Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials

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Abstract

Background Recent data pose the question whether conservative management of chronic kidney disease (CKD) by means of a low-protein diet can be a safe and effective means to avoid or defer transition to dialysis therapy without causing protein-energy wasting or cachexia. We aimed to systematically review and meta-analyse the controlled clinical trials with adequate participants in each trial, providing rigorous contemporary evidence of the impact of a low-protein diet in the management of uraemia and its complications in patients with CKD.

Methods We searched MEDLINE (PubMed) and other sources for controlled trials on CKD to compare clinical management of CKD patients under various levels of dietary protein intake or to compare restricted protein intake with other interventions. Studies with similar patients, interventions, and outcomes were included in the meta-analyses.

Results We identified 16 controlled trials of low-protein diet in CKD that met the stringent qualification criteria including having 30 or more participants. Compared with diets with protein intake of >0.8 g/kg/day, diets with restricted protein intake (<0.8 g/kg/day) were associated with higher serum bicarbonate levels, lower phosphorus levels, lower azotemia, lower rates of progression to end-stage renal disease, and a trend towards lower rates of all-cause death. In addition, very-low-protein diets (protein intake <0.4 g/kg/day) were associated with greater preservation of kidney function and reduction in the rate of progression to end-stage renal disease. Safety and adherence to a low-protein diet was not inferior to a normal protein diet, and there was no difference in the rate of malnutrition or protein-energy wasting.

Conclusions In this pooled analysis of moderate-size controlled trials, a low-protein diet appears to enhance the conservative management of non-dialysis-dependent CKD and may be considered as a potential option for CKD patients who wish to avoid or defer dialysis initiation and to slow down the progression of CKD, while the risk of protein-energy wasting and cachexia remains minimal.

Keywords Low-protein diet; Chronic kidney disease; Glomerular filtration rate; End-stage renal disease; All-cause death; Conservative management; Cachexia; Protein-energy wasting

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Introduction

Chronic kidney disease (CKD) is among the leading causes of death worldwide including emerging giant economies such as India and China. Upon its development, kidney function deteriorates over time until it permanently fails. Management strategies have largely focused on slowing down progression to end-stage renal disease (ESRD), at which time, patients are invariably expected to transition to renal replacement therapy, mostly in the form of maintenance dialysis treatment.
Nevertheless, recent data suggest that attempts to delay or even prevent transition to dialysis therapy may not be inappropriate, including a 2009 study that showed that the initiation of dialysis was associated with a substantial and sustained decline in functional status of the elderly nursing home patients. Many patients with kidney disease prefer to opt to exhaust all conservative management options for CKD, including nutritional strategies, prior to considering dialysis therapy.

Century-old evidence suggests that lower dietary protein intake may help with CKD management including slowing its progression, improving albuminuria, and controlling uraemia. However, results from the Modification of Diet in Renal Disease study in 1994 were inconclusive with regards to the efficacy of a low-protein diet (LPD) in slowing the rate of CKD progression. Several meta-analyses that focused on the rate of CKD progression showed favourable but modest effects of an LPD. Nevertheless, no single study has examined all clinically relevant outcomes, and fewer studies have focused on the role of an LPD in managing uraemia or other CKD complications such as mineral and bone disorders and metabolic acidosis without causing protein-energy wasting or cachexia.

Protein-energy wasting characterized by a decline in body protein mass and energy reserves, including muscle and fat wasting and visceral protein pool contraction, is an underappreciated condition in early to moderate stages of CKD and a strong predictor of adverse outcomes. The applicability of many nutritional interventions and their effects on outcomes in patients with moderate to advanced CKD, including those with protein-energy wasting or at high risk of its development, has not been well studied. The challenge remains as to how to reconcile low dietary protein intake—to avoid or delay dialysis initiation—with adequate nutrient intake and nutritional therapy while insuring favourable nutritional status and to avoid or correct protein-energy wasting. The field lacks an up-to-date systematic review and meta-analysis study on the subject with a focus on the conservative management of CKD. There is an urgency to revisit all traditional and novel options for the non-dialytic management of patients with advanced CKD. Given these considerations and given commonalities and distinctions of the old and emerging controlled trials over the past two decades following the Modification of Diet in Renal Disease study, we aimed to conduct a comprehensive systematic review and meta-analysis study examining the effect of an LPD on the clinical management of patients with CKD.

Materials and methods

K.K.-Z., supported by other coauthors, searched MEDLINE (PubMed) and other relevant sources with no limitation in study type, language, and geographical area using the search terms including ‘low protein diet’, ‘CKD’, and ‘clinical trial’ as well as additional records identified through other sources including prior reviews. A field expert (K. K.-Z) identified any additional relevant studies. The studies were included if they described data from controlled trials (including randomized, self-controlled, parallel, and crossover trials) on CKD patients (excluding prevalent ESRD patients and those receiving dialysis treatment) to compare clinical outcomes across various protein intake levels (i.e. protein-free, very-low-protein, low-protein, moderate-protein, high-protein, very-high-protein, or unrestricted protein diets) or to compare a restricted protein intake with another intervention. An LPD was defined as a diet with a protein content of <0.8 g/kg/day. To ensure meaningful sample size in each study given our focus on the conservative management of CKD, we selected only controlled trials that included at least 30 participants to ensure selection of studies with adequate sample size and higher level of robustness (Figure 1). The aforementioned endeavour was undertaken to both provide a comprehensive roster of relevant randomized controlled trials of LPD for CKD management, which has become Supporting Information, Table S2 of a recently published New England Journal of Medicine review article, titled, ‘Nutritional Management of Chronic Kidney Disease’ by Kalantar-Zadeh and Fouque, and for an additional meta-analysis project that is presented in this manuscript.

We extracted and tabulated the main characteristics and findings of the included studies as well as comments on their methodological quality and clinical significance (Table 1). Also, we evaluated the risk of bias using the Cochrane Collaboration’s tool for assessing risk of bias (Table 2). We examined the effects of an LPD or very-low-protein diet (VLPD) (with or without supplementation with ketoacids or amino acids) on various outcome measures in CKD patients. The corresponding authors of the studies with incomplete results were contacted in order to request further data. Studies with clinical homogeneity (e.g. similar patients, interventions, and outcomes) were included in meta-analyses. Statistical heterogeneity was assessed using the I² statistic. Summary estimates with a corresponding I² ≤ 50% were pooled using fixed-effects meta-analysis while those with a corresponding I² > 50% were pooled using the random-effects model. In addition, in order to ascertain that our results were not dependent on the selected summary estimate or meta-analysis model, we completed sensitivity analyses. Statistical significance was defined as a 95% confidence interval with no overlap with the null effect value (risk difference/mean difference = 0). For statistical procedures, we used Stata 12 (StataCorp., College Station, TX, USA).

Results

Sixteen randomized controlled trials, reported in 17 articles, each with at least 30 participants, were included in our
review (Table 1). Based on the interventions and comparisons, the included studies were divided into the following groups: (i) those comparing LPD with higher-protein diets \(^{10,17-24}\); (ii) those comparing VLPD with LPD \(^{10,25-30}\); and (iii) those involving other comparisons \(^{31,32}\) (Table 1). As all studies were not similar in their recruited patients and/or outcome measures, not all studies in each category were meta-analysed (Figures 2 and 3).

**Low-protein diet vs. higher-protein diets**

For this comparison, LPD was defined as a protein intake of <0.8 mg/kg/day; therefore, VLPD was also considered a subgroup of LPD. Our pooled results showed that the risk of progression to ESRD was significantly lower in those who received LPD compared with those who received higher-protein diets (Figure 2A). In addition, the pooled results indicated a trend towards lower all-cause death in those who received LPD (Figure 2B).

We also meta-analysed other metabolic factors, which showed that 1 year serum bicarbonate was significantly higher in those who received LPD (Figure 2C). However, 1 year serum phosphorus was comparable in the two groups (Figure 2D). We could not meta-analyse results representing parathyroid hormone (PTH), calcium, and other metabolic factors because of their clinical and methodological heterogeneity. In addition to the results of our meta-analysis, some results by individual studies were also informative: serum PTH was not significantly different in the two intervention groups according to the results by Cianciaruso et al.\(^{18}\) and Ihle et al.\(^{22}\) However, Malvy et al.\(^{28}\) completed a longer follow-up (up to 40 months) and revealed a significantly lower PTH in those who received a lower protein intake (mean PTH: 2.71 vs. 5.91 ng/mL; \(P < 0.001\)). Similarly, serum calcium was not significantly different as reported by Ihle et al.\(^{22}\) and Rosman et al.\(^{23}\) However, it was significantly higher in the study by Malvy et al.\(^{28}\) with a longer follow-up duration (serum calcium: 2.42 vs. 2.25 mmol/L; \(P < 0.01\)).

Also, Jiang et al.\(^{17}\) showed that in peritoneal dialysis patients, those who received an LPD had better preservation of glomerular filtration rate (GFR) and residual kidney function. In addition, PTH was significantly lower in those who received ketoacid-supplemented LPD. However, serum phosphorus and calcium were not significantly different between the two intervention groups.

**Very-low-protein diet vs. low-protein diet**

Although the primary aim of this review was to compare LPD with higher-protein diets, we also performed meta-analyses of studies comparing VLPD with LPD. The two dietary groups were respectively defined as those with protein intakes of <0.4 and 0.4–0.8 mg/kg/day. The pooled results showed that the progression to ESRD was significantly lower (Figure 3A) and 1 year GFR was significantly higher (Figure 3C) in those who received VLPD compared with LPD. In addition, the
Table 1  Selected controlled trials (with >30 participants) that have examined the effects of an LPD or VLPD, with or without supplementation with ketoacids or amino acids, on various outcome measures in chronic kidney disease patients

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Participants</th>
<th>Dietary intervention</th>
<th>Outcomes</th>
<th>Follow-Up time</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPD vs. HPD</td>
<td>60 new ESRD pts on PD with RKF</td>
<td>LPD vs. sLPD (LPD + ketoacids) vs. HPD</td>
<td>RKF and nutritional markers on PD</td>
<td>12 months</td>
<td>RKF stable in sLPD group but decreased in the LPD and HPD groups.</td>
<td>No change from baseline on nutritional status in any of the groups during follow-up. Estimated DPI in low vs. high groups was 0.72 vs. 0.92 g/kg/day (P &lt; 0.05). 9 vs. 13 pts in LPD vs. higher DPI stated dialysis.</td>
</tr>
<tr>
<td>Cianciaruso et al.</td>
<td>423 pts with CKD 4–5</td>
<td>Two different DPI levels 0.65 (n = 212) vs. 0.80 g/kg/day (n = 211)</td>
<td>CKD progression and changes in blood and urinary biomarkers</td>
<td>18 months</td>
<td>Reduced urinary excretion of urea, Na, phos in LPD. No differences in phos, albumin, PTH, bicarbonate. No changes in body composition.</td>
<td>Two concurrent randomized controlled trials. Serum albumin increased in both sVLPD and LPD groups and did not differ between groups. Substantial overlap in DPI between two groups.</td>
</tr>
<tr>
<td>MDRD study 1</td>
<td>585 pts with CKD 3–4 (GFR 25–55 mL/min/1.73m²)</td>
<td>Usual protein diet (DPI 1.3 g/kg/day) vs. LPD (0.6 g/kg/day)</td>
<td>CKD progression, blood pressure, proteinuria, nutrition</td>
<td>27 months (mean follow-up)</td>
<td>Projected mean GFR decline at 3 years did not differ significantly between the diet groups. Faster GFR decline in the first 4 months in the LPD group.</td>
<td>Two concurrent randomized controlled trials. Serum albumin increased in both sVLPD and LPD groups and did not differ between groups. Substantial overlap in DPI between two groups.</td>
</tr>
<tr>
<td>Locatelli et al.</td>
<td>456 pts with CKD 3–4</td>
<td>LPD (0.78 g/kg/day) vs. normal DPI (0.9 g/kg/day), both DEI &gt; 30 cal/kg/day</td>
<td>Renal survival defined as dialysis start or doubling of serum creatinine</td>
<td>2 years</td>
<td>Borderline difference, slightly fewer pts assigned to LPD group reached the endpoint (P = 0.059).</td>
<td>Minor weight loss in LPD.</td>
</tr>
<tr>
<td>Williams et al.</td>
<td>95 pts with CKD 4–5</td>
<td>LPD (0.7 g/kg/day) vs. normal diet (DPI 1.02 and 1.14 g/kg/day) and varied phos content</td>
<td>CKD progression rates across three groups</td>
<td>18 months</td>
<td>No differences in the reduction in creatinine clearance, dialysis initiation, or mortality among three groups.</td>
<td>LDP pts lost weight but no change in anthropometric measures or serum albumin. 4 year renal survival improvement in LPD (60 vs. 30%, P &lt; 0.025). PKD pts did not respond to LPD.</td>
</tr>
<tr>
<td>Ihle et al.</td>
<td>72 pts with CKD 4–5</td>
<td>LPD (0.6 g/kg/day) vs. higher DPI (0.8 g/kg/day)</td>
<td>GFR every 6 months</td>
<td>18 months</td>
<td>Stable GFR in LPD vs. loss of GFR in control group (P &lt; 0.05).</td>
<td>LDP pts lost weight but no change in anthropometric measures or serum albumin. 4 year renal survival improvement in LPD (60 vs. 30%, P &lt; 0.025). PKD pts did not respond to LPD.</td>
</tr>
<tr>
<td>Rosman et al.</td>
<td>247 pts with CKD 3–5</td>
<td>0.90–0.95 (CKD 3) vs. 0.70–0.80 g/kg/day (CKD 4–5) vs. unrestricted DPI</td>
<td>GFR after 2 or 4 years</td>
<td>4 years</td>
<td>After 2 years significant slowing of CKD progression in LPD but only in male pts.</td>
<td>(Continues)</td>
</tr>
</tbody>
</table>
Table 1 (continued)

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Participants</th>
<th>Dietary intervention</th>
<th>Outcomes</th>
<th>Follow-Up time</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLPD vs. LPD Gameata et al.</td>
<td>207 non-diabetic pts with CKD 4–5 (eGFR &lt; 30 mL/min/1.73m²) and proteinuria &lt; 1 g/day</td>
<td>LPD (0.6 g/kg/day) vs. sVLPD (vegetarian VLPD 0.3 g/kg/day with KA)</td>
<td>Dialysis initiation or 50% reduction in initial eGFR</td>
<td>15 months</td>
<td>Adjusted NNT (95% CI) to avoid dialysis was 22.4 (21.5–25.1) for pts with eGFR &lt; 30 mL/min/1.73m² but decreased to 2.7 (2.6–3.1) for pts with eGFR &lt; 20 mL/min/1.73m² in ITT analysis.</td>
<td>Correction of metabolic abnormalities occurred only with sVLPD. Compliance to diet was good, with no changes in nutritional measure.</td>
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<tr>
<td>Mircescu et al.</td>
<td>53 non-diabetic CKD 4–5 pts (eGFR &lt; 30 mL/min/1.73m²)</td>
<td>sVLPD (0.3 g/kg/day vegetable proteins) suppl. with KA vs. LPD</td>
<td>Transition to dialysis, eGFR, and laboratory markers</td>
<td>48 weeks</td>
<td>Less dialysis initiation with sVLPD (4 vs. 27%). Stable eGFR in sVLPD but decreased eGFR in controls. Stable GFR in the sVLPD vs. worsening nutritional measures and faster GFR decline in LPD group. Improved markers of bone breakdown in bone.</td>
<td>Open-label randomized, controlled trial. Higher bicarbonate and lower phos in sVLPD group.</td>
</tr>
<tr>
<td>Prakash et al.</td>
<td>34 CKD pts (mean eGFR 28 mL/min/1.73m²)</td>
<td>LPD (0.6 g/kg/day) with placebo vs. sVLPD (0.3 g/kg/day with KA)</td>
<td>Changes in GFR and nutritional markers</td>
<td>9 months</td>
<td>PROSPECTIVE, randomized, double-blind, placebo-controlled single-centre trial.</td>
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<tr>
<td>Malvy et al.</td>
<td>50 pts with CKD 4–5 (eGFR &lt; 20 mL/min/1.73m²)</td>
<td>sVLPD (0.3 g/kg/day with KA vs. LPD (0.65 g/kg/day)</td>
<td>3 mo to eGFR &gt; 5 mL/min/1.73m² or need for dialysis</td>
<td>3 years</td>
<td>Serum albumin increased in both sVLPD and LPD groups and did not differ between groups.</td>
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<tr>
<td>Montes-Delgado et al.</td>
<td>33 pts with CKD 3–5</td>
<td>LPD vs. LPD suppl. with a low-protein and hypercaloric supplement</td>
<td>Renal function and nutritional status</td>
<td>6 months</td>
<td>Slower CKD progression in the supplemented group, with better nutritional status and higher adherence.</td>
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<tr>
<td>MDRD study 2 Klahr et al.</td>
<td>255 pts with CKD 4–5 (GFR 13–24 mL/min/1.73m²)</td>
<td>LPD (0.6 g/kg/day) vs. sVLPD (0.3 g/kg/day with KA)</td>
<td>CKD progression, blood pressure, proteinuria, nutrition</td>
<td>27 months (mean follow-up)</td>
<td>sVLPD group had a marginally slower decline in GFR than LPD group (P = 0.067). Higher Ca, lower phos, alkaline phosphorus, and PTH levels in sVLPD group.</td>
<td>Two concurrent randomized controlled trials.</td>
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<tr>
<td>Lindenau et al.</td>
<td>40 pts with CKD 5 (GFR &lt; 15 mL/min/1.73m²)</td>
<td>LPD with calcium suppl. (n = 18) vs. sVLPD (0.4 g/kg) with KA (n = 22)</td>
<td>Bone and mineral markers including via bone biopsies</td>
<td>12 months</td>
<td>Decreased serum phosphorus with sVLPD, improved markers of bone breakdown in bone.</td>
<td>CKD progression and other outcomes not assessed.</td>
</tr>
</tbody>
</table>
Pooled results revealed trends towards lower GFR decline (Figure 3B) and lower 1 year serum urea (Figure 3D) in those who received VLPD; however, the trends were not significant. The results representing bicarbonate, phosphorus, PTH, and calcium could not be meta-analysed because of their heterogeneity.

Again, in addition to the results of our meta-analysis, we summarize some key results from the individual studies: Garneata et al. observed higher serum bicarbonate (22.9 vs. 16.2 mEq/L, $P < 0.01$), higher serum calcium (4.4 vs. 3.9 mmol/L, $P < 0.01$), and lower serum phosphorus levels (4.4 vs. 6.2 mg/dL, $P < 0.01$) in those who received VLPD vs. LPD. Similarly, Mircescu et al. showed higher serum bicarbonate (23.4 vs. 17.6 mg/dL), higher serum calcium (4.4 vs. 3.9 mmol/L), and lower phosphorus (4.5 vs. 6 mg/dL) in those who received VLPD compared with LPD.

Also, Lindenau et al. reported that in patients with advanced CKD, those who received VLPD showed better control of renal osteodystrophy markers including PTH (0.6 vs. 1.53 ng/mL), osteoid surface (34.3 vs. 51.9), and bone volume (27.9 vs. 25.2); however, most differences did not reach statistical significance.

**Sensitivity analyses**

The results of our sensitivity analyses were comparable with the main meta-analyses, indicating that our results were not dependent upon the selected meta-analysis methods (see Supporting Information, Figures S1 and S2).

**Other comparisons**

Two included studies compared LPD/VLPD with other interventions: Brunori et al. completed a non-inferiority trial of supplemented VLPD vs. dialysis in elderly ESRD patients without diabetes, and they observed that the survival was not higher in those who received VLPD. In the other study, Teplan et al. compared three interventions in CKD patients: (i) LPD supplemented with ketoacids plus human recombinant erythropoietin (EPO); (ii) non-supplemented LPD plus EPO; and (iii) non-supplemented LPD alone. They observed that patients receiving supplemented LPD plus EPO had lower GFR decline and proteinuria and better metabolic profile. None of the studied trials reported increased risk of protein-energy wasting or cachexia despite lower protein intake. There was no safety issue noted in any of the trials.

**Discussion**

Upon meta-analysing contemporary clinical trials of large sample size (>30 participants in each trial) that have examined an
**Table 2 Risk of bias assessment in included studies**

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<tr>
<td>LPD vs. higher PD</td>
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<td>Jiang et al. 17,18</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
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<td>Cianciaruso et al. 19</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>MDRD study 1</td>
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<tr>
<td>Klahr et al. 10</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
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<td></td>
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<tr>
<td>Locatelli et al. 20</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
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<td>Williams et al. 21</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
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<td>Ihle et al. 22</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
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<td>Rosman et al. 23,24</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>VLPD vs. LPD</td>
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<td>Garneaua et al. 25</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
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<td>Mircescu et al. 26</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
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<td>Prakash et al. 27</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
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<td>Malvy et al. 28</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
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<td>Montes-Delgado et al. 29</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
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<td>MDRD study 2</td>
<td></td>
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<td></td>
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<tr>
<td>Klahr et al. 16</td>
<td>Yes</td>
<td>Unclear</td>
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<td>Yes</td>
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<td>Lindena et al. 30</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
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<tr>
<td>Bruni et al. 31</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<td>Teplena et al. 32</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
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</table>

*aBlinding of participants in diet-based interventions is very difficult and almost unattainable.*

LPD for the management of CKD, we found that in comparison with diets with protein intake of >0.8 g/kg/day, diets with restricted protein intake (<0.8 g/kg/day) were associated with higher serum bicarbonate levels, lower phosphorus levels, lower rates of progression to ESRD, and a trend towards lower rates of all-cause death. In addition, VLPD (protein intake: <0.4 g/kg/day) was associated with even greater preservation of kidney function and reduction in the rate of progression to ESRD. These data may have important clinical and public health implications upon the conservative management of CKD.

For over half a century, we have regarded dialysis therapy as a life-saving intervention among patients with advanced kidney failure, in whom survival would otherwise be impossible. To that end, more dialysis and earlier dialysis initiation have been considered to be of immense clinical importance, many clinicians often encounter patients in very late stages of CKD, for example, estimated GFR < 25 mL/min/1.73m², who wish to avoid or defer dialysis therapy by any means possible. Several individual trials as well as meta-analysis studies have shown the benefits of protein restriction for such conservative management of CKD patients.

We found that the risk of progression to ESRD was significantly lower in the LPD compared with higher-protein diets and also found a trend towards greater survival in the former group. The 1 year serum bicarbonate level was significantly higher in those who received an LPD, which is an important metric in the treatment of CKD-associated acidosis and its deleterious effects. We also found lower phosphorus levels and lower azotemia with an LPD, which are important targets for the conservative management of CKD without dialysis. The safety and adherence to an LPD was not inferior to a normal protein diet in individual studies. However, we could not meta-analyse results representing PTH, calcium, and other selected metabolic factors because of the clinical and methodological heterogeneity of the clinical trials. However, these collective results suggest that an LPD may have a potential role in the conservative management of CKD.

As a systematic review and meta-analysis study, our findings were limited by the available data regarding the role of restricted protein intake in the management of CKD patients. The included studies were heterogeneous in their approach and selection of participants, which may have influenced the results.
interventions, and they did not report all relevant clinical outcomes. Also, because of our limited resources, we were unable to search other electronic databases beyond PubMed. Nevertheless, we were inclusive in our data synthesis and reported on the meta-analyses of various clinical outcomes using the most up-to-date evidence, while we excluded studies with <30 participants as our key a priori selection criterion to ensure that only well-designed studies with adequate statistical powers are included. In addition, the external validity of our findings may be less certain, as the efficacy of the LPD in the controlled conditions of RCTs does not necessarily translate into its effectiveness if CKD patients are not adequately compliant to the LPD. Furthermore, we did not assess the risk of publication bias across our included studies because of the few studies pooled together in each meta-analysis. In fact, tests of publication bias, for example, Egger or Begg & Mazumdar may generate inaccurate or misleading results if their ‘sample size’, that is, the number of pooled studies, is small.

In conclusion, the current evidence confirms the effect of restricted dietary protein intake on favourable metabolic surrogates of kidney function including azotemia, bone and mineral disorder, and acidosis, as well as slower kidney function loss, slower progression of CKD, and lower rates of ESRD and death. None of the studied trials reported increased risk of protein-energy wasting or cachexia despite lower protein intake, nor was there any safety issue in any of the trials. Future studies may focus on further examining the selection of appropriate patients for nutritional interventions and other approaches in the conservative management of patients with advanced CKD and investigating the role of adherence to such therapies.

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Online supplementary material

Additional Supporting Information may be found online in the supporting information tab for this article.

Supplemental Figure S1A. Risk of progression to end-stage renal disease in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): Using Random-effects model. Supplemental Figure S1B. Risk of progression to end-stage renal disease in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): Using Relative Risk. Supplemental Figure S1C. Risk of all-cause death in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): Using Relative Risk. Supplemental Figure S1D. 12-month serum bicarbonate (mEq/L) in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): Using Standardized Mean Difference. Supplemental Figure S1E. 12-month serum phosphorus (in mg/dL) in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): Using Standardized Mean Difference. Supplemental Figure S2A. Risk of progression to end-stage...
renal disease in very low protein diet (<0.4 g/kg/day) vs. low protein diet (0.4–0.6 g/kg/day): Using Relative Risk.

Supplemental Figure S2B. 1-year glomerular filtration rate decline (ml/min/1.73m²) in very low protein diet (<0.4 g/kg/day) vs. LPD (0.4–0.6 g/kg/day): Using Standardized Mean Difference (SMD).

Supplemental Figure S2C. 1-year serum urea (mg/dl) in VLPD (<0.4 g/kg/day) vs. LPD (0.4–0.6 g/kg/day): Using Standardized Mean Difference (SMD).

Supplementary Table S2. Selected controlled trials (with greater than 30 participants) that have examined the effects of low-protein or very low-protein diets (with or without supplementation with ketoacids or amino-acids) on various outcome measures in patients with chronic kidney disease.

Conflict of interest statement and disclosure


References

23. Rosman JB, ter Wee PM, Meijer S, Piers Becht TP, Sluiter WJ, Donker AJ. Prospective randomised trial of early


