REVIEW

A Systematic Review of Renal Health in Healthy Individuals Associated with Protein Intake above the US Recommended Daily Allowance in Randomized Controlled Trials and Observational Studies

Mary E Van Elswyk,[1] Charli A Weatherford,[2] and Shalene H McNeill[3]

[1] Van Elswyk Consulting, Inc., Longmont, CO; [2] Weatherford Consulting Services, La Vernia, TX; and [3] National Cattlemen's Beef Association, Centennial, CO

ABSTRACT

A systematic review was used to identify randomized controlled trials (RCTs) and observational epidemiologic studies (OBSs) that examined protein intake consistent with either the US RDA (0.8 g/kg or 10–15% of energy) or a higher protein intake (≥20% but <35% of energy or ≥10% higher than a comparison intake) and reported measures of kidney function. Studies ($n = 26$) of healthy, free-living adults (>18 y old) with or without metabolic disease risk factors were included. Studies of subjects with overt disease, such as chronic kidney, end-stage renal disease, cancer, or organ transplant, were excluded. The most commonly reported variable was glomerular filtration rate (GFR), with 13 RCTs comparing GFRs obtained with normal and higher protein intakes. Most ($n = 8$), but not all ($n = 5$), RCTs reported significantly higher GFRs in response to increased protein intake, and all rates were consistent with normal kidney function in healthy adults. The evidence from the current review is limited and inconsistent with regard to the role of protein intake and the risk of kidney stones. Increased protein intake had little or no effect on blood markers of kidney function. Evidence reported here suggests that protein intake above the US RDA has no adverse effect on blood pressure. All included studies were of moderate to high risk of bias and, with the exception of 2 included cohorts, were limited in duration (i.e. <6 mo). Data in the current review are insufficient to determine if increased protein intake from a particular source, i.e., plant or animal, influences kidney health outcomes. These data further indicate that, at least in the short term, higher protein intake within the range of recommended intakes for protein is consistent with normal kidney function in healthy individuals. *Adv Nutr* 2018;9:404–418.

Keywords: protein intake, renal, kidney, glomerular filtration rate, blood pressure

Introduction

The US RDA for adult men and women is 0.80 g · kg^{-1} · d^{-1} of good-quality protein, based on a calculated protein digestibility corrected amino acid score (1). Similarly, the WHO recommends 0.83 g protein · kg^{-1} · d^{-1} for adults (2). A 2012 report (3) from the European Food Safety Authority established a Population Reference Intake for protein of 0.83 g · kg^{-1} · d^{-1} for adult men and women of all ages. The US acceptable macronutrient distribution range (AMDR) for protein, aimed at chronic disease risk reduction, is 10–35% of caloric intake and is estimated to equate to 1.05–3.67 g · kg^{-1} · d^{-1} based on reference body weights for men and women (1, 4). The current estimated average protein intake in the United States is 165 g/d (5). Although individuals with chronic kidney disease are advised to limit

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Supplemental Tables 1–6 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.

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Address correspondence to MEVE (e-mail: mveconsulting@q.com).

Abbreviations used: AER, albumin excretion rate; AMDR, acceptable macronutrient distribution range; DASH, Dietary Approaches to Stop Hypertension Trial; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; LCD, low-carbohydrate diet; OBS, observational epidemiologic studies; OmniHeart, Optimal Macronutrient Intake Trial to Prevent Heart Disease; RCT, randomized controlled trial; UL, upper limit; WNL, within normal limits.

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protein intake, multiple global and national evidence-based reviews designed to establish DRIs for healthy populations have found insufficient evidence to establish an upper limit (UL) for protein intake (1–3, 6). Despite insufficient evidence to establish a UL, evidence from animal models and individuals with chronic kidney disease have led to the hypothesis that prolonged intake of higher-protein diets could ultimately compromise kidney health and diminish renal function in healthy individuals (7). Several lines of evidence, including adapative renal hyperfiltration without negative consequence during pregnancy and after unilateral nephectromy, suggest otherwise (7). Nevertheless, dietary advice for healthy adults to limit protein intake to the RDA, rather than increase protein intake within the AMDR, even in circumstances when increased protein intake is warranted, persists and may stem at least in part from concerns regarding long-term kidney health (4).

As a wide range of protein intake levels appear acceptable based on current DRI levels, this review was designed to examine published literature investigating the relation of protein intake and indicators of kidney function in healthy adults, with the purpose of understanding whether levels of intake above the currently established US RDA of 0.8 g/kg body weight, but within the AMDR, are consistent with normal kidney health and function. Glomerular filtration rate (GFR) measures filtration rates of normally functioning nephrons, and is thought to provide the best index of normal kidney function (8). To ensure that studies included in the current review were of healthy adults, only studies reporting results of populations with normal GFR of $\geq$90 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} were reviewed.

Methods

Information sources

To identify relevant studies, a literature search was conducted with PubMed up until 9 August 2017. Supplementary literature searches included examining the reference lists of all relevant studies, pertinent review articles, and meta-analyses.

Search strategy

Search terms related to studies of protein intake and kidney health and function were combined in the following strategy: ("dietary proteins" [MeSH] OR "protein intake" [TIAB] OR "high protein" [TIAB] OR "protein consumption" [TIAB] OR "protein supplementation" [TIAB] OR "protein supplement" [TIAB] OR "diet, carbohydrate-restricted" [MeSH] OR "meat" [MeSH] AND "kidney function tests" [MeSH] OR "kidney disease" [MeSH] OR "kidney disease" [TIAB] OR "renal function" [TIAB] OR "renal disease" [TIAB] OR "creatinine" [MeSH] OR "urea" [MeSH] OR "proteinuria" [MeSH] OR "osmolality" [MeSH]) AND "clinical trial" [PT] OR "epidemiologic studies" [MeSH] OR "meta-analysis" [PT] OR "systematic review" [TIAB]) NOT ("case reports" [PT] OR "editorial" [PT] OR "letter" [PT] OR "in vitro" [PT] OR "comment" [PT] OR "animal experimentation" [MeSH] OR "infant" [MeSH] OR "child, preschool" [MeSH] OR "pediatric" [TIAB] OR "critical care" [MeSH] OR "hospitalization" [MeSH] OR "life support care" [MeSH] OR "palliative care" [MeSH] OR "prenatal care" [MeSH] OR "terminal care" [MeSH] OR "pregnancy" [MeSH] OR "lactation" [MeSH] OR "breast feeding" [MeSH] OR "protein-energy malnutrition" [MeSH] OR "renal dialysis" [MeSH] OR "cancer" [MeSH]).

Additionally, PubMed filters were applied to limit results to human studies published in English.

Eligibility criteria

Included studies were randomized controlled trials (RCTs) and observational epidemiologic studies (OBSs) that examined protein intake consistent with either the US RDA for protein (0.8 g $\cdot$ kg body weight^{-1} $\cdot$ d^{-1}or 10–15% of energy) or a higher protein intake ($\geq$20% of energy or $\geq$10% than a comparison intake), and reported measures of kidney function. Studies of healthy, free-living adults (>18 y old) with or without metabolic disease risk factors, such as elevated cholesterol, diabetes, high blood pressure, or obesity, were included. Studies of subjects with overt disease, such as chronic kidney disease, end-stage renal disease, cancer, organ transplant, etc., were excluded. Studies were excluded for the following reasons: *1*) if they were designed to examine outcomes in response to protein type but not protein quantity, i.e., protein source comparison only; *2*) if they supplemented protein in the form of full isoflavone soy, i.e., isoflavones not removed or minimized; *3*) if they were acute feeding studies of $\leq$24 h; *4*) if they were of populations with GFR <90 or albumin excretion rate (AER) >30 or diagnosis of end-stage renal disease; *5*) if they were designed to provide or included subjects with protein intake in excess of 35% of energy or 2.5 g/kg and had no study arm with a lower intake value or protein intake <0.66 g/kg; *6*) if they were designed for weight loss or conducted in a manner where subjects did not maintain energy balance; *7*) if they were designed to provide protein as a purified amino acid bolus or administered intravenously; *8*) if they allowed concomitant intervention with drugs or supplements that influence body weight; *9*) if they comprised letters, abstracts, case reports, case series, position statements, hypotheses, study designs, conference proceedings, prevalence surveys; *10*) if they were published in a language other than English; *11*) if they were conducted in a population nonrepresentative of the general healthy adult population, i.e., pediatric, pregnant and nursing women, vegan-only studies (vegetarians studies included), subjects with significant disease process, i.e., renal disease, cancer, etc., or protein-energy malnutrition; *12*) if they were animal or in vitro studies.

Study selection

Level I screening included a review of all titles and abstracts to check these against eligibility criteria. Full-text publications of any studies not eliminated at Level I were retrieved for complete review at Level II screening, which involved reading the full-text publication to determine that all eliqibility criteria were met and no exclusion criteria were applicable. Study selection was completed by a combination of 1 (Level

I) or 2 reviewers (Level II). Discrepencies were resolved via discussion among all authors.

Data collection process

A data extraction sheet was created in Excel to capture all data of interest from intervention trials. One independent extractor completed data extraction for all studies. The following list of data items (not exhaustive) was extracted from published intervention trials: *1*) study identification details [including study first author; year of study publication; title of publication (first 5 words); country where study was conducted; study type (RCT or OBS); double-blind (yes or no)]; *2*) subject baseline demographics; *3*) intervention details [including protein source; level of protein intake at baseline and incremental supplementation; duration of supplementation (days)]; *4*) dietary details (including baseline diet assessment method; baseline diet information); *5*) data details (including number of completed subjects in each group; number of enrolled subjects; *6*) outcome assessment method; *7*) outcome unit as reported by author; *8*) standard deviations (recorded if reported by author or calculated from available data); *9*) pre- and poststudy outcome means.

Protein intake

In order to make the studies more comparable, protein intake was recorded as grams per day, grams per kilogram per day, and percentage of total energy. Data were taken directly as reported by the author where possible, or calculated from data provided by the authors in the publication when possible.

Bias assessment

For RCTs, bias was assessed with the Cochrane Bias Assessment Tool (9). For prospective cohort studies, bias was assessed with the Newcastle-Ottawa scale (10). To assess bias in cross-sectional studies, an adapted version of the Newcastle-Ottawa scale was used (11). Bias assessments were completed by 2 individuals, results were reviewed collectively, and discrepancies resolved via discussion.

Results

Search results

The Pub Med search yielded 564 publications. An additional 11 publications were discovered via review of pertinent publication bibliographies for a total of 575 publications screened at Level I (i.e., title and abstract). In total, 482 publications were excluded based on initial (Level I) screening of abstracts and titles (**Figure 1**). The most common reason for exclusion of studies at Level I screening was ineligible subject population. Full-text publications of 94 studies were retrieved for complete full-text review at Level II. Sixty-eight studies were excluded at Level II. Citations for studies excluded at Level II with reason for exclusion are listed in **Supplemental Table 1**. Although some trials and observational studies had more than one reason for exclusion, each study was classified into only one exclusion category. A total of 26 studies (18 RCTs and 8 OBSs) were included. For ease of discussion, the studies were grouped according to study type (RCT or OBS) and reported outcomes.

Observational studies

Cross-sectional. Six cross-sectional studies (12–17) of moderate to high risk of bias met our inclusion criteria (**Table 1**, **Supplemental Tables 2** and **3**). Two prospective cohorts (18, 19) of moderate to low risk of bias also met our inclusion criteria (**Table 2**, **Supplemental Table 4**). Ausman et al. (12) reported a cross-sectional study of a small population of women with varying levels and types of dietary protein intake all in excess of the US RDA. Generally speaking, omnivores had higher total protein intake (1.3 g/kg) than vegans (0.96 g/kg), but all outcomes remained within normal limits (WNL) for both groups (Table 1). One study (15) reported differences in urinary and blood outcomes related to kidney function in body builders compared with other athletes. During a 30-d follow-up, estimated protein intake of up to nearly 2.0 g/kg protein intake (protein source not reported) did not appear to negatively influence markers of kidney function in athletes with all outcomes remaining normal (Supplemental Table 2) (15). Teo et al. (16) found no association between protein intake (0.97 ± 0.28 g $\cdot$ kg^{-1} $\cdot$ d^{-1}) and GFR (measured) or serum creatinine in a small sample of healthy Asian adults (Table 1). Ogna et al. (14) found a significant association between creatinine clearance (WNL), but no other kidney function parameter, including estimated glomerular filtration rate (eGFR), in healthy Swiss adults with an average intake of 1.05 g protein/kg (Table 1). Observation of healthy Norwegian adults failed to find an association between protein intake and serum uric acid (17). Finally, Berryman et al. (13) reported on the largest cross-sectional sample of adults and kidney-related outcomes, further delineated according to protein source (i.e. total, animal, dairy, plant). eGFR for all levels of intake ($\leq$1.45 g/kg) was consistent with normal kidney function, and was positively associated with plant and total protein, although this association was nonsignificant after adjustment for common demographic/anthropometric variables, as well as carbohydrate, total fat, saturated fat, and fiber intake. Similarly, plant protein was positively associated with blood pressure, but this observation was also attenuated after adjustment for confounding factors. All protein types and levels were associated with creatinine levels, but after adjustment the association was attenuated for all but total protein. The authors found no evidence of an association between GFR, blood urea nitrogen and creatinine levels with increasing consumption of various protein types (Table 1) (13).

Prospective cohort. The prospective cohort studies (Table 2) (18, 19) included in this review provide limited evidence of an association between level or protein source, and risk of kidney disease. Herber-Gast et al. (18) reported a significant association between increased low-fat dairy and maintenance of normal eGFR in healthy Dutch adults during 15 y of follow-up. No association between total and animal

protein and incidence of kidney disease was noted during 21 y of follow-up in a population of US adults, whereas vegetable protein was associated with a significant 11% decreased risk of kidney disease. While neither study (18, 19) provided information sufficient to calculate grams per kilogram protein intake, both reported protein intake levels consistent with ≥10% of energy, which is consistent with ≥0.8 g/kg based on reference body weights for men and women.

Randomized controlled trials

The majority of included clinical trials were of moderate to high risk of bias (**Supplemental Figure 1**), and were conducted in healthy subjects ($n = 10$) (20–29) or those with either mild hypertension ($n = 2$), hyperlipidemia ($n = 2$) (30, 31), or type 2 diabetes without microalbuminuria ($n = 4$) (32–35). The majority of studies were crossover design of ≥4 d in duration. While many ($n = 7$) studies exceeded 1 mo in duration, no studies were conducted over a period ≥6 mo. Five studies were >1 wk, but <1 mo and 6 studies lasted between 4 and 7 d. Most studies had a small sample size (≤60 subjects; mean = 16). Only 2 studies (36, 37) exceeded 100 subjects. Studies were fairly evenly distributed between those of both men and women and single-sex studies, and those enrolling younger (≤30 y old) or older (40–70 y old) subjects. The majority of studies assessed kidney function by measuring the effect of protein intake on a variety of outcomes including GFR with a fairly even distribution of those reporting eGFR and measured GFR. Several studies ($n = 9$) also reported the influence of protein intake on blood pressure; a few studies ($n = 3$) reported hormone-related variables.

Effect of protein intake on blood pressure. In all studies examining blood pressure outcomes (**Supplemental Table 5**), except one (32), the normal/low-protein group provided ≥0.8 $g \cdot kg^{-1} \cdot d^{-1}$, with most providing ≥1.0–1.5 $g \cdot kg^{-1} \cdot d^{-1}$ for the normal/control group, compared with 2.0–2.5 $g \cdot kg^{-1} \cdot d^{-1}$ for the higher-protein group. One study (32) compared a diet substituting chicken for red meat (1.3 g/kg) with a low-protein diet (0.66 g/kg) in healthy diabetic subjects on various outcomes. The majority of studies supplemented protein either by the addition of animal protein alone (meat and dairy products) or a combination of animal and vegetable protein. Two studies (30, 33) increased protein intake with the use of plant proteins. Regardless of protein

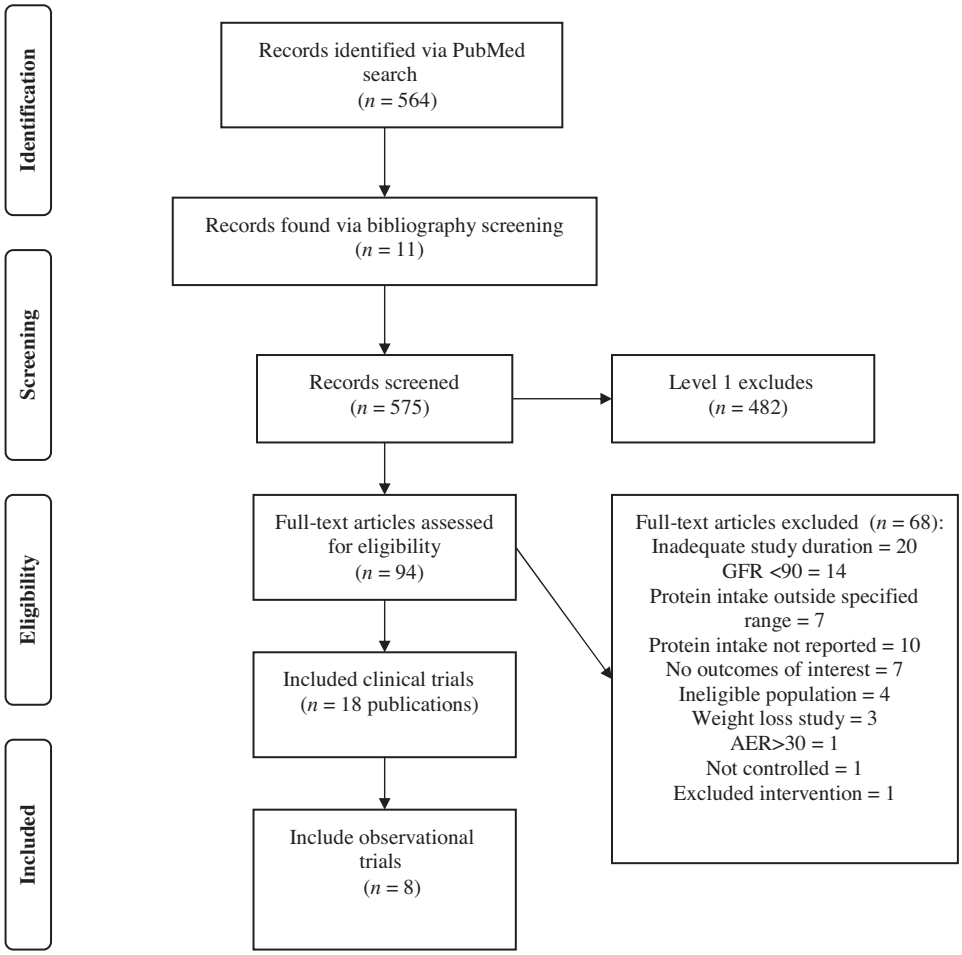

FIGURE 1 Flow diagram of literature search and study selection. AER, albumin excretion rate; GFR, glomerular filtration rate.

TABLE 1 Cross-sectional studies relating protein intake to kidney function outcomes in healthy adults[1]

Study	Subjects	Protein source and distribution (Sodium level)	Protein intake, g/d	Protein intake, g/kg	Protein intake, % kcal	Results and conclusions[2]
Ausman et al., 2008 (12)	Healthy women; age: 23–60 y; cross-sectional	V; $n = 10$ (100 mEq Na/d)	49.4	0.96[3]	NR	Kidney function: Creatinine (mmol · kg^{-1} · d^{-1}) was higher ($P = 0.011$) among OVs (V = 155 vs. LOV = 146 vs. OV = 173); urinary creatinine WNL; pH was intermediate for LOV and different ($P = 0.013$) between V and OV (V = 6.15 vs. LOV = 5.90 vs. OV = 5.74); urinary pH WNL Conclusions: Urinary pH is elevated but WNL among women consuming 1.3 g · kg^{-1} · d^{-1} (OV diet) vs. 0.96 g · kg^{-1} · d^{-1} (V diet). Protein sources cannot be directly compared as intake amounts varied Strengths/limitations: Urine samples collected over 72 h/small sample size; diets not matched for protein intake, so unable to compare sources
		LOV; $n = 16$ (80 mEq Na/d)	57.5	1.0[3]	NR	
		OV; $n = 16$ (109 mEq Na/d)	72.0	1.3[3]	NR	
Berryman et al., 2016 (13)	Healthy US men and women, $n = 11{,}111$; age: 37–50 y	Total (Na NR)	82.3	0.53;0.93;1.45[4]	NR	Kidney function: eGFR = 94.6 mL · min^{-1} · 1.73 m^{-2}) (N); positively associated with plant ($P = 0.0002$) and total protein ($P = 0.04$) intake, NS after adjustment Blood urea nitrogen: 4.7 mmol/L (WNL); all protein levels and sources positively associated except plant protein after further adjustment Serum creatinine: 79 μmol/L (WNL); positively associated with intake and source, attenuated for all except total ($P = 0.038$) after further adjustment Conclusions: "In healthy adults with no history of renal disease, GFR, blood urea nitrogen, and creatinine remain WNL with increasing consumption of animal, dairy, and plant protein." Strengths/limitations: Large sample size; outcome variables measured or from laboratory records (NHANES)/observational design; self-reported dietary data
		Nondairy animal (Na NR)	37.4	0.28;0.45;0.69[4]	NR	
		Dairy (Na NR)	13.4	0.08;0.18;0.29[4]	NR	
		Plant (Na NR)	24.7	0.20;0.30;0.47[4]	NR	
Ogna et al., 2016 (14)	Healthy Swiss adults, $n = 1339$; age: 34.3–63.5 y	Total protein intake assessed via administered questionnaire (3.4 g Na/d)	75.0	1.05[3]	NR	Kidney function: Serum creatinine = 78 μmol/L (WNL); creatinine clearance = 106.8 mL/min (WNL); eGFR = 94.7 mL · min^{-1} · 1.73 m^{-2}) (N); volume 1863 mL (WNL); creatine excretion 151 mmol · kg^{-1} · d^{-1} (WNL) Both protein ($P < 0.001$) and sodium ($P < 0.001$) showed a strong positive linear correlation with measured creatinine clearance. Association between other outcomes and protein NR. Conclusions: Results suggest that sodium may be a modifying factor in the association between eGFR and obesity. Functional outcomes were N or WNL at intake levels >US RDA for protein Strengths/limitations: Large sample size/GFR estimated
Teo et al., 2015 (16)	Healthy Asian adults, $n = 103$	Total protein (Na NR)	58.9	0.91	NR	Kidney function: GFR = 101 mL · min^{-1} · 1.73 m^{-2} (N); serum creatinine = 70 μmol/L (WNL); urine volume = 1580 mL (WNL); no associations reported Conclusions: All functional outcomes were N or WNL at average intake >US RDA for protein. Strengths/limitations: Measured GFR/small sample size; dietary intake methods not described
Zykova et al., 2015 (17)	Healthy Norwegian adults, $n = 3031$	Q1 (Na NR)	77	NR	15	Kidney function: Serum uric acid = 350 μmol/L (WNL); eGFR = 95–96 mL · min^{-1} · 1.73 m^{-2} (N) Conclusions: High-protein low-fat diets are not associated with increased serum uric acid Strengths/limitations: Large sample size/GFR estimated; self-administered FFQ
		Q2 (Na NR)	88	NR	17	
		Q3 (Na NR)	101	NR	18	
		Q4 (Na NR)	228	NR	29	

[1] Normal reference values: GFR = ≥90 mL · min^{-1} · 1.73 m^{-2}; urinary creatinine = 133–221 mmol · kg^{-1} · d^{-1}; urinary pH = 4.5–8; blood pH: 7.35–7.45; blood urea nitrogen: 2.5–8.0 mmol/L; creatinine clearance: 75–125 mL/min; serum creatinine—adult men: 70–120 μmol/L; adult women: 50–90 μmol/L; serum uric acid: 180–420 μmol/L; urinary volume: 800–2000 mL. NS: $P \geq 0.05$. eGFR, estimated glomerular filtration rate; GFR, glomerular filration rate; LOV, lacto-ovo vegetarian; N, normal; NR, not reported; OV, omnivore; Q, quartile; V, vegan; WNL, within normal limits.

[2] Values reported as means by original publication.

[3] Calculated from data provided in study publication.

[4] Reported for deciles 1, 5, and 10.

TABLE 2 Prospective cohort studies relating protein intake to kidney function outcomes in healthy adults[1]

Study	Subjects (follow-up duration)	Protein source and distribution (Sodium levels)	Protein intake, g/d (total cohort)	Protein intake, g/kg (total cohort)	Protein intake,[2] % kcal (total cohort)	Results and conclusions[3]
Herber-Gast et al., 2016 (18)	Healthy Dutch adults, $n = 3798$; age: 35.5–54.9 y (15 y)	Total (Na NR)	82.4	NR	14.5	eGFR: Baseline 108.6 mL · min^{-1} · 1.73 m^{-2}; annual decline −1.01
		Vegetable (Na NR)	30.2	NR	5.3	Conclusions: Intake of total, vegetable, and animal protein are not associated with changes in eGFR over time; increased low-fat dairy was associated with less eGFR decline ($P = 0.0004$)
		Animal (Na NR)	52.0	NR	9.1	
		Nondairy animal (Na NR)	27.6	NR	4.9	
		Dairy (Na NR)	24.5	NR	4.3	Strengths/limitations: Large sample size with adequate follow-up/GFR estimated; self-administered dietary FFQ
Rebholz et al., 2015 (19)	Healthy US adults, $n = 15{,}792$; age: 45–64 y (21 y)	Total (Na NR)	72.4	NR	17.8	Kidney disease incidence: Neither total ($P = 0.40$) nor animal protein ($P = 0.10$) were associated with increased risk of kidney disease (15.6% during follow-up); vegetable protein was associated ($P < 0.004$) with an 11% decrease in kidney disease risk; eGFR = 102–104 mL · min^{-1} · 1.73 m^{-2} (N)
		Vegetable (Na NR)	17.7	NR	4.4	
		Animal (Na NR)	54.6	NR	13.5	Net endogenous acid production (mEq): Higher acid load ($P = 0.004$), with an 8% increased risk of kidney disease
						Conclusions: As total and animal protein intake were not linked to disease, limited vegetable protein intake may, in part, contribute to increased risk
						Strengths/limitations: Large sample size; adequate follow-up/self-administered FFQ: GFR estimated

[1] Normal reference values: GFR = ≥90 mL · min^{-1} · 1.73 m^{-2}. eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; N, normal; NR, not reported.
[2] Calculated from data provided in study publication.
[3] Values reported as means by original publication.

level or source, the majority of studies reported no significant effect of diet on blood pressure outcomes (Supplemental Table 5).

The only studies to report an influence of protein intake on blood pressure were the 2 largest, representing the Dietary Approaches to Stop Hypertension Trial (DASH) ($n = 378$) (36) and the Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) ($n = 164$) (37), which both found that higher protein intake was associated with lower blood pressure in subjects with mild hypertension. Specifically, Jursacheck et al. (37) compared 3 sodium-matched diets (2300 mg/d) designed to provide higher carbohydrate, unsaturated fat, or protein. The carbohydrate and unsaturated fat diets provided 15% of energy from protein, whereas the protein diet provided 25% of energy as protein and resulted in the lowest blood pressure at study end. Similarly, Jacobs et al. (36) compared a normal diet (13.8% of energy), a fruit and vegetable diet (15.1%), and a DASH diet (17.9%) with similar sodium levels (1314–1354 mg/1000 kcal) in hypertensive men and women. Participants consuming the DASH diet consumed the highest level of protein and exhibited the lowest blood pressure at study end.

Urinary measures of kidney health and function. Studies examining urinary measures related to kidney health (**Table 3**) typically compared normal/control protein intakes of 0.7–1.5 g/kg with higher protein intakes of 1.8–2.5 g/kg daily. Four studies did not report the source of added protein. Of the studies reporting protein source, half reported supplementing protein intake with animal protein, either as a combination of meat and dairy or as poultry and fish, compared with a combination of plant and animal protein or plant protein only. Only 2 studies (32, 26) reported urinary measures in response to either plant or animal protein.

The most commonly reported variable of kidney function was measured (as opposed to estimated) GFR, with 13 studies comparing GFRs obtained with normal and higher protein intakes. Most ($n = 8$), but not all ($n = 5$), studies reported significantly higher GFR in response to increased protein intake. No obvious pattern emerged regarding those reporting increased GFR compared with those that did not. Those studies that did not observe increased GFR following increased protein intake were mixed with regard to gender distribution, length of study, source of protein, and whether or not GFR was measured or estimated. Among studies reporting an increased GFR in response to protein intake, rates remained

TABLE 3 Randomized controlled trials in healthy adults relating protein intake to urinary measures of kidney function[1]

Study	Subjects; study design and duration; added protein source	Protein diets (Sodium level)	Protein intake, g/d	Protein intake, g/kg	Protein intake, % kcal	Results and conclusions[2]
Doorenbos et al., 1990 (20)	Healthy men, $n = 8$; age: 21–24 y; 1-wk crossover; red meat	Basal diet (3220 mg Na/d)[3]	79.3[3]	1.0	NR	Urinary factors: ↑ creatinine (16.3 vs. 18.0 mmol · kg^{-1} · d^{-1}; $P < 0.01$); ↑ potassium (76.7 vs. 82.0 mmol/24 h; $P < 0.05$); ↑ uric acid (4.72 vs. 6.77 mmol/24 h; $P < 0.01$); ↑ eGFR (∼120 vs. 130 mL · min^{-1} · 1.73 m^{-2}; $P < 0.01$) (N)
		High protein (3220 mg Na/d)[3]	158.8[3]	2.0	NR	
		High Na (7130 mg Na/d)[3]	79.8[3]	1.0	NR	
		High Na, high protein (7130 mg Na/d)[3]	160.0[3]	2.0	NR	Conclusions: In healthy adults, glucagon may contribute to ↑ GFR in response to ↑ protein intake (1 vs. 2 g/kg)
						Strengths/limitations: Diets matched for sodium content/small sample size; limited duration; GFR estimated
Frank et al., 2009 (21)	Healthy men, $n = 24$; age: 22–26 y; randomized 1-wk crossover; animal protein/milk and milk products	Normal protein (2482 mg Na/d)	88	1.2	13.3	Urinary factors: ↑ urinary albumin excretion (8.7 vs. 18.3 mg/24 h; $P < 0.05$); ↓ pH (6.45 vs. 5.79; $P < 0.05$); ↑ sodium (173.4 mmol/24 h vs. 215.6; $P < 0.05$); ↑ urea nitrogen (mmol/L); ↑ GFR (125 vs. 141 mL · min^{-1} · 1.73 m^{-2}; $P < 0.001$); ↑ renal filtration fraction (23% vs. 28%; $P < 0.05$)
		High protein (2737 mg Na/d)	181	2.4	26.6	Conclusions: A short-term, "high-protein diet in healthy young men induces significant changes in the GFR, the filtration fraction, albuminuria, serum uric acid, and urinary pH values, whereas other indicators of renal function remained unchanged. Although the clinical significance of these findings is unclear, it is recommended that more attention be paid to the monitoring of renal function in humans consuming high protein diets"
						Strengths/limitations: GFR measured/diets not matched for sodium content; short duration
Gross et al., 2002 (32)	Normoalbuminuric, type 2 diabetic men and women, $n = 28$; age: 47–69 y; 4-wk randomized, controlled crossover; chicken leg quarters replaced red meat in usual diet, milk/vegetable protein only in low-protein diet	Usual protein diet (Na NR)	NR	1.43	NR	Urinary factors: ↑ GFR in response to usual vs. chicken diet or low-protein diet (113.4 vs. 101.3 or 93.8 mL · min^{-1} · 1.73 m^{-2}; $P = 0.0029$)
		Chicken-based diet (Na NR)	NR	1.35	NR	
		Low-protein diet (Na NR)	NR	0.66	NR	Conclusions: "A normoproteic diet with chicken as the only source of meat may represent an alternative strategy for treatment of patients with type II diabetes and microalbuminuria"
						Limitations: Dietary sodium levels not reported; GFR measured, but test used prone to overestimation
Jacobs et al., 2009 (36); DASH Trial	Hypertensive men and women, $n = 378$; age: 22–75 y; 8-wk randomized, parallel; mixed protein sources, DASH diet lowest in animal protein including fish, highest in dairy protein	Usual diet (1354 mg Na/1000 kcal)	79	NR	13.8	Urinary factors: In subjects with elevated albumin excretion rate (mg/24 h) at baseline, fruit and vegetable diet (moderate protein) lowered albumin excretion rate vs. usual (lower protein) and DASH (higher protein)
		Fruit and vegetable diet (1314 mg Na/1000 kcal)	82	NR	15.1	
		DASH diet (1324 mg Na/1000 kcal)	95	NR	17.9	Conclusions: "Despite substantially greater protein content in the DASH than the control diet, the DASH diet did not increase albuminuria compared with the control diet"
						Strengths/limitations: Animal protein primarily as dairy/GFR not reported

(*Continued*)

TABLE 3 (*Continued*)

Study	Subjects; study design and duration; added protein source	Protein diets (Sodium level)	Protein intake, g/d	Protein intake, g/kg	Protein intake, % kcal	Results and conclusions[2]
Jenkins et al., 2001 (30)	Hyperlipidemic men and women, $n = 20$; age: 35–71 y; 4-wk crossover; wheat gluten from modified bread (modified bread contributed significantly greater Na compared with control)	High-vegetable protein (Na NR) Control diet (Na NR)	189 111	2.5[3] 1.5[3]	27.4 15.6	Urinary factors: ↑ urea in response to high plant protein (control 432 mmol/d vs. high-vegetable protein 801 mmol/d; $P < 0.001$); ↑ urea clearance in response to high plant protein (control 53 mL/min vs. high-vegetable protein 67 mL/min; $P = 0.005$) Conclusions: Further studies are required to assess the long-term effects of high-vegetable protein intake on renal function Limitations: Diets not matched for sodium; GFR estimated
Jenkins et al., 2003 (31); (companion paper to 30)	Hyperlipidemic men and women, $n = 20$; age: 35–71 y; 4-wk crossover; wheat gluten from modified bread (modified bread contributed significantly greater Na compared with control)	High-vegetable protein (Na NR) Control diet (Na NR)	189 111	2.5[3] 1.5[3]	27.4 15.6	Urinary factors: ↑ sodium (control 3623 mmol/24 h vs. high-vegetable protein 4401 mmol/24 h; $P = 0.013$) and chloride (control 6062 mmol/d vs. high-vegetable protein 7338 mmol/d; $P = 0.011$) (WNL) Conclusions: No changes in kidney function suggested; changes in urinary sodium likely due to increased sodium intake caused by high-vegetable protein bread Limitations: Diets not matched for Na
Jursachek et al., 2013 (37); OmniHeart	Healthy men and women with mild hypertension, $n = 164$; age: ≥30 y; 6-wk crossover with variable 2- to 4-wk washout; plant protein (legumes, grains, nuts, and seeds)	CHO diet (2300 mg Na/d) Unsaturated fat diet (2300 mg Na/d) Protein diet (2300 mg Na/d)	NR NR NR	NR NR NR	15 15 25	Urinary factors: Protein diet ↑ eGFR mL · min^{-1} · 1.73 m^{-2} ($P < 0.001$); baseline = 92.0; mean GFR difference between CHO diet vs. unsaturated fat diet, 0.34; protein diet vs. CHO diet, 4.25; protein diet vs. unsaturated fat diet, 4.58 Conclusions: Increased plant protein diets lowered blood pressure, but increased GFR through independent mechanisms Strengths/limitations: Diets matched for Na/washout period variable; GFR estimated
Kerstetter et al., 1997 (23)	Healthy women, $n = 7$; mean age: 26.7 y; 2-wk crossover; poultry and fish	Low protein (100 mmol Na/d) Medium protein (99.9 mmol Na/d) High protein (99.9 mmol Na/d)	45 63 129	0.7 1.0 2.1	8.6[3] 12.6[3] 26.4[3]	Urinary factors: NS effect of diet on measured GFR (mL · min^{-1} · 1.73 m^{-2}) or sodium (mmol/24 h) Conclusions: No apparent effect of diets on limited measures of kidney function Strengths/limitations: Diets matched for sodium; GFR measured/short duration; very small sample size
Kerstetter et al., 1998 (24)	Healthy women, $n = 12$; age: 21–39 y; 5-d crossover; poultry, fish, and egg whites	Low protein (100 mmol Na/d) High protein (100 mmol Na/d)	45.8 135	0.7 2.1	8.2[3] 26[3]	Urinary factors: ↑ nitrogen (low 477 vs. high 1211 mmol/L; $P = 0.00003$); ↑ GFR (low 101 vs. high 116 mL · min^{-1} · 1.73 m^{-2}; $P = 0.05$) Conclusions: GFR ↑ despite control of sodium intake, but remained N Strengths/limitations: Diets matched for Na; GFR measured/short duration; very small sample size

(*Continued*)

TABLE 3 (*Continued*)

Study	Subjects; study design and duration; added protein source	Protein diets (Sodium level)	Protein intake, g/d	Protein intake, g/kg	Protein intake, % kcal	Results and conclusions[2]
Kerstetter et al., 2000 (25)	Healthy women, $n = 8$; mean age: 23.1 y; 4-d crossover; equal amounts animal and vegetable protein	0.7 g protein/kg body weight diet (100 mmol Na/d)	44.3	0.7	8.0[3]	Urinary factors: NS effect of diet on nitrogen (mmol/L), sodium (mmol/24 h), or GFR (mL · min^{-1} · 1.73 m^{-2}) Conclusions: NS effects of diet on renal function Strengths/limitations: Diets matched for sodium; GFR measured/short duration; very small sample size
		0.8 g protein/kg body weight diet (100 mmol Na/d)	50.2	0.8	9.4[3]	
		0.9 g protein/kg body weight diet (100 mmol Na/d)	56.7	0.9	11.0[3]	
		1.0 g protein/kg body weight diet (100 mmol Na/d)	62.7	1.0	12.4[3]	
Kerstetter et al., 2006 (26)	Healthy women, $n = 20$; mean age: 29.2 y ($n = 12$); mean age: 58.9 ($n = 8$); 4-d crossover; beef, poultry, fish, and dairy (high-meat diet); soy diets free of meat	Low-meat diet (103 mmol Na/d)	45	0.7	8.2[3]	Urinary factors: ↓ titratable acid (mEq) in response to soy; ↑ sodium in response to protein level (low meat, 86 vs. high meat, 102 mmol/24 h; low soy, 86 vs. high soy, 97 mmol/24; $P = 0.04$); ↑ net acid excretion in response to protein level (low meat, 34.8 vs. high meat, 53.2 mmol/d; low soy, 10.8 vs. high soy, 39.4 mmol/d; $P = 0.03$); ↑ GFR (low meat, 94 vs. high meat, 107 mL · min^{-1} · 1.73 m^{-2}; low soy, 94 vs. high soy, 103 mL · min^{-1} · 1.73 m^{-2}; $P < 0.01$) Conclusions: GFR ↑ despite control of sodium intake, but remained N Strengths/limitations: Diets matched for Na; GFR measured/short duration; very small sample size
		High-meat diet (102 mmol Na/d)	134	2.1	25.0[3]	
		Low-soy diet (102 mmol Na/d)	45	0.7	8.5[3]	
		High-soy diet (103 mmol Na/d)	130	2.0	24.0[3]	
Kitazato et al., 2002 (22)	Healthy men and women, $n = 14$; mean age: 21 y; 1-wk crossover; diets with varying combinations of animal, fish, and vegetable proteins	Diet A (mainly animal protein) (Na NR)	83.8	NR	16.2	Urinary factors: ↓ sodium with Diet B (180 vs. 141 mmol/24 h; $P < 0.05$), group I only; ↓ GFR vs. Diet A (159 mL · min^{-1} · 1.73 m^{-2}) in response to Diet B (138 mL · min^{-1} · 1.73 m^{-2}; group I) and Diet C (131 mL · min^{-1} · 1.73 m^{-2}; group II) ($P < 0.05$); ↓ renal plasma flow vs. Diet A (679 mL · min^{-1} · 1.73 m^{-2}) in response to Diet B (536 mL · min^{-1} · 1.73 m^{-2}; group I) and Diet C (606 mL · min^{-1} · 1.73 m^{-2}; group II) ($P < 0.05$) Conclusions: Reduced animal protein diet resulted in favorable change in renal function; additional animal protein did not negate this effect Strengths/limitations: GFR measured/short duration; dietary sodium NR
		Diet B (lower protein, mainly animal) (Na NR)	59.4	NR	12.3	
		Diet C (similar animal/vegetable protein) (Na NR)	79.3	NR	15.7	
Martin et al., 2006 (27)	Healthy men, $n = 5$; mean age: 21 y; 12-wk crossover; NR	High protein (Na NR)	NR	3.6	30	Urinary factors: ↑ renal solute load with increasing protein (674 vs. 1029 vs. 1590 mOsm), significance NR (WNL); ↑ urine-specific gravity (moderate protein, 1.019 vs. high protein, 1.021; $P < 0.05$) Conclusions: Changes in measures of renal function only apparent in response to protein intake 4× the RDA, but remained WNL; no significant changes in measures of renal function with protein intake 2× the RDA Strengths/limitations: Long-term study/small sample size
		Moderate protein (Na NR)	NR	1.8	15	
		Low protein (Na NR)	NR	0.8	10	

(*Continued*)

TABLE 3 (*Continued*)

Study	Subjects; study design and duration; added protein source	Protein diets (Sodium level)	Protein intake, g/d	Protein intake, g/kg	Protein intake, % kcal	Results and conclusions[2]
Nutall et al., 2003 (35)	Healthy, type 2 diabetic men and women, $n = 12$; mean age: NR; 5-wk crossover; NR	15% protein diet (3353 mg Na/d) 30% protein diet (3774 mg Na/d)	NR NR	NR NR	15 30	Urinary factors: ↑ free cortisol (nmol/24 h) 39% in response to 30% ($P < 0.06$); ↓ pH ($P < 0.05$) with 30% diet (6.2 vs. 5.8); ↑ sodium (mmol/24 h) with 30% diet; ↑ creatinine in response to 30% (15.4 vs. 17.5 mmol · kg^{-1} · d^{-1}); ↑ urea in response to 30% (0.22 vs. 0.34 mol); ↑ uric acid in response to 30% (4.0 vs. 5.4 mmol/24 h) Conclusions: Changes in measures of renal function remained WNL for type 2 diabetics with increased protein intake Strengths/limitations: Longer-term study/diets not matched for Na; small sample size
Nutall et al., 2006 (33)	Healthy, type 2 diabetic men, $n = 8$; mean age: 63 y; 5-wk parallel; mix of animal and vegetable protein	Control 15% protein (Na NR) LoBAG 30% protein (Na NR)	NR NR	NR NR	15 30	Urinary factors: ↑ sodium (451 vs. 6923 mmol/24 h; $P < 0.05$); ↓ glucose in response to LoBAG (14 vs. 0.3 mmol/24 h); ↑ creatinine in response to LoBAG (13.3 vs. 20.6 mmol · kg^{-1} · d^{-1}; $P < 0.05$); ↑ urea in response to LoBAG (0.72 vs. 0.90 mol; $P < 0.06$) Conclusions: Improved glucose control and positive nitrogen balance support higher protein diet for older, type 2 diabetics at risk of sarcopenia Strengths/limitations: Longer-term study/small sample size; diets not matched for Na
Roughead et al., 2003 (28)	Healthy, postmenopausal women, $n = 15$; mean age: 60.5 y; 8-wk crossover; primarily beef round, but also pork, turkey, ham, and chicken breast	Low-meat diet (3243 mg Na/d) High-meat diet (3601 mg Na/d)	68 117	0.94 1.62	12 20	Urinary factors: ↑ phosphorus (19.2 vs. 20.3 mmol/24 h; $P < 0.001$); ↑ GFR (1.21 vs. 1.38 mL · min^{-1} · 1.73 m^{-2}; $P < 0.05$), ↑ sodium (100 vs. 120 mmol/24 h;), ↑ potassium (30.0 vs. 45.5 mmol/24 h), ↑ ammonium (35.0 vs. 42.5 mmol/24 h), and ↑ sulfate (2.6 vs. 3.1 mmol/24 h ($P < 0.0001$); ↑ creatinine (7.8 vs. 8.8 mmol · kg^{-1} · d^{-1}) and titratable acid (30.5 vs. 35.4 mEq) Conclusions: Changes in measures of urinary function due to diet diminished over time during the 8-wk study period, suggesting adaptation Strengths/limitations: Longer study period/small sample size; sodium between diets not controlled
Velazquez et al., 2008 (34)	Healthy, type 2 diabetic men and women, $n = 60$ (results reported for $n = 19$ with normoalbuminuria); age: 60–68 y; 4-mo parallel; NR	Normal protein (Na NR) Low protein (Na NR)	87 56	1.2 0.82	16[3] 12.8[3]	Urinary factors: NS effect of diet on GFR (mL · min^{-1} · 1.73 m^{-2}) and urinary albumin excretion rate (mg/24 h) Conclusions: Kidney function appears unaffected by a high-meat diet in older, type 2 diabetics without microalbuminuria Strengths/limitations: Long study duration/small sample size, dietary sodium not reported; GFR estimated

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TABLE 3 (*Continued*)

Study	Subjects; study design and duration; added protein source	Protein diets (Sodium level)	Protein intake, g/d	Protein intake, g/kg	Protein intake, % kcal	Results and conclusions[2]
Walrand et al., 2008 (29)	Healthy men and women, $n = 19$; mean age: 24 y ($n = 10$); mean age: 70 y ($n = 9$); 1-d crossover; NR	Usual protein (Na NR)	72.7 (young); 68.6 (old)	1.04 (young); 0.89 (old)	11.1 (young); 11.8 (old)	Urinary factors: GFR was lower in older participants; ↑ GFR in younger adults (105.9 vs. 127.8 mL · min^{-1} · 1.73 m^{-2}; $P < 0.05$) Conclusions: Difficult to determine if lack of increased GFR in older adults is concerning, or reflects differences in urinary function between populations with insufficient study duration to determine possible adaptation Strengths/limitations: GFR measured/short duration; small sample size
		High protein (Na NR)	147 (young); 137 (old)	2.08 (young); 1.70 (old)	21.8 (young); 23.6 (old)	

[1] Normal reference values: GFR = ≥90 mL · min^{-1} · 1.73 m^{-2}; urinary creatinine: 133–221 mmol · kg^{-1} · d^{-1}; urinary pH: 4.5–8; renal filtration factor: ∼20%; urinary potassium: 25–100 mmol/24 h; urinary uric acid: 1.48–4.43 mmol/24 h; urinary albumin: 50–80 mg/24 h; urinary sodium: 100–260 mmol/24 h; urinary urea nitrogen: 142.84–428.52 mmol/L; C-peptide: 0.26–0.62 nmol/L; urinary chloride: 80–250 mmol/d; specific gravity: 1.005–1.025; urinary sulfate: 7–47 mmol/24 h; urinary cortisol: 9.7–12.4 nmol/24 h; urinary aldosterone: 13.9–52.6 nmol/24 h; urinary phosphorus: 12.9–42 mmol/24 h; urinary magnesium: 3.0–4.3 mmol/24 h; urinary glucose: <2.8 mmol/24 h; microalbumin: <30 mg/24 h. NS: $P \geq 0.005$. CHO, carbohydrate; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; LoBAG, low bioavailable glucose; N, normal; NR, not reported; WNL, within normal limits; ↓, decrease; ↑, increase

[2] Values reported as means by original publication.

[3] Calculated from data provided in study publication.

normal (i.e. ≥90 mL · min^{-1} · 1.73 m^{-2}) for healthy adults. The highest mean GFRs reported were between 125 and 159 mL · min^{-1} · 1.73 m^{-2}) (20–22). Studies reporting the highest GFR were mostly of limited duration (1 wk), in young subjects (aged 21–26 y), and were small in size (≤24 subjects). It is likely that the age of the subjects contributed most to the observation of the high GFR in these studies (rather than duration or sample size) as GFR is influenced by age, and higher in young, compared with older adults (8). Among studies of limited duration that failed to observe an increased GFR, some used diets formulated to have equal levels of sodium intake (23, 25, 26).

Two studies (32, 34) in the current review measured GFR in healthy diabetic subjects (with normal urinary albumin concentrations) in response to increased protein intake up 1.4 g · kg^{-1} · d^{-1}. While providing 1.2 g protein/kg for 4 mo to older (60–68 y) diabetic men and women had no effect on GFR (34), providing 1.4 g/kg to older (47–69 y) diabetic men and women for 4 wk compared with a low-protein diet (0.66 g/kg) significantly increased GFR (from 113 to 93.8 mL · min^{-1} · 1.73 m^{-2}) (32). Two studies (35, 33) in the current review reported urinary glucose concentrations in older type 2 diabetics in response to elevated protein intake. One study (35) found no effect of protein intake on urinary glucose, but the other (33) reported a significant reduction in urinary glucose in response to a diet designed to provide 30% of energy as protein compared with 15%.

Increased risk of kidney stone formation is an additional concern when considering consumption of protein above the US RDA (38, 39). Six studies in the current review examined factors related to kidney stone formation. Doorenbos et al. (20) reported elevated uric acid in 8 young men supplemented with either 1 or 2 g · kg^{-1} · d^{-1} for 1 wk. Similarly, Nutall et al. (35) reported elevated uric acid in 12 type 2 diabetics in response to 30% of energy as protein during a 5-wk study. In contrast, Jenkins et al. (30) found no effect of protein at 1.5–2.5 g/kg on uric acid or uric acid clearance in older men and women ($n = 20$) during a 4-wk study. Kerstetter et al. (26) reported a significant increase, within normal limits, in net acid excretion in women participating in a 4-d study and consuming ≤2.0 g · kg^{-1} · d^{-1}. Finally, studies by Nutall et al. (35, 33) reported no significant effect of protein level on urinary calcium, magnesium, potassium, or phosphorous.

Blood markers of kidney health. Ten studies measured a variety of blood markers of kidney function in response to protein intakes (**Supplemental Table 6**) of 0.7–1.5 g/kg up to higher protein intakes of 1.8–2.5 g/kg daily. Studies were mostly small and conducted with healthy subjects or those with mild hypertension or type 2 diabetes, but with normal kidney function. No studies directly compared plant and animal source protein for effects on blood measures of kidney function. No pattern of abnormality among blood variables, suggestive of adverse effects of increased protein intake, was observed. Generally speaking, increased protein intake had little or no effect on blood markers of kidney function. When changes were evident, for the most part, they remained WNL. One exception is provided by the study of 5 young men participating in a 12-wk crossover study comparing "low" (0.8 g/kg), "moderate" (1.8 g/kg), and "high" (3.6 g/kg) protein intake. In this study, protein intake of 3.6 g/kg significantly increased blood urea nitrogen concentrations beyond the UL of the normal range (i.e. 21.2 in subjects compared with 20 mg/dL UL of normal). Given the very small sample size, it is difficult to know if the observed increase is real or an artifact.

Discussion

The relation between dietary protein intake and systemic blood pressure is an important consideration because certain micronutrients known to impact blood pressure (e.g.

sodium, potassium, calcium) may also increase with increased protein consumption (7). In addition, elevated blood pressure is a prevalent disease risk factor with 31% of Americans hypertensive, 30% prehypertensive, and ~20% hypertensive, yet unaware of their status (40, 41). Evidence indicates only 47% of those with hypertension are adequately controlled (40). Prior research shows that diet and lifestyle modifications, including physical activity, sodium reduction, and fish oil supplementation, can reduce blood pressure, enhance antihypertensive drug efficacy, and decrease cardiovascular disease risk (42). Evidence reported here suggests that protein intake above the US RDA has no adverse effect on blood pressure and may, along with modified sodium intake, help reduce blood pressure. Importantly, our review limited studies of protein intake and blood pressure to only those designed to also measure kidney function. A broader evidence base relating blood pressure to protein intake exists, however. For example, meta-analyses of cross-sectional studies consistently report an inverse association between dietary protein intake and blood pressure, although neither analysis considered the potential impact of displacement of higher-sodium foods by increased protein intake (43, 44). Results from prospective cohorts are limited (43) and suggest either no association between blood pressure and protein intake (44), or an inverse association observed after ≤7 y of follow-up (43) and, in elderly subjects, a positive association between protein intake and risk of hypertension (45). Evidence from RCTs also supports an inverse relation between dietary protein and blood pressure, particularly when protein replaces carbohydrate, in both healthy subjects and those with type 2 diabetes (46, 47). Evidence further suggests that blood pressure reductions are observed regardless of source, with animal and plant proteins resulting in similar reductions (46). Although the mechanism by which protein intake lowers blood pressure is not fully elucidated, hypotheses regarding the observation include adaptive changes in kidney function, particularly increased GFR, and effects of individual amino acids on nitric oxide production (2, 48).

Increased GFR in response to high protein intake is well documented and is believed to be due to increased generation of nitric oxide and increased production of vasoactive kinins (49). The significance of increased GFR in healthy populations is debatable. It has been hypothesized that GFR >125 mL · min^{-1} · 1.73 m^{-2} should be considered "hyperfiltration" and that, over a prolonged period, this higher rate might contribute to the onset and progression of chronic kidney disease (49). Schwingshackl and Hoffman (50) recently conducted a meta-analysis of high- or low-protein RCTs designed for weight loss or weight maintenance. While weight-loss studies and those ≤24 h in duration were excluded from the current review, 30% of the studies of those reviewed by Schwingshackl and Hoffman overlap with the current review. Consistent with our observations, Schwingshackl and Hoffman report an increased mean difference in GFR with higher than with lower protein (+7.18 mL · min^{-1} · 1.73 m^{-2}; 95% CI: –4.45, 9.91 mL · min^{-1} · 1.73 m^{-2}) of unknown clinical relevancy in healthy adults. The authors speculate that the observed increase in GFR "could be interpreted as physiological adaptive mechanism induced by high protein (HP) diet without any clinical relevance." Oyabu et al. (51) conducted a meta-analysis of RCTs designed to examine the effectiveness of long-term (12–24 mo) low-carbohydrate diets (LCDS) for weight loss on kidney function. Both low- and normal-carbohydrate diets resulted in reduced GFR over time but the decrease reported for low-carbohydrate diets was significantly greater (–0.13 mL · min^{-1} · 1.73 m^{-2}; 95% CI: 0.00, 0.26 mL · min^{-1} · 1.73 m^{-2}). The authors concluded that "although the mean change in eGFR in the LCD group was greater than that in the control group, the difference was very low. Therefore, the clinical significance of LCD on renal function might not be great. However, this meta-analysis showed that LCD and the corresponding high-protein diet was not harmful for renal function in overweight and obese individuals without renal dysfunction."

One of the studies included in the current review (29) compared responses of young healthy subjects (mean age 24 y) with those of healthy older subjects (mean age 70 y) to protein intake levels up to twice the US RDA in older adults, and ≤2.0 g/kg in younger adults. GFR declines with age, as does the ability to further increase GFR in response to a high protein load (49). GFR of younger adults increased significantly within the normal range, but older adults did not respond with increased GFR and, in fact, GFR was lower at the end of the study period although the change was nonsignificant ($P = 0.13$). Given the limited duration of the study (10 d), it is impossible to determine if the nonsignificant change in GFR in older adults would be sustained or if GFR would increase were the study prolonged. Data such as these have led to concerns that elderly subjects may be at greater risk of kidney disease in response to higher levels of protein intake (52). However, recent cross-sectional data, although not meeting eligibility criteria for the current review, suggest otherwise. Beasley et al. (53) examined the association between dietary protein intake and GFR in elderly subjects participating in the Cardiovascular Health Study. Consistent with age, GFR in all participants was low (<75 mL · min^{-1} · 1.73 m^{-2} estimated), but interestingly, when stratified according to protein intake, little difference in GFR was observed between the highest (1.63 g/kg) and lowest (1.00 g/kg) quartiles of protein intake. In fact, the maximum GFR (74 ± 18 mL · min^{-1} · 1.73 m^{-2}) was found in the highest quartile of protein intake compared with the GFR of 71 ± 18 mL · min^{-1} · 1.73 m^{-2} found in the lowest quartile of protein intake (P value for linear trend <0.05). Given the importance of protein intake to the maintenance of body protein with age (54), additional research is needed to determine if healthy older adults are at increased risk for kidney disease in response to dietary protein intake.

Based on these limited data, it would appear that type 2 diabetics with normal kidney function may increase protein intake above the RDA, ≤1.2 g/kg, without negative consequence to GFR.

Additional research is needed to elucidate the role of protein intake in glucose homeostasis and maintenance of normal kidney function in older type 2 diabetics.

The evidence from the current review is limited and inconsistent, and cannot be used to draw a conclusion regarding increased protein intake and risk of kidney stones. Similarly, a recent evidence-based review used to establish protein intake recommendations for Norway found the evidence for an association between protein intake and kidney stone formation to be "inconclusive" (6).

Evidence limitations and future research recommendations

It is important to put the current review in perspective regarding level of protein intake. The current review considers "higher" protein intakes, but does not consider studies of "excessive" protein intake, i.e., in excess of the AMDR of 35% of total energy (55, 56). There is limited evidence regarding the long-term consumption of excessive protein; what there is, mainly comes from studies of endurance and strength athletes (56). Nonetheless, after review of renal health and other outcomes in response to excessive protein intake in athletes, Tipton (56) concluded: "This review is in no way intended to advocate high protein intakes for athletes and exercisers. Yet, the risks of high protein intake seem to be minimal for otherwise healthy athletes."

Conclusions drawn from the evidence reviewed herein regarding "higher" protein intake must also be considered with a degree of caution as the majority of studies were found to be of moderate to high risk of bias. While the findings were generally consistent across the included studies, similar consistency from more rigorously conducted trials would increase confidence. It is recommended that future studies in healthy subjects strive to improve study design factors such as randomization and blinding of subjects and personnel to reduce risk of bias results.

With the exception of the 2 included cohort trials, the studies included here were of limited duration, with none exceeding 6 mo. Thus, the long-term consequence of healthy individuals increasing their protein intake to up to twice the US RDA (or within the higher bound of the AMDR) remains somewhat unexplored, although several global and national evidence-based reviews used to establish DRIs have failed to find evidence sufficient to establish a UL (1–3, 6). The unavailability of evidence need to establish a UL, however, cannot be considered the same as lack of evidence of harm. Thus, in an effort to confirm the safety of higher-protein diets for long-term consumption by healthy individuals, RCTs of longer duration are needed to corroborate the observations reported in long-term cohort studies.

Similarly, the evidence base for increased risk of kidney stone formation in healthy individuals consuming higher-protein diets is limited. Measurement of urinary pH is a simple indicator of increased kidney stone risk that could be added to both RCTs and OBSs with limited effort and expense. Finally, evidence regarding kidney function in type 2 diabetics with normal kidney function is limited, so it is difficult to confirm that consuming higher-protein diets is without adverse consequence in this population.

Conclusions

The role of protein in kidney health and function is debated each time recommendations for protein intake are evaluated. Based on the evidence reviewed herein, higher protein intake, at least within the short term, and within the range of DRIs, is consistent with normal kidney function in healthy individuals.

Acknowledgments

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