Nutritional Therapy, Phosphate Control and Renal Protection

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Abstract

Dietary management of chronic kidney disease (CKD) focusses on limiting the intake of substances that might accumulate to toxic levels (such as potassium, phosphorus or salt) and, although still a matter of debate for some, restricting dietary protein to retard kidney damage. Recent evidence brings the opportunity to revisit the role of a healthy diet on disease progression and on some of the cardiometabolic complications of moderate/advanced CKD, such as inflammation or oxidative stress control. This review provides a brief overview of dietary strategies that delay CKD progression and CKD complications, and discusses currently limited data addressing the development of malnutrition and protein-energy wasting before dialysis initiation.

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Introduction

The kidney plays an essential role in nutrient homeostasis and electrolyte and fluid control. Thus, the presence of reduced kidney function and development of chronic kidney disease (CKD) requires specific dietary adaptations. Some of these adaptations are focused on avoiding the retention of specific micro- and macronutrients to toxic levels. Other approaches seek to retard kidney damage and slow progression to end-stage renal disease (ESRD). Finally, the increased prevalence of malnutrition in advanced CKD stages provides another scenario for dietary modification. This review aims at offering a general overview of current dietary recommendations in nondialyzed CKD patients before the start of dialysis.

Nutritional Considerations for Halting CKD Progression

The evidence that lifestyle factors may be involved in the incidence and progression of CKD is mounting. Protein restrictive diets have been the subject of much research and debate, and the inevitable link between salt intake and hypertension demands salt control in patients with reduced renal function. In addition, modern nutritional epidemiology has identified other unhealthy dietary habits that may be associated with the development of CKD. When interpreting the following studies, it should be emphasized, however, that modifying dietary habits is challenging and implies a major change in lifestyle. Indeed, it may be more difficult to implement and evaluate dietary than drug interventions.

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Low-Protein Diets

Animal studies from the 1960s showed that a high-protein diet results in glomerular hyperfiltration and subsequent kidney injury [1], and population-based cohorts seem to confirm these deleterious effects of high intake of nondairy animal protein on renal function [2]. Thus, it is generally recommended that excessive protein intake be avoided by individuals with CKD, and moderate restriction on dietary protein is advocated. The latest KDIGO guidelines suggest the consumption of a high-quality protein diet of around 0.8 g/kg/day among those individuals with CKD stages 3–5 who are highly motivated to follow such a diet [3]. Other recommendations suggest a lower range of protein restriction to 0.6–0.8 g/kg/day, provided that signs of malnutrition are not present [4].

Whether patients with CKD should be prescribed a restricted dietary protein has been a matter of much debate. The largest randomized controlled trial (RCT) performed to date, the Modification of Diet in Renal Diseases (MDRD) study, included about 600 individuals with moderate CKD and showed that a low- versus usual-protein diet (0.58 vs. 1.3 g/kg/day) did not result in slower decline of kidney function [5]. Other smaller RCTs showed that protein restriction to approximately 0.6–0.8 g/kg/day was associated with a modest and not significant benefit on CKD progression [6, 7]. In clinical trials including insulin-dependent diabetic nephropathy patients, low-protein diets (LPDs) resulted in slower decline of glomerular filtration rate (GFR) [8, 9]. A meta-analysis that involved about 1,500 patients suggested a 39% lower risk of kidney failure or death in patients randomly assigned to LPD [10]. A more recent systematic review meta-analyzed studies specifically addressing patients with CKD stages 1–3 and found no reduction in mortality or ESRD after an LPD [11]. Differences in the inclusion criteria, degree of proteinuria or type of protein provided may have affected the results of the studies mentioned above. Because present data are not firmly conclusive, dietary protein restriction cannot be recommended as a *routine* kidney protective strategy for patients with CKD. However, the reported safety of LPDs and their beneficial effects on uremic symptoms are obvious and justify its prescription for most CKD patients.

One concern regarding LPDs is that they might compromise nutritional status in the long term, especially in those individuals with concurrent conditions that would require higher amounts of proteins such as infections, metabolic acidosis or other procatabolic states. Despite this common concern, RCTs show that a LPD does not seem to result in malnutrition [5–7], though patients in studies are subjected to more stringent dietary counseling and control than is common in clinical practice. Monitoring of nutritional status must therefore be implemented if protein-restricted diets are prescribed. Adequate caloric intake must be ensured and at least 60% of the ingested protein must be of high biologic value or contain a high percentage of essential amino acids to ensure net neutral nitrogen balance. Because dietary protein is a source of metabolic acids that stimulate skeletal muscle protein breakdown, LPDs may be associated with less metabolic acidosis. If the patients appear to be at risk of malnutrition, the LPD can be supplemented with essential amino acids and/or keto acids. The use hypercaloric renal-specific supplements in the context of an LPD has been associated with protein intake closer to the target values, better nutritional measures and better adherence to therapy than an LPD alone [12]. Likewise, ketoanalogues of essential amino acids (keto acids) can also be used based on their capacity to neutralize the excessive nitrogen residues through transamination and limit the production of urea, thus breaking the vicious cycle of the disease while at the same time allowing the preservation of nutritional status [13]. It has been postulated that besides the amount of dietary protein, the source of protein could also be important and that vegetable protein or egg whites are preferable [14, 15]. Vegetable sources of protein might have additional benefits that motivate its recommendation in CKD patients such as lower organic phosphorus absorption and, consequently, lower serum phosphate levels and decreased fibroblast growth factor-23 [16]. Vegetarian diets may also decrease the production of uremic toxins such as p-cresyl sulfate and indoxyl sulfate [17], which have been implicated in CKD progression [18]. Finally, a diet high in vegetables might lead to lower endogenous production of acid [19].

Adherence to a protein diet with 0.6 g/kg/day of proteins is often difficult. Nutritional education programs and dietitians' advice are effective in increasing patient adherence to low-protein intake recommendations [20]. The support of the patient by family members and whoever prepares the food is also critical. To maintain this change over time, the LPD prescribed has to be pleasant, varied and not too restrictive. A recent Italian study proposed a simplified approach to an LPD feasible for the patients and for implementation in the clinic [21]. The authors proposed to their patients a simplified vegetarian LPD supplemented with ketoanalogues. The simplified diet was based on a concept of forbidden and allowed foods [forbidden: fish, meat, milk, eggs and derivatives (except in the context of the free-choice meals); every-

thing else is allowed]. The diet was essentially vegan, with an average protein intake of 0.6 g/kg/day and an average energy intake of 30–35 kcal/kg/day, supplemented with ketoanalogues. To improve compliance, 1–3 free-choice meals per week were allowed and the foods are not weighed. Adherence and feasibility were good and the findings were able suggest an easier method to achieve dietary protein restriction.

Salt Restriction

High dietary sodium is an important determinant of blood pressure, predisposing patients with established CKD to salt-sensitive hypertension and fluid retention. Higher dietary sodium intake has been associated with GFR decline in the community [22]. Dietary salt restrictive approaches like the DASH diet [23] are effective in reducing blood pressure. However, there is presently no evidence that a reduction of dietary sodium will retard CKD progression. In individuals with CKD, sodium restriction has been shown to enhance the effects of various antiproteinuric drugs such as angiotensin receptor blockers [24]. More interestingly, an interventional study [25] assigned 176 patients with nondialyzed hypertensive CKD to a low-sodium diet (2,300 mg/day) over 7 days, and reported (vs. a control group) that sodium restriction resulted in a greater reduction in blood pressure as well as a reduction in urine protein excretion. Despite these encouraging findings, intensive reduction in dietary sodium may be difficult to achieve due to poor adherence. The main reasons for poor adherence are (1) worse taste/palatability of low-sodium foods, (2) availability and cost of low-sodium foods, (3) interference with socialization, and (4) lack of perceived benefit and inability to identify low sodium foods. The advice and follow-up of nutritionists is probably needed to improve patient motivation and compliance. Current guidelines recommend an upper limit of 2–3 g of salt per day in nondialyzed CKD patients for blood pressure and volume control as well as for improving the efficacy of antiproteinuric medication [26, 27].

Other Beneficial Dietary Approaches

Recent studies suggest additional potential benefits of healthy eating on CKD progression. In the community, individuals consuming too much saturated fat are more likely to progress to CKD [22]. In those with manifest CKD, a meta-analysis of RCTs addressing the impact of n–3 polyunsaturated fatty acids (present in fish oil) on proteinuria and renal function reported a greater reduction in urine protein excretion with this dietary interven-

tion [28]. When recommending fish intake to CKD patients, however, knowledge of the phosphate-to-protein ratio in different fish species is recommended. Growing evidence suggests potential benefit of dietary fat modification strategies in CKD patients, including increasing the amount of linoleic acid (n–6 PUFA) from vegetable oils and thus reducing the amount of saturated fat ingested [29, 30].

A high consumption of sugary drinks/sodas has been associated with the incidence of albuminuria, CKD and faster GFR decline in the community [31, 32]. However, there is no evidence from interventional studies to support these observational data. An RCT in people with CKD stages 2–3 reported that a low-fructose diet was able to significantly reduce a number of inflammatory biomarkers and blood pressure versus a control group consuming their habitual fructose intake [33]. A recent study found that lower fiber intake was associated with elevated serum CRP levels and increased mortality in people with CKD [34]. Hypovitaminosis D has also been associated with ESRD initiation in people with CKD stages 4–5, an association that is explained in part by fibroblast growth factor-23-dependent pathways [35]. In a series of RCTs, a higher intake of fruits and vegetables was compared to the efficacy of oral bicarbonate in people with CKD stages 1–4. The rationale was that high-alkali fruit intake would reduce the dietary acid load and be able to control acidosis and subsequent kidney injury. In CKD stage 2, both treatments attenuated kidney injury to a similar extent [36]. In CKD stages 3–4, metabolic acidosis was significantly reduced by both treatments (although, as expected, more in the bicarbonate group) [37]. With increased but controlled fruit/vegetable intake, hyperkalemia was not induced [37].

All these associations between healthy nutrients and CKD may be the result of healthy eating in general. Consistent with this notion, increased urine albumin excretion and higher odds of rapid decline in estimated GFR rate have been reported among individuals with consistent Western dietary patterns [2]. In a population-based study, greater adherence to a Mediterranean diet was associated with lower odds of current CKD and was a predictor of mortality in those with manifest CKD [38]. Finally, a healthy diet is often accompanied by other healthy habits that may impact on kidney function. A recent study showed that adherence to a healthy lifestyle (assessed on the basis of smoking habits, BMI, physical activity and dietary quality) was associated with lower all-cause mortality risk in people with CKD stage 3 or more advanced [39].

Phosphate Control and CKD Progression

Because organic phosphorus is bound to protein, the amount of protein eaten will predictably determine phosphorus intake. The intestinal absorption of organic phosphorus is lower if coming from animal sources (absorbed by 40–60%) than from vegetable sources (absorbed by 10–30%). However, inorganic phosphorus presently added to processed foods is almost entirely absorbed in the intestine. Because the amounts of inorganic phosphorus are often not reported in processed food labels, estimation of the real phosphorus intake of CKD patients is challenging and likely exceeds recommendations. Since there are physiological adaptations to counteract excessive phosphorus retention, hyperphosphatemia typically occurs only when patients reach CKD stages 4–5 [40]. This means that dietary phosphorus restriction is generally not necessary in earlier stages. In CKD stage 4–5, elevated phosphate levels were reported to be direct predictors of mortality [41]. Current recommendations for phosphorus intake in CKD stages 3–5 are to reduce intake to 800–1,000 mg/day, in conjunction with use of phosphate binders if considered necessary [4]. Although noncontrolled evidence is not unanimous in this regard, a recent RCT suggested that a low-phosphorus diet is able to decrease serum phosphorus and fibroblast growth factor-23 levels [42]. Another recent RCT showed that the combined prescription of this diet and phosphate binders proved to be more effective than each of these approaches alone [43]. Whenever serum phosphorus is high, regardless of the CKD stage, it seems reasonable to restrict phosphorus intake in addition or not to phosphorus binder prescription.

By reducing the amount of dietary phosphorus absorbed from the gut, phosphate binders help to control serum phosphorus levels and are used by 70–90% of patients receiving hemodialysis in Europe [44]. Clinical trials have confirmed that phosphate binders effectively reduce serum phosphorus in healthy participants, patients not yet undergoing dialysis and patients receiving long-term dialysis for ESRD [45, 46]. Thus, it has been proposed that people with CKD may receive phosphate binders before dietary restrictions are advised. This could help to control serum phosphorus while maintaining high-protein intake and good nutrition, thus avoiding the potential for protein-energy wasting (PEW) and increased mortality associated with protein restriction. In support of this, the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that phosphate binder use was associated with improved survival and better nutritional status [47], perhaps due to a more liberal diet as allowed by phosphate binder use. Prospective interventional studies are needed to confirm these observational data.

Studies have shown that the use of sevelamer- or lanthanum-based phosphate binders can greatly reduce the occurrence of calcification in laboratory models of chronic renal failure. For example, studies of rat vascular smooth muscle cells illustrate that the presence of phosphorus increases the incidence of calcification, and that lanthanum can attenuate this increase [48]. Treatment of rats with chronic renal failure with 3% sevelamer or with 3% lanthanum carbonate reduced the calcification of aortic root lesions to a similar extent [48]. Sevelamer or lanthanum carbonate treatment has been shown to attenuate the development of coronary and aortic calcifications in patients on maintenance hemodialysis to a greater extent than treatment with calcium-based phosphate binders [49]. Two recent studies have shown a similar effect with lanthanum carbonate [50, 51]. However, these potential benefits have not been associated with improved survival in large RCTs.

Phosphorus overload may be detrimental to the cardiovascular prognosis in CKD. Nevertheless, no clinical trial has yet demonstrated that reducing phosphorus intake improves survival in nondialyzed CKD patients or reduces CKD progression. The use of phosphate binders in CKD is based on observational rather than clinical trial data. The few studies available suggest a limited effect of phosphate binders, at least when used in 'normophosphatemic' patients and not in combination with diet [52]. Furthermore, considering the limitations of available studies, more clinical trials and follow-up analyses should investigate the impact of phosphorus metabolism management (nutritional interventions and phosphate binder use) on outcomes at different serum phosphate levels and renal function.

Because oral calcium carbonate affects calcium but not phosphorus balance in CKD stages 3–4 [53], and administration of calcium-containing phosphate binders in hemodialysis patients is associated with increased vascular calcification [54], concern has been raised regarding the safety of excess calcium intake in nondialyzed individuals with CKD. In a calcium balance study, normal individuals and patients with CKD stages 3–4 were in slightly negative to neutral calcium balance on an 800-mg/day calcium diet [55]. Normal individuals were in modest positive calcium balance on a 2,000-mg/day diet, whereas CKD patients on the same diet were in marked positive calcium balance. Furthermore, increased calcium intake significantly decreased 1,25-dihydroxyvitamin D and PTH levels, but it did not alter the serum calcium concentration. On the basis of this study, a diet of 2,000 mg/day of calcium in CKD patients might result in a positive calcium balance with the extra

calcium deposited in tissues leading to calcification. Therefore, it seems reasonable to restrict total calcium intake to the currently recommended dose of 1,500 mg/day [56].

Malnutrition in Patients with Nondialyzed CKD

Complications involving protein-energy status are relatively common in ESRD stages and are associated with poor outcomes and disability. These complications have been collectively termed as PEW. The term PEW was developed in recognition that not all causes of wasting are due to inadequate nutrient intake. PEW is defined as abnormally low levels or excessive losses of body protein mass and energy reserves. Causes of PEW thus include inadequate nutrient intake, but also increased catabolism as induced by systemic inflammation, oxidative stress, imbalance in anabolism/catabolism, metabolic acidosis, abnormal glucose and insulin homeostasis, and vitamin D deficiency [57, 58]. Recently, the role of male hypogonadism (i.e. testosterone deficiency) in nondialyzed CKD patients has attracted renewed attention [59] not only owing to its association with reduced muscle mass and strength [60], but also endothelial dysfunction and risk of cardiovascular events prior to dialysis initiation [61]. Many of these conditions start to become especially apparent in people with CKD when reaching stages 4 and 5. A decline in protein and energy intake is often followed by a worsening in nutritional status. An important aspect to consider in nutritional intake is the content of other nutrients in ingested foods. The dietary restrictions discussed above are necessary in CKD to control hyperkalemia, hyperphosphatemia, and calcium or sodium balance. However, if these restrictions are not accompanied by counseling on alternative food choices, they may result in nutritional deficiencies and appearance of malnutrition. Relatively few studies have addressed the prevalence of malnutrition in nondialyzed CKD patients. Studies defining malnutrition on the basis of hypoalbuminemia report a prevalence of 20–45% [62, 63]. Studies defining malnutrition on the basis of diagnostic tools like subjective global assessment report a prevalence of 18–20% [64–66]. Thus, it is reasonable to state that likely 1 out of 5 people with CKD stages 4–5 will develop PEW prior to initiation of dialysis. The topic of screening and diagnosis of PEW in nondialyzed CKD is not covered in this review, but has been discussed elsewhere [4, 67]. An opinion-based algorithm for clinical assessment and management of malnutrition in nondialyzed CKD has recently been proposed [68].

A critical aspect of malnutrition management in predialysis stages is the amount of energy ingested. Neutral or positive nitrogen balance requires adequate energy intake, and a low-energy intake may directly cause PEW. It is recommended that the daily energy intake in nondialyzed CKD patients be approximately 35 kcal/kg/day in those aged <60 and 30 kcal/kg/day in those aged ≥60 years [56]. These recommendations for energy intake may be modified when examination of an individual's daily energy expenditure indicates different needs. When signs of malnutrition are present, the use of nutritional supplements may be indicated. However, the use of traditional supplements (protein-rich) may be counterintuitive if we advocate an LPD to avoid kidney damage. Hypercaloric supplements providing essential amino acids but with low-protein content could theoretically have some advantages versus traditional supplements, but are more expensive. Unfortunately, no interventional trials of nutritional support in malnourished patients with nondialyzed CKD have yet been published.

Conclusion

Nutrient intake is likely to influence the risk for initiation and progression of CKD as well as some of its associated complications. The evidence linking nutrition with occurrence and prognosis of CKD is unfortunately variable and many nutrients have not been thoroughly investigated. Some topics like salt control and protein restriction have more solid evidence to support their use in clinical practice. However, in the context of present dietary trends, it may not be easy for patients to comply with such restrictions. To date, very little evidence exists on how to manage malnutrition in nondialyzed CKD. Education on nutritional approaches and adaptations in the context of CKD must be a part of patient management at both early and advanced stages. Such programs benefit from the expertise and dedication of nutritionists and dietitians, contributing positively to patient motivation and adherence.

Disclosure Statement

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