The Effects of High-Protein Diets on Kidney Health and Longevity

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ABSTRACT

Although high-protein diets continue to be popular for weight loss and type 2 diabetes, evidence suggests that worsening renal function may occur in individuals with—and perhaps without—impaired kidney function. High dietary protein intake can cause intraglomerular hypertension, which may result in kidney hyperfiltration, glomerular injury, and proteinuria. It is possible that long-term high protein intake may lead to *de novo* CKD. The quality of dietary protein may also play a role in kidney health. Compared with protein from plant sources, animal protein has been associated with an increased risk of ESKD in several observational studies, including the Singapore Chinese Health Study. Potential mediators of kidney damage from animal protein include dietary acid load, phosphate content, gut microbiome dysbiosis, and resultant inflammation. In light of such findings, adopting current dietary approaches that include a high proportion of protein for weight reduction or glycemic control should be considered with care in those at high risk for kidney disease. Given the possibility of residual confounding within some observational studies and the conflicting evidence from previous trials, long-term studies including those with large sample sizes are warranted to better ascertain the effects of high protein intake on kidney health.

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In the United States, >60% of the population meets the criteria for being obese or overweight. In this context, growing interest in low-carbohydrate, high-protein diets has emerged over recent decades. The revived popularity of low-carbohydrate, high-protein diets may be partly fueled by their promotion across social media as an effective means for rapid weight loss and better glycemic control. For patients with CKD or at risk of CKD, high intake of dietary protein, including animal protein, may have detrimental effects on kidney function and long-term kidney health. This review focuses on the potential consequences of high dietary protein intake on kidney health and its relevance in the primary and secondary prevention of CKD.

THE RISE IN POPULARITY OF HIGH-PROTEIN DIETS

The estimated average requirement for protein intake is 0.6 g of protein per kilogram of ideal body weight per day, which corresponds to the amount of protein required to avoid negative nitrogen balance and to meet half of a population's requirements. The recommended daily allowance for protein intake is 0.83 g/kg per day and is calculated to meet the requirements of 97%–98% of the population (two SD above the estimated average requirement).[1] Although there is a lack of consensus regarding the formal definition of a high-protein diet, most definitions set a threshold between 1.2 and 2.0 g/kg per day. Within this range, protein consumption >1.5 g/kg per day is generally considered to be a high-protein diet. Data from the National Health and Nutrition Examination Survey (NHANES) show that the current average consumption of protein in the United States is estimated to be approximately

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Table 1. Summary of observational studies of high dietary protein intake and kidney health across large populations (>1000 participants)

Study Reference	Study or Location	Type	*N* (BMI, kg/m^2)	Mean Age (yr)	Mean eGFR (ml/min per 1.73 m^2)	DM/HTN HTx (%)	Sex (% male)	Protein Intake in the Highest Group (g/kg per d, g/d, or % of total calorie intake)	Duration (yr)	Variable and Outcome
Knight *et al.*[12]	Nurses' Health Study	Prospective cohort	1624 (N/D)	55	90	4/40	0	93 g/d	11	HP was not associated with eGFR decline in normal renal function. However, it was associated with accelerated eGFR decline in mild CKD
Huang *et al.*[74]	Taiwan	Cross-sectional	599 (24.3)	60	22	N/D	54	N/D	N/A	HP was also associated with worsening eGFR at increments of −3.50 ml/min per 1.73 m^2, compared with moderate and low protein intake ($P<0.001$)
Halbesma *et al.*[75]	Prevention of Renal and Vascular ENd-stage Disease (PREVEND)	Prospective cohort	8461 (26.1)	50	81	N/D	N/D	1.4 g/kg per d	7.0	No association between baseline protein intake and rate of renal function decline
Cirillo *et al.* [10]	Gubbio Study	Prospective cohort	1522 (28)	54	84	5/41	44	2.1 g/kg per d	12	1 g/d higher protein intake was related to −4.1 ml/min per 1.73 m^2 more negative eGFR change and 1.78 risk for incidence of eGFR <60 ml/min per 1.73 m^2
Beasley *et al.*[76]	Cardiovascular Health Study	Prospective cohort	3623 (26.5)	72	73	14/55	39	1.63 g/kg per d;24% of total calories	6.4	Protein intake was not associated with change in eGFR ($P>0.05$ for all comparisons)

Table 1. Continued

Study Reference	Study or Location	Type	*N* (BMI, kg/m^2)	Mean Age (yr)	Mean eGFR (ml/min per 1.73 m^2)	DM/HTN HTx (%)	Sex (% male)	Protein Intake in the Highest Group (g/kg per d, g/d, or % of total calorie intake)	Duration (yr)	Variable and Outcome
Lew *et al.*[51]	Singapore Chinese Health Study	Prospective cohort	63,257 (23)	57	N/D	9/23	43	65.3 g/d	15.5	Total protein intake was positively associated with incidence of ESKD in a model that adjusted for basic demographic characteristics (*i.e.*, age, gender, dialect, educational level, and year of interview: HR, 1.55; 95% CI, 1.28 to 1.87) when comparing the highest quartile with the lowest quartile intake. However, the HR was attenuated to 1.19 (95% CI, 0.98 to 1.44) after adjusting for other lifestyle and comorbidity factors
Haring *et al.*[50]	Atherosclerosis Risk in Communities (ARIC) Study	Prospective cohort	11,952 (27)	54	103	11/31	56	109.5 g/d;19.5%	23	Total protein consumption itself was not associated with increasing risk of incident CKD (HR of the highest quintile, 0.89; 95% CI, 0.76 to 1.05)

Table 1. Continued

Study Reference	Study or Location	Type	*N* (BMI, kg/m^2)	Mean Age (yr)	Mean eGFR (ml/min per 1.73 m^2)	DM/HTN HTx (%)	Sex (% male)	Protein Intake in the Highest Group (g/kg per d, g/d, or % of total calorie intake)	Duration (yr)	Variable and Outcome
Malhotra *et al.*[77]	Jackson Heart Study	Observational cohort	3165 (31.8)	55	97	19/57	36	1.0 g/kg per d;19.4%	8	Consumption of protein as percentage of energy intake in lowest and highest quintiles was associated with decline in eGFR among subjects who were diabetic
Esmeijer *et al.*[78]	Alpha Omega Cohort	Prospective cohort	2255 (27.6)	69	82	18/57	80	92 g/d17%	3.5	Patients with a daily total protein intake of ≥1.20 compared with <0.80 g/kg ideal body weight had a twofold faster annual eGFR cysC decline (−1.60 versus −0.84 ml/min per 1.73 m^2) in patients post-MI
Jhee *et al.*[79]	Korean Genome and Epidemiology Study	Prospective cohort	9226 (24.5)	52	94	7/14	48	1.7 g/kg per d	11.5	The highest quartile was associated with 1.32-fold increased risk of rapid eGFR decline (95% CI, 1.02 to 1.73)
Farhadnejad *et al.*[13]	Tehran Lipid and Glucose Study	Prospective cohort	1797 (26.7)	38	76	12/18	46	16%	6.1	The highest tertile of LCHP diet had greater risk of incident CKD (OR, 1.48; 95% CI, 1.03 to 2.15) in comparison to those in the lowest one (*P* for trend=0.027)

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; HTx, heart transplant; N/D, not described; HP, high-protein diet; N/A, not applicable; HR, hazard ratio; cysC, cystatin C; MI, myocardial infarction; LCHP, low-carbohydrate, high-protein diet; OR, odds ratio.

Table 2. Summary of long-term (>6 mo) randomized controlled trials of high dietary protein intake and kidney health

Study Reference	Location	Population Characteristics	Size (LP/HP)	Duration	Protein Intake	Outcome (HP versus LP)
Flechtner-Mors *et al.*[80]	Germany	Obese	110 (55/55)	12 mo	HP, 1.34 g/kg;LP, 0.8 g/kg	Dietary protein was not associated with change of renal function (BUN and creatinine)
Li *et al.*[27]	United States	Obese	85 (41/44)	12 mo	HP, 2.2 g/kg;SP, 1.1 g/kg	CC changes were NS, but hyperfiltration was shown in HP. Albuminuria was not different
Yancy *et al.*[81]	United States	Obese	146 (74/72)	48 wk	HP, 112.2±46.8 g/d;LP, 78.0±35.5 g/d	Creatinine and albuminuria were not different between groups
Larsen *et al.*[26]	Australia	Type 2 DM, obese	99 (46/53)	12 mo	HP, 30%LP, 15%	eGFR and albuminuria were not different between groups, although protein intake measured by urea nitrogen was not significantly different between groups
Wycherley *et al.*[82]	Australia	Obese	68 (35/33)	12 mo	HP, 35%, 1.2 g/kg;LP, 17%, 0.8 g/kg	CC changes were NS, but hyperfiltration was shown in HP
Krebs *et al.*[25]	New Zealand	Type 2 DM, obese	294 (150/144)	24 mo	HP, 30%;LP, 15%	Creatinine and albuminuria was not changed, but protein intake was not regulated well, and it was not different between groups
Friedman *et al.*[16]	United States	Obese	307 (154/153)	24 mo	HP, >15%;LP, 15%	CC was higher in HP group at 12 mo ($P<0.05$), and the change was attenuated at 24 mo. Albumin excretion was not different between groups
Tirosh *et al.*[83]	Israel	Obese	318	24 mo	HP/LC, unlimited protein intake–finally 22%;NP/LP, 18.8%–19.1%	Dietary protein was not associated with increase of eGFR and albuminuria after adjustment. But protein intake of two groups was not different
Tay *et al.*[24]	Australia	Type 2 DM, obese	115 (57/58)	12 mo	HP, 28%;LP, 17%	eGFR and albuminuria were not different
Møller *et al.*[17]	Europe and New Zealand	Prediabetes	309 (206/103)	12 mo	HP, 25%;NP/LP, 15%	There were no associations between increased protein intake and creatinine clearance

LP, low protein intake; HP, high protein intake; CC, creatinine clearance; DM, diabetes mellitus.

1.2–1.4 g/kg per day,[2] which is higher than the recommended amount. Popular weight-loss diets encourage higher amounts of protein while restricting the amount of carbohydrates, based on the assumption that all carbohydrates are undesirable—an assumption that has been refuted in the literature.[3] Although such diets vary, these weight-loss strategies typically recommend that 25%–35% of calories consumed should be from protein and <45% of calories should be from carbohydrates (Supplemental Table 1). In extreme cases, such as the ketogenic diet, <5%–10% of calories are from carbohydrates.

Hyperfiltration from High-Protein Diets and Effects on Kidney Health

In 1928, it was first noted in a frog model that amino acids and peptides could increase blood flow to the kidneys.[4] Subsequent studies in rats and dogs had similar findings.[5–7] In one study of dogs eating meat, the increase in the GFR (a marker of hyperfiltration) was dose dependent, with a maximal GFR increase of nearly 80%.[8]

Human data have also shown hyperfiltration with high protein consumption.[7] The largest short-term (<6 months) trial showed that a high-protein diet (protein

comprising 25% of calories) increased eGFR by 3.8 ml/min per 1.73 m^2 after 6 weeks compared with a lower protein diet (protein comprising 15% of calories).[9,10] In the early stages, glomerular hyperfiltration occurs as a rise in GFR, in proteinuria, or both, but may result in a loss of kidney function over time, particularly in those with underlying CKD, risk factors for CKD, or both.[11]

Several long-term observational studies in humans have shown an association between the consumption of high-protein diets and kidney function decline in individuals with preexisting CKD, including the Nurses' Health Study and the Gubbio Population Study.[10,12] In the Nurses' Health Study, an 11-year observational study of women experiencing mild renal insufficiency (defined as eGFR >55 ml/min per 1.73 m^2 and <80 ml/min per 1.73 m^2), every 10-g increase in protein intake was significantly associated with a change in eGFR of −1.69 ml/min per 1.73 m^2 (95% confidence interval [95% CI], −2.93 to −0.45 ml/min per 1.73 m^2), which was not observed in the population with normal renal function.[12]

In the Gubbio study, a population-based study of 1522 participants aged 45–64 years, a higher protein intake was associated with a lower eGFR after 12 years, including among participants with or without CKD (with CKD defined as an eGFR <90 ml/min per 1.73 m^2). Overall, in a multivariable regression analysis, 1 g/d higher protein intake was related to a −4.1 (95% CI, −5.1 to −3.1) ml/min per 1.73 m^2 more negative eGFR change and to a significantly increased risk for incident eGFR <60 ml/min per 1.73 m^2 (odds ratio, 1.78; 95% CI, 1.15 to 2.78).[10]

Additional long-term observational studies have also described the association of high protein intake with a decline in kidney function, whereas others have not (Table 1). Most recently, a study of nearly 1800 Iranians followed for an average of 6 years showed that those consuming excess protein in the form of a low-carbohydrate, high-protein diet also had a higher risk of CKD (odds ratio, 1.48; 95% CI, 1.03 to −2.15).[13]

However, some observational studies have not observed an association between a high-protein diet and kidney function. Also, randomized clinical trials with a relatively long observation period (>6 months) have generally demonstrated little to no effect on renal function, which may be limited by the use of creatinine-based measurements of kidney function, a sizable attrition in study participants, and the limited duration of these studies (a maximum of 24 months) (Table 2). In one meta-analysis of 30 trials that included short- and long-term trials, a high-protein diet did cause hyperfiltration (as measured by a change in GFR) but caused no change in plasma creatinine.[14] Another meta-analysis of low-carbohydrate diets showed a small increase in eGFR (0.13 ml/min per 1.73 m^2; 95% CI, 0.00 to 0.26 ml/min per 1.73 m^2).[15]

The negligible effects seen in long-term studies also may be attributed to the counterbalancing effects of hyperfiltration (an increase in renal function) and kidney damage from hyperfiltration (a decrease in renal function). For example, a randomized clinical trial of participants who were prescribed the Atkins diet (protein content around 30% of total energy intake) versus a control diet (protein content around 15% of total energy intake) for 12 months reported a rise in creatinine clearance among participants in the Atkins diet arm, suggesting hyperfiltration.[16] However, the differences in creatinine clearance between the Atkins versus control diet groups were attenuated after 24 months of observation,[16] which may indicate that the short-term rise in GFR with high protein intake may be followed by a decline in GFR over time, possibly as a result of renal injury.

Hyperfiltration may also lead to an increased risk of proteinuria. Several studies have shown a link between high protein intake and increased albuminuria or proteinuria as an early indicator of kidney damage. Several observational studies have also demonstrated an increased risk of albuminuria with high dietary protein intake versus standard dietary protein intake, even after accounting for differences in sociodemographics, comorbidities, body anthropometry, health behaviors (*e.g.*, physical activity, energy intake, and smoking status), and medication use.[17–20] However, in another study, the researchers did not consistently observe an association of high protein consumption with albuminuria for the whole population, finding it only among individuals with hypertension and diabetes.[21] In short-term trials with 4–12 weeks of follow-up, in patients with a single kidney or type 2 diabetes, those assigned to high-protein diet interventions (defined as 1.6 g/kg per day or 30% of energy content derived from protein) resulted in a slight increase in urinary albumin excretion compared with participants assigned to a standard diet.[22,23]

However, several long-term (>6 months) trials have not observed an increase in proteinuria with high protein intake,[16,24–27] particularly among participants with normal kidney function. In one trial, the albumin excretion rate did not change between baseline and 12 months, regardless of whether participants were assigned to a high-protein diet (protein comprising 28% of total energy content) or a high-carbohydrate diet (protein comprising 17% of total energy content).[24] Some of these studies were carried out with a small number of participants (<100) and over a relatively short duration of observation (<12 months),[26,27] and the effect of a high-protein diet on proteinuria merits further examination in large-scale, long-term trials. Randomized clinical trials for hyperfiltration of kidney and albuminuria are summarized in Table 2.

PROPOSED PATHWAYS LINKING HIGH-PROTEIN DIETS AND CKD

Mechanistically, high protein intake may lead to increases in kidney volume and weight in humans,[28] which was demonstrated in a mouse model as mesangial matrix expansion with tubulointerstitial

fibrosis.[29] Although research has not fully elucidated the exact mechanisms of protein-induced glomerular hyperfiltration, it is thought to occur as an evolutionary feedback mechanism facilitating the excretion of increased amounts of protein-derived nitrogenous waste. Other factors proposed as underlying mechanisms to facilitate the increased excretion of nitrogenous waste include changes in endocrine mediators (*e.g.*, glucagon and IGF-1), leading to vasodilation, and changes in neurohormonal responses (*i.e.*, tubuloglomerular feedback) within the kidney.[30]

Although some instances of short-term glomerular hyperfiltration, such as that which occurs during pregnancy, may not be associated with a decrease in kidney function, it is possible that prolonged, recurrent glomerular hyperfiltration induced by consumption of a high-protein diet may lead to kidney damage through multiple pathways over time (Figure 1).[31] Experimental data demonstrated that, in a rat model, incrementally higher levels of protein intake (*i.e.*, 20%, 30%, and 45% of total energy content) caused an increase in proinflammatory gene expression in a dose-dependent manner,[32] and that, in pig models, long-term exposure to a high-protein diet (*i.e.*, 35% of energy intake) led to 55% greater renal fibrosis and 30% greater glomerulosclerosis.[33]

HARMFUL METABOLIC CONSEQUENCES OF HIGH-PROTEIN DIETS

In addition to having potential implications of kidney function and structure, high-protein diets may also lead to other metabolic complications.

High dietary intake of protein may lead to higher levels of urea and other nitrogenous waste products. Indeed, several studies have shown that high versus standard dietary protein intake is associated with higher BUN concentrations.[16,34] For example, in a crossover study of 24 healthy young men who consumed a diet with a high level of protein (2.4 g/kg per day) or a diet with a normal level of protein (1.2 g/kg per day) over a 7-day period for each diet (total 14 days), BUN concentrations were significantly higher during the period of higher protein intake than during the period of normal protein intake.[34] Conversely, other studies have shown a proportional reduction in urea generation with dietary protein restriction.[35] One theory holds that high circulating BUN levels, by enhancing protein carbamylation and generating reactive oxygen species, lead to increased oxidative stress, inflammation, endothelial dysfunction, and cardiovascular disease.[30]

A diet with high protein intake might also lead to metabolic acidosis among patients with advanced CKD who have impaired acid excretion and generation of bicarbonate, particularly in the context of protein sourced from animal-based foods. Furthermore, dietary acid might also be a risk factor for CKD through intrarenal mechanisms promoting kidney injury and progressive GFR decline.[36] In an animal model of CKD, chronic metabolic acidosis can stimulate the production of angiotensin II, aldosterone, and endothelin-1, as well as ammoniagenesis, all of which can promote inflammation and fibrosis.[36] The standard American diet, in which protein comprises approximately 15% of energy, is estimated to produce a dietary acid load of approximately 1 mEq/kg per day, the bulk of which is derived from animal sources such as meats, eggs, and cheeses.[37]

In contrast, by including a higher proportion of foods with natural alkali, such as fruits and vegetables, a vegan diet is nearly acid neutral. Plant-based foods can be used to reduce both the dietary acid load and the severity of metabolic acidosis.[38] Similarly, a low protein intake in patients with advanced nondialysis CKD has also been shown to attenuate the severity of metabolic acidosis. NHANES III data have shown that, among 1486 adult participants with CKD, higher dietary acid load ascertained by 24-hour dietary recall was strongly associated with development of ESKD over a median follow-up of 14.2 years.[39] Compared with participants whose dietary acid consumption was in the lowest tertile, those with dietary acid consumption in the highest tertile had triple the risk of incident ESKD, even after accounting for differences in sociodemographics, nutritional factors, clinical factors, baseline eGFR, proteinuria, and serum bicarbonate levels.[39]

Dietary protein intake, which is also strongly correlated with phosphorus intake,[40] may account for 84% of the variance in dietary phosphorus intake.[41] Hyperphosphatemia is a critical factor for morbidity or mortality in patients with CKD.[42] Several large epidemiologic studies have found higher phosphorus

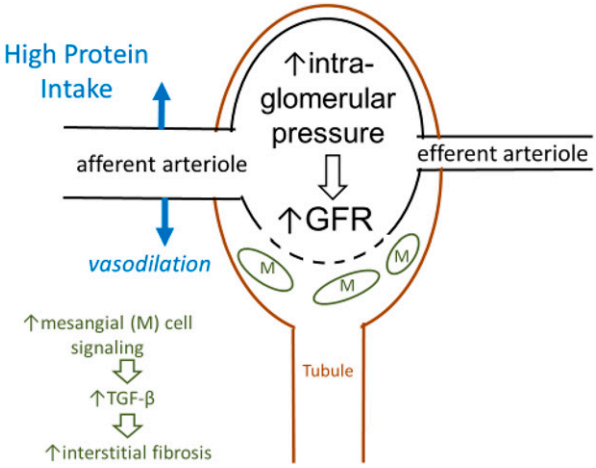

Figure 1. High dietary protein intake leads to the dilation of the afferent arteriole and increased GFR, which may lead to damage to kidney structures over time due to glomerular hyperfiltration.

Table 3. Summary of observational studies of protein source (plant versus animal) and kidney health

Study Reference	Study or Location	Type	Size	Age (yr)	Follow-up Period (yr)	Variable and Outcome
Knight *et al.*[12]	Nurses' Health Study	Prospective cohort study	1624	42–68	11	Consumption of nondairy protein was associated with rapid decline of eGFR among participants with mild CKD
Lin *et al.*[19]	Nurses' Health Study	Prospective cohort study	3121	67	11	HP usually found in Western dietary pattern (red and processed meat, saturated fat, sweets) was associated with albuminuria (OR, 2.17; 95% CI, 1.18 to 3.66) and rapid eGFR decline (OR, 1.77; 95% CI, 1.03 to 3.03). On the other hand, DASH diet (fruits, vegetables, whole grains) had a lower risk of rapid eGFR decline (OR, 0.55; 95% CI, 0.38 to 0.80)
Lin *et al.*[20]	Nurses' Health Study	Prospective cohort study	3348	67	11	Highest quartile of animal fat was associated with higher odds of microalbuminuria (OR, 1.72; 95% CI, 1.12 to 2.64). Consuming two or more servings of red meat/wk was associated with higher odds of microalbuminuria (OR, 1.51; 95% CI, 1.01 to 2.26)
Beasley *et al.*[76]	Cardiovascular Health Study	Prospective cohort study	3623	>65	6.4	There were also no significant associations when protein intake was separated by source (animal versus vegetable)
Lew *et al.*[51]	Singapore Chinese Health Study	Prospective cohort study	63,257	45–74	15.5	Highest quartile of protein intake (from red meat) had 40% increased HR of ESKD (dose dependent). Replacing one serving of red meat with other protein sources was associated with a max relative risk reduction of 62.4%
Haring *et al.*[50]	Atherosclerosis Risk in Communities (ARIC) Study	Prospective cohort study	11,952	44–66	23	Highest quintile of red/processed meat intake had 23% increased HR of incident CKD. On the other hand, highest quintile of vegetable protein intake had 24% reduced HR of incident CKD
Oosterwijk *et al.*[84]	DIAbetes and LifEstyle Cohort Twente-1 Study (DIALECT-1)	Cross-sectional	420	63±9	N/A	The prevalence ratio for the incidence of CKD (<60ml/min per 1.73 m^2) in the fully adjusted model was 0.47 (95% CI, 0.23 to 0.98; P=0.04) in the highest tertile of vegetable protein intake

HP, high-protein diet; OR, odds ratio; DASH, Dietary Attempt to Stop Hypertension; HR, hazard ratio; N/A, not applicable.

levels (even those within the normal range) to be associated with an increased risk of cardiovascular disease morbidity and mortality, even in individuals with normal kidney function.[43,44] Dietary phosphate loading increases expression of fibroblast growth factor 23 (FGF-23), which is a phosphaturic hormone.[45] Elevated FGF-23 levels are associated with vascular calcifications among patients with CKD[46] and left ventricular hypertrophy in experimental animals with uremia.[47] In a long-term observational study over 10 years among an elderly community population, FGF-23

independently associated with all-cause mortality and incidence of heart failure.[48] In addition, in the Ramipril Efficacy In Nephropathy trial, participants with higher serum phosphate levels had faster progression of kidney disease compared with those who had lower levels.[49]

PROTEIN SOURCE (PLANT VERSUS ANIMAL PROTEIN)

Several observational studies have noted the source of dietary protein intake in relation to CKD incidence (Table 3), finding a strong association between intake of animal protein, especially processed red meat consumption, and incidence and progression of CKD. The Atherosclerosis Risk in Communities Study showed an increased risk of incident CKD among participants consuming the highest quintile of red/processed meat compared with those consuming the least.[50] Similarly, in the Singapore Chinese Health Study, consuming red meat strongly associated with ESKD risk in a dose-dependent manner.[51] Data from these studies also demonstrated that red meat, processed meat, or both associated with an increased risk of albuminuria, rapid eGFR decline, or both.[19,51] Substituting one serving of red meat with a plant-based protein such as legumes was associated with a 31%–62.4% reduced risk of CKD.[50,51]

The pathophysiology of the association of animal protein with CKD remains unclear. One proposed mechanism is the link between animal protein consumption and hypertension, which observational studies and controlled trials have repeatedly demonstrated.[52] Conversely, plant-based foods have been shown to have the opposite effect,[53,54] so much so that emphasizing plant-based foods over animal-based foods is one of the principles of the Dietary Attempt to Stop Hypertension (DASH) diet.[55] Animal protein consumption also may lead to weight gain, which might be another predisposing factor for kidney disease. Additionally, studies have demonstrated that, compared with intake of plant protein, intake of animal protein causes an imbalance in the composition of the gut microbiome by producing more ammonia and sulfur-based materials and having a proinflammatory profile, which may result in reduced kidney function and an increased risk of cardiovascular disease.[56–59] Finally, high red meat intake has been associated with an increase in inflammation and oxidative stress, including upregulated inflammatory mediators such as NF-κB and inflammatory cytokines.[60,61]

These differences between the effects of animal-based protein versus plant-based protein may favor the use of the latter in both CKD and ESKD. Plant-based proteins have been previously described as being more than adequate for nutrition in these populations.[62]

THE NEWEST HIGH-PROTEIN DIET: THE KETOGENIC DIET

Although the ketogenic diet has recently received a disproportionate amount of attention because it is purported to help treat obesity and type 2 diabetes, evidence that it actually offers such benefits is limited. Long-term randomized trials have failed to show a clinically significant benefit over comparator diets.[3] Worse, the diet is not without consequence: it may produce adverse effects in the average dieter, such as hyperlipidemia,[3] vitamin and mineral deficiencies, and fatigue. For patients with or at high risk for kidney disease, the ketogenic diet may further tilt the risk/benefit ratio unfavorably by producing kidney-specific risks.

In brief, the ketogenic diet restricts the intake of carbohydrates as an energy source and instead emphasizes the use of (both ingested and stored) fat, resulting in the production of ketones (and giving the diet its name). The diet emphasizes an intake of 1.2–2.0 g/kg of protein per day, which is within the range of a diet with moderately high to high levels of protein.[63] For patients with existing kidney disease, the diet's high protein intake may accelerate the progression of their kidney disease.[64] For individuals without kidney disease, there is limited evidence suggesting that these diets pose danger. However, data from several prospective studies show that animal protein—an integral part of many ketogenic diets—may increase the risk of developing CKD.[19,20,50,51]

Of equal concern for those without CKD is the high amount of fat in the ketogenic diet. Lin *et al.*[19] showed a higher risk of albuminuria among study participants in the highest quartile of animal fat consumption compared with those in the lowest quartile. In another study, Lin *et al.*[20] demonstrated that a dietary pattern that included higher saturated fat intake is also associated with an increased risk of albuminuria and eGFR decline. In addition, studies have demonstrated a protective effect of many foods that are often excluded from the ketogenic diet, including fruits, vegetables, legumes, and whole grains.[65] Exclusion of these foods from the diet may represent an opportunity cost of potential health benefits for the kidney.

Excess consumption of animal protein with the ketogenic diet has also been implicated in the formation of kidney stones.[66,67] This may be one reason why, in the pediatric epilepsy community (where the ketogenic diet is used to treat refractory epilepsy in children), nephrolithiasis has been recurrently listed as an adverse effect of the diet.[68,69]

The acid load consumed and generated among those following a ketogenic diet could also lead to metabolic acidosis and related complications. Case reports exist of ketoacidosis[70] among individuals without kidney disease who consume a low-carbohydrate diet. More modest acidosis is caused by both the dietary acid load in individual foods (especially those from animal-based sources) and ketoacids associated with ketone production, combined with the absence of alkali naturally found in many fruits and vegetables that are partially or totally excluded from the ketogenic diet. Several studies within the pediatric epilepsy literature have documented metabolic acidosis in individuals without CKD.[68,69] For those with CKD, consuming a high

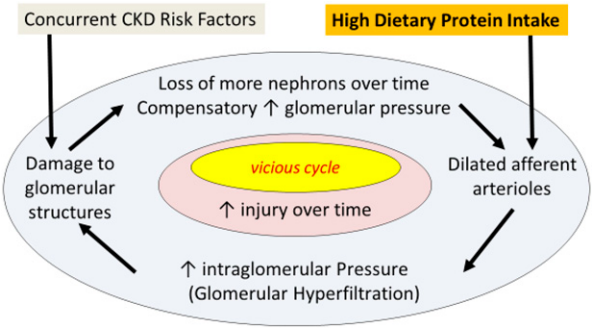

Figure 2. High dietary protein may lead to dilation of afferent arterioles, which results in intraglomerular pressure and glomerular hyperfiltration. It could damage glomerular structure causing compensatory increase of glomerular pressure in remaining glomerulus over time.

dietary acid load has been associated with a higher risk of ESKD.[39] In comparison, consumption of dietary sources of alkali has been shown to delay progression of CKD in a randomized clinical trial.[71] Finally, chronic metabolic acidosis in CKD exacerbated by a high dietary acid load may lead to worsened bone health.[69,72]

HIGH-PROTEIN DIETS AND SOLITARY KIDNEY

Persons with a congenital or acquired solitary kidney—including those who have had a unilateral nephrectomy resulting from living kidney donation, kidney malignancy such as renal cell carcinoma, or trauma—have decreased renal mass. This may lead to glomerular hypertrophy in the setting of increased intraglomerular pressure and glomerular hyperfiltration. These physiologic adaptations of the solitary kidney may lead to unfavorable clinical and renal outcomes over time. Hence, high-protein diets should be avoided, if possible, and plant-based proteins may be recommended. In general, people with one kidney should avoid excessively high dietary protein intake (>1.2 g/kg per day) and high dietary sodium intake; they should also consume adequate dietary fiber and avoid obesity, maintaining a body mass index of <30 kg/m^2. Future studies should help us better understand the optimal target protein intake for persons with a congenital or acquired solitary kidney.[73]

FUTURE DIRECTIONS

There are substantial gaps in our knowledge about the effects of high-protein diets on kidney health, which may result from difficulties in implementing methodologically rigorous research in this area. For example, challenges in maintaining dietary adherence over a protracted period may partly explain the paucity of randomized clinical trials examining the long-term effects of a high-protein diet on kidney health. Indeed, a number of hypotheses regarding long-term effects of a high-protein diet have been extrapolated from short-term interventional studies.

In addition, the lack of a uniform definition of a high-protein diet (including the total quantity of protein intake), as well as variation in sources of protein across studies, may have contributed to mixed findings. Although there have been numerous observational studies examining associations of long-term high protein intake exposure with kidney function, interpretation of these data are limited by residual confounding as well as challenges in the accurate measurement of protein intake consumption over a prolonged period. For example, although food frequency questionnaires are the preferred method for ascertaining dietary intake in epidemiologic studies, these tools are known to underestimate nutrient consumption, particularly in CKD. Measurement of urinary nitrogen excretion may provide a more accurate assessment of dietary protein intake, but it may be difficult to implement this tool in long-term studies.

CONCLUSION

Although there has not been a full elucidation of the underlying mechanisms by which high protein intake may adversely affect kidney function, particularly in the context of CKD, existing data suggest that glomerular hyperfiltration caused by a high-protein diet may lead to an increase in albuminuria and an initial rise and subsequent decline in GFR (Figure 2). Furthermore, growing evidence suggests that high-protein diets may be associated with a number of metabolic complications that may be detrimental to kidney health. Given the rise in popularity of high-protein diets and the high prevalence of CKD in the United States population—including many individuals who may be unaware of their CKD status, further studies are needed to investigate how differences in dietary protein quantity and quality affect short- and long-term outcomes in patients with or without CKD.

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SUPPLEMENTAL MATERIAL

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Supplemental Table 1. Comparison of macronutrient contents of selected popular diets.

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Supplemental table of contents

Table 1 - Comparison of macronutrient contents of selected popular diets for weight control

Diet Type	Protein	Carbohydrate	Fat	Fruits and Vegetables	Sodium and Potassium
Ketogenic diet[1]	1.2 – 2.0 g/kg	5-10%	65-85%	Only low-carbohydrate fruit and berries are used	Sodium is sometimes added in the early stage to reduce symptoms caused by diuresis from ketosis
Atkins [2]	No limit (20-35%)	Initially severely restricted and gradually introduced afterward (5 progressing to 15%)	55-70%	Fruit and berries are out of diet especially in early stage of diet	Easily added sodium especially in the early stage to reduce symptoms caused by diuresis due to ketosis
Mediterranean [3]	15-20% (tendency to avoid protein from meat)	~50% (high fiber intake)	~30% (high content with unsaturated fatty acid with olive oil)	Large amounts of fruit and vegetables encouraged	Sodium intake is not restricted much, Potassium intake is high from fruit and vegetables.
Paleo [4]	20-35% (lean meat and fish, avoid dairy product)	20-40% (nuts and seeds, avoiding grains, legume, and sugar)	25-50% (oil from nuts and seed)	Unrestricted	Very low sodium and high potassium

% is expressed for content among total energy intake

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