Bon Appétit: Time to Eat for Better Kidney Health

We all need to eat (and each of us almost always has a number of extreme food likes and dislikes), which may be why research on dietary factors and medical conditions continues to garner substantial interest well beyond the traditional scientific community and consistently infiltrates the general public media. Yet under the surface of each tidy sound bite or headline with proclamations such as "Lycopene Linked to Reduced Stroke Risk" in the New York Times[1] or "Diet Sodas May Hurt Kidneys" on National Public Radio,[2] the science of studying nutrition and chronic diseases is complex and challenging.

For example, with the possible exception of interventional trials of single nutrient supplements (eg, eicosapentaenoic acid fish oils or cholecalciferol), how individual dietary intake is assessed in large study cohorts is often complicated. Do we focus on quantifying individual nutrients (eg, fiber, protein, or vitamin E), specific foods (eg, number of eggs or grams of alcohol intake), or dietary patterns (Western, Mediterranean, or DASH-style diet)? How accurately is dietary intake quantified using semiquantitative food frequency questionnaires, of which there are several different versions? Is it really a sound approach to even use short-term daily food diaries as the gold standard to validate food frequency questionnaires?

Although performing timed 24-hour urine collections to evaluate sodium intake or using gas chromatography on adipose tissue to assess fatty acid intake may be more accurate, these measures are cumbersome, and the additional expense may be exorbitant in large cohort studies. Moreover, all these considerations apply for each time point at which dietary intake may be measured; longitudinal studies with repeated measures of dietary factors add an additional methodologic complication of intraperson variation in diet over time. For example, sequential surveys of the US population between 1988 and 2004 suggest that total meat consumption has increased in men but decreased in women over time.[3] Correspondingly, this complexity raises the issue of whether cumulative effects of diet over many years versus recent shorter term dietary effects are of concern.

The impact of diet also depends on the disease outcome of interest. For example, acute asthma exacerbations or other short-term medical outcomes would focus on more immediate and recent dietary intake. In contrast, whether defined as estimated glomerular filtration rate decline or increasing albuminuria/proteinuria, CKD progression is an entity that often takes many years to unfold. Therefore the challenges of studying associations between diet and decline of kidney function include accurate measurements of dietary intake, estimated glomerular filtration rate, and albuminuria in a repeated longitudinal manner. Although baseline low levels of albuminuria, even in the traditional "normal" range (<30 μg/mg) have been identified as an important predictor of cardiovascular disease and all-cause mortality in the general population,[4,5] assessing albuminuria changes with repeated measures longitudinally is challenging because of decreased accuracy in measuring urinary albumin-to-creatinine ratios when albumin concentrations are less than 20 mg/L[6] and because there is relatively large intraperson day to day variability in urinary albumin concentration (mg/L), timed urinary albumin excretion rate, or albumin-to-creatinine ratios.[7] In fact, mean within-person coefficients of variation are reported as 34% to 40%.

This issue of *Advances in Chronic Kidney Disease* spotlights the current medical knowledge in nutrition and kidney diseases. Although the hypotheses around high dietary protein intake and progressive kidney disease through a mechanism of hyperfiltration have been taught for decades, relatively recent scientific advances in nutritional epidemiology have resulted in an opportunity to further examine relationships between diet and CKD. Importantly, nutritional epidemiology has moved beyond quantifying individual nutrients to looking at individual foods or dietary patterns.

Historically, malnutrition has been a major clinical focus in kidney disease. However, caloric excess and obesity are probably more common than malnutrition now among adults with all stages of kidney disease. Obesity itself is a known risk factor for end-stage kidney disease, and this may be due to acceleration of decline in kidney function mediated by obesity and obesity-related comorbidities. Dr. Tuttle and colleagues discuss potential mechanisms whereby obesity may heighten risk for end-stage kidney disease. Although obesity may be detrimental to an individual with early stages of kidney disease, overall survival may be better in patients receiving dialysis who are obese than in patients receiving dialysis who are not obese. Dr. Friedman discusses the potential difficulties in assessing the impact of obesity on overall survival in dialysis patients. He also summarizes findings from short-term studies assessing weight loss in patients who have undergone kidney transplantation or who are receiving maintenance dialysis.

Obesity is the result of an imbalance between caloric intake and caloric expenditure. Diets high in processed

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foods and low in fruits and vegetables tend to be calorically dense. More than 2 decades ago, high caloric intake was shown to promote kidney injury in animal models. In fact, caloric restriction strongly ameliorates glomerulosclerosis after subtotal nephrectomy. The article by Dr. Kramer postulates that high caloric intake itself modulates adiponectin expression by the energy-dependent NAD-dependent deacetylase sirtuin 1 (silent mating type information regulation 2 homolog). Thus higher caloric intake itself should also be considered a mediator or comediator of kidney injury in the obese state.

Diets high in processed foods are also high in sodium and phosphorus additives, which are both linked to direct and indirect risks for CKD progression. The review by Dr. Guiterrez provides an in-depth look at the historical aspects of sodium additives and how the current government regulation of food additives may impact future attempts to lower the sodium and phosphorus added to processed food.

In addition to sodium and phosphorous, high fructose corn syrup may be the most common food ingredient in processed foods; it is included in soda, breads, pancake syrup, ketchup, jelly, cereal, and cookies. The potential harm from consumption of high fructose corn syrup has been reviewed in several previous articles. In this issue of *Advances in Chronic Kidney Disease*, however, Dr. Shoham and colleagues summarize data from existing observational studies and conclude that no convincing association has been demonstrated between high fructose corn syrup consumption and the incidence or progression of kidney disease. However given the strong overlap between high fructose corn syrup consumption, total caloric intake, and potential factors that may heighten the risk of kidney disease, such as diabetes and obesity, it may be difficult if not impossible to disentangle the impact of one particular nutritional factor such as high fructose corn syrup on kidney disease risk. For example, as discussed by Drs. Scialla and Anderson, the dietary acid load of a meal may influence kidney disease progression, especially among individuals with reduced nephron mass. Their review provides an elegant discussion of how the dietary acid load of a meal depends not only on its protein content but also on the absolute amounts of fruits and vegetables. In the setting of a high dietary acid load, each nephron must augment ammoniagenesis, and this may be maladaptive in the setting of a limited number of nephrons. Diets enriched with fruits and vegetables may be beneficial in kidney disease because of a lower dietary acid load.

Diets high in fruits and vegetables in addition to low-fat dairy products may also benefit individuals with kidney stone disease. Drs. Heilberg and Goldfarb review the current state of science for optimal nutrition for kidney stone prevention while emphasizing that the effectiveness of nutritional interventions for kidney disease are not supported by randomized controlled trials, and long-term adherence to a particular diet remains uncertain. Thus primary and secondary kidney stone disease prevention must continue to emphasize the importance of increasing fluid intake to reduce the concentrations of stone-forming salts.

Nutritional factors may be one of the most important modifiable risk factors in patients with stage 3 and stage 4 CKD for slowing disease progression. Ms. Filipowicz' and Dr. Beddhu's survey of the relevant published medical literature suggests that lower dietary sodium and higher fruit and vegetable intake may be key components to preserving kidney function in moderate to severe CKD, but rigorous randomized trials are required to validate associations identified in observational studies.

Finally, optimizing nutrition for individuals receiving hemodialysis and peritoneal dialysis continues to challenge clinicians who care for adults and children with kidney disease. Dr. Ikizler provides an in-depth look at mechanisms whereby protein energy wasting (PEW) develops in patients who are dependent on dialysis. He also discusses studies that have examined intervention strategies for adults with PEW who are receiving dialysis. PEW is also a concern in patients receiving chronic peritoneal dialysis, and Drs. Tennankore and Bargman review the diagnostic tools available to diagnose PEW and present therapeutic strategies for maximizing nutritional status in the peritoneal dialysis population.

Over the past several decades, treatment of kidney disease has focused mainly on pharmaceutical interventions for blood pressure and glucose control as well as management of anemia. Nutritional management should be a cornerstone therapy for any chronic medical disease, including all stages of kidney disease. The wide range of topics covered in this issue of *Advances in Chronic Kidney Disease*, including nutritional considerations in kidney stones, kidney disease prevention and progression, and end-stage kidney disease, not only summarize existing studies but also highlight evidence gaps whereby future research may provide the greatest impact.

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