 (7.7)<br>18 months: 79.7 (7.0)<br>RM_ANOVA reported as F=4.35 P=0.016 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| HERNANDEZ2008 | | | | | | | DQoL, 46-item instrument with a 5-point Likert scale and 4 subscales (1-5, lower scores indicate better QOL) | Baseline: 93.3 (18.7)<br>6 months: 126.2 (26.8)<br>12 months: 88.1 (17.4)<br>18 months: 120.9 (22.3)<br><br>RM_ANOVA reported as F=18.5 P=0.000 | |
| | | | | | | | Hospitalisation, number of events | Baseline: 0.8 (2.2)<br>6 months: 0.1 (0.4)<br>12 months: 0.1 (0.5)<br>18 months: 0.2 (0.4)<br><br>RM_ANOVA reported as F=1.11 P=0.37 | |
| | | | | | | | Driving incidents, number of events | Baseline: 0.3 (0.7)<br>6 months: 0.1 (0.3)<br>12 months: 0.3 (0.8)<br>18 months: 0.1 (0.5)<br><br>RM_ANOVA reported as F=1.00 P=0.41 | |

**Table 292: HOPKINS 2012[66]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Hopkins et al., 2012. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care: 35: 1638-1642.<br><br>REF ID: HOPKINS2012 | Retrospective observational case-series<br><br>DAFNE courses<br><br>UK | n=539 (subgroup of n=215 with impaired awareness)<br>Inclusion:<br>• Attending DAFNE course<br>• Subgroup with impaired awareness: those reporting symptom onset at BG <3mmol/litre or not at all were considered to have impaired awareness of hypoglycaemia.<br>Exclusion: | Age, mean (SD)<br>Not reported for subgroup<br><br>Male, %<br>Not reported for subgroup<br><br>Disease duration:<br>Not reported for subgroup<br><br>% patients with impaired awareness:<br>100% (215/215)<br><br>HbA1c, %:<br>Not reported for subgroup | DAFNE course (Dose adjustment for normal eating) – 5 day course focusing on adjustment of insulin for carbohydrate intake and reflective use of home BG monitoring data. | none | 1 year (300-420 days) | % patients with impaired awareness (n=215), those reporting symptom onset at BG <3mmol/litre or not at all | 97/215 (45%) | Funding: broader program funded by the UK NIHR. G.T. employed as the national director of the DAFNE program and funded by the UK DAFNE collaborative.<br><br>No data available for impaired awareness outcome at follow-up for 26/215 (12%) |
| | | | | | | | Severe hypoglycaemia, self-reported episodes requiring assistance to treat hypoglycaemia due to incapacity, mean (SD) number of episodes per patient-year | Year preceding: 3.6 (13.6)<br>Year post-DAFNE:<br>1.3 (5.9) | |
| | | | | | | | QOL | Not reported for subgroup with impaired awareness of hypoglycaemia | |
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**Table 293: LEELARATHINA 2013[92]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Leelarathina et al., 2013A. Restoration of Self-Awareness of Hypoglycaemia in Adults With Long-Standing Type 1 Diabetes: Hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. Diabetes Care: 36: 4063-4070<br><br>REF ID: LEELARATHINIA2013 | Prospective case series<br>HypoCOMPaSS trial (this paper reports the case-series study data for all treatment arms)<br><br>July 2010-June 2011, 96 adults recruiter to main HypoCOMPaSS trial across 5 UK tertiary centres | n=18<br><br>Inclusion:<br>• 18-74 years<br>• Type 1 diabetes according to WHO criteria<br>• IAH (Gold score ≥4 with or without history of SH in preceding 12 months defined by ADA)<br>• Serum C-peptide <50pmol/litre with simultan | Age, mean (SD) 50 (9.0)<br><br>Type 1 diabetes duration 35.0 (10.0)<br><br>HbA1c 8.1 (1.0) | Hypoglycaemia avoidance (6 months)<br><br>HypoCOMPaSS education tool (at start of 24-week RCT period: individualised education session aimed at avoidance and early detection of BG <4mmol/litre). Followed by 24-week using:<br>1) MDI + SMBG<br>2) MDI + SMBG and RT-CGM<br>3) CSII + SMBG<br>4) CSII + SMBG and RT-CGM | This study reports the before and after clamp study data from the trial | 6 months | Edinburgh Hypo Score (at end of clamp study): 11 items rating 4 autonomic symptoms & 5 neuroglycopenic symptoms (omitted non-specific symptoms nausea and headache from analysis). Each item scored 1-7 (absent-maximal) – converted to scale 0-6 with min-max possible range 0-54) | Total symptoms AUC<br>Before intervention: 500 (365-685)<br>After intervention: 650 (365-1285)<br>Reported as P=0.02 | Funding:<br>Diabetes UK grant and Cambridge NIHR BRC. No pharmaceutical company or device manufacturer funded the trial. Authors have received sponsorship, consultancy fees and sit on advisory boards for various companies.<br><br>30 consented to baseline clamp and 27 to post-RCT clamp. 25 completed at baseline and 22 post-RCT. Termination of clamp |
| | | | | | | | Self-awareness of hypoglycaemia (clamp study), plasma glucose at which first felt hypoglycaemic, mmol/litre, mean (SD) | Before intervention: 2.6 (0.1)<br>After intervention: 3.1 (0.2)<br>Reported as P=0.017 | |
| | | | | | | | Severe hypoglycaemia, | 6 months preceding intervention: | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A | | eous exclusion of biochemical hypoglycaemia<br><br>Exclusion:<br>• Unwilling to undertake intensive insulin therapy and study devices<br>• History of intolerance to glargine<br>• Additional exclusion for clamp study (>60 | | PRIMARY GOAL OF INSULIN DOSE TITRATION THROUGHOUT THE 24-WEEK RCT PERIOD WAS ABSOLUTE AVOIDANCE OF ALL BG LEVELS <4mmol/litre<br><br>Of 18 participants in clamp study:<br>CSII n=9 & MDI n=9<br>SMBG n=11 & CGM n=7 | | | annualised rate (not clamp study), median (IQR) | 4 (0-7)<br>RCT-period:<br>0(0-0)<br>Reported as P=0.001 | mainly due to cannula issues. Results presented for 18 participant for whom paired clamp data available.<br><br>Area Under the Curve calculated using trapezoid rule after linear interpolation of any missing data |
| | | | | | | | IAH, Gold score, range 1-7, mean (SD) | Baseline:<br>5.2 (0.2)<br>Post-RCT:<br>4.3 (0.4)<br>Reported as P=0.009 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | years); history of epilepsy or ischemic heart disease | | | | | | | |

**Table 294: LEITAO 2008[94]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Leitao et al., 2008. Restoration of hypoglycaemia awareness after islet transplantation. Diabetes Care: 31: 2113-2115.<br><br>REF ID: LEITAO 2008 | Retrospective observational case-series<br><br>US | n=31<br><br>Inclusion:<br>• Islet transplantation alone (n=25) or islet transplantation after kidney (n=6)<br><br>Exclusion: | Age, mean 43.8 (8.7)<br><br>Type 1 diabetes duration 29.3 (11.8)<br><br>Male %: 42%<br><br>Mean Clarke score 5.29 (1.51)<br><br>Number of patients with HU (Clarke | Islet transplantation (n=25) or islet transplantation after kidney (n=6) | none | 47.2 (21.3) months after first intervention | Clarke score (minimum =0; maximum =7), mean (SD)<br><br>Number of patients with HU (Clarke score ≥4) | Before: 5.29 (1.51)<br>After: 1.35 (1.92)<br><br>Before: 27/31 (87%)<br>After: 4/31 (13%) | Funding: Supported by NIH/NCRR; Juvenile Diabetes Research Foundation International; NIH/NIDDK; the State of Florida and the Diabetes Research Institute Foundation. Author scholarship from Conselho Nacional de |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | score ≥4): 27/31 (87%) | | | | | | Desenvolvimento Cientifico e Tecnologico. |

**Table 295: LIU 1996[97]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Liu et al., 1996. Improved counter-regulatory hormonal and symptomatic responses to hypoglycaemia in patients with insulin-dependent diabetes mellitus after 3 months of less strict glycemic control. Clinical and | Prospective case series observational before and after study | n=7 (plus 12 healthy controls)<br><br>Inclusion:<br>• IDDM<br>• Intensive insulin therapy and achieved strict glycaemic control<br>• Recurrent hypoglycaemia (BG<3mmol/litre more than twice a week for 5 months and at least one SH requiring assistance during the last 2 years.<br>Exclusion:<br>• Autonomic neuropathy<br>• Other chronic | Male:Female<br>3:4<br><br>Age, mean (SE)<br>36 (3.0)<br><br>Duration of diabetes, mean (SE)<br>18 (4.0)<br><br>HbA1c %, mean (SE)<br>6.9 (0.3) | 3 months less strict glycaemic control aimed at increasing daily mean BG to 8-10mmol/litre based on 4-times daily SMBG. Telephone consultation once a week | None | 3 months | HbA1c %, mean (SE) | Baseline: 6.9 (0.3)<br>3 months: 8.0 (0.3)<br>Reported as P<0.05) | Funding: Grant from the Juvenile Diabetes Foundation International |
| | | | | | | | Autonomic/neuroglycopenic symptom scores, scores from 0-10 on a VAS, mean (SE) | Sweating<br>Baseline: 1.1 (0.4)<br>3 months: 5.2 (1.9)<br>Reported as P<0.05)<br>Lack of concentration<br>Baseline: 0.2 (0.2)<br>3 months: 4.0 (1.1)<br>Reported as P<0.05)<br>Hunger; | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| investigative medicine: 19: 71-82<br><br>REF ID: LIU1996 | | diabetic complications, other diseases influence glucose metabolism or medications influencing HU. | | | | | | Palpitation; Tremor; Fatigue all reported as NS difference | |

**Table 296: MEYER 1998[107]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Meyer et al., 1998. Improved glucose counter regulation and autonomic symptoms after intraportal islet transplants alone in patients with long-standing type I diabetes mellitus. | Prospective case series observational before and after study<br><br>Germany | n=3 (plus 10 healthy controls)<br><br>Inclusion:<br>• Type 1 diabetes<br>• Multiple episodes of protracted SH requiring hospitalisation and glucagon or IV glucose<br>Exclusion: | Male:Female 2:1<br><br>Age, years, mean (SD)<br>35.3 (4.0)<br><br>Duration of diabetes, years, mean (SD)<br>25.7 (7.4)<br><br>HbA1c %, mean (SD)<br>8.0 (0.5) | Islet transplant<br><br>One developed insulin-independence over 14 days after transplant, the other two patients required insulin for ~3 weeks. At FU, graft function had slightly declined and all required insulin. Islet transplants were rejected approx. 2 months after | None | | HbA1c %, mean (SD) | Before: 8.0 (0.5)<br>After: 8.2 (0.3)<br>Reported as NS | Funding: not reported |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Transplantation: 66: 233-240<br><br>REF ID: MEYER1998A | | • Autonomic and peripheral neuropathy | | withdrawal of immunosuppressant therapy in all patients (approx. 1 month after re-examination) | | | | | |

**Table 297: RYAN 2005[132]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Ryan et al., 2005. Five-year follow-up after clinical islet transplantation. Diabetes: 54: 2060-2069.<br><br>REF ID: 2027 | Retrospective observational case-series<br><br>Canada | n=65<br><br>Inclusion:<br>• Received islet transplantation<br>Exclusion: | Male %<br>43%<br><br>Age years, mean (SE)<br>42.9 (1.2)<br><br>Duration of diabetes, mean (SE)<br>27.1 (1.3)<br><br>% with problematic hypoglycaemia (frequent recurrent episodes of | Islet transplantation (52 had two transplants and 11 had three transplants) | None | 5 year<br><br>Median (range) months, 35.5 (4.1-67.8) | HYPO score | Reported to improve significantly post-transplant | Funding:<br>Juvenile Diabetes Foundation International |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | hypoglycaemia, usually associated with HU and more recently notified with HYPO score ≥1047): 52/65 80% | | | | | | |

**Table 298: RYAN 2009[133]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Ryan et al., 2009. Use of continuous glucose monitoring system in the management of severe hypoglycaemia. Diabetes Technology and Therapeutics: 11: 635-639 | Prospective observational case-series<br><br>Canada | n=16<br><br>Inclusion:<br>• Type 1 diabetes treated with MDI<br>• Elevated baseline HYPO-score >75th percentile for type 1 diabetes population (>423) and had at least one | Male:Female<br>10:6<br><br>Age years, mean (SE)<br>52.0 (2.3)<br><br>Duration of diabetes, mean (SE)<br>29.4 (2.8)<br><br>HbA1c %, mean (SE)<br>8.4 (0.3) | CGMS<br><br>1 month run-in period with CGMS (Medtronic) with built in alarm. Following by 1 month study period with CGMS. | None (SMBG) | 2 month | Modified HYPO score: current 4 week BG (higher scores for more values <3mmol/litre and more points for lack of symptoms), mean (SE) | 1 month baseline: 857 (184)<br>Study month: 444 (92) | Funding:<br>Part financed by Medtronic Canada<br><br>2 drop-outs |
| | | | | | | | HbA1c %, mean (SE) | Before: 8.4 (0.3)<br>After: 8.2 (0.3) | |
| | | | | | | | | | |
| | | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| REF ID: RYAN2009 | | SH within the last year<br>Exclusion: | | | | | | | |

**Table 299: THOMAS 2007[153]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Thomas et al., 2007. A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or | RCT<br>UK | n=21<br>Adults<br>Inclusion:<br>• Type 1 diabetes<br>• At least one episode of SH according to ADA criteria in the preceding 6 months<br>• Naïve to MDI insulin analogue therapy | Male:Female 11:10<br>Age years, mean 43 (10)<br>Duration of diabetes, mean 25 (10)<br>HbA1c % baseline, mean (SD)<br>Education: 8.5 (1.1)<br>Analogue: 8.6 (1.1)<br>CSII: 8.5 (1.9)<br>Altered hypoglycaemia awareness (score | Education alone (n=7) – maintenance of current insulin regimes and relaxation of SMBG targets (fasting and preprandial BG 7-8.5mmol/litre; post-prandial and pre-bed BG >7mmol/litre)<br>ALL:<br>Uniform structured re- | 1) Analogue (n=7) – preprandial insulin lispro and evening insulin glargine with conventional BG targets (fasting 4.5-7; preprandial 5-7.5; postprandial 6-8; pre-bed 6.5-8.5)<br>2) CSII insulin lispro (n=7) delivered by | 24 weeks | HbA1c %, mean (SD)<br>Altered hypoglycaemia awareness (score ≥4 in validated questionnaire), no. of patients:<br>DQOL, mean (SD) lower scores=better QOL<br>HFS, mean (SD) lower scores=better QOL | Education: 8.3 (1.0)<br>Analogue: 7.6 (0.7)<br>CSII: 7.4 (1.0)<br>Education: 2/7<br>Analogue: 4/7<br>CSII: 3/7<br>Education: 58 (16)<br>Analogue: 70 (11)<br>CSII: 74 (20)<br>Education: 81 (14)<br>Analogue: 83 (26)<br>CSII: 64 (16) | Funding: supported by unrestricted donations from Sanofi-Aventis and Medtronic<br>2 drop-outs from education arm |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| education alone. Diabetic Medicine: 24: 778-783<br><br>REF ID: THOMAS2007 | | • Recurrent severe hypoglycaemia confirmed in all participant<br>• Questionnaire confirmed altered hypoglycaemia awareness<br>Exclusion: | ≥4 out of 7 in validated questionnaire), number of patients:<br>Education: 7/7<br>Analogue: 7/7<br>CSII: 7/7 | education aimed at rigorous avoidance of biochemical hypoglycaemia while maintaining overall glycaemic control | Medtronic 508 pump with conventional BG targets | | | | |

# G.7 Ketone monitoring

## G.7.1 Ketone self-monitoring and in-hospital monitoring

**Table 300: KURU 2014[86]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| B. Kuru, M. Sever, E. Aksay, T. Dogan, N. Yalcin, Eren E. Seker, and F. | Prospective case series<br><br>1 centre in Turkey | n=256<br><br>Inclusion criteria:<br>• Patients admitted to ED<br>• Age >14 years | Baseline:<br>Mean age (SD): 62 (14.9); range 15-96 years.<br>44% male | **Point of care testing – frequency of monitoring is not mentioned – appears to be once only)**<br>• Capillary blood ketones: Optimum-meter, Optimum TM exceed, TM/Abbott. | | n/a | BLOOD vs. URINE KETONES<br>n=221 (83.4%) - no ketones found in urine<br>n=29 (13.1%) of these patients had positive blood ketones. 3 of these patients were severely ketonaemic, 6 moderately | | Funding: Not mentioned<br><br>Risk of bias: Consecutiv |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Ustuner. Comparing finger-stick beta-hydroxybutyrate with dipstick urine tests in the detection of ketone bodies. Turk.Acil Tip Derg. 14 (2):47-52, 2014.<br><br>REF ID: KURU 2014 | | • Serum glucose ≥150 mg/dl<br>Exclusion criteria:<br>• Patients whose tests could not be performed | Drop-outs: n/a | Measured at bedside using β-ketone test strips. No ketonaemia = 0-0.5 mmol/litre; mild ketonaemia = 0.6-1.5 mmol/litre); moderate = 1.6 – 3.1 mmol/litre; severe = ≥3.2 mmol/litre. Positive blood ketones (ie. ketonaemia) = >0.5 mmol/litre.<br><br>• Urine ketone bodies: urine ketone dipstick tests (DIRUI H800 analyser).<br><br>DKA diagnosis: ADA criteria. | | | ketonaemic, and 20 mildly ketonaemic.<br>79.6% - no ketones found in blood<br>53.7% of these patients had no ketones in urine. 8 of these patients were severely ketonaemia, 12 moderately ketonaemic, and 34 mildly ketonaemic. | | e recruitment<br>Prospective study |
| AUTHORS' CONCLUSIONS: Performing a capillary blood ketone measurement instead of a urine ketone measurement, was a better predictor of ketonaemia | | | | | | | | | |

**Table 301: LAFFEL 2006[88]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| L. M. B. Laffel, K. | RCT | n=123 | | Bld n=62 | Uri n=61 | Capillary blood ketone | Urine ketone monitoring ( | 6 months | ER use, no episodes | Bld: 8<br>Urine: 14 | Funding: Abbott Laboratories |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wentzell, C. Loughlin, A. Tovar, K. Moltz, and S. Brink. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with type 1 diabetes: A randomized clinical trial. Diabet.Med. 23 (3):278-284, 2006.<br><br>REF ID: LAFFEL | 2 centres in the USA | (n=62 Blood group; n=61 urine group)<br><br>Inclusion criteria:<br>• Children, adolescents and young adults: age range 3-22 years<br>• Type 1 diabetes attained age ≤22 years<br>• Duration of diabetes ≥12 months<br>• insulin dose of≥0.5 U/kg/day if age > 5 years or≥0.3 U/kg/day if age ≤5<br>• Routine glucose monitoring ≥3 times | Age, years (SD) | 14.3 (4.6) | 13.2 (5.0) | monitoring (β-OHB)<br><br>ITT: n=62<br><br>Precision Xtra System (Abbott), which measures blood 3-OHB and glucose levels with their respective test strips<br><br>Patients in both groups were encouraged to check glucose levels ≥ 3 times daily and to check ketones during acute illness or stress, when glucose levels were | β-OHB)<br><br>ITT: n=61<br><br>Precision QID system with blood glucose strips and urine ketone strips (Ketostix, Bayer) | follow-up | Hospitalisation, no. of episodes | Bld: 3<br>Urine: 8 | Risk of bias:<br>Randomisation = unclear (done at each site, by patient, but details not given)<br>To ensure equal representation of insulin pump and non-pump users and to avoid confounding by glycaemic control, patients were randomized according to pump status and glycated haemoglobin (HbA1c)<br>Allocation concealment = not mentioned<br>Blinding = not mentioned<br>ITT analysis (no drop-outs) |
| | | | Women, % | 61 | 53 | | | | HbA1c, % (SD) | Bld: 8.3 (1.5)<br>Urine: 7.7 (1.2) | |
| | | | Diabetes, mean years (SD) | 7.5 (4.6) | 7.3 (4.7) | | | | | | |
| | | | HbA1c, % | 8.3 (1.5) | 7.9 (1.3) | | | | HbA1c: after controlling for baseline HbA1c values, there was NS difference in HbA1c at end of the study and NS change from baseline in either group.<br><br>Patient preference: overall more people preferred to check blood than urine ketones, as easier to perform | | |
| | | | | | | | | | Authors conclusions:<br>Blood ketone monitoring during sick days appears acceptable to and preferred by young people with Type 1 diabetes. Routine implementation of blood 3-OHB monitoring for the management of sick days and impending DKA can | | |
| | | | NS differences between groups for any of the baseline characteristics<br><br>Drop-outs (6 months): None mentioned | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 2006 | | daily<br>Exclusion criteria:<br>• Recurrent DKA<br>• Known emotional problems | | consistently elevated (≥13.9 mmol/litre on two consecutive readings), or when symptoms of DKA were present.<br><br>Participants continued routine diabetes care throughout the study, including 24-h access to an on-call physician | | | potentially reduce hospitalization /emergency assessment compared with urine ketone testing and offers potential cost savings. | | No mention of powering<br>Drop-outs = acceptable (<20%) |

**Table 302: BEKTAS 2004[13]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| F. Bektas, | Observational | n=139 | Baseline: | **Point of care testing –** | | Approximately | Sensitivity and specificity of | | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| O. Eray, R. Sari, and H. Akbas. Point of care blood ketone testing of diabetic patients in the emergency department . Endocr.Res. 30 (3):395-402, 2004.<br><br>REF ID: BEKTAS 2004 | (prospective case series xxxxxx)<br><br>1 centre in Turkey | included as met criteria and had full records (11,383 screened)<br><br>Inclusion criteria:<br>• Newly diagnosed or known diabetic patients<br>• Patients presenting to the ED with any medical (non-trauma) complaint<br>• patients with blood glucose ≥200 mg/dL by finger stick testing and blood capillary β-HBA ≥0.1mmol/li | Mean age (SD): 57 (14)<br>42% female<br><br>Drop-outs:<br>n/a<br><br>Outcomes:<br>Diabetic ketosis/ketonaemia: venous blood β-HBA ≥0.42 mmol/litre<br>DKA: as above but also pH <7.3<br>Sensitivity/specificity of DK and DKA detection: lab tests of serum glucose (>200 mg/dL) and β-HBA ≥0.42 mmol/litre were used as the gold /reference standards. | **frequency of monitoring was done weekly (according to the statistical analysis section of the paper)**<br>• Capillary blood ketones: Medisense Optimum Sensor fingertip probe for measuring β-HBA (range between 0.1 to 9.0 mmol/litre) .<br>• Urine ketone bodies: urine ketone dipstick tests were used (positive values ranging from 0-4). | | 6 months | ketone measurements:<br>n=30 DK; n=18 DKA<br><br>Detecting DK<br>Capillary β-HBA: sensitivity 91/specificity 56<br>Urine β-HBA: sensitivity 82/specificity 54<br>Detecting DKA<br>Capillary β-HBA: sensitivity 72/ specificity 82<br>Urine β-HBA: sensitivity 66/ specificity 78<br><br>Hyperketonaemic vs. Normoketonaemic patients<br>SS difference between the 2 groups for capillary, venous and urine β-HBA measurements.<br>Hyperketonaemic = ≥0.42 mmol/litre venous blood β-HBA ≥0.42<br>n=48 hyperketonaemic hyperglycaemia.<br>n=91 normoketonaemic hyperglycaemia.<br><br>Capillary β-HBA<br>Hyper = 1.48 (1.89)<br>Hypo = 0.23 (0.19); p<0.001<br>Venous β-HBA | | Not mentioned<br><br>Risk of bias: |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | tre were included.<br><br>Exclusion criteria:<br>• Chief complaint of trauma<br>• Using L-dopa or its metabolites | | | | | Hyper = 1.56 (1.62)<br>Hypo = 0.18 (0.13); p<0.001<br>Urine β-HBA<br>Hyper vs. hypo: p=0.007<br><br>DKA vs. DK patients<br>SS difference between the 2 groups for capillary and venous β-HBA mmts<br>but NS difference for urine β-HBA mmts.<br>DK venous blood β-HBA ≥0.42<br>DKA venous blood β-HBA ≥0.42 + pH<7.3<br>n=30 DK; n=18 DKA<br><br>Capillary β-HBA<br>DK = 0.88 (1.27)<br>DKA = 2.87 (2.26); p=0.002<br>Venous β-HBA<br>DK = 1.15 (0.57)<br>DKA = 2.16 (2.40); p<0.001<br>Urine β-HBA<br>DK vs. DKA: p=0.07 (NS) | | |
| AUTHORS' CONCLUSIONS: A rapid, bedside capillary blood ketone test for β-HBA can accurately measure blood concentrations of β-HBA in an ED setting, and can be used as an accurate diagnostic test to detect emergency metabolic problems in patients such as DK or DKA. | | | | | | | | | |

**Table 303: ARORA 2011C[11]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| S Arora, SO. Henderson, T Long, and M Menchine. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: [49]-hydroxybutyrate versus the urine dipstick. Diabetes Care 34 (4):852-854, 2011.<br><br>REF ID: ARORA 2011C | Observational (prospective case series xxxxxx)<br><br>1 centre in USA | n=516 included as met criteria and had full records (859 screened)<br><br>Inclusion criteria:<br>• Convenience sample of patients presenting to the ED<br>• Patients with capillary blood glucose ≥250 mg/dL.<br><br>Exclusion criteria:<br>• Critically ill<br>• acute psychosis<br>• unable to give informed | Baseline:<br>Median (IQR): DKA n=54: No DKA n=462<br>Age, years: 41: 48<br>Female, %: 27.8: 35.3<br>+ urine dipstick ketones: 98.1%: 64.9%<br>β-OHB, mmol/litre: 0.3 (0.2-1.2): 4.9 (3.7-5.6)<br><br>Drop-outs:<br>None mentioned<br><br>Outcomes:<br>DKA (ADA criteria): serum glucose. ≥250 mg/dL; anion gap >10 mmol/litre; Co2 ≤18 mmol/litre; and pH≤7.3. | **Point of care testing – frequency of monitoring not mentioned**<br>• Capillary blood ketones: Medisense/Abbot precision Xtra meter for measuring β-OHB.<br>• Urine ketone bodies: urine ketone dipstick tests were used (positive or negative).<br>Diagnostic accuracy: Blood capillary using cut-off of >1.5 mmol/litre (considered positive test). Difference in specificity for blood and urine ketones was assessed. | | Approx. 2 years | Sensitivity and specificity of ketone measurements:<br>n=462 No DKA; n=54 DKA<br><br>Detecting DKA<br>Capil β-HBA: sensitivity 98.1/specificity 78.6<br>Urine β-HBA: sensitivity 98.1/ specificity 35.1<br>Difference for specificity is SS (p<0.01)<br>Capillary β-HBA were stable across a wide range of potential cut-offs.<br>The ROC suggested that optimal β-HBA cut-off is >2 mmol/litre (sensitivity remains 98.1% but spec improves to 82.3%)<br><br>AUTHORS' CONCLUSIONS:<br>Point of care blood β-OHB and the urine dipstick are equally sensitive for detecting DKA (98.1%). However, blood β-OHB is more specific (78.6% vs. 35.1%), offering the potential to significantly reduce unnecessary DKA work-ups among hyperglycaemic patients in the ED. | | Funding:<br>Donation of test strips by Abbot Laboratories.<br><br>Risk of bias:<br>Sample size calculation of n=54 (study sample stopped after enrolling this number of patients)<br>xxx<br>xxx |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | consent | | | | | | | |

**Table 304: HARRIS 2005[59]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| S. Harris, R. Ng, H. Syed, and R. Hillson. Near patient blood ketone measurements and their utility in predicting diabetic ketoacidosis. Diabet.Med. 22 (2):221-224, 2005.<br><br>REF ID: HARRIS 2005 | Observational (retrospective case series, review of records xxxxxxxx)<br><br>1 centre in UK | n=50 (records of first 50 people to have β-OHB measured)<br><br>Inclusion criteria:<br>Hyperglycaemic or unwell<br>Patients presenting to the ED<br>patients with blood glucose >11 mmol/litre by finger stick testing | Baseline:<br><br>DKA (n=9) / DK (n=8) / Others (n=33)<br>Age, years: median<br>23 / 35 / 61<br>Female, %<br>11 / 50 / 39<br>Diabetes new diagnosis, %<br>11 / 38 / 21<br>Blood β-OHB, mmol/litre<br>≥6.0 / 3.4 / 0.3<br>Urine dipstick >1.5 mmol/litre<br>100% (7/7) / 86% (6/7) / 33% (5/15)<br><br>Drop-outs:<br>None mentioned<br><br>Outcomes: | **Point of care /near patient testing – frequency of monitoring was not reported**<br>• Capillary blood ketones: Medisense /Abbot Optimum for measuring β-OHB from finger-prick (range between 0.0 to 6.0 mmol/litre) .<br>• Urine ketone bodies: urine ketone dipstick tests | | Retrospective thus n/a<br><br>However patients were followed for 48hrs in their records or telephone to see if developed DKA. | Sensitivity and specificity of ketone measurements:<br>n=9 DKA; n=8 DK; n=33 other<br><br>Detecting DKA<br>Capil β-OHB >1 mmol/litre: sensitivity 100/ spec 76<br>Capil β-OHB >3 mmol/litre: sensitivity 100/ spec 88<br>Urine β-OHB: sensitivity 100/spec 52<br><br>Detecting patients requiring treatment with IV insulin:<br>Capil β-OHB >1 mmol/litre: sensitivity 100/ spec 86<br>Capil β-OHB >3 mmol/litre: sensitivity 100/ spec 100<br>Urine β-OHB: sensitivity 100/spec 65<br><br>AUTHORS' CONCLUSIONS:<br>Measuring β-OHB when a | | Funding:<br>Not mentioned<br><br>Risk of bias:<br>Gold standard includes blood β-OHB test. therefore have used another classification system on whether the patients was treated with IV insulin for anything other than procedural reasons. |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | Ketonaemia: urine dipstick (acetoacetate >1.5 mmol/litre or β-OHB >1.0 mmol/litre<br>Diabetic ketosis: ketonaemia (as above) plus metabolic acidosis (pH >7.3 and HCO3 15-24 mmol/litre)<br>DKA: metabolic acidosis (as above) secondary to ketonaemia (as above) but also pH <7.3<br>Hypoglycaemia alone = all other patients<br>Diagnostic accuracy: for detecting DKA the gold standard would include the β-OHB blood test and thus calculation will overestimate the power of the test. Therefore have used another classification system for detecting whether the patients was treated with IV insulin for anything other than procedural reasons. | | | | hyperglycaemic patients is identified, could offer a simple method of identifying at an early stage those patients at highest risk of DKA (β-OHB >3.0 mmol/litre) and redirecting the search for a diagnosis in others (β-OHB >1.0 mmol/litre) | | |

**Table 305: TABOULET 2007**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| P. Taboulet, N. Deconinck, A. Thurel, L. Haas, J. Manamani, R. Porcher, C. Schmit, J. P. Fontaine, and J. F. Gautier. Correlation between urine ketones (acetoacetate) and capillary blood ketones (3-beta-hydroxybutyrate) in hyperglycaemic patients. Diabetes Metab. 33 (2):135-139, 2007.<br><br>REF ID: TABOULET 2007 | Observational (retrospective case series, review of records xxxxxxxx)<br><br>1 centre in France | n=529<br><br>Inclusion criteria:<br>• Hyperglycaemic patients<br>• Patients measured for blood ketones, urine ketones and blood glucose Patients presenting to the ED<br>• patients with blood glucose ≥250 mmol/litre<br>• Determined NCGCNews@rcplondon.ac.uk on patients with malaise, polydyspepsia-poluria, disorders of consciousnes | Baseline: | Point of care /near patient testing – tested on all patients with blood glucose >13.75 mmol/litre<br><br>• Capillary blood ketones: Medisense /Abbot Optimum for measuring β-OHB from finger-prick (maximum 6.0 mmol/litre) .<br>• Urine ketone bodies: urine ketone dipstick tests (acetoacetate) | | Retrospective thus n/a<br><br>However patients data was from a period of 32 months | Relationship between presence of ketone bodies and ketoacidosis:<br>Incidence of ketoacidosis was 7.7%<br>Ketoacidosis rate increased with elevation of blood ketones and to a lesser degree with elevation of urine ketones<br>Area under ROC curve for capacity to predict ketoacidosis was SS higher for blood ketones (0.984) than for urine ketones (0.941); p<0.0001.<br>The % of patients with ketoacidosis ranged from 0% (at 0.1 mmol/litre blood ketones) to 78% (at ≥3 mmol/litre blood ketones) and 6% (+ urine ketones) to 49% (+++ urine ketones).<br><br>Relationship between presence of ketone bodies and hospitalisation:<br>Incidence of hospitalisation was 49.7%<br>Hospitalisation rate increased with elevation of blood | | Funding:<br>Not mentioned<br><br>Risk of bias:<br>xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | s, life-threatening situations and in all known diabetic patients. | | | | | ketones and to a lesser degree with elevation of urine ketones<br>Area under ROC curve for capacity to predict hospitalisation was SS greater for blood ketones (0.704) than for urine ketones (0.620); p<0.0001.<br>The % of patients who were hospitalised with ketoacidosis ranged from 42% (at 0.1 mmol/litre blood ketones) to 94% (at ≥3 mmol/litre blood ketones)and 51% (+ urine ketones) to 84% (+++ urine ketones).<br><br>AUTHORS' CONCLUSIONS:<br>In hyperglycaemic patients in the ED, a good correlation was observed between urine ketones and blood ketones for low values, but a poor correlation for high values. Either test can therefore be used to exclude ketosis, but the capillary ketones test is more accurate to confirm ketoacidosis. | | |

# G.8 Arterial risk control

## G.8.1 Aspirin

LARGE TRIALS ACCORD and ACCEPT-D are in progress - ACCEPT-D not complete for several years as recruitment slow

**Table 306: Hansen 2000[58]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HANSEN 2000[58] [RM Note: Search dates – check old GLs] | RCT (cross-over after 4 weeks) 1 centre in Denmark | n=17 (n=8 Aspirin group; n=9 placebo group) Inclusion criteria: • Type 1 diabetes with persistent low-level (micro) albuminuria (urinary AER between 30 and 300 mg/24h in at least 2 of 3 sterile urine samples) • Insulin dependent from time of | | Aspirin n=8 | Placebo n=9 | Low dose aspirin (150 mg) ITT: n=8 Aspirin given as one 150 mg tablet/day 4 weeks of treatment and then 2 week wash-out then crossed over to 4 weeks of placebo Concomitant medication: In both groups, n=15 | Placebo ITT: n=9 Placebo tablet 4 weeks of placebo and then 2 week wash-out then crossed over to 4 weeks of aspirin | 4 weeks treatment | AEs | NS difference (data not given) | Funding: Danish Diabetes Association; drugs supplied by Leo Pharmaceutical products, Denmark. Risk of bias: • Wash-out period = adequate (2 weeks; mean 19.4 days) • Randomisation = unclear (as details not given) • Allocation concealment |
| | | | Age, years (SD) | 43 (9) | | | | | Dyspepsia | Aspirin: 3 Placebo:3 (NS diff) | |
| | | | Women, % | 71% | | | | | HbA1c, % (95% CI) | Aspirin: 8.4 (8.0, 9.0) Placebo:8.5 (8.1, 9.0) MD: -0.1 (-0.4, 0.2);p=0.41 | |
| | | | Diabetes, mean years (SD) | 28 (8) | | | | | | | |
| | | | Anti-HT treatment, %: ACE/ non-ACE/ none | 82/6/12 | | | | | SD calculated for HbA1c | Aspirin: 0.60 Placebo: 0.59 | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures (6 months) | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | diagnosis<br>• Receiving at least 2 daily injections of insulin<br>Exclusion criteria:<br>• SBP >200 mmHg<br>• User of COX-inhibitors<br>• acute gastritis or peptic ulcer disease<br>• pregnant | Retinopathy, %: non/simplex, proliferative | 18/41/41 | patients received their usual a-HT treatment (n=14 ACEi, n=11 and/or non-ACEi) | | | UER and GFR | Also NS difference | = yes it was done, but unclear (as details not given)<br>Blinding = double (but details not given)<br>ITT analysis (no drop-outs)<br>Powered study (urinary AER)<br>Drop-outs = acceptable (<20%) |
| | | | Smokers, % | 53 | | | | | | |
| | | | NS differences between groups for any of the baseline characteristics<br><br>Drop-outs (6 months): None mentioned | | | | | | | |

**Table 307: ETDRS 1992[40]**

| Reference | Study type | Number of patients | Patient characteristics (type 1 diabetes subgroup) | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ETDRS 1992[40] | RCT | n=3711 Type 1 diabetes and | | Aspirin n=559 | Placebo | High dose aspirin (650 | Placebo | 5 years (averag | Mortality (all | Aspirin: 29/559 | Funding: National Eye |

| Reference | Study type | Number of patients | Patient characteristics (type 1 diabetes subgroup) | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 22 centres in the USA. | type 2 diabetes (n=1130 Type 1 diabetes; 30%)<br><br>Aspirin group: n=1856 (all patients) n=559 (Type 1 diabetes)<br><br>Placebo group: n=1855 (all patients) n=571 (Type 1 diabetes)<br><br>Inclusion criteria:<br>• Diabetes mellitus and 1 of following categories of diabetic | | | n=571 | mg/day)<br><br>Type 1 diabetes - ITT: n=559<br><br>Aspirin given as two 325 mg tablets once/day<br>During the trial lower doses were considered due to possibility of less AEs, but decided to continue on 650 mg/day.<br><br>Concomitant medication:<br>Not mentioned | Type 1 diabetes - ITT: n=571<br><br>Placebo tablet | e); range 4-9 years. | cause): end of follow-up | Placebo: 39/571 | Institute, USA.<br><br>Risk of bias:<br>Randomisation = unclear (just says randomised)<br>Allocation concealment = good (drug assignment not known to patient or personnel)<br>Blinding = double (patient or personnel unaware of drug assignment)<br>ITT analysis<br>Powered study (compliance and mortality)<br>Drop-outs = acceptable (<30% for |
| | | | Age, years, %<br><30<br>30-49<br>≥50 | 51<br>46<br>3 | 46<br>50<br>4 | | | | Mortality (all cause): 5 years life table* | Aspirin: 17/559<br>Placebo: 27/571<br>RR given: NS difference | |
| | | | | | | | | | Mortality (CV): end of follow-up | Aspirin: 17/559<br>Placebo: 26/571 | |
| | | | Women, % | 40 | 36 | | | | Mortality (CV): 5 years life table* | Aspirin: 10/559<br>Placebo: 18/571<br>RR given: NS difference | |
| | | | Diabetes, %<br><10 years<br>10-19<br>≥20 years | 3<br>62.1<br>34.9 | 4<br>58<br>38 | | | | | | |
| | | | HbA1c ≥10%, % | 45.1 | 51.9 | | | | MI (fatal and non-fatal): end of follow-up | Aspirin: 25/559<br>Placebo: 31/571 | |

| Reference | Study type | Number of patients | Patient characteristics (type 1 diabetes subgroup) | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | retinopathy: mild non-proliferative with macular oedema, moderate to severe non-proliferative or early proliferative (less severe than the high risk proliferative stage) with or without macular oedema<br>• Visual acuity required to be better than 20/40 in each eye (or 20/400 if acuity was reduced as a result of diabetic macular oedema. | 50% of patients had CV disease history§<br>25% of patients had proliferative retinopathy in one or both eyes.<br><br>§NOTE: History of CV disease was defined a history of any of the following: coronary artery disease, congestive heart failure, MI or intermittent claudication. Patients reporting any of the following drug use were also considered to have CV disease history: long-term anti-anginal agents, BBs, vasodilators, digitalis, antiarrhythmic agents, diuretics or other a-HT agents. Patients with SBP ≥160 mmHg were also considered to have CV disease history. | | | | MI (fatal and non-fatal): 5 years life table* | Aspirin: 13/559<br>Placebo: 21/571<br>RR given: NS difference | long-term study) |
| | | | | | | | Stroke (fatal and non-fatal): end of follow-up | Aspirin: 7/559<br>Placebo: 12/571 | |

| Reference | Study type | Number of patients | Patient characteristics (type 1 diabetes subgroup) | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | • Adults age 18-70 years<br><br>Exclusion criteria:<br>• SBP >210 mmHg and/or DBP >110 mmHG despite use of a-HT medication<br>• History of GI haemorrhage or diagnosis of active G ulcer in past 2 years<br>• inability or unwillingness to stop taking a-coagulants or a-platelet drugs<br>• allergy to aspirin<br>• pregnancy or lactation | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics (type 1 diabetes subgroup) | Intervention | Comparison | Length of follow-up | Outcomes | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | • poor prognosis for 5 years of follow-up because of a prior major CV event, cancer, or another chronic disease | | | | | | | | |
| | | | Comparable between groups for all of the baseline characteristics<br><br>Drop-outs:<br>Not given for type 1 diabetes subgroup<br>Overall study drop-outs:<br>3144/3711 survivors<br>2807 (24%) completed final visit (164 alive, 706 died, 34 unable to contact). | | | | | Stroke (fatal and non-fatal): 5 years life table* | Aspirin: 4/559<br>Placebo: 10/571<br>RR: 0.60 (0.18-2.04)<br>RR given: NS difference<br>Data for these outcomes should be presented as HRs (Hazard ratios), however data reported in | |

| Reference | Study type | Number of patients | Patient characteristics (type 1 diabetes subgroup) | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | paper is insufficient to calculate these. They have not provided the log-rank or Cox-regression p-values, but have calculated the RRs | |

**Table 308: ETDRS unpublished data (provided with permission, from personal communication with the authors) (February 2013) - CV events in type 1 diabetes ETDRS participants that had no previous CVD**

| | Total | | Aspirin | | | |
|---|---|---|---|---|---|---|
| | | | No | | Yes | |
| | N | Col% | N | Row% | N | Row% |
| Total | 1393 | 100.0 | 710 | 51.0 | 683 | 49.0 |
| CV event[a] | 119 | 8.5 | 64 | 53.8 | 55 | 46.2 |
| Yes | | | | | | |
| No | 1274 | 91.5 | 646 | 50.7 | 628 | 49.3 |
| CV death | 72 | 5.2 | 40 | 55.6 | 32 | 44.4 |

| | Total | | Aspirin | | | |
|---|---|---|---|---|---|---|
| | | | No | | Yes | |
| | N | Col% | N | Row% | N | Row% |
| Yes | | | | | | |
| No | 1321 | 94.8 | 670 | 50.7 | 651 | 49.3 |
| MI | 85 | 6.1 | 48 | 56.5 | 37 | 43.5 |
| Yes | | | | | | |
| No | 1308 | 93.9 | 662 | 50.6 | 646 | 49.4 |
| Stroke | 30 | 2.2 | 13 | 43.3 | 17 | 56.7 |
| Yes | | | | | | |
| No | 1363 | 97.8 | 697 | 51.1 | 666 | 48.9 |

*(a) CV events = CV death, MI or stroke, CVD = MI, CAD, CHF, stroke, TIA*

# G.9 Inpatient management

## G.9.1 IV insulin

**Table 309: Christiansen 1988 [27]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Christiansen CL et al. Insulin treatment of the insulin-dependent diabetic patient undergoing minor | RCT | n=20<br><br>Inclusion criteria:<br>• Adults<br>• Insulin-dependent diabetic admitted for minor | | IV infusion of glucose, insulin & potassium (GIK) for 24 hours<br>Glucose 55g/litre, potassium chloride 20mmol/litre and insulin<br>Insulin | Pre-op SC insulin<br>0.5 x usual daily dose if BG ≤8 mmol/litre<br>0.66 x usual daily dose if BG >8 and ≤15 mmol/litre<br>Concomitant glucose infusion 55g/litre at | 3 days (day of operation and 2 days post-op) | Achieving target blood glucose levels (5-10mmol/litre), reported as % of values within the target range not no. of patients | During all 3 days:<br>IV GIK: 48%<br>SC: 26% (reported as P<0.01)<br>During infusion period:<br>IV GIK: 67% | Funding: Danish Diabetic Association and Nordic Insulin Foundation<br>Risk of |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| surgery. Anaesthesia. 1988; 43:533-537<br><br>REF ID: 1909 | | surgery<br>Exclusion criteria:<br>• Steroid or β-blocker treatment<br>• BG > 15 mmol/litre at 07:00 on the day of op | | | | 8units/litre if BG ≤4 mmol/litre; 16 units/litre if BG 4.1-6.9 mmol/litre; 24units/litre if BG 7-11.9 mmol/litre; 32 units/litre if BG 12-15 mmol/litre;<br>Insulin = Velosulin (Nordisk insulin) | 100ml/h for 24 hours<br>Insulin = Insulatard (Nordisk Insulin) | | | SC: 28% (reported as P<0.0001)<br><br>Hyperglycaemia, no. of patients with ≥1 BG level >15mmol/litre<br>IV GIK: 6/10<br>SC: 10/10 | bias: Randomisation = unclear<br>Allocation concealment = unclear<br>Blinding = none reported |
| | | | | IV GIK | SC | | | | | | |
| | | | N | 10 | 10 | | | | | | |
| | | | Age, median (range) | 52 (25-74) | 52 (29-76) | | | | | | |
| | | | % male | 40 | 40 | | | | | | |
| | | | HbA1c %, median (range) | 8 (7.5-9) | 8.8 (7.7-9.2) | | | | | | |
| | | | Drop outs: | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | None reported | BOTH GROUPS:<br>Allowed to eat post-op<br>Aim to maintain BG between 5-10mmol/litre<br>If BG >15mmol/litre, 12 units of Velosulin insulin given SC | | | | | |
| | | | | | | | Hypoglycaemia, no. of patients with ≥1 BG level <5mmol/litre | IV GIK: 6/10<br>SC: 4/10 | |
| | | | | | | | Time spent out of target glucose | Not reported | |
| | | | | | | | Duration of IV treatment | Not reported | |
| | | | | | | | inpatient stay, days, median (range) | IV GIK: 5 (1-10)<br>SC: 5 (2-7) | |
| | | | | | | | Inpatient mortality | Not reported | |
| | | | | | | | Infection rate/wound healing | Not reported | |
| | | | | | | | QoL (SF-36, DQoL, DSQoL) | Not reported | |

**Table 310: Corney 2012** [28]

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Corney SM et al. Compariso | Retro-spective cohort | n=99 cases (75 unique individuals | | IV | CSII | CSII suspension. | IV insulin infusion: | CSII: Continue CSII with | Inpatient stay | Achieving target blood glucose | % of cases with ≥1 intra-op hyperglycaemia | Funding: Investigator |

| Reference | Study type | Number of patients | Patient characteristics | | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n of Insulin Pump Therapy (CSII) to Alternate Methods for Perioperative Glycemic Management in Patients with Planned Postoperative Admissions. J of Diabetes Science and Technology. 2012; 6(5):1003-1015<br><br>REF ID: CORNEY 2012 | study | Inclusion criteria:<br>≥18 years<br>type 1 diabetes/type 2 diabetes<br>Elective surgery<br>Exclusion criteria:<br>Pregnancy<br>CSII discontinued prior to admission<br>Immediate or long-acting basal insulin administered. | N | 20 | 53 | 19 | Convert from SCII to IV insulin infusion pre-operatively | supplemental SC or IV insulin if required.<br>Suspend CSII: suspend SCII with or without SC or IV insulin boluses | | levels<br><br>% with intra-op target BG, hypo, moderate and severe hyper only reported graphically (no data). Comparison reported as P=0.034. | (BG >179mg/dl)<br>IV: 40%<br>CSII.: 45.3%<br>CSII suspension.: 84.2%<br><br>Mean BG mg/dl (all intra-op measurements and 1st post-op)<br>IV: 152.3 (28.9)<br>CSII.: 163.5 (58.5)<br>CSII suspension.: 188.3 (44.9)<br>P=0.128 as reported. | grant from sanofi-aventis<br>Risk of bias:<br>Study design – case-series<br>Consecutive patients included<br>ACA<br>SS baseline diffs in pre-op BG |
| | | | Age | 51.6 (11.9) | 51.5 (10.4) | 55.3 (10.5) | | | | | | |
| | | | % M | 35 | 28.3 | 21 | | | | | | |
| | | | % Type 1 diabetes | 90 | 86.8 | 84.2 | | | | | | |
| | | | HbA1c % | 7.49 (1.0) | 7.63 (1.2) | 8.29 (1.1) | | | | | | |
| | | | BG mg/dl | 196.8 (79.9) | 146.1 (62.8) | 160 (86.3) | | | | | | |
| | | | Drop outs: 7 (5 excluded as CSII status unavailable, 2 dropped from analysis as CSII had been suspended) | | | | ALL GROUPS:<br>Intravenous dextrose treatment given as judged appropriate for all groups. | | | Hypoglycaemia (severe intra-op; BG <40mg/dl) | IV: 0/20<br>CSII.: 0/53<br>CSII suspension.: 0/19 | |
| | | | | | | | | | | Time spent out of target glucose (hypo/hyper) | Not reported | |
| | | | | | | | | | | Duration of IV treatment | Not reported | |
| | | | | | | | | | | Duration inpatient | Not reported | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | stay | | |
| | | | | | | | Inpatient Mortality | Not reported | |
| | | | | | | | Infection rate/wound healing | Not reported | |
| | | | | | | | QoL (SF-36, DQoL, DSQoL) | Not reported | |

**Table 311: Husband 1986** [68]

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Husband DJ et al.. Management of Diabetes during Surgery with Glucose-Insulin-Potassium Infusion. Diabetic Medicine. 1986; 3:69-74 | Prospective case series | n=128 (n=41 IDDM)<br>Inclusion criteria:<br>• Mainly adults<br>• Type 1 diabetes or type 2 diabetes<br>• Elective ops involving general or | | | IV infusion of glucose, insulin & potassium (GIK)<br>SC insulin omitted on the morning of op and GIK infused at 100ml/h (at least 1 hour before op; 16U Actrapid insulin, 10mmol potassium chloride and 500ml 10% glucose)<br>Before infusion, if BG < 5mmol/litre insulin decreased to 12U/500ml and | None | 3 days (day of operation and 2 days post-op) | Achieving target blood glucose levels<br>Pre-op: 5-10 mmol/litre<br>Op day: 5-12 mmol/litre (with no hypoglycaemia <3 mmol/litre) | Pre-op: 26/41<br>Operation day: 31/41 (reason for unacceptable below, hypo/hyper)<br><br>BG values, mmol/litre, mean (SD)<br>Pre-op: 8.2 (3.0)<br>Post-op: 9.6 (3.4)<br>Mean op day: 8.9 (2.3) | Funding:<br>DJH supports by grant from Newcastle-upon-Tyne Health Authority and ACT. British Diabetic Association.<br>Risk of bias:<br>• Study design case-series |
| | | | N | 41 (IDDM) | | | | | | |
| | | | Age, median (range) | No type 1 diabetes subgroup data | | | | | | |
| | | | Pre-op BG (fasting), mean SD | 8.2 (3.0) | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: HUSBAND 1986 | | epidural anaesthesia<br>Exclusion criteria:<br>• Cardiopulmonary bypass op | | | if > 13mmol/litre increased to 20U/500ml<br>GIK infusion adjusted in steps of 4U/500ml to maintain BG 5-10 mmol/litre<br>GIK continued until first post-op meal (SC regime reinstituted) | | | | Mean post-op day 1 (n=14): 9.4 (1.9)<br>Mean post-op day 2 (n=9): 10.2 (2.8) | |
| | | | % male | Not reported | | | | | | |
| | | | Drop outs:<br>None reported | | | | | | | |
| | | | | | | | | Hypoglycaemia | On operation day, no. of patients with BG level <5mmol/litre 4/41<br>Hyperglycaemia : On operation day, no. of patients with BG level >12mmol/litre 6/41 | |
| | | | | | | | | Time spent out of target | Not reported | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | glucose | | |
| | | | | | | | Duration of IV treatment | Not reported | |
| | | | | | | | inpatient stay | Not reported | |
| | | | | | | | Inpatient mortality | Not reported | |
| | | | | | | | Infection rate | Not reported | |
| | | | | | | | QoL (SF-36, DQoL, DSQoL) | Not reported | |

**Table 312: McCavert 2010** [103]

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| McCavert et al.. Peri-operative blood glucose management in general surgery – A potential element for improved diabetic patient outcomes. | Prospective case series | n=69 (n=35 type 1 diabetes)<br><br>Inclusion criteria:<br>• Diabetic patients having elective or emergency surgery<br>Exclusion criteria: | n=35 (Type 1 diabetes)<br>Elective n=21<br>Emergency n=14 | IV infusion of glucose, insulin & potassium (GIK; based on Alberti Regimen)<br>Type 1 diabetes commenced on GIK before, during and after surgery<br>BG measured pre-op (6am), post-op (6pm), post-op day 1 (6am) and post- | None | 3 days (day of operation and 2 days post-op) | Achieving target blood glucose levels, mean % for all 4 time points (6.1-10 mmol/litre) | Elective patients (n=21):<br><6.1mmol/litre: 7.4%<br>6.1-10mmo/litre: 25.9%<br>>10mmol/litre: 55.6%<br>Not checked: 11%<br><br>Emergency patients (n=14):<br><6.1mmol/litre: 4.5%<br>6.1-10mmo/litre: | Funding:<br>None reported<br><br>Risk of bias:<br>• Study design case-series<br><br>Adherence to GIK<br>20/35 Type 1 diabetes received the GIK infusion (elective 14, |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Int. J of Surgery. 2010; 8(6):494-498<br><br>REF ID: McCAVERT 2010 | | | | | op day 2 (6am) | | | | 22.7%<br>>10mmol/litre: 65.9%<br>Not checked: 6.8% | emergency 6)<br>5/21 elective patient not treated according to protocol<br>11/14 emergency patient not treated according to protocol |
| | | | Age, median (range) | No Type 1 diabetes subgroup data | | | | hypoglycaemia | 'No hypoglycaemic episodes were reported' | |
| | | | % male | | | | | Time spent out of target glucose | Not reported | |
| | | | Drop outs:<br>None reported | | | | | Duration of IV treatment | Not reported | |
| | | | | | | | | inpatient stay | Not reported for Type 1 diabetes subgroup | |
| | | | | | | | | Inpatient mortality | Not reported | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Infection rate | Wound infection:<br>Elective patients: 2/21<br>Emergency patients: 1/14<br>Peritonitis:<br>Elective patients: 1/21<br>Emergency patients: 0/14<br>Septicaemia:<br>Elective patients: 0/21<br>Emergency patients: 2/14 | |
| | | | | | | | QoL (SF-36, DQoL, DSQoL) | Not reported | |

**Table 313: Poppe 2004** [126]

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Poppe AY, Vautour L, Yale J-F, Wing SS. Evaluation of a Protocol for the | Retrospective case series (consecutive chart review | n=50<br>Inclusion criteria:<br>• Treated with SC insulin or oral agents | Type 1 diabetes (n=12, 24%) or type 2 diabetes (n=38, 76%)<br><br>Age, mean | Perioperative IV insulin protocol<br>SC insulin discontinued morning of surgery<br>IV insulin (0.5 | None | Inpatient stay<br>(first 24 hours of infusion for these outcomes) | Achieving target blood glucose levels | % of levels in the hyperglycaemic range (>12mmol/litre; first 24 hours; type 1 diabetes):<br>49.7%<br>Mean BG level (first | Funding: not reported<br>Risk of bias:<br>Study design – case-series<br>Consecutive patients |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Perioperative Administration of Intravenous Insulin in Patients with Diabetes. Canadian Journal of Diabetes. 2004; 28(2):00-00.<br><br>REF ID: POPPE2004 | | • Surgical procedure as inpatient (treated with IV insulin during surgery)<br>• Survived for at least 1 day after surgery<br>Exclusion criteria:<br>• Caesarean section<br>• Remained in ICU for >48hours | (SE): 62.0 (1.8) not reported for type 1 diabetes subgroup<br><br>M/F: 30/20 not reported for type 1 diabetes subgroup<br><br>Drop outs:<br>26 patients remained on the IV insulin protocol at 24 hours not reported for type 1 diabetes subgroup | patient's daily dose ÷ 24, per hour) with glucose (5g/hour).<br>Initial rate decreased by 50% in patients with BG <6mmol/litre.<br>Insulin adjustments made if outside target BG range 8.1-12mmol/litre (increased 25-50% if 12.1-16mmol/litre and by 50-100% if >16mmol/litre) | | | | 24 hours; type 1 diabetes only):<br>12.1 (1.1) mmol/litre | included<br>26/50 patients remained on the IV protocol at 24 hours (not reported if analysis done on ACA or ITT)<br>Subgroup:<br>Type 1 diabetes n=12 (24% of patients). But, type 1 diabetes subgroup analysis performed (not in all outcomes) |
| | | | | | | | Hypoglycaemia | No type 1 diabetes subgroup data | |
| | | | | | | | Time spent out of target glucose (hypo/hyper) | Not reported | |
| | | | | | | | Duration of IV treatment | Not reported | |
| | | | | | | | Duration inpatient stay | Not reported | |
| | | | | | | | Inpatient Mortality | Not reported | |
| | | | | | | | Infection rate/wound healing | Not reported | |
| | | | | | | | QoL (SF-36, DQoL, DSQoL) | Not reported | |

**Table 314: Wagner 1999** [164]

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Wagner A, Risse A, Brill H-L, Wienhausen-Wilke V, Rottmann M, Sondern K, Angelkort B. Therapy of Severe Diabetic Ketoacidosis. Diabetes Care. 1999; 22(5):674-677<br><br>REF ID: WANGER 1999 | Prospective case series<br><br>Paper also reports retrospective chart review of DKA admissions (Total n=114) | n=114<br>(15 repeat patients)<br>Prospective insulin intervention study (n=65)<br>Inclusion criteria:<br>• Adults and young people with type 1 diabetes<br>• Severe ketoacidosis, admitted to ICU<br>Exclusion criteria: | Age, mean (SD): 34 (16)<br>Range 11-74 years not reported for intervention study separately<br><br>M/F: 60% male not reported for intervention study separately<br>Diabetes duration: 12.2 (10.8). Range 0-41 years not reported for intervention study separately<br><br>Drop outs | 'Very low-dose insulin application'. IV insulin infusion 1U/h (0.4-4.0U/h). Initially small insulin boli of 2.0-15.0U given. Target – reduction in BG level of 50mg/dL/h. If BG drop more than 100mg/dL/h, 5% glucose given. Ringer lactate fluid substitution, potassium replacement and heparin. | None | Inpatient stay | Achieving target blood glucose levels<br>(reported as mean (range) BG mg/dl at each time point) | Admission: 606(86-1191)<br>After 1hr: 468(96-1075<br>After 4hr: 376(66-1003<br>After 8hr: 283(107-738)<br>After 12hr: 251(89-614) | Also reports results from retrospective case-series review of DKA admissions (not relevant).<br>Funding: not reported<br>Risk of bias:<br>Study design – case-series<br>Consecutive patients included |
| | | | | | | | hypoglycaemia | Not reported | |
| | | | | | | | Time spent out of target glucose (hypo/hyper) | Not reported | |
| | | | | | | | Duration of IV treatment | Not reported | |
| | | | | | | | Duration inpatient stay | Not reported (duration of ICU stay only) | |
| | | | | | | | Inpatient Mortality | Not reported | |
| | | | | | | | Infection rate/wound healing | Not reported | |
| | | | | | | | QoL (SF-36, DQoL, DSQoL) | Not reported | |

# G.10 Complications

## G.10.1 Gastroparesis

### G.10.1.1 The 2 relevant STUDIES FROM THE ORIGINAL 2004 GUIDELINE

**Table 315: JANSSENS 1990[70]**

| Q59 What is the optimum method of managing autonomic neuropathy in adults with Type 1 diabetes? | |
|---|---|
| **Author/Title/Reference/Yr** | Janssens, J., Peeters, T. L., Vantrappen, G., Tack, J., Urbain, J. L., De Roo, M., Muls, E., & Bouillon, R. 1990, "Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies", *N Engl J Med*, vol. 322, no. 15, pp. 1028-1031. |
| **n=** | n=10 in cross over design<br>Belgium |
| **Research Design** | Randomised controlled trial |
| **Aim** | To examine the effect of erythromycin on the impaired gastric emptying of people with severe diabetic gastroparesis |
| **Population** | Type 1 diabetes |
| **Intervention** | 200 mg of erythromycin was infused intravenously over a 15-minute period after the meal. |
| **Comparison** | A control was infused placebo |
| **Outcome** | The outcomes measured were percentages of both solids and of liquid remaining in the stomach after the standard meal, at 1 hour and 2 hours after digestion of the meal<br>The simultaneous gastric emptying of liquids and solids was determined scintigraphically with a double-isotope technique. The technique used a standardized meal consisting of one scrambled egg , two slices of bread, and 150 ml of water. The weight of the solids was 110 g, and they contained 0.966 MJ (231 kcal), consisting of 35 percent fat, 47 percent carbohydrate, and 18 percent protein. The meals were eaten in a mean (±SE) period of 8±2 minutes.<br>Images were obtained every 10 minutes for one hour and then every 15 minutes for another hour. The results were expressed as the percentages of solids and liquids remaining in the stomach over time after the completion of the meal. |
| **Characteristics** | Age =51years, Male =30%, Duration of Diabetes =24years, HbA1c =8.0%, Type 1 diabetes =100% |
| **Results** | Erythromycin markedly accelerated the extremely slow gastric emptying of solids in those with diabetic gastroparesis. With 85 ±7% of solids remaining in the stomach with placebo at 1 hour compared to 21 ±5% with erythromycin (pless than0.005), |

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| | this effect was also seen at 2 hours<br>Erythromycin accelerated the severely impaired emptying of liquids in the people with diabetes, with only 22 ±5% of liquid remaining in the stomach at 1 hour with IV erythromycin compared to 54 ±5% with placebo<br>There were no outcomes recorded regarding adverse events during the cross-over study period |
| **Hierarchy of Evidence Grading** | Ib |
| **Comments** | Study is too short to allow valid conclusions about the effect of the drug on long-term control of diabetes.<br>The participants' blood glucose concentrations were maintained between 5.5 and 8.3 mmol per litre by combined infusions of insulin and glucose during the fast and the subsequent study period. No other concomitant therapy was given to either group<br>The effect of erythromycin on gastric emptying in people with severe diabetic gastroparesis seems to confirm the drug's strong gastro-kinetic effect<br>All people in study had chronic gastroparesis that was refractory to other treatments.<br>Small sample size makes extrapolation to a wider population difficult |
| **Reference/Citation** | 266 |
| **ADDITIONAL DATA REQUIRED FOR 2015 GUIDELINE** | **RCT: 1 day of erythromycin vs. 1 day placebo (cross-over); 1 day wash-out inbetween.**<br>**Follow-up: All patients were then treatment with erythromycin for 4 weeks**<br><br>**HbA1c (at end of 4 weeks): 7.6% (range 5.1 – 10.0)**<br>**Baseline was: 8.0% (range 5.3 – 11.6)** |

**Table 316: SAMSOM 1997[134]**

| Q59 What is the optimum method of managing autonomic neuropathy in adults with Type 1 diabetes? | |
|---|---|
| **Author/Title/Reference/Yr** | Samsom, M., Jebbink, R. J., Akkermans, L. M., Bravenboer, B., van Berge-Henegouwen, G. P., & Smout, A. J. 1997, "Effects of oral erythromycin on fasting and postprandial antroduodenal motility in patients with type I diabetes, measured with an ambulatory manometric technique.", *Diabetes Care*, vol. 20, no. 2, pp. 129-134. |
| **n=** | n=12 in crossover design |
| **Research Design** | Randomised controlled trial |
| **Aim** | To evaluate the effects of oral erythromycin on inter-digestive and postprandial gastrointestinal motility and dyspeptic |

| | |
|---|---|
| | symptoms in people with type 1 diabetes |
| **Population** | Type 1 diabetes The people with diabetes were selected on the presence of dyspeptic symptoms, such as nausea, vomiting, early satiety, fullness, bloating, and abdominal pain. Mechanical obstruction or other diseases responsible for these symptoms were ruled out by means of endoscopy of the upper intestinal tract and ultrasound examination |
| **Intervention** | Erythromycin stearate 250g (orally) three times daily, 30 min before the meal for 14 weeks |
| **Comparison** | This was compared to a placebo tablet for the same period |
| **Outcome** | The inter-digestive phases were defined as follows: 2) phase I: motor quiescence starting after the end of phase III, 2) phase II: pressure waves greater than2 kPa occurring at a rate higher than two per 10 min and less than the maximum frequency of the antrum (three contractions/min) or the duodenum (10-12 contractions/min), and 3) phase III rhythmic contractile activity at the maximum frequency (three contractions/min) in poi] the antrum for at least 1 min and in the duodenum (10-12 contractions/min) for at least 2 min. Phase III had to be propagated over at lea over at least two recording sites and followed by motor quiescence. The manometric data were analysed visually to determine the position of the pressure transducers and to examine pathological motility patterns, using commercially available software, this was carried out over a 20hour period. Symptom scores for the severity of dyspeptic symptoms were also recorded daily for 14 days<br>Antro-duodenal motility was studied during a 20-h period, using a commercially available meal (stew, mixed vegetables, and potatoes; 1,805 kj; 27 g protein, 29 g carbohydrate, 23 g fat; together with 200 ml water or tea was taken at 6:00 P.M. At 8:00 A.M., they took a standardized breakfast consisting of two slices of bread with margarine and jam (1,140 kj; 1 g protein, 48 g carbohydrate, 10 g fat) and 200 ml water or tea. At 12:0 Antro-duodenal motility was recorded using a six-channel solid-state manometric catheter connected to a portable data logger<br>The symptoms of nausea, vomiting, early satiety, bloating, fullness, and abdominal pain were each scored at10:00 P.M. daily, according to a 3 point grading system, validity not specified,<br>A surveillance for adverse events included weekly visits to the hospital with biochemical analysis of blood samples |
| **Characteristics** | Age =43years, Male =25%, Duration of diabetes =26years, HbA1c =9%, Type 1 diabetes =100% |
| **Results** | No clinical or bio- chemical side effects were observed during erythromycin treatment. The blood glucose concentrations during 2 weeks of erythromycin or placebo treatment showed no statistically significant difference<br>During fasting The total number of phase III during erythromycin treatment was 62, compared with 48 during placebo which was not significant<br>There was a decrease in the length of the migrating motor complex (MMC) during erythromycin treatment, compared with placebo 86.2 ± 25.3 Vs. 118.9 ± 46.0 min (P = 0.03).<br>The postprandial pattern showed erythromycin significantly decreased the duration of the post- prandial motor Pattem, from 417.0 ± 137.9 to 348.8 ± 93.8 min (P = 0.04).<br>After dinner the number of distal antral contractions (P less than 0.01) and motility index (P less than 0.03) were significantly |

| | |
|---|---|
| | increased by erythromycin. After breakfast, there were no such increases<br>In the total group, the mean symptom score did not improve during erythromycin treatment compared to placebo<br>No correlation between antroduodenal motility parameters and the individual symptoms, except for phase III, which was invariably associated with nausea. |
| **Hierarchy of Evidence Grading** | Ib |
| **Comments** | It is unlikely that blood glucose concentrations have influenced the results of erythromycin treatment presented in this study.<br>There is no validation of symptom scoring and therefore results may not be reproducible, with unknown effects on outcomes<br>There was a one week washout period but no test to see if this was adequate, with potential contamination of intervention and therefore decreased treatment effect. |
| **Reference/Citation** | 265 |
| **ADDITIONAL DATA REQUIRED FOR 2015 GUIDELINE** | • STUDY LIMITATIONS: randomised, double blind, washout period (1 week), not mention allocation concealment , no dropouts<br>• 2 weeks treatment with erythromycin vs. 2 weeks treatment with placebo (and crossed-over)<br>• HbA1c (at baseline was: 9.39% (SD 2.34) – post-treatment data not given!<br>• Mean symptom severity score - out of total of 3: 3= worse severity - (SD): placebo period 1.81 (0.86); erythromycin period 1.53 (0.67); NS difference<br>• NS improvement in any of the individual symptoms either. |

# G.11 The new studies from the new guideline search

**Table 317: OLAUSSEN 2014**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EA. Olausson, S Storsrud, H Grundin, M Isaksson, S Attvall, and M Simren. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. Am J Gastroenterol 109 (3):375- | RCT<br><br>Sweden | n=56 diabetes with gastroparesis (64% Type 1 diabetes)<br><br>Inclusion criteria:<br>• Insulin-treated diabetes mellitus<br>• Age 18-70 years<br>• Clinical suspicion of gastroparesis<br>• Delayed gastric emptying (scintigraphy)<br>• No evidence of mechanical obstruction<br>• Able to understand | ALL PTS BASELINE | | | Small particle diet<br>Eat foods with small particle size or food items that could easily be processed into small particle size.<br><br>BOTH GROUPS: received instruction from dietician how to fill out questionnaires and dietary food record, and advice on having the | Normal diabetes diet<br>Food usually recommender for people with diabetes.<br>Large particle size acceptable and food should be low GI. | 20 weeks | 20 weeks treatment | Diet | Control | Funding: None specific for this study.<br><br>Risk of bias:<br>Randomisation = unclear (details not given)<br>Allocation concealment = not mentioned<br>Blinding = not mentioned<br>ITT analysis: yes – LOCF<br>Drop-outs: unacceptable (>10% differential |
| | | | | Intervention diet n=28 | Usual diabetes diet n=28 | | | | Weight, kg, mean (SD) | 77.9 (16) | 78.5 (15.8) | |
| | | | Age, years; mean | 51.5 | 55.0 | | | | Weight change, mean difference, kg | -0.012 (-1.6 to 1.6), p=0.99 no difference | | |
| | | | Female | 64% | | | | | HbA1c, % (SD) | 7.4 (0.8) | 7.8 (1.1) | |
| | | | HbA1c, % (SD) | 7.4 (0.8) | 7.9 (1.2) | | | | SF-36 PCS, out of 100 (SD) | 40.2 (10.9) | 35.5 (12.8) | |
| | | | Mean duration of diabetes, years | 28.2 | 23.6 | | | | SF-36 MCS, out of 100 (SD) | 43.8 (15.2) | 41.5 (14.8) | |
| | | | Weight, kg, mean (SD) | 78.4 (16.3) | 79.0 (15.6) | | | | Severity of nausea/vomiting, | -0.56 (-1.01 to -0.11), p=0.01 favours diet | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 385, 2014.<br><br>REF ID: OLAUSSEN 2014 | | verbal and written information and complete questionnaires in Swedish.<br>•<br>Exclusion criteria:<br>• Previous GI surgery except appendectomy<br>• Severe psychiatric disease<br>• Sequelae after cerebrovascular disease<br>• Serum creatinine >150 micromole/litre<br>• Untreated disease with a potential impact on gastric emptying or GI symptoms | | | | same meal scheme: breakfast, snack, lunch. Snack, dinner, and evening snack.<br>Also received dietary advice from the same dietician at 7 out-patient visits during the 20 weeks. | | | mean change difference | | between groups) |
| | | | SF-36 PCS, out of 100 (SD) | 39.0 (11.4) | 37.6 (12.0) | | | | Severity of fullness/early satiety, mean change difference | -0.61 (-1.14 to -0.08), p=0.02 favours diet | |
| | | | SF-36 MCS, out of 100 (SD) | 41.5 (15.9) | 42.1 (13.3) | | | | Severity of bloating, mean change difference | -0.86 (-1.48 to -0.25), p=0.006 favours diet | |
| | | | | | | | | | Severity of upper abdominal pain, mean change difference | -0.36 (-1.01 to -0.28), p=0.27 NS difference | |
| | | | Drop-outs :<br>n=1 (3.6%) intervention<br>n=5 (18%) control | | | | | | Severity of lower abdominal pain, mean change difference | -0.50 (-1.15 to -0.14), p=0.12 NS difference | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | SEVERITY SCORES (PAGI-SYM): 20 items, 6 subscales (nausea/vomiting; fullness/early satiety; bloating; upper abdominal pain; lower abdominal pain; heartburn/regurgitation).<br>Score of 0-6 (6-point Likert scale). 0 = no symptoms, 5 = very severe symptoms. | | |

**Table 318: SNAPE 1982**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| W. J. Snape, Jr., W. M. Battle, S. S. Schwartz, S. N. Braunstein, H. A. Goldstein, and A. Alavi. Metoclopramide to treat gastroparesis due to | RCT (cross-over)<br><br>USA | n=10 Type 1 diabetes and gastroparesis<br><br>Inclusion criteria:<br>• IDDM adults<br>• Symptoms of gastric retention, vomiting, bloating, and | ALL PTS BASELINE | | Metoclopramide (10 mg tablets) four times daily 30 minutes before breakfast, lunch, and dinner, and before sleep. | Placebo | 3 weeks (each cross-over period) | 3 weeks treatment on each | Met | Placebo | Funding: none mentioned.<br><br>Risk of bias:<br>No wash-out period.<br>Randomisation = unclear (details not given)<br>Allocation concealment |
| | | | Age, years; mean | 31.4 | | | | Weight loss, no. of patients | 3 | 6 | |
| | | | Mean duration of diabetes) | 16.2 years | | | | Symptoms 'felt better', no. of patients | 7 | 0 | |
| | | | Mean insulin dose – LA | 40.5 (6.6 | | | | No vomiting, | 6 | 0 | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| diabetes mellitus: a double-blind, controlled trial. Ann.Intern. Med. 96 (4):444-446, 1982.<br><br>REF ID: SNAPE 1982 | | early satiety<br><br>Exclusion criteria:<br>None mentioned. | insulin (NPH or Lente) | U) | | | | no of patients | | | = not mentioned<br>Blinding = double<br>ITT analysis: yes – no drop-outs<br>Drop-outs: acceptable (none) |
| | | | | | | | | AEs (abdominal pain), no. of patients | 0 | 3 | |
| | | | | | | | | Questionnaire given to patients - symptoms were classified as present, not present, mild, moderate, or severe. | | | |
| | | | Drop-outs :<br>None mentioned | | | | | | | | |

**Table 319: RICCI 1985**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D. A. Ricci, M. B. Saltzman, C. Meyer, C. Callachan, and R. W. Mccallum. Effect of metoclopra | RCT (cross-over)<br><br>USA | n=13 Type 1 diabetes and gastroparesis<br><br>Inclusion criteria:<br>• IDDM adults<br>• Symptoms of | ALL PTS BASELINE | | Metoclopramide (10 mg tablets) four times daily 30 minutes before breakfast, lunch, and | Placebo | 3 weeks (each cross-over period) | 3 weeks treatment on each | Met | Placebo | Funding: Grant from AH Robins Company, and from NIHR. |
| | | | Age, years; mean | 44.1 | | | | Overall mean symptom score – frequency (SD); max | 26.5 (21.6) | 45.3 (45.5) | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| mide in diabetic gastroparesis. J.Clin.Gastroenterol. 7 (1):25-32, 1985.<br><br>REF ID: RICCI 1985 | | gastric stasis<br>• Objective documentation of delayed gastric emptying (radionuclide solid meal)<br>• Symptoms of nausea, vomiting, epigastric fullness, bloating and distension, early satiety, and anorexia.<br><br>Exclusion criteria:<br>• Organic causes of delayed gastric emptying (such as ulceration, obstruction).<br>• Other causes of delayed gastric emptying<br>• Contraindicatio n to | | | dinner, and before sleep. | | | score = 100 | | | Risk of bias:<br>1-week wash-out period.<br>Randomisation = unclear (details not given)<br>Allocation concealment = not mentioned<br>Blinding = double<br>ITT analysis: yes – no drop-outs<br>Drop-outs: acceptable (none) |
| | | | Female | 54% | | | | Mean symptom score (total of 100): 5 symptoms (epigastric fullness, pressure and bloating; nausea; vomiting; anorexia; early satiety. Each rated grades 0-20 (0= symptom not experienced, 10= daily frequency; 15= 2-3 times/day; 20= 4 or more times/day) | | | |
| | | | Mean duration of diabetes, years | 12.6 (range 3-28) | | | | | | | |
| | | | Mean duration of gastric stasis symptoms, years | 2.5 (3 months to 7 years) | | | | | | | |
| | | | Mean symptom scores, mean (SD) | Met = 50.0 (19.5)<br>Placebo = 52.7 (21.6) | | | | | | | |
| | | | Drop-outs :<br>None mentioned | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | metoclopramide<br>• Taking other dopamine antagonists<br>• Other drugs with known delaying effects on gastric emptying. | | | | | | | |

**Table 320: MCCALLUM 1983**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R. W. Mccallum, D. A. Ricci, H. Rakatansky, J. Behar, J. B. Rhodes, G. Salen, J. Deren, A. Ippoliti, H. W. Olsen, K. Falchuk, and | RCT<br><br>USA | n=44 diabetes and gastroparesis (95% type 1 diabetes)<br><br>Inclusion criteria:<br>• Diabetes<br>• Delayed gastric emptying (test meal study or roentgenologic study) | ALL PTS BASELINE | | | Metoclopramide (10 mg tablets) four times daily<br><br>30 minutes before breakfast, lunch, and dinner, and | Placebo | 3 weeks | | Met | Placebo | Funding: partly by Medtonic.<br><br>Risk of bias:<br>Randomisation = unclear (details not given)<br>Allocation concealmen |
| | | | | Metoclop)<br><br>n=20 | Placebo n=24 | | | | | | | |
| | | | Age, years; mean | 40 | 42 | | | | No. of patients getting Improvement of ≥2 on severity scale (for patients with initial rating of moderate or more) | | | |
| | | | Male | 45% | 29% | | | | Vomiting, | 6/1 | 4/8 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| . A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. Diabetes Care 6 (5):463-467, 1983.<br><br>REF ID: MCCALLUM 1983 | | Exclusion criteria:<br>• Ulceration, obstruction, and other organic aetiologies of gastric retention<br>• Other causes of delayed gastric emptying<br>• Contraindication to metoclopramide<br>• Taking other dopamine antagonists<br>• Other drugs with known delaying effects on gastric emptying.<br>• All disorders other than diabetes | Nausea | 15 (75%) | 18 (75%) | before bedtime. | | | no of patients | 0 | | t = not mentioned<br>Blinding = double<br>ITT analysis: no<br>Drop-outs: 2 in each group (<20% and no differential between groups) |
| | | | Vomiting, n | 11 (55%) | 10 (43%) | | | | AEs, no. of patients | 11/ 18 | 20/22 | |
| | | | Duration of diabetes, years | 12.6 (range 3-28) | | | | | Patient diaries used to record frequency and severity of symptoms.<br><br>5-point Scale: 0=absent, 1 = slight, 2=moderate, 3 = marked, 4 = extreme | | | |
| | | | Duration of gastroparesis symptoms, years | 2.5 (range 3 months -7 years) | | | | | | | | |
| | | | Drop-outs :<br>n=2 in each group (10% and 8% respectively) | | | | | | | | | |

**Table 321: TIMRATANA 2013[157] – subgroup analysis done in the diabetic patients**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| P. Timratana, K. El-Hayek, H. Shimizu, M. Kroh, and B. Chand. Laparoscopic Gastric Electrical Stimulation for Medically Refractory Diabetic and Idiopathic Gastroparesis. J.Gastrointest.Surg. 17 (3):461-470, 2013.<br><br>REF ID: TIMRATANA 2013 | Case-series (prospective)<br><br>USA | n=110 gastroparesis (n=55 diabetes; the rest = idiopathic)<br><br>Inclusion criteria:<br>• Age >18 years<br>• Typical symptoms of gastroparesis<br>• Have failed medical management or unable to tolerate medications<br>• Diabetic or idiopathic causes of gastroparesis<br>• Off all narcotics and pro-motility agents for 2 weeks prior to the study<br><br>Exclusion criteria:<br>• Prior gastric surgery. | DIABETIC SUBGROUP (n=55) | | IMPLANTED GES system - Laparoscopic<br><br>Neurostimulator (Enterra Therapy System, Medtronic)<br><br>Programmed to standardised parameters (3V; cycle ON for 0.1 seconds). | No comparison group | Mean 27 months 1-113) | Results DIABETIC SUBGROUP | Pre-op (baseline) | Follow-up | Funding: None<br><br>Risk of bias: No checklist for before-after studies/case-series |
| | | | Age, years; mean | 41.3 | | | | HbA1c (SD) | Pre-op n=37 7.6 (1.3) | Post-op n=17 8.7 (1.8) | |
| | | | Male/female, | 17/38 | | | | Nausea | SS change, p<0.01 | | |
| | | | Duration diabetes, years | 18 (1-40) | | | | Vomiting<br>Pain<br>Bloating | SS change, p<0.01<br>SS change, p=0.009<br>NS change, p=0.165 | | |
| | | | Duration gastroparesis, years | 6.4 (1-20) | | | | AEs (post-surgical complications) | n=5 | | |
| | | | Insulin<br>Pancreas transplant | n=48<br>n=2 | | | | Death | n=4 at mean 14.5 months (1-26) | | |
| | | | | | | | | TSS, severity, mean (SD) | 6 months: 10.7 (1.7); p<0.05.<br>12 months: 9.2 (1.5); p<0.05 | | |
| | | | SF-36 mental, mean (SE) | 37.3 (3.5) | | | | | | | |
| | | | GET | 2hrs: 80 | | | | SF-36, | 6 months: 32.0 | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | (gastric emptying), % retention, median (IQR) | (69-88); 4hrs: 46 (28-68) | | | | physical, mean (SE) | (2.0); p<0.025.<br>12 months: 35.2 (2.9); p<0.025 | |
| | | | | | | | | SF-36, mental, mean (SE) | 6 months: 42.0 (3.5).<br>12 months: 47.3 (2.2). | |
| | | | Drop-outs :<br>None in first 2 months<br>6 months cumulative n=5 diabetics<br>12 months cumulative n=6 | | | | | 2hrs GET, median (IQR) | 6 months: 67 (50-79).<br>12 months: 46 (29-61) | |
| | | | | | | | | 4hrs GET, median (IQR) | 6 months: 44 (21-67).<br>12 months: 16 (1-30), p<0.05. | |
| | | | | | | | | TSS = sum of severity of ratings for 6 symptoms: 5-point symptom questionnaire: 0=absent, 1= mild, 2=moderate, 3=severe, 4= extremely severe. Symptoms measured were upper GI tract symptoms: vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain). | | |

**Table 322: ABELL 2003[5] – subgroup analysis done in the diabetic patients**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T. Abell, R. W. Mccallum, M. Hocking, K. Koch, H. Abrahamsson, I. Leblanc, G. Lindberg, J. Konturek, T. Nowak, E. M. M. Quigley, G. Tougas, and W. Starkebaum. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology 125 (2):421-428, 2003.<br><br>REF ID: | RCT (cross-over)<br><br>11 centres in USA, Canada, and Europe. | n=33 gastroparesis (n=17 diabetes; n=16 idiopathic)<br><br>Inclusion criteria:<br>• >1 episode of vomiting/week<br>• Delayed gastric emptying (>60% retention at 2 hours and >10% at 4 hours (scintigraphic method for solid meals)<br>• Symptoms consistent with gastroparesis for >12 months<br>• Refractories or intolerance to 2 of 3 classes of prokinetic drugs (cholinergics, motilin receptor agonists, dopamine receptor agonists) and 2 of 3 classes | Diabetic subgroup (n=17) | | Implanted GES system ON (then off)<br><br>Neurostimulator (Medtronic model 4300) with 2 implanted leads In the muscularis propria of the greater curvature<br><br>Programmed to standardised parameters (14Hz, 5mA, 330µs; cycle ON for 0.1 seconds, cycle OFF for 5 seconds).<br><br>Mean surgery duration: 1.6 hours | Implanted GES system OFF (then on)<br><br>BOTH GROUPS - Concomitant medication: Patients continued their current antiemetic or prokinetic treatment during the study | 1 month of treatment on or off, then switched.<br><br>Then 10 months open-label with stimulator ON | RCT results (1 month treatment) DIABETIC SUBGROUP | GES ON | GES OFF | Funding: partly by Medtonic.<br><br>Risk of bias:<br>Wash-out period = none mentioned.<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not reported<br>Blinding = double<br>ITT analysis: not reported<br>Not powered study; enrolment stopped early due to difficulty in recruiting patients.<br>Drop-outs =none for phase 1 RCT (thus ITT analysis) |
| | | | Age, years; mean | 38.1 | | | | WVF, episodes/ week; median (IQR) | 6.0 (3.0-14.8) | 12.8 (5.5-24.2) | |
| | | | Male/female, | 9/8 | | | | TSS; severity, mean (SD) | 11.3 (1.5) | 13.2 (1.7) | |
| | | | BMI, Kg/m$^2$; mean (SD) | 24.7 (4.7) | | | | 6 and 12 month data (below) is given for DIABETIC SUBGROUP. All had machine ON. | | | |
| | | | WVF Weekly vomiting frequency | 13.4 (8.8-55.6) | | | | WVF | 6 months: 2.6 (0.9-12.5); p<0.05. 12 months: 4.9 (0.1-7.4); p<0.05 | | |
| | | | Total symptom score (TSS); mean (SE) | 16.87 (1.2) | | | | TSS, severity, mean (SD) | 6 months: 10.7 (1.7); p<0.05. | | |
| | | | SF-36 physical, mean (SE) | 26.1 (2.3) | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| ABELL 2003 | | of antiemetics (a-histamines, serotonin receptor antagonists, and dopamine receptor antagonists)<br><br>Exclusion criteria:<br>• Documented intestinal pseudo-obstruction, prior gastric surgery, vagotomy, organ transplantation, seizures, primary swallowing disorders, chemical dependency, pregnancy, or psychogenic vomiting<br>• Medically unstable or at high surgical risk. | SF-36 mental, mean (SE) | 37.3 (3.5) | | | | | 12 months: 9.2 (1.5); p<0.05 | |
| | | | GET (gastric emptying), % retention, median (IQR) | 2hrs: 80 (69-88); 4hrs: 46 (28-68) | | | | SF-36, physical, mean (SE) | 6 months: 32.0 (2.0); p<0.025.<br>12 months: 35.2 (2.9); p<0.025 | |
| | | | | | | | | SF-36, mental, mean (SE) | 6 months: 42.0 (3.5).<br>12 months: 47.3 (2.2). | |
| | | | Drop-outs :<br>None in first 2 months<br>6 months cumulative n=5 diabetics<br>12 months cumulative n=6 | | | | | 2hrs GET, median (IQR) | 6 months: 67 (50-79).<br>12 months: 46 (29-61) | |
| | | | | | | | | 4hrs GET, median (IQR) | 6 months: 44 (21-67).<br>12 months: 16 (1-30), p<0.05. | |
| | | | | | | | | TSS = sum of severity of ratings for 6 symptoms: 5-point symptom questionnaire: 0=absent, 1= mild, 2=moderate, 3=severe, 4= extremely severe. Symptoms measured were upper GI tract symptoms: vomiting, nausea, early satiety, bloating, | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | postprandial fullness, epigastric pain). | | |

**Table 323: ABELL 2011[6] – subgroup analysis done in the diabetic patients**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T. L. Abell, W. D. Johnson, A. Kedar, J. M. Runnels, J. Thompson, E. S. Weeks, A. Minocha, and M. E. Griswold. A double-masked, randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for | RCT (cross-over)<br><br>1 centres in USA | n=58 gastroparesis (n=13 diabetes; n=38 idiopathic; n=7 postsurgical)<br><br>Inclusion criteria:<br>• 18-70 years old<br>• Gastroparesis symptoms >1 year (diabetic, postsurgical or idiopathic etiology)<br>• 7 or more episodes of chronic vomiting and/or nausea per week, | ALL patients BASELINE | | | Implanted GES system ON (then off)<br><br>Neurostimulator (Medtronic Enterrra stimulator),.<br><br>Programmed to standardised parameters (14Hz, 5-10mA, 330µs; cycle ON for 0.1 – 1.0secs, cycle OFF for 5-4 seconds). | Implanted GES system OFF (then on) | 72 hours of treatment on or off, then switched. | RCT results (3 days treatment) DIABETIC SUBGROUP: n=13 | GES ON | GES OFF | Funding: partly by Medtonic.<br><br>Risk of bias:<br>Wash-out period = 24 hrs.<br>Randomisation = unclear (details not given)<br>Allocation concealment = none (unmasked)<br>Blinding = double<br>ITT analysis: no<br>Powered |
| | | | | Group A (on/off)<br><br>n=28 | Group B (off/on) n=30 | | | | | | | |
| | | | Age, years; mean | 47 | 45 | | | | Vomiting score | -0.31 units/day (-0.64, 0.02) with stimulation (p=0.069) | | |
| | | | Male | 28% | 13% | | | | | | | |
| | | | BMI, Kg/m$^2$; mean (SD) | 29.4 (7.4) | 27.5 (7.7) | | | | | | | |
| | | | Vomiting score (likert 1-5) | 1.82 (1.55) | 2.68 (1.61) | | | | | | | |
| | | | Total | 12.8 | 14.6 | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| gastroparesis. Gastrointest.Endosc. 74 (3):496, 2011.<br><br>REF ID: ABELL 2011 | | irrespective of gastric emptying time<br>• Refractory or intolerant to antiemetic drug classes (antihistamines and phenothiazines, serotonin receptor antagonists, dopamine receptor antagonists)<br><br>Exclusion criteria:<br>• Active infection of any kind<br>• Enrolled in another medical device or drug study<br>• Pregnant<br>• Unsuitable for endoscopy<br>• Unwilling or unable to return for | sympto m score (TSS); mean (SD) | (4.95) | (3.8) | | | | | | study.<br>Drop-outs = <20% and <10% differential between arms. |
| | | | Nausea score (likert 1-5) | 3.27 (0.92) | 3.33 (1.03) | | | | | | |
| | | | GET (gastric emptying), % retention, mean (SD) | 2 hours : 45.5 (24.1)<br><br>4hr: 24.5 (26.5) | 2 hours : 38.7 (26.2)<br><br>4hr: 19.4 (25.4) | | | | | | |
| | | | Drop-outs :<br>n=6 in group A and n=7 in group B. All due to dislodged electrode they discontinued treatment. | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | follow-up visits. | | | | | | | |

**Table 324: BRAUN 1989[18]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention<br>Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| A. P Braun. Domperidone in the treatment of symptoms of delayed gastric emptying in diabetic patients. Adv.Ther. (6):51-62, 1989.<br><br>REF ID: BRAUN 1989 | RCT – cross-over (with run-in and extension phase all patients on domperidone)<br><br>USA | n=13 Type 1 diabetes and type 2 diabetes with gastroparesis (95% Type 1 diabetes) – in the RCT phase<br><br>Inclusion criteria:<br>Diabetes<br>• At least 1 symptom of delayed gastric emptying at moderate to severe intensity<br><br>Exclusion criteria:<br>• Total gastrectomy<br>• Pregnant or likely to become p0regnant<br>• Conditions or illnesses that | All patients baseline | | Domperidone 10 or 20 mg/day<br>vs.<br>Placebo<br><br>Domperidone<br>9/10 patients 10mg/day<br>4/13 = 20 mg/day at 15-30 minutes before meals and at bedtime.<br><br>IN BOTH GROUPS:<br>There was a 12 week run-in (open Domperidone treatment phase. Patients received 10mg tablet before each meal and bedtime. If insufficient improvement seen, dose could increase to 20mg. All patients who showed improvement at this phase were entered for 2 year maintenance programme (2 further months of treatment on Dom, then RCT, then extension)<br>The RCT phase followed (1 | 12 week run-in (open Domperidone treatment phase); then 1 month RCT phase (1 month each treatment); then long-term open domperidone treatment phase (up to 2 years – mean 467 days). | RCT results (1 monthly treatment) n=13 | | Funding: None reported.<br><br>Risk of bias:<br>Wash-out period = 24 hrs.<br>Randomisation = unclear (details not given)<br>Allocation concealment = unclear (details not given)<br>Blinding = double<br>ITT analysis: no<br>No mention of powering.<br>Drop-outs in RCT = <20% and <10% differential between |
| | | | Final population of n=18 for efficacy phase | Male: 33%<br>Mean age: 51<br>Weight: 68kg | | | Change from baseline: there was SS deterioration in TSS frequency in placebo group, but NS for TSS intensity. | | |
| | | | NO OTHER BASELINE DETAILS GIVEN | | | | Domperidone was SS better than placebo for:<br>frequency and intensity of early satiety (p<0.05)<br>TSS frequency (p<0.05)<br>TSS intensity (p=0.05).<br><br>There was NS difference between Domperidone and Placebo for:<br>Nausea<br>Vomiting<br>Anorexia<br>Distention/bloating | | |
| | | | | | | | After the RCT: most physicians rated domperidone as excellent/good (Phys global assessment) | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention<br>Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | could interfere with evaluation of the study drug.<br>• No concurrent medications that could mask GI symptoms or compromise efficacy assessment were allowed during study or 1 week before. | | | month cross-over of Dom vs. placebo)<br>Last extension phase followed – all patients received open therapy with Dom (up to 2 years). | | Open phase 1 (12 weeks treatment on Domperidone, before RCT): n=18<br>12/18 patients had dose increased to 20mg.<br>SS decrease in intensity and severity of all individual symptoms, and TSS severity and frequency (p<0.05) | | arms. |
| | | | Drop-outs :<br>• n=20 patients started open phase; n=2 not included in analysis<br>• n=13 started RCT phase. | | | | Open phase 2 (up to 2 years on Domperidone, after RCT): n=13<br>SS decrease in TSS frequency, intensity and severity (p<0.05). | | |
| | | | | | | | NOTE: TSS (both frequency and intensity) is on a scale of 0-3; with 3 being worse. There were 5 symptoms.<br>5 symptoms assessed were: anorexia, nausea, vomiting, distention/bloating, early satiety. | | |

*NOTE: only patients who improved on domperidone in run-in phase, entered the subsequent RCT phase of the study.*

**Table 325: FRIEDENBERG 2008[50] – subgroup analysis done in the diabetic patients**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F. K. Friedenberg, A. Palit, H. P. Parkman, A. Hanlon, and D. B. Nelson. Botulinum toxin A for the treatment of delayed gastric emptying. Am.J.Gastroenterol. 103 (2):416-423, 2008.<br><br>REF ID: FRIEDENBERG 2008 | RCT<br><br>1 centres in USA. | n=32 gastroparesis (n=18 diabetes; n=13 idiopathic; n=1 post-surgical)<br><br>Inclusion criteria:<br>• 18-75 years<br>• Symptoms consistent with delayed gastric emptying (GCSI score >27)<br>• Delayed gastric emptying (scintigraphy; within past 3 months)<br>• Diabetics required to be under good metabolic control fBG <140 mg/dL) for 1 month before study<br>• Patients on prokinetics with partial effectiveness had to have stable dose at least 4 | ALL PTS (n=32); n=16 in each group | | | BOTOX (BoNT/A)<br>200U BoNT/A (5 mL volume) injected into the pylorus.<br>Clear and odourless reconstitution from powder. Injection administered after an overnight fast and standard upper endoscopy) | PLACEBO<br>Sterile saline injection – 5 mL (administered after an overnight fast and standard upper endoscopy)<br><br>BOTH GROUPS - Concomitant medication:<br>PTS ON PROKINETICS (if partially effective) DISCONTINUED the treatment 48hrs | 1 month post-treatment (single injection) | 1 month post-treatment: DIABETIC SUBGROUP | BoTOX | Placebo | Funding: none mentioned.<br><br>Risk of bias:<br>Randomisation = ok (although just says randomisation table)<br>Allocation concealment = yes – independent study coordinator accessed.<br>Blinding = double<br>Powered study.<br>Drop-outs =none (thus ITT analysis) |
| | | | Age, years; mean | 41.6 | 40.4 | | | | GCSI score reduction, mean (SD)<br>p=0.79 | 11.4 (9.8) | 13.7 (16.3) | |
| | | | Male | 19% | 19% | | | | 2hr GES, %<br>4hr GES, %<br>NS | 15<br>8 | 11<br>9 | |
| | | | Gastric retention % (SD) 2hrs | 67 (11.3) | 64 (13.7) | | | | | | | |
| | | | Gastric retention %, (SD) 4hrs | 29 (17.8) | 28 (22.8) | | | | | | | |
| | | | GCSI, (SD) | 34.4 (4.2) | 36.4 (4.8) | | | | | | | |
| | | | GVAS (SD) | 603 (139) | 584 (131) | | | | | | | |
| | | | Previous treatment: | 14 | 11 | | | | SYMPTOM SEVERITY SCORES: | | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | weeks before study.<br><br>Exclusion criteria:<br>• Pregnant<br>• Unfit to undergo upper endoscopy<br>• Prior abdominal surgery except for hernia repair or appendectomy<br>• Received prior BoNT/A or known allergy to the protein<br>• Unable to stop medications known to exacerbate delayed gastric emptying (eg. Narcotic analgesics) | Metoclop<br><br>Domperid<br>Erythrom y<br>Tegasero d<br>PPI | 3<br>2<br>2<br>8 | 2<br>3<br>2<br>9 | | before GES. Patients on ineffective prokinetics were discontinued the treatment 4 weeks before study. | | 1. GCSI score (Gastroparesis Cardinal Symptoms Index): 9 symptoms, scale 0 (none) – 5 (very severe). Total score = 45. Score ≥27 = moderate to severe symptoms. | | |
| | | | | | | | | | GVAS score (Gastroparesis VAS): 8 symptoms, all post-prandial assessed for severity. 100mm VAS; max score 800.<br>QoL (impact of symptoms on QoL and ability to attend and function in work or school. 5-point Likert scale used. | | |
| | | | Drop-outs :<br>None | | | | | | GES: normal emptying with test meal = ≤50% retention at 2hrs and ≤10% at 4 hrs. | | |

**Table 326: FROKJAER 2008[52]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| J. B. Frokjaer, N. Ejskjaer, P. Rask, Andersen S. Due, H. Gregersen, A. M. Drewes, and P. Funch-Jensen. Central neuronal mechanisms of gastric electrical stimulation in diabetic gastroparesis. Scand.J.Gastroenterol. 43 (9):1066-1075, 2008.<br><br>REF ID: | RCT (cross-over)<br><br>1 centres in Denmark. | n=7<br>Diabetes with gastroparesis (n=6 Type 1 diabetes)<br><br>Inclusion criteria:<br>• Symptomatic diabetic autonomic neuropathy (minimum of 2 symptoms from different organ systems)<br>• Classic symptoms suggestive of gastroparesis (nausea, vomiting, early satiety and bloating) which were refractory to antiemetics and prokinetics.<br>• Verified delayed gastric emptying of a solid meal and liquids (assessed by either | All patients (n=7) | | IMPLANTED GES system ON (then off)<br><br>Neurostimulator (Medtronic 3116). 2 electrodes. Greater curvature of the pylorus.<br><br>Programmed to standardised parameters (14Hz, 5mA, 330µs; cycle ON for 0.1sec, cycle OFF for 5 seconds). | IMPLANTED GES system OFF (then on)<br><br>BOTH GROUPS - Concomitant medication: At start of study 2 patients were taking medication affecting GI function; rest were not treatment because of previous insufficient response to various drugs. All | 1 month treatment, then crossed-over | | ON period | OFF period | Funding: Danish Research Council, Aarhus County, Danish Diabetes Association, Research Council of North Jutland, Aarhus University Hospital, Toyota Foundation, and SparNord Foundation.<br><br>Risk of bias:<br>No washout period between cross-over<br>Randomisation = ok (although just says |
| | | | Age, years; mean | 39 years (25-55) | | | | Vomiting episodes/ day, mean (SEM) | 1.13 (0.50)<br>SD calculated: 1.32 | 0.33 (0.13)<br>SD calculated: 0.34 | |
| | | | Male/Female | 4/3 | | | | | | | |
| | | | Diabetes type | n=6 Type 1 diabetes; man 25 years duration | | | | | | | |
| | | | Vomiting episodes/ day, mean (SEM) | 0.61 (0.26) | | | | | | | |
| | | | Nausea duration, hours/day, mean (SEM) | 4.1 (0.7) | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | Drop-outs : n=1 | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| FROKJAER 2008 | | scintigraphy, or paracetamol absorption method). Thus patients had severe emptying disorder.<br><br>Exclusion criteria:<br>• Pregnant<br>• Psychogenic vomiting<br>• Prior abdominal surgery<br>• Pseudo-obstruction<br>• Uraemia<br>• Primary eating and swallowing disorders | | | medication affecting GI function was paused 2 days before all investigation periods. | | | | randomisation table)<br>Allocation concealment = not mentioned.<br>Blinding = double<br>No mention of powering.<br>Not ITT analysis<br>Drop-outs: N<20% |

**Table 327: HOROWITZ 1985[67] Data presented for cases (diabetics) only**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| M. | Prospe | n=12 | All type 1 diabetes | DOMPERIDON | N/A | 35 - 51 | Anorexia/naus | 0.42 (.67) | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Horowitz, P. E. Harding, B. E. Chatterton, P. J. Collins, and D. J. Shearman. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. Dig.Dis.Sci. 30 (1):1-9, 1985.<br><br>REF ID: HOROWITZ 1985 | ctive case-series<br><br>Australia | Type 1 diabetes with autonomic neuropathy<br><br>n=22 normal volunteers also recruited (but not designed as case-control study)<br><br>Inclusion criteria:<br>Type 1 diabetes for at least 10 years<br>Autonomic neuropathy<br>Other complications of diabetes<br>Non-smokers<br>Not taking medication known to affect GI motility<br><br>Also normal healthy controls recruited<br><br>Exclusion criteria:<br>None reported | patients (n=12) | | E<br>20mg 3x/day, 30-60 minutes before meals<br><br>Patients were tested immediately after given 40mg domeperidone vs. placebo<br><br>Then later part of trial (results for this are reported here as matched protocol) patients received longer term treatment with domperidone. | | days treatment (median 38 days) | ea, mean (SD) | | Janssen Pharmaceutic Patienty. Ltd.<br><br>Risk of bias:<br>No NICE checklist for case-series |
| | | | Age, years; mean | 43 (21-61) | | | | Early satiety, mean (SD) | 0.75 (0.97) | |
| | | | Male/Female | 6/6 | | | | Epigastric fullness/upper abdominal discomfort, mean (SD) | 0.58 (0.79) | |
| | | | Diabetes type | All type 1 diabetes Duration >10 years | | | | | | |
| | | | Anorexia/ nausea, mean (SD) | 1.17 (1.03) | | | | Post-prandial vomiting, mean (SD) | 0.08 (0.29) | |
| | | | Early satiety, mean (SD) | 1.75 (0.97) | | | | TSS severity, mean (SD) – total score of 4 symptoms/max. 12 | 1.83 (1.99) | |
| | | | Epigastric fullness/upper abdominal discomfort, mean (SD) | 1.75 (1.23) | | | | Episodes of Hypo | 5 patients observed more episodes while taking domperidone (no details given) and reduced their insulin dose | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | HbA1c, % MEDIAN (range) | 7.5 (5.6 – 12.1); NS change from baseline | |
| | | | Post-prandial vomiting, mean (SD) | 0.42 (0.79) | | | | • Symptoms severity of GP were SS reduced by domperidone treatment (p<0.001):<br>• baseline median 4.5, range 1-10<br>• End of treatment median 1.5, range 0-6 | | |
| | | | TSS severity, mean (SD) – total score of 4 symptoms /max. 12 | 5.08 (3.09) | | | | Each Symptom score on scale of 0-3 (higher = more severe) | | |
| | | | HbA1c, % MEDIAN (range) | 8.5 (6.8-10.9) | | | | | | |
| | | | | | | | | | | |

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**Table 328: LACY 2004 (case-control)[87]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| B. E. Lacy, M. D. Crowell, A. Schettler-Duncan, C. Mathis, and P. J. Pasricha. The treatment of diabetic Gastroparesis with botulinum toxin injection of the pylorus. Diabetes Care 27 (10):2341-2347, 2004.<br><br>REF ID: LACY 2004 | Prospective case control<br><br>Open label trial with age and sex-matched control subjects from a tertiary care referral centre for patient with Gastroparesis | n=8 with type 1 diabetes<br>Control group consisted of age and sex-matched control subjects without diabetes and without any complaints.<br><br>Inclusion criteria:<br>• Details not given<br>Exclusion criteria:<br>• Pregnancy<br>• Known allergy to eggs, botulinum toxin, or lidocane<br>• Previous surgery to the stomach, pylorus, or | Eight type 1 diabetes who had failed standard therapy were enrolled | | Injection of the pylorus with 200 units of botulinum toxin A during upper endoscopy. Patient was observed for 1-2 h in the recovery area and then discharged home.<br><br>Patients underwent esophagogastroduodenoscopy (before intervention) to rule out mechanical obstruction. | N/A | 12 weeks | | Before | After | Funding: study funded donations to the Marvin M. Shuster Centre for Digestive and Motility Disorders and by unrestricted educational grants<br><br>Risk of bias:<br>NO NICE CHECK LIST |
| | | | Age, years; mean (range) | 41 (36-46) | | | | *Mean symptom score | 27.0 (n=8) | 12.2 (n=8) at week 8 | |
| | | | | | | | | Symptom scores of the seven patients who completed all 12 weeks follow up after only one injection of botulinum toxin were not significantly different | | | |
| | | | Male/ female, | 2/6 | | | | SF-36 questionnaire scores | In the six patients who completely filled out both pre- and post-injection SF-36 questionnaires, total scores did not change significantly. | | |
| | | | Insulin use, years; mean (range) | 24.4 (10-40) | | | | Physical function domain of SF-36 | Improvement noted ($p<0.05$) | | |
| | | | Diabetes duration, mean | 25.3 (10-40) | | | | HbA1c (%) | HbA1c obtained at 8 weeks follow up visit was not significantly different from | | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | small bowel<br>• Previous Nissen fundoplication or other antireflux surgery<br>• Known pyloric stricture<br>• Previous stroke, TIA, or chronic diseases involving the CNS<br>• Concurrent use of opiates or anticholinergics | years (range) | | | | | | | baseline. | |
| | | | HbA1c (%) | Baseline value not given | | | | | Hospital admission | Not reported | |
| | | | | | | | | | Severe hypoglycaemia | Not reported | |
| | | | Drop-outs : | | | | | | *mean symptom score: each patient filled out a symptom questionnaire. Each question asked the patient to rate symptoms from none (0 points) to severe (3 points); the maximum score was 36. | | |

**Table 329: MCCALLUM 2010B[102]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| R. W. | RCT | n=45 | All patients (n=45) | IMPLANTED | IMPLANTED | 1.5 | During | ON | OFF | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mccallum, W. Snape, F. Brody, J. Wo, H. P. Parkman, and T. Nowak. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. Clin.Gastroenterol.Hepatol. 8 (11):947-954, 2010. | (cross-over)<br><br>8 centres in USA | Diabetes with gastroparesis (94% insulin dependent)<br><br>Inclusion criteria:<br>≥18 years old<br>Symptomatic requiring treatment for ≥1 year<br>Unresponsive or intolerant to prokinetic or antiemetic drugs for >1 month<br>At least 7 episodes of vomiting during 7 consecutive days in the 28-day diary<br>Gastric retention: >10% at 4hrs (or >60% at 2hrs if patients unable to complete 4hr test)<br>On a stable does of prokinetic agents at least 30 days before baseline and willing | | | GES system ON (then off)<br><br>Neurostimulator (Enterra system, Medtronic 7425G or 3116). 2 electrodes. Greater curvature of the stomach.<br><br>Programmed to standardised parameters (14Hz, 5mA, 330µs; cycle ON for 0.1sec, cycle OFF for 5 seconds).<br><br>BOTH GROUPS – Prior to randomisation, all patients had device turned on for 1.5 | GES system OFF (then on)<br><br>BOTH GROUPS - Concomitant medication: Not mentioned. | months all patients on treatment;<br>3 months treatment randomisation (each period of cross-over)<br>Then follow-up at 12 months (4.5 months all patients on treatment). | randomised phase | period | period | Medtronic, Inc.<br><br>Risk of bias:<br>No washout period between cross-over<br>Randomisation = not enough details given just says randomised, 1:1 ratio stratified by centre in block size of 4.<br>Allocation concealment = not sufficient (unblinded person in sealed envelopes).<br>Blinding = double |
| | | | Age, years; mean | 38.3 years | | | | WVF: Vomiting episodes/ week, median (IQR) | 3.81 (0.75-14.03) | 4.25 (0.38-15.13) | |
| | | | Female | 65% | | | | Frequency symptom scores, mean (SD) *=SS difference between gps | | | |
| | | | BMI, kg/m$^2$ | 26.4 (range 17-42) | | | | Vomiting | 2.31 (1.43) | 2.03 (1.48) | |
| | | | WVF – weekly vomiting frequency: episodes/ week, median | 16.8 | | | | Nausea | 2.81 (1.31) | 2.42 (1.56) | |
| | | | | | | | | Early satiety | 1.89 (1.47) | 1.47 (1.44) | |
| | | | | | | | | Bloating | 1.83 (1.58) | 2.03 (1.58) | |
| | | | | | | | | Post-prandial fullness | 1.44 (1.38)* | 1.64 (1.46)* | |
| | | | | | | | | Epigastric pain | 1.31 (1.37) | 1.28 (1.41) | |
| | | | Gastric retention | 75.5% at 2hrs<br>46.5% at 4hrs | | | | Epigastric burning | 0.92 (1.18) | 1.03 (1.34) | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| REF ID: MCCALLUM 2010B | | to continue through the study.<br><br>Exclusion criteria:<br>Diagnosis of any underlying illness that affects GI motility<br>Current primary disorders such as psychogenic vomiting, eating disorder or swallowing disorder<br>Previous gastric surgery for total or partial gastric resection, fundoplication, and vagotomy<br>Daily narcotic analgesia for abdominal pain<br>Drug or alcohol dependency within past 12 months<br>Life expectancy <1 year<br>Patients with other implantable | Mean HbA1c | 7.95% (range 4.6 – 12.4) | months to allow for recovery from the surgery. | | | TSS | 12.5 (7.10) | 11.89 (7.48) | Powered study.<br>Not ITT analysis<br>Drop-outs: N<20% |
| | | | All patients had delayed gastric emptying | | | | | Frequency symptom score: 0 = absent, 4 = extremely frequent (≥7 per week).<br>Total symptom frequency score (TSS) = sum of all individual symptoms | | | |
| | | | Drop-outs :<br>n=6 (13%) | | | | | Severity symptom scores, mean (SD) *=SS difference between gps | | | |
| | | | | | | | | Vomiting | 2.06 (1.26) | 1.64 (1.27) | |
| | | | | | | | | Nausea | 2.44 (1.30) | 2.03 (1.30) | |
| | | | | | | | | Early satiety | 1.39 (1.20) | 1.11 (1.06) | |
| | | | | | | | | Bloating | 1.39 (1.29) | 1.53 (1.25) | |
| | | | | | | | | Post-prandial fullness | 1.36 (1.29) | 1.33 (1.20) | |
| | | | | | | | | Epigastric pain | 1.25 (1.38) | 1.25 (1.36) | |
| | | | | | | | | Epigastric burning | 1.00 (1.29) | 0.92 (1.25) | |
| | | | | | | | | TSS | 10.89 | 9.81 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | neurostimulators, pacemakers or defibrillators<br>Pregnant<br>Planning to receive diathermy treatment<br>Undergone radiation treatment of upper abdomen<br>Planning on having MRI | | | | | | (6.73) | (6.47) | |
| | | | | | | | Severity symptom score: 0 = absent, 4 = extremely severe (requiring bed rest)<br>Total symptom severity score (TSS) = sum of all individual symptoms | | | |
| | | | | | **Data has also been reported for 12 month follow-up (ie. All on treatment for 4.5 months)**<br>12 months data shows:<br>• SS improvement from baseline for: in-hospital days, Frequency symptom score, severity symptom score, SF-36, % gastric retention at 2hrs and 4hrs.<br>• NS difference for: BMI, HbA1c, weekly hypoglycaemic attack | | | | | |

**Table 330: PATTERSON 1999 (RCT)[123]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| D. | RCT | n=95 with type | | Domperidone | Metaclopramide | 4 weeks | | DOM | METO | Funding: |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patterson, T. Abell, R. Rothstein, K. Koch, and J. Barnett. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am.J.Gastroenterol. 94 (5):1230-1234, 1999.<br><br>REF ID: PATTERSON 1999 | 5 Centres, USA | 1 diabetes with Gastroparesis<br><br>Inclusion criteria:<br>• Age ≥18 years<br>• Type 1 diabetes and at least 3 months of 2 gastroparesis symptoms<br>• TSS severity of 4 symptoms (nausea, vomiting, bloating/distention, early satiety) had to be at least 5/12.<br><br>Exclusion criteria:<br>• GI tract cancer or major illnesses<br>• Receiving | Age, years; median (range) | 39 (19-69) | n=48<br>20 mg (4 times a day)<br><br>BOTH GROUPS:<br>Insulin treatment details not given | n=45<br>10 mg (4 x/day)<br><br>Placebo tablet also taken as there were less tablets required for metocopramide than there were for domperidone.<br><br>BOTH GROUPS:<br>Tablets taken 15-30 minutes before meals and at bedtime.<br>Medications that could mask the effect of study drugs were not permitted during study. Other drugs affecting GI system were discouraged. | | | | | Janssen Research Foundation.<br><br>Risk of bias:<br>Randomisation = details not given – just says randomised.<br>Allocation concealment = not mentioned.<br>Blinding = double<br>No mention of powering.<br>Not ITT analysis<br>Drop-outs: N<20% (19%) |
| | | | HbA1c %, mean (range) | Not reported | | | | 4 symptoms: nausea, vomiting, bloating/distention, early satiety | | | |
| | | | Male/ female | 33/62 | | | | | | | |
| | | | Symptom severity | Comparable in both groups | | | | Individual symptoms | NS difference between the treatment groups. | | |
| | | | Weight, kg; median (range) | 68.2 (41-122) | | | | TSS severity score: 4 symptoms (out of 12) | DOM: 4.71 (0.46); 41% reduction | METO: 5.09 (0.5); 38.9% reduction | |
| | | | TSS severity score – 4 symptoms (out of 12) | DOM: 8.0 (0.32)<br>MET: 8.33 (0.29) | | | | | | | |
| | | | Drop-outs/missing data: n=18 (Of these, 6 dom and 10 meto discontinued treatment prematurely). n=9 patients discontinued | | | | | | | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | dialysis<br>• Undergone prior gastric surgery<br>• Receiving illicit drugs<br>• Received either study drug in past 30 days<br>• Pregnant or likely to become pregnant. | due to AEs (most patients was due to adverse CNS effects).; n=3 dom, and n=6 meto. | | | | | | | |

**Table 331: SHARMA 2011 (before-after study)[144]**

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| D. Sharma, G. Morrison, F. Joseph, T. S. Purewal, and P. J. Weston. The role of continuous | Prospective, case-series<br><br>2 Centres, UK | n=26 with type 1 diabetes with Gastroparesis<br><br>• Inclusion criteria:<br>• Type 1 diabetes with gastroparesis | | | CSII pump therapy<br><br>Initiated using flat basal rate to provide 24hr insulin delivery; then tailored to individual. | N/A<br><br>Pre-CSII, patients were on MDI. | 12 months after starting CSII | | Baseline | 12 months | Funding: None reported.<br><br>Risk of bias:<br>NO NICE CHECK LIST |
| | | | Age, years; mean (range) | 38.4 (24-53) | | | | Weight gain, mean kg | 2.9 kg at 6 months | | |
| | | | HbA1c %, mean | 9.9 (6 - 15.3) | | | | BMI reduction, | -1.0 kg/m$^2$ at 6 months | | |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| subcutaneous insulin infusion therapy in patients with diabetic gastroparesis. Diabetologia 54 (11):2768-2770, 2011.<br><br>REF ID: SHARMA 2011 | | • Managed previously with MDI then CSII<br>• Gastroparesis Diagnosis based on symptoms (delayed gastric emptying by scintigraphy<br><br>Exclusion criteria:<br>Structural abnormalities that may cause similar symptoms (as observed by ultrasound and oesophagogastroduodenoscopy). | (range) | | Boluses delivered to cover each meal. Boluses given in extended form with extension times determined by composition of food, severity of symptoms and the results of the gastric emptying studies. As symptoms improved, bolus doses for carbs were modified by shortening the extension times or by adopting a multi-wave delivery whereby 10% of the total insulin dose was infused as 1st-phase insulin. | | | mean kg/m$^2$ | | | |
| | | | Male/ female | 2/24 | | | | | | | |
| | | | Diabetes duration | 21 (8-34) | | | | HbA1c, % median (range) | SS improvement: 8.0% (5.6-14.3%) vs. 9.8% (6-15.3%); p<0.05 | | |
| | | | BMI, kg/m$^2$, mean (range) | 23.9 (16-33) | | | | Hospital admission related to gastroparesis – inpatient bed days; median days/patients/year (range) | 8.5 (0-144) | 0 (0-15) days<br><br>P<0.05 | |
| | | | Weight, kg, mean (range) | 65.4 (42-99) | | | | | | | |

**Table 332: SILVERS 1998[146]**

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D. Silvers, M. Kipnes, V. Broadstone, D. Patterson, E. M. M. Quigley, R. Mccallum, N. K. Leidy, C. Farup, Y. Liu, and A. Joslyn. Domperidone in the management of symptoms of diabetic Gastroparesis: Efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. Clin.Ther. | Multicentre two-phase (single-masked phase and double masked phase) withdrawal study. Single masked phase not randomised. Double masked phase randomised. | Double masked RCT n=208<br><br>(n=105 Domperidone; n=103 placebo)<br><br>Inclusion criteria:<br>• Type 1 diabetes, be between 18 and 70 years<br>• Able to take oral medication and have experienced symptoms suggestive of Gastroparesis for at least 6 months | | Domperidone n=105 | Placebo n=103 | Double masked 4-week phase: Domperidone (two 10-mg tablets) four times daily<br><br>Only patients (from the single non-randomised phase) whose total symptom score had improved were eligible for entry into the second phase (double masked phase) of the study.<br><br>Patients receiving cisapride or metoclopramide were required to undergo a | Double masked 4-week phase: Placebo (two identical dummy tablets) four times daily | 4 weeks | Double masked phase | Domperidone | Placebo | Funding: support provided by Janssen Research Foundation, Titusville, New Jersey<br><br>Risk of bias:<br>Wash-out period = 1 week<br>Randomisation = unclear (as details not given)<br>Allocation concealment = not reported<br>Blinding = double (but details not given)<br>ITT analysis: details not given<br>Powered study. 93 per |
| | | | Age, years; mean (SD) | 45 (SD 12.6) | 45.3 (SD 11.9) | | | | Quality of Life (QoL) – *SF36: physical component scale (PCS); mean (SD) | 0.65 (SD 0.75) n=104 | -1.77 (SD 0.75) n=99 | |
| | | | Male/ female, (%) | 34/71 | 31.1/68.9 | | | | Quality of Life (QoL) – *SF36: mental component scale (MCS) | -1.08 (SD 1.13) n=104 | -0.96 (SD 0.89) n=99 | |
| | | | History of gastroparetic symptoms, years; mean (SD) | 3.5 (SD 3.6) | 4.3 (SD 5.4) | | | | | | | |
| | | | Smokers, % | 32.4% | 17.5% | | | | Mean change in **total symptom scores | 0.1 | 0.94 | |
| | | | Diabete | | | | | | Mean | 0.03 | 0.32 | |

| Reference | Study type | Number of patients | Patient characteristics | | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 (3):438-453, 1998.<br><br>REF ID: SILVERS 1998 | | Exclusion criteria:<br>• Gastric surgery (including vagotomy) before study entry<br>• History of cancer of the gastrointestinal tract or abdominal radiotherapy<br>• Previous (within the past 30 days) or planned concurrent use of an investigational drug<br>• Previous participation in a study involving domperido | s, mean years (SD) | | | washout period of 1 week before enrolment. | | | change in nausea | | | treatment group to detect a difference of 30% at the end of double masked treatment phase at an α level of 0.05 and 80% power<br>Drop-outs = none mentioned<br>All patients underwent scintigraphy to evaluate to evaluate their gastric-emptying status within 4 weeks of enrolment |
| | | | | | | | | | Mean change in early satiety | -0.04 | 0.19 | |
| | | | | | | | | | Adverse events | 63 n=105 | 65 n=103 | |
| | | | | | | | | | Vomiting (%) | 0 n=105 | 5 (4.9) n=103 | |
| | | | Patients were required to have a minimum symptom severity score of 2 (moderate) on a scale of 0-3 for each of nausea, abdominal distension/bloating, early satiety, vomiting, and abdominal pain. Their combined total symptom severity score (sum of the 5 individual symptom scores) had to be ≥8 (out of a possible 15) for entry into the first phase of the study.<br>For entry into the second phase, patients were required to have a total | | | | | | *SF36 consists of 36 items across 8 domains that can be reduced to 2 indexes –the physical and mental component summaries (PCS and MCS respectively).<br>**Total symptom score calculated by totalling the severity scores of the five individual symptoms of Gastroparesis. Responses were rated on a scale of 0 to 3, in which 0 = none; 1 = mild (awareness of a sign or symptom, symptoms easily tolerated); 2 = moderate (enough discomfort to interfere with usual activities); or 3 = severe (incapacitating | | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | ne or a compassionate clearance program, and dialysis for renal failure<br>• Pregnancy or child bearing potential<br>• Severe cardiac disease | symptom score of ≤6 at the end of the first phase and a decrease (improvement) in their total severity score of ≥5 units from the baseline visit.<br><br>NS differences were found between the domperidone and placebo groups at the selection visit, except in smoking behaviour: more patients randomised to domperidone (32.4%) were smokers compared with those randomised to placebo (17.5%)<br><br>Drop-outs :<br>None mentioned | | | | symptoms, inability to work or engage in usual activities). | | |

**Table 333: VANDERVOORT 2005 (before-after study)[160]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| I. R. van der Voort, J. C. Becker, K. H. Dietl, J. | A prospective case series | n=17 with type 1 diabetes with Gastroparesis refractory to | Eight type 1 diabetes who had failed standard therapy were enrolled | All included patients received an electrical | N/A | 12 months | | Baseline | 12 months | Funding: supported by Medtronic Europe, |

| Reference | Study type | Number of patients | Patient characteristics | | Intervention | Comparison | Length of follow-up | Outcome measures | Effect sizes | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| W. Konturek, W. Domschke, and T. Pohle. Gastric electrical stimulation results in improved metabolic control in diabetic patients suffering from Gastroparesis. Exp.Clin.Endocrinol.Diabetes 113 (1):38-42, 2005.<br><br>REF ID: VANDERVOORT 2005 | single centre study | conventional medical therapy.<br>Prior to entry, upper GI ENDOSCOPY was performed to exclude mechanical causes of gastric outlet obstruction.<br><br>Inclusion criteria:<br>• Details not given<br>Exclusion criteria:<br>• Patients with intestinal pseudo-obstruction<br>• Primary swallowing disorders<br>• Seizures<br>• Psychogenic vomiting<br>• Pregnancy<br>• Previous surgery to the stomach, pylorus, or small bowel<br>• Vagotomy<br>• Organ transplantation | Age, years; range | 25-73 years | stimulation system consisting of a stimulator (Itrel 3, Model 7425, Medtronic Kerkrade, the Netherlands)and two unipolar intramuscular electrodes | | | Weekly vomiting frequency; mean (range) | 26 (19-41) | 4 (0-13)* | Tolochenaz, Switzerland<br><br>Risk of bias:<br>NO NICE CHECK LIST |
| | | | | | | | | Weekly nausea frequency; mean (range) | 34 (21-49) | 12 (2-20) | |
| | | | Male/ female, | 5/12 | | | | HbA1c (%) | Significantly reduced at 6 months and 12 months compared to baseline values. Compared to baseline, the mean value improved by 28% at 6 months and 24% at 12 months.<br>Prior to implantation of the device, no patient had presented with HbA1c values of less than 7.5% | | |
| | | | Diabetes duration | At least 10 years | | | | Hospital admission | Not reported | | |
| | | | HbA1c (%) | not given | | | | Severe hypoglycaemia | Not reported | | |

## G.11.1 Acute painful neuropathy

**Table 334: Gibbons 2010[54]**

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| Gibbons C. H., Freeman R. Treatment induced diabetic neuropathy – a reversible painful autonomic neuropathy. Ann Neurol: 67(4): 534-541. 2010 | Prospective case-series<br><br>Setting: US | n=16 (Type 1 diabetes n=9)<br>Inclusion criteria:<br>• Acute painful neuropathy after rapid and sustained glycaemic control | For type 1 diabetes only n=9:<br><br>HbA1c = 15.5 (1.3)%<br>HbA1c after intensive BG control, baseline before treatment = 6.4(0.6)%<br><br>Age = 24.9 (3.3)<br><br>Female% = 78%<br><br>Duration of type 1 diabetes = 9.6 (2.3) years<br><br>Initial pain score (following | Medications to reduce neuropathic pain, all patients on different treatments (alone or in combination):<br>Anti-epileptics (gabapentic, pregabalin, lamotrigine or topiramate)<br>TCAs (amitriptyline, nortriptyline or desipramine)<br>Tramadol<br>Methadone<br><br>Anti-epileptics + TCA + Tramadol n=2<br>Anti-epileptics + TCA n=1<br>Anti-epileptics | 18 months or more | Duration of treatment for a 50% reduction in pain[a] | 15 months (range 12-28) | Funding:<br>Juvenile Diabetes Research Foundation<br><br>Risk of bias:<br>Study design – case series<br>IENFDL outcome data only available for 6/9 type 1 diabetes patients and FU only available in 3/6 patients<br>7/9 patients had a remote history of diabetic anorexia and other 2 subjects had historically poor BG control due to treatment non-compliance<br>All patients experienced life event causing them to radically improve BG control |
| | | | | | | Pain, 0-10 Likert scale, 0=no pain; 10=worst pain imaginable) [a] | Baseline, mean (SD) = 10 (0)<br>Follow-up: 7-9 | |
| | | | | | | Retinopathy, no. of patients[a] | Baseline: 7/16<br>6 months of sustained BG control: 16/16 | |
| | | | | | | Microalbinuria, number of patients[a] | Baseline: 8/16<br>1 year: 13/16 | |
| | | | | | | Neuropathy impairment score in lower limb (NIS-LL; muscle strength graded as normal, zero, to max score of 64 if paraplegic, reflexes graded zero to 8 and sensation graded 0 to 16)[b] | Baseline: 5.1(1.4)<br>1 year: 5.3 (1.3) reported NS | |
| | | | | | | Autonomic symptoms (11 point Likert scale; (0=no symptoms; 10=severe symptoms), baseline vs. 18 months[b] | SS improvement reported in the following scores: orthostatic lightheadedness, orthostatic dizziness, pre-syncope, syncope, orthostatic symptoms | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | intensive BG control), 0-10 likert scale = 10 (0) | + SNRI n=1<br>Anti-epileptics + SNRI + tramadol n=2<br>Anti-epileptics + tramadol n=1<br>Anti-epileptics + SNRI + methadone n=1<br>SNRI + tramadol n=1 | | | worse with standing, nausea, vomiting, diarrhoea, early satiety<br>NS difference reported in the following scores:<br>Orthostatic symptoms after meals, loss of appetite, urinary frequency, nocturia, hyperhidrosis, anhidrosis, erectile dysfunction. | |
| | | | | | | Autonomic dysfunction* | Abnormal HR response deep breathing<br>Baseline: 69%<br>18 months: 48%<br>Abnormal inspiratory-expiratory ratio<br>Baseline: 62%<br>18 months: 19%<br>Valsalva ratio<br>Baseline: 56%<br>18 months: 43%<br>Orthostatic hypotension<br>Baseline: 69%<br>18 months: 31% | |
| | | | | | | Intra-epidermal nerve fibre density distal leg (IENFDL), number of patients with normative values | Baseline: 0<br>One year: 1 | |

| Reference | Study type | Number of patients | Patient characteristics | Intervention | Length of follow-up | Outcome measures | Effect sizes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | (reported in 6 type 1 diabetes patients, outcome data NA at 1 year for 3 patients)** | | |

*(a) Data from mixed population of type 1 diabetes and type 2 diabetes*
*(b) Data from type 1 diabetes subgroup analysis*

## G.11.2 Thyroid disease – frequency of monitoring

### G.11.2.1 Prevalence of thyroid disease in type 1 diabetes patients

**Table 335: Allen 2008**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Allen S, Huber J, Devendra D. Prevalence of organ-specific autoantibodies in childhood and adult onset type 1 diabetes. Immunology of Diabetes. 2008; 1150:260-262.<br><br>Ref ID: ALLEN 2008 | Cross-sectional<br><br>prevalence study conducted over 5 years from 2001 to 2006<br>Records from 5 NHS trust diabetic clinics in the UK | Number of patients<br>Total number of patients who attended diabetic clinics from 2001 to 2006 was 599, of which 271 were excluded as part of exclusion in inclusion criteria<br>Inclusion criteria:<br>• Adults 16 years and above<br>• Exclusion criteria:<br>• If multiple organ-specific antibodies tested for on separate occasions<br>• If organ specific | | | Thyroid peroxidase autoantibodies (TPO)<br><br>Thyroid receptor autoantibodies (TRABs)<br><br>Information on test type or threshold for positive/negative result not reported | Thyroid disease<br><br>Prevalence of type 1 diabetes patients with positive antibodies to: TPO=11.5% (13/113) and TRAB=9.1% (5/55) in adult onset<br><br>Prevalence of type 1 diabetes patients with positive antibodies to TPO=11.8% (11/93) and TRAB=1.9% (1/54) in childhood onset |
| | | | Number of patients | n=180/328 type 1 diabetes adults | | |
| | | | Age (years), mean (SD) | Median age at onset diabetes:18 years | | |
| | | | Gender (m/f) | Not reported | | |
| | | | Duration of diabetes (years), mean (SD) | Reported as median of 21 (75%CI12-27) | | |
| | | | HbA1c (%) | Not measured | | |
| | | | BMI (kg/m$^2$), mean (SD) | Not measured | | |
| | | | Treatment | | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | antibodies were measured after the diagnosis of an autoimmune condition was confirmed | subgroups | | | |
| | | | Diabetes control | | | |

**Table 336: Bianchi 1995**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Bianchi G, Montanari P, Fabbri A, Gamberini A, Zoli M, Marchesini. Thyroid volume in type 1 diabetes patients without overt thyroid disease. Acta Diabetologica. 1995; 32:49-52.<br><br>Ref ID: BIANCHI 1995 | Cross-sectional prevalence study<br><br>Patients admitted to hospital<br>In Italy, but setting not reported | Inclusion criteria:<br>45 patients with type 1 diabetes with no history of previous thyroid disorders/and or use of drugs known to affect thyroid homeostasis<br>Exclusion criteria:<br>• Not reported | | | fT3 (pmol/litre)<br>fT4 (pmol/litre)<br>TSH (mU/litre)<br><br>Normal values for TSH: 0.4-3.5 mU/litre<br>Normal values for fT3: 4.0-8.9pmol/litre<br>Normal values for fT4:9.0-23.0pmol/litre<br><br>Positive titres for anti-microsome antibodies:>50U/ml<br>Positive titres for anti-thyroglobulin:>100U/ml | Thyroid disease<br>Prevalence of anti-microsomal antibodies: 33%<br>Prevalence of anti-thyroglobulin antibodies: 16% |
| | | | Number of patients | n=45 type 1 diabetes adults | | |
| | | | Age (years), mean (SD) | 16-68 (median 40 years) | | |
| | | | Gender (m/f) | 20m/25f | | |
| | | | Duration of diabetes (years), mean (SD) | All type 1 diabetes patients, but duration of diabetes not reported | | |
| | | | HbA1c (%) | 8.9% (SD 1.8%, range 5.1% to 12%) | | |
| | | | BMI (kg/m$^2$), mean (SD) | Not reported | | |
| | | | Diabetes | diabetic ketosis or for | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | | control | evaluation and treatment of complications of diabetic disease | | |

**Table 337: CARDOSO 1995**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Cardosa C, Ohwovoriole AE, KuKu SF. A study of thyroid function and prevalence of thyroid autoantibodies in an African diabetic population | Cross-sectional prevalence study<br>Lagos university teaching hospital, NIgeria and Eko hospital, Lagos, Nigeria | 40 consecutive insulin-treated diabetic patients (attending clinics at hospital?)<br>Exclusion criteria:<br>• Not reported | | | T3 (0.8ng/ml)<br>T4 (50-138ng/ml)<br>TSH(0.6-6.0ng/ml)<br>Serum thyroid autoantibodies:<br>Significantly positive thyroid microsomal antibodies:≥50IU/ml<br>Significantly positive thyroglobulin antibodies:≥100IU/ml | Thyroid disease/function<br>Subclinical hypothyroidism<br><br>Prevalence of thyroid autoantibody positivity in type 1 diabetes patients was 46.6% (13/28) |
| | | | Number of patients | n=28 adults with type 1 diabetes | | |
| | | | Age (years), mean (SD) | 36.46 years (SEM 2.10) | | |
| | | | Gender (m/f) | 12m:16f | | |
| | | | Duration of diabetes (years), mean (SD) | 12.69 years (SEM 1.90) | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI ($kg/m^2$), mean (SD) | Not reported | | |
| | | | Treatment subgroups | Subclinical hypothyroidism | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | | Diabetes control | 29/40 patients had fairly good control, 11/40 had poor control, but authors do not specify whether type 1 diabetes patients | | |

**Table 338: DAGDELEN 2009**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Dagdelen S, Hascelik G, Bayraktar M. Simultaneous triple organ specific autoantibody profiling in adult patients with type 1 diabetes mellitus and their first-degree relatives. International Journal of Clinical Practice. 2009;63(3):449-456. | Cross-sectional matched case-control/prevalence study<br>Patients visiting adult outpatient endocrinology and metabolism department at a tertiary university hospital between 2002 and 2004 | Inclusion criteria:<br>Patients with type 1 diabetes with onset below 35 years and an interval of <3 years between diabetes onset and insulin requirement, and body mass index, patients with past or present seropositivity for GAD antibodies, IA2, anti-islet or anti-insulin | | | T3<br>T4<br>TSH<br>Serum thyroid autoantibodies:<br>Significantly positive thyroid microsomal antibodies:≥50IU/ml<br>Significantly positive thyroglobulin antibodies:≥100IU/ml | Thyroid disease/function<br>Subclinical hypothyroidism<br><br>Prevalence of thyroid autoantibody positivity in type 1 diabetes patients was 46.6% (13/28) |
| | | | Number of patients | n=65 adults with type 1 diabetes | | |
| | | | Age (years), mean (SD) | 29.2 (+/-9.4) | | |
| | | | Gender (m/f) | 52% male:48% female | | |
| | | | Duration of diabetes (years), mean (SD) | 9.8 years (+/-8.3) | | |
| | | | HbA1c (%) | 7.4 (+/-1.4) | | |
| | | | BMI ($kg/m^2$), mean (SD) | <25$kg/m^2$ | | |
| | | | Treatmen | N/A | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Ref ID:DAGDELEN 2009 | | autoantibodies without acanthosis nigricans<br><br>Exclusion criteria:<br>Age <18 years, duration of diabetes <2 years, secondary diabetes or pancreatic insufficiency and presence of selective immunoglobuli n A deficiency | t subgroups | | | |
| | | | Diabetes control | | | |

**Table 339: DUFAITRE 2006**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Dufaitre-Patouraux L, Riveline JP, Renard E, Melki V, Belicar-Schaepelynck | Cross-sectional prevalence study, 14 EVADIAC centres, comparative | Inclusion criteria:<br>275 Male or female patients between ages 18-70 years already treated | | | LT4 treatment and presence of anti-TPO antibodies to determine hypothyroidism<br><br>Grave's disease was | At time of inclusion (T0):<br>• prevalence of Hashimoto's disease in CIPII patients=8.4% (13/154) vs. 7.4% (9/121) CSII treated patients<br>• prevalence of Grave's disease in CIPII patients=1.3% (2/154) vs. 2.4% (3/121) CSII patients |
| | | | Number of patients | n= patients with type 1 diabetes, 139 patients in the CIPII group and 108 patients in the CSII group | | |
| | | | Age (years), | CIPII group=47±10.2 | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| P, Selam JL et al. Continuous intraperitoneal insulin infusion does not increase the risk of organ-specific autoimmune disease in type 1 diabetic patients: results of a multicentric, comparative study. Diabetes and Metabolism. 2006; 32(5 Patient 1):427-432. Ref ID:DUFAITRE 2006 | study in France to determine whether implanted pumps enhance the frequency of autoimmune diseases. | by CIPII or CSII for C-peptide negative type 1 diabetes<br><br>Exclusion criteria: Patients presenting clinical thyroid autoimmune disease at the time of inclusion to study | mean (SD) | years<br>CSII group=46.3±11.2 years | determined by history of treatment for hyperthyroidism and presence of anti-TSH binding inhibitor or anti-TPOab<br><br>Subclinical diseases were defined by the presence of antiTPOab with normal T3 and T4 for thyroiditis<br><br>For TSH measurement:<br>Normal thyroid function=0.4-4mU/litre<br><br>Hyperthyroidism=4-20mU/litre<br><br>Hypothyroidism=>20 mU/litre<br><br>Threshold for positive anti-TPOab=60U/litre | Prevalence of subclinical autoimmune disease by measurement of anti-TPOab:<br>25.9% (36/139) CIPII patients vs. 30.6% (33/108) CSII patients<br><br>Total study group prevalence of thyroid autoimmune disease =9.8% for clinical disease and 28% for subclinical disease<br><br>No new case of autoimmune disease recorded at T1 (1 year after inclusion) |
| | | | Gender (m/f) | 79m:75f | | |
| | | | Duration of diabetes (years), mean (SD) | CIPII group=24.8±10.2 years<br>CSII group=24.8±10.2 years | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI (kg/m$^2$), mean (SD) | Not reported | | |
| | | | Treatment subgroups | | | |
| | | | Diabetes | | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | | control | | | |

**Table 340: FIALKOW 1975**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Fialkow PJ, Zavala C, Nielsen R. Thyroid autoimmunity: increased frequency in relatives of insulin-dependent diabetes patients. Annals of Internal Medicine. 1975; 83(2):170-176.<br>Ref ID FIALKOW 1975 | Cross-sectional prevalence<br><br>Patients were assessed from the diabetes instruction classes of the metabolic section at Mason clinic (private practice) in Seattle, USA | Inclusion criteria:<br>Type 1 diabetes patients (male and female) between ages 30 and 45 years and followed up for two years after the study was initiated for insulin status<br><br>Exclusion criteria:<br>Patients below 20 years age | | | Antibodies to thyroid globulin (TGab) and thyroid microsomal antibodies (TPO) were determined by tanned red cell agglutination and indirect immunofluorescence | Prevalence of thyroid antibodies in type 1 diabetes patients=35% (18/52)<br><br>Prevalence of type 1 diabetes patients with Graves' disease= 1.9% (1/52)<br><br>Prevalence of type 1 diabetes patients with surgery/goitre=1.9% (1/52)<br>In the age group 20-30, 18/30 patients tested positive for thyroid antibodies. 7/30= TPO+ (low titre), 4/30= TPO+ (high titre), 5/30=TGab+ (low titre), 2/30=TGab+ (high titre)<br><br>In the age group 40-59, 22 patients tested positive for thyroid antibodies. 2/22=<br><br>Frequencies of antibodies to thyroglobulin and to thyroid cytoplasm were equally elevated in type 1 diabetes patients<br><br>Presence of antibodies was not correlated significantly with duration of disease or of insulin therapy (P>0.1) |
| | | | Number of patients | 52 adults with type 1 diabetes | | |
| | | | Age (years), mean (SD) | 37.6 | | |
| | | | Gender (m/f) | 26m:26f | | |
| | | | Duration of diabetes (years), mean (SD) | Not reported | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI ($kg/m^2$), mean (SD) | Not reported | | |
| | | | Treatmen | Age 20-39 | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | | t subgroups | Age 40-59 | | |
| | | | Diabetes control | Not reported | | |

**Table 341: GOMEZ 2003**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Gomez JM, Maravall FJ, Guma A, Abos R, Soler J, Fernandez-Castaner M. Thyroid volume as measured by ultrasonography in patients With type 1 diabetes mellitus without thyroid dysfunction. Hormone and Metabolic Research. 2003; 35(8):486-491. | Cross-sectional study in patients with type 1 diabetes attending an endocrine unit in Spain, younger than 40 years | Inclusion criteria:<br>36 patients with type 1 diabetes<br><br>Exclusion criteria:<br>Patients who had previous autoimmune thyroid dysfunction, or positive serum anti-thyroid peroxidase antibodies | | | TSH normal=<40 IU/ml | Basal TSH levels in males =1.6%±1.14 compared to control group=1.5%±0.78 (95%CI -0.56 to 0.41; P=0.76)<br><br>Basal TSH levels in females=1.69%±1.08 compared to control group=1.59%±0.96 (P=0.48) |
| | | | Number of patients | n=36 patients with type 1 diabetes | | |
| | | | Age (years), mean (SD) | 26.8±5.1 | | |
| | | | Gender (m/f) | Not reported | | |
| | | | Duration of diabetes (years), mean (SD) | Newly diagnosed diabetes | | |
| | | | HbA1c (%) | 6.6±1.4 (baseline) | | |
| | | | BMI ($kg/m^2$), mean (SD) | M:24.6±2.8<br>F:24.9±3.48 | | |
| | | | Treatment subgroups | N/A | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Ref ID GOMEZ2003 | | | Diabetes control | Insulin requirement =0.65±0.25U/kg | | |

**Table 342: Hanukoglu 2003**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Hanakoglu A, Mirachi A, Dalal L, Admoni O, Rakover Y, Bistritzer Z, Levine A, Somekh E, Lehmann D, Tuval M, Boaz M, Golander A. Extrapancreatic autoimmune manifestations in type 1 diabetes patients and their first-degree relatives. Diabetes care. 2003; 26(4):1235-1240<br>REF ID: HANUKOGLU 2003 | Cross-sectional study of young patients with type 1 diabetes and their first degree relatives in a multicentre study in Israel | Inclusion criteria:<br>Type 1 diabetic patients who were diagnosed before the age of 18 years and first degree relatives and a group of healthy subjects with no history of autoimmune disease served as a control group | | | Thyroid antibodies directed to thyroglobulin (TG) and to microsomal antigens (TG and TPO) were determined by enzyme linked immunosorbent assay. TG and TPO titres<br><br>1/180 and 1/80, respectively, were considered diagnostic for autoimmune thyroid disease. In all patients screened for thyroid antibodies, free T4 and thyrotropin concentrations were also determined. | The prevalence of autoimmune thyroid disease as determined by positive TPO and/or TG antibody rates among type 1 diabetes probands was 27%, with 6% of those being hypothyroid<br><br>The corresponding rates among screened first-degree relatives (positive TPO and/or TG 25%, hypothyroid Hashimoto disease 8%) did not significantly differ from the rates found in probands, but were significantly higher than rates in control subjects<br><br>The frequencies of positive TPO and TG antibodies alone and together were 18, 19, and 11%, respectively, in probands. The corresponding rates among first-degree relatives were quite similar (19, 17, and 10%, respectively)<br><br>The TPO titres in three control subjects were only slightly elevated (1/84, 1/118, and 1/98), whereas they were markedly elevated in most probands and family members (5-fold in 13 probands and 12 relatives and 2.5-fold in 3 probands |
| | | | Number of patients | Probands=109<br>Relatives screened=100<br>Relatives interviewed=312<br>Control subjects=78 | | |
| | | | Age (years), mean (SD) | Probands=9.4+/-4.2 )(at diagnosis)<br>Relatives screened=29+/-15.5<br>Relatives interviewed=29=/-16.4<br>Control subjects=14.9+/-10.4 | | |
| | | | Gender (m/f) | Probands=62/47<br>Relatives screened=42/58<br>Relatives interviewed=159/153<br>Control subjects=41/37 | | |
| | | | Duration of diabetes (years), mean (SD) | | | |
| | | | HbA1c (%) | | | |
| | | | BMI ($kg/m^2$), mean (SD) | | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | | | | | and 6 relatives)<br><br>In first degree relatives who were screened, medical history revealed pre-existing Hashimoto thyroiditis in five and Graves disease in one<br><br>The frequency of pre-existing autoimmune thyroiditis detected by interview only, was low (1%)<br><br>Probands with Hashimoto thyroiditis did not have more relatives with positive antibodies than probands with normal antibody titres. Among 50 probands whose relatives were screened, 12 probands with thyroiditis had 8 relatives with positive antibodies and 13 relatives with normal antibody titres. Among 13 probands without thyroiditis, the corresponding numbers were 16 (positive) and 17 (normal) relatives |
| | | | Treatment subgroups | | | |
| | | | Diabetes control | | | |

**Table 343: JIN 2011**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Jin P, Huang G, Lin J, Yang L, Xiang B, Zhou W et al. High titre of antiglutamic acid decarboxylase autoantibody is a strong predictor of the development of thyroid autoimmunity in patients with type 1 diabetes and latent autoimmune diabetes in adults. Clinical Endocrinology. 2011; 74(5):587-592.<br>Ref ID: JIN2011 | Cross-sectional study<br><br>Prevalence Study<br><br>setting: Second Xiangya Hospital of Central South University from January 2001 and December 2003 in China | Patients with type 1 diabetes and patients with LADA<br><br>Inclusion criteria:<br>LADA patients age of onset ≥30 years, persistently positive for GAD65Ab at least 1 year after diagnosis, no ketosis within the first 6 months of diagnosis, no insulin treatment within the first 6 months of the initial diagnosis<br><br>After 4 years follow-up, 184 patients with type 1 diabetes and 130 patients with | | | Anti-TPOab positivity=3.6<br>Anti-TGab positivity=3.0<br>Normal TSH range=0.35-5.5mU/litre<br>Normal T3 range=0.6-1.81nmol/litre<br>Normal T4 range=45-109 pmol/litre<br><br>Hypothyroidism=elevated TSH level (≥5.5mU/litre) with or without decreased serum thyroid hormone level<br>Hyperthyroidism=decreased serum thyroid hormone level with or without elevated thyroid hormone levels | • TGAb prevalence in type 1 diabetes=23.7% vs. 16.3% LADA<br>• TPOab prevalence in type 1 diabetes=24.7% vs. 18.5% LADA<br>• Overall prevalence of thyroid autoantibody= 27.4% in type 1 diabetes vs. 21.5% in LADA patients<br>• Prevalence of sub/clinical, hypo/hyperthyroidism= 9.5% in type 1 diabetes vs. 11.1% in LADA, with most having subclinical hypothyroidism<br><br>After 4 years follow-up:<br>• Prevalence of TGab=24.5% (45/184) in type 1 diabetes vs. 17.7% (23/130) in patients with LADA<br>• Prevalence of TPOab= 25.5% (47/184) in type 1 diabetes vs. 20.0% (26/130) in patients with LADA<br>• Prevalence of thyroid dysfunction=14.1% in type 1 diabetes vs. 15.3% in patients with LADA<br>• The prevalence of antibodies and thyroid dysfunction increased insignificantly during the 4 year follow-up<br>• Patients (95%) with positive thyroid antibodies tested positive at beginning of study and also during follow-up |
| | | | Number of patients | n=190 type 1 diabetes patients<br>n=135 LADA patients | | |
| | | | Age (years), mean (SD) | 24.9±14.1 years (type 1 diabetes)<br>49.6±12 years (LADA) | | |
| | | | Gender (m/f) | 110m:80f (type 1 diabetes)<br>79m:56f (LADA) | | |
| | | | Duration of diabetes (years), mean (SD) | 1.9±1.7 years (type 1 diabetes)<br>2.3±2.1 years (LADA) | | |
| | | | HbA1c (%) | Type 1 diabetes+Tab+=8.4±2.3<br>Type 1 diabetes+Tab-=8.2±2.1<br>LADA+Tab+=8.2±2.1<br>LADA+Tab-=8.1±2.4 | | |
| | | | BMI ($kg/m^2$), mean (SD) | Type 1 diabetes+Tab+=18.8±3.2<br>Type 1 diabetes+Tab-=19.7±3.4<br>LADA+Tab+=23.4±3.4<br>LADA+Tab-=22.8±3.1 | | |
| | | | Treatmen | | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | LADA were included. | t subgroups | | | |
| | | | Diabetes control | Not reported | | |

**Table 344: JUNIK 2006**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Junik R, Kozinski M, Debska-Kozinska K. Thyroid ultrasound in diabetic patients without overt thyroid disease. Acta Radiologica. 2006; 47(7):687-691.<br>Ref ID JUNIK2006 | Cross-sectional study/prevalence<br><br>Patients were referred to the department of endocrinology and diabetology at Nicolaus Copernicus university, Poland | 98 patients with diabetes mellitus | | | TSH (thyrotropin) normal range=0.35mIU/litre -4.94mIU/litre<br><br>FT3 normal range=1.71-3.71pg/ml<br><br>FT4 normal range =0.7-1.48ng/dl | Subclinical hyperthyroidism=7% (2/30)<br><br>Subclinical hypothyroidism=3% (1/30)<br><br>TSH levels in patients was within normal range (0.97 (0.61-1.58) mIU/litre) |
| | | | Number of patients | n=30 patients with type 1 diabetes | | |
| | | | Age (years), (median) | Median 43 (range 28-50) | | |
| | | | Gender (m/f) | 12m:18f | | |
| | | | Duration of diabetes (years), mean (SD) | Not reported | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI ($kg/m^2$), mean (SD) | Not reported | | |
| | | | Treatment | Subclinical hyperthyroidism | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | | subgroups | Subclinical hypothyroidism | | |
| | | | Diabetes control | Poorly controlled diabetes | | |

**Table 345: KUCERA 2003**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Kucera P, Novakova D, Behanova M, Novak J, Tlaskalova-Hogenova H, Andel M. Gliadin, endomysial and thyroid antibodies in patients with latent autoimmune diabetes of adults (LADA). Clinical and Experimental Immunology. | Cross-sectional/prevalence study<br>Patients selected from the epidemiological study of the diabetes centre at the 3rd medical faculty, Charles university, and also from several out-patient diabetes clinics in Prague and | Consecutive sera from 158 diabetic LADA (type 1 diabetes) or type 2 diabetes patients | | | TPOab<br>TGab<br><br>Normal or positive thresholds not reported | • Positive TPOab=22.1%(15/68)<br>• Positive TGab=8.82%(6/68) |
| | | | Number of patients | Group A=68 LADA (type 1 diabetes) patients | | |
| | | | Age (years), mean (SD) | 64.4±10.0 | | |
| | | | Gender (m/f) | 29m:39f | | |
| | | | Duration of diabetes (years), mean (SD) | 10.6±7.6 | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI ($kg/m^2$), mean (SD) | Not reported | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| 2003; 133(1):139-143.<br><br>Ref ID: KUCERA 2003 | Melnik | | Treatment subgroups | Not reported | | |
| | | | Diabetes control | Not reported | | |

**Table 346: LUPI 2013**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Lupi I, Raffaelli V, Di CG, Caturegli P, Manetti L, Ciccarone AM et al. Pituitary autoimmunity in patients with diabetes mellitus and other endocrine disorders. Journal of Endocrinological Investigation. 2013; 36(2):127-131. | Cross-sectional study/prevalence<br>Patients were evaluated from 2009 to 2011 in the department of endocrinology and metabolism at the university of Pisa, Italy | 111 patients with type 1 diabetes | | | FT4 (normal=7-17 pg/ml)<br>FT3 (normal=2.7-5.7 pg/ml)<br>TSH (normal=0.4-3.4 µU/ml)<br>TPOab (normal=<10U/ml)<br>TGab (normal=<30U/ml)<br>TSHreceptor(normal=<2 U/litre) | • 40.5% (45/111) type 1 diabetes patients found to have one or more autoimmune diseases<br>• Prevalence of Hashimoto's disease =31.5% (35/111)<br>• Prevalence of Grave's disease=6.3% (7/111) |
| | | | Number of patients | n=111 patients with type 1 diabetes previously on multiple dose insulin therapy | | |
| | | | Age (years), mean (SD) | 38.7±1.3 | | |
| | | | Gender (m/f) | 44m:67f | | |
| | | | Duration of diabetes (years), mean (SD) | 28.3±1.19 | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI ($kg/m^2$), mean (SD) | $25kg/m^2$ | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | | Treatment subgroups | | | |
| | | | Diabetes control | Not reported | | |

**Table 347: PALMA 2013**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Palma CCSS, Pavesi M, Nogueira VG, Clemente ELS, Vasconcellos MDFB, Pereira LC et al. Prevalence of thyroid dysfunction in patients with diabetes mellitus. Diabetology and Metabolic Syndrome. 2013; 5(1).<br>Ref ID:PALMA 2013 | Cross-sectional study/prevalence<br><br>Patients were recruited from the out-patient clinic of the unit of diabetes at hospital universitario Pedro Ernesto, Rio de Jeneiro, Brazil | 386 patients (type 1 diabetes and type 2 diabetes) regularly attending the out-patient clinic<br>Inclusion criteria:<br>Duration of diabetes mellitus longer than one year for those with type 1 diabetes<br>Diagnosis was based on clinical | | | Anti-TPOab=<34IU/ml, 3.4-7.6<br><br>FT4=0.93-1.7 ng/dl, 1.8-3.0<br><br>TSH=0.27-4.20µg/Ul/ml<br><br>Thyroid dysfunction was classified as clinical hypothyroidism if TSH levels were >4.20µUl/ml and FT4 lower than 0.93ng/dl<br><br>Subclinical hypothyroidism= TSH | 14.6% (12/82) type 1 diabetes positive anti-TPOab autoimmunity<br><br>Prevalence of subclinical hypothyroidism without previous thyroid dysfunction was 13% in type 1 diabetes patients<br><br>New cases of subclinical hypothyroidism in patients with type 1 diabetes was (9/82 (13%)<br><br>Type 1 diabetes patients with previous thyroid dysfunction had TSH and FT4 levels in the normal range |
| | | | Number of patients | n=82 patients with type 1 diabetes | | |
| | | | Age (years), mean (SD) | 33.5±15.8 | | |
| | | | Gender (m/f) | 39m:43f | | |
| | | | Duration of diabetes (years), mean (SD) | 14.6±11.7 | | |
| | | | HbA1c (%) | 12.3±3.1 | | |
| | | | BMI ($kg/m^2$), mean (SD) | 24.4±5.2 $kg/m^2$ | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | presentation: variable degree of weight loss, polyuria, polydipsia, polyphagia and the need to use insulin continuously since the diagnosis without discontinuation, medical follow-up was at least one year | | | levels >4.20µUl/ml and FT4 ranging from 0.93-1.7ng/dl<br><br>Subclinical hyperthyroidism= TSH levels lower than 0.27µUl/ml and FT4 higher than 1.7ng/dl<br><br>Autoimmunity=anti-TPOab levels >34IU/litre | |
| | | | Treatment subgroups | Clinical hypothyroidism<br>Subclinical hypothyroidism<br>Clinical hyperthyroidism<br>Subclinical hyperthyroidism | | |
| | | | Diabetes control | | | |

**Table 348: PERROS 1995**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Perros P, McCrimmon RJ, Shaw G, Frier BM. | Cross-sectional study/prevalence | A random sample of 1310 adult diabetic patients were | | | Thyroid function tests:<br>FT4<br>TSH | Prevalence of hypothyroidism=5.9% in males vs. 14.5% in females<br>Prevalence of hyperthyroidism=1.1% in males vs. 6.4% in females |
| | | | Number of patients | n=406 type 1 diabetes patients | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabetic Medicine. 1995; 12(7):622-627.<br><br>Ref ID:PERROS 1995 | Patients were randomly selected from the diabetic outpatient clinic in the royal infirmary, Edinburgh for more than one year and were screened for thyroid dysfunction one year prior to recruitment | predominantly urban and Caucasian | Age (years), mean (SD) | Reported as mean sample age of all diabetic patients =53.8±16.3 | Normal range of FT4=9-23nmol/litre<br>Normal range for TSH=0.15-3.5mU/litre<br><br>Normal thyroid function=FT4 and TSH in normal range<br><br>Hypothyroidism=FT4 <9nmol/litre and TSH greater than 3.5mUl/litre<br><br>Hyperthyroidism=FT4 >23nmol/litre and TSH <0.15 mUl/litre<br><br>Subclinical hypothyroidism=FT4 within normal range and TSH >3.5mU/litre<br><br>Subclinical hyperthyroidism=FT4 within normal range and TSH <0.15mUl/litre | Prevalence of subclinical hypothyroidism=5.4% in males vs. 9.5% in females<br><br>Prevalence of subclinical hyperthyroidism=0% in males vs. 0.9% in females<br><br>New cases of thyroid disease:<br>Prevalence of hypothyroidism=1.6% in males vs. 1.8% in females<br><br>Hyperthyroidism=0% in males vs. 1.4% in females<br><br>Subclinical hypothyroidism=4.8% in males vs. 8.6% in females<br><br>Subclinical hyperthyroidism=0% in males vs. 0.5% in females<br><br>Action taken as a result of screening:<br>Clinical management was influenced in 49 patients<br><br>23 patients received thyroxine replacement treatment for primary hypothyroidism, subclinical hypothyroidism<br>One patient received radioiodine therapy for hyperthyroidism secondary to Graves' disease<br>7 patients with hyperthyroidism were treated with antithyroid drugs or radioiodine |
| | | | Gender (m/f) | 186m:220f | | |
| | | | Duration of diabetes (years), mean (SD) | One year previous to recruitment | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI ($kg/m^2$), mean (SD) | Not reported | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | | | | | Doses of thyroxine for hypothyroidism and carbimazole for hyperthyroidism were adjusted |
| | | | Treatment subgroups | Hypothyroidism<br>Subclinical hypothyroidism<br>Hyperthyroidism<br>Subclinical hyperthyroidism | | |
| | | | Diabetes control | Not reported | | |

**Table 349: PRAZNY 1999**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Prazny M, Skrha J, Limanova Z, Hilgertova J. The evaluation of thyroid and islet autoantibodies in type 1 diabetes mellitus. Sbornik Lekarsky. | Cross-sectional study/prevalence study<br><br>Patients were randomly selected from a Czech Republic population<br><br>Blood samples were | Type 1 diabetes patients | | | Anti-TPOab<br>Anti-TGab<br>TSH<br>T4<br><br>Thyroid disease= anti-TPOab >50U/ml and >100U/ml anti-TG | Prevalence of positive antiTPO and antiTG antibodies higher in women than men<br><br>Prevalence of antiTPO=14% (3/21) in men vs. 21% (5/34) in women<br>11% (6/55) patients were positive for both antiTPO and antiTG antibodies |
| | | | Number of patients | n=55 | | |
| | | | Age (years), mean (SD) | 39±13 | | |
| | | | Gender (m/f) | 21m:34f | | |
| | | | Duration of diabetes (years), | 18±13 | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| 1999; 100(3):205-211.<br>Ref ID:PRAZNY 1999 | taken from patients with type 1 diabetes after overnight fasting , and serum was used for thyroid function testing | | mean (SD) | | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI (kg/m$^2$), mean (SD) | 24.1±2.6 | | |
| | | | Treatment subgroups | IA-2 ab<br>GAD ab | | |
| | | | Diabetes control | Not reported | | |

**Table 350: RATTARASARAN 2000**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Rattarasarn C, Diosdado MA, Ortego J, Leelawattana R, Soonthornpun S, Setasuban W et al. Thyroid autoantibodies in Thai type 1 diabetic patients: clinical | Cross-sectional study /prevalence<br><br>Patients with type 1 diabetes were selected from a Thai population attending a diabetic clinic at prince of Songkla | 50 patients with type 1 diabetes and previous history of ketonuria or ketoacidosis at onset or a history of primary or secondary failure to oral hypoglycaemic agents within three years | | | Anti-TPOab positivity=titres of ≥1:10<br>Anti-TGab=titres of ≥1:100<br>TSH normal range=0.25-4.0mU/litre<br><br>Follow-up in patients without obvious thyroid dysfunction=19months (SD±8) | Prevalence of positive TGab=18% (9/50)<br><br>Prevalence of positive anti-TPOab=30% (15/50)<br><br>Prevalence of combined anti-TGab and anti-TPOab positivity<br><br>13% (2/16) patients with anti-TPO and anti-TG positivity had previous hyperthyroidism prior to diabetes onset at time of study<br><br>Of the remaining group of thyroid antibody positive group, two patients had newly diagnosed hyperthyroidism, one patient had |
| | | | Number of patients | n=50 patients with type 1 diabetes<br>n=47/50 adults | | |
| | | | Age (years), mean (SD) | 36.5±17.5 | | |
| | | | Gender (m/f) | 31m:19f | | |
| | | | Duration of diabetes (years), mean (SD) | 5.2±4.1 | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| significance and their relationship with glutamic acid decarboxylase antibodies. Diabetes Research and Clinical Practice. 2000; 49(2-3):107-111.<br><br>Ref ID: RATTARASARAN 2000 | university hospital, Thailand | | HbA1c (%) | Not reported | | clinical hypothyroidism<br><br>16% patients were anti-TG or anti-TPO positive (8/50) at time of study. At 19 months follow-up, 25% (2/8) patients developed hypothyroidism<br>13% (1/8) had elevated TSH levels after 20 months follow-up<br>One patient had elevated TSH levels after 35 months follow-up<br><br>Patients with thyroid antibodies but without history of thyroid disease had a higher frequency of thyroid dysfunction at the time of study<br><br>25% (2/8) patients were at a higher risk of developing thyroid dysfunction at 3 years follow-up<br><br>68% (34/50) were thyroid antibody negative |
| | | | BMI ($kg/m^2$), mean (SD) | Not reported | | |
| | | | Treatment subgroups | NA | | |
| | | | Diabetes control | All patients were treated with insulin at the start of study | | |

**Table 351: UMPIERREZ 2003**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Umpierrez GE, Latif KA, | Cross-sectional | 58 patients with type 1 | | | TSH, T4, T3 measured yearly | Prevalence of thyroid dysfunction=33% (19/58) |
| | | | Number | 58 patients with type 1 | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Murphy MB, Lambeth HC, Stentz F, Bush A et al. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. Diabetes Care. 2003; 26(4):1181-1185. Ref ID:UMPIERRE Z 2003 | study /prevalence<br><br>Patients enrolled in the diabetes control and complication trial at the university of Tennessee health science centre in 1993 and prospectively followed up for 18 years | diabetes<br><br>Exclusion criteria: hypothyroidism prior to diabetes onset | of patients | diabetes with or without hypothyroidism | Anti-TPOab measured at 4 year intervals<br><br>Anti-TPOab normal range=<32IU/ml<br><br>TSH normal range=0.4-4.0 mU/ml | Prevalence of primary hypothyroidism=31% (18/58)<br><br>Hypothyroidism was more common in females (44%) vs. males (19%)<br><br>Patients who are anti-TPO positive were 17.91 times as likely to develop hypothyroidism compared with anti-TPO negative patients |
| | | | Age (years), mean (SD) | Hypothyroidism+=18±2<br>Hypothyroidism-=16±1 | | |
| | | | Gender (m/f) | 26m:32f | | |
| | | | Duration of diabetes (years), mean (SD) | 8±4 | | |
| | | | HbA1c (%) | No difference between groups | | |
| | | | BMI ($kg/m^2$), mean (SD) | Hypothyroidism+=24±1<br>Hypothyroidism-=22±0.3 | | |
| | | | Treatment subgroups | Hypothyroidism+<br>Hypothyroidism- | | |
| | | | Diabetes control | Monitoring of glycaemic control and diabetes complications | | |

**Table 352: VONDRA 2004**

| Reference | Study details | Number of patients | Patient characteristics | Tests | Results |
|---|---|---|---|---|---|
| Vondra K, | Cross- | 109 patients | | AntiTPO at least | Prevalence of type 1 diabetes patients with |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Vrbikova J, Sterzl I, Bilek R, Vondrova M, Zamrazil V. Thyroid autoantibodies and their clinical relevance in young adults with type 1 diabetes during the first 12 year after diabetes onset. Journal of Endocrinological Investigation. 2004; 27(8):728-732.<br>Ref ID VONDRA2004 | sectional study<br><br>Young adults aged 18-35 years at the time of diagnosis, with newly diagnosed type 1 diabetes were followed up for 12 years after initial diagnosis since 1990s in the institute of endocrinology, Prague | with type 1 diabetes | Number of patients | n=109 | twice yearly. Cut-off value=1U/ml (>1U/ml=positive)<br>AntiTgab at least twice yearly. Cut-off value=3.8 U/ml (>5.0 U/ml=positive)<br>TSH level greater than 4.5mlU/litre with normal thyroid hormone levels was considered as subclinical hypothyroidism, and was measured twice yearly. Normal range of TSH=0.17-4.05mlU/litre | positive antiTPO+antiTG antibodies= 25% (27/109)<br><br>Prevalence of type 1 diabetes patients with positive antiTPO antibody only=26% (28/109)<br><br>Prevalence of type 1 diabetes patients with negative thyroid antibodies=49% (54/109) |
| | | | Age (years), mean (SD) | 18-35 (at time of diagnosis) | | |
| | | | Gender (m/f) | 58m:51f | | |
| | | | Duration of diabetes (years), mean (SD) | Newly diagnosed diabetes | | |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI ($kg/m^2$), mean (SD) | Group I=22.5<br>Group II=21.7<br>Group III=22.7 | | |
| | | | Treatment subgroups | AntiTPO+AntiTgl<br>AntiTPO only<br>T-ab negative | | |
| | | | Diabetes control | Not reported | | |

**Table 353: WALTER 2007**

| Reference | Study details | Number of patients | Patient characteristics | Tests | Results |
|---|---|---|---|---|---|
| Walter M, | Cross- | 124 type 1 | | Serum TSH | Autoimmune thyroid disease=31% (38/124) |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| McDonald CG, Paty BW, Shapiro AMJ, Ryan EA, Senior PA. Prevalence of autoimmune diseases in islet transplant candidates with severe hypoglycaemia and glycaemic lability: previously undiagnosed coeliac and autoimmune thyroid disease is identified by screening. Diabetic Medicine. 2007; 24(2):161-165.<br>Ref ID:WALTER 2007 | sectional/prevalence study based<br>in Canada | diabetes patients with severe hypoglycaemia and/or glycaemic lability undergoing assessment for islet transplantation and known cases of autoimmune disease , including previous radioiodine therapy or anti-thyroid drug therapy, and individuals receiving L-thyroxine | Number of patients | n=124 consecutive patients with type 1 diabetes | (threshold 4.5 mU/litre)<br><br>Anti-TPO antibodies (range/threshold not reported)<br><br>Patients with elevated TSH and anti-TPOab positivity remaining high were identified as new cases | New cases of thyroid disease=11% (4/38)<br><br>Known cases=87% (33/38)<br><br>Detection rate for new cases=5.8% (4/86)<br><br>True prevalence=35%<br><br>Thyroid disease was more common in women (43% 33/77) than men (21% 10/47) |
| | | | Age (years), mean (SD) | 44 ( range 23-65) | | |
| | | | Gender (m/f) | 47m:77f | | |
| | | | Duration of diabetes (years), mean (SD) | 28.4 (range 5-52) | | |
| | | | HbA1c (%) | 8.0±1.3 | | |
| | | | BMI ($kg/m^2$), mean (SD) | 24.9±3.5 | | |
| | | | Treatment subgroups | Autoimmune disease<br>No autoimmune disease | | |
| | | | Diabetes control | Severe hypoglycaemia and/or glycaemic lability, hypoglycaemia unawareness despite optimised insulin therapy | | |

**Table 354: WHITEHEAD 2010**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Whitehead C, Lunt H, Pearson JF, Cawood TJ. Is screening for hypothyroidism in the diabetes clinic effective? Practical Diabetes International. 2010; 27(3):113-117.<br>Ref ID WHITEHEAD2010 | Cross-sectional study /prevalence and laboratory results of patients attending the diabetes centre in Christchurch hospital, New Zealand<br><br>Missing data: none | 800 patients included in study<br>Inclusion criteria:<br>Attendance of patients between January 2007 and January 2009<br>hypothyroidism to include only patients with autoimmune hypothyroidism<br>Exclusion criteria:<br>Patients residing outside the Canterbury district health board catchment area of under 500,000 people, and not having type 1 diabetes<br>Patients who are post-radioiodine or | | | Normal TSH not reported<br>Normal FT4 not reported | Prevalence of hypothyroidism (including subclinical hypothyroidism) in type 1 diabetes patients=10.8% (43/400)<br><br>Prevalence of subclinical hypothyroidism=4% (16/400)<br><br>Prevalence of autoimmune hypothyroidism requiring thyroxine treatment=7% (27/400)<br><br>Prevalence of hypothyroidism due to surgery or radioiodine treatment or hyperthyroidism=2% (6/400)<br><br>Prevalence of hyperthyroidism or subclinical hyperthyroidism=1% (2/400)<br><br>Average dose of thyroxine replacement in patients with hypothyroidism requiring thyroxine treatment and type 1 diabetes=104µg<br>Annual thyroid hormone testing to detect hypothyroidism requiring thyroxine treatment=1.8% patients with type 1 diabetes<br><br>Median time of patients to attend a diabetic clinic=9.5 years<br><br>Prevalence of hypothyroidism requiring |
| | | | Number of patients | n=400 patients with type 1 diabetes | | |
| | | | Age (years), mean (SD) | >20 | | |
| | | | Gender (m/f) | 53%m:47%f | | |
| | | | Duration of diabetes (years), mean (SD) | Development of diabetes before the age of 40 years and requirement for insulin treatment within 1 year of diagnosis | | |
| | | | HbA1c (%) | NA | | |
| | | | BMI (kg/m$^2$), mean (SD) | NA | | |
| | | | Treatment subgroups | Hypothyroidism<br>Subclinical hypothyroidism<br>Hypothyroidism+thyroxine | | |
| | | | Diabetes control | Not reported | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | post-thyroidectomy treatment, or who are on 'block and replace' treatment with an antithyroid drug plus thyroxine.<br>Hypothyroidism was defined as patients with a diagnostic label of hypothyroidism, or who are on thyroxine treatment in the absence of non-autoimmune aetiology of hypothyroidism or patients with TSH above the reference range with a normal FT4, who were not on thyroxine treatment | | | | thyroxine treatment increased with age, particularly after 50 years |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| | | Autoimmune hypothyroidism requiring treatment was defined as those with hypothyroidism and who were also on thyroxine treatment | | | | |

**Table 355: YAMAGUCHI 1991**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Yamaguchi Y, Chikuba N, Ueda Y, Yamamoto H, Yamasaki H, Nakanishi T et al. Islet cell antibodies in patients with autoimmune thyroid disease. Diabetes. 1991; 40(3):319- | Cross-sectional study /prevalence study<br><br>Patients with type 1 diabetes and autoimmune thyroid disease were seen in the outpatient | Total=316 patients with autoimmune disease<br><br>Exclusion criteria: juvenile onset of type 1 diabetes group without autoimmune disease | | | T4 normal range=4.5-11.5µg/dl<br><br>FT4 normal range=0.6-2.3ng/dl<br><br>T3 normal range=91-143ng/dl<br><br>FT3 normal range=2.2-6.7pg/ml<br><br>TSH normal | 87.5% (18/21) type 1 diabetes patients were positive for anti-thyroidal autoantibodies |
| | | | Number of patients | n=21 type 1 diabetes patients with autoimmune thyroid disease | | |
| | | | Age (years), mean (SD) | Not reported | | |
| | | | Gender (m/f) | Not reported | | |
| | | | Duration of diabetes (years), mean (SD) | Not reported | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| 322.<br>Ref ID YAMAGUCHI1991 | endocrinology and metabolism clinic of Nagasaki university hospital, Japan, during 1982-1988 | | HbA1c (%) | Not reported | range=0.5-5.0µl/ml<br><br>Anti-thyroid microsomal antibodies and anti-thyroglobulin antibodies were considered positive with a dilution > 1x102 | |
| | | | BMI (kg/m$^2$), mean (SD) | Not reported | | |
| | | | Treatment subgroups | Not reported | | |
| | | | Diabetes control | Not reported | | |

**Table 356: YASMIN 2006**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Yasmin T, Ghafoor F, Malik T, Ruhy N, Khan AU. Pattern of thyroid autoimmunity in type 1 and type 2 diabetics. Journal of the College of Physicians and Surgeons-- | Cross-sectional study<br><br>Patients were seen at the diabetic clinic of Shaikh Zayed hospital, Lahore, Pakistan from August 2004 and April | 163 patients | | | Hypothyroidism= FT4 values <60nmol/litre and TSH >5mlU/litre)<br><br>Hyperthyroidism=TSH<0.3mlU/litre<br>Thyroid disease=anti-TPO>100IU/ml | 61% (31/51) of type 1 diabetes patients had high levels of anti-TPOab and 84 % (43/51) of these patients had high FT4 levels<br><br>Anti-TPOab positivity was higher in females than males |
| | | | Number of patients | n=51 type 1 diabetes patients | | |
| | | | Age (years), mean (SD) | 36.8±4.7 | | |
| | | | Gender (m/f) | Not reported | | |
| | | | Duration of diabetes (years), mean (SD) | Not reported | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Pakistan. 2006; 16(12):751-754.<br>Ref ID YASMIN2006 | 2005 (8 months) | | HbA1c (%) | Not reported | | |
| | | | BMI (kg/m$^2$), mean (SD) | 25.6±4.2 | | |
| | | | Treatment subgroups | Not reported | | |
| | | | Diabetes control | Not reported | | |

## G.11.3 Monitoring of thyroid disease in type 1 diabetes patients

**Table 357: BIANCHI 1995**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Bianchi G, Montanari P, Fabbri A, Gamberini A, Zoli M, Marchesini G. Thyroid volume in type 1 diabetes patients without overt thyroid disease. Acta Diabetologica. 1995; | Case control study<br><br>Patients were admitted to hospital for diabetic ketosis or for evaluation and treatment of complication of their diabetic disease | 45 patients with type 1 diabetes and with no history of previous thyroid disorders and/or use of drugs known to affect the thyroid homeostasis | | | Immunometric methods:<br>FT3 normal range=4.0-8.9pmol/litre<br><br>FT4 normal range=9.0-23.0pmol/litre<br><br>TSH normal range=0.4-3.5mU/litre<br><br>Anti-TPOab | All patients had FT4 levels higher than the normal range and FT3/FT4 ratio was reduced<br><br>4/45 patients had high levels of FT4 and FT3 and TSH at levels below the detection limit<br><br>2/4 patients had anti-TPOab positivity and an ultrasound result showing dis-homogeneous thyroid parenchyma and were confirmed with Hashimoto's thyroiditis (hypothyroidism)<br><br>1/4 patient was confirmed to have asymptomatic Graves' disease and 1/4 patient was confirmed to have hyperthyroidism |
| | | | Number of patients | n=45 patients with type 1 diabetes | | |
| | | | Age (years), (median) | 16-68 (median 40 years) | | |
| | | | Gender (m/f) | 20m:25f | | |
| | | | Duration of diabetes (years), mean (SD) | Not reported | | |
| | | | HbA1c (%) | 8.9% (range 5.1% to | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| 32(1):49-52. Ref ID BIANCHI1995 | Duration of study not reported<br><br>Country: Italy<br><br>No missing data | | | 12.0%) | positivity= titres>50U/ml<br><br>Anti-TGab positivity= titres>100 U/ml<br><br>Ultrasound=evaluation of thyroid morphology | |
| | | | BMI (kg/m$^2$), mean (SD) | Not reported | | |
| | | | Treatment subgroups | Not reported | | |
| | | | Thyroidism at baseline | Not reported | | |
| | | | Diabetes control | Poor control | | |

**Table 358: VONDRA 2004**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Vondra K, Vrbikova J, Sterzl I, Bilek R, Vondrova M, Zamrazil V. Thyroid autoantibodies and their clinical relevance in young adults with type 1 | Cross-sectional study<br><br>Young adults aged 18-35 years at the time of diagnosis, with newly diagnosed type 1 | 109 patients with type 1 diabetes | | | AntiTPO at least twice yearly. Cut-off value=1U/ml (>1U/ml=positive)<br>AntiTgab at least twice yearly. Cut-off value=3.8 U/ml (>5.0 U/ml=positive)<br>TSH level greater than 4.5mlU/litre with normal thyroid hormone levels was | Annual and cumulative incidence of patients with newly detected concurrent positivity of both antiTPO and antiTgI during follow-up<br><br>All new concomitant detection of both thyroid antibodies were made in the first four years from onset of diabetes (96% of all cases), with one patient who was positive for both antibodies in year 8 from onset of diabetes<br><br>The cumulative incidence of concomitant positivity of both antibodies in 109 patients |
| | | | Number of patients | n=109 | | |
| | | | Age (years), mean (SD) | 18-35 (at time of diagnosis) | | |
| | | | Gender (m/f) | 58m:51f | | |
| | | | Duration of | Newly diagnosed diabetes | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| diabetes during the first 12 year after diabetes onset. Journal of Endocrinological Investigation. 2004; 27(8):728-732. Ref ID VONDRA2004 | diabetes were followed up for 12 years after initial diagnosis since 1990s in the institute of endocrinology, Prague<br><br>No missing data | | diabetes (years), mean (SD) | | considered as subclinical hypothyroidism, and was measured twice yearly. Normal range of TSH=0.17-4.05mIU/litre | reached 25% and remained at this level throughout the follow-up period<br><br>Annual and cumulative incidence of patients with newly detected anti-TPO positivity varied between 2-8% and reached a cumulative value of 26% in year 9 of the follow-up period. During years 10, 11 and 12 there were no new detected cases |
| | | | HbA1c (%) | Not reported | | |
| | | | BMI ($kg/m^2$), mean (SD) | Group I=22.5<br>Group II=21.7<br>Group III=22.7 | | |
| | | | Treatment subgroups | AntiTPO+AntiTgl<br>AntiTPO only<br>T-ab negative | | |
| | | | Diabetes control | Not reported | | |

**Table 359: UMPIERREZ 2003**

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A et al. Thyroid dysfunction in patients with type 1 diabetes: a | Cross-sectional study<br><br>Patients with type 1 diabetes were previously enrolled in the DCCT RCT | 58 patients with type 1 diabetes | | | AntiTPOab normal=<30 IU/ml<br><br>TSH normal=0.4-4.0mU/ml<br><br>T3 and T4 assays were performed as recommended by the manufacturers | Presence of TPO antibodies was associated with an increased risk of hypothyroidism<br><br>Most patients with TPO positive antibodies tested positive at beginning of the study remained positive throughout the study<br><br>Patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95%CI 3.89- |
| | | | Number of patients | 58 patients with type 1 diabetes | | |
| | | | Age (years), mean (SD) | 19±2 | | |
| | | | Gender (m/f) | 26m:32f | | |
| | | | Duration of | Type 1 diabetes+hypothyroidism | | |

| Reference | Study details | Number of patients | Patient characteristics | | Tests | Results |
|---|---|---|---|---|---|---|
| longitudinal study. Diabetes Care. 2003; 26(4):1181-1185.<br>Ref ID UMPIERREZ2003 | and were followed prospectively for 18 years in Tennessee, USA | | diabetes (years), mean (SD) | =18±2<br><br>Type 1 diabetes only=16±1 | | 82.54) (controlled for age at onset of diabetes<br><br>Cox proportional hazard analysis for prediction of development of hypothyroidism from age of onset, sex and TPO status (likelihood ratio X2=15.88, df=3, P=0.001)<br>Adjusted hazard ratio for TPO status=8.99 (95%CI 2.35-34.36) showing that patients positive for antiTPO were much more likely to develop hypothyroidism than those patients who were TPO negative<br><br>Patients who are TPO negative remain TPO negative throughout 12-28 duration of diabetes. The percentage of patients who tested positive at onset rapidly developed hypothyroidism as the duration of diabetes increased (years), and most of these patients developed subclinical hypothyroidism |
| | | | HbA1c (%) | No difference between subgroups | | |
| | | | BMI ($kg/m^2$), mean (SD) | Type 1 diabetes+hypothyroidism =24±1<br><br>Type 1 diabetes only=22±0.3 | | |
| | | | Treatment subgroups | Normal<br>Hypothyroidism<br>Subclinical hypothyroidism<br>Hyperthyroidism | | |
| | | | Diabetes control | Not reported | | |

# G.12 Methodological limitations of observational studies in the guideline

## G.12.1 Review question: Diagnosis

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Amrouche 2008 | ✓ | ✓ | ✓ | n/a |
| Arikan 2005 | ✓ | ✓ | ✓ | n/a |
| Andersen 2014 | ✓ | ✓ | ✓ | n/a |
| Arslan 2014 | X | ✓ | ✓ | n/a |
| Bodalska 2006 | ✓ | ✓ | ✓ | n/a |
| Barker 2014 | ✓ | ✓ | ✓ | n/a |
| Bell 2004 | ✓ | ✓ | ✓ | n/a |
| Cerna 2003 | ✓ | ✓ | ✓ | n/a |
| Davies 2008 | ✓ | ✓ | ✓ | n/a |
| Davis 2003 | ✓ | ✓ | ✓ | n/a |
| Hamaguchi 2004 | ✓ | ✓ | ✓ | n/a |
| Hampe 2013 | ✓ | ✓ | ✓ | n/a |
| Hawa 2013 | ✓ | ✓ | ✓ | n/a |
| Hillman 2009 | ✓ | ✓ | ✓ | n/a |
| Hope 2013 | ✓ | ✓ | ✓ | n/a |
| Hosszu 2003 | ✓ | ✓ | ✓ | n/a |
| Huang 2013 | ✓ | ✓ | ✓ | n/a |
| Lu 2014 | ✓ | Partially - mixed adults + young-people | ✓ | n/a |
| Mahadeb 2014 | ✓ | ✓ | ✓ | n/a |
| Maraschin 2013 | ✓ | ✓ | ✓ | n/a |
| McDonald 2011 | ✓ | ✓ | ✓ | n/a |
| Murao 2008 | ✓ | ✓ | ✓ | n/a |
| Paschke 2013 | ✓ | ✓ | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| Rajalakshmi 2014 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Rogowicz 2014 | ✓ | ✓ | ✓ | n/a |
| Roh 2013 | X | ✓ | ✓ | n/a |
| Shishikura 2014 | ✓ | ✓ | ✓ | n/a |
| Sorgjerd 2012 | ✓ | ✓ | ✓ | n/a |
| Szepietowska 2012 | ✓ | ✓ | ✓ | n/a |
| Thanabalasingham 2012 | ✓ | ✓ | ✓ | n/a |
| Wilmot 2013 | ✓ | ✓ | ✓ | n/a |
| Yang 2008 | ✓ | ✓ | ✓ | n/a |
| Zampetti 2012A | ✓ | ✓ | ✓ | n/a |
| Bottazzo 2005 | ✓ | ✓ | ✓ | n/a |
| Castleden 2006 | ✓ | ✓ | ✓ | n/a |
| Trabucci 2012 | ✓ | ✓ | ✓ | n/a |
| Desai 2007 | ✓ | ✓ | ✓ | n/a |
| Chowta 2010 | ✓ | ✓ | ✓ | n/a |
| Monge 2004 | ✓ | ✓ | ✓ | n/a |
| Kim 2007 | ✓ | ✓ | ✓ | n/a |
| Aggarwal 2010 | ✓ | ✓ | ✓ | n/a |
| Zhang 2012A | ✓ | ✓ | ✓ | n/a |
| Hwangbo 2012 | ✓ | ✓ | ✓ | n/a |
| Maioli 2010 | ✓ | ✓ | ✓ | n/a |
| Vaziri 2010 | ✓ | ✓ | ✓ | n/a |
| Lindholm 2004 | ✓ | ✓ | ✓ | n/a |
| Radtke 2009 | ✓ | ✓ | ✓ | n/a |
| Lee 2011A | ✓ | ✓ | ✓ | n/a |
| Vlad 2004 | ✓ | ✓ | ✓ | n/a |
| Besser 2011 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Borg 2003 | ✓ | Partially - mixed adults + young people | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| Brunova 2002 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Fan 2013 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Laadhar 2007 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| McDonald 2011 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Ota 2005 | ✓ | Partially – mixed all ages | ✓ | n/a |
| Scholin 2004 | ✓ | ✓ | ✓ | n/a |
| Scholin 2004A | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Scholin 2004B | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Scholin 2011 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Tridgell 2011 | ✓ | Partially - mixed all ages | ✓ | n/a |
| Vermeulen 2011 | ✓ | ✓ | ✓ | n/a |
| Wenzlau 2010 | ✓ | Partially - mixed adults + young people | ✓ | n/a |

### G.12.2 Review question: Education

No non-comparative observational studies were included for this review

### G.12.3 Review question: Carbohydrate counting

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Brazeau 2013 | ✓ | ✓ | ✓ | X |
| Dias 2010 | ✓ | ✓ | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| Franc 2009 | ✓ | ✓ | ✓ | n/a |

### G.12.4 Review question: GI diet

No non-comparative observational studies were included for this review

### G.12.5 Review question: HbA1c

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Araszkiewicz 2006 | ✓ | ✓ | ✓ | ✓ |
| Eeg-Olofsson 2010 | X | ✓ | ✓ | ✓ |
| Forrest 2000 | ✓ | ✓ | ✓ | ✓ |
| Guerci 1999 | ✓ | ✓ | ✓ | ✓ |
| Hietala 2013 | ✓ | ✓ | ✓ | ✓ |
| Kullberg 1994 | X | ✓ | ✓ | ✓ |
| LeCaire 2013 | ✓ | Partially - mixed adults + young people | ✓ | ✓ |
| Nordwall 2009 | X both retro and pros | Partially - mixed adults + children | ✓ | ✓ |
| Rossing 1996 | ✓ | ✓ | ✓ | ✓ |
| Weinstock 2013 | ✓ | ✓ | ✓ | ✓ |
| Aiello 2014 | ✓ | ✓ | ✓ | ✓ |
| Jacobson 2013 | ✓ | ✓ | ✓ | ✓ |
| Lind 2011 | ✓ | ✓ | ✓ | ✓ |
| Zoffmann 2014 | ✓ | ✓ | ✓ | ✓ |
| Agardh 1997 | ✓ | ✓ | ✓ | ✓ |
| Brinchmann-Hansen 1992 | ✓ | ✓ | ✓ | ✓ |
| DCCT/EDIC 2005; DCCT/EDIC 2008 | ✓ | ✓ | ✓ | ✓ |
| Nathan 2005; White 2008 | ✓ | ✓ | ✓ | ✓ |
| Diamante 1997 | ✓ | ✓ | ✓ | ✓ |
| Eid Fares 2010 | X | Partially - mixed adults + young people | ✓ | ✓ |
| Hislop 2008 | ✓ | Partially - mixed adults + young people | ✓ | ✓ |

| | | | | |
|---|---|---|---|---|
| Lehto 1999 | ✓ | Partially - only men | ✓ | ✓ |
| Lustman 2005 | ✓ | ✓ | ✓ | ✓ |
| Perez Mendez 2007 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Pittsburgh EDC 2002 (Olson 2002A) | ✓ | Partially – mixed all ages | ✓ | ✓ |
| Pittsburgh EDC 2003 (Orchard 2003) | ✓ | Partially – mixed all ages | ✓ | ✓ |
| Shaban 2006 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Tabaei 2004 | ✓ | ✓ | ✓ | ✓ |
| Van Tillburg 2001 | ✓ | Partially - Mixed ages | ✓ | ✓ |
| WESDR 1998A (Klein 1998A) | ✓ | Partially - mixed adults + young people | ✓ | ✓ |
| WESDR 1994 (Moss 1994A) | ✓ | ✓ | ✓ | ✓ |
| WESDR 1999 (Moss 1999) | ✓ | ✓ | ✓ | ✓ |
| WESDR 1998 (Klein 1998) | X | ✓ | ✓ | ✓ |
| WESDR 1995 (Klein 1995; 1996) | ✓ | ✓ | ✓ | ✓ |
| Wikblad 1996 | X | ✓ | ✓ | n/a |
| Wikblad 1991 | X | ✓ | ✓ | n/a |

### G.12.6 Review question: SMBG - frequency and timing

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Abdelgadir 2006 | ✓ | ✓ | ✓ | n/a |
| Bott 1994 | ✓ | Partially – mixed adults + children | ✓ | ✓ |
| Bragd 2003 | ✓ | ✓ | ✓ | ✓ |
| Cox 2007 | ✓ | ✓ | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| Evans 1999 | X | Partially – mixed adults + children | ✓ | ✓ |
| Hillman 2004 | X | Partially - unclear age | ✓ | ✓ |
| Karter 2001 | X | ✓ | ✓ | ✓ |
| Klein 1992 | ✓ | ✓ | ✓ | n/a |
| Minder 2013 | ✓ | ✓ | ✓ | ✓ |
| Nathan 1996 | ✓ | Partially – mixed all ages | ✓ | ✓ |
| Pickup 2006 | ✓ | ✓ | ✓ | ✓ |
| Schiffrin 1992 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Schutt 2006 | ✓ | ✓ | ✓ | ✓ |
| Service 2007 | ✓ | Partially - mixed adults + young people | ✓ | ✓ |
| Shimizu 2008 | ✓ | ✓ | ✓ | X |
| Tildesley 2004 | ✓ | Partially - mixed adults + young people | ✓ | X |
| Weitgasser 1994 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Willey 1993 | ✓ | ✓ | ✓ | n/a |
| Ziegler 1993 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Araszkiewicz 2008 | ✓ | ✓ | ✓ | X |
| Bell 1994 | ✓ possibly retro | Partially - Mixed all ages | ✓ | |
| Bell 1984 | ✓ | Partially - Mixed all ages | ✓ | n/a |
| Bruttomesso 1992 | X | ✓ | ✓ | X |
| Chan 2009 | ✓ | ✓ | ✓ | ✓ |
| Brinchmann-Hansen 1992 | ✓ | ✓ | ✓ | ✓ |
| Gonder 1988 | ✓ | ✓ | ✓ | X |
| Hartemann 2001 | ✓ | ✓ | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| Lloyd 1993 | ✓ | ✓ | ✓ | ✓ |
| Merimee 1984 | ✓ | Partially - % type 1 diabetes unclear | ✓ | n/a |
| McClean 2005 | ✓ | ✓ | ✓ | ✓ |
| Miller 2013 | ✓ | ✓ | ✓ | ✓ |
| Nayak 2011 | ✓ | Partially - Mixed diabetes and ages | ✓ | ✓ |
| Sjoberg 1988 | ✓ | ✓ | ✓ | X |
| Van Tilburg 2001 | ✓ | Partially – Mixed all ages | ✓ | ✓ |
| Woo 2011 | ✓ | Partially - unclear ages | ✓ | n/a |
| Ziegler 1989 | ✓ | Partially - Mixed all ages | ✓ | unclear |
| Ziegler 2012 | ✓ | Partially - Mixed all ages | ✓ | unclear |

### G.12.7 Review question: SMBG – glucose targets

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Cox 1994 | ✓ | ✓ | ✓ | X |
| Kovatchev 2000 | ✓ | Partially - unclear age | ✓ | n/a |
| Mulhauser 1998 | ✓ | ✓ | ✓ | ✓ |
| Service 2001 | ✓ | Partially - mixed adults + young people | ✓ | ✓ |
| Vervoort 1996 | ✓ | ✓ | ✓ | n/a |
| Wei 2014 | ✓ | Partially - age unclear | ✓ | n/a |

### G.12.8 Review question: SMBG – technologies

No non-comparative observational studies were included for this review

### G.12.9 Review question: SMBG versus CGM

No non-comparative observational studies were included for this review

### G.12.10 Review question: Insulin therapy –rapid-acting

No non-comparative observational studies were included for this review

### G.12.11 Review question: Insulin therapy - long-acting

No non-comparative observational studies were included for this review

### G.12.12 Review question: Insulin therapy - mixed

No non-comparative observational studies were included for this review

### G.12.13 Review question: Insulin therapy - adjuncts

No non-comparative observational studies were included for this review

### G.12.14 Review question: Insulin therapy - needle length, site and rotation

No non-comparative observational studies were included for this review

### G.12.15 Review question: Pancreas transplant and islet cell transplantation

No non-comparative observational studies were included for this review

### G.12.16 Review question: Hypoglycaemia - identification & quantification of impaired awareness of hypoglycaemia

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Hendrieckx 2014 | X | ✓ | ✓ | ✓ |
| Hopkins 2012 | X | ✓ | ✓ | n/a |
| Choudhary 2010A | ✓ | ✓ | ✓ | n/a |
| Clarke 1995 | ✓ | ✓ | ✓ | n/a |
| Geddes 2007 | ✓ | ✓ | ✓ | n/a |
| Geddes 2008 | ✓ | ✓ | ✓ | X |
| Gimenez 2009 | ✓ | ✓ | ✓ | n/a |
| Gold 1994 | ✓ | ✓ | ✓ | n/a |
| Hoihansen 2010 | ✓ | ✓ | ✓ | n/a |
| Janssen 2000A | ✓ | ✓ | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| Pedersen 2003 | ✓ | ✓ | ✓ | n/a |
| Ryan 2004 | ✓ | Partially - mainly type 1 diabetes | ✓ | n/a |
| Schopman 2011 | ✓ | ✓ | ✓ | n/a |
| Streja 2005 | ✓ | ✓ | ✓ | ✓ |

### G.12.17 Review question: Hypoglycaemia - recovering hypoglycaemia awareness

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Brooks 2013 | X | ✓ | ✓ | n/a |
| Choudhary 2013 | X | ✓ | ✓ | n/a |
| Cranston 1994 | ✓ | ✓ | ✓ | n/a |
| De Zoysa 2014 | ✓ | ✓ | ✓ | n/a |
| Fanelli 1993 | ✓ | ✓ | ✓ | n/a |
| Fritsche 2001 | ✓ | ✓ | ✓ | n/a |
| Gimenez 2010 | ✓ | ✓ | ✓ | n/a |
| Hernandez 2008 | ✓ | ✓ | ✓ | n/a |
| Hopkins 2012 | X | ✓ | ✓ | n/a |
| Leitao 2008 | X | ✓ | ✓ | n/a |
| Liu 1996 | ✓ | ✓ | ✓ | n/a |
| Meyer 1998 | ✓ | ✓ | ✓ | n/a |
| Ryan 2005 | X | ✓ | ✓ | n/a |
| Ryan 2009 | ✓ | ✓ | ✓ | n/a |
| Leelarantha 2013A | ✓ | ✓ | 6 months | n/a |

### G.12.18 Review question: Ketone monitoring - self-monitoring & in-hospital monitoring

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Bektas 2004 | ✓ | Partially - % type 1 diabetes | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| | | not given | | |
| Arora 2011C | ✓ | Partially - % type 1 diabetes not given | ✓ | n/a |
| Kuru 2014 | ✓ | Not very - mixed ages + % type 1 diabetes not given | ✓ | n/a |
| Harris 2005 | X | Partially - % type 1 diabetes not given | ✓ | n/a |
| Taboulet 2007 | X | Not very - mixed adults + young people, and % type 1 diabetes not given | ✓ | n/a |

### G.12.19 Review question: Arterial risk control

No non-comparative observational studies were included for this review

### G.12.20 Review question: Inpatient management – IV insulin

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Corney 2012 | X | Partially - >70% type 1 diabetes | ✓ | n/a |
| Husband 1986 | ✓ | Partially - ages unclear | ✓ | n/a |
| McCavert 2010 | ✓ | ✓ | ✓ | n/a |
| Poppe 2004 | ✓ | ✓ | ✓ | n/a |
| Wagner 1999 | ✓ | Partially - mixed adults + young people | ✓ | n/a |

### G.12.21 Review question: Complications – gastroparesis

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Timratana 2013 | ✓ | Partially - % | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| | | type 1 diabetes unclear | | |
| Horowitz 1985 | ✓ | ✓ | ✓ | n/a |
| Sharma 2011 | ✓ | ✓ | ✓ | n/a |
| Vandervoot 2005 | ✓ | ✓ | ✓ | n/a |

### G.12.22 Review question: Complications – acute painful neuropathy

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Gibbons 2010 | ✓ | Partially - 55% type 1 diabetes | ✓ | n/a |

### G.12.23 Review question: Complications – thyroid disease

| Study ID | Study design: prospective or cross-sectional | Representative population sample | Outcomes adequately measured | Appropriate statistical analysis (adjusted for confounders where applicable) |
|---|---|---|---|---|
| Allen 2008 | ✓ | ✓ | ✓ | n/a |
| Bianchi 1995 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Cardoso 1995 | ✓ | ✓ | ✓ | n/a |
| Dagdelen 2009 | ✓ | Partially - mixed adults + young people + children | ✓ | n/a |
| Dufaitre 2006 | ✓ | ✓ | ✓ | n/a |
| Fialzok 1997C??? /fialkow 1975? | ✓ | ✓ | ✓ | n/a |
| Gomez 2003 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Hanukoglu 2003 | ✓ | Partially - children | ✓ | n/a |
| Jin 2011 | ✓ | ✓ | ✓ | n/a |
| Junik 2006 | ✓ | ✓ | ✓ | n/a |
| Kucera 2003 | ✓ | ✓ | ✓ | n/a |

| | | | | |
|---|---|---|---|---|
| Lupi 2013 | ✓ | ✓ | ✓ | n/a |
| Palma 2013 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Perros 1995 | ✓ | ✓ | ✓ | n/a |
| Prazny 1999 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Rattarassaran 2000 | ✓ | Partially - mixed adults + young people | ✓ | n/a |
| Umpierrez 2003 | ✓ | Partially - mixed adults + young people | ✓ | ✓ |
| Vondra 2004 | ✓ | ✓ | ✓ | n/a |
| Walter 2007 | ✓ | ✓ | ✓ | n/a |
| Whitehead 2010 | ✓ | ✓ | ✓ | n/a |
| Yamaguchi 1991 | ✓ | ✓ | ✓ | n/a |
| Yasmin 2006 | ✓ | Partially - mixed adults + young people | ✓ | n/a |

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