# CHAPTER 7-CKD GUIDELINE

## CONTENTS:

### 7.1. MODIFICATION OF LIFESTYLE

### 7.2. DIETARY INTERVENTION AND RENAL OUTCOMES

### 7.1. MODIFICATION OF LIFESTYLE

**In adults with CKD, do improving lifestyle habits decrease progression of CKD?**

<table>
<thead>
<tr>
<th>Ref ID: 414</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castaneda C, Gordon PL, Uhlin KL et al. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial.[see comment]. <em>Annals of Internal Medicine.</em> 2001;</td>
<td>RCT 1+ Randomised, blinded 1 centre USA Not ITT</td>
<td>N =26</td>
<td>Drop out rate 0% in each arm</td>
<td>Inclusion criteria: people &gt; 50 years with CKD (creatinine 133-442 micromol/l or 1.5-5.0 mg/dl)</td>
<td>N=14 Resistance training + low protein diet Procedure: Nutrition status and adherence to low-protein diet (0.6 g/kg body weight per day) was observed for 2-8 weeks run-in. Participants randomised to resistance group + low protein diet (three exercise sessions/week supervised by a blinded trainer with increasing workloads on five weight resistance machines) or to sham training + low protein diet (gentle movements of upper and lower body while standing, sitting and bending designed to have no physiologic impact). Muscle strength tests determined at baseline and after 12 weeks of training. GFR (125I-iothalamate), biochemical measures</td>
<td>N=12 Sham training + low protein diet</td>
<td>3 months</td>
<td>Change in muscle strength Change in GFR Total body K</td>
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<td>Exclusion criteria: MI in past 6 months, unstable chronic condition, dementia, alcoholism, dialysis or RRT, current resistance training, recent involuntary weight change (2 kg), albumin &lt; 30 g/l, proteinuria &gt; 10 g/d, abnormal stress test result at screening</td>
<td>Baseline characteristics: NS differences between people randomised to resistance training or</td>
<td>**Baseline characteristics: NS differences between people randomised to resistance training or</td>
<td>**Baseline characteristics: NS differences between people randomised to resistance training or</td>
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</table>
### Effect size
Adherence to resistance training was 91% and to sham training was 90%. NS difference.
Adherence to low protein diet: resistance training group consumed 108% of target protein levels and sham group consumed 112% of target protein levels (NS between groups).

### Change in muscle strength:
People who took resistance training + low protein diet had an increase in muscle strength (+32%, N=14), whereas the sham training + low protein diet had decreased overall muscle strength (-13%, N=12). P<0.001 between groups.

### Change in Total body Potassium:
Resistance training increased total body potassium in the resistance training + low protein diet (+4%, N=12), whereas potassium decreased in the sham training + low protein diet (-6%, N=11), p=0.014 between groups.

### Change in GFR:
GFR increased in people with resistance training + low protein diet (+ 1.18 ml/min/1.73m$^2$ absolute change, N=14), whereas GFR decreased in the sham training + low protein diet group (-1.62 ml/min/1.73m$^2$ absolute change, N=12). P=0.048 between groups.

No exercise adverse events or injuries were reported in either group.
Assessment of bias: small study may not be adequately powered to detect changes between groups.

### Reference Study type/Evidence level

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<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eidemak I, Haaber AB, Feldt RB et al. Exercise training and the progression of chronic renal failure.[see RCT 1+</td>
<td>RCT 1+ Randomised, blinding not applicable</td>
<td>N =30 Drop out rate 20% in exercise 26% in usual</td>
<td><strong>Inclusion criteria:</strong> nondiabetic people with moderate progressive CKD (median GFR 25 ml/min/1.73m$^2$, range 10-43 ml/min/1.73m$^2$)</td>
<td>N=15 Exercise training Procedure: Patients randomised to exercise group (mainly bicycle ergometer exercise in the patient’s home, running, swimming, and walking) or to control group (patients maintained their usual, mostly</td>
<td>N=15 Usual (sedentary lifestyle)</td>
<td>1.5 years or until death or RRT (median 20 month)</td>
<td>Change in maximal aerobic work capacity Progression of renal disease (slope of GFR vs time) Blood lipids</td>
<td>University of Copenhagen, Medical Foundation if Greater Copenhagen</td>
</tr>
</tbody>
</table>
Baseline characteristics: NS differences between people randomised to exercise training or control (usual, sedentary lifestyle) for gender, age (45 years), GFR (26 ml/min) aerobic work capacity, BP, progression of nephropathy (reciprocal of serum creatinine vs time)

sedentary lifestyle). Exercise duration and intensity gradually increased up to 60-75% of maximal exercise capacity determined by exercise testing. Exercise tests were performed before randomisation and at the end of the study. Exercise testing consisted of cycling on an electronically braked bicycle ergometer coupled to a cardiopulmonary gas exchange system. Plasma creatinine, physical exam, and clinical chemistry tests performed at baseline and every month. GFR ($^{51}$Cr-EDTA clearance) was measured at baseline, and every 3-9 months.

<table>
<thead>
<tr>
<th>Effect size</th>
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<tbody>
<tr>
<td>3 people in the exercise group started dialysis, N=2 in the control group started dialysis.</td>
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<td>N=1 control died (unknown reason)</td>
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<td>N=1 control withdrew after 10 months for personal reasons.</td>
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</table>

Change in maximal aerobic work capacity:
Maximal aerobic work capacity significantly increased in the exercise group (N=15; 25 ml O$_2$/ (min X kg BW) at baseline to 27 ml O$_2}$/ (min X kg BW) after 18 months, p<0.05), whereas maximal aerobic work capacity did NS change in the control group (N=15, 21 ml O$_2$/ (min X kg BW) at baseline to 19 ml O$_2$/ (min X kg BW) after 20 months, p NS).

Change in GFR:
Median GFR decreased in both control (N=15; -0.28 ml/min/month) and exercise groups (N=15; -0.27 ml/min/month, NS between treatments)

Blood Lipids: NS changes from baseline in triglycerides, VLDL, HDL, LDL cholesterol in exercise or control groups. Total cholesterol significantly increased from baseline in the exercise group, p<0.05. NS changes from baseline for total cholesterol in the control group.

Assessment of bias: No blinding (not possible), small study N=15 in each arm may not be adequately powered to detect changes between groups. Authors note that renal function did not decline with exercise and suggest that exercise is neither detrimental nor overly beneficial to this population. Exercise could have other benefits (cardiovascular, feelings of well-being, etc)

Ref ID: 318

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Number of</th>
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<th>Length of</th>
<th>Outcome measures</th>
<th>Source of</th>
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<tbody>
<tr>
<td>Chronic kidney disease: evidence tables DRAFT</td>
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<table>
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<tr>
<th>level</th>
<th>patients</th>
<th>Inclusion criteria: chronic (&gt; 1 year duration) proteinuric (&gt; 1 g/24-h urine protein on at least 3 consecutive determinations in preceding 6 months) nephropathy of diabetic or nondiabetic origin, BMI &gt; 27 kg/m²)</th>
<th>Low calorie diet N=20 Procedure: Prior to the study, all patients completed a 2 month observation period with a full history, exam, blood pressure, BMI, and lab tests. ACE inhibitors, nondihydropyridine CCBs, and ARBs were withdrawn 6 weeks prior to randomisation. Statins and antihypertensive agents (other than ACE, ARB, or CCB) permitted as long as dose remained the same throughout. BP targeted to &lt; 140/90 mm Hg (doxazosin as first choice, then amlodipine if needed) Patients randomised 2:1 to low-calorie normo-protein diet group or control (usual diet) group. The low-calorie normo-protein diet was a reduction of 500 kcal with respect to the individual's usual diet (determined from 3 day food diaries) and consisted of 25-30% fat and 55-65% carbohydrate of total caloric intake. Protein content was adjusted to 1 to 1.2 g/kg/day. Physical exam, BMI, BP, weight, interview with dietician performed at baseline and weeks 1, 3, and 5 after randomisation. Laboratory evaluations performed at baseline, 1 and 5 months later. CrCl estimated from Cockcroft Gault.</th>
<th>Usual diet N=10</th>
<th>5 months</th>
<th>BMI Change in protein excretion Change in CrCl Change in serum creatinine</th>
<th>Not stated</th>
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<tbody>
<tr>
<td>RCT 1+</td>
<td>N=30</td>
<td>Not blinded</td>
<td>Spain</td>
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<td>Inclusion criteria: chronic (&gt; 1 year duration) proteinuric (&gt; 1 g/24-h urine protein on at least 3 consecutive determinations in preceding 6 months) nephropathy of diabetic or nondiabetic origin, BMI &gt; 27 kg/m²)</td>
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<td>Exclusion criteria: Unstable renal disease, nephrotic syndrome requiring diuretic therapy, immunosuppressive therapy, hypertension requiring &gt; 2 antihypertensive agents</td>
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<tr>
<td>Baseline characteristics: NS differences between people randomised to low calorie or usual diet</td>
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**Table:**

| Inclusion criteria: chronic (> 1 year duration) proteinuric (> 1 g/24-h urine protein on at least 3 consecutive determinations in preceding 6 months) nephropathy of diabetic or nondiabetic origin, BMI > 27 kg/m²) | Low calorie diet N=20 Procedure: Prior to the study, all patients completed a 2 month observation period with a full history, exam, blood pressure, BMI, and lab tests. ACE inhibitors, nondihydropyridine CCBs, and ARBs were withdrawn 6 weeks prior to randomisation. Statins and antihypertensive agents (other than ACE, ARB, or CCB) permitted as long as dose remained the same throughout. BP targeted to < 140/90 mm Hg (doxazosin as first choice, then amlodipine if needed) Patients randomised 2:1 to low-calorie normo-protein diet group or control (usual diet) group. The low-calorie normo-protein diet was a reduction of 500 kcal with respect to the individual's usual diet (determined from 3 day food diaries) and consisted of 25-30% fat and 55-65% carbohydrate of total caloric intake. Protein content was adjusted to 1 to 1.2 g/kg/day. Physical exam, BMI, BP, weight, interview with dietician performed at baseline and weeks 1, 3, and 5 after randomisation. Laboratory evaluations performed at baseline, 1 and 5 months later. CrCl estimated from Cockcroft Gault. | Usual diet N=10 | 5 months | BMI Change in protein excretion Change in CrCl Change in serum creatinine | Not stated |
**Effect size**

**Weight:**
Weight significantly decreased after 5 months of a low calorie diet (87.5 kg at baseline to 83.9 kg after 5 months, p<0.01, N=20), whereas weight increased significantly in the usual diet group (96.1 kg at baseline to 98 kg at 5 months, p<0.05, N=10) and p<0.05 between groups.

**BMI:**
BMI significantly decreased after 5 months of a low calorie diet (33 kg/m² at baseline to 31.6 kg/m² after 5 months, p<0.01, N=20) and significantly increased in the usual diet group (34.3 kg/m² at baseline to 35 kg/m² after 5 months, p<0.05, N=10) and p<0.05 between groups.

**BP:**
NS changes in SBP and DBP in either low calorie or usual diet groups.

**Change in CrCl:**
There were NS changes in CrCl after 5 months of low calorie diet, however CrCl significantly decreased in the usual diet group (61.8 ml/min/1.73 m² at baseline to 56 ml/min/1.73 m² after 5 months, p<0.05) NS changes between groups.

**Change in serum creatinine:**
There were NS changes in serum creatinine after 5 months of a low calorie diet, whereas creatinine significantly increased after 5 months of a usual diet (1.6 mg/dl at baseline to 1.8 mg/dl at 5 months, p<0.05) NS between groups.

**Change in protein excretion:**
Urinary protein excretion significantly decreased after 5 months of a low calorie diet (2.8 g/24-h at baseline to 1.9 g/24-h at 5 months, -31% reduction, p<0.05).
There was a NS increase in proteinuria in the usual diet group (3 g/24-h at baseline to 3.5 g/24-h at 5 months, NS). (p<0.05 between groups).

Weight loss was significantly correlated with a decrease in UPE (r=0.62, p<0.01), but not BP or creatinine clearance.

Results were similar when diabetic and nondiabetic people were analysed separately.

Assessment of bias: small study N=30 and short follow-up (5 months) No blinding, Cockcroft Gault less accurate to estimate CrCl in obese people.

<table>
<thead>
<tr>
<th>Ref ID: 558</th>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparis on</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of fundin g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hovind P, Rossing P, Tarnow L et al. Smoking and progression</td>
<td>Prospective cohort</td>
<td>N total = 301</td>
<td>Inclusion: patients with type 1 diabetes and nephropathy (persistent albuminuria &gt; 300 mg/24-h in at least 2 of 3 consecutive 24-h urine collections, presence of diabetic retinopathy)</td>
<td>Smokers N = 176</td>
<td>Median 7 years (range 3-14 years)</td>
<td>decline in GFR</td>
<td>Danish Diabetes Foundati on, Hansen</td>
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</tbody>
</table>

- **N non-smokers = 94**
- **N ex-smokers = 31**
- **1 centre study: Steno clinic, Denmark**

Exclusion criteria: other renal disease

Population baseline characteristics:
- NS between groups for duration of diabetes, retinopathy, albuminuria, HbA1C.
- Ex-smokers (mean 35 years) were significantly older than non-smokers (35 years) or smokers (36 years). Smokers had significantly lower SBP and DBP than non-smokers or ex-smokers.
- Schmokers had significantly higher GFR (92 ml/min/1.73m²) versus non-smokers (86 ml/min/1.73m²) or ex-smokers (80 ml/min/1.73m²).

Effect size
- Median cigarettes was 20/day in the smokers and had been 20/day in ex-smokers.

**Effect of Smoking on GFR**
- After adjustment for BP, albuminuria, HbA1C and cholesterol, there was NS difference in the rate of GFR decline between non-smokers (mean 4.4 ml/min/year), ex-smokers (mean 3.4 ml/min/year), and smokers (mean 4.0 ml/min/year).

Albuminuria, cholesterol, MAP, and HbA1C were all significant independent predictors of progression.

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</thead>
<tbody>
<tr>
<td>Ibanez L, Morlans M, Vidal X et al. Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. <em>Kidney International.</em></td>
<td>Case control</td>
<td>2+</td>
<td>Cases with ESRD = 520 Controls without ESRD = 982</td>
<td>Inclusion criteria: Cases: all patients entering dialysis program because of ESRD between June 1995 and Nov. 1997 in all dialysis centers in Barcelona, Spain. Controls: randomly selected from hospital admission lists, including acute conditions not</td>
<td>Users of analgesics and NSAIDS in Cases with ESRD = 122 Users of analgesics and NSAIDS in controls = 166 Procedure: Two controls were age (within 5 years).</td>
<td>Nonusers of analgesics and NSAIDS in Cases with ESRD = 398 Nonusers of</td>
<td>Not applicable</td>
<td>Risk of ESRD</td>
<td>Dept of Health and Social Security</td>
</tr>
</tbody>
</table>

Chronic kidney disease: evidence tables DRAFT
**Effect of Analgesic and NSAID use on Risk for ESRD:**

Compared with non-users (N=398 cases, N=816 controls), users of analgesics and NSAIDS (N=122 cases, N=166 controls) had NS risk of ESRD [adjusted OR 1.22 (95% CI 0.89 to 1.66)].

**Sub-analysis: Effect of Aspirin use and Risk for ESRD**

Users of aspirin (N=81 cases, N=94 controls) had a significantly increased risk of ESRD compared with nonusers [adjusted OR 1.56 (95% CI 1.05 to 2.30)]. The effect of aspirin was related with the cumulative dose (p trend =0.012) and duration of use (p trend= 0.012).
Sub-analysis: Effect of Pyrazolone use and Risk for ESRD

Users of pyrazolones (N=34 cases, N=51 controls) had NS risk of ESRD compared with nonusers [adjusted OR 1.03 (95% CI 0.60 to 1.76)]

Sub-analysis: Effect of non-aspirin NSAID use and Risk for ESRD

Users of non-aspirin NSAIDs (N=37 cases, N=51 controls) had NS risk of ESRD compared with nonusers [adjusted OR 0.94 (95% CI 0.57 to 1.56)]

When the exposure time was increased to 6 months prior to any symptom of renal disease, the OR for ESRD by each drug category was similar.

Smoking and ESRD:

Smokers (N=320 cases, N=557 controls) had a significantly increased risk of ESRD compared with non-smokers [adjusted OR 1.54 (95% CI 1.14 to 2.07)]

Note: possible recall bias may have caused misclassification of analgesic use.

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<tbody>
<tr>
<td>Orth SR, Stockmann A, Conradt C et al.</td>
<td>Retrospective Case-control 2+</td>
<td>N pairs = 102 N matched IgA-GN pairs = 54 N matched ADPKD pairs = 48 European multi-centre study: Austria, Germany, Italy</td>
<td>Inclusion: biopsy-proven IgA-glerulonephritis (IgA-GN) or ultrasonography-proven autosomal dominant polycystic kidney disease (ADPKD) Exclusion criteria: systemic diseases involving the kidney (diabetes, lupus), immunosuppressive therapy, age at renal failure &lt; 21 years Population baseline characteristics: NS difference between case (patients with ESRD) and matched controls (renal disease; no ESRD) with respect to age at renal death of cases compared to mean age of controls, age at diagnosis of renal disease, overall</td>
<td>5-15 pack years (cigarettes) N males = 28 males &gt;15 pack years (cigarettes) N males=43 Procedure: Medical records searched to identify case and control patients, and to retrieve clinical and demographic data. Case patients were defined by the presence of ESRD (need for chronic haemodialysis or kidney transplant). Control patients were identified by the failure to progress to serum creatinine value &gt; 3 mg/dl during a minimum observation period of 1 year</td>
<td>N/A Dropouts: 17.9% of controls and 12.2% of cases failed to return smoking questionnaires</td>
<td>ESRD</td>
<td>Not stated</td>
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</tbody>
</table>
Antihypertensive medication use, serum cholesterol, low protein diet, lipid lowering medication use. Male cases and controls were similar with respect to DBP, calcium channel blocker use. SBP was higher in male cases than controls (146 vs 139 mm Hg). ACE inhibitor use was significantly lower in male cases than controls (25% vs 42%). Female cases and controls were similar with respect to SBP and ACE inhibitor use.

Effect size

Analysis was restricted to male cases and matched controls (N=72 pairs), as the female pairs (N=30 pairs) were too few. In females, smoking was NS associated with risk of ESRD.

IgA-GN and ADPKD pairs were combined in the analysis as separate analyses showed similar effects of smoking on ESRD.

**Effect of Smoking on progression to ESRD**

CRUDE analysis: Compared to men who smoked for 0-5 pack-years (N=73 total; N cases=26, N controls=47), men who smoked 5-15 pack years (N=28 total; N cases = 17, N controls = 11) had a significantly increased odds of ESRD [unadjusted OR 3.5 (95% CI 1.3 to 9.6), p=0.017].

Compared to men who smoked for 0-5 pack-years (N=73 total; N cases=26, N controls=47) men who smoked >15 pack years (N=43 total; N cases=29, N controls = 14) had a significantly increased odds of ESRD [unadjusted OR 5.8 (95% CI 2.0 to 17), p=0.001].

There was significant interaction between the smoking variable and ACE inhibitor use (p=0.026). Patients treated with ACEi (N cases=18, N controls = 30). Patients not treated with ACEi (N cases = 54, N controls = 42).

Compared to men who did not receive ACE inhibitors and smoked for 0-5 pack-years, men who smoked > 5 pack years and did not receive ACEi had a significantly increased odds of ESRD [adjusted OR 10.1 (95% CI 2.3 to 45), p=0.002]. adjusted for SBP

Compared to men who received ACE inhibitors and smoked for 0-5 pack-years, men who smoked > 5 pack years and received ACEi had NS risk of ESRD [adjusted OR 1.4 (95% CI 0.3 to 7.1), p=0.65]. adjusted for SBP

Note: limitations – females were excluded from analysis due to low frequency of smoking in this group, confounding by other variables?

<table>
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</table>

Chronic kidney disease: evidence tables DRAFT

Prospective cohort  
2 +  
N total = 185  
N smokers = 44  
N never smokers = 141  
1 centre study: Germany

Inclusion: patients with type 1 or 2 diabetes attending the clinic  
Exclusion criteria: people with GFR < 60 ml/min/1.73m², ex-smokers

Population baseline characteristics: 60% had type 1 diabetes. 72% non-smokers and 86% smokers had proteinuria > 0.15 g/d. Smokers were significantly younger (47 vs 54 years), more likely to be male, and had a lower GFR than non-smokers (95 vs 107 ml/min). NS difference between smokers and non-smokers with respect to BMI, diabetes type 1, insulin use, duration of diabetes, HbA1c, retinopathy, proteinuria, hypertension, SBP, DBP, ACEi use, CAD, PVD, stroke.

Smokers N = 44  
Procedure: At baseline, patients had a physical exam (BP, anthropometry, spot urine test, serum creatinine, cholesterol, triglycerides), an interview, and completed a standardised questionnaire to assess smoking status. GFR was estimated with MDRD equation. Patients had at least 4 annual follow-up visits. Patient management was left to GP in interim.

Never smokers N = 141  
Procedure: As for intervention

Median 5.1 years  
20% decline in GFR  
Change in proteinuria  
Not stated

Effect size  
BP at baseline was well controlled for both smokers (135/80 mm Hg) and non-smokers (138/79 mm Hg) and improved during follow-up.

**Effect of Smoking on GFR**  
GFR remained stable during follow-up in non-smokers (107 to 106 ml/min) but decreased significantly in smokers (95 to 83 ml/min, p<0.001). Smokers had a significantly increased odds of a 20% decline in GFR compared to non-smokers [OR 2.52 (95% CI 1.06 to 5.99), p<0.01]. This relationship persisted after adjustment for diabetes type or control, retinopathy, age, BMI, ACEi use, BP, proteinuria (F-ratio=65.9, p<0.0001).

Male gender and diabetes type independently influenced course of renal function in smokers compared to non-smokers. Male smokers had a significantly increased odds of a 20% decline in GFR compared to male non-smokers [OR 5.32 (95% CI 1.49 to 18.9), p<0.05]. Smokers with type 1 diabetes had a significantly increased odds of a 20% decline in GFR compared with non-smokers with type 1 diabetes [OR 4.49 (95% CI 1.36 to 14.7), p<0.05]. NS for presence or absence of retinopathy, proteinuria, or ACEi use.

**Effect of Smoking on Proteinuria**  
Proteinuria increased from baseline to the end of the study in smokers (0.36 to 0.44 g/24-h, N=44) and non-smokers (0.47 to 0.54 g/24-h, N=141), but there was NS differences between the two groups.

Ref ID: 149
**Saiki A, Nagayama D, Ohhira M et al. Effect of weight loss using formula diet on renal function in obese patients with diabetic nephropathy.**


<table>
<thead>
<tr>
<th>Before and after prospective observational study</th>
<th>N =22</th>
<th><strong>Inclusion criteria:</strong></th>
<th>After low calorie formula diet N=22</th>
<th><strong>Exclusion criteria:</strong></th>
<th><strong>Baseline characteristics:</strong> Mean age 53.6 years, BMI 30.4 kg/m², CrCl 0.68 ml/s/1.73 m²</th>
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</thead>
<tbody>
<tr>
<td>Japan</td>
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<td>Obese (BMI &gt; 25 kg/m²) diabetic people with proteinuria (urinary albumin &gt; 300 mg/day), serum creatinine &lt; 265.2 micromol/l and diabetic retinopathy.</td>
<td>Procedure: Patients all received a daily caloric intake of 25-30 kcal/kg and 0.8 g/kg protein for at least 3 months. Statins, antihypertensive agents permitted providing they were prescribed for more than 2 months prior to study and that the doses were unchanged. All patients then switched to a low calorie diet (740 or 970 kcal/day or 11-19 kcal/kg) for 4 weeks. A formula diet providing 170 kcal/pack was used. Patients either consumed one meal of formula diet and 2 ordinary meals (total 970 kcal/day) or 2 formula diet meals and 1 ordinary meal (total 740 kcal/day). Salt intake was 2.79 g/day (740 kcal diet) or 4.90 g/day (970 kcal diet). Plasma creatinine, CrCl (24-h urine collections) physical exam, weight, BP, BMI, and clinical chemistry tests performed at baseline and every week for 4 weeks. Visceral fat measured before and after 4 weeks.</td>
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<td>Unstable diabetic retinopathy, pleural effusion, severe leg edema</td>
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**Effect size**

**Body weight:**

Weight significantly decreased after four weeks of a low calorie formula diet (85.2 kg at baseline to 79.0 kg after 4 weeks, p<0.0001)

**BMI:**

BMI significantly decreased after four weeks of a low calorie formula diet (30.4 kg/m² at baseline to 28.2 kg/m² after 4 weeks, p<0.0001)

**BP:**

SBP and DBP each significantly decreased (p<0.05) after four weeks of a low calorie formula diet.
**Change in CrCl:**
There was NS change in CrCl after four weeks of a low calorie formula diet (0.68 ml/s/1.73 m² at baseline to 0.77 after 4 weeks, p NS)

**Change in serum creatinine:**
Serum creatinine significantly decreased after 4 weeks of a low calorie-formula diet (172.4 micromol/l at baseline to 130.8 micromol/l after 4 weeks, p<0.0001)

**Change in protein excretion:**
Urinary protein significantly decreased after 4 weeks of a low calorie-formula diet (3.27 g/24-h at baseline to 1.50 g/24-h after 4 weeks, p<0.0001)

Weight loss was significantly correlated with a decrease in serum creatinine (r=0.621, p=0.0021) and with a decrease in protein excretion (r=0.487, p=0.0215). Decrease in visceral fat was significantly correlated with decreases in serum creatinine (r=0.579, p=0.0475) and with a decrease in protein excretion (r=0.575, p=0.0496).

Changes in BP (SBP or DBP) were NS correlated with changes in creatinine or urinary protein excretion.

Assessment of bias: small study N=22 and all patients were hospitalised. Before and after study.

<table>
<thead>
<tr>
<th>Ref ID: 1319</th>
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</thead>
<tbody>
<tr>
<td>Reference</td>
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<tr>
<td>Study type/ Evidence level</td>
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<tr>
<td>Number of patients</td>
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<td>Patient characteristics</td>
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<td>Intervention</td>
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<td>Comparison</td>
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<td>Length of follow-up</td>
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<td>Outcome measures</td>
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<td>Source of funding</td>
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<tr>
<td>Before and after prospective observational study</td>
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<tr>
<td>3 Italy</td>
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<tr>
<td>N =24</td>
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<tr>
<td>Inclusion criteria: obese type 1 and type 2 diabetic people with overt nephropathy (urinary protein excretion &gt; 500 mg/day on six consecutive visits), and diabetic retinopathy.</td>
</tr>
<tr>
<td>Baseline characteristics: NS different between type 1 and 2 diabetics, therefore results were</td>
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<tr>
<td>After low calorie diet N=24</td>
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<tr>
<td>Procedure: Prior to the study, all patients received a mean daily caloric intake of 1870 kcal/day (220 kg carbohydrate, 81 g protein, 63 g fat). All patients then switched to a low calorie diet (1410 kcal/day consisting of 170 g carbohydrate, 58 g protein, 49 g fat) for 12 months. Drugs for arterial hypertension were discontinued. Plasma creatinine, creatinine clearance, urinary protein excretion rate, urinary albumin excretion rate, GFR (99Tc m) physical exam, weight, BP, BMI, and clinical chemistry tests performed at baseline and after 12 months.</td>
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<tr>
<td>Before low calorie diet N=24</td>
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<tr>
<td>12 months</td>
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<tr>
<td>BMI</td>
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<tr>
<td>Change in protein excretion</td>
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<td>Change in albumin excretion</td>
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<td>Change in CrCl</td>
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<tr>
<td>Change in GFR</td>
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<tr>
<td>Not stated</td>
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</table>
Effect size

**BMI:**
BMI significantly decreased after 12 months of a low calorie diet (33.5 kg/m² at baseline to 26.2 kg/m² after 12 months, p<0.001)

**BP:**
SBP and DBP each significantly decreased (p<0.002) after 12 months of a low calorie diet.

**Blood lipids:**
Total cholesterol (p<0.01) and triglycerides (p<0.002) significantly decreased and HDL cholesterol (p<0.05) significantly increased after 12 months of a low calorie diet.

**Change in CrCl:**
CrCl significantly increased after 12 months of low calorie diet (80 ml/min/1.73 m² at baseline to 90 ml/min/1.73 m² after 12 months, p<0.01)

**Change in GFR:**
GFR significantly increased after 12 months of low calorie diet (64 ml/min/1.73 m² at baseline to 80 ml/min/1.73 m² after 12 months, p<0.01).

**Change in serum creatinine:**
Serum creatinine significantly decreased after 12 months of a low calorie diet (145.2 micromol/l at baseline to 101.2 micromol/l after 12 months, p<0.001)

**Change in protein excretion:**
Urinary protein excretion significantly decreased by 51% after 12 months of a low calorie diet, p<0.01. Reduction was seen in all 24 patients. 5/24 had UPE below overt nephropathy levels after 12 months of low calorie diet.

**Change in albumin excretion:**
Urinary albumin excretion significantly decreased by 31% after 12 months of a low calorie diet, p<0.01.

Weight loss was NS correlated with a decrease in UPE or UAE.
Changes in BP (SBP or DBP) were NS correlated with decreases in urinary protein excretion or UAE.

Assessment of bias: small study N=24. Before and after study.
<table>
<thead>
<tr>
<th>Non-randomised controlled trial</th>
<th>N total = 26</th>
<th>N water-based exercise = 17</th>
<th>N sedentary control = 9</th>
<th>N water-based exercise = 26</th>
<th>N water-based exercise = 17</th>
<th>N sedentary control = 9</th>
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<tr>
<td>Procedure:</td>
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<td>At baseline and after 12 weeks</td>
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<td>of intervention, patients had a</td>
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<td>physical exam (BP, anthropometry,</td>
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<td>spot urine test, serum creatinine</td>
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<td>cystatin C, triglycerides) and</td>
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<td>Water-based aerobic exercise was</td>
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<td>performed twice/week for 30</td>
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</table>

### Effect size

**Change in GFR**
There were NS changes in GFR from baseline to 12 weeks in people who took aerobic water-based exercise (62.9 ml/min at baseline to 67.1 ml/min at 12 weeks, NS), and there were NS changes in GFR in the sedentary control group (69.8 ml/min at baseline to 66.3 ml/min at 12 weeks, NS).

**Change in cystatin C**
Cystatin C significantly decreased in the exercise group (1.7 mg/l at baseline to 1.4 mg/l at 12 weeks, p<0.05), whereas there were NS changes in cystatin C in the sedentary control (1.7 mg/l at baseline to 2.0 mg/l at 12 weeks, NS).

**Change in proteinuria**
Proteinuria significantly decreased in the exercise group (0.7 g/g PCR at baseline to 0.4 at 12 weeks, p<0.05), whereas there were NS changes in proteinuria in the sedentary control (1.4 mg/l g/g PCR at baseline to 1.5 at 12 weeks, NS).

**Cardiorespiratory parameters**
Peak O2 pulse, peak ventilation, and peak load all significantly increased (improved) from baseline to 12 weeks in people who took aerobic water-based exercise (p<0.05), whereas as there were NS changes in these parameters in the sedentary control group. There were NS changes in either group for peak VO2.

**Blood lipids**

---


Non-randomised controlled trial

<table>
<thead>
<tr>
<th>Study: Estonia</th>
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</table>

Inclusion: patients with moderate CKD

Exclusion criteria: not stated

Population baseline characteristics: NS differences between two groups for age, sex, BP, GFR (62 vs 69 ml/min, exercise vs control), cystatin C, peak VO2

Procedur: As for intervention

3 months

Change in GFR

Not stated

Change in cystatin C

Change in proteinuria

Cardiorespiratory parameters

Blood lipids
There were NS changes in either group for total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglycerides

Note: very small trial, no assessment of power, uneven distribution to each arm, not randomised, no mention of blinding, no mention of loss to follow-up

<table>
<thead>
<tr>
<th>Reference Study/ Evidenc e level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparis on</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of fundin g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perneger TV, Whelton PK, Puddey IB et al. Risk of end-stage renal disease associated with alcohol consumption. American Journal of Epidemiology. 1999; 150(12):1275-1281. Ref ID: 527</td>
<td>Case-control 2 - USA</td>
<td>N cases (people with new ESRD) = 716 N controls (age matched from general population) = 361</td>
<td>Inclusion: Cases: people with new-onset ESRD requiring dialysis diagnosed between Jan.-July 1991 identified through ESRD registry. Controls: general population identified by random number dialling. Exclusion criteria: not stated Population baseline characteristics: NS difference between case (ESRD) and age matched controls (general population) with respect to age (47 years). 42% of cases were female, 65% controls were female. 54% of cases were black, only 14% of controls were black.</td>
<td>N=716 cases Increasing drinks/month or day Procedure: Age matching between cases and controls. Participants interviewed via telephone about alcohol consumption, amount, frequency, and potential confounders (diabetes, hypertension, acetaminophen use, cigarette smoking, drug use, income, education</td>
<td>N=361 controls Abstainer Procedure: As for intervention</td>
<td>N/A 90% of controls and 95% of cases completed the telephone interview</td>
<td>ESRD Not stated</td>
</tr>
</tbody>
</table>

**Effect size**

**Effect of Alcohol consumption on progression to ESRD**

Univariate analysis: Compared with abstainers (N=246 cases and N=124 controls), people who drank > 2 alcoholic drinks/day and ≤ 4 drinks/day (N=41 cases, N=7 controls) had a significantly greater odds of ESRD [OR 3.0 (95% CI 1.3 to 6.8)]

Compared with abstainers (N=246 cases and N=124 controls), people who drank > 4 drinks/day (N=61 cases, N=5 controls) had a significantly greater odds of ESRD [OR 6.1 (95% CI 2.4 to 15.7)]

After excluding N=68 people who drank moonshine and adjusting for age, sex, race, hypertension, income, diabetes, acetaminophen use, smoking, and opiate use...
(total N=912), people who drank > 2 alcoholic drinks/day had a significantly greater odds of ESRD [OR 4.0 (95% CI 1.2 to 13.0)] than abstainers.

There was NS odds of ESRD for people who drank moderate amounts of alcohol ( < 1 drink/day or 1-2 drinks/day) compared with abstainers (adjusted as above)

Note: limitations – The following weren’t addressed in the methodology: The same exclusion criteria are used for both cases and controls, Comparison is made between participants and non-participants to establish their similarities or differences. Cases are clearly defined and differentiated from controls. Is it clearly established that controls are non-cases? Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment.

### 7.2 DIETARY INTERVENTION AND RENAL OUTCOMES

**What dietary interventions are associated with improved renal outcomes in adults with CKD?**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
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<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fouque D, Laville M, Boissel JP. Low protein diets for chronic kidney disease in non diabetic adults. Cochrane Database of Systematic Reviews. 2007;(2):CD001892. Ref ID: 1692</td>
<td>Systematic review and meta-analysis Search MEDLINE, EMBASE CENTRAL from 1966 to Dec. 2004, 1+</td>
<td>N=1524; 8 studies in nondiabetic renal disease populations</td>
<td>Inclusion: Non-diabetic people with moderate to severe CKD estimated by creatinine, CrCl, or GFR. Studies had to be randomised, controlled in adults. Studies had to have a minimum follow-up of 1 year. Exclusion: diabetic populations, children with renal failure 5/8 studies included people with Stage 4-5 CKD</td>
<td>Low protein diet (LPD: 0.3 to 0.6 g/kg/day) N=763</td>
<td>Usual (free or unrestricted ≥ 0.8 g/kg/day) protein diet N=761</td>
<td>Trials lasted at least 12 months</td>
<td>Renal death (death due to any cause, initiation of dialysis, or kidney transplant)</td>
<td>None</td>
</tr>
</tbody>
</table>
The mean difference in protein intake between LPD and unrestricted diets was 0.2 g/kg/day.

**Renal death:**

103 renal deaths in LPD and 148 in usual protein diet

A LPD significantly decreased the risk of renal death compared with an unrestricted protein diet (8 studies, N=1524; RR 0.69 (95% CI 0.56 to 0.86), p=0.0007) in nondiabetic CKD populations. There was NS heterogeneity (chi square = 5.72, p=0.57).

Sensitivity analysis

People with nondiabetic CKD randomised to a LPD (0.6 g/kg/day) had NS risk of renal death compared with people on an unrestricted diet (3 studies, N=1116; RR 0.76 (95% CI 0.54 to 1.05), p=0.1). There was NS heterogeneity (chi square = 1.37, p=0.50).

People with nondiabetic CKD randomised to a very LPD (0.3 to 0.6 g/kg/day) had a significantly reduced risk of renal death compared with people on an unrestricted diet (5 studies, N=408; RR 0.65 (95% CI 0.49 to 0.86), p=0.002). There was NS heterogeneity (chi square = 3.91, p=0.42). 4/5 Studies were conducted in people with Stage 4-5 CKD.

Note: no quality assessment of each trial was performed, although randomisation method was checked. This meta-analysis combines Stage 3-5 CKD populations.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
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<tbody>
<tr>
<td></td>
<td>Search MEDLINE from 1966 to Dec. 1994, references of published studies</td>
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Inclusion: NONDIABETIC populations meta-analysis: studies had to be randomised, controlled in adults. Studies had to have a minimum follow-up of 1 year, and include information on the number of patients who developed renal failure or died. DIABETIC populations meta-analysis: studies had to be randomised, concurrent control design or a nonrandomised cross-over design with a minimum follow-up period of 9 months.

Exclusion: not stated
**Effect size**

**NONDIA Betic Renal Disease:** N=1413; 5 studies; dropout rate ranged from 1.8% to 38.8%.

The protein intake in the LPD group ranged from 0.4g/kg/day to 0.6g/kg/day.

Baseline renal function was consistent with moderate CKD.

**Occurrence of death or ESRD**

There was a significant reduction in the occurrence of death or ESRD in people with nondiabetic renal disease on a LPD compared with those on a usual diet (5 trials; N=1413 RR 0.67, 95% CI 0.50 to 0.89, p=0.007). There was no significant interstudy heterogeneity (p>0.2).

**GFR change:** A beneficial effect on GFR change with a LPD was seen in 1 RCT (Ihle et al). A possible beneficial effect on GFR change was seen in the MDRD study (Klahr et al).

**CrCl decline:**

1 study showed NS differences in CrCl between LPD and usual diet (Williams et al).

**Serum creatinine change:**

One study showed NS differences between LPD and usual diet for serum creatinine changes (Locatelli et al), whereas another study (Rosman et al) showed a beneficial effect of a LPD for this outcome.

**MAP:**

The difference in MAP between the LPD and usual diet group was only – 2.9 mm Hg (95% CI -10.4 to +4.9 mm Hg, NS), thus the beneficial effect of the LPD did not appear to be the result of an effect on BP.

EC extracted specific data from each trial:

**Change in body weight:**

Williams et al. 1991: Body weight decreased in usual diet group (N=32) and LPD group (N=33), but NS differences between groups.

**Change in mid-arm circumference**

Williams et al. 1991: NS differences between usual diet group (N=32) and LPD group (N=33) for changes in mid-arm circumference.

**Diabetic Renal Disease:** N=108; 5 studies; dropout rate ranged from 0% to 41%.

The protein intake in the LPD group ranged from 0.50 g/kg/day to 0.85 g/kg/day.

Baseline protein excretion was consistent with albuminuria in all studies, except Dullart et al. (microalbuminuria or above normal albumin excretion)

Only 9/108 patients were on ACEi (N=6 on LPD and N=3 in usual diet)
Changes in GFR or creatinine clearance, or urinary albumin excretion rate

In people with type 1 diabetic renal disease (N=108; 5 studies) A LPD significantly reduced the risk for a decline in GFR or creatinine clearance or an increase in urinary albumin excretion rate [RR 0.56 (95% CI 0.40 to 0.77), p<0.001]. There was no significant interstudy heterogeneity (p>0.2).

**MAP:**
The difference in MAP between the LPD and usual diet group was only – 2.6 mm Hg (95% CI -6.1 to +1.0 mm Hg, NS), thus the beneficial effect of the LPD did not appear to be the result of an effect on BP.

**Glycosylated haemoglobin**
The difference in glycosylated haemoglobin between the LPD and usual diet group was only 0.03% (95% CI -0.58% to +0.65%, NS), thus the beneficial effect of the LPD did not appear to be the result of an effect on glycaemic control.

Note: In the nondiabetic renal disease studies, all analysed had GFR < 55 ml/min. Protein intake was significantly lower in the LPD group compared with usual diet, but not always achieving the target protein level. Also no analysis of malnutrition the meta-analysis as not all studies reported such data. Authors support a LPD of 0.6 g/kg/day. In the diabetic renal disease studies, there were only 109 people total, so authors feel evidence is less compelling for a LPD. Suggest a LPD in people with diabetic renal disease with progressive proteinuria despite good glycaemic control and use of ACEi.

<table>
<thead>
<tr>
<th>Ref ID: 4050</th>
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<tbody>
<tr>
<td><strong>Reference</strong></td>
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<tr>
<td>Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. Cochrane Database of Systematic Reviews. 2007; Ref ID: 4050</td>
</tr>
</tbody>
</table>
**Effect size**

**ESRD or death**
ESRD or death occurred in 27% of people with type I diabetes and nephropathy randomised to usual diet compared with 10% of people randomised to LPD (1 study, N=82, p=0.04). The risk of ESRD or death was significantly lower in people with type I diabetes and nephropathy randomised to LPD compared with usual diet [RR 0.23 (95% CI 0.07 to 0.72, p=0.01 after adjustment for baseline CVD].

**Change in GFR**
In people with type 1 diabetes and nephropathy, there was NS improvement in GFR in those randomised to a LPD compared with usual diet [7 RCTs, N=222, change in GFR WMD +0.14 ml/min/month (95% CI -0.06 to +0.34)] . There was significant heterogeneity (I²=62%, p=0.01).

In people with type 2 diabetes and nephropathy, there was a NS improvement in GFR in the LPD group (-0.4 ml/min/month) compared with the usual diet (-0.3 ml/min/month; 1 RCT, N=160).

Another RCT in people with type 2 diabetes and nephropathy (N=37) showed a similar decline in GFR in the LPD (-0.51 ml/min/month) compared with the usual diet (-0.52 ml/min/month) group.

In an RCT in which type 1 and type 2 diabetic people with nephropathy were analysed as a single population (N=80), there was NS differences in GFR decline between those randomised to LPD (-0.48 ml/min/month) compared with a usual (-0.50 ml/min/month) diet.

**Quality of Life:**
No study assessed this outcome.

**Compliance:**
The intended protein intake in the LPD group ranged from 0.3 to 0.8 g/kg/day, however compliance was low as the actual protein intake ranged from 0.6 to 1.1 g/kg/day

**Adverse Effects: Nutritional Status**
9 studies assessed nutritional status, but only 1 study found evidence of malnutrition (definition not provided) as serum pre-albumin and serum albumin significantly decreased in the LPD group.

EC extracted specific data from each trial:

**Change in body weight:**
Meloni et al. 2004: NS change in body weight in people with diabetic nephropathy on usual diet (N=40), whereas body weight significantly decreased after 12 months
of a LPD (N=40; 65.7 kg at baseline to 61.4 kg after 12 months, p<0.01)

Hansen et al. 2002: NS differences between LPD group (N=41) and usual diet (N=41) for body weight changes (data not shown) in people with type 1 diabetes and nephropathy.

Dullart et al. 1993: Body weight significantly increased from baseline to 24 months on the usual diet (N= 16), whereas there were NS changes in body weight in the low protein diet (N=14) in people with type 1 diabetes and AER 10-200 g/min

**Change in BMI:**
Meloni et al. 2004: NS change in BMI in people with diabetic nephropathy on usual diet (N=40), whereas BMI significantly decreased after 12 months of a LPD (N=40; 26.8 kg/m2 at baseline to 24.2 kg/m2 after 12 months, p<0.05)

**Changes in serum albumin:**
Meloni et al. 2004: NS change in serum albumin or serum prealbumin in people with diabetic nephropathy on usual diet (N=40) or on LPD (N=40). NO signs of malnutrition.

Hansen et al. 2002: NS differences between LPD group (N=41) and usual diet (N=41) for changes in serum albumin (data not shown) in people with type 1 diabetes and nephropathy.

Dullart et al. 1993: NS changes in serum albumin in either the usual diet (N=16) or LPD groups (N=14) in people with type 1 diabetes and AER 10-200 g/min.

Raal et al. 1994: NS changes in serum albumin in either the LPD group (N=11) or the usual diet group (N=11) after 6 months of the diet treatment in people with type 1 diabetes and nephropathy.

**Changes in mid-arm circumference:**
Hansen et al. 2002: NS differences between LPD group (N=41) and usual diet (N=41) for changes in mid arm circumference (data not shown) in people with type 1 diabetes and nephropathy.

Note: authors note that compliance to LPD is poor, and review does not establish what level of LPD should be advised, if at all, as evidence is not very compelling. Authors state that LPD could delay dialysis by 1 to 2 months if compliance is high.