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

Yu Pan, Li Li Guo, and Hui Min Jin

ABSTRACT
Background: A low-protein diet (LPD) has been proposed for many years to delay the progression of diabetic nephropathy. However, the efficacy of an LPD with respect to renal outcome is disputed.
Objective: We aimed to determine the effect of an LPD on renal function in patients with type 1 or 2 diabetic renal diseases by using a meta-analysis of randomized controlled trials.
Design: Medline, EMBASE, and the Cochrane Central Register of Controlled Trials were searched. Eight studies met the inclusion criteria for our meta-analysis: a duration of >6 mo, use of a randomized control group, availability of outcome data for changes in glomerular filtration rate (GFR) or creatinine clearance rate (CCR), and albuminuria or proteinuria in patients with type 1 or 2 diabetic nephropathy. Data were combined by means of a fixed-effects model. Weighted mean differences (WMD) were calculated for the change in GFR or CCR, glycated hemoglobin (HbA1c), and serum albumin between the LPD and control groups. A random-effects model was also used to calculate the standardized mean difference for the change in urinary albumin excretion or proteinuria.
Results: Overall, a change in WMD for GFR or CCR was not significantly associated with an LPD, but a decrease in WMD for HbA1c was significant in the LPD group (P = 0.005). Although the benefit of LPD therapy on proteinuria was significant (P = 0.003), great heterogeneity was observed. In a subgroup analysis, LPD resulted in lower serum albumin concentrations.
Conclusion: LPD was not associated with a significant improvement of renal function in patients with either type 1 or 2 diabetic nephropathy.

INTRODUCTION
Diabetic nephropathy, whether associated with type 1 (T1DM) or type 2 (T2DM) diabetes mellitus, is a leading cause worldwide of end-stage renal disease (ESRD) (1, 2). Treatment strategies include limitation of dietary protein, improved glycemic control, and inhibition of the renin-angiotensin system (3–6). A low-protein diet (LPD) has been proposed for many years to delay the progression of ESRD in patients both with and without diabetes (3, 7). Clinical trials and several meta-analyses suggest that an LPD is potentially beneficial for patients with nondiabetic renal disease (3, 7). However, for diabetic nephropathy, the efficacy of an LPD is disputed with respect to renal outcome (8–10). A previous systematic review pooling the data from 5 studies of insulin-dependent diabetes mellitus conducted before 1996 found that an LPD significantly slowed the increase in urinary albumin concentration or the decline in glomerular filtration rate (GFR) or creatinine clearance rate (CCR), with no significant differences seen between the LPD and control groups in glycated hemoglobin (HbA1c) (3). These results suggested that an LPD may slow the progression of ESRD in T1DM patients. However, nonrandomized crossover designs were selected for the diabetic nephropathy studies in the present meta-analysis. Over the years, this result has been challenged by several clinical trials (8–10), and doubt remains as to whether an LPD improves renal function and decreases urinary albumin or protein excretion in diabetic renal disease, despite the B-level evidence recommended by American Diabetes Association (11). Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the effect of an LPD on markers of renal function decline and urinary protein excretion.

MATERIALS AND METHODS
Search strategy and inclusion criteria
RCTs were identified via MEDLINE (PubMed, 1966–2007), EMBASE (1974–2007), www.clinicaltrials.gov, and the Cochrane Controlled Clinical Trials Register Database. The key words of the first step were “protein-restricted” diet OR “diet, protein-restricted” OR “low protein diet” AND “diabetic nephropathies.” From these searches, we obtained 50 articles. In the second step, we kept all of the clinical trials and deleted reviews and animal experiments; 24 studies were excluded. The rest of the steps are shown in Figure 1. The bibliographies of all retrieved articles also were checked manually. Eight studies met the inclusion criteria for our meta-analysis: a duration of >6 mo, use of a randomized control group, availability of outcome data for changes in GFR or CCR, and albuminuria or proteinuria in patients with type 1 or 2 diabetic nephropathy. All included trials were published in English-language medical journals. Because of carryover effects and the tendency of diabetic nephropathy to...
progress quickly during the disease course, we excluded all crossover trials in our meta-analysis (12).

Data on participants’ characteristics (age, sex, and type and duration of diabetes or diabetic nephropathy), interventions (low or normal protein intake), duration of follow-up, and outcomes (GFR, CCR, or evaluated GFR, proteinuria or similar index, HbA1c, and serum albumin concentrations) were extracted from all included trials. Any disagreement in data extraction was resolved by discussion between 2 of us (HMJ and YP) and by consultation with the third author (LLG).

Outcome measures

The primary outcome was the rate of change in GFR (mL·min⁻¹·1.73 m²). Although CCR is conceptually different, it is commonly used as an estimate of GFR (13); therefore, CCR was used interchangeably with GFR in this analysis to assess the primary outcome.

As a secondary outcome, we assessed the changes in urinary protein excretion and serum albumin concentration from baseline to end of follow-up. Results from analysis of timed urine specimens for proteinuria and albuminuria were converted to grams per 24 h. HbA1c and serum albumin values were also included as secondary outcomes.

Statistical analysis

Data were combined by means of a fixed-effects model. The SDs were imputed by using interquartile ranges and full ranges. The methods of calculating the change-from-baseline SD are referenced in the Cochrane Handbook (14). The standardized mean difference (SMD), which is calculated by dividing the mean values by the SD and which can be used to compare studies that report continuous outcomes by using different scales, was used to pool results from all studies that reported untransformed changes in urinary protein excretion. The weighted mean difference (WMD) was used to pool the change-from-baseline values for GFR, HbA1c, and serum albumin concentrations, which were reported by using the same scale of measurement among all studies.

We used REVIEW MANAGE for WINDOWS software (version 4.2.7; The Nordic Cochrane Centre, Copenhagen, Denmark) to pool the data and calculate mean differences. Meta-regression was employed to examine the association between certain variables (changes in GFR, proteinuria, HbA1c, and serum albumin concentrations) and the effect of an LPD on the outcome. Two a priori sensitivity analyses, assessing the relative effects of LPD and GFR among different clinical types of diabetes, were planned. We evaluated the statistical heterogeneity of the study results by using the F statistic, which measures the extent of inconsistency among the studies’ results and which is interpreted as approximately the proportion of total variation in study estimates that is due to heterogeneity rather than to sampling error. We used STATA software (version 10.0; Stata Corporation, College Station, TX) to calculate publication bias, which was assessed by using weighted regression. Statistical significance was set at P < 0.05 for all analyses.

RESULTS

Trial flow and study characteristics

The decision process that was used to differentiate among studies considered for inclusion is shown in Figure 1. Eight eligible studies with a total of 519 participants were included in the present review—253 subjects in the treatment group and 266 subjects in the control group (8–10, 15–19). Two of the selected trials focused on patients with T2DM, 4 focused on patients with T1DM, and the remaining 2 trials included patients with either T1DM or T2DM. All of these trials provided data on the rate of change in GFR or CCR. Seven trials provided data on the changes in HbA1c, but only 4 trials recorded the changes in serum albumin concentration. The different trials provided varied data on proteinuria, and those variations led to heterogeneity. The characteristics of the included studies—and the Jadad scores as an indication of the quality of the studies—are shown in Table 1. As seen there, the average protein intake in the LPD groups during all trials was 0.91 g·kg⁻¹·d⁻¹, whereas that in the control groups was 1.27 g·kg⁻¹·d⁻¹ (P = 0.04). However, the intake in the LPD group was 20% higher than the Recommended Dietary Allowance.

Assessment of publication bias

There was little asymmetry in the funnel plot. The weighted regression test indicated no statistical evidence of publication bias (bias = 0.53, P = 0.43).

Effect of the low-protein diet on the rate of change in glomerular filtration rate

None of the observed changes in GFR were significantly associated with the effects of the LPD (Figure 2). Overall, the
<table>
<thead>
<tr>
<th>Study</th>
<th>Jadad score</th>
<th>Type of diabetes</th>
<th>Male subjects</th>
<th>Mean age</th>
<th>Course of DM Subjects</th>
<th>Duration of study Subjects</th>
<th>Protein intake Prescribed</th>
<th>Protein intake Actual</th>
<th>Baseline GFR</th>
<th>Baseline proteinuria Subjects</th>
<th>Baseline proteinuria Value</th>
<th>Baseline proteinuria Measure</th>
<th>Protein intake (actual)</th>
<th>Baseline GFR</th>
<th>Baseline proteinuria Subjects</th>
<th>Baseline proteinuria Value</th>
<th>Baseline proteinuria Measure</th>
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<tbody>
<tr>
<td>Ciavarella et al (15)</td>
<td>2</td>
<td>T1DM</td>
<td>56</td>
<td>37.1</td>
<td>17.7</td>
<td>9</td>
<td>0.6</td>
<td>0.71</td>
<td>97 ± 34</td>
<td>AER</td>
<td>434 ± 244</td>
<td>9</td>
<td>1.44</td>
<td>103 ± 28</td>
<td>452 ± 200</td>
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</tr>
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<td>Dullaart et al (16)</td>
<td>4</td>
<td>T1DM</td>
<td>90</td>
<td>40.8</td>
<td>23</td>
<td>24</td>
<td>0.6</td>
<td>0.79</td>
<td>131 ± 34</td>
<td>UAE</td>
<td>36 (16, 83)</td>
<td>16</td>
<td>1.09</td>
<td>122 ± 26</td>
<td>31 (19, 51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raal et al (17)</td>
<td>2</td>
<td>T1DM</td>
<td>36</td>
<td>30</td>
<td>20</td>
<td>6</td>
<td>0.8</td>
<td>0.87</td>
<td>50 ± 19</td>
<td>UAE</td>
<td>884 (87–9110)</td>
<td>11</td>
<td>2.0</td>
<td>66 ± 28</td>
<td>1167 (80–4180)</td>
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<td></td>
</tr>
<tr>
<td>Pijls et al (18)</td>
<td>4</td>
<td>T2DM</td>
<td>61</td>
<td>64</td>
<td>12</td>
<td>12</td>
<td>0.8</td>
<td>0.93</td>
<td>81 ± 19</td>
<td>Albuminuria</td>
<td>21.4 (10, 40)</td>
<td>63</td>
<td>1.12</td>
<td>85 ± 24</td>
<td>21.3 (8, 4634)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansen et al (19)</td>
<td>3</td>
<td>T1DM</td>
<td>65</td>
<td>40</td>
<td>27</td>
<td>48</td>
<td>0.6</td>
<td>0.89</td>
<td>69 ± 30</td>
<td>Albuminuria</td>
<td>690 (547, 871)</td>
<td>34</td>
<td>1.02</td>
<td>67 ± 32</td>
<td>721 (502, 1036)</td>
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<td></td>
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<tr>
<td>Pijls et al (8)</td>
<td>4</td>
<td>T2DM</td>
<td>63</td>
<td>63</td>
<td>6.7</td>
<td>24</td>
<td>0.8</td>
<td>1.10</td>
<td>82 ± 19</td>
<td>Albuminuria</td>
<td>—</td>
<td>68</td>
<td>1.14</td>
<td>85 ± 23</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meloni et al (9)</td>
<td>3</td>
<td>T1DM or T2DM</td>
<td>55</td>
<td>43</td>
<td>22</td>
<td>12</td>
<td>0.8</td>
<td>0.86</td>
<td>43.9 ± 4.7</td>
<td>24-h proteinuria</td>
<td>2.4 ± 1.1</td>
<td>40</td>
<td>1.24</td>
<td>45 ± 5.1</td>
<td>2.6 ± 0.8</td>
<td></td>
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</tr>
<tr>
<td>Dussol et al (10)</td>
<td>3</td>
<td>T1DM or T2DM</td>
<td>83</td>
<td>52</td>
<td>15</td>
<td>24</td>
<td>0.8</td>
<td>1.10</td>
<td>82 ± 21</td>
<td>Microalbuminuria (g/d)</td>
<td>—</td>
<td>25</td>
<td>1.03</td>
<td>89 ± 27</td>
<td>—</td>
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</tr>
</tbody>
</table>

1 DM, diabetes mellitus; GFR, glomerular filtration rate; AER, albumin excretion rate; UAE, urine albumin excretion; T1DM, type 1 DM; T2DM, type 2 DM.
2 x ± SD (all such values).
3 Measured as mg/24 h.
4 x; 95% CI in parenthese.
5 x; range in parentheses.
6 Geometric x; 95% CI in parentheses.
7 Measured as g/24 h.
8 Measured as g/d.
change in WMD for GFR was not statistically significant \((P = 0.61)\). Furthermore, neither patients with T1DM nor those with T2DM showed benefits from LPD therapy \((P = 0.63 \text{ and } 0.81, \text{ respectively})\). There was no significant heterogeneity among the trials \((I^2: 38.7-0\%)\).

**Effects of the low-protein diet on proteinuria or albuminuria**

Five different measurements of protein excretion were reported in the 8 trials: albumin excretion rate \((\text{mg/24 h})\), microalbuminuria \((\text{g/d})\), urine albumin excretion \((\text{UAE}) \text{ (mg/24 h)}\), and albuminuria \((\text{mg/24 h})\). Therefore, the SMD was used to compare these diverse measures. Overall, the change in the SMD for proteinuria was statistically significant, and there was a decrease of 0.69 units in the LPD group \((95\% \text{ CI: } -3.8, -1.04)\). Another study assessed proteinuria in g/24 h and also found a benefit from LPD therapy \((0.1 \text{ g/24 h}; 95\% \text{ CI: } -0.67, 0.48 \text{ g/24 h})\). The data from the remaining 6 trials, expressed as microalbuminuria, UAE, or albuminuria, did not differ significantly between the LPD and control groups \((P > 0.1)\). However, the obvious heterogeneity cannot be ignored \((Figure 3)\). When \(P < 0.10\) is used to determine statistical significance, a random-effects model is used to incorporate heterogeneity among trials. Because variability in the treatment effects on proteinuria led to the statistical heterogeneity \((P < 0.10)\), we choose the random-effects rather than the fixed-effects model, although the random-effects estimate may not reflect the actual effect in any particular population being studied.

**Effect of the low-protein diet on glycated hemoglobin**

The point estimate for the effect of LPD on the rate of change in HbA1c was favorable in 7 of 8 trials \((Figure 4)\). The change in the WMD for HbA1c was significantly different \(\text{(reduction of } 0.31\%; 95\% \text{ CI: } -0.53, 0.09\%)\), and the heterogeneity disappeared \((I^2 = 34\%)\). Hence, LPD was associated with a significant decrease in HbA1c.

**DISCUSSION**

To our knowledge, this publication is the first systematic review of RCTs in humans to evaluate the renal effects of LPD in diabetic nephropathy. We included 8 RCTs that studied the efficacy of LPD intervention in patients with types 1 and 2 diabetic nephropathy. Our analysis showed that, when compared with consumption of a normal-protein diet, treatment with an LPD was not associated with a significant improvement in kidney function as estimated by GFR; however, a significant decrease in proteinuria or albuminuria was observed in the LPD group. Our findings contradict those of 3 earlier meta-analyses \((3, 20, 21)\). This difference in results may reflect variations in study inclusion criteria. For example, in the earlier meta-analyses, crossover trials were included. However, a particular concern with respect to a crossover design is the risk of a carryover effect \((12)\), in which the treatment in the first period has an effect that carries over into the second period. Freeman \((22)\) showed that the crossover strategy is seriously flawed and that it often leads to biased conclusions. Considering the fact that the crossover design could not incorporate heterogeneity among trials, the analysis may not reflect the actual effect in any particular population being studied.

**FIGURE 2.** Changes in glomerular filtration rate \((\text{GFR; mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2)\) in patients with type 1 (T1DM) or type 2 (T2DM) diabetes mellitus who were following the low-protein diet \((\text{Treatment})\) compared with changes in those following a normal protein diet \((\text{Controls})\). Changes are expressed as weighted mean difference \((\text{WMD})\).
mask the effects of an intervention such as LPD on long-term outcomes such as renal function, we excluded studies with crossover designs from the present meta-analysis. We chose to include patients with either type 1 or type 2 diabetic nephropathy because, in both types of diabetes, chronic hyperglycemia is the primary characteristic of the disease, and structure-functional relations are similar in most respects (23).

An important factor that could influence the efficacy of the LPD for kidney function is the duration of the intervention. Some reports have suggested that initiation of an LPD in T1DM patients with elevated urinary albumin excretion induced a faster initial (3–4 wk) and a slower subsequent (4 mo) decline in GFR (24–27). In the present analysis, however, LPD was not associated with a beneficial change in GFR, regardless of whether patients treated for <12 mo were considered separately from those treated for >12 mo.

Intensive glycemic control is thought to be associated with a beneficial kidney outcome (5), and a study by Rigalleau et al (28) involving 193 diabetes patients concluded that estimations of GFR correlate significantly with the HbA1c values. In contrast, the results of the present meta-analysis, in which an LPD is helpful for decreasing HbA1c values but is not beneficial for slowing decreases in GFR, support the findings from our group’s earlier study (29), which showed that glycemic control, as indicated by lower HbA1c concentrations, was not significantly associated with slower progression of renal failure. It has been reported that, in clinical trials, postprandial blood glucose elevation, which is a marker of metabolic control, but not HbA1c is correlated with the decline in GFR in T2DM patients (30).

Albuminuria or proteinuria is used clinically as a marker of nephropathic risk and progression of renal disease in T1DM and T2DM (1, 31). However, it has been recognized that the

![FIGURE 3. Change in proteinuria in patients following the low-protein diet (Treatment) compared with changes in those following a normal protein diet (Controls). Changes are expressed as standardized mean difference (SMD).](https://academic.oup.com/ajcn/article-abstract/88/3/660/4649080)

![FIGURE 4. Changes in glycated hemoglobin (HbA1c) in patients following the low-protein diet (Treatment) compared with changes in those following a normal protein diet (Controls). Changes were expressed as weighted mean difference (WMD).](https://academic.oup.com/ajcn/article-abstract/88/3/660/4649080)
probability of progression to macroalbuminuria in microalbuminuric subjects is not as high as once thought (31). Although albuminuria or proteinuria tended to decrease in the present meta-analysis, it is difficult to assess this result because of the differences in the variables observed among the 8 studies. When reductions in albuminuria, UAE, and proteinuria were considered together, the SMD for the effect of LPD on proteinuria was statistically significant. However, it should be noted that, although the SMD allowed us to compare these different measures, a degree of caution is needed in interpreting the significance of the proteinuria or albuminuria results, which were reported with the use of different scales.

The risk of malnutrition in patients treated with LPD is another serious concern, because malnutrition per se results in the progression of renal failure. The serum albumin concentration is a common variable for assessing nutritional status in practice, but only 4 of the studies we reviewed reported changes in serum albumin concentrations. Amelioration of albuminuria or proteinuria is generally associated with an improvement in serum albumin concentrations. However, in the present meta-analysis, decline in proteinuria is not accompanied by an improvement in serum albumin concentrations. Amelioration of albuminuria or proteinuria results, which were reported with the use of different scales.

Compliance is an important confounding factor in assessing the effect of an LPD on the progression of chronic renal disease in patients with diabetic nephropathy. Nonadherence to the prescribed LPD by some patients would result in an underestimation of the diet’s true effect. Compliance with an LPD is defined as an actual intake equal to ±20% of the prescribed protein intake. In well-controlled studies, actual protein intake tends to exceed prescribed intake by 10% to ±20% (32–34). Of the 8 trials reviewed in the present meta-analysis, actual or achieved mean protein intake in the LPD groups exceeded the prescribed protein intake by an average of 0.91 g · kg body wt⁻¹ · d⁻¹ (range: 0.7–1.0 g · kg body wt⁻¹ · d⁻¹), as assessed by 24-h urinary urea nitrogen excretion or dietary history. Nevertheless, the average mean protein intake in the LPD group was significantly lower than that in the normal protein diet group (1.27 g · kg body wt⁻¹ · d⁻¹; \( P = 0.04 \)).

Although the present analysis was based on RCTs, it has several limitations that should be considered. First, the present review included only 8 articles from English-language journals, of which several were rather short, and 2 of which had Jadad scores of only 2. Second, there was considerable variation in study subjects (type 1 or type 2 diabetic nephropathy), level of reduction of dietary protein, outcome analysis (GFR or estimates of GFR and proteinuria), and duration of study. These differences may explain some of the heterogeneity observed. Third, only one trial followed patients for \( \geq 2 \) y, and a span of \( \leq 2 \) y may not be sufficient to capture differences on GFR. Fourth, we defined the main outcome by using the decline in GFR and proteinuria as a proxy for renal death, but this information was not recorded in most of the included articles.

Despite these limitations, the present meta-analysis suggests that an LPD was not associated with a significant improvement in markers of renal function in patients with either type 1 or type 2 diabetic nephropathy, notwithstanding a decline in HbA₁c and urinary protein excretion. Although these results do not rule out the possibility that an LPD is beneficial for patients with T1DM or T2DM, there does not seem to be a large benefit with respect to renal function, and the potential for harm due to malnutrition should not be ignored. Large, multicenter RCTs should be performed to better understand the actual effect of an LPD on kidney outcome in diabetic nephropathy.

The authors’ responsibilities were as follows—YP, LLG, and HMJ: participated in the design of the study, collected the data, and contributed to the data analysis; HMJ: designed the study, was responsible for the data analysis and interpretation, and wrote the draft of the manuscript; and LLG and YP contributed equally to this manuscript. None of the authors had a personal or financial conflict of interest.

### REFERENCES


