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TABLE OF CONTENTS

[Intervention Review]

Protein restriction for diabetic kidney disease

Shimin Jiang[1], Jinying Fang[2], Wenge Li[1]

[1]Department of Nephrology, China-Japan Friendship Hospital, Beijing, China. [2]China-Japan Friendship Institute of Clinical Medicine, Beijing University of Chinese Medicine, Beijing, China

Contact: Wenge Li, wgli_zrsn@126.com.

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ABSTRACT

Background

Diabetic kidney disease (DKD) continues to be the leading cause of kidney failure across the world. For decades dietary protein restriction has been proposed for patients with DKD with the aim to retard the progression of chronic kidney disease (CKD) towards kidney failure. However, the relative benefits and harms of dietary protein restriction for slowing the progression of DKD have not been addressed.

Objectives

To determine the efficacy and safety of low protein diets (LPD) (0.6 to 0.8 g/kg/day) in preventing the progression of CKD towards kidney failure and in reducing the incidence of kidney failure and death (any cause) in adult patients with DKD. Moreover, the effect of LPD on adverse events (e.g. malnutrition, hyperglycaemic events, or health-related quality of life (HRQoL)) and compliance were also evaluated.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 17 November 2022 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We included randomised controlled trials (RCTs) or quasi-RCTs in which adults with DKD not on dialysis were randomised to receive either a LPD (0.6 to 0.8 g/kg/day) or a usual or unrestricted protein diet (UPD) (≥ 1.0 g/kg/day) for at least 12 months.

Data collection and analysis

Two authors independently selected studies and extracted data. Summary estimates of effect were obtained using a random-effects model. Results were summarised as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes and mean difference (MD) or standardised MD (SMD) with 95% CI for continuous outcomes. Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

We identified eight studies involving 486 participants with DKD. The prescribed protein intake in the intervention groups ranged from 0.6 to 0.8 g/kg/day. The prescribed protein intake in the control groups was ≥ 1.0 g/kg/day, or a calculated protein intake ≥ 1.0 g/kg/day if data on prescribed protein intake were not provided. The mean duration of the interventions was two years (ranging from one to five years). Risks of bias in most of the included studies were high or unclear, most notably for allocation concealment, performance and detection bias. All studies were considered to be at high risk for performance bias due to the nature of the interventions.

Most studies were not designed to examine death or kidney failure. In low certainty evidence, a LPD may have little or no effect on death (5 studies, 358 participants: RR 0.38, 95% CI 0.10 to 1.44; I^2 = 0%), and the number of participants who reached kidney failure (4 studies, 287 participants: RR 1.16, 95% CI 0.38 to 3.59; I^2 = 0%). Compared to a usual or unrestricted protein intake, it remains uncertain whether a LPD slows the decline of glomerular filtration rate over time (7 studies, 367 participants: MD -0.73 mL/min/1.73 m^2/year, 95% CI -2.3 to 0.83; I^2 = 53%; very low certainty evidence).

It is also uncertain whether the restriction of dietary protein intake impacts on the annual decline in creatinine clearance (3 studies, 203 participants: MD -2.39 mL/min/year, 95% CI -5.87 to 1.08; I^2 = 53%). There was only one study reporting 24-hour urinary protein excretion. In very low certainty evidence, a LPD had uncertain effects on the annual change in proteinuria (1 study, 80 participants: MD 0.90 g/24 hours, 95% CI 0.49 to 1.31). There was no evidence of malnutrition in seven studies, while one study noted this condition in the LPD group. Participant compliance with a LPD was unsatisfactory in nearly half of the studies. One study reported LPD had no effect on HRQoL. No studies reported hyperglycaemic events.

Authors' conclusions

Dietary protein restriction has uncertain effects on changes in kidney function over time. However, it may make little difference to the risk of death and kidney failure. Questions remain about protein intake levels and compliance with protein-restricted diets. There are limited data on HRQoL and adverse effects such as nutritional measures and hyperglycaemic events. Large-scale pragmatic RCTs with sufficient follow-up are required for different stages of CKD.

PLAIN LANGUAGE SUMMARY

Low protein diets for adults with diabetic kidney disease

What is the issue?

For people with diabetic kidney disease (DKD) not requiring dialysis, it may be recommended to limit the amount of protein in the diet to slow the progression of chronic kidney disease. However, uncertainty remains about how much protein should be consumed.

What did we do?

We reviewed the evidence about the effect of low protein diets on the progression of kidney disease in adult patients with DKD, not on dialysis. The evidence is current to 17 November 2022. All studies were combined, provided that they compared a low protein diet (0.6 to 0.8 g/kg/day) with a usual or unrestricted protein diet (≥ 1.0 g/kg/day) for 12 months or more.

What did we find?

We identified eight studies enrolling 486 people who had DKD at different stages of chronic kidney disease. Studies included type 1 and type 2 diabetes. The results showed that a low protein diet has uncertain effects on slowing the decline of glomerular filtration rate. Compared with a usual or unrestricted protein diet, a low protein diet may have little or no effect on the number of people who died or progress to kidney failure needing dialysis. The vast majority of studies reported nutritional status, with only one study indicating potential malnutrition in the low protein diet group. There may be little or no difference in health-related quality of life; however, only one study reported this outcome. Compliance with the low protein diet was unsatisfactory in four of the eight studies

For the most part, the included studies were poorly conducted, and data were often not reported; therefore, the overall certainty of the evidence for our outcomes of interest was either low or very low.

Conclusions

Because there were insufficient data and difficulties in adherence to such a low protein diet, we are uncertain whether a low protein diet slows the progression of kidney disease for people with DKD not on dialysis. More high-quality studies with large samples and sufficient follow-up are needed.

Summary of findings 1. Low protein diet versus usual or unrestricted protein diet for adults with diabetic kidney disease

Low protein diet versus usual or unrestricted protein diet for adults with diabetic kidney disease

Patient or population: adults with DKD
Settings: all settings
Intervention: low protein diet (0.6 to 0.8 (g/kg/day)
Comparison: usual or unrestricted protein diet (≥ 1 g/kg/day)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual or unrestricted protein diet	Low protein diet				
Death (any cause)	**45 per 1000**	**17 per 1000** (4 to 65)	**RR 0.38** (0.1 to 1.44)	358 (5 studies)	⊕⊕⊖⊖ **low**[1,2]	Eleven participants died in the 5 studies reporting this outcome
Kidney failure	**34 per 1000**	**40 per 1000** (13 to 123)	**RR 1.16** (0.38 to 3.59)	287 (4 studies)	⊕⊕⊖⊖ **low**[1,2]	Eleven participants developed kidney failure in the 4 studies reporting this outcome
Change in GFR	The mean decline in GFR with a low protein diet was **0.73 mL/min/1.73 m²/yearlower** (2.3 lower to 0.83 higher) than a usual or unrestricted protein diet		-	367 (7 studies)	⊕⊖⊖⊖ **very low**[1,3,4]	-
Change in 24-hour urinary protein excretion	The mean decline in 24-hour urinary protein excretion with a low protein diet was **0.9 g/24 hours higher** (0.49 to 1.31 higher) than a usual or unrestricted protein diet		-	80 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]	-
Malnutrition	See comment	See comment	-	471 (7 studies)	See comment	Six studies showed no evidence of malnutrition, while one study noted malnutrition in the low protein diet group. The number of participants was not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in the footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
DKD: Diabetic kidney disease; **CI:** Confidence interval; **RR:** Risk ratio; **GFR:** Glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

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[1] Small studies and wide CIs that include the potential for important benefits and harms
[2] Most of the included studies did not contribute to the outcome evaluated
[3] Study limitations were due to high or unclear risks of bias
[4] Important and unexplained heterogeneity present

BACKGROUND

Description of the condition

Diabetes is a major public health concern that has reached alarming levels. In 2021, it is estimated that 10% of adults around the world (537 million people) are living with diabetes, and this number is projected to reach 783 million by 2045 (IDF 2021). The increased prevalence of diabetes has led to an increase in patients with diabetic kidney disease (DKD) and kidney failure across the world (Dabelea 2017; IDF 2021). It is estimated that approximately 40% of patients with diabetes will develop chronic kidney disease (CKD) (Parving 2006; Unnikrishnan 2007), an entity referred to as DKD (Tervaert 2010). DKD is a diagnosis that refers to specific pathologic structural and functional changes seen in the kidneys due to diabetes (ADA 2014; KDOQI 2007; KDIGO 2020). These changes lead to a clinical presentation characterised by increased urinary albumin excretion and progressive reductions in kidney function. The natural history of DKD in patients in longitudinally studied populations with type 2 diabetes is similar to that in those with type 1 diabetes. It typically includes several stages, starting with apparent normality in the first few years after diagnosis, followed by incipient nephropathy (known as microalbuminuria), and then by overt nephropathy that will progress to kidney failure requiring dialysis or transplantation, or both (Gross 2005).

DKD continues to be the leading cause of kidney failure in most developed countries (JSDT 2019; UKRR 2020; USRDS 2019) and increases the risk of death, mainly from cardiovascular causes (Sabanayagam 2019). For patients with DKD undergoing dialysis, the healthcare cost increases by an average of 2.8 times/year compared with CKD patients who are not on dialysis (Li 2013). Studies in patients with type 2 diabetes and early stages of kidney disease demonstrated that multifactorial interventions had a long-term benefit for the development of microvascular and macrovascular complications and death (Gaede 2003; Gaede 2016). Therefore, a target-driven, long-term, intensified intervention targeting multiple risk factors, such as lifestyle modification (including dietary counselling, smoking cessation, and adequate physical activity) and pharmacological intervention, may stabilise early-stage DKD. Furthermore, other diet-related factors, such as poorer glycaemic control, obesity, and malnutrition, may also impact on severity and progression of DKD (KDIGO 2020; KDOQI 2020).

Description of the intervention

In patients with diabetes and CKD, dietary recommendations change depending on the stage of kidney disease and treatment modality. However, there is uncertainty around dietary recommendations for those with diabetes and non-dialysis-dependent CKD as two recent guidelines slightly differ (KDIGO 2020; KDOQI 2020). In adult patients with diabetes with decreased glomerular filtration rate (GFR) (GFR < 60 mL/min/1.73 m^2) and not on dialysis, KDOQI 2020 recommended that it was reasonable to prescribe a daily protein intake of 0.6 to 0.8 g/kg/day. According to the recommendation of the World Health Organization on daily protein intake for healthy people, KDIGO 2020 recommended daily protein intake should be maintained at approximately 0.8 g/kg/day for those with diabetes and non-dialysis-dependent CKD.

In addition, the optimal diet for diabetes from the perspective of diabetologists (ADA 2019) is low-energy and low-carbohydrate because carbohydrate is a readily available source of energy and the primary dietary influence on postprandial blood glucose, which may be applied in a variety of eating patterns that meet individualized dietary plans. Therefore, restricting the amount of dietary protein below 0.8 g/kg/day in a person with diabetes, who may have also been counselled to restrict carbohydrates and fat, may significantly decrease the caloric content of the diet. This severely restricted diet, if followed, may lead to a decline in the quality of life (QoL) and an increase in the risk of malnutrition (Pan 2008; Robertson 2007). However, in CKD with reduced GFR, a high protein intake is associated with the development of increased intra-glomerular pressure and glomerular hyperfiltration, which in turn contributes to accelerating the decline in kidney function (Hostetter 1986). Thus, nephrologists (KDOQI 2020) state a recommendation of normal/high energy (25 to 35 kcal/kg/day) and low protein diets (LPD) (0.6 to 0.8 g/kg/day) as an option in patients with DKD not on dialysis. Because of the reduced energy amount resulting from the lower protein intake, a protein restriction diet needs more carbohydrates to meet energy requirements, whilst high carbohydrates may worsen glycaemic control in diabetes. These are two competing views. Thus, the impact of protein/diet restrictions on DKD should balance the benefits and harms.

Most adults, especially those in developed countries, have a usual protein intake of more than 1.0 g/kg/day. Traditionally, a LPD is rigid and restrictive, which is prescribed using an exchange system to include both high and low-biological value proteins. In general, a focus on vegetables, fruits, whole grains, fibre, legumes, right plant-based proteins, unsaturated fats and less meat may help DKD patients achieve this protein restriction (KDIGO 2020). Compliance with a LPD is typically assessed by regular measurement of 24-hour urinary excretion of urea nitrogen using the Maroni formula (Maroni 1985). Considering the uncertainty around recommendations for optimal dietary protein intake in people with DKD not on dialysis, whether limiting protein intake to less than 0.8 g/kg/day (i.e. 0.6 to 0.8 g/kg/day) provides more benefits to patients with DKD than a usual or unrestricted protein diet (UPD) (≥ 1.0 g/kg/day) needs to be further explored.

How the intervention might work

In the 1980s, it was hypothesised that lower dietary protein intake could reduce glomerular hyperfiltration and delay the progression of chronic renal insufficiency in experimental animal models (Klahr 1983). Since then, clinical trials have compared different levels of protein intake in CKD patients with or without diabetes and demonstrated the beneficial role of LPD in delaying the gradual loss of kidney function (Barsotti 1988; Ciavarella 1987; Giordano 2014; Jungers 1987). Other long-term studies in rats have demonstrated that LPD ameliorates diabetes-induced kidney injuries, including the accumulation of abnormal mitochondria, tubular cell damage and inflammation, which is related to autophagy restoration and inhibition of the mTORC1 pathway (Kitada 2016). In 2007, a Cochrane review (Robertson 2007) was published with the aim of assessing the role of LPD in DKD patients. Robertson 2007 reported that a LPD appeared to slow the progression of DKD, although in a non-significant way. Another Cochrane review (Hahn 2020) evaluated the efficacy of LPD in patients with non-diabetic CKD. Hahn 2020 found that a LPD probably reduced the number of people with CKD stage 4 or 5 (moderate certainty evidence). Therefore, such a diet may have the potential to protect the kidneys. This is partly because limiting protein intake contributes

to a significant decrease in urinary urea nitrogen output and a concomitant decrease in kidney workload. It is suggested that dietary protein restriction also favours the correction of metabolic acidosis and CKD-metabolic bone disease (Garneata 2016; Williams 1991). Additionally, a low protein intake may ameliorate oxidative stress and insulin resistance (Chauveau 2011; Gao 2010; Kim 2010), which are the common features of accelerated atherosclerosis in patients with DKD. These experimental and clinical data suggest that dietary protein restriction in people with DKD may prevent the natural progression of CKD towards kidney failure.

Why it is important to do this review

This is an update of the Cochrane review, which was first published in 1997 (Waugh 1997) and updated in 2007 (Robertson 2007) with the aim to explore whether dietary protein restriction benefits adults with DKD by delaying the onset of kidney failure and/or slowing the rate of decline in GFR. The 2007 update analysed a total of seven RCTs with 222 patients and reported that limiting protein intake may slow the decline of GFR, but more studies were needed (Robertson 2007). However, few events (e.g. death and kidney failure) were observed with LPD compared with those occurring with UPD. Overall there remains considerable controversy as to whether dietary protein restriction does retard the rate of decline in kidney function in people with DKD at different stages of CKD. During the latest decade, several new RCTs assessing dietary protein restriction in DKD have been published. Thus, in this review, we aimed to update Robertson 2007 to determine whether the addition of further RCTs could modify previous findings.

OBJECTIVES

To determine the efficacy of LPD (0.6 to 0.8 g/kg/day) in preventing the progression of CKD towards kidney failure and in reducing the incidence of kidney failure and death (any causes) in adult patients with DKD. Moreover, the effect of LPD on adverse events (e.g. malnutrition, hyperglycaemic events, or health-related (HR) QoL) and compliance was also evaluated.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) or quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods). Interventions should last a minimum of 12 months. Cross-over studies were excluded for primary outcomes but were considered for secondary outcomes if the starting period of the intervention was randomly allocated and each intervention was in place for at least 12 months.

Types of participants

Inclusion criteria

- Adults with type 1 or type 2 diabetes as defined by authors in each study. In studies that included a minority of non-diabetic patients, analyses were restricted to patients with diabetes only.
- Clinically and/or pathologically diagnosed DKD. Clinical diagnosis of DKD was based on the presence of albuminuria and/or reduced GFR in the absence of signs or symptoms of other causes of kidney disease and should adhere to the standard guidelines (ADA 1999; ADA 2008; ADA 2010; ADA 2018; KDOQI 2007). If necessary, we used the authors' definition of DKD. Information on glycaemic control and antihyperglycaemic treatment should be stated.

Exclusion criteria

- Design or analysis flawed, for example, if anti-hypertensive treatment was started or increased at the same time as the diet was changed. However, studies with antihyperglycaemic treatment being started or increased at the same point in time were not excluded because a restricted protein intake may not provide sufficient energy, and as a result, needs more carbohydrates to reach the energy request and, in turn, worsens the control of diabetes.
- Because of the difficulty of controlling confounding factors and the major concern for LPD in DKD, studies including pregnant women or malnourished patients were excluded.
- Studies were excluded if insufficient details of protein diet were given or if the intervention was carried out immediately in pre-dialysis patients.

Types of interventions

1. Studies comparing a reduced or modified protein diet (0.6 to 0.8 g/kg/day) with a UPD (≥ 1.0 g/kg/day) for at least 12 months
2. Studies in which people received supplements of essential amino acids, keto-analogues, or both, were included, provided that the total nitrogen intake differed between the experimental and the control groups
3. Studies in which people received different types of protein (animal or plant) were also included, provided that the daily protein intake met the request of the treatment groups.

Types of outcome measures

Primary outcomes

- Kidney failure: defined by the need to initiate chronic dialysis or to receive a kidney transplant during follow-up
- Change in GFR: defined by the mean annual change in GFR from baseline to end of follow-up. In this analysis, estimated (e) GFR was used interchangeably with measured GFR
- Death (any cause).

Secondary outcomes

- Change in creatinine clearance (CrCl) as defined by the mean annual change from baseline to end of follow-up
- Change in 24-hour urinary protein excretion as defined by the mean annual change from baseline to end of follow-up
- End of study body weight
- End of study body mass index (BMI)
- Adverse effects, e.g. development of malnutrition as defined by the study authors, hyperglycaemic events, or other adverse events during follow-up reported in included studies
- Measures of compliance with LPD, assessed by urinary urea, dietary interview, or other useful methods
- HRQoL measured using validated scales, e.g. the short-form 36 Health Status Questionnaire (SF-36) (Ware 1992), the EuroQol-5 Dimension (EQ-5D) (EuroQol 1990), or similar.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies (up to 17 November 2022) through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals and the proceedings and abstracts from major kidney and transplant conferences
4. Searching the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website under CKT Register of Studies.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.
3. Grey literature sources (e.g. abstracts, dissertations, and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, were not searched.

Data collection and analysis

Selection of studies

The initial version of this review was undertaken in 1997 (Waugh 1997) and updated in 2007 (Robertson 2007).

This new review was undertaken by three authors. The search strategy described was used to obtain titles and abstracts of studies that were relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however, studies and reviews that might include relevant data or information on trials were retained initially. Two authors independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria. Disagreements were resolved in consultation with a third author.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one report of a study was identified, data from the most complete report were extracted, but the remaining reports were checked for additional information. We also contacted principal investigators for missing data whenever necessary. Any discrepancy between published versions was evaluated and highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2021) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

For dichotomous outcomes (death, kidney failure and adverse effects), results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (GFR, CrCl, urinary protein excretion, body weight, and BMI), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales had been used. Where standard deviations (SD) for continuous outcomes were missing and not available from triallists, these were imputed (Higgins 2021). Any standard errors (SE) and CIs were transformed into SDs where appropriate.

Unit of analysis issues

Data from cross-over studies were planned to be analysed for secondary outcomes, provided that separate data for the first part of the study were available. No eligible cross-over studies were identified.

Dealing with missing data

Any further information required from the original author was requested by emailing the corresponding author/s, and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients, as well as intention-to-treat, as-treated and per-protocol population, was carefully performed. Attrition rates, for example, drop-outs, losses to follow-up and withdrawals, were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2021).

Assessment of heterogeneity

We assessed the heterogeneity by visual inspection of the forest plot. We quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test or a CI for I^2) (Higgins 2021).

Assessment of reporting biases

There were insufficient data to generate funnel plots to assess for the potential existence of small study bias for the outcomes of kidney failure, death (any cause), change in GFR and change in proteinuria. Where there were multiple publications from the same trial, the primary publications and additional reports were reviewed to identify all outcomes to reduce the risk of selective outcome reporting bias.

Data synthesis

Data were pooled using the random-effects model; however, the fixed-effects model was also used to ensure the robustness of the model chosen and susceptibility to outliers when appropriate.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to assess differences in results possibly related to participant groups, different ways of measuring the change in GFR, dietary compliance, study quality and disease severity. There were too few studies in each analysis to allow meaningful subgroup analyses.

Sensitivity analysis

There were insufficient extractable data to perform the following sensitivity analyses in order to explore the influence of the following factors on effect size:

- Repeating the analysis, excluding unpublished studies
- Repeating the analysis taking account of the risk of bias, as specified
- Repeating the analysis, excluding any very long or large studies, to establish how much they dominated the results.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in a 'Summary of findings' table. The table presents key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2021a). The 'Summary of findings' table also includes an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. This was assessed by two authors. The certainty of a body of evidence involves consideration of the within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates and risk of publication bias (Schunemann 2021b). We presented the following outcomes in the 'Summary of findings' table.

- Death (any cause)
- Kidney failure
- Change in GFR
- Change in 24-hour urinary protein excretion
- Adverse effects: nutritional status.

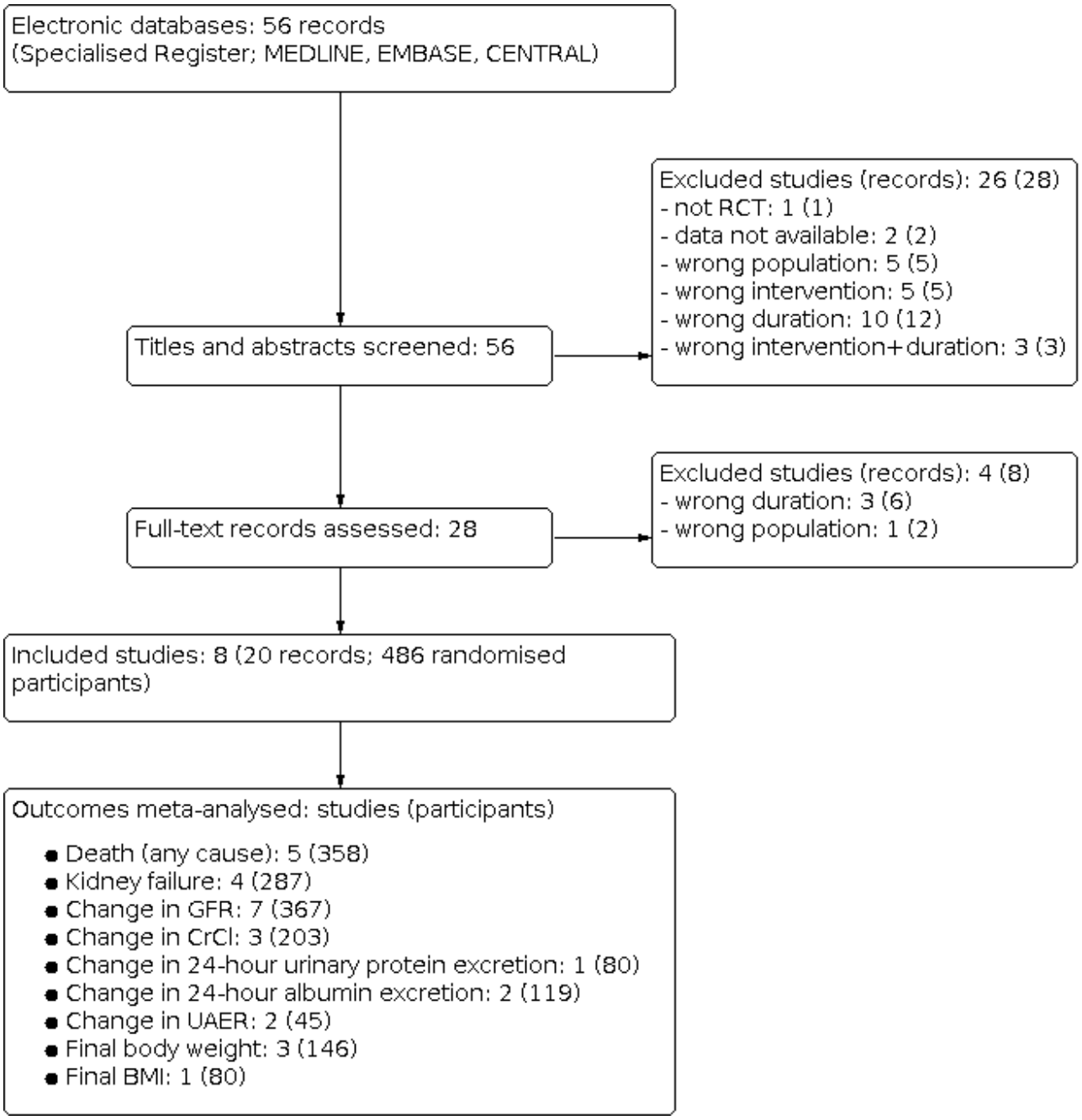
RESULTS

Description of studies

Results of the search

After searching the Specialised Register, a total of 56 records were identified. After screening titles and abstracts and full-text review, eight studies (20 records) were included, and 30 studies (36 records) were excluded. No ongoing studies were identified (Figure 1).

Figure 1. Flow diagram of study selection



Included studies

See Characteristics of included studies; Table 1.

Eight studies (486 participants) were included (Brouhard 1990; Dullaart 1993; Dussol 2004; Hansen 2002; Koya 2009; Meloni 2002; Meloni 2004; Zeller 1991). Four studies (Brouhard 1990; Dullaart 1993; Hansen 2002; Zeller 1991) were carried out in patients with type 1 diabetes, one study (Koya 2009) in patients with type 2 diabetes, and three studies (Dussol 2004; Meloni 2002; Meloni 2004) in patients with type 1 and type 2 diabetes. Sample sizes ranged from 15 to 112 patients. The mean duration of the interventions was two years (ranging from one to five years).

In four studies (Brouhard 1990; Dussol 2004; Hansen 2002; Koya 2009), most participants with DKD had CKD stages 1 to 3 (KDIGO 2020). One study (Dullaart 1993) only included participants with CKD stage 1.

In two studies (Meloni 2002; Meloni 2004), the majority of participants had CKD stage 3. Many of the patients appear to overlap as the biochemical data were similar or identical for both the baseline and post-intervention data in both the LPD and the UPD groups. Therefore, data from Meloni 2004 were extracted, and Meloni 2002 was checked for additional information. Zeller 1991 included participants with CKD stages 2 to 4.

In all but two studies, participants in both groups were balanced in terms of baseline characteristics. In Brouhard 1990, the unrestricted group had slightly worse factors at baseline but none significant, while in Dullaart 1993, the baseline BMI was significantly higher in the LPD group.

In all studies, the intervention group was a LPD containing prescribed protein intake from 0.6 to 0.8 g/kg/day. Five studies (Brouhard 1990; Dullaart 1993; Dussol 2004; Koya 2009; Zeller 1991) prescribed a UPD (≥ 1.0 g/kg/day) as the comparison intervention. In the other three studies (Hansen 2002; Meloni 2002; Meloni 2004), the comparison intervention was a free protein diet without data on the specific level of prescribed protein intake, and the actual calculated protein intake was higher than 1.0 g/kg/day.

Excluded studies

See Characteristics of excluded studies.

Thirty studies (36 records) were excluded.

- One study was not randomised (Garcia Garcia 1990)
- Six studies enrolled participants with diabetes but without kidney disease (Pecis 1994; Pedersen 1989; Pijls 1999; Rudberg 1988; Stephenson 2005; Wiseman 1987)
- Eight studies investigated interventions not relevant to this review (Azadbakht 2003; Barsotti 1993; Chen 2012h; Ciarambino 2012; Facchini 2003; Qiu 2012a; Suratkal 2012; Wheeler 2002)
- Thirteen studies followed up for less than one year (Bending 1988; Ciavarella 1987; Cohen 1987; Effendi 2000; Gross 2002; Hansen 1999; Parillo 1988; Pinto 1991; Raal 1994; Rosenberg 1987; Velazquez Lopez 2008; Zeller 1986; Zucchelli 1988b).
- Two studies did not report the exact number of participants with DKD in each group (Aoyagi 2006; Silan 2003).

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

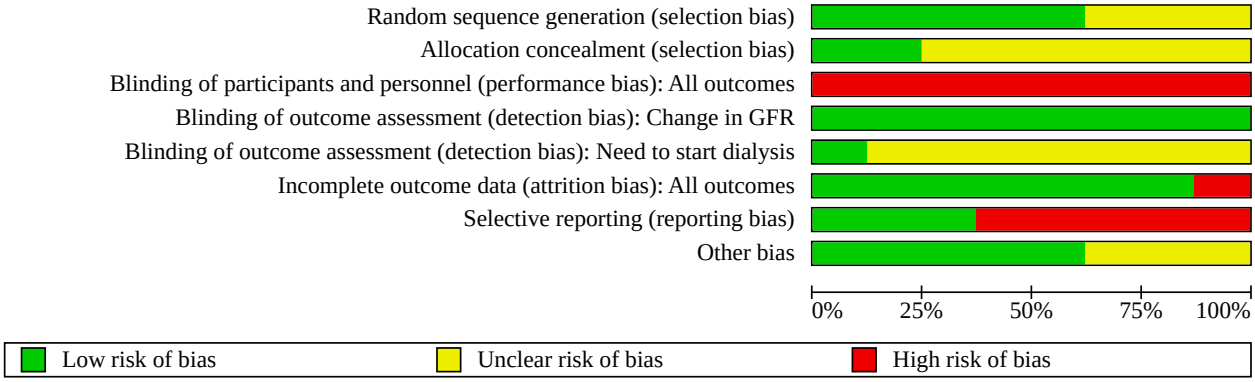
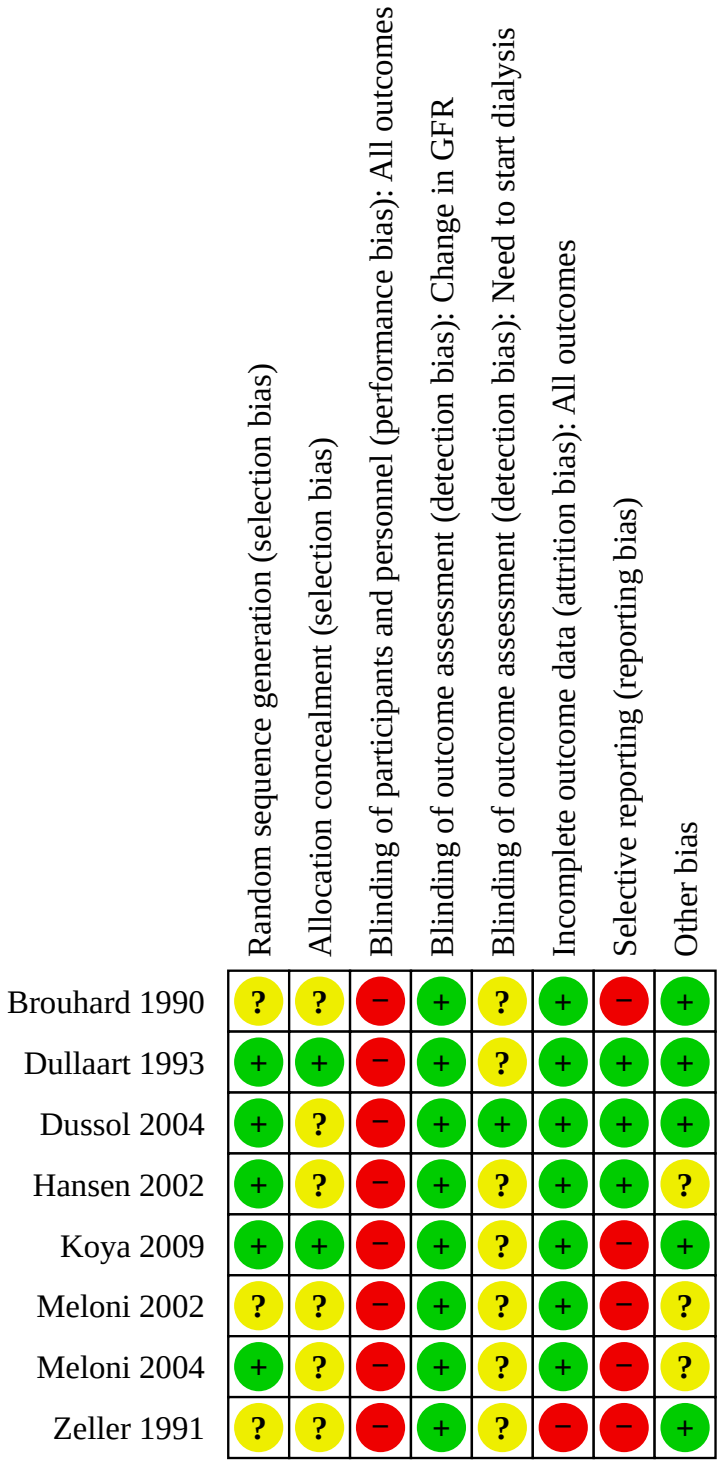


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Random sequence generation

Five studies (Dullaart 1993; Dussol 2004; Hansen 2002; Koya 2009; Meloni 2004) specified appropriate methods for random sequence generation and were considered to be at low risk of bias. The risk of bias from random sequence generation methods was unclear in the remaining three studies.

Allocation concealment

Two studies (Dullaart 1993; Koya 2009) were judged to have adequate allocation concealment and were judged to be at low risk of bias. The risk from allocation concealment was unclear in the remaining six studies.

Blinding

Performance bias

Participants underwent different diet procedures that could not be blinded. Therefore, all eight studies were open-label and judged to be at high risk of performance bias.

Detection bias

Detection bias (blinding of outcome assessment) was recorded separately for GFR and kidney failure. Since GFR was measured or calculated based on laboratory data and unlikely to be influenced by a lack of blinding, all studies reported this outcome and were considered to be at low risk of detection bias. For kidney failure (the need to initiate chronic dialysis), only Dussol 2004 was rated with a low risk of detection bias, as the authors provided information to indicate that GFR < 15 mL/min/1.73 m^2 was the criteria for the onset of kidney failure, which was unlikely to be affected by investigators knowledge of the dietary assignment. The remaining seven studies did not provide any information on how to assess the onset of kidney failure or information on whether the onset of kidney failure was determined by personnel independent of the study investigators.

Incomplete outcome data

Attrition bias was assessed to be at low risk in seven studies (Brouhard 1990; Dullaart 1993; Dussol 2004; Hansen 2002; Koya 2009; Meloni 2002; Meloni 2004). Zeller 1991 was considered to be at high risk of attrition bias as 25% of participants were lost to follow-up or discontinued diet, and two patients in the LPD group whose mean protein intake exceeded 0.8 g/kg/day were excluded from the general analysis.

Selective reporting

Studies were considered to be at high risk if data were provided in a format which could not be entered into the meta-analyses or if the study did not provide data on death, GFR, the requirement for dialysis, urinary protein/albumin excretion, or the nutritional status of the participants. Selective reporting was considered to be at low risk in three studies (Dullaart 1993; Dussol 2004; Hansen 2002), and the remaining five studies were judged to be at high risk of bias (Brouhard 1990; Koya 2009; Meloni 2002; Meloni 2004; Zeller 1991).

Other potential sources of bias

Five studies (Brouhard 1990; Dullaart 1993; Dussol 2004; Koya 2009; Zeller 1991) were considered to be at low risk for other potential biases as they were funded by education or government organisations. In the remaining three studies, it was unclear as there was insufficient information to permit judgement regarding funding sources.

Effects of interventions

See: **Summary of findings 1** Low protein diet versus usual or unrestricted protein diet for adults with diabetic kidney disease

See Summary of findings 1.

Death (any cause)

Five studies (Brouhard 1990; Hansen 2002; Koya 2009; Meloni 2002; Meloni 2004) reported the number of deaths. Of these, three studies (Brouhard 1990; Meloni 2002; Meloni 2004) did not specifically report deaths, but there appeared to be no deaths, which was inferred from part of the information provided about participant recruitment or attrition during the study follow-up. The certainty of the evidence was considered low (Summary of findings 1) because of imprecision and potential publication bias. A LPD may have little or no effect on deaths compared with a UPD (Analysis 1.1 (5 studies, 358 participants): RR 0.38, 95% CI 0.10 to 1.44; I^2 = 0%).

Kidney failure

Four studies (Dullaart 1993; Dussol 2004; Hansen 2002; Koya 2009) reported the number of participants reaching kidney failure. The certainty of the evidence was considered low (Summary of findings 1) because of imprecision and potential publication bias. A LPD may make little or no difference to the number of participants who progressed to kidney failure compared with a UPD (Analysis 1.2 (4 studies, 287 participants): RR 1.16, 95% CI 0.38 to 3.59; I^2 = 0%).

Change in glomerular filtration rate

All eight studies reported the annual change in GFR. Since the data from Meloni 2002 and Meloni 2004 were almost the same at baseline and at the end of the study, we considered these two studies overlapped; therefore, we only used the data from Meloni 2004 in our meta-analysis. Studies used different methods to evaluate the change in GFR. Because of study limitations (high or unclear risks of bias), moderate heterogeneity (imprecision), and few participants (potential publication bias), the certainty of the evidence was considered to be very low (Summary of findings 1). It is uncertain whether a LPD impacts the annual change in GFR when compared with a UPD (Analysis 1.3 (7 studies, 367 participants): MD -0.73 mL/min/1.73 m^2/year, 95% CI -2.3 to 0.83; I^2 = 53%). Heterogeneity was reduced by the removal of Brouhard 1990 and Zeller 1991, but it was unclear why the data provided by these studies differed from the other studies.

Change in creatinine clearance

Three studies (Koya 2009; Meloni 2004; Zeller 1991) reported the change in CrCl and were included in the meta-analysis. Because of moderate heterogeneity, imprecision, and a high or unclear risk of bias in most studies, the certainty of the evidence was considered to be very low. It is uncertain whether a LPD influences the annual decline in CrCl when compared with a UPD (Analysis 1.4 (3 studies, 203 participants): MD -2.39 mL/min/year, 95% CI -5.87 to 1.08; I^2 = 53%). The removal of Zeller 1991 reduced this heterogeneity to 12%. There were attrition bias and unclear selection bias in Zeller

1991, so it is possible that an increased risk of bias in these domains might contribute to the heterogeneity.

Change in 24-hour urinary protein excretion

Meloni 2004 reported 24-hour urinary protein excretion at baseline and at follow-up. Because of small numbers, a high risk of bias and imprecision, the certainty of the evidence was considered to be very low (Summary of findings 1). Therefore, it is uncertain whether a LPD reduces the 24-hour urinary protein excretion (Analysis 1.5 (1 study, 80 participants): MD 0.90 g/24 hours, 95% CI 0.49 to 1.31).

Two studies (Dussol 2004; Hansen 2002) reported data on 24-hour urinary albumin excretion, and two studies (Brouhard 1990; Dullaart 1993) reported urinary albumin excretion rate (UAER). Because a surrogate outcome of change rate (%) in UAER was used in Dullaart 1993 (not the change value), we estimated SMD for UAER. Compared with the UPD, LPD has uncertain effects on the decline in 24-hour urinary albumin excretion (Analysis 1.6 (2 studies, 119 participants): MD 0.00 g/24 hours, 95% CI -0.07 to 0.07; I^2 = 0%; very low certainty evidence), but may decrease UAER in patients treated with LPD (Analysis 1.7 (2 studies, 45 participants): SMD 0.68, 95% CI 0.08 to 1.29; I^2 = 0%).

Adverse effects and nutritional status

No studies reported hyperglycaemic events or other adverse events. Seven studies (Dullaart 1993; Dussol 2004; Hansen 2002; Koya 2009; Meloni 2002; Meloni 2004; Zeller 1991) reported nutritional status. Six studies reported no evidence of malnutrition, while Meloni 2002 reported malnutrition in the LPD group (as measured by serum levels of albumin and prealbumin and anthropometric parameters). The definition of malnutrition and the number of participants involved in Meloni 2002 were not given, but serum prealbumin and serum albumin decreased in the LPD group.

Three studies (Dullaart 1993; Dussol 2004; Meloni 2002) reported final body weight. Because of imprecision and potential publication bias, the certainty of the evidence was considered to be low. LPD may make little or no difference to the final body weight (Analysis 2.1 (3 studies, 146 participants): MD 1.03 kg, 95% CI -3.04 to 5.09; I^2 = 23%).

Meloni 2004 reported final BMI. The certainty of the evidence was rated very low because of a high or unclear risk of bias, imprecision and small participants. Thus a LPD had uncertain effects on final BMI (Analysis 2.2 (1 study, 80 participants): MD -1.20 kg/m^2, 95% CI -2.60 to 0.20; very low certainty evidence).

Compliance

All eight studies assessed dietary compliance and measured at one to six monthly intervals or regularly, either by an independent measurement of urinary urea excretion (Brouhard 1990; Dullaart 1993; Meloni 2004) or by a combination of urinary urea excretion and food record (Dussol 2004; Hansen 2002; Koya 2009; Meloni 2002; Zeller 1991). This was facilitated by dietitians. The prescribed protein intake across the included studies in intervention groups ranged from 0.6 to 0.8 g/kg/day, but the calculated protein intake ranged from 0.68 to 1.0 g/kg/day. Brouhard 1990 did not report the calculated protein intake, and in four studies (Dussol 2004; Hansen 2002; Koya 2009; Meloni 2004), the calculated protein intake exceeded 0.8 g/kg/day in the intervention groups, indicating that participant compliance to a restricted protein diet in nearly half of the studies was unsatisfactory.

Health-related quality of life

Koya 2009 assessed the QoL using the SF-36 questionnaire (physical function, social function, physical role, emotional role, mental health, energy, pain and general health perceptions). There were no significant differences in HRQoL between the LPD and UPD groups during the study period.

DISCUSSION

Summary of main results

This review summarises eight small RCTs involving 486 people with DKD, which compared a LPD (0.6 to 0.8 g/kg/day) with a UPD (≥ 1.0 g/kg/day). Dietary protein restriction was evaluated with the mean duration of interventions ranging from one to five years. The studies included people with CKD stages 1 to 4. The risks of bias in the included studies were often high or unclear, and these risks, combined with the imprecision in effect estimates, resulted in low or very low confidence in the results.

For the primary outcomes, a LPD may make little or no difference to the number of participants who died regardless of cause (low certainty evidence) or those who progressed to kidney failure (low certainty evidence). It remains uncertain whether a LPD impacts the annual decline in GFR compared to a UPD (very low certainty evidence).

Many studies were not designed to assess the effect of dietary protein restriction on the change in proteinuria or albuminuria. As a result, there was uncertainty about the effect of protein restriction on this outcome.

Seven studies assessed nutritional status. Six studies had no participants with malnutrition, while one study noted malnutrition in the LPD group on a prescribed intake of 0.6 g/kg/day, as measured by serum levels of prealbumin and albumin. No study formally assessed hyperglycaemic events in the participants. Only one study reported that QoL was assessed and that the LPD regimen did not affect HRQoL. Nearly half of the studies reported that compliance with a LPD of 0.6 to 0.8 g/kg/day was unsatisfactory.

Overall, these data suggest that current evidence for dietary protein restriction in the setting of DKD is of low or very low certainty and insufficient as a guide for clinical practice.

Overall completeness and applicability of evidence

One major limitation was the relatively small number of included studies, with only one study enrolling more than 100 participants (Koya 2009). All the included studies were published before 2009.

Many confounding variables, such as type of diabetes, different ways of measuring the change in GFR, dietary compliance, and different stages of CKD (CKD 1-5, not on dialysis), were not reported in detail. Thus subgroup analysis allowing for variations in these aspects could not be properly carried out due to the paucity of studies. Many studies were of low methodological quality or did not present adequate data. For the primary outcomes, such as death and kidney failure, there were too few studies of sufficient size or duration to examine these outcomes, and an adequate follow-up

interval should be at least three to five years. Numerical data on weight loss were provided in a few studies though nearly all the studies reported that participants' body weight was measured.

Quality of the evidence

The quality of study evidence was assessed using the Cochrane risk of bias tool together with GRADE methodology. Most studies had unclear risk methods for allocation concealment and were rated at high risk of bias in the selective reporting domain. None of the participants or study investigators were considered to be masked to treatment allocation as all studies were open-label. We assessed detection bias for GFR and kidney failure separately. Because GFR measurement was a laboratory outcome, all studies were considered at low risk of detection bias. For the outcome assessment of kidney failure, most studies were judged to be at an unclear risk of detection bias, as information on how to assess the onset of kidney failure was not provided.

We downgraded for the possibility of publication bias due to the very low numbers of data observations for each outcome or the small number of included studies. Confidence in evidence for death (any cause), kidney failure, change in GFR or 24-hour urinary protein excretion, and weight loss was low or very low, meaning future researches are likely to offer different results.

Potential biases in the review process

This review adhered as closely as possible to our published protocol (Jiang 2021). A comprehensive search of the Cochrane Kidney and Transplant's Specialised Register was performed by the Information Specialist, which reduced the likelihood of potential studies being omitted from the review. As with most systematic reviews, there remains the possibility that unpublished studies with positive or negative results may not have been identified. We are aware of the potential for publication bias due to the small number of studies in the review. At least two authors independently evaluated all the identified studies in an effort to address any bias or errors in study selection, data extraction and risk of bias assessment.

Agreements and disagreements with other studies or reviews

In 1997, a published Cochrane review evaluated protein restriction among adults with DKD who followed a LPD for at least four months, but there was no evidence from RCTs that explored the impact of dietary protein on kidney failure or death (Waugh 1997). The 2007 update (Robertson 2007) identified one RCT exploring the number of participants who died or developed kidney failure (Hansen 2002), and pooled data from seven RCTs in patients with type 1 diabetes showed a non-significant reduction of GFR decline in the LPD group. In this review, with interventions lasting for a minimum of 12 months, it seems to be more powerful than in the 2007 version. However, there was also very limited data available to assess the impact of protein restriction on death or kidney failure, although we were able to report on these outcomes separately.

Two recently published systematic reviews (Li 2019; Zhu 2018) evaluated the effects of protein restriction in participants with DKD, both of which evaluated change in GFR or proteinuria but did not evaluate the number of participants dying or reaching kidney failure. Zhu 2018 evaluated eleven RCTs (687 participants) that had a mean length of follow-up of more than two months. In this review, a LPD (0.6 to 0.8 g/kg/day) compared with a UPD did not seem to slow down the decline in GFR and the increase in urinary protein level. Similarly, 20 RCTs with at least three months of follow-up, including 1,372 participants with DKD, were reviewed by Li 2019. The authors noted the dietary protein restriction was significantly effective for decreasing proteinuria and that the final GFR in the LPD group seemed to be higher than in the UPD group, although in a non-significant way. In this review, pooling of the seven RCTs with at least one-year follow-up resulted in a non-significant improvement in GFR of 0.73 mL/min/1.73 m^2/year in the LPD group. Variation among participants also needs to be taken into account. Studies did not give sufficient details to quantify this, or a small sample size could not provide great statistical power to observe differences between treatment groups. Thus a small average benefit may conceal larger benefits in some patients.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, available data from RCTs outlined in this review suggest that current evidence of dietary protein restriction in the setting of DKD is of low or very low certainty and insufficient to guide clinical practice. There were also very limited data available on adverse effects (e.g. weight loss and hyperglycaemia events) and participants' QoL, which could be affected by difficulties in maintaining dietary compliance. In practice, the optimum level of dietary protein intake would probably be a compromise between efficacy and compliance. Although a dietary protein intake of 0.6 to 0.8 g/kg/day was recommended by the KDOQI Clinical Practice Guideline 2020 as a dietary intervention for diabetic adults with CKD 3-5, not on dialysis (KDOQI 2020), clinicians should inform their patients of the lack of high-quality evidence for these benefits as well as the well-recognised adverse effects of this intervention. It remains uncertain whether a dietary protein intake of 0.6 to 0.8 g/kg/day should be indicated in adults with DKD at high risk of progression to kidney failure. We still cannot determine what level of protein intake is most effective at different stages of CKD in such a population.

Implications for research

Given that the sample sizes of the existing studies are generally small and insufficient to determine the effect of LPD on death and kidney failure, there is a need for more large-scale pragmatic RCTs with an emphasis on different stages of CKD as well as adequate follow-up. In addition, clinical trials comparing different levels of protein intake or altering protein type in those with DKD are also necessary. Outcome measures should include not only albuminuria, proteinuria, and change of GFR but also the incidents of kidney failure and death. QoL and other adverse events, including weight loss, incidents of malnutrition, and hyperglycaemic events, should be of greater concern. Further information on the role of compliance with restricted protein intake on definite outcomes is also required. With satisfactory adherence to the diet and without compromising the QoL, whether patients with DKD should be offered the option of a reduced protein intake in order to retard the progression of kidney failure needs to be further evaluated (Piccoli 2016).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brouhard 1990

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: before March 1990 • Duration of follow-up: 12 months
Participants	General information • Setting: single centre • Country: USA • Inclusion criteria: patients with type 1 diabetes and microalbuminuria (≥ 30 µg/min); SCr ≤ 8 mg/dL; BP ≤ 140/90 mmHg, which was measured at least three times within 3 weeks or more prior to the study start • Exclusion criteria: not reported Baseline characteristics • Number: LPD group (8); UPD group (7) • Mean age ± SD (years): LPD group (36 ± 13); UPD group (30 ± 12) • Sex (M/F): LPD group (5/3); UPD group (4/3) Comorbidities/other information • Many were hypertensive, and all had either background or proliferative retinopathy

Brouhard 1990 *(Continued)*

	• Patients maintained their usual insulin regimen and other medications. Blood pressure medications other than the ACEIs were adjusted to maintain BP at or below 140/90 mmHg
Interventions	LPD group • Prescribed protein intake: 0.6 g/kg/day • Calculated protein intake: not reported UPD group • Prescribed protein intake: 1.0 g/kg/day • Calculated protein intake: not reported Co-interventions • Treatment for hypertension
Outcomes	Outcomes relevant to this review • Rate of decline in GFR • Change in UAER by calculating the difference in means and SDs between the baseline and follow-up • Compliance assessed by urinary urea excretion (a 3-month trial period)
Notes	• Funding source: Texas Methodist Foundation, Austin, Texas; Juvenile Diabetes Foundation International, New York; General Clinical Research Centre Program of the Division of Research Resources, National Institutes of Health, Bethesda, Maryland • Conflicts of interest: not reported • Other: no significant differences in any of the baseline measurements between groups but the UPD group had slightly worse factors; no mention of malnutrition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on the method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Masking of patients or study investigators was not reported; participants underwent different diet procedures that could not be blinded
Blinding of outcome assessment (detection bias) Change in GFR	Low risk	Laboratory measurement of GFR was unlikely to be influenced by a lack of blinding
Blinding of outcome assessment (detection bias) Need to start dialysis	Unclear risk	No information was provided; need to start dialysis was not recorded as a study outcome
Incomplete outcome data (attrition bias)	Low risk	All participants appeared to have completed follow-up

Brouhard 1990 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Only GFR and UAER were reported, but chronic dialysis and nutritional status were not reported. Deaths were also not reported, but there appeared to be no deaths
Other bias	Low risk	Grants from Texas Methodist Foundation, and Juvenile Diabetes Foundation International, and Grant RR73 from General Clinical Research Centre Program of the Division of Research Resources

Dullaart 1993

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: before April 1992 • Duration of follow-up: 2 years
Participants	General information • Setting: single centre, outpatient department • Country: the Netherlands • Inclusion criteria: patients with type 1 diabetes and microalbuminuria (10 to 200 µg/min); SCr < 120 µmol/L; GFR ≥ 90 mL/min/1.73 m^2; absence of hypertension; duration of diabetes ≥ 5 years; age between 21 and 65 years • Exclusion criteria: patients with renal tract abnormality, other renal disease, or planning to become pregnant Baseline characteristics • Number: LPD group (14); UPD group (16) • Mean age ± SD (years): LPD group (43 ± 13); UPD group (39 ± 13) • Sex (M/F): LPD group (14/0); UPD group (13/3) Comorbidities/other information • 86% (12/14) of participants in LPD group and 75% (12/16) of participants in UPD group had concomitant background or proliferative retinopathy
Interventions	LPD group • Prescribed protein intake: 0.6 g/kg/day • Calculated protein intake: 0.79 ± 0.16 g/kg/day UPD group • Prescribed protein intake: > 1.0 g/kg/day • Calculated protein intake: 1.09 ± 0.21 g/kg/day Co-interventions • The diet was supplemented with methionine tablets if necessary • Sodium intake was unrestricted • Both groups received an isocaloric diet
Outcomes	Outcomes relevant to this review

Dullaart 1993 *(Continued)*

- Annual change in GFR (renal clearance of I^{125} iothalamate) by calculating the difference in means and SDs between the baseline and follow-up
- Annual change in UAER by using the regression coefficients
- Compliance assessed by urinary urea excretion
- Malnutrition assessed by calorie intake, BMI and serum albumin
- Final body weight

Notes

- Funding source: the Dutch Diabetes Research Fund
- Conflicts of interest: not reported
- Other: no significant differences in baseline measurements between groups, except BMI was significantly higher in the LPD group; no evidence of malnutrition; seven participants in the LPD group showed good compliance using a protein intake consistently < 0.8 g/kg/day

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Masking of patients or study investigators was not reported. Actually, participants underwent different diet procedures that could not be blinded
Blinding of outcome assessment (detection bias) Change in GFR	Low risk	GFR was measured by ^{125}I iothalamate and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Need to start dialysis	Unclear risk	No information was provided. Need to start dialysis was not recorded as a study outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient from the LPD group after randomisation decided not to participate further. Data were available for all the remaining participants
Selective reporting (reporting bias)	Low risk	Reported GFR, UAER and body weight. Data for death and the need to start dialysis were not reported but there appeared to be no deaths and no patients needing dialysis
Other bias	Low risk	Grant from the Dutch Diabetes Research Fund

Dussol 2004

Study characteristics

Methods

- Study design: parallel RCT
- Duration of study: June 1999 to June 2001
- Duration of follow-up: 2 years

Dussol 2004 *(Continued)*

Participants	General information • Setting: single centre, outpatient department • Country: France • Inclusion criteria: patients with type 1 or type 2 diabetes and DKD (either pathologically or clinically confirmed; disease duration > 10 years; presence of diabetic retinopathy); age between 18 and 75 years • Exclusion criteria: clinical or laboratory evidence of other kidney or urinary tract disease; absence of nephropathy; kidney failure requiring dialysis; presence of pregnancy; cachexia; BMI > 33 kg/m^2 Baseline characteristics • Number (randomised/analysed): LPD group (30/22); UPD group (33/25) • Mean age ± SD (years): LPD group (52 ± 12); UPD group (63 ± 9) • Sex (M/F): LPD group (19/3); UPD group (20/5) Comorbidities/other information • not reported
Interventions	LPD group • Prescribed protein intake: 0.8 g/kg/day • Calculated protein intake: 0.83 ± 0.15 g/kg/day UPD group • Prescribed protein intake: pre-study diet (if participants had a high-protein diet before study, they were recommended to decrease their protein intake to 1.2 g/kg/day) • Calculated protein intake: 1.0 ± 0.1 g/kg/day Co-interventions • Renin-angiotensin blockers (ACEIs or ARBs) • Both groups received isocaloric diet
Outcomes	Outcomes relevant to this review • Kidney failure requiring dialysis • Annual change in GFR (measured using ^{99m}Tc-DTPA) • Annual change in 24-hour urinary albumin excretion • Final body weight • Compliance assessed by dietary records and urinary urea excretion • Malnutrition assessed by energy intake, body weight, serum albumin and serum Hb
Notes	• Funding source: Programme Hospitalier de Recherche Clinique 1998 • Conflicts of interest: not reported • Other: concomitant medications were similar in the two diet groups at baseline and follow-up; no evidence of malnutrition; six patients in the LPD group maintained a protein intake ≤ 0.8 g/kg/day • No evidence of malnutrition • Six patients in the LPD group maintained a protein intake ≤ 0.8 g/kg/day • Funding source: Programme Hospitalier de Recherche Clinique 1998

Dussol 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to the type of diabetes (type 1 or type 2) and performed using random numbers
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked
Blinding of outcome assessment (detection bias) Change in GFR	Low risk	GFR was measured using ^{99m}Tc-DTPA and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Need to start dialysis	Low risk	End-stage kidney disease (GFR < 15 ml/min/1.73m^2) was the criteria for starting dialysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups (24% in the LPD group; 27% in the UPD group), with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Reported dialysis, GFR and nutritional status. Deaths were not reported but there appeared to be no deaths
Other bias	Low risk	Grant from Programme Hospitalier de Recherche Clinique 1998

Hansen 2002

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: May 1995 to April 1996 • Duration of follow-up: 4 years
Participants	General information • Setting: single centre, outpatient department • Country: Denmark • Inclusion criteria: patients with type 1 diabetes and albuminuria (≥ 300 mg/24 hours); SCr < 120 µmol/L; GFR > 20 mL/min/1.73 m^2 and progressive DKD (pre-study decline in GFR ≥ 2 mL/min/year); presence of diabetic retinopathy; duration of diabetes ≥ 10 years (an onset before the age of 35 years); age between 18 and 60 years • Exclusion criteria: other kidney or urinary tract disease; presence of pregnancy; history of congestive heart failure or myocardial infarction or coronary bypass surgery within the last 3 months

Hansen 2002 *(Continued)*

	Baseline characteristics • Number: LPD group (41); UPD group (41) • Mean age ± SD (years): LPD group (40 ± 8); UPD group (41 ± 9) • Sex (M/F): LPD group (30/11); UPD group (23/18) Comorbidities/other information • Most participants were hypertensive • 27% (11/41) of participants in LPD group and 24% (10/41) of participants in UPD group had concomitant coronary heart disease or stroke at the time of randomisation • 44% (18/41) of participants in LPD group and 46% (19/41) of participants in UPD group smoked, respectively
Interventions	LPD group • Prescribed protein intake: 0.6 g/kg/day + supplementation of calcium of 500 mg/day • Calculated protein intake: 0.89 g/kg/day (0.83 to 0.95) UPD group • Prescribed protein intake: pre-study diet • Calculated protein intake: 1.02 g/kg/day (95% CI 0.95 to 1.1) Co-interventions • Both groups received isocaloric diet
Outcomes	Outcomes relevant to this review • Kidney failure requiring dialysis • Death (any cause) • Slope of GFR over time by kidney clearance of ^{51}Cr-EDTA • Annual change in 24-hour urinary albumin excretion • Compliance monitored by dietary interview and UAER • Malnutrition assessed by mid-arm circumference, serum albumin and body weight
Notes	• Funding source: not reported • Conflicts of interest: not reported • Other: at baseline and during follow-up, a comparable number of patients in both diet groups received antihypertensive treatment, ACEIs, diuretics, alpha and beta blockers, CCBs, low-dose acetylsalicylic acid and lipid lowing agents, respectively; malnutrition indicators (mid-arm circumference, serum albumin and body weight) were comparable in 2 groups (data not shown)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	With concealed randomisation the patients were in blocks of two according to the level of GFR
Allocation concealment (selection bias)	Unclear risk	Concealed randomisation stated but no information on method used is available

Hansen 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unmasked
Blinding of outcome assessment (detection bias) Change in GFR	Low risk	GFR was measured using ^{51}Cr-EDTA and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Need to start dialysis	Unclear risk	No information provided on the criteria used to commence dialysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study, and no patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes (death, commencement of dialysis, GFR, nutritional status) were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Koya 2009

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: 1 December 1997 to 30 April 2006 • Duration of follow-up: 5 years
Participants	General information • Setting: multi-centre, outpatient department • Country: Japan • Inclusion criteria: type 2 diabetes and overt nephropathy (proteinuria between 1.0 and 10 g/day; UAER of more than 200 µg/min at least twice in a 1-year period); SCr < 176 µmol/L; presence of diabetic retinopathy; age between 30 and 70 years; usual protein diet (1.2 g/kg/day) • Exclusion criteria: type 1 diabetes; other kidney diseases; body weight less than 80% of ideal body weight; clinically significant illness (such as heart failure, hepatic disease, recent myocardial infarction and stroke); UTI; being treated with a low-protein diet and/or ACEIs or ARBs Baseline characteristics • Number: LPD group (56); UPD group (56) • Mean age ± SD (years): LPD group (57.5 ± 7.8); UPD group (56.3 ± 8.7) • Sex (M/F): LPD group (33/23); UPD group (33/23) Comorbidities/other information • 63% and 68% of participants in LPD and UPD groups, respectively, had hypertension
Interventions	LPD group • Prescribed protein intake: 0.8 g/kg/day • Calculated protein intake: 0.9 ± 0.2 g/kg/day (assessed by food record); 1.0 ± 0.2 g/kg/day (assessed by 24-hour urinary nitrogen excretion)

Koya 2009 *(Continued)*

	UPD group • Prescribed protein intake: 1.2 g/kg/day • Calculated protein intake: 1.1 ± 0.2 g/kg/day (assessed by food record); 1.0 ± 0.2 g/kg/day (assessed by 24-hour urinary nitrogen excretion) Co-interventions • Not reported
Outcomes	Outcomes relevant to this review • Kidney failure requiring dialysis • Slope of GFR decline over time by using modified MDRD formula • Slope of CrCl decline over time • Death (any cause) • Compliance monitored by food record and urinary nitrogen excretion every 3 months • Malnutrition assessed by body weight • HRQoL assessed annually using the SF-36
Notes	• Funding source: the Ministry of Health, Labour and Welfare of Japan • Conflicts of interest: none • Other: participants for both groups were balanced for baseline characteristics; no significant differences in HRQoL between the two groups during the study period; malnutrition indicators comparable in 2 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Minimization
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not masked
Blinding of outcome assessment (detection bias) Change in GFR	Low risk	GFR was calculated using modified MDRD formula and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Need to start dialysis	Unclear risk	No information provided on the criteria used to commence dialysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	21% lost to follow-up/discontinued diet but all participants included in analysis
Selective reporting (reporting bias)	High risk	The data of proteinuria/albuminuria provided in a format that could not be extracted to calculate the change over time
Other bias	Low risk	Grant from the Ministry of Health, Labour and Welfare of Japan

Meloni 2002

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: before 2002 • Duration of follow-up: 12 months
Participants	General information • Setting: single centre, outpatient department • Country: Italy • Inclusion criteria: 32 patients with type 1 diabetes and 37 patients (63.2 ± 19.3 years) with type 2 diabetes; overt nephropathy and hypertension • Exclusion criteria: not reported Baseline characteristics • Number: LPD group (35); UPD group (34) • Mean age ± SD (years): LPD group (52.7 ± 15.3); UPD group (56.3 ± 16.0) • Sex (M/F): LPD group (21/14); UPD group (17/17) Comorbidities/other information • Protein intake was free in all participants before starting the study
Interventions	LPD group • Prescribed protein intake: 0.6 g/kg/day • Calculated protein intake: 0.68 ± 0.21 g/kg/day UPD group • Prescribed protein intake: free protein diet • Calculated protein intake: 1.39 ± 0.28 g/kg/day Co-interventions • All patients received ACEIs and CCBs
Outcomes	Outcomes relevant to this review • Mean decline of GFR over time by a radioisotope technique with chromium ^{51}Cr-EDTA clearance • Annual decline of CrCl by calculating the difference in means and SDs between the baseline and follow-up • Final body weight • Annual change in 24-hour urinary protein excretion • Compliance monitored by diet questionnaire and urinary urea excretion • Malnutrition measured by serum albumin, serum pre-albumin, and anthropometric parameters (body weight, ideal weight, and obesity index)
Notes	• Funding source: not reported • Conflicts of interest: not reported • Other: malnutrition noted in LPD group

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Meloni 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Masking of patients or study investigators was not reported. Actually, participants underwent different diet procedures that could not be blinded
Blinding of outcome assessment (detection bias) Change in GFR	Low risk	GFR was measured using ^{51}Cr-EDTA and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Need to start dialysis	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants appeared to have completed follow-up
Selective reporting (reporting bias)	High risk	Reported GFR and nutritional status. Deaths were not reported, but there appeared to be no deaths. Patients needing to start dialysis during follow-up were not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Meloni 2004

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: 1 January to 31 December 2001 • Duration of follow-up: 12 months
Participants	General information • Setting: single centre, outpatient department • Country: Italy • Inclusion criteria: 24 patients (46.7 ± 9.8 years) with type 1 diabetes and 56 patients (63.2 ± 19.3 years) with type 2 diabetes; overt nephropathy and hypertension • Exclusion criteria: patients had signs of malnutrition; uncontrolled BP (SBP > 140 mm Hg or DBP > 85 mm Hg) Baseline characteristics • Number: LPD group (40); UPD group (40) • Mean age ± SD (years): 54.5 ± 15.6 • Sex (M/F): 39/41 Comorbidities/other information • 27 of 80 participants (33.7%) had cardiovascular pathology

Meloni 2004 *(Continued)*

	• Protein intake in all participants was free before starting the study
Interventions	LPD group • Prescribed protein intake: 0.8 g/kg/day • Calculated protein intake: 0.86 ± 0.12 g/kg/day UPD group • Prescribed protein intake: free protein diet • Calculated protein intake: 1.24 ± 0.44 g/kg/day Co-interventions • All patients received ACEIs and CCBs
Outcomes	Outcomes relevant to this review • Mean decline of GFR by a radioisotope technique with ^{51}Cr-EDTA clearance • Annual decline of CrCl by calculating the difference in means and SDs between the baseline and follow-up • Final BMI • Malnutrition measured by serum albumin, serum pre-albumin, and anthropometric parameters (body weight, ideal weight, and obesity index) • Annual change in 24-hour urinary protein excretion • Compliance monitored by urinary urea excretion
Notes	• Funding source: not reported • Conflicts of interest: not reported • Other information: no reported malnutrition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple randomisation using dedicated software generating casual numbers to assign participants to treatment groups and remaining participants were placed in control group"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Masking of patients or study investigators was not reported. Actually, participants underwent different diet procedures that could not be blinded
Blinding of outcome assessment (detection bias) Change in GFR	Low risk	GFR was measured using ^{51}Cr-EDTA and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Need to start dialysis	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants appeared to have completed follow-up

Meloni 2004 *(Continued)*

Selective reporting (reporting bias)	High risk	Reported GFR and nutritional status. Deaths were not reported, but there appeared to be no deaths. Patients needing to start dialysis during follow-up did not report
Other bias	Unclear risk	Insufficient information to permit judgement

Zeller 1991

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: before 1991 • Duration of follow-up: at least 12 months (mean: 34.7 months)
Participants	General information • Setting: single centre • Country: USA • Inclusion criteria: patients with type 1 diabetes and clinically evident nephropathy (24-hour urinary protein excretion > 0.5 g); presence of diabetic retinopathy • Exclusion criteria: contraindications to a LPD, such as severe infection, cancer, or pregnancy, a history of brittle diabetes; < 18 years or > 60 years; other causes of kidney disease Baseline characteristics • Number: LPD group (20); UPD group (15) • Mean age ± SD (years): LPD group (33 ± 9); UPD group (35 ± 8) • Sex (M/F): LPD group (11/9); UPD group (10/5) Comorbidities/other information • Some participants had hypertension
Interventions	LPD group • Prescribed protein intake: 0.6 g/kg/day • Calculated protein intake: 0.72 ± 0.06 g/kg/day UPD group • Prescribed protein intake: at least 1.0 g/kg/day • Calculated protein intake: 1.08 ± 0.10 g/kg/day Co-interventions • A standard multivitamin preparation
Outcomes	Outcomes relevant to this review • Slope of GFR decline over time by measurement of ^{125}I-labeled iothalamate clearance • Slope of CrCl decline over time • Compliance assessed on the basis of dietary history and measurement of urinary excretion of urea nitrogen • Malnutrition measured by body weight, mid-arm circumference, and serum albumin
Notes	• Funding source: the Juvenile Diabetes Foundation and the Texas Kidney Foundation and a General Clinical Research Center grant (MOI-RR00633)

Zeller 1991 *(Continued)*

- Conflicts of interest: not reported
- Other information: no significant differences in any of baseline measurements between groups; malnutrition measures showed no significant change

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Masking of patients or study investigators was not reported. Actually, participants underwent different diet procedures that could not be blinded
Blinding of outcome assessment (detection bias) Change in GFR	Low risk	GFR was measured using ^{125}I-labeled iothalamate clearance and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Need to start dialysis	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	25% lost to follow-up/discontinued diet. Two patients in the LPD group whose mean protein intake exceeded 0.8 g/kg/day were excluded from the general analysis
Selective reporting (reporting bias)	High risk	Reported deaths, GFR and nutritional status. Patients needing to start dialysis during follow-up did not report. Change in proteinuria could not be extracted
Other bias	Low risk	Grants from the Juvenile Diabetes Foundation and the Texas Kidney Foundation and a General Clinical Research Center grant (MOI-RR00633)

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BMI: body mass index; BP: blood pressure; CCBs: calcium channel blockers; CrCl: creatinine clearance; DBP: diastolic blood pressure; DKD: diabetic kidney disease; GFR: glomerular filtration rate; Hb: haemoglobin; HRQoL: health-related quality of life; LPD: low protein diet; MDRD: Modification of Diet in Renal Disease; RCT: randomised controlled trial; SBP: systolic blood pressure; SCr: serum creatinine; SD: standard deviation; SF-36: short-form 36 Health Status Questionnaire; UAER: urinary albumin excretion ratio; UPD: usual or unrestricted protein diet; UTI: urinary tract infection; ^{51}Cr-EDTA: chromium-51 ethylenediamine tetra-acetic acid; ^{99m}Tc-DTPA: technetium-99m-diethylene triamine penta-acetic acid

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aoyagi 2006	RCT comparing regular protein restriction diet (0.6 g/kg/day) with mild protein restriction diet (1.1 g/kg/day) in type 2 diabetic patients with nephropathy under angiotensin II receptor blockade; the number of patients in each group could not be determined
Azadbakht 2003	Wrong intervention and duration: cross-over design comparing a diet containing 0.8 g/kg protein (70% animal and 30% vegetable protein) with a similar diet containing 0.8 g/kg protein (35% soy protein, 30% vegetable protein and 35% animal protein); the starting period of the intervention was only 7 weeks

Study	Reason for exclusion
Barsotti 1993	Wrong intervention: low protein intake (0.7 g/kg/day) versus very low protein intake (0.3 g/kg/day); it was unclear whether randomisation was used
Bending 1988	Wrong duration: cross-over study with patients only studied for 3 weeks in each phase
Chen 2012h	Wrong intervention: keto-amino acids (100 mg/kg/day) versus no addition in participants on low protein intake (0.8 g/kg/day)
Ciarambino 2012	Wrong intervention and duration: low protein intake (0.8 g/kg/day, 7 days a week) versus a protein diet (0.8 g/kg/day, 6 days a week) in participants with a usual protein intake (1.2 g/kg/day); follow-up only 4 weeks
Ciavarella 1987	Wrong duration: 3 to 6 months duration only
Cohen 1987	Wrong duration: cross-over study with participants only studied for 3 weeks in each phase
Effendi 2000	Wrong duration: standard protein diet (> 1 g/kg/day) versus a LPD (0.8 g/kg/day) but duration of follow-up is only 4 weeks
Facchini 2003	Wrong intervention: carbohydrate-restricted, low-iron-available, polyphenol-enriched diet (not an unrestricted diet) versus conventional standard-of-care dietary treatment
Garcia Garcia 1990	Not randomised
Gross 2002	Wrong duration: cross-over study with participants only studied for 4 weeks in each phase
Hansen 1999	Wrong duration: low protein intake versus UPD but duration only 8 weeks
Parillo 1988	Wrong duration: 10 days duration only
Pecis 1994	Wrong population and duration: diabetic participants with normoalbuminuria; duration only 3 weeks
Pedersen 1989	Wrong population and duration: cross-over study comparing an UPD with limited protein intake in diabetic patients with normoalbuminuria; each intervention for 4 weeks only
Pijls 1999	Wong population: more than 60% diabetic participants with normoalbuminuria
Pinto 1991	Wrong duration: cross-over study comparing low protein intake with a UPD; each intervention for 3 weeks only
Qiu 2012a	Wrong intervention: LPD (0.6 g/kg/day) + keto-analogues versus dietary protein intake of 0.8 g/kg/day (< 1.0 g/kg/day)
Raal 1994	Wrong duration: 6 months duration only
Rosenberg 1987	Wrong duration: cross-over study comparing low protein intake with a high protein diet; each intervention for 11 days only
Rudberg 1988	Wrong population and duration: cross-over study including diabetic patients with normoalbuminuria; only studied for 10 days in each phase
Silan 2003	RCT comparing a LPD (0.6 g/kg/day) with a UPD in type 1 diabetic patients with progressive DKD; the number of patients in each group could not be determined

Study	Reason for exclusion
Stephenson 2005	Wrong population and duration: cross-over study including diabetic patients with normoalbuminuria; only studied for 8 weeks in each phase
Suratkal 2012	Wrong intervention: keto-analogues versus no supplements in participants on the same LPDs
Velazquez Lopez 2008	Wrong duration: 4 months duration only
Wheeler 2002	Wrong intervention and duration: cross-over study comparing plant-based protein intake with predominantly animal-based protein diet in participants on macronutrients equivalent between the two diets; each intervention for 6 weeks only
Wiseman 1987	Wrong population and duration: cross-over study in diabetic patients with normoalbuminuria comparing low protein intake with UPD; each intervention for 3 weeks only
Zeller 1986	Wrong duration: patients followed for only a mean of 6.7 months
Zucchelli 1988b	Wrong duration: 4 weeks only

LPD: low protein diet; RCT: randomised controlled trial; UPD: usual or unrestricted protein diet

DATA AND ANALYSES

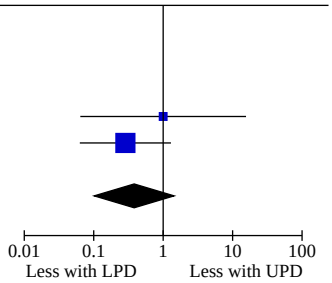
Comparison 1. Low protein diet versus usual or unrestricted protein diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death (any cause)	5	358	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.10, 1.44]
1.2 Kidney failure	4	287	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.38, 3.59]
1.3 Change in GFR [mL/min/1.73 m^2/year]	7	367	Mean Difference (IV, Random, 95% CI)	-0.73 [-2.30, 0.83]
1.4 Change in CrCl [mL/min/year]	3	203	Mean Difference (IV, Random, 95% CI)	-2.39 [-5.87, 1.08]
1.5 Change in 24-hour urinary protein excretion	1	80	Mean Difference (IV, Random, 95% CI)	0.90 [0.49, 1.31]
1.6 Change in 24-hour urinary albumin excretion	2	119	Mean Difference (IV, Random, 95% CI)	0.00 [-0.07, 0.07]
1.7 Change in UAER	2	45	Std. Mean Difference (IV, Random, 95% CI)	0.68 [0.08, 1.29]

Analysis 1.1. Comparison 1: Low protein diet versus usual or unrestricted protein diet, Outcome 1: Death (any cause)

Study or Subgroup	Low protein diet (LPD) Events	Total	Usual protein diet (UPD) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brouhard 1990	0	8	0	7		Not estimable
Meloni 2002	0	35	0	34		Not estimable
Meloni 2004	0	40	0	40		Not estimable
Koya 2009	1	56	1	56	23.2%	1.00 [0.06 , 15.59]
Hansen 2002	2	41	7	41	76.8%	0.29 [0.06 , 1.29]
Total (95% CI)		**180**		**178**	**100.0%**	**0.38 [0.10 , 1.44]**
Total events:	3		8			

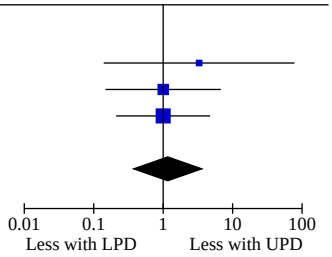
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Low protein diet versus usual or unrestricted protein diet, Outcome 2: Kidney failure

Study or Subgroup	Low protein diet (LPD) Events	Total	Usual protein diet (UPD) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dullaart 1993	0	14	0	16		Not estimable
Dussol 2004	1	30	0	33	12.7%	3.29 [0.14 , 77.82]
Hansen 2002	2	41	2	41	34.8%	1.00 [0.15 , 6.76]
Koya 2009	3	56	3	56	52.5%	1.00 [0.21 , 4.74]
Total (95% CI)		**141**		**146**	**100.0%**	**1.16 [0.38 , 3.59]**
Total events:	6		5			

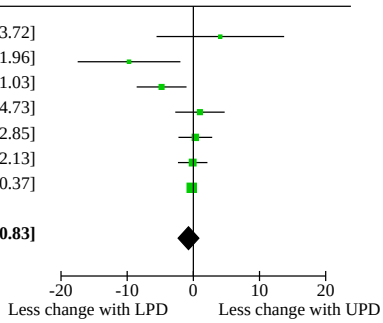
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable



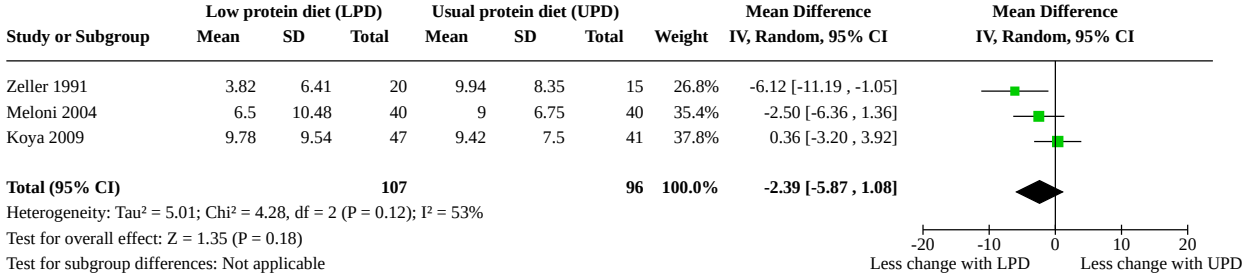
Analysis 1.3. Comparison 1: Low protein diet versus usual or unrestricted protein diet, Outcome 3: Change in GFR [mL/min/1.73 m²/year]

Study or Subgroup	Low protein diet (LPD) Mean	SD	Total	Usual protein diet (UPD) Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dullaart 1993	9	14.76	14	4.92	11.76	16	2.4%	4.08 [-5.56 , 13.72]
Zeller 1991	3.02	4.82	20	12.74	14.76	15	3.6%	-9.72 [-17.48 , -1.96]
Brouhard 1990	3.36	1.8	8	8.16	4.8	7	11.5%	-4.80 [-8.57 , -1.03]
Dussol 2004	3.5	5.5	22	2.5	7.5	25	11.6%	1.00 [-2.73 , 4.73]
Koya 2009	6.1	6.5	47	5.8	5.7	41	18.0%	0.30 [-2.25 , 2.85]
Hansen 2002	3.8	4.2	38	3.9	5.3	34	20.3%	-0.10 [-2.33 , 2.13]
Meloni 2004	5.78	1.5	40	6.03	1.3	40	32.7%	-0.25 [-0.87 , 0.37]
Total (95% CI)			**189**			**178**	**100.0%**	**-0.73 [-2.30 , 0.83]**

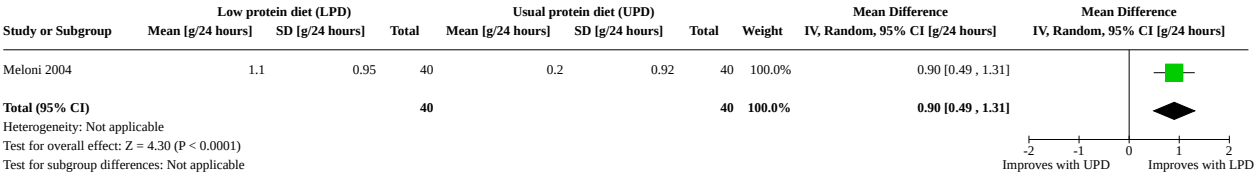
Heterogeneity: Tau² = 1.84; Chi² = 12.66, df = 6 (P = 0.05); I² = 53%
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



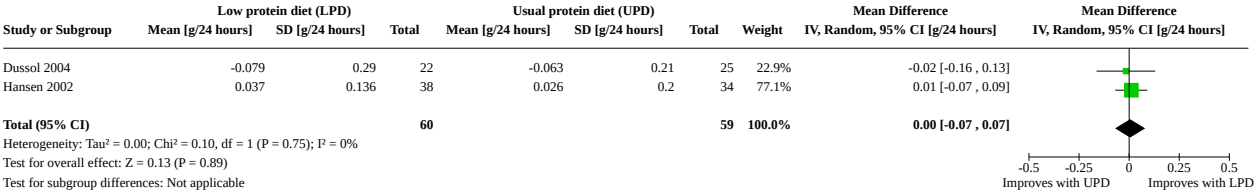
Analysis 1.4. Comparison 1: Low protein diet versus usual or unrestricted protein diet, Outcome 4: Change in CrCl [mL/min/year]



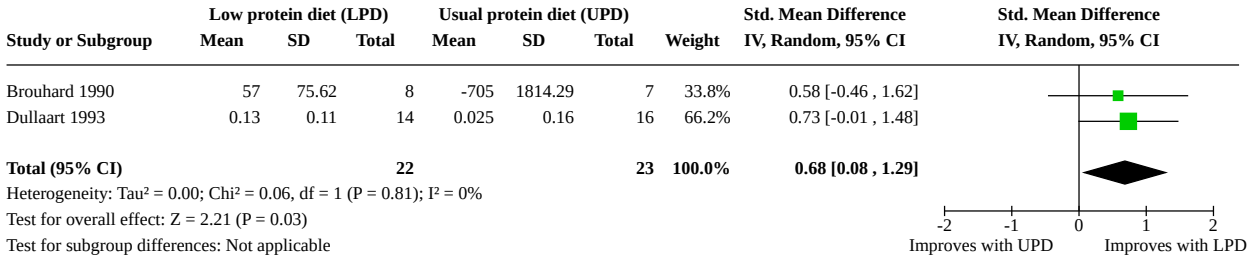
Analysis 1.5. Comparison 1: Low protein diet versus usual or unrestricted protein diet, Outcome 5: Change in 24-hour urinary protein excretion



Analysis 1.6. Comparison 1: Low protein diet versus usual or unrestricted protein diet, Outcome 6: Change in 24-hour urinary albumin excretion



Analysis 1.7. Comparison 1: Low protein diet versus usual or unrestricted protein diet, Outcome 7: Change in UAER



Comparison 2. Nutritional measures

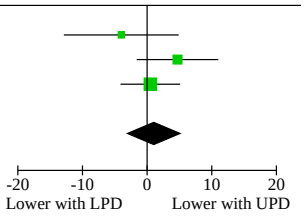
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Final body weight	3	146	Mean Difference (IV, Random, 95% CI)	1.03 [-3.04, 5.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Final body mass index	1	80	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.60, 0.20]

Analysis 2.1. Comparison 2: Nutritional measures, Outcome 1: Final body weight

Study or Subgroup	Low protein diet (LPD) Mean [kg]	SD [kg]	Total	Usual protein diet (UPD) Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Dussol 2004	78	10	22	82	20	25	18.2%	-4.00 [-12.88 , 4.88]
Dullaart 1993	79.1	7.65	14	74.4	9.94	16	32.0%	4.70 [-1.61 , 11.01]
Meloni 2002	60.8	7.3	35	60.3	11.7	34	49.8%	0.50 [-4.12 , 5.12]
Total (95% CI)			**71**			**75**	**100.0%**	**1.03 [-3.04 , 5.09]**

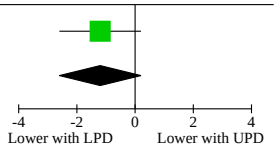
Heterogeneity: Tau² = 3.07; Chi² = 2.58, df = 2 (P = 0.27); I² = 23%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Nutritional measures, Outcome 2: Final body mass index

Study or Subgroup	Low protein diet (LPD) Mean [kg/m²]	SD [kg/m²]	Total	Usual protein diet (UPD) Mean [kg/m²]	SD [kg/m²]	Total	Weight	Mean Difference IV, Random, 95% CI [kg/m²]
Meloni 2004	24.2	2.6	40	25.4	3.7	40	100.0%	-1.20 [-2.60 , 0.20]
Total (95% CI)			**40**			**40**	**100.0%**	**-1.20 [-2.60 , 0.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Summary of included studies at time of randomisation

Study	No. of participants	Mean age ± SD (years)	Men %	Type of diabetes	CKD stage	Mean GFR ± SD (mL/min/1.73 m²)	Follow-up (years)
Brouhard 1990	15	33 ± 13	60	Type 1	1-3	81.1 ± 32.4	1
Dullaart 1993	30	41 ± 13	90	Type 1	1	126 ± 30	2
Dussol 2004	63	58 ± 12	83	Mixed	1-3	86 ± 24	2
Hansen 2002	82	40.5 ± 8.5	65	Type 1	1-3	68 ± 31	4
Koya 2009	112	56.9 ± 8.2	59	Type 2	1-3	62.3 ± 25.2	5
Meloni 2002	69	54.4 ± 15.3	55	Mixed	3	44.4 ± 4.9	1
Meloni 2004	80	54.5 ± 15.6	49	Mixed	3	44.5 ± 4.9	1
Zeller 1991	35	34 ± 8	60	Type 1	2-4	47.4 ± 23.8	2.8

CKD: chronic kidney disease; GFR: glomerular filtration rate

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. (diabet* near/2 (nephropath* or kidney or renal)):ti,ab,kw 2. diabetes:ti,ab,kw 3. proteinuria:ti,ab,kw 4. albuminuria:ti,ab,kw 5. microalbuminuria:ti,ab,kw 6. macroalbuminuria:ti,ab,kw 7. "urinary albumin excretion rate":ti,ab,kw 8. UAER:ti,ab,kw 9. {OR #3-#8} 10.#2 and #9 11.#1 or #10 12.(protein near/2 (restrict* or reduc* or low)):ti,ab,kw 13.dietary next protein*:ti,ab,kw 14.protein next intake:ti,ab,kw. 15.{OR #12-#13} 16.#11 and #15 in Trials
MEDLINE	1. Diabetic Nephropathies/ 2. (diabet* adj2 (nephropath* or kidney or renal)).tw. 3. or/1-2 4. Diabetes Mellitus/ 5. exp Diabetes Mellitus, Type 1/ 6. exp Diabetes Mellitus, Type 2/ 7. diabetes.tw. 8. or/4-7 9. Albuminuria/ 10.albuminuria.tw. 11.microalbuminuria.tw. 12.urinary albumin excretion rate.tw. 13.UAER.tw. 14.Proteinuria/ 15.proteinuria.tw. 16.or/9-15 17.and/8,16 18.or/3,17 19.Diet, Protein-Restricted/ 20.(protein adj2 (restrict* or reduc* or low)).tw. 21.Dietary Proteins/ 22.or/19-21 23.and/18,22
EMBASE	1. diabetic nephropathy/ 2. (diabet* adj2 (nephropath* or kidney or renal)).tw. 3. or/1-2 4. diabetes mellitus/

(Continued)

5. insulin dependent diabetes mellitus/
6. non insulin dependent diabetes mellitus/
7. diabetes.tw.
8. or/4-7
9. exp proteinuria/
10. albuminuria.tw.
11. microalbuminuria.tw.
12. macroalbuminuria.tw.
13. proteinuria.tw.
14. urinary albumin excretion rate.tw.
15. UAER.tw.
16. or/9-15
17. and/8,16
18. or/3,17
19. protein restriction/
20. (protein adj2 (restrict* or reduc* or low)).tw.
21. protein intake/
22. or/19-21
23. and/18,22

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

(Continued)

interventions by participants and personnel during the study	*High risk of bias*: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

(Continued)

	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

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CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: SJ
2. Study selection: SJ, JF
3. Extract data from studies: SJ, JF
4. Enter data into RevMan: SJ
5. Carry out the analysis: SJ
6. Draft the final review: SJ, WL
7. Disagreement resolution: WL
8. Update the review: SJ, WL

DECLARATIONS OF INTEREST

- Shimin Jiang: no relevant interests were disclosed
- Jinying Fang: no relevant interests were disclosed
- Wenge Li: no relevant interests were disclosed

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Diabetes Mellitus; *Diabetic Nephropathies; Diet, Protein-Restricted [adverse effects]; *Hyperglycemia; *Kidney Failure, Chronic [prevention & control]; *Malnutrition; Randomized Controlled Trials as Topic; *Renal Insufficiency, Chronic

MeSH check words

Adult; Humans