Why the Nutritional Management of Acute Versus Chronic Kidney Disease Should Differ

DOES EATING LESS or more protein affect kidney health? To answer this question, it is important to better understand the pathophysiology of renal function as it pertains to protein intake. Consistent data in both animal models and human subjects suggest that a high-protein diet leads to dilation of the afferent arterioles of the glomeruli. This is usually the result of an amino acid surge in the circulation upon a protein-rich meal. Consequently, increased intraglomerular pressure ensues, which results in elevated glomerular filtration rate (GFR), a phenomenon also known as "glomerular hyperfiltration." Hence, there are two important but opposing scenarios vis-à-vis the quantity of the dietary protein intake and kidney function: (1) Higher protein intake can increase intraglomerular pressure, which is useful in the short term when we eat a large protein meal with high-protein content, so that we can ensure effective clearance of nitrogenous end products that are produced from eating too much protein, but in the long term, the resultant glomerular hyperfiltration may cause wear and tear and more loss of nephrons in the kidneys.[1,2] (2) Less protein intake, on the other hand, leads to lower amounts of circulating amino acids, tighter afferent arterioles, lower intraglomerular pressure, and decreased GFR in the short term, which may help protect kidney glomeruli and confer kidney health longevity in the long term.[3] As to what types of proteins (animal- versus plant-based) can accentuate or mitigate these effects, there are limited and inconsistent data.[4,5] A 1990 study by Kontessis *et al*[6] showed that an animal-based protein diet increased GFR more than similar amounts of plant-based proteins and that glomerular hyperfiltration was observed in those eating meat and not vegetable-derived proteins. Nevertheless, until additional studies on the putative differential effects of a plant- versus animal-based diet become available, it is prudent to assume that higher dietary protein of any source increases GFR and may cause glomerular hyperfiltration.

If an amino acid surge in the circulation dilates afferent arterioles and increases blood perfusion and intraglomerular pressure leading to glomerular hyperfiltration, would eating a low-carbohydrate, high-protein diet lead to higher risk of *de novo* chronic kidney disease (CKD)? On the other hand, should patients with acute kidney injury (AKI) receive high-protein nutrition during the acute event, regardless of their underlying CKD, so that glomerular perfusion would be accentuated? In this issue of the ***Journal of Renal Nutrition***, a large cohort study of almost 1,800 healthy adults in Iran by Farhadnejad *et al*[7] shows provocative findings that the highest versus lowest tertile of a low-carbohydrate, high-protein diet was associated with a 48% greater risk of incident CKD.[1] Among the strengths of this study are its prospective design, long follow-up duration of 6.1 years, the large representative study population, and the use of a validated food-frequency questionnaire. Some limitations include measuring the serum creatinine level only once and potential selection bias of having healthier persons. However, the latter limitation would dilute the found associations so that it is possible that a low-carbohydrate, high-protein diet would have an even more deleterious impact across kidney health among populations at large. The evidence from the study by Farhadnejad *et al*[7] suggests that higher adherence to a low-carbohydrate, high-protein diet may increase the risk of incident CKD. There have been several recent studies with similar findings. A recent study in the *Journal of Renal Nutrition* by Malhorta *et al*[8] suggested that among diabetic African-Americans, higher dietary protein intake was associated with greater decline in estimated GFR. A recent study by Esmeijer *et al*[9] reported on the dietary and kidney data of the Alpha-Omega Cohort, a prospective study of 4,837 Dutch patients aged 60-80 years with a prior history of myocardial infarction who took part in a clinical trial of low-dose omega-3 fatty acids.[10] Esmeijer et al found that for each 0.1 g per kilogram ideal body weight per day (g/kg/day) increase in dietary protein intake, the annual GFR decline was accelerated by -0.12 mL/min/1.73 m^2 per year. In yet another study by Jhee *et al*[11] in 9,226 South Koreans from a large national contemporary (2001-2014) cohort, the multivariate adjusted likelihood of kidney hyperfiltration was 3.5-fold higher in the highest versus lowest quartile of the dietary protein intake. As in the Dutch study by Esmeijer *et al*,[9] the Korean study demonstrated a loss of renal function that was faster across higher quartiles of dietary protein intake.[11] Hence, it can be

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argued that while a high-protein diet poses potential harm to the kidneys' health, a low-protein diet extends the kidneys' longevity.

A reasonable question that emerges as a result of the recent population-based studies is whether a high-protein nutrition should be avoided at all costs in the context of any types of kidney disease. Given that elevated amino acid levels in the blood dilate afferent arterioles of the glomeruli and increase renal perfusion and intraglomerular pressure, it can be argued that during an AKI event, patients with or without CKD should receive high-protein nutrition in an effort to increase glomerular perfusion and to ensure faster recovery of the nephrons. This poses the question as to what the best nutritional intervention should be for patients with AKI across different levels of severity of AKI. In this issue of the ***Journal of Renal Nutrition***, Hellerman *et al*[12] conducted a prospective multicenter study on a number of critically ill patients with AKI receiving enteral or parenteral nutritional support in Israel and compared administered, prescribed, and used carbohydrates and lipids. Resting energy expenditure was measured by indirect calorimetry, and the protein catabolic rate was calculated from urine urea nitrogen excretion in nonoliguric patients or by urea kinetic-based methods in patients on renal replacement therapy. The average resting energy expenditure measurement and urea nitrogen appearance were 1,736 ± 409 kcal/day and 12.4 ± 7.0 g/day, respectively. The mean calculated lipid oxidation was 101 ± 74 g/day, the prescribed and administered lipids were on average lower, i.e., 67 ± 33 g/day and 63 ± 37 g/day, respectively. Discrepancies in the opposite direction were observed with carbohydrate oxidation analyses, in that carbohydrate utilization was 106 ± 132 g/day, which was much lower than the prescribed carbohydrate utilization of 187 ± 74 g/day. Hellerman *et al*[12] concluded that critically ill patients with AKI do not receive adequate amounts of macronutrients to support their needs given the large discrepancy observed between measured carbohydrates and lipids and their utilization, in that they use 57% less carbohydrates than expected, while oxidizing 150% more lipids. One relevant issue that was not adequately discussed is whether providing higher protein content in the nutritional supplements for AKI would remedy the said nutrient gap and could enhance kidney injury recovery. Most standard enteral and parenteral nutritional formulas provide a high proportion of energy from carbohydrate followed by lipids, while protein content might not be adequate. The study by Hellerman *et al*[12] shows that 52% of the energy used in patients with AKI was from lipids and 24% from carbohydrates, suggesting that the remaining 24% was from protein, but the investigators did not show amino acid metabolic data analyses of their study. Critically ill patients with AKI often exhibit a hypermetabolic state with high rates of protein nitrogen appearance and lipid oxidation, whereas gluconeogenesis in the kidney may be decreased under AKI, where higher activation of catabolic hormones and excessive release of proinflammatory cytokines exist. Given that an amino acid surge not only dilates afferent arterioles to glomeruli leading to a rise in GFR but it can also provide a resilient source of energy under gluconeogenesis and lipid oxidation impairments, nutritional supplements with higher amounts of protein including essential amino acids should be designed for patients with AKI. There are some guideline discrepancies pertaining to recommended nutritional support in AKI, in that the *European Society of Parental and Enteral Nutrition* (ESPEN)[13] recommends 20-30 Cal/kg/day but only 0.6-0.8 g/kg/day of protein administration, and these ESPEN guidelines also suggest adjusting the latter target for patients under extracorporeal therapy (such as intermittent dialysis) and those under continuous renal replacement therapy to increase protein to 1.0-1.5 and up to 1.7 g/kg/day, respectively. Guidelines from the *American Society of Parental and Enteral Nutrition*, on the other hand, recommend 25-30 kcal/kg/day, including a target protein administration of 1.2-2.0 g/kg/day.[14] Given that higher protein and amino acid administration in AKI may have salutary impacts on both GFR and unmet nutritional needs, the ESPEN and *American Society of Parental and Enteral Nutrition* guidelines could benefit from amendments to highlight the importance of higher protein administration for patients with AKI.

It is important to note that high ranges of protein intake of 1.2-1.4 g/kg/day or higher, be it parenteral or enteral, may also be temporarily recommended to any patient with CKD, regardless of CKD stage, with signs of protein-energy wasting (PEW) or at imminent risk of PEW, while low-protein diets of 0.6-08 g/kg/day should be the default target for stable CKD patients at all times.[3] Relevant to the unmet need to more effectively identify patients at risk of PEW, in this issue of the ***Journal of Renal Nutrition***, Tan *et al*[15] report that a bioelectrical impedance analysis-derived phase angle can reliably predict PEW in chronic hemodialysis patients. However, while dialysis patients at risk of PEW may benefit more attention with focused nutritional interventions, we believe that in all chronic dialysis patients without residual kidney function, a relatively high protein intake target of 1.2-1.4 g/kg/day should be the recommended base, and these patients should also eat during hemodialysis.[16] In a recent issue of the ***Journal of Renal Nutrition***, Choi *et al*[17] evaluated the safety of providing supplemental meals during hemodialysis to boost the protein intake. They found no adverse effects of the meals consumed during dialysis treatment, and, most notably, they were able to use a varied meal plan that included a vegan approach.[17] However, an important challenge is to maintain a high protein intake while avoiding concomitant high-salt consumption. In this issue of the

Journal of Renal Nutrition, Hu *et al*[18] assessed the impact of baseline dietary self-efficacy on the effect of a dietary intervention to reduce sodium intake in patients receiving maintenance hemodialysis and found that younger age and perceived income inadequacy were among the determining factors for a low self-efficacy in these patients. These findings[18] may suggest that those with low self-efficacy may benefit the most from interventions that are based on social cognitive therapy to reduce dietary sodium, and hence, more attention should be paid to underlying behavioral constructs such as self-efficacy.

Of note, a low-sodium diet is also important for the management of earlier stages of CKD, including for the management of proteinuria where a low-protein diet is preferred. The renoprotective effects of a low-protein diet can be synergistically enhanced with the direct effect of a low-sodium diet, as well as the effect of angiotensin pathway modulators such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which dilate the efferent arteriole and reduce intraglomerular pressure and glomerular damage.[3] In this issue of the ***Journal of Renal Nutrition***, Jardine *et al*[19] examined the impact of sustained dietary salt reduction on albuminuria in approximately 2,000 adults who had participated in a cluster randomized trial in 120 villages in rural China, where villages were randomized to a sodium-reduction program of education and access to reduced-sodium salt substitute or control.

The investigators reported that the program resulted in a 0.322-g/day decrease in sodium intake and less albuminuria (8.85 mg/g versus 10.53 for intervention vs control) with an odds ratio for albuminuria of 0.67 (95% confidence interval, 0.46-0.99). These findings suggest that the multifaceted intervention reduced the likelihood of albuminuria by 33%.[19] In another study from rural China in this issue of the ***Journal of Renal Nutrition***,[20] the variations in body mass index, waist circumference, and waist-to-height ratio as predictors of CKD were examined among 4,221 adults aged 27 to 95 years, and associations between these abnormalities in body composition metrics and CKD were found in this rural Chinese population. Of note, in a review of literature on obesity paradox and reverse epidemiology in this issue of the ***Journal of Renal Nutrition***, Imam and Coleman[21] have suggested that survival advantages of higher body mass index in dialysis patients may not hold in peritoneal dialysis patients, in whom obesity may be associated with worse outcomes.

There are other relevant articles on food consumption as well as nutritional status, interventions, and outcomes in this issue of the ***Journal of Renal Nutrition*** including a review article on food additives that can worsen the potassium burden and increase the risk of hyperkalemia.[22] Given that the use of potassium additives in processed foods has been growing with potassium amounts far exceeding naturally occurring potassium levels in fresh fruits and vegetables and other heart-healthy foods and given that added potassium may be more readily absorbable than the natural potassium in high-fiber whole foods, a new approach to dietary potassium restriction by relaxing the healthy food intake and focusing on restricting processed foods is warranted.[23]

In another study, to better understand the implication of CKD and its severity on food consumption according to sociodemographic and geographical characteristics and CKD treatment, Santin *et al*[24] analyzed the data from 60,202 Brazilians who participated in their National Health Survey including 5,480 treated and 5,294 untreated patients with CKD, as well as 548 patients receiving dialysis and 517 patients with a kidney transplant. The investigators reported that the CKD group, in particular those undergoing dialysis therapy, exhibited a lower regular consumption of beans, alcoholic beverages, and salt in excess and reflected that food consumption in people with CKD may be substantially influenced by sociodemographic and geographical characteristics.[24] In a pilot study by Hage *et al*[25] of 20 patients with nondialysis CKD stage 3 to 5 with a serum bicarbonate level below 22 mmol/L, administering 1 g of oral sodium bicarbonate 3 times a day for 4 weeks increased urinary excretion of soluble α-Klotho but did not increase serum α-Klotho. Given that increased serum Klotho levels may confer protective cardiovascular effects in CKD, additional studies are warranted to examine whether nutritional interventions can modulate Klotho levels in patients with CKD.[26] Finally, in a large contemporary cohort study of 29,124 US veterans with advanced CKD who transitioned to dialysis therapy between 2007 and 2015, Hsiung *et al*[27] showed both lower levels of serum albumin and a decline in serum albumin over time were associated with higher risk of mortality and hospitalization rates in the first year after transition to dialysis therapy. A low serum albumin level is among the strongest predictors of mortality in both nondialysis and dialysis-dependent CKD patients and heralds the impending or preexisting PEW, a condition characterized by metabolic and nutritional changes leading to depleted visceral and peripheral stores of protein and energy. The study by Hsiung *et al*[27] highlights, for the first time, the residual deleterious effect of low serum albumin level that can last even after transitioning to maintenance dialysis therapy. As to whether a low serum albumin level in patients with CKD is amenable to nutritional interventions, we expect that discussion will be continued on this and other topics and hope that the *Journal of Renal Nutrition* continues to provide the ultimate platform for such productive scientific debates and discoveries.[28]

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