Food for Thought: Diet as a Risk Factor for CKD

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There are over 15.5 million people with stage III CKD in the United States [1]. Although stage III CKD is sometimes dismissed as ‘age-related eGFR decline’ and not a true pathological process, in large meta-analyses, compared to a reference eGFR of 95 ml/min/1.73 m², those with stage III CKD had twofold higher cardiovascular mortality after adjusting for age and other factors [2, 3]. Given the large number of individuals with stage III CKD and its cardiovascular relevance, stage III CKD is very important from a public health perspective.

Therefore, interventions that can potentially decrease the incidence of CKD are also of public health importance. However, this has been an understudied topic. The first reason is probably the above-stated dismissal of stage III CKD as biologically irrelevant. The second reason is the difficulty of studying this topic as an examination of incident CKD involving a large number of people who do not have kidney disease at baseline over a long duration of follow-up, perhaps a decade or even longer.

In the current issue of the Journal, Rebholz et al. [4] in an elegant study examined 15,055 middle-aged (mean aged 54) community dwelling adults from the Atherosclerosis Risk in Communities dataset. A food frequency questionnaire was used to assess dietary intake at baseline (1986–1989) and visit 3 (1993–1995). They calculated the potential renal acid load from estimated protein, phosphorus, potassium, magnesium and calcium intakes. The

median follow-up was for 21 years. During this really long follow-up, they identified 2,351 cases of incident CKD. They carefully chose the definition of incident CKD. It was defined as eGFR <60 ml/min/1.73 m² at any follow-up visit accompanied by >25% decline in eGFR from baseline. This definition is important, as it excludes those whose eGFR merely dropped from 61 to 59 ml/min/1.73 m². In addition, they also identified incident CKD based upon ICD 9/10 codes for CKD stage 3 or higher in hospitalizations (by active surveillance of the cohort) or cause of death (by linking to National Death Index) or incident ESRD (by linking to USRDS).

Those in the lowest quartile of potential renal acid load had negative acid load implying that their diet was alkaline. Compared to that group, those in the highest quartile of renal acid load had statistically significant 13% higher odds of developing incident CKD. While a 13% increased risk appears small, it has to be interpreted in the context that there are millions of Americans with stage 3+ CKD and even if there is only a 10% reduction, that would translate into several hundreds of thousands of fewer people with CKD with an intervention that could be inexpensive and essentially nontoxic.

It is of importance to note that while potential renal acid load is a biological construct, it was calculated from many dietary variables including estimated protein, phosphorus, potassium, magnesium and calcium intakes.

Thus, the observed relationship of potential renal acid load with incident CKD could be driven by one or more of those variables. Rebholz et al. [4] examined the associations of these individual variables with incident CKD. While total protein, animal protein and potassium intakes were not associated with incident CKD, however, higher plant protein, magnesium, calcium and phosphorus intakes were associated with lower risk of incident CKD.

Higher plant protein intake is associated with decreased mortality in CKD [5]. Hence, the associations of plant protein intake with incident CKD is not surprising. However, for us nephrologists who are used to the paradigm that high calcium and high phosphorous intakes are detrimental, the associations of higher calcium and phosphorus intakes with lower risk of incident CKD are very surprising indeed. However, when one realizes that nuts, soybeans, tofu, whole grains, and so on are high in both calcium and phosphorus, these observations do make biological sense. Similarly, nuts and whole grains are also high in magnesium [6].

This gets us to the issue of unmeasured confounders. As nicely noted by Rebholz et al. [4], high-potential renal acid load could lead to kidney damage via multiple mechanisms including complement activation. However, these observed associations might also be the result of other factors that are in a diet that are less acid generating. In other words, it might be the dietary pattern and not any one single ingredient by itself that could be either harmful or beneficial.

Diabetes and hypertension are the leading causes of CKD in the United States. Therefore, diets that decrease the incidence of these 2 conditions could also reduce

CKD. Consumption of Mediterranean diet that is high in nuts, unsaturated fats, seeds, whole grains, fruits and vegetables decreased the incidence of type 2 diabetes in a randomized controlled trial (RCT) [7]. Dietary Approaches to Stop Hypertension (DASH)-style diet (higher intake of fruits, vegetables, legumes, fish, poultry, and whole grains) significantly lowered systolic blood pressure [8]. Furthermore, DASH style dietary pattern was associated with lower risk of rapid eGFR decline (OR 0.55, 95% CI 0.38–0.80) in the Nurse's Health Study [9].

It is customary to call for RCTs when there is a promising result from an observational study. The effect size was only 13% in this study. As discussed earlier, even a 10% reduction of incident CKD will have huge benefits from the public health policy point of view. However, will it be realistic to conduct an RCT that is adequately powered to detect an effect size of 13% over a very long duration of follow-up that might last for a decade or two? Such a trial will involve tens of thousands of people. It is unlikely that such a mega trial will ever be carried out.

What about a trial of sodium bicarbonate to prevent CKD? Well, the above limitations will apply to such a trial too.

Hence, we are left to make our decisions based on our intuition and clinical judgement. As RCT data show that Mediterranean diet can reduce diabetes [7], it is prudent to advocate such a diet with the hope that the incidence of CKD can be reduced.

Acknowledgements

This work is supported by NIDDK R01 DK091437.

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