Optimizing Diet to Slow CKD Progression

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Due to the unique role of the kidney in the metabolism of nutrients, patients with chronic kidney disease (CKD) lose the ability to excrete solutes and maintain homeostasis. Nutrient intake modifications and monitoring of nutritional status in this population becomes critical, since it can affect important health outcomes, including progression to kidney failure, quality of life, morbidity, and mortality. Although there are multiple hemodynamic and metabolic factors involved in the progression and prognosis of CKD, nutritional interventions are a central component of the care of patients with non-dialysis CKD (ND-CKD) and of the prevention of overweight and possible protein energy-wasting. Here, we review the reno-protective effects of diet in adults with ND-CKD stages 3–5, including transplant patients.

Keywords: chronic kidney disease, protein restricted diet, nutrition, salt restriction, renoprotection

INTRODUCTION

Advanced chronic kidney disease (CKD) is a systemic disorder which is associated with high mortality and poor quality of life. Different treatments and lifestyle modifications are needed to avoid progression to kidney failure, which requires of kidney replacement therapy (maintenance dialysis or transplantation), and exceedingly costly therapy to Society (1–3). Chronic kidney disease progression is largely conditioned by hemodynamic and metabolic factors independent of the primary kidney disease, many of them, such as the high blood pressure (BP), the hyperfiltration, or the proteinuria are highly influenced by diet (4). Moreover, due to the kidney’s unique role in nutrient metabolism, patients with advanced CKD are unable to maintain adequate nutrient homeostasis, developing metabolic disorders as sodium and volume overload, hyperkalemia, hyperphosphatemia, metabolic acidosis, altered hormone regulation, and inflammation. Accordingly, nutritional interventions should be a fundamental strategy in the treatment of patients with CKD (5–7).

In recent years, several studies, trials, and meta-analyses have evidenced the effectiveness of protein restriction and other nutritional interventions on kidney outcomes (8–17). This evidence was judged to increase the strength of recommendations for the nutritional management of patients with CKD in the 2020 update of the KDOQI guidelines (18). In this review, we aim to summarize recent studies on the role of diet, focusing on salt and protein restriction, as well as the use of supplements with essential amino acids (AAs) and keto analogs (KAs) to delay the progression of CKD and, at the same time, to preserve the nutritional status of patients with ND-CKD.
DIETARY REQUIREMENTS IN PATIENTS WITH KIDNEY DISEASE

Table 1 shows current recommendations for nutritional requirements in adult patients with non-dialysis CKD (ND-CKD), and kidney transplant recipients (KTR) (18, 19). A caloric intake of 25–35 kcal/kg/day is recommended to counteract the excess resting energy expenditure secondary to inflammation and comorbidities, as well as for preserving a neutral or positive nitrogen balance. However, this recommendation should be individualized according to the patient’s profile, including age, lean body mass (which is the primary determinant of energy expenditure), physical activity, and the underlying etiology of kidney disease (20, 21). According to the 2020 KDOQI guidelines, the recommended protein intake for stable patients with ND-CKD 3–5 dialysis is 0.55–0.60 g/kg/day, which can be reduced to 0.28–0.43 g/kg/day if it is supplemented with 7–15 g/day of KAs and essential AAs. In the case of diabetic patients, guidelines suggest a higher protein intake up to 0.6–0.8 g/kg/day to glycemic control. Any intercurrent catabolic episode may require increasing energy and protein intake independently of CKD stage (22). Regarding protein quality, there is no consensus on whether the protein source impacts differently on the risk of CKD progression (18).

Kidney transplant recipients require a different nutritional management depending on the post transplantation period. During the perioperative period, KTR need to adequate their intake of energy to 35–40 kcal/kg/day and of proteins up to 1.4 g/kg/day for at least 4 weeks (19) to compensate the increase in protein catabolism subsequent to the use of steroid and surgical stress. However, in the maintenance phase, the goal is to optimize the nutritional status with a slight reduction of the caloric intake down to 30 kcal/kg/day. Obese KTR should reduce their caloric consumption to levels lower than their energy expenditure, being values close to 25 kcal/kg/day an adequate approximation (19). Due to the lack of available studies in this population (23), it has been proposed that those with normal kidney function should follow similar recommendations to the general population, whereas for KTR with chronic allograft dysfunction, it is recommended to provide a protein-restricted diet just as in ND-CKD (19).

A modest sodium restriction (<2.3 g/day) is recommended for the management of CKD patients to achieve better volume control, reducing BP, and proteinuria synergistically with available pharmacologic interventions (18). A daily fiber intake of 25–30 g/day or more for CKD patients may be suggested, being this amount similar to recommendations for the general population (7). Potassium restriction in CKD may prevent from complying with this recommendation but in general terms CKD patients do not require aggressive dietary potassium restriction until advanced stages or if hyperkalemia risk is judged high (24–26). Recently, it has been suggested to avoid high potassium foods with poor nutritional value (i.e., bran products, or salt substitutes) and correct other causes of hyperkalemia, such as metabolic acidosis or use of renin-angiotensin-aldosterone system (RAAS) inhibitors, before restricting healthy foods (27). Acidosis is a key risk factor in the progression of CKD, being fruits and vegetables an alternative to oral alkali that may reduce the risk for volume retention and/or hypertension related to bicarbonate supplementation (28). Given the role of calcium balance and the serum phosphate in the development of cardiovascular calcifications, several experts recommend limiting total dietary calcium intake to 800–1,000 mg/day or

| TABLE 1 Nutritional requirements for patients with non-dialysis CKD according to 2020 KDOQI Guidelines (15). |
|-------------------------------------------------|-------------------------------------------------|
| **Energy (kcal/kg ideal weight/day)** | **Protein (g/kg/day)** |
| ND-CKD stage 3–5 | Transplantation |
| 25–35 | 25–35 in maintenance KTR |
| 25–35 | 25 (obesity) |
| 25–35 | 35–40 for the first 4 weeks after transplantation |
| 0.55–0.60 or 0.28–0.43 plus keto/amino acid supplementation | 0.8 |
| 0.80–0.90 (diabetes) | 0.6–0.8 (CKD stages 3–5 T) |
| 1.0 (illness) | ≥ 1.4 (for the first 4 weeks after transplantation or if high doses of prednisone is required) |
| Sodium (g/day) | Potassium[^a] |
| <2.3 | Adjust dietary potassium intake to maintain serum potassium within the normal range |
| | Adjust dietary potassium intake to maintain serum potassium within the normal range |
| Calcium (mg/day) | 800–1,000[^b] |
| 25–38 | Insufficient data to define optimal dietary calcium intake in KTR (research priority) |
| 25–38 | |
| Fiber (g/day) | Vitamin D (IU/day) |
| 2.4 | 600–800 |
| 600–800 | 600–800 |
| Folic acid (µg/day)^[^c] | 400 |
| 400 | 400 |
| Vitamin B12 (µg/day)^[^d] | 90 (M), 75 (W) |
| 2.4 | 90 (M), 75 (W) |
| | Vitamin E (mg/day)^[^e] |
| 15 | 15 |
| | Vitamin K (µg/day)^[^f] |
| 120 (M), 90 (W) | 120 (M), 90 (W) |
| | Selenium (µg/day)^[^g] |
| 55 | 55 |
| | Zinc (mg/day)^[^h] |
| 11 (M), 8 (W) | 11 (M), 8 (W) |

[^a] Energy and protein intake should be adapted to age, gender, level of physical activity, body composition, weight status goals, CKD stage, and concurrent illness or presence of inflammation to maintain normal nutritional status. If present, priority should be given to the correction of protein-energy wasting.

[^b] Not enough evidence to make a statement on protein sources.

[^c] Guidelines do not suggest specific dietary K range (restriction per se may favor other nutrient deficiencies). Before restricting healthy foods, other causes of hyperkalemia (acidosis, constipation…) should be corrected.

[^d] Including dietary calcium, calcium supplementation, and calcium-based phosphate/potassium binders.

[^e] When making decisions about phosphorus restriction treatment, consider the bioavailability of phosphorus sources (e.g., animal, vegetable, additives).

[^f] No specific recommendations are provided by KDOQI guidelines. In the absence of evidence specific for persons with CKD, recommended Dietary Allowances for Adult General Population should apply.
less (including dietary calcium, calcium supplementation, and calcium-based phosphate binders) in adults with CKD 3–4 not taking active vitamin D analogs. Although phosphate intake to 800–1,000 mg/day (800–1,300 in KTR) was recommended previously (29, 30), new guidelines suggest adjusting dietary phosphorus intake to maintain serum phosphate levels in the normal range (18). Limiting processed foods with phosphorous-based additives and encouraging home-cooked meals from fresh ingredients (preferably plant-based foods) should be the first-line interventions for phosphorus restriction (31). As in the general population, vitamin D intake for CKD patients is recommended at 600–800 IU/day, but the optimal vitamin D levels in serum remain controversial (31, 32).

PRACTICE STRATEGIES: NEED FOR INDIVIDUALIZED AND NOT TOO RESTRICTIVE DIET

Because a “kidney” diet comes with many restrictions, adherence to such a diet can be difficult and problematic (5). Too many restrictions should be avoided (18), as they can lead to poor intake. Modifications in diet are rarely required for patients with a GFR ≥60 ml/min/1.73 m². Such patients should be advised to follow the same dietary recommendations as for the general population [low sodium and refined sugar, avoidance of red and processed meats, and high content of fruits, vegetables, legumes, fish, poultry, and whole grains (33)]. However, in the later stages of CKD, diet must be modified across the spectrum of the disease, according to the type of renal replacement therapy if any, and the presence of other comorbidities (5).

ADEQUATE PROTEIN INTAKE TO SLOW CKD PROGRESSION

Biosynthesis and Degradation of Proteins

Protein digestion includes the process of breaking down proteins into their constituent AAs, which can be used either to create proteins or as an energy source, the latter especially in times of starvation (34). Unlike carbohydrates and fats, if proteins are consumed in excess, the body has no capacity for their storage. As a result, excess AAs consumed are processed, being hydrocarbon skeletons stored as fat, while the surplus of nitrogen must be removed, in as much as nitrogenous waste products are harmful, and there are no nitrogenous compounds in energy-transduction pathways (35). This is especially relevant for CKD patients, in whom consuming diets rich in protein leads to the accumulation of nitrogenous waste products and ions, causing the uremic syndrome. Transamination reactions are reversible and can thus be used to synthesize AAs from α-ketoacids (36, 37). However, human beings cannot synthesize all of the AAs (the so-called essential AAs), which must be supplied in the diet. A deficiency of even a single AA leads to a negative nitrogen balance. In this state, more protein is degraded than is synthesized, so more nitrogen is excreted than is ingested (38). The latter is particularly relevant for CKD patients under low protein diet (LPD), who may be at risk for developing protein-energy wasting (PEW) if not adequately monitored.

Effects of Amino Acids and Proteins on Renal Hemodynamics

Excess nutritional load of AAs dilates the “afferent” arteriole, increasing intraglomerular pressure and resulting in “glomerular hyperfiltration” and increased renal plasma flow (39). Glomerular hyperfiltration may contribute to progression of CKD (40–43). Conversely, a lower protein intake leads to greater constriction of the afferent arteriole, resulting in a reduction in GFR (Figure 1). In addition to hemodynamic-mediated mechanisms, protein restriction may protect against CKD progression by changes in cytokine expression and matrix synthesis (5).

Metabolic Adaptation to a Reduction in Protein Intake

Most authors agree that, in the absence of intercurrent disease, the protein requirements for patients with CKD are not substantially different from those of healthy subjects (44). In normal healthy adults, the minimum dietary protein intake to prevent negative nitrogen balance is approximately 0.6 g/kg/day. Maintaining this LPD or a very low protein diet (VLPD) of nearly 0.3 g/kg/day supplemented with AAEs and KAs are sufficient to achieve nitrogen balance and normal nutritional parameters (45, 46). As in healthy subjects, CKD patients, can improve AA utilization and nitrogen balance during LPD and VLPD by activating appropriate adaptive responses (47). These include normal anabolic responses to dietary protein restriction (suppression of AA oxidation) and feeding (stimulation of protein synthesis and inhibition of protein degradation), and the recycling of AAs derived from protein breakdown (35, 36). It is important to note that these diets require sufficient caloric intake to effectively use dietary protein (48).

Benefits of Protein Restriction on Kidney Outcomes

The benefits of LPDs include slowing the progression of CKD and reducing uremic symptoms and metabolic disorders (20, 21, 48, 49). Nearly 20 RCTs have assessed the effects of protein restriction on several renal outcomes, including CKD progression, proteinuria, phosphate levels, acidemia, and BP, which have been summarized in several meta-analyses and two Cochrane reviews (8–11, 15, 16, 50–56). Overall, the balance of evidence suggests a benefit of dietary protein restriction. The 2020 KDOQI guidelines recommend, in non-diabetic adults with CKD 3–5 who are metabolically stable, protein restriction for reducing the risk of progression to end-stage renal disease (ESRD) and death (evidence 1A), and improve quality of life (1C). In adults with CKD 3–5 and who have diabetes, the guidelines suggest (with an evidence grade of “opinion”) a higher protein intake up to 0.8–0.9 g/kg/day (18). For the study of the effect of LPD on survival, they identified five RCTs. Three studies clearly indicated a beneficial effect of moderate restriction in dietary protein in the development of
The effects of different nutritional interventions to slow progression of CKD. Schematic representation of reno-protective mechanisms related to protein and diet restriction. These effects can be synergistic with the mechanisms of angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers, which dilate the efferent arteriole and reduce intraglomerular pressure and glomerular damage. Adapted from Kalantar-Zadeh and Fouque (5). CKD, chronic kidney disease; GFR, glomerular filtration rate; TGF-β, transforming growth factor beta.
chronic kidney rejection. Low protein diet was associated with a significant improvement in plasma renin activity without any change in BP, GFR, or renal plasma flow. Studies are needed to establish the efficacy and the safe level of dietary protein restriction in KTR (78).

**Challenges and Risks for Protein Restriction Diets**

Major concerns for LPD/VLPD are adherence and safety (79–81). Patients’ adherence to these dietary regimens is low, being the knowledge and the satisfaction that the patients obtain from diet compliance the main determinants of adherence (82). Even if the patients are well-informed about the benefits of LPD/VLPD, some of them may find it difficult to adapt their lifestyles to the diet. Accordingly, it is of paramount importance to educate patients about the role of diet therapy with protein restriction for the treatment of CKD, taking into account their eating habits and preferences (81, 83). Regarding nutritional security, it has been definitively demonstrated that PEW is extremely rare in patients with CKD provided that the energy intake is in the normal-high range (30–35 kcal/kg/day), the protein intake is increased in case of acute illness or hospitalization, and provided that a nutritional assessment is periodically conducted (7, 18, 80). Consequently, trained personnel (ideally a registered dietitian nutritionist) is strongly recommended to develop individualized dietary programs and routinely monitor and advise patients (18, 80, 82, 84). However, this approach is time and money consuming (80). An option for those centers in which dedicated personnel (i.e., dietitian) is not available or the expertise of the nephrologist in managing diets is not optimal may be found in simplified and practical approaches to LPD (80, 85, 86). Indeed, even small reductions in protein intake as low as 0.2 g/kg/day may also delay the need for dialysis treatment (10, 56, 80). In these Nephrology Units devoid of dieticians, protein intake may be assessed by urinary urea-N excretion, whereas weight and other anthropometric methods (e.g., skinfold thickness) may be useful for indirectly monitoring caloric intake and body fat (85, 87).

**Effects of the Nature of Protein. Is a Vegetarian Diet an Option?**

There is insufficient evidence to recommend a particular protein type (plant vs. animal) in terms of the effects on CKD progression or nutritional status (18). However, several observational studies have suggested that plant proteins may have more renoprotective effects than animal proteins. A diet rich in protein from plant sources may slow the progression of CKD (88–92), decrease proteinuria (93, 94), lower the level of uremic toxins (94–99), phosphorus intake, and the endogenous production of acid (89, 90, 100, 101). Moreover, that such diet could potentially improve survival (102). However, the confounding factors inherent in a diet rich in plant-based protein (i.e., higher intakes of vitamins and antioxidants) make it difficult to draw definite conclusions (103, 104). In a RCT, Garneata et al. compared a KA-supplemented vegetarian VLPD with conventional LPD in 207 CKD patients (89). The probability to reach the end point (i.e., KRT or a >50% eGFR reduction) was lower in the supplemented VLPD group than in the LPD group.

**DIETARY SALT RESTRICTION**

Dietary sodium intake is a modifiable factor that can impact on the risk of CKD progression as well as on cardiovascular disease in CKD patients. Previous reports have demonstrated the effect of sodium intake on fluid overload and hypertension, both predictors of kidney progression and cardiovascular remodeling (105–109). In addition, high sodium intake might have direct toxic effects on blood vessels (109, 110). High salt intake is also a well-established risk factor for hypertension in KTR and can result in decreased graft survival (2, 111).

Conversely, salt restriction RCTs demonstrate a reduction in BP and proteinuria, with potential benefits on CKD progression and survival (5). A Cochrane review summarized the effects of salt restriction in CKD (8). Unfortunately, these studies did not show collectively a beneficial effect of a lower sodium intake on mortality, cardiovascular events, or CKD progression, probably due to their short follow-up and the limited sample size. It is interesting to highlight a significant decrease in proteinuria associated to a low salt diet, that was observed in all the RCTs that reported this outcome (112–115). The 2020 KDOQI guidelines recommend in adults with CKD 3–5 (1B), CKD 5D (1C), or posttransplantation (1C), a limitation in the sodium intake to <2.3 g/d (<100 mmol/d) to achieve a BP reduction, an improvement in volume control and a decrease in proteinuria levels (2A) (18). Nevertheless, the lack of long-term RCTs assessing the effectiveness and safety of dietary salt restriction on CKD progression and survival prevents any firm conclusions about these hard outcomes.

**REDUCED PHOSPHORUS INTAKE**

Phosphate-specific diet therapy provided by a dietitian may reduce phosphate levels in CKD, although overall certainty of evidence is low (116). However, association between hyperphosphatemia and adverse cardiovascular outcomes and CKD progression is robust in this population (117–124), also in KTR (125–127). Altogether, it seems reasonable to recommend adjusting dietary phosphorus intake to maintain serum phosphate levels in the normal range (18, 105).

**DIETARY CALORIC RESTRICTION**

Obesity constitutes a risk factor for diabetic and non-diabetic kidney disease (128), and there is some evidence suggesting that weight reduction through diet and lifestyle modifications could be considered as a component of the reno-protective regimen of obese patients with ND-CKD (129). Bariatric surgery reduces risk factors implicated in the progression of kidney injury in obesity and type 2 diabetes mellitus (130, 131). Dietary calorie restriction and exercise may reduce oxidative stress and inflammatory in patients with moderate to severe CKD.
(132), whereas weight loss may lead to better BP control and reduction of the obesity-related glomerular hyperfiltration and proteinuria (133–136).

**FIBER INTAKE AND PROBIOTICS**

Evidence is emerging for the effects of fiber intake on uremic toxins generation (104, 137, 138). In a placebo-controlled RCT involving 30 patients with ND-CKD, total plasma p-cresol concentration was reduced by 40% after taking a synbiotic for 4 weeks (139). According to a recent meta-analysis involving eight studies of 261 patients with CKD stages 3–5D, probiotics supplementation may reduce the levels of p-cresol sulfate and elevate the levels of IL-6, thereby protecting the intestinal epithelial barrier of patients with CKD (14). However, it remains uncertain if increasing fiber intake to normalize intestinal microflora could delay CKD progression.

**DIETARY PATTERNS AND CKD PROGRESSION**

Historically, research recommendations and guidelines have focused primarily on modifying the single intake of micro or macronutrients (57). However, eating habits generally remain little over time for each individual, so that the overall dietary pattern may be more decisive for patients than an excess or deficiency in one specific nutrient (103). Adherence to healthy diet patterns as the Mediterranean and the DASH (The Dietary Approach to Stop Hypertension) diets has been linked to less rapid kidney function decline and favorable effects on cardiovascular morbidity and mortality in ND-CKD patients, including KTR (140, 141). Plant-based diets could also mitigate metabolic acidosis in patients with CKD and potentially slow the progression of kidney disease, but evidence is limited (104). Conversely, a Western diet (rich in saturated fat, red and processed meat, and sweets) has been associated with an increased risk of CKD progression and albuminuria (142). The evidence is not conclusive as not all studies associate healthy dietary patterns and risk of ESRD (143). Evidence from interventional studies is also very limited (144, 145). Altogether, there is a possibility that healthy dietary patterns may prevent the development of ESRD (5, 81, 146).

**CONCLUSIONS**

Close monitoring to adherence to dietary recommendations and frequent evaluation of nutritional status is fundamental in the management of patients with CKD, since it can affect important health outcomes, including CKD progression, quality of life, morbidity, and mortality. Within these nutritional measures, salt restriction, LPD and VLPD supplemented with AAs and KAs of nitrogen-free AAs, have been shown in recent meta-analyses of RCTs to be effective in modifying the natural history of CKD, delaying the fall of the GFR, decreasing proteinuria, BP levels, or bone mineral disorder parameters, without increasing the risk of PEW. Patients’ preferences and compliance have to be considered when prescribing LPD/VLPD in order to increase the adherence. Additional nutritional measures to delay CKD progression, some of them considered as experimental, may include the limitation of phosphate and calorie intake, the increase of fiber intake, and the promotion of healthy dietary patterns.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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