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Revisiting glomerular hyperfiltration and examining the concept of high dietary protein-related nephropathy in athletes and bodybuilders

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Purpose of review
High-protein diets (HPDs) are popular but their consequences for kidney health, especially among athletes and bodybuilders who typically maintain a high protein intake for a long time, have not been investigated. This review focused on recent studies of the association of HPD with long-term kidney health and the concept of high dietary protein-related nephropathy.

Recent findings
Several long-term observational studies including large populations have reinforced the notion that HPDs are associated with a rapid decline of kidney function. An increase in renal blood flow and glomerular hyperfiltration caused by vasodilation, and increased levels of endocrine and paracrine factors (glucagon, IGF-1, prostanoids, and nitric oxide), facilitates the excretion of protein-derived nitrogenous waste. Inhibition of tubule-glomerular feedback and increased proximal tubular Na^+ reabsorption after a HPD augment glomerular hyperfiltration and may trigger synthesis of proinflammatory cytokines and receptor for advanced glycation end-products (RAGE). Focal segmental glomerulosclerosis reported in association with anabolic steroid may indeed be a HPD nephropathy given that HPD results in progressive glomerulosclerosis, especially in remnant glomeruli or in diabetic kidney disease but can happen in any high-risk situation, such as solitary kidney and polycystic kidneys.

Summary
HPD among athletes and bodybuilders in an extreme way across a long-term period may pose a risk to renal health including high incidence of HPD nephropathy.

Keywords
anabolic steroid nephropathy, glomerular hyperfiltration, high protein-induced nephropathy, kidney health

INTRODUCTION

In recent decades, high-protein diets (HPDs) and low carbohydrate consumption has become popular. HPDs are widely promoted on social media for rapid weight reduction. Professional athletes and bodybuilders use very high amount of HPDs to increase their lean body mass and muscle strength. However, the effects on health, especially kidney function have not been clearly stated. Several studies of HPDs including animal protein have shown detrimental effects on kidney health because of glomerular hyperfiltration, especially in patients with chronic kidney disease (CKD) or a risk thereof. This review focuses on the consequences of an HPD on glomerular hyperfiltration and renal health.

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KEY POINTS

- A high-protein diet increases renal blood flow and glomerular hyperfiltration.
- Vasodilation induced by endocrine factors and inhibition of tubule-glomerular feedback caused by a high-protein diet lead to glomerular hyperfiltration.
- Persistent glomerular hyperfiltration caused by the consumption of a high-protein diet was associated with a rapid decline of kidney function in observational studies.
- Athletes and bodybuilders maintaining a high protein intake over long periods may be at risk of progression to advanced chronic kidney disease.
- Nutritional approaches emphasizing protein quantity and quality should be established.

INDEX CASE

The index case is a 33-year-old man who presented with proteinuria and rapid deterioration of renal function. The patient was diagnosed with Focal Segmental Glomerulosclerosis (FSGS) 5 months prior to this evaluation. He was a fitness trainer and bodybuilder consuming a HPD (>3.5 g/kg/day; 40–50% of total energy intake), along with dietary supplements, such as creatine monohydrate and branched-chain amino acids, before being diagnosed with FSGS. He denied using anabolic steroids. After being diagnosed with FSGS, he had been prescribed an angiotensin-receptor blocker. However, his compliance was poor and he has not reduced his protein intake much. His BMI was 37 kg/m^2, with a height of 175 cm and a weight of 143 kg. His blood pressure was 150/90 mmHg. Serum creatinine was 2.8 mg/dl. The proteinuria in 24 h urine collection was measured as 6.1 g/day, representing a marked increase from the 1.7 g/day recorded at the time of diagnosis. The creatinine clearance rate was 24 ml/min/1.73 m^2. In addition to uncontrolled hypertension and low medication compliance, the continuation of HPD may have not only engendered but also promoted rapid progression to advanced CKD because of FSGS.

HYPERFILTRATION CAUSED BY A HIGH PROTEIN DIET: EVIDENCE FROM ANIMAL EXPERIMENTS

The effect of HPD on kidney health was first investigated in animal models, and glomerular hyperfiltration was suggested by an increased glomerular filtration rate (GFR) after HPD. Intake of a meal containing 10 g/kg meat increased creatinine clearance in dogs [1▪]. A similar effect of an HPD on kidney hemodynamics was observed in pigs; the HPD group had a markedly higher GFR than the normal-protein diet (NPD) group at 4 months, resulting in 55 and 30% higher fibrosis and glomerulosclerosis rates, respectively. In a longer term study, rats consuming an HPD for 17 months had larger glomeruli, 17% heavier kidneys, an approximately three-fold higher rate of proteinuria, and a 27% higher creatinine clearance rate compared with those consuming an NPD [2,3]. HPDs increase renal blood flow (RBF), which promotes the excretion of nitrogen products via dilatation of afferent arterioles after an increase in amino acids [4]. A protein-rich meal induced a 150% increase in RBF in seals, accompanied by a similar increase in GFR.

Impaired tubule-glomerular feedback also occurred after HPD, *in vivo* and *in vitro*, maintaining and exacerbating the increase in RBF and GFR in an HPD group [5▪]. Increased RBF and GFR may increase intraglomerular pressure and accelerate progressive glomerular sclerosis, especially in remnant glomeruli with decreased renal mass because of previous injuries, which reflects compensatory hyperfiltration as an adaptive hemodynamic change [6].

Phenotypic changes in diabetic nephropathy, such as glomerular hyperfiltration and hypertrophy, may also be affected by an HPD. Indeed, in animal models of diabetic nephropathy with leptin deficiency (*ob/ob*), this manifested as increased GFR and proteinuria in *ob/ob* mice fed an HPD [7▪]. After 6 months of an HPD (50% of total calories) in streptozotocin-induced type 1 diabetic rats, significant alterations of glomerular morphology were seen, with an increased mesangial fraction and reduced filtration surface compared with a standard protein diet group (20% of total calories). Hemodynamic changes, such as increased GFR and RBF, were also observed [8]. Administration of sodium-glucose cotransporter 2 inhibitor, which attenuates glomerular hyperfiltration, alleviated the increase in GFR caused by an HPD in diabetic mice [9].

LONG-TERM CONSEQUENCES OF A HIGH PROTEIN DIET FOR KIDNEY HEALTH: EVIDENCE FROM HUMAN STUDIES

The largest short-term (< 6 months) trial of optimal macronutrient intake (Omni-Heart) showed that an HPD (25% of calories) increased the estimated GFR (eGFR) by 3.8 ml/min/1.73 m^2 after 6 weeks compared with a standard protein diet (15% of calories) [2]. In a randomized controlled study including more than 300 participants, glomerular hyperfiltration associated with HPD manifested in the early stages as an increase in the GFR, which lasted for up to 12 months. However, the difference was

diminished at 24 months, suggesting that the increase of GFR with glomerular hyperfiltration by HPD is not sustained and resulted in rapid decline of kidney function after that [10].

Hyperfiltration may also increase the risk of proteinuria. An HPD is associated with increased albuminuria/proteinuria. There is an increased risk of albuminuria when on an HPD compared with a standard diet, even after adjustment for differences in sociodemographics, comorbidities, body anthropometry, health behaviors, and medication [1▪,11]. However, the association was only seen in those with preexisting kidney dysfunction, such as a single kidney, hypertension, and diabetes [12]. The effect of an HPD on proteinuria should be examined in large-scale, long-term randomized controlled trials.

The effects of HPDs on kidney dysfunction have been typically evaluated in observational studies based on large populations. Several long-term, observational human studies have shown an association of consumption of an HPD with a rapid decline of kidney function in those with preexisting CKD. In the Nurses' Health Study, an 11-year observation study of women with mild renal insufficiency (eGFR = 55–80 ml/min/1.73 m^2), every 10 g increase in protein intake was associated with a significant change in the eGFR of −1.69 (95% CI: −2.93 to −0.45 ml/min/1.73 m^2) but this was not observed in a population with normal renal function [1▪].

Most of the large observational studies on the association of HPD with kidney outcomes yielded similar results, irrespective of population characteristics and location. Recently, there were many reports regarding the association of HPD with long-term kidney function. In a study of 2017 based on observational data from 63 257 Chinese people with a mean follow-up of 15.5 years, higher quartiles of protein intake, especially red-meat consumption, were associated with a dose-dependent risk of end-stage kidney disease (ESKD) [13]. In the Jackson Heart study, an observational cohort study of African-Americans in Mississippi with a median follow-up of 8 years, the highest quintile of protein intake was associated with rapid decline of eGFR among participants with diabetes, and the risk was also elevated in the lowest quintile [14]. Another study, based on the Alpha and Omega cohort of 2255 Dutch patients with a history of myocardial infarction (MI) within the past 10 years, evaluated the association of dietary protein intake with decline of kidney function after MI, which doubles the risk of kidney dysfunction. Each 0.1 g/kg/day increase in protein was associated with a −0.12 ml/min/1.73 m^2 (95% CI −0.19 to −0.04) annual decline in the eGFR during the post MI period [15▪]. An observational study based on the Korean Genome and Epidemiology Study, which included a community-based cohort of 9226 middle-aged persons, showed that the relative risk of renal hyperfiltration was 3.48-fold higher in the highest than lowest quartile of protein intake, and the highest quartile of protein intake was also associated with a 1.32-fold increased risk of a rapid eGFR decline (95% CI 1.02–1.73) [16▪▪]. A study of 1800 Iranians followed for an average of 6 years reported that those with lower carbohydrate and higher protein intake had a greater risk of CKD (OR 1.48; 95% CI 1.03–2.15) [17]. In addition to the association of HPD with CKD, a high daily protein intake of at least 1.4 g/kg/day was also associated with higher mortality among participants with impaired kidney function (<60 ml/min/1.72 m^2; hazard ratio 1.37; 95% CI 1.02–1.85) in an analysis of 27 604 continuous adult NHANES participants (1999–2010) but not among participants with normal kidney function [18▪▪].

However, a significant association of an HPD with decreased kidney function was not observed in one study [19]. Few long-term randomized controlled trials have analyzed the effect of HPDs on renal function [20▪]. In a recent meta-analysis, an HPD caused hyperfiltration and changes in the GFR, but there was no significant change in serum creatinine [21]. Recent observational studies regarding the association of HPD with long-term kidney function are summarized in Table 1.

POTENTIAL MECHANISMS LINKING HIGH PROTEIN DIET AND CHRONIC KIDNEY DISEASE: GLOMERULAR HYPERFILTRATION

A protein load (or amino acid infusion) increases RBF and GFR via vasodilation of afferent arterioles and a decrease in vascular resistance [22]. This is believed as an evolutionary feedback mechanism to enhance the excretion of protein-derived nitrogenous waste. An HPD increases Na^+ reabsorption in proximal tubules, contributing to the increased RBF and GFR seen after HPD [7▪].

The increased levels of vasodilatory mediators, such as prostanoids and nitric oxide, caused by changes in endocrine and paracrine factors (e.g. glucagon and insulin-like growth factor I) may mediate the changes seen in renal hemodynamics after HPD [5▪,23▪▪]. The remaining nephrons show functional overactivity in association with metabolic and hormonal factors, of which the most important are hyperglycemia and obesity [24▪▪].

Altered neurohormonal responses within the kidney that inhibit tubule glomerular feedback (TGF) have been posited as a mechanism underlying

Table 1. Recent studies published within 5 years about the association of high-protein diet with outcome of kidney function or mortality

Authors	Study location (cohort)	Study type	Sample size	Mean age (years)	Mean eGFR	Protein intake in the highest group	Study duration (years)	Results
Lew *et al.*, 2017 [13]	Singapore Chinese Health Study	Prospective cohort	63 257	57	N/D	65.3 g/day	15.5	The highest quartile of total protein intake was positively associated with incidence of ESRD in a model that adjusted for basic demographics (hazard ratio 1.55, 95% CI 1.28–1.87) compared with the lowest quartile. Highest quartile of animal protein intake (from red meat) had 40% increased HR of ESRD.
Haring *et al.*, 2017 [19]	Atherosclerosis Risk in Communities (ARIC) Study	Prospective cohort	11 952	54	103	109.5 g/day (19.5% of total calories)	23	Total protein consumption itself was not associated with increasing risk of incident CKD (hazard ratio of the highest quintile 0.89, 0.76–1.05)
Malhotra *et al.*, 2018 [14]	Jackson Heart study	Observational cohort	3165	55	97	1.0 g/kg/day (19.4% of total calories)	8	Consumption of protein as percentage of energy intake in lowest and highest quintiles was associated with decline in eGFR among diabetic subjects
Esmeijer *et al.*, 2019 [15▪]	Alpha-Omega cohort	Prospective cohort	2255	69	82	92 g/day (17% of total calories)	3.5	Subjects with a daily total protein intake of at least 1.20 compared with less than 0.80 g/kg ideal body weight had a two-fold faster annual eGFRcysC decline (−1.60 vs. −0.84 ml/min/1.73 m^2) in 10-year post-MI period
Jhee *et al.*, 2019 [16▪▪]	Korean Genome and Epidemiology Study	Prospective cohort	9226	52	94	1.7 g/kg/day	11.5	Renal hyperfiltration was 3.48-fold higher in the highest quartile of protein intake than in the lowest. The highest quartile was associated with 1.32-fold increased risk of rapid eGFR decline (95% CI 1.02–1.73).
Farhadnejad *et al.*, 2019 [17]	Tehran Lipid and Glucose Study	Prospective cohort	1797	38	76	16% of total calories	6.1	The highest tertile of LCHP diet had greater risk of incident CKD (OR 1.48; 95% CI: 1.03–2.15) in comparison to those in the lowest one (*P* for trend 0.027).
Narasaki *et al.*, 2021 [18▪▪]	National Health and Nutritional Examination Survey (1999–2010)	Retrospective study	27 604	72	eGFR <60: 47 eGFR ≥60: 100	1.4 g/kg/day	eGFR <60: 3.8 eGFR ≥60: 4.7	A high DPI of at least 1.4 g/kg ABW/day was associated with higher mortality (hazard ratio 1.37, 95% CI 1.02–1.85) only in subjects with impaired kidney function (eGFR <60 ml/min/1.72 m^2)

the increase in GFR after HPD [25]. Increase of proximal tubular Na^+ reabsorption after HPD may led to the increased delivery of Na^+ to the macula densa, which inhibits the normalization of the TGF system, and it is possibly mediated in part by the renin–angiotensin–aldosterone system (RAAS) as RAAS inhibition attenuated the response additionally along with low protein diet [26].

An increase in GFR and intraglomerular pressure in a single nephron leads to tensile and shear stresses on the endothelial cells in the capillary wall and podocytes [27]. An increase in glomerular capillary hydraulic pressure leads to glomerular injury and nephron loss, which exacerbates hyperfiltration in the remaining nephrons [24▪▪]. Hyperfiltration increases the oxygen required to reabsorb the increased filtered load, which may be associated with increased oxidative stress and upregulation of proinflammatory and profibrotic cytokines, such as TGF-β and type IV collagen [26]. Incremental increases in protein intake (i.e. 20, 30, and 45% of total energy intake) increase proinflammatory gene expression in a dose-dependent manner [28]. Moreover, the increased proinflammatory cytokine gene expression caused by an HPD may be associated with structural damage and hyperfiltration in the remaining glomeruli [28].

In glomerular cells, podocytes and mesangial cells, high amino acid supplementation induced apoptosis and inflammation, especially under high-glucose conditions. Receptor for advanced glycation end-products (RAGE) is a key mediator of inflammation, and advanced glycation end-products (AGE) were increased in glomerular cells. Greater kidney hypertrophy and reduced numbers of podocytes were observed in diabetic mice on an HPD (40% of total calories). In humans, increased protein intake was directly correlated with urinary AGE excretion [29]. It may be also hypothesized that tubular cell injury by increase of filtrated albumin under glomerular hyperfiltration especially in diseased conditions with damage of filtration barrier might be implicated [30].

The matter of the source of dietary protein intake on kidney health has been investigated. Though there has not been demonstration clearly with randomized controlled trials especially among athletes and bodybuilders about the impact of the protein source, the findings in many observational studies that high consumption of red/processed meat was associated with increased risk of kidney dysfunction may be applied in this population [13,19]. Poor blood pressure control, weight gain, unfavorable changes in gut microbiome, inflammation and oxidative stress after animal protein consumption have been suggested as underlying mechanisms, though it is not clearly revealed yet [1▪]. Further studies should be needed.

The various processes mentioned above that occur after an HPD may lead to the increases in hemodynamic and metabolic burden in the kidneys followed by deterioration of long-term kidney function. Especially in athletes and bodybuilders, who typically maintain a very high protein intake for long periods and often have CKD or at risk of CKD thereof [31▪], HPD may lead to high dietary protein-induced nephropathy (Fig. 1).

CONSUMPTION OF A HIGH PROTEIN DIET BY ATHLETES AND BODYBUILDERS

The recommended daily allowance (RDA) of protein in the general population is 0.83 g/kg/day, which meets the protein-intake requirement for 97–98% of the population. Protein consumption exceeding 1.5 g/kg/day is usually considered as an HPD. However, professional athletes and bodybuilders consume around 4.3 g/kg/day (in male individuals) and 2.8 g/kg/day (in female individuals), which far exceed the recommended amounts [32]. Fat-free mass increased with increasing protein intake in a meta-analysis, peaking at 1.6 g/kg/day (almost twice the RDA). However, the fat-free mass plateaued after 1.6 g/kg/day, and muscle mass did not increase with any further increase in protein intake. Therefore, protein intake beyond this point may exert a negative effect on kidney health without any further increases in muscle mass and strength [33].

Athletes and bodybuilders may be at risk of kidney dysfunction. A high BMI may be associated with development and progression of CKD, and acute kidney injury caused by rhabdomyolysis and the use of nonsteroidal anti-inflammatory drugs (NSAID) may compromise kidney health. Some supplements are considered to be associated with kidney dysfunction as high-dose vitamin D injection lead to progressive nephrocalcinosis [34▪].

Use of anabolic steroid has been also suggested to cause kidney dysfunction in athletes and bodybuilders. Especially several case series of collapsing variant of focal segmental glomerulonephritis have been reported in bodybuilders having anabolic steroid [35,36]. However, recent two studies, which were based on biopsy-proven data of 15 and 22 bodybuilders with kidney dysfunction, respectively, demonstrated that the distribution of causes for kidney dysfunction were not significantly different in bodybuilders compared with general population even after consideration and adjustment of anabolic steroid use [34▪,37]. And, most of the participants were under consumption of HPD. So it is suggested that HPD may impose a burden to cause rapid

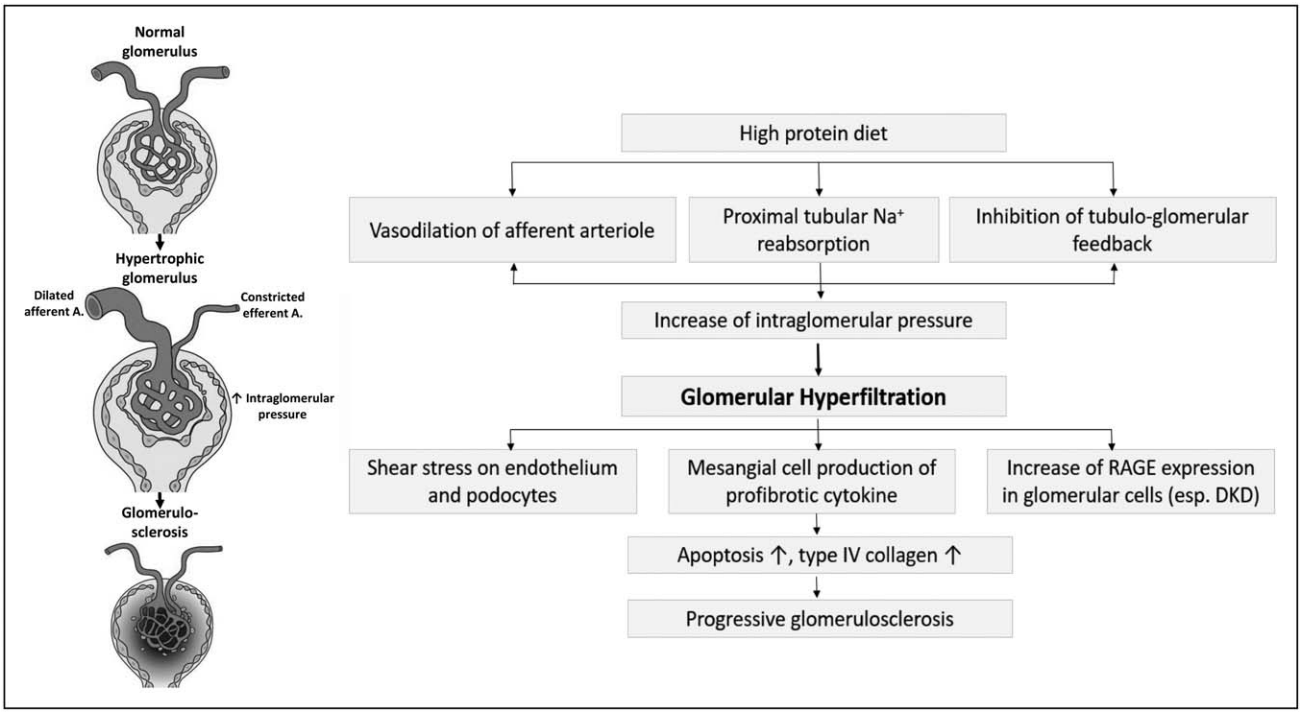

FIGURE 1. Schema of the proposed mechanism of high dietary protein-induced nephropathy.

aggravation of underlying kidney disease among bodybuilders, and it may also contribute to development of secondary FSGS in combination with postadaptive changes driven by rapid and extreme increase of lean body mass. Hence, we believe that focal segmental glomerulosclerosis reported in the above cases in association with anabolic steroid may be a type of HPD-induced nephropathy given that HPD results in progressive glomerulosclerosis, especially in remnant glomeruli and diabetic kidney disease but can happen in any high-risk situation, such as solitary kidney and polycystic kidneys. More studies should be needed.

Therefore, protein intake in athletes and bodybuilders should be managed carefully, and a cost–benefit analysis is warranted. Moreover, protein supplements are commonly used by young athletes, the proportion of whom using protein supplements

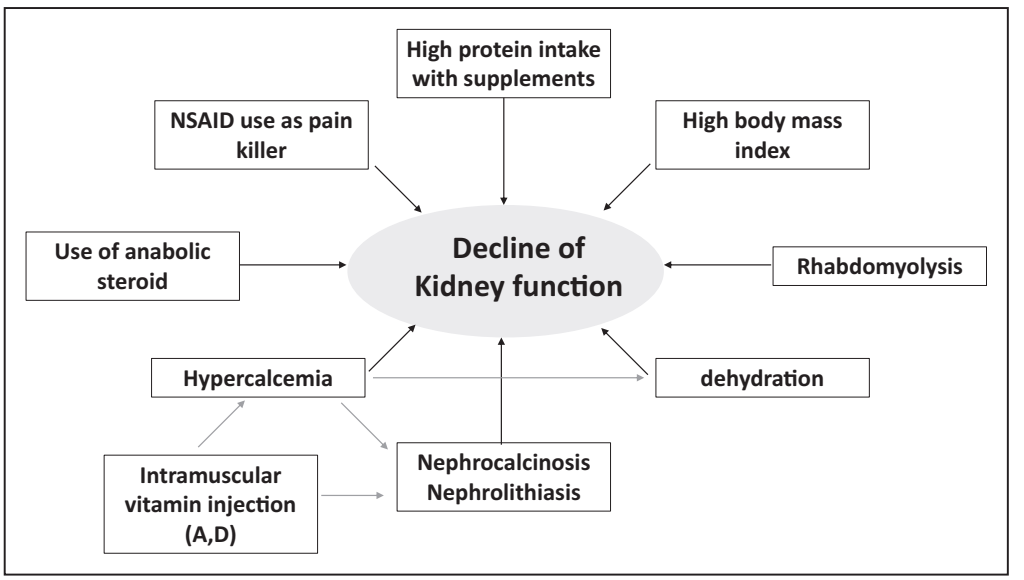

FIGURE 2. Various risk factors for kidney dysfunction among athletes and bodybuilders.

was reportedly higher (41.7%) than in the general population (17%) [38]. This increases glomerular hyperfiltration, resulting in HPD-induced nephropathy. Regular examinations of kidney function and appropriate nutritional strategies for maintaining kidney health are needed for athletes and bodybuilders. Risk factors associated with kidney dysfunction in athletes and bodybuilders were summarized in Fig. 2.

CONCLUSION

In the HPD era, it is necessary to accurately evaluate the health risks and benefits (including kidney function) of dietary patterns. An HPD may have detrimental effects on kidney health, especially in athletes or bodybuilders who typically remain on an HPD for long periods. Focal segmental glomerulosclerosis previously reported in association with anabolic steroid is likely a type of HPD nephropathy in the form of progressive glomerulosclerosis and can be observed among persons with athletic or body and muscle building goals who consumes high amounts of dietary protein. Specific recommendations regarding protein quality and quantity are needed [39▪▪].

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Conflicts of interest

There are no conflicts of interest.

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