Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials

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CRD summary
This review assessed the effect of consuming a low protein diet, compared to a normal protein intake, on renal outcomes in people with diabetes. The authors concluded that no strong improvements in kidney function were demonstrated. Despite poor reporting of some aspects of the review process, this conclusion is likely to be reliable.

Authors' objectives
To evaluate the effect of low protein diets on renal outcome in patients with diabetic nephropathy

Searching
MEDLINE and EMBASE were searched from inception to 2007, alongside the Cochrane Central Register of Controlled Trials (CENTRAL) and the website www.clinicaltrials.gov. Search terms were reported. Reference lists of all retrieved papers were searched manually.

Study selection
Randomised controlled trials (RCTs) of low protein diets in participants with any type of diabetes were included (no definition of the comparator 'normal' protein diet was provided). Trials using a crossover design were excluded due to the possibility of carry-over effects. Included trials had to have a minimum follow-up period of six months and report at least one of the following outcomes: change in glomerular filtration rate or creatinine clearance rate, albuminuria or proteinuria. Change in glomerular filtration rate or creatinine clearance rate was the primary outcome.

Five different methods of assessing protein excretion were used amongst the included trials: albumin excretion rate (mg/24 hours), micro-albuminuria (g/day), urine albumin excretion (mg/24 hours), 24 hour proteinuria (g/24 hours) and albuminuria (mg/24 hours). Included trials studied participants with type 1 diabetes only, type 2 diabetes only or included participants with either type of diabetes. The mean age of included participants ranged from 30 to 64, the percentage of males ranged from 36 to 90%, and baseline glomerular filtration rate ranged from 43.9 to 131 mL per minute per 1.73m². Prescribed protein intake in the low protein diet groups was either 0.6 or 0.8 g/kg/day; actual intake ranged from 0.71 to 1.10 g/kg/day. Protein intake in the normal diet group ranged from 1.02 to 2.0 g/kg/day.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The Jadad scale was used for the quality assessment of RCTs, but the content of the scale was not reported. Up to 5 points could be awarded for the presence of adequate randomisation and allocation concealment, blinding and description of withdrawals and drop-outs.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Changes from baseline in glomerular filtration rate or creatinine clearance rate (used interchangeably to estimate change in glomerular filtration rate), urinary protein excretion and serum albumin concentration were extracted. Results from analysis of timed urine specimens for proteinuria and albuminuria were converted to grams per 24 hours. Data on glycated haemoglobin (HbA₁𝑐) and serum albumin were also extracted.

Data were extracted by two reviewers and any disagreements were resolved by discussion between them and by consultation with the third author.

Methods of synthesis
A fixed-effect model was used to combine data; in the presence of statistical heterogeneity (P<0.10), a random-effects model was employed. Weighted mean differences (WMD) were combined for changes from baseline in glomerular filtration rate, HbA1c, and serum albumin concentrations. For outcomes assessed using different measurement scales, i.e. changes in urinary protein excretion, the standardised mean difference (SMD) was estimated. Standard deviations (SDs) were imputed using interquartile ranges and full ranges.

Statistical heterogeneity was assessed using the $I^2$ statistic. Meta-regression used to examine any effect from potential sources of heterogeneity: changes in glomerular filtration rate, proteinuria, HBA1c, and serum albumin concentrations. A priori sensitivity analyses of the relative effects of low protein diets on glomerular filtration rate according to type of diabetes were conducted. Publication bias was assessed by using weighted regression and presentation of data in a funnel plot.

**Results of the review**

Eight RCTs with 519 participants were eligible for inclusion. Three trials had a Jadad score of 4 out of 5 points, three scored 3 and two scored 2 out of 5 points. No further details of the quality assessment were provided. No evidence of publication bias was identified visually on the funnel plot or statistically (p=0.43). Average protein intake in the low protein diet group was 1.27g/kg/day compared to 0.91g/kg/day in the normal protein diet group, but nevertheless was around 20% greater than the recommended dietary allowance.

Low protein diets were found to have no statistically significant effect on changes in glomerular filtration rate either overall (WMD: 0.50mL.min$^{-1}$1.73m$^{-2}$, 95% CI -1.43 to 2.42; eight RCTs) or for those with type 1 or type 2 diabetes, and no significant heterogeneity was identified (overall $I^2$=0%, p=0.53).

A significant decrease in proteinuria was identified in the low protein diet group compared to the normal protein diet group (SMD -0.69 units, 95% CI -0.14 to -0.23; eight RCTs), but the trial results were significantly heterogeneous ($I^2$=81.4%), so the reported result was taken from a random-effects model.

A significant reduction in glycated haemoglobin of 31% was reported for the low protein diet group compared to the normal protein group (WMD -0.31%, 95% CI -0.14 to -0.23; eight RCTs), but the trial results were significantly heterogeneous ($I^2$=8.14%), so the reported result was taken from a random-effects model.

**Authors’ conclusions**

The authors concluded that there did not appear to be any large benefit from low protein diets on renal outcome in patients with diabetic nephropathy and that there may be potential for harm in terms of malnutrition.

**CRD commentary**

The aim and inclusion criteria for this review were clear and appropriate. A well-recognised tool for the quality assessment of RCTs was used to evaluate trials. Comprehensive trial details were provided, but no details of how the trials rated on individual quality criteria were given, which made it impossible to judge their relative merits. The search covered more than one database and included an attempt to identify grey literature, which helped to reduce any publication bias. Review methods were detailed only in terms of the approach to data extraction and this was not explicitly stated to have been conducted independently by two reviewers; this left open the possibility of reviewer bias in study selection and validity assessment, and possibly in data extraction. The statistical synthesis of included trials was appropriate, as were the methods used, but the validity assessment was not used to inform the synthesis. Appropriate caution was attached to the use of the standardised mean difference to compare certain outcomes assessed using different measurement scales. Overall, the quality of reporting of the review could have been better, but the authors’ conclusions were based on the data presented and appear reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.
The authors stated that large multicentre RCTs are needed to fully understand any effect from low protein diets on kidney outcome in patients with diabetic nephropathy.

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