Primary Versus Secondary Prevention of Chronic Kidney Disease: The Case of Dietary Protein

Related Articles, p. 235 and p. 245

THE PROCLAMATION THAT *"the greatest medicine of all is to teach people how not to need it"* (Hippocrates. 460-370 BC, Greece) is the basic principle of primary disease prevention, which aims to prevent disease before it ever occurs. Preventing exposures to hazards that cause disease, such as altering unhealthy behaviors, is one example of primary disease prevention. Secondary or tertiary disease prevention, however, refers to reducing the impact of a disease that has already occurred, or limiting the impact of an ongoing illness that has lasting effects, respectively. Salutary diets or lifestyles for primary versus secondary/tertiary disease prevention may not necessarily align.

In patients with manifest chronic kidney disease (CKD), a low-protein diet remains the first line of nutrition therapy for *secondary prevention* of CKD.[1,2] Potential effects of low-protein diets are the preservation of residual renal function, better control of uremia, reduced kidney stone formation, hyperphosphatemia, or gut-derived uremic toxins.[3,4] However, there remains conflicting data on the benefits of low-protein diets in retarding the progression to end-stage kidney disease[5] or lowering the risk of mortality,[6] and the potential to promote undernutrition in the elderly.[2] It is possible that conflicting evidence is explained by patient-centered experiences following this restrictive dietary approach.[7] In fact, compliance to a low-protein diet is commonly between 14% and 50% in CKD trials,[2] and approximately, 70% of nephrologists report hesitation in prescribing it.[8]

In contrast to the low-protein diet advice in CKD, a high protein, low carbohydrate diet has been touted as a quick fix solution to today's epidemics of obesity and type 2 diabetes. Commentary has followed related to its safety, with several reports, and lay media raising concern that such diets in the general population may be detrimental to the healthy kidney.[9-12] Yet, the current state of the evidence is uncertain, with little to no evidence to support these claims. To date, randomized controlled trials of a high-protein diet in individuals free from CKD have generally observed no adverse effect on renal function decline (Table 1). Existing studies are nonetheless too short in duration to meaningfully detect estimated glomerular filtration rate (eGFR) changes (<2 years), often include younger participants, and choose creatinine-based eGFR as a study outcome, which may be compromised when intervening on protein intake.[23] Similar conclusions were reached in a recent meta-analysis of randomized controlled trials that showed that a high-protein diet in populations free from CKD stimulated the renal reserve causing increases in eGFR, but no evidence of renal damage or eGFR decline was found.[24] Observational evidence also points to a lack of a clear association between a high-protein diet and renal function in the general population (Table 2). Finally, real-world examples support this contention, within the body-building community[11] and in historical accounts of extreme protein intakes (e.g., men in the famous Lewis and Clark expedition across America in 1804 reportedly ate as much as nine pounds of buffalo meat (>600 g protein) each day with no ill effects[32]).

In this issue of *JREN,* we are presented with two studies examining the effects of dietary protein on the healthy kidney. Cirillo et al.[30] present a post hoc analysis of the Gubbio study, an Italian population-based study of 4,679 adults. Dietary protein intake was measured from overnight urine urea nitrogen (UUN), with low protein intake defined as the lowest quartile of UUN distribution. CKD progression was defined as an eGFR reduction of less than or equal to 1 standard deviation from baseline. Over 16 years of follow-up, they found no association between low UUN and the odds of eGFR decline. Interestingly, when the analysis was restricted for those participants with reduced renal function at baseline (defined as eGFR decline from equal to or below a Z-score of -1 baseline eGFR), a low protein intake was significantly associated with lower odds of eGFR decline (odds ratio: 0.44 [95% confidence interval 0.22, 0.85]). Also in this issue, Malhotra et al.[31] present another observational analysis based on 3,165 participants from the Jackson Heart study. The sample included African–American adults who were mostly female (65%) and had dietary protein intake ascertained at baseline from food frequency questionnaires. Change in GFR was calculated as the final visit GFR minus the baseline GFR, using the CKD Epidemiology Collaboration

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Table 1. Results of Studies Examining High Protein Intake and Renal Outcomes in Randomized Controlled Trials Conducted in Populations Free From CKD With Study Durations Greater Than 3 Months

Study Citation	Population	Duration	Protein Exposure	High Protein Intake and Change in Renal Function
Randomized controlled trials				
Campos-Nonato et al. 2017[13]	Mexican adults; 20-60 y; BMI 25-45 kg/m^2; metabolic syndrome; n = 118	6 mo	High protein: 1.3 g/kg Low protein: 0.8 g/kg	No significant change in renal function
Freidman et al. 2012[14]	Adults; 18-65 y; BMI 27-40 kg/m^2; n = 307	24 mo	High protein: >15% Low protein: 15%	No significant change in renal function
Krebs et al. 2012[15]	Adults; 30-75 y; type 2 diabetes; BMI >27 kg/m^2; n = 419	24 mo	High protein: 30% Low protein: 15%	No significant change in renal function
Larsen et al. 2011[16]	Adults; type 2 diabetes; BMI 27-40 kg/m^2; n = 99	12 mo	High protein: 30% Low protein: 15%	No significant change in renal function
Li et al. 2010[17]	Adults; >30 y; BMI 27-40 kg/m^2; n = 100	12 mo	High protein: 30%; 2.2 g/kg Low protein: 15%; 1.1 g/kg	No significant change in renal function
Noakes et al. 2005[18]	Adults; 20-65 y; BMI 27-40 kg/m^2; n = 100	3 mo	High protein: 37% Low protein: 17%	No significant change in renal function
Skov et al. 1999[19]	Adults; BMI 25-34 kg/m^2; n = 65	6 mo	High protein: 25% Low protein: 12%	Increase in GFR of 5 mL/min No adverse renal effects reported
Tay et al. 2015[20]	Adults; type 2 diabetes; n = 115	12 mo	High protein: 28% Low protein: 17%	No significant change in renal function
Tirosh et al. 2013[21]	Adults; 40–65 y; BMI >27 kg/m^2; n = 318	24 mo	High protein: 22% Low protein: 19%	High protein increased eGFR by 5% Albuminuria decreased in the low protein intervention. No adverse renal effects reported
Wycherley et al. 2012[22]	Adults; 20-65 y; BMI 27-40 kg/m^2; n = 68	12 months	High protein: 35%; 1.2 g/kg Low protein: 17%; 0.8 g/kg	No significant change in renal function

BMI, body mass index; CKD, chronic kidney disease.

equation. The primary finding of this study was a lack of significant association between protein intake and GFR decline over 8 years of observation. However, when the analysis was stratified by diabetes status, participants with diabetes had a higher incidence of eGFR decline across the lowest (-20.0 ± 1.7 mL/min/1.73 m^2) and highest (-15.9 ± 2.8 mL/min/1.73 m^2) quintiles of protein intake, as compared to those with middle quintile (-12 ± 1.6 mL/min/1.73 m^2).

These 2 studies add to the body of evidence that restricting protein intake may not be beneficial in the primary prevention of CKD. Nonetheless, they also suggest that a lower protein intake may be beneficial in some high-risk populations, including those with some mild degree of renal impairment or diabetes. This agrees with preceding observational reports, such as the Nurses' Health study, where an association of low protein intake with less rapid decline of kidney function over time was only observed in the subgroup of 489 participants with established mild renal impairment.[28] There is also the suggestion that quality of the ingested protein (animal vs. plant-based) within an overall healthy dietary pattern, may be more important than the total protein ingested.[33] Indeed, acute laboratory studies suggest that animal protein stimulates the renal reserve more so than plant-based proteins.[34] As recently shown in *JREN*,[27] people consuming the highest quartile of vegetable protein had a 24% reduced risk of incident CKD over a 23-year follow-up period, but the analysis of overall protein intake yielded no association. When the analysis targeted individual food items, there was an increased CKD risk for those who consumed more protein from red and processed meats (HR 1.23; $P < .01$), and a reduced CKD risk for those who consumed more protein from dairy products, nuts, and legumes. While an important limitation of all these studies is their observational nature because of the lack of adequately powered and well-designed intervention trials. Such evidence forms the basis for many nutrition guidelines in primary and secondary prevention.

The Science of Nutrition is a science of "virtue in moderation", where any excess nutrient intake or deficit is a risk for more harm than good. Concerns relating to a high-protein diet are likely because of harmful effects other than kidney damage. Some of the adverse effects attributed to excessive protein intake include disorders of bone and calcium homeostasis, renal stone formation, possible increased risk of cancer, disorders of liver function, hypertension, and coronary artery disease.[10,35] It is