NICE National Institute for Health and Care Excellence

Appendix A3: Summary of evidence from surveillance

2019 surveillance of Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015) NICE guideline NG18

Contents:

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the whole guideline.

We found 31 studies in a search for randomised control trials (RCTs) and Cochrane reviews published between 1 June 2014 and 7 December 2018 for children and young people with type 1 diabetes and published between 26 August 2014 and 19 February 2019 for children and young people with type 2 diabetes.

The search dates differ as the literature search for evidence on children and young people with type 1 diabetes was part of a wider search for populations of any age with type 1 diabetes which was developed to identify evidence relevant to both NICE guideline NG17 on type 1 diabetes in adults and NICE guideline NG18. The second search strategy was developed specifically for evidence on children and young people only with type 2 diabetes. The start dates reflect the last date of searches performed for the evidence reviews of NICE guideline NG17 and NG18 respectively, and the end dates reflect differences in when work on each surveillance review started.

We also included:

- One relevant RCT from a total of 3 identified by topic experts, plus 6 additional non-RCT publications

- Two RCTs and 1 additional publication identified through comments received after publication of the guideline
- One RCT and 2 additional publications identified by stakeholders

From all sources, we considered 32 studies and 9 additional publications to be relevant to the guideline.

See summary of evidence from surveillance below for details of all evidence considered, and references.

Selecting relevant studies

Studies were included if they met the following criteria:

- they included children and young people with type 1 or type 2 diabetes. There was some flexibility given to studies that included young people older than 18 years old: these were included if the sample also clearly included children aged younger than 18 years old.
- were RCTs with a sample size of at least 40 or
- a Cochrane review.

Ongoing research

We checked for relevant ongoing research. Of the ongoing studies identified, 3 were assessed as having the potential to change recommendations, however the medications listed are not currently licenced for use in children and young people with type 1 or type 2 diabetes. These will be considered as relevant evidence in the future if these medications gain a licence for use in this population. During stakeholder consultation relevant ongoing research and an *in press* article was identified. We plan to check the publication status regularly and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- A Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (>=10 to <18 Years) With Type 2 Diabetes Mellitus
- Phase 3 Alogliptin Pediatric Study
- A Study of SIMPONI® to Arrest Beta-cell Loss in Type 1 Diabetes (T1GER)
- Continuous Glucose Monitoring Intervention in Teens and Young Adults With Type 1 Diabetes (CITY)
- Strategies to Enhance New Continuous Glucose Monitoring Use in Early Childhood (SENCE)

- Ibanez-Bruron MC, et al Sight-threatening diabetic eye disease in children and young people in the UK. The Royal College of Ophthalmologists Annual Congress; Liverpool, 2017. *In press.*

Intelligence gathered during surveillance

Views of topic experts

For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to NICE guideline NG18.

We sent questionnaires to 20 topic experts and received 5 responses. The topic experts were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty.

Four of the experts felt that the guideline should be updated, whereas one was unsure. Areas identified for update included: the effectiveness of newer insulins and cheaper biosimilar insulins for type 1 diabetes, the use of FreeStyle Libre for glucose monitoring (flash), the definition of hypoglycaemia, changing the frequency of diabetic retinopathy screening, fluid therapy for children and young people with diabetic ketoacidosis, and the use of new technologies such as online education as an alternative to current structured education offerings. Further details are provided in the relevant 'Intelligence gathering' sections below.

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline.

A full list of guideline recommendations can be found on the website at the following link: https://www.nice.org.uk/guidance/ng18

1.1 Diagnosis

Surveillance proposal

This section should not be updated.

Editorial amendments

Recommendation 1.1.6 is currently worded to indicate that 'rarely or never developing ketone bodies in the blood (ketonaemia) during episodes of hyperglycaemia' is a criterion for considering other types of diabetes than type 1 or type 2 diabetes (i.e. other insulin resistance syndromes, or monogenic or mitochondrial diabetes), however this can also be an indicator for type 2 diabetes, an amendment is required to clarify this.

2019 surveillance summary

Diagnosis of type 1 diabetes (T1D) in children and young people

No relevant evidence was identified.

Diagnosis of type 2 diabetes (T2D) in children and young people

One cluster RCT (n=1,369) assessed the effectiveness of an automated T2D screening module added to a computerised clinical decision support tool (CDST) compared to a standard CDST on screening for T2D and diagnosing T2D in paediatric patients at high risk for T2D. The tool led to a significant improvement in screening of patients who met the American Diabetes Association criteria for T2D and in them attending scheduled follow-up appointments with primary care clinicians. [1]

See Table 1 for study details.

Diagnosis of other types of diabetes

No relevant evidence was identified.

Intelligence gathering

A topic expert highlighted the use of new technologies such as a new diabetes platform and online education as an alternative to the current structured education offerings, however no evidence was provided by topic experts and none was identified in the literature search.

A stakeholder highlighted the International society for pediatric and adolescent diabetes (ISPAD) Clinical Practice Consensus Guidelines on The diagnosis and management of monogenic diabetes in children and adolescents. This provides recommendations on diagnosing monogenic diabetes, including that 'All patients diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of monogenic neonatal diabetes mellitus (NDM), as type 1 diabetes is extremely rare in this subgroup. In patients diagnosed between 6 and 12 months of age, testing for NDM should be limited to those without islet antibodies as the majority of patients in this age group have type 1 diabetes.'

Impact statement

There are no recommendations concerning the use of automated tools or systems to assist the identification and diagnosis of children and young people with T2D. While the new

evidence indicates that an automated T2D screening module added to a CDST improves attendance at a screening appointment, the impact on diagnosis is not stated. It is therefore proposed that this is not an area for update. Further research in this area will be looked for in the next surveillance review. The ISPAD recommendations on criteria that indicates a child may have monogenic diabetes is in line with current recommendations. While there are no recommendations on testing for islet antibodies, no evidence on diagnostic accuracy or cost-effectiveness of tests for antibodies was identified. As such, this is not currently considered as an area for update.

New evidence is unlikely to change guideline recommendations.

1.2 Type 1 diabetes

Surveillance proposal

This section should be updated.

Editorial amendments

Recommendation 1.2.32 lists the 'sulphonylureas', these are now spelled 'sulfonylureas', so should be changed to this new spelling. 'Glyburide' is listed but that name isn't used in the UK and is a synonym for 'glibenclamide', which is already listed. 'Glyburide' should therefore be removed from this recommendation.

Recommendation 1.2.63 which recommends considering ongoing real-time continuous glucose monitoring for 'children and young people who undertake high levels of physical activity (for example, sport at a regional, national or international level)' should be amended to include other examples of 'high levels of physical activity'.

In recommendation 1.2.110 requires the following footnote adding: "screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme."

2019 surveillance summary

Study details for the evidence in this section are provided in Table 2.

Education and information for children and young people with type 1 diabetes

No relevant evidence was identified.

Smoking and substance misuse

No relevant evidence was identified.

Immunisation

No relevant evidence was identified.

Insulin therapy for children and young people with type 1 diabetes

Five RCTs assessed different insulin regimens in children with T1D. Four RCTs reported that the following regimens were non-inferior at reducing HbA1c:

- a co-formulation of basal and bolus insulin (insulin degludec/insulin aspart) injected once-daily with insulin aspart for remaining meals compared to insulin detemir (IDet) injected once-daily or twice-daily plus mealtime insulin aspart (n=362) [2]
- insulin degludec injected once-daily compared with IDet injected once or twice-daily, with prandial insulin aspart [3]
- Insulin degludec plus fast-acting insulin aspart (faster aspart) post-meal compared with mealtime insulin degludec plus insulin aspart [4]
- continuous subcutaneous insulin infusion (CSII) compared to multiple daily injections (MDI) initiated within 14 days of T1D diagnosis (n=293); however, CSII was more expensive than MDI, with no additional QALY gains, indicating that it is not cost-effective. [5]

However 1 RCT also reported that mealtime insulin degludec plus faster aspart provided superior HbA1c control compared with mealtime insulin degludec plus insulin aspart [4]

One RCT compared 48 to 72 hours IV insulin therapy to multiple subcutaneous injections at diagnosis of T1D and found a significant improvement in mean plasma glucose after the first 2 full days of insulin therapy but no differences at 24 months follow-up (n=54). [6]

One RCT investigated the psychosocial benefits of CSII compared to MDI for 6 months followed by CSII in children with T1D and their families (n=211). Results indicated that children with T1D aged 8-11 years old had a significantly improved diabetes-specific health-related quality of life (DHRQOL) in the CSII group compared to MDI group but that adolescents (aged 12-16 years old) did not. There was also a significant decline of overall diabetes burden reported by caregivers in the CSII compared to MDI group. [7]

One RCT assessed the effectiveness of different types of insulin pump therapy: hybrid closed-loop therapy compared to sensor-augmented pump therapy in children with sub-optimally controlled T1D (n=86). It was reported that the hybrid closed-loop therapy led to significant improvements in glucose control and reduced the risk of hypoglycaemia. [8]

Oral medicines for children and young people with type 1 diabetes

Two RCTs compared metformin to placebo in children with T1D as an adjunct to insulin. One RCT (n=90) reported that HbA1c levels significantly improved when metformin was given for 12 months compared to placebo [9]; while the other RCT (n=140) reported significant improvements in HbA1c levels with metformin compared to placebo at 13 weeks follow-up but not at 26 weeks follow-up. [10] Significant improvements in vascular function, insulin

dose and body mass index (BMI) score were also reported in the metformin compared to placebo groups; and both RCTs reported that there were no significant differences in gastrointestinal side effects between those receiving metformin compared to those given a placebo.

Dietary management for children and young people with type 1 diabetes

A cluster RCT (31 UK paediatric centres; n=396) reported that compared to usual care, a 5-day structured dietary education course led to significant improvements in quality of life at 6 and 12 months but no differences in HbA1c at 24 months in children and young people with T1D. [11]

Exercise for children and young people with type 1 diabetes

No relevant evidence was identified.

Blood glucose targets

A Cochrane review of 12 RCTs (n=2,230) assessed the effects of intensive versus conventional glycaemic targets in patients with T1D. Only 1 RCT included children (n=not reported in the abstract). Results from this trial were not reported separately. Overall, the authors concluded that tight blood sugar control reduces the risk of developing microvascular diabetes complications such as retinopathy, nephropathy and neuropathy in younger patients at early stages of T1D, with the effects becoming weaker once complications have manifested; but that 'there is no firm evidence for specific blood glucose targets' and 'treatment goals need to be individualised taking into account age, disease progression, macrovascular risk, as well as the patient's lifestyle and disease management capabilities'. [12]

Blood glucose monitoring

An RCT (n=90) reported that compared to no incentive, a 3-month financial incentive intervention that rewarded daily blood glucose monitoring of 4 or more checks per day, led to significant improvements in adherence to glucose monitoring at the end of the 3-month intervention, but not at 3 months follow-up in young people with T1D. The intervention had no effect on changes in HbA1c levels at either the end of the intervention or 3 months follow-up [13]

One RCT in young people with poorly controlled T1D and who were poorly compliant with blood glucose self-monitoring (n = 182) compared an intervention involving an experimental blood glucose meter which integrates blood glucose testing with a smartphone (iBGStar™ + DMApp) with a standard glucose monitor. There were no significant differences in HbA1c levels, self-monitoring compliance or quality of life after 6 months between the intervention and control groups. [14]

HbA1c targets and monitoring

See [13, 14] above and Table 2 for study details.

Hyperglycaemia, blood ketone monitoring and intercurrent illness in children and young people with type 1 diabetes

No relevant evidence was identified.

Hypoglycaemia in children and young people with type 1 diabetes

No relevant evidence was identified.

Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes

No relevant evidence was identified.

Surgery for children and young people with type 1 diabetes

No relevant evidence was identified.

Psychological and social issues in children and young people with type 1 diabetes

Three RCTs assessed the impact of psychological interventions on mental wellbeing and/or HbA1c levels. Compared with usual care, a clinic-based structured educational group incorporating psychological approaches (n=362) and motivational interviewing and problem-solving skills training (n=258) for children with T1D were found to have no significant impact on HbA1c levels at follow-up of between 12 to 24 months [15, 16]. While no significant improvements in HbA1c levels were found when cognitive behavioural therapy (CBT) was compared to non-directive supportive counselling (n=85), children in the CBT group maintained HbA1c levels, while those in the non-directive supportive counselling showed a significant deterioration in HbA1c levels at the 12 months follow-up; CBT was also reported to significantly improve psychological outcomes compared to non-directive supportive counselling. [17]

Monitoring for complications and associated conditions of type 1 diabetes

No relevant evidence was identified.

Diabetic retinopathy in children and young people with type 1 diabetes

No relevant evidence was identified.

Diabetic kidney disease in children and young people with type 1 diabetes

No relevant evidence was identified.

Intelligence gathering

Insulin therapy for children and young people with type 1 diabetes

Topic experts said that evidence for newer long-acting insulins such as degludec (Tresiba) should be reviewed. No evidence in children was provided.

Other analogue and biosimilar insulins were highlighted by topic experts, however only medicines licenced for children and evidence which included children as participants were considered in this surveillance review.

Initial intelligence identified MiniMed 640G system with SmartGuard for managing blood glucose levels in people with type 1 diabetes (February 2016) MIB51. The MiniMed 640G integrated sensor-augmented pump therapy system with SmartGuard is a continuous glucose monitoring and insulin delivery system for people with type 1 diabetes. It can automatically suspend insulin delivery if blood glucose is predicted to drop below a pre-set level within 30 minutes. The Medtech Innovation Briefing indicates that the evidence is still in proof of concept phase.

Blood glucose monitoring

Initial intelligence identified FreeStyle Libre for glucose monitoring (July 2017) MIB110. This MIB summarises the evidence on FreeStyle Libre (flash glucose monitor) which measures glucose levels from a sensor applied to the skin as an alternative to routine finger-prick blood glucose testing. It is intended as a replacement for glucose monitoring via the fingertip prick test.

Topic experts also asked that evidence on this be considered as NHS England have released guidance on Flash Glucose Monitors for Type 1 diabetes patients in March 2019 which highlights which people with T1D should receive a flash glucose monitor – specific ages are not provided. Topic experts also highlighted the November 2018 Regional Medicines Optimisation Committee FreeStyle Libre Position Statement. The advice of this group to Area Prescribing Committees is that: "Until further trial data is available, it is recommended that audit data on the use of FreeStyle Libre® is collected through its use in limited and controlled settings where patients are attending for Type 1 diabetes care. It is recommended that FreeStyle Libre® should only be used for people with Type 1 diabetes, aged 4 and above, attending specialist Type 1 care using multiple daily injections or insulin pump therapy, who have been assessed by the specialist clinician" and meet specific criteria.

Stakeholders also highlighted Diabetes UK's Type 1 diabetes technology: A consensus guideline which states that children aged 4 years and older may receive a flash glucose monitor (if other conditions are met). They also reported that flash glucose monitors are being prescribed to some children and young people with type 1 diabetes on the NHS.

A stakeholder also reported that there are issues with the interpretation of recommendation 1.2.63 which recommends considering ongoing real-time continuous glucose monitoring for 'children and young people who undertake high levels of physical activity (for example, sport at a regional, national or international level)'. They reported that clinical commissioning groups often refuse continuous glucose monitoring for children undertaking high levels of physical activity that is not at the high level of competition given as an example within the recommendation.

Hypoglycaemia in children and young people with type 1 diabetes

A topic expert noted that they thought the definition of hypoglycaemia should be updated. They highlighted a discussion paper that described internationally agreed upon definitions for hypoglycaemia and discussed potential regulatory approaches for recognising and labelling diabetes therapies in order to facilitate personalised care.

Diabetic retinopathy in children and young people with type 1 diabetes

Topic experts highlighted new evidence that indicates screening for diabetic retinopathy could take place less frequently than annually without leading to a delay in diagnosing clinically significant disease:

- Screening Intervals for Diabetic Retinopathy and Implications for Care
- Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes.

Initial intelligence gathering identified that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme.

Initial intelligence gathering also identified an NIHR Health Technology Assessment (HTA) on What works to increase attendance for diabetic retinopathy screening? An evidence synthesis and economic analysis. This reported that quality improvement incorporating behaviour change techniques such as goal-setting and providing additional social support increased diabetic retinopathy screening attendance by 12% on average compared with usual care, with a high probability of being cost-effective at a societal willingness to pay threshold of £20,000/QALY.

Uptake data for NICE guideline NG18 derived from the Royal College of Paediatrics and Child Health National Paediatric Diabetes Audit indicates that between 2015 and 2017 there have been annual increases in the percentage of children aged 12 years or older with T1D having an eye screening or a referral for eye screening (64.9%, 66.2% and 74.4%).

Impact statement

Insulin therapy for children and young people with type 1 diabetes

Evidence was identified which supports the existing recommendation 1.2.19 to offer children and young people with T1D MDI basal–bolus insulin regimens from diagnosis, and to then offer CSII or pump if injections aren't appropriate. While it was reported in 1 RCT that there are psychosocial benefits of CSII compared to MDI for children with T1D and benefits for carers of children with T1D, the current recommendations make it clear that patient choice is taken into consideration when advising on and choosing an insulin regimen (recommendation 1.2.18).

New evidence was also identified which supports both the use of the long-acting insulin degludec in children with T1D, which can be delivered as a once-daily injection and may be enhanced by the addition of fast-acting insulin aspart at mealtime, or alternatively the use of detemir injected once- or twice-daily. Evidence on degludec was not reviewed during the

original guideline development of NICE guideline NG18 but evidence for other long-acting insulins (glargine and detemir) was searched for; however at the time there were no published studies investigating the effectiveness of insulin glargine or insulin detemir specifically in children and young people and it was concluded that further research was needed. The committee also noted that 'there is no substantive evidence to suggest that any particular type of intermediate or long-acting insulin has greater clinical effectiveness than any other'. The evidence base remains limited, with only 3 published RCTs investigating long-acting insulin use in children and young people with T1D, with most of the data indicating non-inferiority in HbA1c control between the different intermediate or long-acting insulins, as such it is proposed that this is not currently an area for update.

Recommendation 1.2.30 advises that if a child or young person with T1D does not have optimal blood glucose control, that if necessary, they can be offered an alternative insulin regimen, including an insulin pump. New evidence from 1 RCT was identified concerning pumps that use new technology which automatically adjusts the delivery of insulin (hybrid closed-loop therapy). The results indicate that these newer devices may be superior to sensor-augmented pump therapy in controlling glucose and reducing the risk of hypoglycaemia in people with T1D of all ages, including children with sub-optimally controlled T1D. As the evidence base for this new technology is still emerging it is proposed that this is not currently an area for update.

New evidence is unlikely to change guideline recommendations.

Oral medicines for children and young people with type 1 diabetes

Recommendation 1.2.31 advises that metformin in combination with insulin is only given in the context of research studies 'because the effectiveness of this combined treatment in improving blood glucose control is uncertain'. New evidence from 2 RCTs indicates that compared with placebo, metformin given to children and young people with T1D as an adjunct to insulin does result in improved HbA1c levels, although the results were mixed concerning the long-term effectiveness. Given that the evidence base remains limited, with only 2 published RCTs, and the use of metformin in children and young people with T1D is off-label, it is proposed that this is not currently an area for update.

New evidence is unlikely to change guideline recommendations.

Dietary management for children and young people with type 1 diabetes

New evidence from 1 cluster RCT reported that a dietary education course led to significant improvements in quality of life but no differences in HbA1c. This does not have an impact on current recommendations which highlight the need for children and young people with T1D to be aware of the importance of healthy eating on their health, and that they should be supported in making changes to their food choices.

New evidence is unlikely to change guideline recommendations.

Blood glucose targets and monitoring

In line with current recommendations, a Cochrane review assessing the effects of intensive versus conventional glycaemic targets in patients with T1D concluded that 'treatment goals need to be individualised taking into account age, disease progression, macrovascular risk, as well as the patient's lifestyle and disease management capabilities'. Financial incentives for achieving daily blood glucose monitoring are not discussed in NICE guideline NG18 and the evidence from 1 RCT indicates that this is only effective while incentives are in place, indicating that this is not an effective long-term strategy for getting young people to monitor their blood glucose. The use of monitors integrated with smartphone technology are also not discussed in NICE guideline NG18, however current evidence from 1 RCT indicates that a blood glucose meter that integrates blood glucose testing with a smartphone App does not lead to additional improvements in blood glucose monitoring in comparison to using a traditional glucose meter in young people with T1D.

In relation to equipment for monitoring blood glucose, NICE guideline NG18 recommends offering a choice of equipment in order to optimise blood glucose control in response to adjustment of insulin, diet and exercise (recommendation 1.2.60). It also recommends offering ongoing real-time continuous glucose monitoring with alarms to children and young people with T1D who have frequent severe hypoglycaemia, or impaired awareness of hypoglycaemia associated with adverse or an inability to recognise, or communicate about, symptoms of hypoglycaemia (recommendation 1.2.62); and recommends considering ongoing real-time continuous glucose monitoring for neonates, infants and pre-school children, children and young people who undertake high levels of physical activity, children and young people who have comorbidities or are receiving treatments that can make blood glucose control difficult (recommendation 1.2.63).

There are no recommendations specifically on the use of a flash glucose monitor but the MIB describing the technology is available in the NICE Diabetes in Children and Young people interactive flowchart. While no evidence was identified concerning the effectiveness of a flash glucose monitor on blood glucose control and the new NHS England guidance, Regional Medicines Optimisation Committee statement and Diabetes UK guideline on prescribing this technology are not at odds with the recommendation to offer a choice of equipment, practitioners are prescribing these devices to some children with T1D and are not currently sure of NICE's position on the technology; it is therefore proposed that this is an area for update.

New evidence identified that may change current recommendations.

HbA1c targets and monitoring

New evidence from 1 RCT indicates that financial incentives given to young people with T1D have no impact on HbA1c levels, as such this evidence has no impact on existing recommendations.

New evidence is unlikely to change guideline recommendations.

Hypoglycaemia in children and young people with type 1 diabetes

A discussion paper on internationally agreed upon definitions for hypoglycaemia and proposed regulatory approaches for recognising and labelling diabetes therapies in order to facilitate personalised care was identified by a topic expert, however development and regulatory issues are not within scope for NICE guideline NG18. No definitions of hypoglycaemia are specified in the guideline recommendations 1.2.76 to 1.2.86 but reference is made to mild, moderate and severe hypoglycaemia. The full guideline reports that "there is no consistent or agreed definition of hypoglycaemia. In theory, hypoglycaemia is the level of blood glucose at which physiological neurological dysfunction begins. In practice, neurological dysfunction can be symptomatic or asymptomatic, and the level at which it occurs varies between individuals, may vary with time and circumstance, and is affected by antecedent hypoglycaemia or hyperglycaemia. Symptoms usually occur in most people when the blood glucose level is less than 3.0 mmol/l, although for some it may be as low as 2.0 mmol/l or as high as 3.5 mmol/l."

New evidence is unlikely to change guideline recommendations.

Psychological and social issues in children and young people with type 1 diabetes

While evidence from 3 RCTs indicates that psychological interventions have little impact on HbA1c levels in children and young people with T1D, there is evidence that CBT improves mental wellbeing. This is in line with the current recommendation to consider providing a programme of behavioural intervention therapy or behavioural techniques in order to improve health-related quality of life but does not indicate that such programmes necessarily help with treatment adherence or improved HbA1c levels (recommendation 1.2.103).

New evidence is unlikely to change guideline recommendations.

Diabetic retinopathy in children and young people with type 1 diabetes

While topic experts highlighted new evidence on the optimum frequency of screening for diabetic retinopathy, this area falls under the remit of the NHS Diabetic Eye Screening Programme and is therefore not considered in the surveillance review. The current recommendations to offer children and young people with T1D (or T2D) monitoring for diabetic retinopathy annually from 12 years of age is in line with the recommendations from the NHS Diabetic Eye Screening Programme. A footnote will be added to clarify that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme. We will ensure that we keep up-to-date with any changes made by the NHS Diabetic Eye Screening Programme that may impact on existing recommendations and review accordingly.

There was however evidence from an NIHR HTA that indicates attendance at screening for retinopathy could be improved by incorporating behaviour change techniques such as goal-setting and providing additional social support into services.

New evidence identified that may change current recommendations.

1.3 Type 2 diabetes

Surveillance proposal

This section should be updated.

Editorial amendments

Recommendation 1.3.14 highlights that in children or young people who have type 2 diabetes (T2D) and are overweight or obese, the benefits of physical activity and weight loss are addressed, and children supported in making lifestyle changes. There are cross-references to NICE guideline NG7 on 'preventing excess weight gain' and NICE guideline CG189 on 'obesity: identification, assessment and management'; however given that there are several relevant NICE guidelines in these areas, it is proposed that cross-references are made instead to the NICE physical activity, obesity and diet pathways.

In recommendation 1.3.43 on offering children and young people with type 2 diabetes annual monitoring, the bullet point that recommends 'diabetic retinopathy from 12 years' should have a footnote added noting that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme.

After recommendation 1.3.44 add the following recommendation: 'for guidance on managing non-alcoholic fatty liver disease in children and young people with type 2 diabetes, see the NICE guideline on Non-alcoholic fatty liver disease (NAFLD)'.

2019 surveillance summary

Study details for the evidence in this section are provided in Table 3.

Education and information for children and young people with type 2 diabetes

One RCT (n=90) reported that a nursing intervention in children with T2D resulted in significant improvements in compliance with dietary control, exercise, and drug use and significantly better blood glucose, blood lipids, blood pressure and body mass when compared to those receiving usual care. [18]

Smoking and substance misuse

No relevant evidence was identified.

Immunisation

No relevant evidence was identified.

Dietary management for children and young people with type 2 diabetes

See [18] above and Table 3 for study details.

Metformin

Three RCTs report on data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial, a large trial (n=699) comparing the efficacy and safety of 3 interventions: metformin, metformin plus rosiglitazone or metformin with an intensive lifestyle intervention incorporating nutrition, physical activity, and behaviour modification in children and young people aged 10-17 year olds with T2D. The following results were reported:

- A significant improvement in glycaemic control in the metformin with rosiglitazone compared to the metformin group [19]
- A non-significant improvement in glycaemic control in the metformin with lifestyle intervention compared to the metformin group [19]
- No difference in weight in the metformin with lifestyle intervention compared to the metformin or metformin with rosiglitazone group [20]
- No differences in metabolic syndrome between the 3 intervention groups. [21]

One RCT (n=91) also compared outcomes in 10-19 year olds with impaired glucose tolerance or T2D given metformin alone for 12 months or 3 months of insulin glargine followed by 9 months of metformin. No significant differences were found between the groups in HbA1c, fasting glucose, oral glucose tolerance test 2-h glucose results, beta-cell function or BMI percentile. [22]

HbA1c targets and monitoring for children and young people with type 2 diabetes

See [18] above and Table 3 for study details.

Surgery for children and young people with type 2 diabetes

No relevant evidence was identified.

Psychological and social issues in children and young people with type 2 diabetes

No relevant evidence was identified.

Monitoring for complications and associated conditions of type 2 diabetes

No relevant evidence was identified.

Hypertension in children and young people with type 2 diabetes

No relevant evidence was identified.

Dyslipidaemia in children and young people with type 2 diabetes

No relevant evidence was identified.

Diabetic retinopathy in children and young people with type 2 diabetes

No relevant evidence was identified.

Diabetic kidney disease in children and young people with type 2 diabetes

No relevant evidence was identified.

Intelligence gathering

Diabetic retinopathy in children and young people with type 2 diabetes

Initial intelligence gathering identified that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme. An NIHR HTA on What works to increase attendance for diabetic retinopathy screening? An evidence synthesis and economic analysis was also identified. This reported that quality improvement incorporating behaviour change techniques such as goal-setting and providing additional social support increased diabetic retinopathy screening attendance by 12% on average compared with usual care, with a high probability of being cost-effective at a societal willingness to pay threshold of £20,000/QALY.

Uptake data for NICE guideline NG18 derived from the Royal College of Paediatrics and Child Health National Paediatric Diabetes Audit indicates that for children aged 12 years or older with T2D 64.9% had an eye screening or a referral for eye screening in 2015, 47.2% had retinopathy in 2016, which increased to 54.8% in 2017.

Impact statement

Education and information for children and young people with type 2 diabetes

Recommendations 1.3.1 and 1.3.2 highlight the importance of providing children and young people with T2D and their family members or carers a continuing programme of tailored education on HbA1c monitoring and targets, the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control. The findings from 1 RCT on a nursing intervention in children with T2D that led to improvements in diet, exercise, drug use, blood glucose, blood lipids, blood pressure and body mass when compared to those receiving usual care, supports this recommendation.

New evidence is unlikely to change guideline recommendations.

Metformin

Overall, the evidence supports recommendation 1.3.22 to offer standard-release metformin from diagnosis to children and young people with T2D. While there is evidence that compared to metformin alone, glycaemic control is significantly improved if rosiglitazone and

metformin are prescribed, rosiglitazone has been suspended in the UK and as such it would not be appropriate to consider its use in children with T2D. There is evidence from 1 RCT on the use of insulin and metformin in children and young people with T2D. This RCT reported no differences in blood glucose measurements between those receiving insulin followed by metformin, compared to those given metformin alone. As evidence is based on 1 relatively small RCT, it is proposed that NICE guideline NG18 is not updated in relation to evidence concerning the use of metformin and insulin in children and young people with T2D.

New evidence is unlikely to change guideline recommendations.

Diabetic retinopathy in children and young people with type 2 diabetes

A footnote will be added to recommendation 1.3.43 to clarify that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme. We will ensure that we keep up-to-date with any changes made by the NHS Diabetic Eye Screening Programme that may impact on existing recommendations and review accordingly.

Evidence was identified that indicates attendance at screening for retinopathy could be improved by incorporating behaviour change techniques such as goal-setting and providing additional social support into services. Uptake data indicates that eye screening attendance is at a low rate in children aged 12 years or older who have T2D. As current recommendations do not discuss how attendance could be encouraged, this should be considered as an area for update.

New evidence identified that may change current recommendations.

1.4 Diabetic ketoacidosis

Surveillance proposal

This section should be updated.

2019 surveillance summary

Study details for the evidence in this section are provided in Table 4.

Recognition, referral and diagnosis of diabetic ketoacidosis

No relevant evidence was identified.

Initial management of diabetic ketoacidosis

No relevant evidence was identified.

Fluid and insulin therapy

A Cochrane review of 5 RCTs (n=201) assessed the effects of subcutaneous rapid-acting insulin analogues for the treatment of diabetic ketoacidosis (DKA) in any people with T1D or T2D and DKA. Only 1 of the trials (n=60) included younger diabetic participants and children. This trial found no significant difference in the time to reach a glucose level of 250 mg/dL between insulin lispro and intravenous (IV) regular insulin in children with DKA. This was in line with the overall findings of the Cochrane review that there were 'neither advantages nor disadvantages when comparing the effects of subcutaneous rapid-acting insulin analogues versus intravenous regular insulin for treating mild or moderate DKA'. The authors reported the evidence was mostly low- to very low-quality. [23] Five RCTs compared different doses and rates of administration of oral fluids and insulin therapy for the treatment of DKA:

- One RCT (n=50) reported that time to metabolic normalisation was significantly better in children and young people with T1D and DKA given IV fluid at high volume (20 mL/kg bolus + 1.5 × maintenance rate) compared to those given IV fluid at low volume (10 mL/kg bolus + 1.25 × maintenance rate), although there were no differences between the groups in overall hospital length of treatment. [24].
- Across the remaining 4 RCTs, there were no significant differences in outcomes reported between the following interventions:
  - a balanced salt solution (Hartmann's solution) versus 0.9% normal saline (n=77); but there was a significant improvement in time for plasma bicarbonate to reach 15 mmol/L in the children described as having 'severe' DKA who were given Hartmann's solution compared to 0.9% normal saline [25]
  - 3% saline versus 0.9% saline (n=40) [26]
  - different sodium chloride content of IV fluids (0.9% or 0.45%) and rate of administration (rapid or slow) (n=1,255) [27]
  - low-dose insulin infusion (0.05 U/kg per hour) versus standard dose insulin infusion (0.1 U/kg per hour) (n=50). [28]

Monitoring during therapy

No relevant evidence was identified.

Complications of diabetic ketoacidosis

Hypokalaemia

One RCT reported no differences in hypokalaemia in children with DKA (n=50) given a low-dose insulin infusion (0.05 U/kg per hour) compared with a standard dose insulin infusion (0.1 U/kg per hour). [28]

Avoiding future episodes of diabetic ketoacidosis

No relevant evidence was identified.

Intelligence gathering

Initial intelligence gathering and topic experts identified guidance from ISPAD: ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state which states that in children with DKA 'an assumed fluid deficit between 5% and 10% of body weight should be replaced over 24 to 48 hours along with maintenance fluids, using fluids with a sodium content between 0.45% and 0.9% saline. The risk of cerebral injury does not appear to be associated with differences in fluid protocols within these ranges. Therefore, clinicians should not unnecessarily restrict fluid administration if clinical signs suggest the need for circulatory volume expansion.' This recommendation is based on the findings of [27], a publication which topic experts also highlighted. One topic expert reported concern that current fluid therapy is "very conservative and my clinical impression is there are high rates of transient acute kidney injury with current recommendations." Published evidence concerning the impact on kidney injuries was not provided.

Topic experts also highlighted Fluid treatment for children with diabetic ketoacidosis: How do the results of the pediatric emergency care applied research network Fluid Therapies Under Investigation in Diabetic Ketoacidosis (FLUID) Trial change our perspective which discusses implications of the findings of [27] on fluid therapy on DKA. This report concludes that 'rapid fluid infusion does not cause brain injury (within the range of infusion rates evaluated). Furthermore, although the main trial results showed no significant differences in neurological outcomes in the study arms, subanalyses in children with the most severe DKA suggested more rapid improvements in mental status with more rapid fluid infusion rates. These findings emphasize that fluid infusion for DKA treatment should not be restricted because of concerns about causing brain injury. Most, if not all, children with DKA require a fluid bolus of 20 mL/Kg, and additional fluid boluses should be administered if peripheral perfusion remains poor or there are other clinical signs of circulatory compromise after the initial fluid bolus.'

Impact statement

Fluid and insulin therapy

The new evidence supports existing recommendations 1.4.22-49 in that there is evidence that both subcutaneous rapid-acting insulin analogues and IV regular insulin are effective for treating mild or moderate DKA and that 0.9% sodium chloride is an appropriate fluid. However, the new evidence, notably from [27], indicates that rapid fluid infusion at volumes higher than those recommend in recommendation 1.4.31 is not associated with an increased risk of cerebral oedema in children and young people with DKA; and that in the case of severe DKA, more rapid fluid infusion rates may be associated with faster improvements in mental status. This evidence, along with international guidance and topic expert opinion indicates that this should be an area for update.

New evidence identified that may change current recommendations.

1.5 Service provision

Surveillance proposal

This section should not be updated.

2019 surveillance summary

Study details for the evidence in this section are provided in Table 5.

Service provision

A Cochrane review of 93 RCTs (n=22,047) assessed the effects of telemedicine compared to usual care in people with various chronic conditions, including diabetes (21 RCTs, n=2,768), of which 3 studies included young people (n=217). Overall, it was reported that telemedicine can improve the control of blood glucose in those with diabetes. [29]

An RCT with adolescents with T1D or T2D (n=146) assessed the effectiveness of a multisystemic therapy involving an intensive, home and community-based family treatment on patient-provider relationships. It reported some improvements in aspects of patient-provider relationships. [30]

An RCT with children with T2D in India (n=90) reported that a nursing intervention resulted in significant improvements in drug compliance in comparison to usual care. [18]

Transition from paediatric to adult care

A Cochrane review of 4 RCTs (n=238) assessed the effectiveness of interventions designed to improve the transition of care for adolescents from paediatric to adult health services. All chronic conditions that required ongoing clinical care were included. One trial assessed a structured comprehensive transition programme with a transition co-ordinator for adolescents with T1D (n=26). The trial found that at 12-month follow-up, there was no significant difference in rates of transfer from paediatric to adult diabetes services nor in risk of disease-related hospital admissions. The quality of the evidence was rated as low. Data from this trial was also combined with another trial which evaluated a technology-based intervention for adolescents with a range of different conditions on the use of health services. It was reported that these interventions may lead to slightly more young people taking positive steps to initiate contact with health professionals themselves, but the quality of the evidence was rated as low, and results were non-significant. [31]

There was also an RCT with young adults aged between 17 to 19 years old with T1D (n=120) that assessed the effect of an appointment-management intervention on clinic attendance and disengagement after transition of care from paediatric to adult services. They found no improvements in clinic attendance or disengagement from services 0-12 months post-transition from the intervention but did find significant improvements at 12-24 months after transition. [32]

Intelligence gathering

No evidence was identified.

Impact statement

The evidence supports existing recommendations that include the need for a multidisciplinary team to provide care (recommendation 1.5.1) and the provision of 24-hour telephone access (telemedicine; recommendation 1.5.4). While the evidence was mixed concerning the effectiveness of interventions on improving the transition from paediatric to adult care, the the quality of the evidence was rated as low in the Cochrane review and there is overall only a small number of trials in this area. The evidence does not indicate that the principles in recommendations 1.5.9-1.5.13 do not hold.

New evidence is unlikely to change guideline recommendations.

Research recommendations

Research recommendation	Summary of findings
What is the clinical and cost effectiveness of a programme of structured education from diagnosis for children and young people with type 1 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the impact of training in teaching skills for healthcare professionals on the effectiveness of education for children and young people with type 1 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the effectiveness of education programmes in which young people with type 1 diabetes provide training for their peers?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Research is needed to compare the effectiveness of continuous subcutaneous insulin infusion (or insulin pump therapy) and multiple daily injection regimens in children and young people with type 1 diabetes.	There is new evidence from 1 RCT that indicates there is no difference in effectiveness between CSII and MDI in reducing HbA1c, but that CSII may not be cost-effective.

Research recommendation	Summary of findings
Research is needed to evaluate the effectiveness of long-acting insulin analogues in children and young people with type 1 diabetes.	The new evidence from 2 RCTs supports the use of the long-acting insulin degludec in children with T1D.
Further research is required to evaluate the effectiveness of insulin delivery systems in children and young people with type 1 diabetes.	The new evidence from 1 RCT indicates that pumps that use new technology may be superior to sensor-augmented pump therapy in children with sub-optimally controlled T1D in controlling glucose and reducing the risk of hypoglycaemia
Research is needed to compare the effectiveness of insulin delivery modes (for example, dermal, nasal, oral and pulmonary) in children and young people with type 1 diabetes.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the clinical and cost effectiveness of non-insulin agents (for example, metformin) combined with insulin treatment in children and young people with type 1 diabetes?	The new evidence from 2 RCTs indicates that compared with placebo, metformin given to children and young people with T1D as an adjunct to insulin does result in improved HbA1c levels.
What is the impact of educating children and young people with type 1 diabetes and their family members or carers (as appropriate) about their glycaemic index from diagnosis?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the optimal upper limit and timing for blood glucose measurements after meals for children and young people with type 1 diabetes to reach an HbA1c level of 48 mmol/mol (6.5%) without unacceptable hypoglycaemia?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the clinical and cost effectiveness of real-time continuous glucose monitoring systems compared to 5 or more capillary blood glucose tests per day in children aged 5 years or younger with type 1 diabetes who use insulin pump therapy?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Research is needed to investigate the clinical implications of alternative site monitoring (for example, the arm as opposed to the finger) in children and young people with type 1 diabetes.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
Further research is needed to evaluate the effects of persistent hypoglycaemia and recurrent diabetic ketoacidosis on neurocognitive function.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Further studies are needed to evaluate the effectiveness of behavioural and social interventions on anxiety and depression, eating disorders, behavioural and conduct disorders, and adherence to therapy in children and young people with type 1 diabetes, especially in adolescence, from diagnosis and in established diabetes.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Further research is needed to evaluate the effectiveness of screening for cardiovascular risk factors in children and young people with type 1 diabetes.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the correlation between changes in body mass index standard deviation scores and absolute HbA1c measurements or changes in HbA1c in children and young people with type 2 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the long-term comparative clinical and cost effectiveness of different metformin preparations for treating type 2 diabetes in children and young people?	The new evidence shows that metformin administered in tablet form using a standard dosage improves glycaemic control: metformin was provided as 1000mg capsules in the TODAY trial [19-21] and the dosage/preparation was not described in the abstract of the other RCT [22]. Different metformin preparations were not compared with one another.
What is the clinical and cost effectiveness of psychological interventions for children and young people with type 2 diabetes?	There is new evidence from 3 RCTs which indicates that psychological interventions have little impact on HbA1c levels in children and young people with T1D, but that CBT improves mental wellbeing.

Research recommendation	Summary of findings
What is the optimal dosage of intravenous insulin for managing diabetic ketoacidosis (DKA) in children and young people?	The new evidence indicates that larger dosages of insulin than those recommended in NICE guideline NG18 are not associated with an increased risk of cerebral oedema in children with DKA. This should be considered in an update to the guideline.
Further research is needed to evaluate the effects of low blood glucose levels on learning, attendance at school and educational attainment.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Further research is needed to investigate young people's experiences of transition from paediatric to adult services for people with type 1 diabetes.	The new evidence from a Cochrane review and an RCT was mixed concerning the effectiveness of interventions on improving the transition from paediatric to adult care.

Data summary tables

Table 1. Diagnosis

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Diagnosis of T2D in children and young people							
Hannon, T. S.; et al. (2017) [1]	cRCT	1,369	Children aged 10 years or older with T2D or at risk of T2D	T2D module to a computerised clinical decision support	usual computerised clinical decision support	screening for T2D	Improvement with intervention
						attending a scheduled follow-up appointment	Improvement with intervention
*Type of study cRCT = cluster randomised controlled trial n = number of participants T2D = type 2 diabetes							

Table 2. Type 1 diabetes

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Insulin therapy for children and young people with type 1 diabetes							
Battelino, T.; et al. (2018) [2]	RCT	362	1 - <18 years old with T1D	Insulin degludec/insulin aspart (IDegAsp) once-daily (OD) plus insulin aspart (Asp) for remaining meals	insulin detemir (IDet) OD or twice-daily plus mealtime Asp (Idet + Iasp)	HbA1c	No improvement with intervention (non-inferior)
Thalange, N., et al. (2015) [3]	RCT	350 (for 26 weeks), 280 (for 26 weeks extension)	1 – 17 years old with T1D	Insulin degludec (IDeg) OD	IDet once- or twice-daily, with prandial insulin aspart	HbA1c at 26 and 52 weeks	No improvement with intervention (non-inferior)
						change in mean fasting plasma glucose	Improvement with intervention
						hypoglycaemia	No improvement with intervention (non-inferior)
						hyperglycaemia with ketosis	Improvement with intervention

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Bode, B.W., et al. (2019) [4]	RCT	777	1 - <18 years old with T1D	Fast-acting insulin aspart (faster aspart) plus IDeg at mealtime	IDegAsp at mealtime	HbA1c (at 26 weeks follow-up)	Improvement with intervention
						Change from baseline in 1-h postprandial glucose increment	Improvement with intervention
						hypoglycaemia	No improvement with intervention (non-inferior)
				Faster aspart plus IDeg post-meal	IDegAsp at mealtime	HbA1c (at 26 weeks follow-up)	No improvement with intervention (non-inferior)
						Change from baseline in 1-h postprandial glucose increment	NR
						hypoglycaemia	No improvement with intervention (non-inferior)
Blair, Joanne; et al. (2018) [5]	RCT	293	7 months - 15 years with T1D	Continuous subcutaneous insulin infusion (CSII) (SCIPI RCT)	Multiple daily injections (MDI) initiated within 14 days of T1D diagnosis	HbA1c (at 12 months follow-up)	No improvement with intervention
						Cost effectiveness	No improvement with intervention
Enander, R.; et al. (2018) [6]	RCT	54	2.8 - 14.9 years old with T1D	48 to 72 hours IV insulin therapy at diagnosis	multiple subcutaneous injections	mean plasma glucose (first 2 full days of insulin therapy)	Improvement with intervention
						HbA1c (at 24 months follow-up)	No improvement with intervention
						insulin doses (at 24 months follow-up)	No improvement with intervention
						maximal mixed-meal tolerance test (at 24 months follow-up)	No improvement with intervention
Mueller-Godeffroy, Esther; et al. (2018) [7]	RCT	211	6 - 16 years old with T1D (receiving MDI)	Immediate CSII (PUMPKIN trial)	MDI for 6 months before transferring to CSII	Patient-reported diabetes-specific quality of life for age group 12-16 years	No improvement with intervention

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
						Patient-reported diabetes-specific quality of life for age group 8-11 years	Improvement with intervention
						Diabetes burden of main caregiver	Improvement with intervention
Tauschmann, M.; et al. (2018) [8]	RCT	86 (33 were aged 6–12 years and 19 were aged 13–21 years)	>6 years old with sub-optimally controlled T1D (population had an insulin pump)	Hybrid closed-loop therapy	Sensor-augmented pump therapy	HbA1c	Improvement with intervention
						Proportion of time glucose concentration was within target range (glucose control)	Improvement with intervention
Oral medicines for children and young people with type 1 diabetes							
Anderson, J. J. A.; et al. (2017) [9]	RCT	90	8 - 18 years old with T1D	Metformin	Placebo	HbA1c at 3 and 12 months	Improvement with intervention
						Vascular function	Improvement with intervention
						Gastrointestinal side effects	No improvement with intervention
						Insulin dose	Improvement with intervention
Libman, I. M.; et al. (2015) [10]	RCT	140	12.1 - 19.6 years with T1D	Metformin	Placebo	HbA1c at 13 weeks follow-up	Improvement with intervention
						HbA1c at 26 weeks follow-up	No improvement with intervention
						Total daily insulin (per kg of body weight)	Improvement with intervention
						BMI score	Improvement with intervention
						Gastrointestinal side effects	No improvement with intervention
Dietary management for children and young people with type 1 diabetes							

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Price, K. J.; et al. (2016) [11]	cRCT	396	11-16 years old with T1D	Structured education course (KICk-OFF: Kids in Control of Food)	Usual care	HbA1c	No improvement with intervention
						Generic quality of life scores at 6 and 12 months follow-up	Improvement with intervention
Blood glucose targets							
Fullerton, B.; et al. (2014) [12]	CR	12 RCTs (n=2,230; 1 RCT with children with T1D n=NR))	T1D (all ages)	tighter ('intensive') blood glucose control)	less intense treatment targets ('conventional' glucose control)	risk of developing microvascular diabetes complications	Improvement with intervention
Blood glucose monitoring, HbA1c targets and monitoring							
Wong, C. A.; et al. (2017) [13]	RCT	90	14 - 20 years old with T1D	Financial incentive ($60 monthly) (BE IN CONTROL)	No incentive	Adherence to glucose monitoring at end of intervention	Improvement with intervention
						Adherence to glucose monitoring at 3 months follow-up	No effect with intervention
						Change in HbA1c levels at end of intervention	No effect with intervention
						Change in HbA1c levels at 3 months follow-up	No effect with intervention
Di Bartolo, P.; et al. 2017 [14]	RCT	182	14 – 24 years old with poorly controlled T1D and poorly compliant with blood glucose self-monitoring	Experimental glucose meter with an App (iBGStar™ + DMApp) (i-NewTrend)	Standard glucose monitoring	Change in HbA1c at 6 months	No effect with intervention
						Achievement of compliance with self-monitoring of blood glucose at 6 months	No effect with intervention
						Quality of life at 6 months	No effect with intervention
Psychological and social issues in children and young people with type 1 diabetes							

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Christie, Deborah; et al. (2016) [15]	cRCT	362	8 - 16 years old with T1D	Clinic-based structured educational group incorporating psychological approaches (CASCADE)	Standard care	HbA1c	No improvement with intervention
						HbA1c measured at 12 or 24 months	No improvement with intervention
						Diabetes-specific QoL	No improvement with intervention
Mayer-Davis, Elizabeth J.; et al. (2018) [16]	RCT	258	13 - 16 years old with T1D	Motivational interviewing and problem-solving skills training (FLEX)	Usual care	HbA1c at 18 months	No improvement with intervention
Wei, C.; et al. (2018) [17]	RCT	85	11 - 16 years old with T1D	Cognitive behavioural therapy	Non-directive supportive counselling	HbA1c at 24 months	No improvement with intervention
						Psychological outcomes	Improvement with intervention

*Type of study CR = Cochrane review; cRCT = cluster randomised controlled trial; RCT = randomised controlled trial.

n = number of participants. The number of participants was not always reported in the abstract (NR).

CSII = continuous subcutaneous insulin infusion; IDeg = insulin degludec; IDet = insulin detemir; IDegAsp = Insulin degludec and insulin aspart; NR = not reported in the abstract; MDI = Multiple daily injections; OD = once-daily; T1D = type 1 diabetes;

Table 3. Type 2 diabetes

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Education and information for children and young people with type 2 diabetes							
Hezang, B.; et al. (2017) [18]	RCT	90	Children with T2D	nursing intervention	usual care	dietary control compliance	Improvement with intervention
						exercise treatment compliance	Improvement with intervention
						blood glucose, blood lipids, blood pressure and body mass	Improvement with intervention
Metformin							

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Narasimhan, S.; Weinstock, R. S. (2014) [19]	RCT	699	Obese youth aged 10 - 17 years old with new-onset T2D	metformin with rosiglitazone	monotherapy with metformin	glycaemic control	Improvement with intervention
				metformin with an intensive lifestyle intervention (TODAY trial)	monotherapy with metformin	glycaemic control	No improvement with intervention
Marcus, M. D.; et al. (2017) [20]	RCT	595	11 - 17 years old with T2D	metformin with an intensive lifestyle intervention	monotherapy with metformin	Change in weight	No improvement with intervention
				metformin with an intensive lifestyle intervention (TODAY trial)	metformin with rosiglitazone	Change in weight	No improvement with intervention
Weinstock, R. S.; et al. (2015) [21]	RCT	679 at baseline; 625 at 6 months follow-up; 545 at 24 months.	Youth with T2D	metformin with rosiglitazone metformin with an intensive lifestyle intervention (TODAY trial)	monotherapy with metformin	metabolic syndrome	No improvement with intervention
Consortium, Rise (2018) [22]	RCT	91	Overweight or obese 10 - 19 years old with IGT or T2D	3 months insulin glargine followed by 9 months metformin (RISE)	12 months metformin alone	beta-cell function	No improvement with intervention
						BMI percentile	No improvement with intervention
						HbA1c, fasting glucose, oral glucose tolerance test 2-h glucose results	No improvement with intervention

*Type of study RCT = randomised controlled trial

n = number of participants.

IGT = impaired glucose tolerance; T2D = type 2 diabetes.

Table 4. Diabetic ketoacidosis (DKA)

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Andrade-Castellanos, C. A.; et al. (2016) [23]	CR	5 RCTs (n=201; 1 RCT with children with DKA n=60)	People (all ages) with DKA	subcutaneous rapid-acting insulin analogues	standard IV insulin infusion	time to reach a glucose level of 250 mg/dL	No improvement with intervention
Bakes, K.; et al. (2016) [24]	RCT	50	0 - 18 years old with T1D and DKA	IV fluid at high volume (20 mL/kg bolus + 1.5 × maintenance rate)	IV fluid at low volume (10 mL/kg bolus + 1.25 × maintenance rate)	time to metabolic normalisation	Improvement with intervention
						Normalisation of PH	Improvement with intervention
						Normalisation of serum bicarbonate	No improvement with intervention
						length of hospital treatment and time to discharge	No improvement with intervention
Yung, M.; Letton, G.; Keeley, S. (2017) [25]	RCT	77	Children with DKA	a balanced salt solution (Hartmann's solution)	0.9% normal saline	time for plasma bicarbonate to reach 15 mmol/L	No improvement with intervention
Shaf, O.; Kumar, V. (2018) [26]	RCT	40	Children with moderate to severe DKA	3% saline	0.9% saline	hemodynamic improvement, the resolution of acidosis and the correction of hyperglycaemia	No improvement with intervention
Kuppermann, N.; et al. (2018) [27]	RCT	1,255	Children with DKA	sodium chloride content of IV fluids (0.9% or 0.45%) and rate of administration (rapid or slow)	sodium chloride content of IV fluids (0.9% or 0.45%) and rate of administration (rapid or slow)	neurological outcomes	No improvement with intervention (non-inferior)
Nallasamy, K.; et al. (2014) [28]	RCT	50	≤ 12 years old with DKA	low-dose insulin infusion (0.05 U/kg per hour)	standard dose insulin infusion (0.1 U/kg per hour)	rate of decrease in blood glucose until to 250 mg/dL or less	No improvement with intervention (non-inferior)
						time to resolution of acidosis	No improvement with intervention (non-inferior)
						episodes of treatment failures	No improvement with intervention (non-inferior)

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
						hypokalaemia	No improvement with intervention (non-inferior)
						hypoglycaemia	No improvement with intervention (non-inferior)

*Type of study CR = Cochrane review; RCT = randomised controlled trial

n = number of participants.

DKA = diabetic ketoacidosis; T1D = type 1 diabetes

Table 5. Service provision

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Service provision							
Flodgren, G., et al. (2015) [29]	CR	21 RCTs with people with diabetes (3RCTs with young people, n=217)	People with chronic conditions including diabetes	Telemedicine	Usual care	Blood glucose control	Improvement with intervention
Carcone, A. I.; et al. (2015) [30]	RCT	146	Adolescents with T1D or T2D	multisystemic therapy	telephone support	Patient-provider relationships: Coordinated and Comprehensive Care scale	Improvement with intervention
						Patient-provider relationships: Respectful and Supportive Care scale; Enabling and Partnership Scale; Providing Specific Information scales	No improvement with intervention
Hezang, B.; et al. (2017) [18]	RCT	90	Children with T2D	nursing intervention	usual care	drug compliance	Improvement with intervention
Transition from paediatric to adult care							

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Campbell, F.; et al. (2016) [31]	CR	4 RCTs (n=238; 1 RCT with adolescents with T1D n=26)	Adolescents with chronic conditions including T1D	comprehensive transition programme	Usual care	rates of transfer from paediatric to adult diabetes services	No improvement with intervention
						risk of disease-related hospital admissions	No improvement with intervention
White, Mary; et al. (2017) [32]	RCT	120	17 - 19 years old with T1D	Transition from paediatric to adult care (TrACeD)	Standard care	Clinic attendance 0-12 months post-transition	No improvement with intervention
						Clinic attendance 12-24 months post-transition	Improvement with intervention
						Disengaged from services 0-12 months post-transition	No improvement with intervention
						Disengaged from services 12-24 months post-transition	Improvement with intervention

*Type of study CR = Cochrane review; RCT = randomised controlled trial.

n = number of participants.

T1D = type 1 diabetes; T2D = type 2 diabetes.

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