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

Author

Kelly, Jaimon T, Campbell, Katrina L, Carrero, Juan J

Published

2018

Journal Title

Journal of Renal Nutrition

Version

Accepted Manuscript (AM)

DOI

10.1053/j.jrn.2018.04.006

Editorial

Primary versus secondary prevention of chronic kidney disease: the case of dietary protein

Jaimon T. Kelly, RD[1], Katrina L. Campbell, RD, PhD[1], Juan J. Carrero, Pharm, PhD[2]

[1] Faculty of Health Sciences and Medicine, Bond University, Australia

[2] Department of Medical Epidemiology and Biostatistics. Karolinska Institutet, Stockholm, Sweden

Short title: Low protein diets for CKD

Financial Disclosure: None.

Address correspondence to

Juan Jesus Carrero

Department of Medical Epidemiology and Biostatistics (MEB)

Karolinska Institutet, Stockholm, Sweden.

E-mail: juan.jesus.carrero@ki.se

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 behaviours, is one example of primary disease prevention. Secondary or tertiary disease prevention, however, refer 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 (ESKD)[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 14-50% 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 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.[13] 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.[14] 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 (for example, men in the famous Lewis and Clark expedition across America in 1804 reportedly ate as much as nine pounds of buffalo meat (>600 grams protein) each day with no ill effects[15]).

In this issue of *JREN,* we are presented with two studies examining the effects of dietary protein on the healthy kidney. Cirillo *et al.*[16] 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 one 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%CI 0.22, 0.85]). Also in this issue*,* Malhotra *et al.*[17] 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-EPI 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 two 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.[18] There is also the suggestion that quality of the ingested protein (animal versus plant-based) within an overall healthy dietary pattern, may be more important than the total protein ingested.[19] Indeed, acute lab studies suggest that animal protein stimulates the renal reserve more so than plant-based proteins[20]. As recently shown in JREN[21] 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<0.01), 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, due to 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.[10,22] It is interesting, in this sense, that Malhotra and co-workers[17] observed a U-shape association between protein intake and mortality. Neither too little nor too much protein intake may be good for health, as it was similarly shown in other population-based studies.[18,23]

These two interesting studies leave us with two conclusions. First, they align with current evidence, which does not support the assertion that a high protein diet leads to incident CKD in the community, at least in those with normal renal function. Interestingly however, is a call for caution about prescribing high-protein diets in populations at high-risk of CKD, such as those with minimal renal impairment or diabetes. There is a need to better understand lifestyle advice for the primary prevention of CKD separately from secondary prevention, preferably in randomized controlled trials.

Second, these studies make us realize that although a healthy diet is likely to be effective for primary CKD prevention,[24] the characteristics of such a diet are, to date, poorly defined.[25] The case of dietary protein and CKD illustrated in these two studies is an excellent example that primary and secondary prevention strategies are not always aligned. There is still much to be learned in the case of dietary protein, and more improvement is needed for effective strategies to minimize the burden of CKD in the community. After all, CKD afflicts one in 10 adults and causes as many deaths as diabetes.[26,27]

References

1. Kopple JD, Fouque D. Pro: The rationale for dietary therapy for patients with advanced chronic kidney disease. *Nephrology Dialysis Transplantation.* 2018;33(3):373-378.
2. Woodrow G. Con: The role of diet for people with advanced Stage 5 CKD. *Nephrology Dialysis Transplantation.* 2018;33(3):380-384.
3. Kovesdy CP. Traditional and novel dietary interventions for preventing progression of chronic kidney disease. *Journal of Renal Nutrition.* 2013;23(3):241-245.
4. Black AP, Anjos JS, Cardozo L, et al. Does Low-Protein Diet Influence the Uremic Toxin Serum Levels From the Gut Microbiota in Nondialysis Chronic Kidney Disease Patients? *J Ren Nutr.* 2018.
5. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *The New England journal of medicine.* 1994;330(13):877.
6. Fouque D, Laville M, Boissel J. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database of Systematic Reviews.* 2009;3.
7. Kelly JT, Campbell KL, Hoffmann T, Reidlinger DP. Patient experiences of dietary management in chronic kidney disease: a focus group study. *J Ren Nutr.* 2017.
8. Kalantar-Zadeh K, Moore LW, Tortorici AR, et al. North American experience with Low protein diet for Non-dialysis-dependent chronic kidney disease. *BMC Nephrology.* 2016;17:90.
9. Marckmann P, Osther P, Pedersen AN, Jespersen B. High-protein diets and renal health. *Journal of Renal Nutrition.* 2015;25(1):1-5.
10. Delimaris I. Adverse Effects Associated with Protein Intake above the Recommended Dietary Allowance for Adults. *ISRN Nutrition.* 2013;2013:6.
11. Manninen AH. High-protein diets are not hazardous for the healthy kidneys. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2005;20(3):657-658; author reply 658.
12. Luyckx VA, Mardigan TA. High protein diets may be hazardous for the kidneys. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2004;19(10):2678-2679.
13. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *New England Journal of Medicine.* 2012;367(1):20-29.
14. Schwingshackl L, Hoffmann G. Comparison of High vs. Normal/Low Protein Diets on Renal Function in Subjects without Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *PLOS ONE.* 2014;9(5):e97656.
15. Anderson S, Brenner BM. The aging kidney: structure, function, mechanisms, and therapeutic implications. *Journal of the American Geriatrics Society.* 1987;35(6):590-593.
16. Cirillo M, Cavallo P, Bilancio G, Lombardi C, Vagnarelli OT, Laurenzi M. Low Protein Intake in the Population: Low Risk of Kidney Function Decline but High Risk of Mortality. *Journal of Renal Nutrition.* 2018.
17. Malhotra R, Lipworth L, Cavanaugh KL, et al. Protein Intake and Long-term Change in Glomerular Filtration Rate in the Jackson Heart Study. *Journal of Renal Nutrition.* 2018.
18. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. *Annals of Internal Medicine.* 2003;138(6):460-467.

19. Kelly JT, Carrero JJ. Dietary Sources of Protein and Chronic Kidney Disease Progression: The Proof May Be in the Pattern. *Journal of Renal Nutrition.* 2017;27(4):221–224.
20. Hostetter TH, Troy JL, Brenner BM. Glomerular hemodynamics in experimental diabetes mellitus. *Kidney international.* 1981;19(3):410-415.
21. Haring B, Selvin E, Liang M, et al. Dietary protein sources and risk for incident chronic kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. *Journal of Renal Nutrition.* 2017;27(4):233-242.
22. Golzarand M, Bahadoran Z, Mirmiran P, Azizi F. Protein Foods Group and 3-Year Incidence of Hypertension: A Prospective Study From Tehran Lipid and Glucose Study. *J Ren Nutr.* 2016;26(4):219-225.
23. Halbesma N, Bakker SJ, Jansen DF, et al. High protein intake associates with cardiovascular events but not with loss of renal function. *Journal of the American Society of Nephrology.* 2009;20(8):1797-1804.
24. Kelly JT, Palmer SC, Wai SN, et al. Healthy Dietary Patterns and Risk of Mortality and ESRD in CKD: A Meta-Analysis of Cohort Studies. *Clinical Journal of the American Society of Nephrology.* 2016;12(2):272-279.
25. Campbell KL, Carrero JJ. Diet for the Management of Patients With Chronic Kidney Disease; It Is Not the Quantity, but the Quality That Matters. *Journal of Renal Nutrition.* 2016;26(5):279-281.
26. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017;390(10100):1151-1210.
27. Thomas B, Matsushita K, Abate KH, et al. Global Cardiovascular and Renal Outcomes of Reduced GFR. *J Am Soc Nephrol.* 2017;28(7):2167-2179.
28. Campos-Nonato I, Hernandez L, Barquera S. Effect of a High-Protein Diet versus Standard-Protein Diet on Weight Loss and Biomarkers of Metabolic Syndrome: A Randomized Clinical Trial. *Obesity facts.* 2017;10(3):238-251.
29. Friedman AN, Ogden LG, Foster GD, et al. Comparative effects of low-carbohydrate high-protein versus low-fat diets on the kidney. *Clinical journal of the American Society of Nephrology.* 2012;7(7):1103-1111.
30. Krebs J, Elley C, Parry-Strong A, et al. The Diabetes Excess Weight Loss (DEWL) Trial: a randomised controlled trial of high-protein versus high-carbohydrate diets over 2 years in type 2 diabetes. *Diabetologia.* 2012;55(4):905-914.
31. Larsen RN, Mann NJ, Maclean E, Shaw J. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. *Diabetologia.* 2011;54(4):731-740.
32. Li Z, Treyzon L, Chen S, Yan E, Thames G, Carpenter CL. Protein-enriched meal replacements do not adversely affect liver, kidney or bone density: an outpatient randomized controlled trial. *Nutrition Journal.* 2010;9(1):72.
33. Noakes M, Keogh JB, Foster PR, Clifton PM. Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. *Am J Clin Nutr.* 2005;81(6):1298-1306.
34. Skov AR, Toubro S, Bulow J, Krabbe K, Parving HH, Astrup A. Changes in renal function during weight loss induced by high vs low-protein low-fat diets in overweight subjects. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* 1999;23(11):1170-1177.
35. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Long-Term Effects of a Very Low Carbohydrate Compared With a High Carbohydrate Diet on Renal Function in Individuals With Type 2 Diabetes: A Randomized Trial. *Medicine.* 2015;94(47):e2181.

36. Tirosh A, Golan R, Harman-Boehm I, et al. Renal function following three distinct weight loss dietary strategies during 2 years of a randomized controlled trial. *Diabetes Care.* 2013;36(8):2225-2232.
37. Wycherley T, Brinkworth G, Clifton P, Noakes M. Comparison of the effects of 52 weeks weight loss with either a high-protein or high-carbohydrate diet on body composition and cardiometabolic risk factors in overweight and obese males. *Nutrition & diabetes.* 2012;2(8):e40.
38. Dunkler D, Dehghan M, Teo KK, et al. Diet and kidney disease in high-risk individuals with type 2 diabetes mellitus. *JAMA Intern Med.* 2013;173(18):1682-1692.
39. Haring B, Selvin E, Liang M, et al. Dietary Protein Sources and Risk for Incident Chronic Kidney Disease: Results From the Atherosclerosis Risk in Communities (ARIC) Study. *Journal of Renal Nutrition.* 2017.
40. Lew Q-LJ, Jafar TH, Koh HWL, et al. Red Meat Intake and Risk of ESRD. *Journal of the American Society of Nephrology.* 2016;28(1):304-312.

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 [28]	Mexican adults; 20-60 years; BMI 25-45kg/m^2; metabolic syndrome; n=118	6 months	High protein: 1.3 g/kg Low protein: 0.8 g/kg	No significant change in renal function
Freidman et al 2012 [29]	Adults; 18-65 years; BMI 27-40kg/m^2; n=307	24 months	High protein: >15% Low protein: 15%	No significant change in renal function
Krebs et al 2012 [30]	Adults; 30-75 years; type 2 diabetes; BMI >27kg/m^2; n=419	24 months	High protein: 30% Low protein: 15%	No significant change in renal function
Larsen et al 2011 [31]	Adults; type 2 diabetes; BMI 27-40kg/m^2; n=99	12 months	High protein: 30% Low protein: 15%	No significant change in renal function
Li et al 2010 [32]	Adults; >30 years; BMI 27-40kg/m^2; n=100	12 months	High protein: 30%; 2.2g/kg Low protein: 15%; 1.1g/kg	No significant change in renal function
Noakes et al 2005 [33]	Adults; 20-65 years; BMI 27-40kg/m^2; n=100	3 months	High protein: 37% Low protein: 17%	No significant change in renal function
Skov et al 1999 [34]	Adults; BMI 25-34kg/m^2; n=65	6 months	High protein: 25% Low protein: 12%	Increase in GFR of 5ml/min. No adverse renal effects reported
Tay et al 2015 [35]	Adults; type 2 diabetes; n=115	12 months	High protein: 28% Low protein: 17%	No significant change in renal function
Tirosh et al 2013 [36]	Adults; 40–65 years; BMI >27kg/m^2; n=318	24 months	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 [37]	Adults; 20-65 years; BMI 27-40kg/m^2; n=68	12 months	High protein: 35%; 1.2g/kg Low protein: 17%; 0.8g/kg	No significant change in renal function

Table 2. Results of studies examining high protein intake and renal outcomes in observational studies conducted in populations free from CKD.

Study citation	Population	Duration	Protein exposure	High protein intake and change in renal function
Dunkler et al 2013[38]	ONTARGET cohort; n=6123	5.5 years	Protein intake analysed across tertiles High protein: 1g/kg Low protein: 0.4g/kg	Lowest tertile of total and animal protein intake had an increased risk of CKD compared with participants in the highest tertile
Halbesma et al 2009 [23]	PREVEND cohort; n=8461	6.4 years	Protein intake analysed across quintiles. High protein quintile = 3.3g/kg	No significant change observed in renal function
Haring et al[39]	ARIC cohort; n= 11,952	23 years	Protein intake analysed across quintiles. High protein quintile: 110g/day	No significant change observed in renal for total protein intake Red and processed meat consumption associated with risk of CKD Protective associations from plant, egg and fish protein sources
Knight et al 2003 [18]	Nurses' Health Study cohort; n=1624	11 years	Protein intake analysed across quintiles. High protein quintile: 93g/day	No significant change observed in renal function in non-CKD Significant association to renal function decline in those with established CKD
Lew et al 2016[40]	Singapore Chinese Health Study cohort; n=63,257	15.5 years	Protein intake analysed across quartiles of animal, poultry, fish and plant sources High protein quintile: 64g/day Low protein quintile: 53g/day	Red meat consumption associated with risk of ESRD Protective associations from plant, egg and fish protein sources
Cirillo et al 2018[16]	Gubbio study cohort; n=4679	15.9 years	Lowest protein: 20% of the sample's UUN distribution	No significant change observed in renal function in non-CKD Significant association to renal function decline in those with established CKD
Malhotra et al 2018[17]	Jackson Heart study cohort; n= 3165	8 years	Protein intake analysed across quartiles High protein quintile: 19%; 1g/kg Low protein quintile: 10%; 0.6g/kg	No significant change observed in renal function in non-CKD Significant association to renal function decline in those with uncontrolled diabetes

Abbreviations – NHANES: US National Health Nutritional Examination Survey, ARIC: Atherosclerosis Risk in Communities, ONTARGET: The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, PREVEND: Prevention of Renal and Vascular End-Stage Disease, ESRD: end-stage renal disease, UUN: urine urea nitrogen.