Nutritional Management of Patients with Chronic Kidney Disease Through Low-Protein Diets

Authors: Stephen Jeffreys,[1] *Melanie Steinmair[2]

1. Medical Writer, Shrewsbury, UK
2. Dr Schär, Burgstall, Italy

*Correspondence to melanie.steinmair@drschaer.com

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Abstract

Chronic kidney disease (CKD) is a global health problem, affecting approximately 10% of the adult population. It has a significant impact on patient quality of life and mortality rates, and increases costs for healthcare systems. Nutrition plays an important role in disease prevention, as it can help prevent hypertension and Type 2 diabetes mellitus, the two major underlying causes in CKD development. Medical nutrition therapy with protein reduction is an important pillar in the conservative management of patients with chronic renal failure and may improve overall patient outcomes. Its effects on uraemia, proteinuria, and metabolic acidosis have been demonstrated in numerous studies. Hence, the 2020 update to the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in CKD has taken this into account, and recommends, with the highest level of evidence (1A), a diet with reduced protein intake in metabolically stable, nondialysis-dependent patients with CKD Stages 3–5. In practice, low-protein diets are often not particularly used for several reasons, such as concerns about the potentially increased risk for protein-energy wasting and poor adherence expectations. However, there is further evidence to show that a low-protein diet with adequate energy intake and high biological value protein supply, regularly followed by a trained dietitian, is safe and patient adherence increases with a personalised dietary approach, tailored to individual patient needs and considerations for dietary habits. Also, medical foods can help to facilitate reaching nutritional targets and preventing malnutrition, as they are a good source of almost nitrogen-free energy, providing only little amounts of protein, sodium, phosphorus, and potassium.

INTRODUCTION

Dependent on their level of residual kidney function and the presence of comorbidities, such as diabetes, hypertension,[1] and cardiovascular disease,[2,3] patients with chronic kidney disease (CKD) have differing nutritional requirements. A medical nutritional therapy, the so-called low-protein diet (LPD) maintains good nutritional status, reduces uraemic toxicity and metabolic alterations,[4] and decreases proteinuria,[5] and thus may play a part in lessening a declining kidney function and improving overall outcome. A plant-dominant, high-fibre, LPD may also bring additional benefits by altering the gut microbiome to enhance gut barrier performance, reduce inflammation, and delay CKD progression.[6]

LOW-PROTEIN DIET IN CHRONIC KIDNEY DISEASE

Recently, the National Kidney Foundation (NKF), in conjunction with the Academy of Nutrition and Dietetics (AND), published the 2020 update to the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in CKD.[7] A specific set of guidelines have been developed for the amount of protein recommended for CKD patient populations differentiated by diabetes:

- For those adults Stage 3–5, without diabetes, and who are metabolically stable and not on dialysis, patients should have an LPD of 0.55–0.60 g dietary protein/kg body weight/day, with or without ketoanalogues, or a very low-protein diet (VLPD) that provides 0.28–0.43 g dietary protein/kg body weight/day supplemented with ketoanalogues or amino acids.[7]
- Whereas for adult patients Stage 3–5, not on dialysis, and with diabetes, it is thought reasonable to prescribe a dietary protein intake of 0.60–0.80 g dietary protein/kg body weight/day to maintain a stable nutritional status and optimise glycaemic control.[7]

The most recent Kidney and Transplant Specialised Register Cochrane Review examined randomised controlled trials (RCT) for nondiabetic adults with CKD who had yet to require dialysis, and compared differing dietary protein regimes including VLPD (0.3–0.4 g/kg/day), LPD (0.5–0.6 g/kg/day), or normal protein intake (≥0.8 g/kg/day) for 12 months or more.[8] Evidence from 17 RCT (N=2,996) were examined, and it was concluded that VLPD compared with LPD, or normal protein diet, probably reduced the number of patients with advanced kidney failure who progress to dialysis.[8]

SUPPLEMENTING LOW-PROTEIN DIET WITH ESSENTIAL AMINO ACIDS AND KETOANALOGUES

LPD, especially if the protein amount is drastically restricted (VLPD), can be considered challenging to facilitate, owing to poor patient compliance and risk for protein-energy wasting (PEW) leading to malnutrition.[9] PEW is frequently encountered in patients with CKD and is distinguished by sarcopenia, weight loss, and low serum levels of albumin or transthyretin.[10]

In a Medline search for PEW in the title, Koppe et al.[10] identified 327 papers; a number of these specified PEW as a strong predictor of mortality in CKD. From this meta-analysis, the estimated prevalence of PEW in 16,434 haemodialysis patients ranged from 28 to 54%, and it increased as renal function declined.[10] To remove the risk of malnutrition and PEW in VLPD, ketoanalogues, precursors of essential amino acids, have been used as supplements. These analogues are converted into amino acids by transaminase while consuming ammonia molecules during this process. Aparicio et al.,[11] in their consensus statement for protein-restricted diets supplemented with keto acid therapy, advocated for the many benefits of following this strategy, including decreased uraemic toxins, reduced proteinuria, and improved insulin sensitivity. They have made recommendations for keto dosage depending on CKD staging.[11] A meta-analysis of 9 studies (N=410) with ketoanalogue supplementation was conducted by Jiang et al.,[12] who found there is a significant effect of supplemented VLPD/LPD in the protection of estimated glomerular filtration rate (eGFR), potentially reducing the progression of CKD.[12] Chewcharat et al.[13] conducted a more recent metanalysis of 17 RCT with over 1,400 patients and also concluded restricted protein diets supplemented with ketoanalogues helped preserve eGFR and

reduce proteinuria, serum phosphate, parathyroid hormone levels, blood pressure, and serum cholesterol. For patients to be able to benefit from such diet and lifestyle changes, centres have successfully deployed trained dietitians to counsel patients with CKD[14]

PHOSPHORUS HOMEOSTASIS AND AVOIDANCE OF SECONDARY PARATHYROIDISM

Patients with advanced CKD experience mineral disturbances as kidney function decreases. The ability to excrete phosphorus is reduced, leading to a positive phosphorus balance and triggering phosphaturia induced through increases in fibroblast growth factor 23 (FGF23) and parathyroid hormone.[15] Hyperphosphataemia is recognised as an independent risk factor for mortality in patients undergoing dialysis. A large observational study (n=3,490) was carried out in patients with CKD by Kestenbaum et al.[16] Associations between elevated serum phosphate, mortality risk, and myocardial infarction were found, which were independent of known confounding factors, including renal function.[16] After adjustment, they noted a relationship between serum phosphate levels >3.5 mg/dL and increased mortality risk; this increased linearly with each subsequent 0.5 mg/dL increase in serum phosphate levels.

To maintain serum phosphate levels in the normal range for patients with CKD Stages 3–5, it is recommended to restrict dietary phosphate to 800–1,000 mg/day.[7] However, the source of protein may have some bearing on the amount of available phosphorus. Moe et al.[15] reported on a trial in patients with CKD (n=8) to compare vegetarian and meat diets with equivalent nutrients prepared by clinical research staff. Results showed that after 1 week of a vegetarian diet, lower serum phosphorus levels and decreased FGF23 levels were achieved compared with a meat diet. It was concluded that protein source can have an impact on phosphorus levels in patients with CKD. Further, it was recommended that patients with CKD receiving dietary counselling should be informed about phosphate levels and protein sources for phosphates.[15] The phosphate in plant-based proteins is only 30–50% bioavailable due to being bound to phytates, compared with 70–80% bioavailability for animal-based foods, such as dairy.[16]

Sullivan et al.[17] reported on the risk of hyperphosphataemia due to consumption of phosphorus-rich food additives found in processed and fast foods; it is estimated that food additives contribute 30% of overall phosphate intake in a USA diet.[18] Sullivan conducted an RCT (N=279) in patients with end-stage renal disease that compared phosphorus levels; one group (n=145) were educated about avoiding phosphorus-rich food additives in groceries and fast foods, while the controls (n=134) followed usual care. They found that the educated patients resulted in a modest (0.6 mg/dL) but clinically significant improvement in serum phosphorus levels. Sullivan et al. concluded that this decline in average phosphorus level among the intervention cohort corresponds to a 5–15% reduction in relative mortality risk in observational studies.[17]

REDUCING METABOLIC ACIDOSIS IN CHRONIC KIDNEY DISEASE

Metabolic acidosis is a common complication in CKD and can trigger metabolic, endocrine, and musculoskeletal abnormalities.[19] Vegetable-based foods are rich in organic anion salts, which are directly absorbed by the gut to release bicarbonates. This results in a neutral or alkaline situation in the gut.[20] It has been estimated that consuming a fruit and vegetable diet can reduce acid excretion, equivalent to consuming 0.5 mEq/kg/day of sodium bicarbonate.[21] This can also lead to reduced proteinuria and decreased blood pressure in certain patients with CKD.[21] Extracellular sodium cations are responsible for fluid homeostasis, which is controlled through the renin–angiotensin–aldosterone system (RAAS).[7] This mechanism regulates sodium excretion through the kidneys and therefore exerts control on extracellular fluid volume and arterial blood pressure.[22] Excess sodium intake is excreted in the urine, with serum levels tightly controlled. However, in CKD, the system can be compromised by excessive dietary sodium consumption and/or kidney capability to excrete sodium becoming inadequate.

Humalda et al.[23] conducted a review to examine the evidence for the protective effect of dietary sodium restriction in patients with CKD specifically. In CKD cohorts, sodium intake is generally elevated, often above population average. For both diabetic and nondiabetic patients with CKD, a moderately lower sodium consumption was associated with better long-term outcomes of RAAS-blockade due to improved effects on proteinuria, independent of blood pressure. On the basis of an observed J-curve for sodium intake and outcome, with higher risk at both higher and lower sodium intakes, concerns have been expressed on the safety of rigorous sodium restriction. However, in their review, Humalda et al. concluded there are considerable potential benefits for most patients with CKD to have a moderately restricted sodium diet.[23] The KDOQI Clinical Practice Guideline for adults with CKD Stages 3–5 recommended that to control blood pressure and proteinuria, the amount of dietary sodium consumed should be <100 mmol/day (or <2.3 g/day).[7]

McMahon et al.[24] conducted a small, double-blind, placebo-controlled randomised crossover study of 25 nondialysed, nontransplanted patients with CKD. Using blood pressure, proteinuria, extracellular fluid volume, and arterial stiffness as markers of cardiovascular progression in CKD populations, they aimed to evaluate dietary sodium intake on these markers. They found a dietary sodium restriction of 60–80 mmol daily intake significantly decreased ambulatory blood pressure by 10/4 mmHg (systolic/diastolic) over the 24 hours. Also, for extracellular volume, albuminuria, and proteinuria, significant reductions were observed, with the latter two occurring independent of blood pressure changes. In this study, dietary sodium restriction reduced the incidence of most risk factors without significant adverse effects; however, symptomatic hypotension was observed and was resolved by modifying the antihypertensive regime.[24]

CARDIOVASCULAR RISK FACTOR MANAGEMENT IN CHRONIC KIDNEY DISEASE

In patients with CKD, inflammatory cytokine and advanced glycation end-product concentrations are often raised.[25] Susceptibility to inflammatory diseases, such as atherosclerosis and stroke, is heightened in this group of patients.[26] A vegetarian diet can confer cardiovascular benefits due to lower BMI, reduced blood pressure, a decreased incidence of hypertension, and reduced risk of Type 2 diabetes mellitus.[27] The large EPIC-Oxford study (n=37,875) grouped people into their expressed dietary preference for meat, fish, vegetarian, or vegan, and demonstrated age-adjusted mean BMI was highest in meat-eaters and lowest in vegans.[28] Several studies have reported reducing blood pressures when moving from a meat-based diet to a vegetarian one.[17,29]

Klahr et al.[30] conducted the Modification of Diet in Renal Disease (MDRD) Study in 840 patients to determine the effects of dietary protein restriction and blood pressure control on the progression of CKD. In Study 1, 585 patients with eGFR ranging from 25 to 55 mL/min/1.73m^2 were randomly assigned to usual protein diet or LPD and to usual or low blood pressure groups. After a mean of 2.2 years, the projected decline in eGFR did not differ significantly between diets or blood pressure groups. In Study 2, 255 patients with an eGFR of 13–34 mL/min/1.73m^2 were randomly assigned to LPD or VLPD and a usual or low blood pressure group. On follow-up, the VLPD group had a marginally slower decline in eGFR compared with the LPD group (p=0.07). In their conclusions, the authors stated there was no statistical difference between diet groups in time to end-stage renal disease or death.[30] A subsequent reanalysis by Levey et al.[31] suggested that the patient cohort on a diet of 1.30 g protein/kg/day, compared with the group allocated a diet of 0.58 g protein/kg/day and lower phosphorus intakes, experienced significantly more kidney function loss after the first 4 months from the start of the programme. After other known risk factors had been ruled out, a reduced protein consumption was associated with a 29% lower risk of CKD progression and no additional benefit from supplementation with ketoanalogues.[32] In the VLPD group, the causes of renal disease were hypertensive-vascular nephropathies (38%), glomerulonephritis (20%), tubule-interstitial nephropathies (15%), and unknown causes (27%); in the control group the percentages were similar: 41%, 18%, 16%, and 24%, respectively. Moreover, the frequency of cardiovascular complications (angina, infarction, stroke) was

46% in VLPD group, and 42% in control group (p=not significant).[5]

PLANT-BASED DIETS FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

Kalantar-Zadeh et al.[33] have recently proposed a plant-dominant, low-protein diet as a pragmatic approach to facilitating CKD progression.[33] The proposition is for a diet that delivers daily protein ingestion of 0.6–0.8g/kg/day with at least 50% as plant-based sources, preferably whole unrefined and unprocessed foods; a low ~ sodium intake of <3 g/day; higher dietary fibre of 25–30g/day; and adequate nutritional energy intake of 30–35 kcal/kg/day.[33]

Potassium homeostasis and excretion are commonly impaired in patients with CKD, and hyperkalaemia is particularly concerning in late-stage CKD. Hyperkalaemia has an association with increased mortality and may contribute to peripheral neuropathy in patients with CKD.[7] The KDOQI recommendations for adults with CKD Stages 3–5 or post-transplantation should have dietary potassium intake adjusted to maintain normal serum potassium levels.[7] For adults with CKD Stages 3–5 or post-transplantation with either hyperkalaemia or hypokalaemia, dietary or supplemental potassium intake should be based on individual needs. It is suggested that when treating hyperkalaemia, the patient should recommend fruit and vegetables low in potassium.[7] It has been shown that double boiling can reduce the potassium concentration in potatoes and other tuberous root vegetables.[34,35] Eating a plant-dominant, high-fibre, low-protein diet may lead to favourable alterations in the gut microbiome. Among other things, the gut microbiota plays an essential role in the production of short-chain fatty acids. Dietary fibre enables the gut microbiota to generate short-chain fatty acids, which in turn become energy sources for gut bacteria and maintain intestinal epithelial barrier permeability.[36] Gut microbiome dysbiosis, resulting from alterations of composition and function of the gut microbiota and disruption of gut barrier function, is seen in pateints with CKD.[37] This gut flora disruption can generate large amounts of uraemic toxins, which can translocate into the systemic circulation due to the impairment of the intestinal barriers.[38] Uraemic toxaemia has been associated with the development of cardiovascular disease, CKD progression, and raised mortality risk in patients with CKD.[33,39]

PRACTICAL STRATEGIES

There is a need for practical applications in the management of dietary recommendations in CKD, which will turn the clinical guidance already set out into a set of pragmatic approaches. It is essential to engage with patients on their terms and make the clinical guidance a living reality for them.

Each diagnosis of CKD will require extensive and long-term changes to food and lifestyle for the patient. Virtually all dietary interventions require significant effort from the healthcare team, requiring expertise often outside the focus of most practising nephrologists.[40] Beto et al.[9] reported poor adherence to diet, medications, and treatments, estimated to vary between 20 and 70%, which could contribute to increased morbidity and mortality.[9] Delivering practical nutritional advice to patients with CKD requires co-ordination of many dietary components to cover calories, protein, carbohydrates, fats, electrolytes, and fluid, especially in patients with comorbidities, such as hypertension, diabetes, and cardiovascular diseases. Dietary intake studies have experienced adherence difficulties with the scope and complexity of CKD diet parameters. In Italy, nephrologists have a long-standing tradition of successfully implementing LPD for CKD. This has been due, in part, to the availability of low-protein foods, which have been available in Italy for decades. These products are carbohydrate-rich, low in salt, and virtually free of phosphorus, potassium, and nitrogen. They can effectively replace analogous food staples, such as bread, pasta, or biscuits, making it possible to reduce or replace protein of low biological value with higher value proteins, such as animal or legume proteins, and ensure a high energy intake.[41] D'Alessandro et al.[42] investigated the practicalities of such low-protein foods consumed by 100 patients with CKD prescribed LPD. Of these patients, 92% believed nutritional counselling with a trained dietitian was beneficial in successfully following their diet.[42] There are two main factors that enable successful LPD adherence: the prevention of PEW and the continual implementation of the dietary plan. For this reason, skilled teams

of nephrologists and dietitians are needed to frequently monitor patients on LPD and provide comprehensive nutritional support for their patients with CKD.[39]

Furthermore, D'Alessandro et al. mapped out simplified dietary regimens for these patients. They observed that low-protein products, which have a particularly favourable energy/phosphate ratio and can be high in plant fibre, are very important tools for the safe and successful implementation of dietary plans for patients with CKD.[14] Cost-effectiveness studies have been conducted to evaluate the economic benefits of pursuing a VLPD compared with dialysis in patients with Stage 5 CKD. Scalone et al.[43] followed 57 elderly patients with Stage 5 CKD who were randomised to dialysis or VLPD over 3 years. It was concluded that VLPD was a safe and beneficial strategy for these patients and allowed economic resources to be reallocated for further investments into the healthcare system.[43] Mennini et al.[44] compared the cost-effectiveness of LPD versus normal diet in patients with CKD Stages 4–5 over 10 years. A Quality-Adjusted Life Year (QALY) assessment showed LPD was both more effective in terms of good quality of life gained and was less expensive than normal diet.

CONCLUSION

Given the high incidence of CKD, nutritional therapy interventions have a significant role to play in delaying the progression of CKD, improving overall patient outcomes, and are significantly more cost-effective to healthcare systems compared with the cost of dialysis and transplantation. To deliver patient-centric dietary plans effectively, the involvement of dedicated dietitians in the patient management team is crucial. Food choice is a vital part of taking patients on this nutritional journey. Specific low-protein products, such as pasta, breads, and biscuits, can help patients to adhere to a LPD, assist in the facilitation of disease management, and provide better overall outcomes.

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