

Editorial

Dietary sources of protein and CKD progression: the proof may be in the pattern

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The medieval philosopher Moses Maimonides (Spain, 1135-1204) wrote that “*No disease that can be treated by diet should be treated with any other means*”. Not so long ago, before we had the means of dialysis therapy, and still today in many parts of the world, diet represents the sole management strategy in end-stage kidney disease (ESKD).

Arguably the most common dietary prescription for people with CKD is a low protein diet, on the premise it may retard chronic kidney disease (CKD) progression, ameliorate uremia, kidney stone formation, gout, hyperphosphatemia, and gut-derived uremic toxins.¹ However, the effectiveness of low protein diets have been debated for decades, particularly the paucity and often conflicting evidence underpinning progression to ESKD² or all-cause mortality.³ One potential explanation for the conflicting evidence, which is gaining momentum in the literature, is the discussion of the optimal level and source of dietary protein, specifically the type of animal versus plant-based proteins.⁴

Emerging studies suggest that plant proteins are more protective than animal protein diets in the primary prevention of CKD. A recent analysis of NHANES III participants with reduced eGFR showed that protein consumption from plant-based sources was associated with significant lower risks of death compared to animal proteins (HR 0.85, 95% CI 0.75-0.96;p=0.01).⁵ In the Nurses’ Health Study,⁶ women with mild CKD consuming a high

animal protein diet had significantly greater decline in GFR than women consuming more plant protein (show data). A small clinical study in healthy volunteers initially supported the notion that plant-proteins are less harmful than animal proteins, even when matched for total protein intake, and independent of fiber added to the diet.⁷ Meta-analysis of high versus normal protein diets demonstrate a diet high in animal protein significantly decreases the GFR in subjects without CKD. Conversely, the authors found insufficient evidence to prove plant-proteins delay the onset of CKD more so than animal proteins.⁸

In this issue of the *Journal*, we are presented with a large longitudinal data set from the Atherosclerosis Risk in Communities (ARIC) Study⁹ involving 11,952 U.S. community-dwelling adults free of CKD, diabetes, cardiovascular disease and heart failure. Sources of dietary protein intake were ascertained from validated food frequency questionnaires grouping protein from unprocessed red meat, processed red meat, red and processed meat intake (combined), poultry, fish and seafood, eggs, high-fat dairy products, low-fat dairy products, nuts, and legumes. During a mean follow up of 23 years, individuals consuming the highest quartile of vegetable protein had a reduced Hazard Ratio (HR) of incident CKD of 24% in a multi-adjusted analysis ($p < 0.002$). Across all levels of protein intake, there was no significant protection of delaying incident CKD. However, when the analysis targeted individual food groupings, the deleterious effects of red meat proteins on kidney health became more apparent. There were significant increased risks of developing CKD for those who consumed more protein from red and processed meats (HR 1.23; $p < 0.01$), whereas the CKD risk was lower among those with a higher consumption of low-fat dairy proteins (HR 0.75; $p < 0.001$), fish and seafood (HR 0.89; $p < 0.01$), nuts (HR 0.81; $p < 0.01$), and legumes (HR 0.83; $p < 0.03$). Haring and colleagues go a step further in their analysis, showing that if an individual could simply substitute one serving of red and processed meats for one serving per day of the abovementioned protein sources, the risk of incident CKD would be significantly reduced from 20%, 18%, 14% and 31%, respectively.

This well-performed epidemiological analysis complements a previous investigation from the Singapore Chinese Health Study, that similarly reported on the deleterious effects of high red meat intake and progression to ESKD in an Asian population.¹⁰ That study suggested that simply substituting one serving of red meat with either one serving of poultry, fish, eggs, or soy/legumes can result in significant declines in ESKD risk, of 62%, 49%, 45%, and 50%, respectively. In comparison, the Asian estimates of these substitution exercises are markedly more pronounced than the analysis from Haring et al., an issue perhaps attributed to the distinctly different habitual dietary pattern in Singapore versus the U.S. (lower consumption of fish, higher consumption of red meat and processed foods).^{11,12} In any case, evidence goes in line with a recent meta-analysis concluding that a plant-protein based dietary pattern to significantly reduce the risk of all-cause mortality in individuals with CKD.¹³

Are these associations explained by plant-protein *per se*, by the overall dietary pattern that aligns with a higher plant-protein intake, or by the healthier lifestyle that presumably accompanies a plant-rich diet?

Animal proteins, in comparison to plant proteins, are of high biologic value (higher proportion of amino acids are absorbed by the gut) and more ‘complete’ in their amino acid profile. They have therefore been historically viewed as superior (in terms of the quality of nutrients provided) to non-animal (plant-based) sources.⁴ However, these differences in amino acid composition may render different effects on kidney function. Individuals with high plant protein and low animal protein intake consume greater proportions of cysteine,

proline, glycine, alanine and serine and smaller proportions of the other 13 amino acids versus individuals with lower plant protein and higher animal protein intake. Seminal studies dating back 25 years suggested these differences, particularly in glycine and alanine content, may make protein sources impact differently on kidney damage.^{14,15}

Plant-proteins are predominantly alkaline-inducing, higher in inorganic phosphates (phytates, which have a poor absorption in the intestine), and come from foods that are inherently lower in saturated fat and overall calories (**Table**). A diet with a higher plant-based protein intake was found to be associated with higher bicarbonate levels and improved phosphorous balance in patients with non-dialysis CKD.¹⁶ Clinical investigations support this association, finding that higher intake of fruits and vegetables reduce the renal acid load, blood pressure, and overall body weight in people with established CKD.¹⁷ Diets rich in plant-based proteins have also been found to decrease serum creatinine, C-reactive protein, and proteinuria in CKD,¹⁸⁻²⁰ which in addition, when paired to higher fiber intake, is associated with reduced nephro-vascular uremic toxin production.²¹ In a crossover trial in 9 patients with non-dialysis CKD, one week of a predominantly plant protein diet prepared by clinical research staff, equivalent in nutrients to a meat-based diet led to decreased serum phosphorus and fibroblast growth factor 23 levels.¹⁰

Nonetheless, a person consuming a diet rich in plant-protein is perhaps more aware of healthy eating or a healthy lifestyle, and these are residual confounding factors that make drawing conclusions from epidemiology in this area challenging. In fact, the benefits of consuming a plant-rich dietary pattern probably go beyond source of protein, and could be attributed to the overall foods and nutrients consumed together²² (**Table**). Further differences in diets with a plant-based intake also include a higher intake of fruit and vegetables (with vitamins and antioxidants),²³ fish and omega-3 fatty acids,²⁴ legumes, wholegrain cereals and nuts,^{25,26} and at the same time a lower consumption of sodium,²⁷ red meat,²⁸ saturated fats,²⁹ and common phosphate additives.³⁰ At the end of the day, this evidence is in keeping with the dietary advice given in healthy eating guidelines to the general population,⁴ and may give rationale to public health strategies for primary CKD prevention. Although it is a tempting argument, based on these emerging data, that the CKD diet should be more liberalised to 'allow' for these higher plant-based intake, we must bear in mind that observational analyses in population samplings with low eGFR may not necessarily extrapolate to referred patients undergoing dietary management with CKD. Observational and interventional studies are required in these referred and managed patients in order to test the hypothesis of the beneficial effects of liberalized diets in the context of the delicate equilibrium of phosphate and potassium intake.³¹

To conclude, the exciting paper of Haring et al.⁹ suggests we should consider the differences between protein sources in retarding CKD progression. Because plant protein is not consumed in isolation, the way of implementing these observations into clinical practice is by targeting changes in the overall pattern of eating. Adopting a patient-centered educational approach which shifts focus onto foods, such as wholegrains, fruits, vegetables, as well as proteins from poultry and seafood, rather than 'protein' per se, may be of benefit for both the translation of the message and also for disease management. This article furthers our understanding on how substituting foods rather than nutrients affect clinical outcomes for CKD patients. We hope this paper encourages these discussions and may lead to future intervention studies to test this impeding question: can a plant-based dietary pattern matched for protein be more effective in retarding CKD progression than a low protein diet alone?

Table: Key differences in the nutrition profile of plant and animal proteins

	Plant protein	Animal protein
Calories	Low	High
Essential amino acids	Not complete – exception is quinoa. <i>Simple meal planning allows patients to complete the essential amino acid profile</i>	Complete
Saturated fat	Low	High
Unsaturated fat	High	Low
Fiber	High	Low
Iron	Non-haem iron*# <i>Present in beans, spinach, raisins, cashews, oatmeal, cabbage, tomato juice</i>	Haem iron Highly bioavailable
Sodium	Low	High
Potassium	High Low potassium options if required	Low
Phosphate	Low* Lower phosphate-protein ratio	High Higher phosphate-protein ratio
Uremic toxins	Low Harbors saccharolytic bacteria	High Harbors proteolytic bacteria
Antioxidants	High	Low
B ₁₂	Low <i>Present in brown bread, muesli, pickled cucumber, sauerkraut</i>	High
Calcium	Low* <i>Present in tofu, mustard and turnip greens, bok choy, kale, spinach</i>	High in dairy foods
Folate	High	Low
Magnesium	High	Low <i>Meat and fish are sources of magnesium</i>
Zinc	Low* <i>Present in wholegrain breads, cereals, oats, brown rice, nuts, seeds, legumes, tofu, soy, fortified breakfast cereals</i>	High

*Higher intake of phytic acid in plant protein diets can decrease absorption. # Vitamin C foods increase absorption.

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