Title
The Future of Nutrition in Kidney Disease: Plant-Based Diets, Gut Microbiome, and Beyond

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Authors
Joshi, Shivam
Moore, Linda W
Kalantar-Zadeh, Kamyar

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The Future of Nutrition in Kidney Disease: Plant-Based Diets, Gut Microbiome, and Beyond

THE FUTURE OF nutrition in kidney disease looks different from its past. Historically, the so-called "renal diets," aimed predominantly at reducing potassium content, have eschewed consideration of the microbiome, the inclusion of plant foods or the bioavailability of micronutrients such as potassium and phosphorus, but as this issue of the *Journal of Renal Nutrition* shows, these concepts are here to stay. Several recent narrative reviews have extensively discussed the potential benefits of a plant-based diet and a low-protein, plant-dominant diet, also known as a "PLADO diet."[1,2] For reference, plant-dominant diets derive at least 50% of the protein from plant sources but less than those seen in plant-based diets. These types of diets have the potential to ameliorate metabolic acidosis, chronic kidney disease (CKD) progression, hyperphosphatemia, pill burden, CKD-related hypertension, nephrolithiasis, mortality, and the health of the microbiome. Further, plant-based diets have the added benefit of possibly improving the two main causes of CKD and end-stage kidney disease: diabetes and essential hypertension. Despite these positive effects, these types of diets have been avoided for an equally long list of potential risks and barriers, including hyperkalemia, hyperphosphatemia, palatability, cost, and tradition. However, as evidence accumulates, it is becoming clearer that a low-protein, plant-based diet such as PLADO may not create these issues. Some risks, such as hyperkalemia, may have been overstated.[3] Furthermore, other issues, such as serum phosphorus levels may actually improve. Consequently, our perception of the risk-benefit ratio has gradually been tilting in favor of the PLADO strategy.

The rising popularity of this dietary approach within kidney disease can be seen in the titles of some of the articles in this issue, mention of plants and plant-based diets within the text, and the references to other articles on the subject. Several articles in this issue devote themselves entirely to this subject. For example, Picard et al.[4,5] builds off her previous work on potassium additives and bioavailability published in this Journal in 2019 by analyzing the content of patient handouts on dietary potassium restriction in an article published in the current issue. In total, 18 handouts from Canadian health agencies in six provinces were analyzed. The five most commonly restricted foods were bananas, potatoes, oranges, cantaloupe, and avocados, likely based on their total potassium content. However, as Picard[5] has pointed out previously, the reduced bioavailability of plant-based potassium may reduce absorption of potassium as opposed to unnaturally added potassium as preservatives or the potassium found in animal foods. Indeed, potassium additives and animal-based potassium may have higher bioavailability and may be more clinically meaningful on the burden of potassium in CKD and end-stage kidney disease, especially because plant food consumption has been historically low in patients with kidney disease.[6]

Given the evolving evidence of plant-based and plant-dominant diets in the kidney community, Moore[7] has written a patient education article in this issue to help frame this diet for patients with kidney disease. In this short review article, Moore[7] provides a half-dozen key points on plant-based diets in CKD that are supplemented with important references on the topic along with a multicolored patient-friendly handout on the subject. Not only can the article and handout be used to educate patients but it can also be used to educate healthcare workers who take care of patients with CKD. Although this brochure does recommend limiting high-potassium fruits and vegetables in CKD stages 4 and 5 to avoid hyperkalemia, it is likely that future handouts will be clearer and more unified as more evidence, such as the work of Picard et al.,[4,5] emerges.

Embedded in this issue is the theme of phosphorus metabolism in kidney disease, which has important overlaps with plant-based diets. In an article in this issue, a group of Irish kidney dietitians have written an updated review on their national low-phosphorus kidney diet sheet by considering four key concepts in phosphorus metabolism.[8] In their update, Byrne et al.[8] first discuss the issue of phosphorus bioavailability, which is affected by the proportion of dietary phytate from plant sources, given that the human gut lacks the enzyme phytase to release phosphorus from phytate, and whether phosphorus additives are present with near 100% bioavailability. The second concept reviewed is the safety and benefit of increasing plant protein, which they recommend a "judicious

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Address correspondence to Shivam Joshi, MD, Department of Medicine, NYU School of Medicine, 550 First Avenue, New York, NY 10016. E-mail: shivam.joshi@nyulangone.org

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approach" given potential concern of hyperkalemia. Although not discussed in detail, the existing evidence suggesting hyperkalemia with plant-based protein is slim to none and a less reserved recommendation may have been warranted given the potential benefits of these foods.[2] Third, the authors discuss the phosphorus:protein ratio but neglect to incorporate their first point regarding phosphorus bioavailability. When taking into account phosphorus bioavailability, plant proteins have a more favorable phosphorus:protein ratio.[9] Finally, the authors discuss their fourth topic: phosphorus additives, which is a recurring issue in both industrialized and emerging economies globally. In the United States, phosphorus additives are disclosed, but not quantified, making dietary restriction instructions difficult. Nonetheless, phosphate additives should be avoided in patients with kidney disease of any type, stage, or severity.

Building on the issue of how difficult phosphorus restriction is in industrialized countries, Conley et al.[10] published their findings in this issue of a substudy of the "IMPROVE-CKD Study" analyzing phosphorus intake in ninety Australian adults with CKD stages 3b and 4. The researchers found that mean phosphorus intake was 1,544 mg/day and 96% of individuals exceeded the daily intake of phosphorus (1,000 mg/day). The single largest contributor to daily dietary intake as per the minor food group was poultry (Table S2). Rounding out the top five were milk, beef, and cheese, which is not surprising given their higher phosphorus bioavailability when compared with plant foods and the relative high consumption of animal-based proteins in industrialized societies.

Dietary phosphorus restriction is also difficult for children with kidney disease. In this issue, Oladitan and Van-Sickle[11] describe an innovative point system that was used to successfully help a 14-year-old male with stage 4 CKD limit dietary phosphorus intake. The point system is based on the conversion of 50 mg of dietary phosphorus to 1 point and daily points are limited to 20 points of phosphorus ingested, which is equivalent to 1,000 mg of dietary phosphorus per day. In this case study, his recorded phosphorus intake remained 1,000 mg each day without signs of malnutrition.

The gut microbiome in kidney disease is another area of growing interest, especially when considered with the putative effects of plant-based diets. In this issue, Stanford et al.[12] performed a cross-sectional analysis of twenty-two adults in a clinical trial receiving maintenance hemodialysis therapy to evaluate associations between plant-based diet quality, uremic toxins, and the microbiome constellation. In this pilot study, authors found that patients on dialysis who had a higher adherence to a plant-based diet index were associated with a lower level of indoxyl sulfate, a common uremic toxin. This finding has been shown previously when omnivorous diets have been compared with vegetarian diets in patients on dialysis and also as per fiber intake.[13-15] However, Stanford et al.[12] also showed that an *unhealthy* plant-based diet index was associated with a higher level of indoxyl sulfate, adding to the existing evidence that plant-based diets are not all created equally.[16]

Another article in this issue also combines the popular topics of plant-based diets and gut microbiome in the form of a review on the organic compound trimethylamine N-oxide (TMAO). TMAO has been associated with cardiovascular disease and mortality in patients with CKD. TMAO levels rise with declining kidney function *and* with the consumption of certain animal-based foods high in the precursors of TMAO, such as carnitine and choline, which are found in red meat, eggs, and some nonfish seafoods. Plant-based diets do not lead to significant TMAO production. Much of the current evidence on TMAO comes from patients without CKD as there are no experimental or clinical studies of plant-based diets on TMAO in CKD. However, the existing evidence is suggestive that a plant-based diet may have the potential to reduce the risk of cardiovascular disease, mortality, and even CKD progression through a reduction in TMAO levels and presents itself as an exciting area of future research within the domain of plant-based diets and renal nutrition.

While we await direct research of plant-based diets on TMAO production in CKD, we can contemplate the results of the study by Lim et al.[17] also published in this issue. In their randomized, double-blind, placebo-controlled trial, Lim et al.[17] evaluated the effect of a probiotic supplement on various biomarkers in a group of 56 patients on hemodialysis. The study demonstrated that 6 months of probiotic supplementation did not affect hemoglobin, blood urea nitrogen, blood sugar, inflammatory markers, or p-cresyl sulfate, a uremic toxin. However, 6 months of probiotic supplementation did beneficially lower indoxyl sulfate levels compared with those in the placebo group. This adds to an existing collection of studies that has produced mixed results on the effects of probiotics on uremic toxin production and may be related to several study-specific factors, including the strain of the probiotic used, the dose of probiotics used, and the length of the study. However, it should be noted that a recent study of a mouse model of CKD has shown that a diet of sulfur-containing amino acids reduced uremic toxin production through inhibition of the enzyme tryptophanase.[18]

This issue of the *Journal of Renal Nutrition* features another article on the use of probiotic supplements in end-stage kidney disease, specifically patients on peritoneal dialysis. In their randomized controlled trial, Pan et al.[19] evaluated 166 patients on peritoneal dialysis randomly assigned to either a control group or a daily dose of probiotics for 2 months and found decreases in the levels of hs-CRP and IL-6 in the intervention group. They also noted higher serum albumin levels, upper arm circumference, triceps skinfold thickness, physical function, and social functioning in those receiving the probiotics. The mechanisms for the significant improvements after probiotic supplementation are not well understood but are thought to be related to resultant changes in the gut microbiome.

In this issue, several articles are unrelated to either plant-based diets or the microbiome but have other importance for renal nutrition. Tuokkola et al.[20] evaluated the patient records of 33 children receiving dialysis to better understand levels of micronutrient intake, which is important for the growth and development of children. Children receiving a renal-specific formula met their age-specific requirements for vitamins and minerals, but children who were not on supplementary feeding demonstrated low intakes of zinc, iron, calcium, and vitamins D, B1, B2, and B6 and may need a multivitamin and mineral supplement.

On a similar note, adults on dialysis are also susceptible to inadequate nutrition in the form of protein-energy wasting partly due to the reduction in food consumption in those with kidney impairment. Mouillot et al.[21] studied the desire of protein-rich foods in dialysis-dependent patients during their days with versus without dialysis. In this pilot study of 24 patients, the desire of protein-rich foods was higher on dialysis treatment days than on days without dialysis and correlated with decreased concentrations of plasma amino acids suggesting that protein-rich foods may be recommended during and immediately after dialysis treatment to facilitate protein ingestion. This evidence builds on previous studies that have shown benefits of the consumption of high-protein meals during dialysis.[22,23]

As seen in this issue of the *Journal of the Renal Nutrition*, the current state of kidney nutrition is evolving, not only in evidence but also in topic. We are now witnessing an explosion of research in areas such as the microbiome, the bioavailability of elements such as phosphorus and potassium, and plant-based and plant-dominant diets. Ultimately, this research will help improve the care of patients with kidney disease, one meal at a time.

Shivam Joshi, MD
Department of Medicine, New York University School of Medicine, New York, New York

Department of Medicine, NYC Health + Hospitals/Bellevue, New York, New York

Linda W. Moore, PhD, RDN
Houston Methodist Hospital, Houston, TX

Kamyar Kalantar-Zadeh, MD, MPH, PhD
University of California Irvine, Orange, CA

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