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REVIEW ARTICLE

High Protein Diets and Glomerular Hyperfiltration in Athletes and Bodybuilders: Is Chronic Kidney Disease the Real Finish Line?

Alberto de Lorenzo[1,2] · **Andrew S. Bomback**[3] · **Niko Mihic**[4]

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Abstract
Several observational and experimental studies in humans have suggested that high protein intake (PI) causes intraglomerular hypertension leading to hyperfiltration. This phenomenon results in progressive loss of renal function with long-term exposure to high-protein diets (HPDs), even in healthy people. The recommended daily allowance for PI is 0.83 g/kg per day, which meets the protein requirement for approximately 98% of the population. A HPD is defined as a protein consumption > 1.5 g/kg per day. Athletes and bodybuilders are encouraged to follow HPDs to optimize muscle protein balance, increase lean body mass, and enhance performance. A series of studies in resistance-trained athletes looking at HPD has been published concluding that there are no harmful effects of HPD on renal health. However, the aim of these studies was to evaluate body composition changes and they were not designed to assess safety or kidney outcomes. Here we review the effects of HPD on kidney health in athletes and healthy individuals with normal kidney function.

1 Introduction

Glomerular filtration rate (GFR) is considered the best index of kidney function in health and disease. As GFR cannot be measured easily in clinical practice, it is estimated from equations such as the Modification of Diet in Renal Disease (MDRD) Study equation and the CKD-EPI creatinine equation. The first uses serum creatinine, age, race, sex, and body size, and the latter logarithm of serum creatinine, sex, race, and age. The CKD-EPI creatinine equation is as accurate as the MDRD Study at GFR less than 60 ml/min/1.73 m^2 and more accurate at higher levels of estimated GFR, although precision remains suboptimal [1]. In clinical practice, an increase in estimated GFR (eGFR) means an improvement in kidney function while a decrease implies the opposite. Equations do not overcome limitations of serum creatinine as an endogenous filtration marker. All creatinine-based equations should be used with caution in people with abnormally high or low levels of muscle mass. Thus, it is clear that they will not work equally well in all populations including athletes. eGFR calculations can be imprecise in those with high lean body mass or in healthy populations [2–5]. These equations are used to assess the burden of CKD in epidemiologic studies and public health [1].

Chronic kidney disease (CKD) is a public health problem with a prevalence of approximately 13%, with significant effects on morbidity and mortality. CKD poses a significant burden to national healthcare systems, resulting in national efforts worldwide to reduce its incidence and progression [6]. Diabetes mellitus (DM) and hypertension are the leading etiologies of CKD, but in population studies, CKD etiology is often uncertain. Some experimental and observational human studies have suggested that high protein intake (HPI) may increase the rate of CKD progression and even cause CKD in healthy people [7, 8].

The Modification of Diet in Renal Disease (MDRD) study supports the role of dietary protein restriction in the management of patients with CKD to slow the progression of kidney failure, but did not yield convincing results for preventing onset of kidney disease [9]. In fact, there are conflicting recommendations in the literature about

✉ Alberto de Lorenzo
albertodelorenzoalvarez@gmail.com

1 Department of Nephrology, Hospital Universitario HM Sanchinarro, Madrid, Spain

2 Department of Nephrology, Hospital Universitario de Getafe, Universidad Europea de Madrid, Madrid, Spain

3 Division of Nephrology, Department of Medicine, Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, USA

4 Chief Medical Officer of Real Madrid CF, Madrid, Spain

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Key Points

A high-protein diet induces an increase in renal function as a physiological adaptation, suggesting a kidney function reserve. The maintenance of this situation over time may induce an exhaustion of this reserve, a fall in kidney function to normal, and eventually further declines in renal filtration to chronic kidney disease over time.

The vast majority of surveys performed in athletes are short-term studies, with a small sample size and lacking control groups of normal protein intake. The brief follow-up periods prevent a true assessment of the renal reserve and its expected progressive decline due to oxidative stress, inflammation, apoptosis, and glomerular damage.

Athletes choosing a high-protein diet should be aware of the potential long-term risks and should discuss them with their physicians, following individualized recommendations according to their personal health status. A follow-up of renal function during a high protein diet and after discontinuation is highly recommended.

how much protein is safe for subjects with normal kidney function; in general, sports societies, fitness professionals, and coaches have been more generous in their recommendations than nephrologists. The estimated average requirement for PI 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 50% of the population's requirements. The recommended daily allowance (RDA) for PI is 0.83 g/kg per day, which meets the protein requirement for 97–98% of the population [10]. People with an eGFR below 60 ml/min/1.73 m^2 should restrict protein to 0.55–0.60 g/kg/day or below to slow the progression of CKD [11].

A high-protein diet (HPD) is defined by most guidelines, societies and authors as a protein consumption > 1.5 g/kg per day (> 15–16% of total energy), or an intake within the range between 1.2 and 2.0 g/kg/day. Athletes and bodybuilders are often encouraged to follow HPDs to optimize muscle protein balance, increase lean body mass, and enhance performance [5]. The use of protein supplements by young athletes is more than twofold higher than the use in general population (41.7% versus 17%), and at least 80% of bodybuilders report use of these supplements [12, 13]. The International Society of Sports Nutrition (ISSN) recommends "an overall daily PI in the range of 1.4–2.0 g protein/kg body weight/day (g/kg/d) for building and maintaining muscle mass … for most exercising individuals." Furthermore, the ISSN states that "higher PI (> 3.0 g/kg/day) may have positive effects on body composition in resistance-trained individuals" [14]. These kinds of diets are also recommended on social media for rapid weight loss by restricting the amount of carbohydrates, advocating that 25–35% of calories consumed should be from protein and < 45% of calories should be from carbohydrates [15, 16].

High dietary PI increases renal blood flow (RBF) and causes intraglomerular hypertension, leading to hyperfiltration and more efficient excretion of nitrogenous waste products. This phenomenon has been well reported in both animal and clinical models [16] and confirmed in a meta-analysis including 30 randomized controlled trials (RCTs) [17]. Kidney hyperfiltration, progressive glomerular injury leading to sclerosis, and resultant increase in albuminuria may result in progressive loss of kidney function with long-term exposure to HPD [15, 18–20]. It is unclear, however, whether individuals with normal kidney function have the same risk for these effects of HPD compared to those with preexisting kidney disease.

The Nurses' Health study of 1624 women (42–68 years of age) was the first large-scale observational study of the impact of HPD on kidney function in the general population. This study found a longitudinal association of HPI with accelerated eGFR decline after 11-year follow-up in women with eGFR 55-80 ml/min/1.73 m^2 at baseline, but not in those with eGFR > 80 ml/min/1.73 m^2 [21]. In men and women aged 28–75 years without kidney disease, the PREVEND study reported the lack of association between PI and eGFR or eGFR change after 6-year follow-up [22]. Both these studies were based on methods for eGFR calculation with low accuracy in the range of normal to high GFR. Cirillo et al. conducted a study with 1522 participants (aged 45–64 years) with normal kidney function and 12-year follow-up and demonstrated that high protein is associated with higher GFR decline over time [8]. There are additional studies with conflicting results for the impact of HPD on renal function decline in the general population [22].

2 Hyperfiltration Secondary to High-Protein Diet

Brenner et al. [23] hypothesized that an increase in GFR and glomerular pressure, called hyperfiltration, might cause renal dysfunction and raise the risk for renal injury 40 years ago. It is known that uninephrectomy increases renal blood flow and GFR by about 40% in the remnant kidney and leads to moderate acceleration of glomerular sclerosis and proteinuria [24]. Brenner states that these increases in remnant-kidney function (also observed in other models of renal

disease) are due to arteriolar vasodilatation, which causes elevations in the flows and pressures in the capillaries of remnant glomeruli that contribute to the eventual destruction of the hyperfunctioning remnant nephrons. This work highlights that restoration of glomerular hemodynamics to a near-normal level by protein restriction was associated with preservation of glomerular architecture and absence of proteinuria [23].

Many works have been published on the effect of proteins in increasing GFR, probably as a physiological adaptation process suggesting a kidney function reserve [25, 26]. This was first investigated in animal models: mammals fed acute or chronic HPD exhibited increases in GFR and renal blood flow [27]. An intake of 10 g/kg of protein caused an increase in creatinine clearance in dogs [15] and a rise in GFR and higher fibrosis and glomerulosclerosis in pigs at 4-month follow-up [13]. In rats fed a HPD for 17 months, Hostetter et al. reported glomerulomegaly, a 30% increase in creatinine clearance rate, and threefold higher rate of proteinuria compared with rats consuming normal PI [28]. A long-term study in rats fed a HP diet, 35% of total energy consumption (TEC), resulted in 17% higher kidney weights, a threefold rise in proteinuria, larger glomeruli, and a 27% increase in creatinine clearance as compared with the normal protein (NP)-fed rats (15% of TEC) [29]. However, there are a number of studies in animals that were unable to demonstrate the association of HPD with long-term kidney function [30, 31].

A protein load increases RBF and GFR via vasodilation of afferent arterioles and a decrease in vascular resistance [13]. This hyperfiltration improves the excretion of nitrogen products [32]. Nevertheless, the increase in RBF may cause an increase in intraglomerular pressure that leads to nephron loss, which enhances hyperfiltration in the remaining glomeruli [33]. Hyperfiltration increases oxygen consumption, which may lead to an increase of oxidative stress, resulting in upregulation of proinflammatory and profibrotic cytokines (transforming growth factor-β, type IV collagen). In turn, these cytokines produce inflammation and apoptosis, provoking glomerular structural damage, and again, increasing hyperfiltration in healthy nephrons [34] (Fig. 1). Moreover, a PI of more than 30–45% of total energy triggers the overexpression of proinflammatory genes in a dose-dependent way [35]. HPD may also increase sodium reabsorption in proximal tubules, raising intraglomerular pressure even more, refeeding this mechanism of glomerular damage [36]. The increased delivery of sodium to the macula densa inhibits the normalization of tubulo-glomerular feedback, possibly mediated in part by the renin–angiotensin–aldosterone system (RAAS), as RAAS inhibition attenuated the response similarly to a low-protein diet [35]. Recently, Noorgard et al. confirmed progression of nephropathy in diabetic

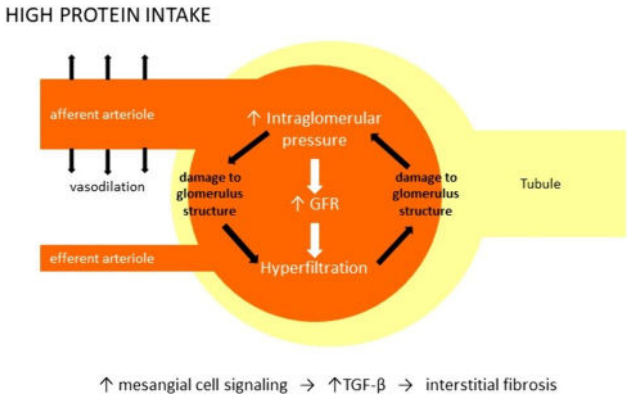

Fig. 1 High dietary protein intake induces vasodilation of the afferent arteriole increasing glomerular filtration rate which may lead to damage to renal structures over time due to glomerular hyperfiltration. *GFR* glomerular filtration rate, *TGF-β* transforming growth factor β

mice with HPD that was abrogated by the sodium-glucose transport protein 2 (SGLT2) Inhibitor dapagliflozin [37].

All these mechanisms described above have been found to accelerate CKD in animal and human studies, but this has not been clearly demonstrated among subjects with normal kidney function [38]. Increased RBF and chronic vasodilation cause glomerular damage and may have an effect on long-term kidney function, especially in athletes and bodybuilders who follow a high PI for long periods. This is of special importance in subjects with risk factors or established CKD. In addition, as some athletes could have unknown kidney disease, screening for kidney disease should be recommended in those who intend to start on HPD or in those already on such a diet (Fig. 2).

3 Implications in Subjects with Normal Kidney Function

Schwingshackl et al. published a meta-analysis of 30 randomized controlled trials (RCTs) including 2160 subjects, all of them without CKD (eGFR > 60 ml/min/1.73 m^2), to investigate the impact of HPD on parameters of kidney function [17]. HPD was associated with a significant increase in GFR (7.18 ml/min/1.73 m^2; 95% CI 4.45–9.91; $p < 0.001$) when compared with low and normal PI [17]. Another more recent meta-analysis conducted by Devries et al. [39] of 28 RCTs (15 of them included in the study by Schwingshackl et al. [17]) with 1358 participants analyzed GFR after HPI and the change in GFR from pre-intervention to post. Post-intervention GFR was higher after HPD (0.19 ml/min; 95% CI 0.07–0.31; $p = 0.002$). The change in GFR pre/post was not statistically significant, however (0.11 ml/min; 95% CI − 0.05 to 0.27; $p = 0.16$). The authors concluded that HP

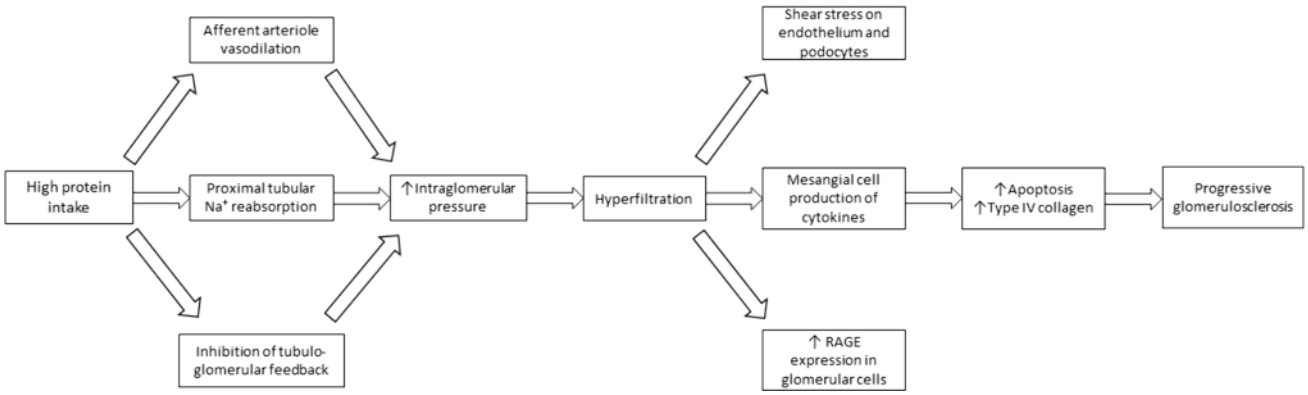

Fig. 2 Protein-induced nephropathy and its possible pathophysiological mechanism. *Na*$^+$ sodium, *RAGE* receptor for advanced glycation end-products

intakes do not adversely influence kidney function in healthy adults.

Some comments are needed with respect to both meta-analyses. Nearly half of the studies collected in both used estimated GFR to measure renal function, which loses accuracy in subjects with normal kidney function. Although these studies were not designed to assess long-term kidney outcomes, we highlight that only 6 studies out of 30 had a follow-up period of at least of 1 year, with a median follow-up of only 6 weeks. This period is likely insufficient to obtain robust conclusions or demonstrate any reliable change in kidney function in terms of PI effects. More studies are needed with longer follow-up periods and more accurate methods of kidney function measurement. Juraschek et al. published the largest short-term (< 6 months) trial of optimal macronutrient intake (Omni-Heart) and concluded that HPD raised eGFR by 3.8 ml/min/1.73 m^2 after 6 weeks [40]. Studies regarding the association of HPD with renal function [40–78] are listed in Table 1.

Epidemiologic studies have shown disparate results regarding the association of HPD with long-term kidney function. An Iranian cohort study conducted on 1797 participants followed-up for a mean of 6.1 years found that the highest tertile for reported PI (15.8 ± 2.1% of energy) had a nearly 50% greater risk of CKD with an odds ratio (OR) of 1.48 (OR 1.48; 95% CI 1.03–2.15) [9]. A total of 9226 participants in the Korean Genome and Epidemiology Study, a community-based prospective study, were enrolled and classified into quartiles according to daily amount of PI on the basis of food frequency questionnaires [7]. The relative risk of renal hyperfiltration was 3.48-fold higher in the highest than in the lowest PI quartile after adjustment for confounding factors (95% CI 1.39–8.71; $p = 0.01$). The mean eGFR decline rate was faster as quartiles of PI increased. Furthermore, the highest quartile was associated with a 1.32-fold increased risk of rapid eGFR decline (95% CI 1.02–1.73; $p = 0.03$) [7]. Conversely, the Nurses' Health Study in the USA, with 1624 women enrolled and an 11-year follow-up period, found that a HPI (76.7 ± 13.6 g/day) was not associated with changes in eGFR in women with eGFR > 80 ml/min/1.73 m^2 (0.25 mL/min/1.73 m^2; 95% CI 0.78–1.28). In women with eGFR 55–80 mL/min/1.73 m^2, however, PI was significantly associated with a change in eGFR of − 7.72 mL/min/1.73 m^2 (95% CI − 15.52 to 0.08) per 10-g increase in PI [21].

An interesting RCT including more than 300 individuals conducted by Ko et al. demonstrated hyperfiltration secondary to HPD lasting for 12 months. At 24 months, however, the difference was reduced, suggesting that hyperfiltration by HPD is not sustained and can result in decline of kidney function over longer periods of time [79]. The Singapore Chinese Health Study, a prospective population-based cohort with 63,257 adults (aged 45–74 years) with a mean follow-up of 15.5 years, showed that the three higher quartiles of total PI combined had a hazard ratio (HR) for end-stage renal disease (ESRD) of 1.24 (95% CI 1.05–1.46) compared with the lowest quartile. Red meat intake strongly associated with ESRD risk in a dose-dependent manner, with a HR for highest quartile versus lowest quartile of 1.40 (95% CI 1.15–1.71; $p < 0.001$) [80]. In an observational cohort study of 3165 African Americans followed up for a median of 8 years, the highest quintile of PI (≥ 80th percentile of energy from protein) was associated with a decline in eGFR among diabetic subjects [38]. Haring et al. did not demonstrate a relationship between HPD and decreased renal function in a study of 11,952 adults (44–66 years) free of DM and cardiovascular disease and with an eGFR ≥ 60 mL/min/1.73 m^2. However, red and processed meat was associated with increased CKD risk in contrast with higher dietary intake of nuts, legumes and low-fat dairy products [81]. A Dutch study of 2255 participants with previous myocardial infarction found that each 0.1 g/kg/day increase in PI was associated with a 0.12 ml/min/1.73 m^2 (95% CI 0.19–0.04) annual decline in eGFR after 3.4 years of follow-up [82].

Table 1 Studies published involving participants with normal renal function taking a high-protein diet in whom glomerular filtration rate was measured

Study	Design	Duration (weeks)	*N* (% female)	Mean age (years)	Daily PI	GFR method	GFR pre	GFR post
Bergstrom et al. [41]	X-over	1	8 (50)	26	2 g/kg/d 0.3 g/kg/d	Inulin clearance (mL/min)	NS NS	113 ± 12 100 ± 14
Brinkworth et al. [42]	PG	68	29 (72)	52	30% 15%	Creatinine clearance (mL/min)	100 ± 44 102 ± 27	100 ± 14 113 ± 30
Brinkworth et al. [43]	PG	52	68 (63)	51	35% 24%	eGFR (MDRD ml/min/1.73 m^2)	90 ± 17 84 ± 14	91 ± 18 84 ± 12
Cao et al. [44]	X-over	7	16 (100)	56	1.6 g/kg/d 0.8 g/kg/d	eGFR (not specified, mL/min)	NS NS	NS NS
Chu et al. [45]	X-over	2	6 (0)	25	150 g 75 g	Creatinine clearance (mL/min)	NS NS	122 ± 15 105 ± 14
Ferrara et al. [46]	RCT	24	15 (0)	26	1.9 g/kg/d 1.3 g/kg/d	eGFR (not specified, mL/min)	NS NS	NS NS
Frank et al. [47]	X-over	1	24 (0)	24	2.4 g/kg/d 1.2 g/kg/d	Sinistrin clearance (mL/min)	NS NS	141 ± 8 125 ± 5
Friedman et al. [48]	PG	104	307 (68)	46	Unlimited 15%	Creatinine clearance (mL/min)	135 ± 35 133 ± 42	139 ± 35 130 ± 42
Gross et al. [49]	X-over	4	15 (27)	57	1.2–1.5 g/kg/d 0.5–0.8 g/kg/d	Cr-EDTA clearance (mL/min)	NS NS	101 ± 23 94 ± 20
Hegsted and Linkswiler [50]	X-over	9	6 (100)	25	123 g 46 g	Creatinine clearance (mL/min)	NS NS	103 ± 5 91 ± 3
Jenkins et al. [51]	X-over	4	20 (25)	56	27.4% 15.6%	Creatinine clearance (mL/min)	NS NS	110 ± 31 104 ± 36
Jesudason et al. [52]	RCT	48	45 (22)	60	30% 20%	eGFR (MDRD ml/min/1.73 m^2)	NS NS	NS NS
Johnston et al. [53]	PG	6	16 (90)	19–54	31.5% 15%	Creatinine clearance (mL/min)	104 ± 25 82 ± 17	85 ± 25 85 ± 22
Juraschek et al. [40]	X-over	6	156 (45)	54	25% 15%	eGFR (CKD epi, cystatin C, ml/min/1.73 m^2)	92 ± 16 92 ± 16	96 ± 8 92 ± 10
Kerstetter et al. [54]	X-over	1	7 (100)	26	2.1 g/kg/d 0.7 g/kg/d	eGFR (not specified, mL/min)	104 ± 13 98 ± 12	116 ± 22 102 ± 10
Kim and Linkswiler. [55]	X-over	1.5	6 (0)	21–29	142 g 47 g	Creatinine clearance (mL/min)	NS NS	116 ± 7 105 ± 10
Krebs et al. [56]	RCT	52	419 (60)	58	30% 15%	Creatinine clearance (mL/min)	NS NS	NS NS
Larsen et al. [57]	PG	52	99 (52)	59	30% 15%	eGFR (not specified, mL/min)	70 ± 12 73 ± 15	73 ± 18 76 ± 18
Leidy et al. [58]	PG	12	46 (100)	50	30% 15%	eGFR (MDRD ml/min/1.73 m^2)	86 ± 9 74 ± 14	84 ± 9 78 ± 10
Li et al. [59]	RCT	52	100 (62)	49	2.2 g/kg/d 1.1 g/kg/d	Creatinine clearance (mL/min)	129 ± 60 117 ± 44	139 ± 40 117 ± 43
Liu et al. [60]	RCT	12	50 (100)	47	LC 18%	NS	NS NS	NS NS
Longland et al. [61]	PG	4	40 (0)	23	2.4 g/kg/d 1.2 g/kg/d	eGFR (MDRD ml/min/1.73 m^2)	109 ± 9 114 ± 11	114 ± 11 117 ± 11
Luger et al. [62]	PG	12	42 (55)	62	30% 15%	eGFR (MDRD ml/min/1.73 m^2)	71 ± 15 66 ± 15	74 ± 14 69 ± 19
Luscombe-Marsh et al. [63]	PG	12	57 (56)	50	40% 20%	Creatinine clearance (mL/min)	121 ± 37 117 ± 52	141 ± 45 124 ± 60
Noakes et al. [64]	PG	12	98 (100)	49	34% 17%	Creatinine clearance (mL/min)	82 ± 23 82 ± 23	77 ± 20 73 ± 21
Nuttall et al. [78]	X-over	5	8 (0)	63	30% 15%	NS	NS NS	NS NS

Table 1 (continued)

Study	Design	Duration (weeks)	*N* (% female)	Mean age (years)	Daily PI	GFR method	GFR pre	GFR post
Pomerleau et al. [65]	X-over	3	20 (33)	58	1.9 g/kg/d 0.8 g/kg/d	Technicum-DTPA plasma clearance (ml/s/1.73 m^2)	NS NS	NS NS
Roughead et al. [66]	X-over	8	15 (100)	60	25% 12%	Creatinine clearance (mL/min)	NS NS	83 ± 11 73 ± 11
Sargrand et al. [67]	RCT	8	12 (75)	47	30% 15%	NS	NS NS	NS NS
Skov et al. [68]	PG	24	50 (76)	40	25% 12%	Cr-EDTA clearance (mL/min)	106 ± 15 114 ± 19	111 ± 18 105 ± 16
Stern et al. [69]	RCT	4	41 (65)	53	LC 15%	NS	NS NS	NS NS
Tay et al. [70]	PG	52	115 (43)	58	28% 17%	eGFR (CKD epi, ml/min/1.73 m^2)	96 ± 12 92 ± 12	92 ± 12 90 ± 12
Teunissen-Beekman [71]	PG	4	48 (30)	55	1.5 g/kg/d 1 g/kg/d	Inulin clearance (mL/min)	130 ± 25 137 ± 26	127 ± 25 134 ± 26
Tirosh et al. [72]	RCT	104	318 (14)	51	LC Med LF	eGFR (MDRD ml/min/1.73 m^2)	NS NS NS	+ 5.3% + 5.2% + 4.0%
Velázquez-lopez et al. [73]	RCT	4	41 (65)	67	1–1.2 g/kg/d 0.6–0.8 g/kg/d	eGFR (Cockroft-Gault, ml/min)	NS NS	NS NS
Wagner et al. [74]	X-over	1	12 (67)	31	2 g/kg/d 0.5 g/kg/d	eGFR (MDRD ml/min/1.73 m^2)	NS NS	95 ± 11 92 ± 10
Wagner et al. [74]	X-over	1	10 (70)	60	2 g/kg/d 0.5 g/kg/d	eGFR (MDRD ml/min/1.73 m^2)	NS NS	77 ± 9 69 ± 10
Walrand et al. [75]	X-over	1.5	10 (50)	24	2.1 g/kg/d 1 g/kg/d	Iothalamate clearance (mL/ min/SA)	NS NS	128 ± 6 106 ± 4
Walrand et al. [75]	X-over	1.5	9 (44)	70	2.1 g/kg/d 1 g/kg/d	Iothalamate clearance (mL/ min/SA)	NS NS	74 ± 6 81 ± 7
Westman et al. [76]	RCT	24	84 (78%)	51	VLC 15%	eGFR (MDRD ml/min/1.73 m^2) and Creatinine clearance (mL/min)	NS NS	NS NS
Wycherly et al. [77]	PG	52	64 (0)	51	35% 17%	Creatinine clearance (mL/min)	10,625 103 ± 23	110 ± 40 101 ± 27

Values are means ± SDs

DTPA, diethylenetriamine pentaacetic acid; eGFR, estimated GFR; GFR, glomerular filtration rate; GFR pre, GFR pre-intervention; GFR post, GFR post-intervention; LC, low-carbohydrate diet; LF, low-fat diet; Med, Mediterranean diet; NS, not specified; PG, parallel-group study; PI, protein intake; RCT: randomized controlled trial; SA, surface area; VLC, very low-carbohydrate diet; X-over, randomized crossover design; 24-h Cr clearance, 24-h creatinine clearance

Studies published within the last 20 years assessing HPD and kidney health across large populations [7, 8, 21, 22, 38, 80–85] are summarized in Table 2.

Hyperfiltration may lead to an increased risk of proteinuria. Several studies have shown a relation between HPD and increased albuminuria or proteinuria as an early indicator of kidney damage [86–88]. However, some authors did not observe this link for the whole population [48, 56, 70], finding it only among subjects with hypertension and DM [89]. Some of these studies were carried out with a small number of participants and with short follow-up periods. The effect of a HPD on proteinuria merits further examination in large-scale, long-term trials.

4 Studies in Athletes and Bodybuilders

As PI improves muscle protein synthesis, many athletes use nutritional supplements to achieve an optimization of their performance in terms of endurance and resistance [14]. Professional athletes and bodybuilders consume around 4.3 g/kg/day (men) and 2.8 g/kg/day (women) of protein, exceeding the recommended daily amounts [90]. Nevertheless, Morton et al., in their meta-analysis, concluded that muscle mass did not increase with any further increase in PI over 1.6 g/kg/day (twice the RDA), while negative consequences on kidney function may still ensue [91].

Table 2 Summary of observational studies published within 20 years investigating high dietary protein intake and kidney health across large populations (> 1000 participants)

Reference	Study or location	Type	*N*	Mean age (years)	Mean eGFR (ml/min/1.73 m^2)	Protein intake in the highest group	Duration (years)	Results
Knight et al. [21]	Nurses' Health Study	PC	1624	55	90	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
Halbesma et al. [22]	Prevention of Renal and Vascular ENd-stage Disease (PREVEND)	PC	8461	50	81	1.4 g/kg/d	7	No association between baseline PI and rate of GFR decline
Cirillo et al. [8]	Gubbio Study	PC	1522	54	84	2.1 g/kg/d	12	1 g/d higher PI was related to 4.1 ml/min/1.73 m^2 more negative eGFR change and 1.78 risk for incidence of eGFR < 60 ml/min/1.73 m^2
Beasley et al. [83]	Cardiovascular Health Study	PC	3623	72	73	1.63 g/kg/d	6.4	PI was not associated with change in eGFR
Lew et al. [80]	Singapore Chinese Health Study	PC	63,257	57	NS	65.3 g/d	15.5	Total PI was positively associated with incidence of ESRD adjusted for basic demographic characteristics (HR 1.55) when comparing the highest quartile with the lowest quartile intake. However, the HR fell to 1.19 after adjusting for other lifestyle and comorbidity factors
Haring et al. [81]	Atherosclerosis Risk in Communities (ARIC) Study	PC	11,952	54	103	109.5 g/d	23	Total PI was not associated with increasing risk of incident CKD
Malhotra et al. [38]	Jackson Heart Study	OC	3165	55	97	1.0 g/kg/d	8	PI as percentage of energy intake in lowest and highest quintiles was associated with decline in eGFR among diabetics
Esmeijer et al. [82]	Alpha Omega Cohort	PC	2255	69	82	92 g/d	3.5	Patients with a daily total PI ≥ 1.20 g/kg/d compared with < 0.80 g/kg/d had a twofold faster annual eGFR decline in patients post-MI
Jhee et al. [7]	Korean Genome and Epidemiology Study	PC	9226	52	94	1.7 g/kg/d	11.5	The highest quartile was associated with 1.32-fold increased risk of rapid eGFR decline
Farhadnejad et al. [84]	Tehran Lipid and Glucose Study	PC	1797	38	76	16%	6.1	The highest tertile of LCHP diet had greater risk of incident CKD in comparison with those in the lowest one
Narasaki et al. [85]	National Health and Nutritional Examination Survey	RS	27,604	72	eGFR < 60: 47 eGFR > 60: 100	1.4 g/kg/d	4.7	A high PI of at least 1.4 g/kg/d was associated with higher mortality (HR 1.37) in subjects with eGFR < 60 ml/min/1.73 m^2

CKD, chronic kidney disease; CS, cross-sectional; ESRD, end-stage renal disease; LCHP, low-carbohydrate–high-protein diet; LP, low protein; MI, myocardial infarction; OC, observational cohort; PC, prospective cohort; PI, protein intake; RS, retrospective study

Sports and fitness studies, including those from the ISSN [14, 92–96], stated that HPD, even over 3.0 g/kg/day, has no adverse effects on healthy kidneys. A series of studies in resistance-trained athletes consuming HPDs aimed to evaluate body composition changes and was not designed to assess safety or kidney outcomes. The authors still have consistently published claims of safety. The first of these studies examined the effect of 3.4 g/kg/day on body composition in 48 subjects randomly assigned to HPD (3.4 g/kg/day) or so-called "normal" protein diet (2.3 g/kg/day) followed up for 6 weeks. The investigators concluded that HPD may confer benefits in body composition and improved performance without any deleterious effects given that changes in eGFR or creatinine were not observed [93]. The same authors conducted a 16-week crossover study of 12 resistance-trained men in two 8-week treatment periods (normal diet and HPD) [94]. The study mean PI was 2.9 ± 0.9 g/kg/day. No significant changes in body composition or markers of health were observed, so the authors asserted there were no side effects regarding HPD. Although they highlighted that no deleterious effects on kidney function appeared, one of the two individuals with the highest recorded PIs (4.66 g/kg/day and 6.59 g/kg/day) increased his eGFR from 88 ml/min/1.73 m^2 to 122 ml/min/1.73 m^2. Another randomized crossover study by this group followed 14 resistance-trained men for 1 year, and a case study of five of the participants reported outcomes for an additional year [92]. For the first year, participants alternated their usual PI with 6 months of HPD (> 3.0 g/protein/kg/day). Again, no significant changes were seen in creatinine or eGFR, although this study lacked adequate statistical power to evaluate overall safety. For the second year, five individuals were provided supplements and asked to self-report dietary intake. At baseline, the mean PI was 2.5 ± 1.0 g/kg/day and then increased by the second year to 3.5 ± 1.4 g/kg/day. Two of these patients showed worse kidney function between the first and second year, with an increase in creatinine from 0.85 to 1.3 mg/dl and a fall in eGFR from 97 ml/min/1.73 m^2 to 61 ml/min/1.73 m^2. However, the authors reported that HPD up to 3.5 g/kg/day for 2 years showed no evidence of kidney damage [95]. Poortmans et al. published one of the few studies in which kidney function was measured by creatinine clearance (CrCl) in 24-h urine output. This study included 37 subjects divided in two groups—bodybuilders and other athletes—that completed a 7-day nutrition record representative of typical training days. Resting and exercise blood samples with 24-h urine were obtained on day 7 of the study. In post-exercise analysis, there were no differences between groups, with both suffering both a slight increase in creatinine (3–4% reduction in CrCl) and increase in albumin excretion. The authors concluded that PI under 2.8 gr/kg/day did not impair kidney function in well-trained athletes [96]. Studies in athletes or bodybuilders [92–96] are listed in Table 3.

5 Discussion

Most of the published studies on the effect of PI on kidney function of athletes and healthy individuals focused on short-term effects. In contrast, little information is available on the effect of chronic dietary PI, especially HPD. The studies carried out by non-nephrologist physicians or experts in sports nutrition referenced above [92–96] are designed to evaluate body composition and not kidney outcomes or safety.

HPD followed by athletes and bodybuilders are mostly based on animal protein. Several observational studies have noted a strong association between intake of animal protein and incidence and progression of CKD [80, 81, 83, 86], as well as an increased risk of albuminuria, rapid eGFR decline, or both [23, 80, 86]. The pathophysiology of these associations remains unclear. One proposed mechanism is the link between animal protein consumption and hypertension [97] or weight gain [98]. Conversely, plant-based foods have been shown to have the opposite effect [99, 100]. 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 [101–104]. Phosphorus may play an important role in this process. Proteins are an important source of phosphorus, with a linear relationship between protein intake and phosphoremia. Its intake can be both naturally in foods rich in protein, and through inorganic phosphate additives present in different foods, including protein supplements which have high bioavailability [105]. From the early stage of CKD, dietary phosphate loading increases expression of fibroblast growth factor 23 (FGF-23), a phosphaturic hormone synthesized to excrete the excess phosphorus [106]. Studies have shown that phosphate load leads to a faster decline in renal function as the damaged kidney is not able to achieve an adequate phosphaturia [107]. Enhanced extracellular and intracellular phosphorus concentrations may accelerate the progression of kidney damage by generating endothelial dysfunction and oxidative stress [108], along with the role of FGF-23 in stimulating cell proliferation and upregulating the renin–angiotensin system [109, 110]. To date, several observational studies converged to indicate that phosphate might have an independent pathogenic role in the onset and progression of CKD [111–113]. Animal-based proteins also yield a higher dietary acid load, which increases acidosis, especially in kidney patients with impairments of both acid excretion and bicarbonate generation. Furthermore, dietary acid might also be a risk factor for CKD through intrarenal mechanisms promoting kidney injury and progressive GFR

Table 3 Studies of HPD in athletes with renal function measurement

Study	Design	Duration (weeks)	*N* (% female)	Mean age (years)	Daily PI (gr/Kd/day)	GFR method	GFR pre (ml/min/1.73 m^2)	GFR post (ml/min/1.73 m^2)	
Antonio et al. [92]	X-over	24	14 (0)	26	2.6 3.3	eGFR[b]	96 ± 20[a] 95 ± 19[a]	102 ± 18 98 ± 16	
Antonio et al. [93]	RCT	6	48 (23)	26	2.3 3.4	eGFR[b] (only in 23 subjects)	101 ± 12 90 ± 13	100 ± 15 90 ± 9	
Antonio et al. [94]	X-over	8	12 (0)	26	2.6 3.3	eGFR[b]	96 ± 20[c]	102 ± 18 101 ± 18	
Antonio et al. [95]	CR	104	5 (0)	30	2.2	eGFR[b]	68 126 76 125 89	w52ww 66 117 97 135 95	104w 72 117 61 125 99
Poortmans et al. [96]	PG	1	37 (0)	28	1.94 1.35	24-h Cr clearance	NS	148 ± 6[a] 143 ± 5[a]	

Values are means ± SDs

CR, case reports; eGFR, estimated GFR; GFR, glomerular filtration rate; GFR pre, GFR pre-intervention; GFR post, GFR post-intervention; PG, parallel-group study. NS, not specified; PI, protein intake; X-over, randomized crossover design; 24-h Cr clearance, 24-h creatinine clearance; 52w, GFR after 52 weeks; 104w, GFR after 104 weeks

[a]ml/min

[b]Not specified, presumed to be Modification of Diet in Renal Disease (MDRD-4) equation as authors stated normal values > 60 ml/min/1.73 m^2

[c]Mean eGFR of participants

decline [114]. As plant-based foods are rich in natural alkali they may be used to reduce both the dietary acid load and the severity of metabolic acidosis [115].

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 [80, 81]. These differences between the effects of animal-based protein versus plant-based protein may favor the use of the latter in CKD. Plant-based proteins have been previously described as being more than adequate for nutrition in individuals with impaired renal function [116]. To date, there appears to be a lack of literature that discusses how to manage vegan diets for athletic purposes since vegetable sources generally lack one or more of the essential amino acids. Empirical research is needed to examine the effects of vegan diets in athletic populations in terms of performance, body composition and renal health. Most of the studies listed in Table 1 were performed with animal protein [41, 42, 45–48, 57, 58, 60, 61, 63–65, 67, 69, 70, 75–78], some with animal- and plant-based proteins [40, 42, 44, 47, 49, 53–55, 59, 62, 68], only two with the latter [51, 66], and three did not specify the source [52, 56, 74]. Unfortunately, these studies did not compare results between the different sources of protein.

It is known that HPD induces an increase in GFR presumably as a physiological adaptation, suggesting a kidney function reserve [25, 26]. This reserve is diminished or absent in patients with CKD due to the reduced number of nephrons, so it is recommended to restrict protein to 0.55–0.80 g/kg/day or below to slow the progression of renal disease [11]. In subjects with normal renal function, the maintenance of this situation over time is likely unsustainable, and instead may induce an exhaustion of this reserve, a fall in GFR from hyperfiltration to normal, and eventually further declines in GFR to CKD over time. Jhee et al., in a community-based prospective cohort study of 9226 subjects followed-up for a median of 11.5 years, all with normal renal function and without any underlying kidney disease at baseline, demonstrated that a high-protein diet increases the risk of renal hyperfiltration and a rapid renal function decline [7]. Participants were classified into quartiles according to daily amount of protein intake on the basis of food frequency questionnaires. After full adjustment for confounding factors, the highest quartile group showed higher odds ratios for renal hyperfiltration and for rapid decline in eGFR than the lowest quartile group (OR 3.48, 95% CI 1.39–8.71; $p = 0.01$; OR 1.32, 95% CI 1.02–1.73; $p = 0.03$, respectively). Subjects were then divided into two groups according to renal hyperfiltration status. Each group was further categorized into four groups according to daily protein intake quartiles. Mean eGFR decline rate was faster in the renal hyperfiltration group than in the non-renal hyperfiltration group (3.1 versus 2.1 mL/min/1.73m^2/year, respectively; $p < 0.001$). The highest protein intake group showed increased risk of the occurrence of eGFR < 60 mL/min/1.73 m^2. Moreover,

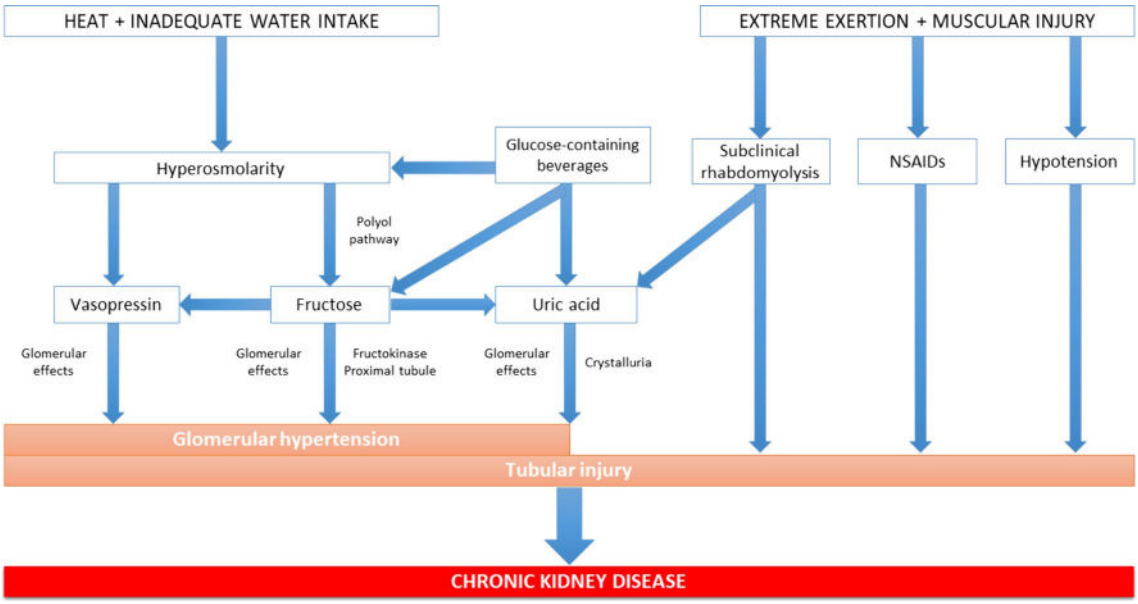

Fig. 3 Mechanisms potentially involved in the development of heat-associated chronic kidney disease. Hyperosmolarity produced by recurrent dehydration induces vasopressin release and production of fructose due to the activation of the polyol pathway (aldose reductase and sorbitol dehydrogenase). Vasopressin causes an increase in intraglomerular pressure and fructose is metabolized by fructokinase in the proximal tubule, re-stimulating the release of vasopressin. This situation provokes an increase in oxidative stress and in uric acid production, leading to tubular injury. Rehydration with glucose-containing beverages will provide higher amounts of substrate, amplifying vasopressin reponse and uric acid production. There are a number of different mechanisms which may simultaneously appear in athletes taking part in this renal injury as subclinical rhabdomyolysis, NSAIDs consumption and hypotension due to volume depletion. The latter activates the renin–angiotensin–aldosterone system, playing an important role in chronic kidney disease. *NSAIDs* non-steroidal anti inflammatory drugs

when the subjects were divided into with or without renal hyperfiltration, in the hyperfiltration group there was consistent association that the highest protein intake was related to increased risk for the occurrence of eGFR < 60 mL/min/1.73 m^2.

The vast majority of surveys performed in athletes are short-term studies in which the brief follow-up period prevents a true assessment of the renal reserve and its expected progressive decline due to oxidative stress, inflammation, apoptosis, and glomerular damage [34]. The meta-analysis conducted by Devries et al. concluded that HPI does not adversely influence GFR in healthy adults. Of note, 12 of the 30 studies included kidney function assessment with eGFR (formula not stated in most of these studies), which has lower accuracy in the range of normal to high GFR [2–4]. Moreover, only 6 studies had at least 1 year of follow-up period; 2 used 6-month follow-up, and the remaining 22 studies followed individuals for between 1 and 12 weeks. We highlight that in five of the studies with longest follow-up period, an increase in GFR occurred after HPD, in three cases measured by creatinine clearance [39].

To the best of our knowledge, all published studies performed in athletes lacked control groups of normal PI, most of them comparing two different versions of HPDs. No study utilized a follow-up period long enough or a sample size robust enough to obtain conclusions about the implications of chronic HPD for kidney health. A minority of studies measured kidney function with 24-h urine output for creatinine clearance, which is a better measurement of kidney function in young individuals with higher GFR values than using eGFR [5], which was used in most studies. Creatinine is a byproduct of creatine and may increase with high dietary animal-based PI or increased muscle mass. Due to this, eGFR calculations can be imprecise in those with high lean body mass or in healthy populations. These limitations, and the potential for glomerular hyperfiltration, make eGFR a suboptimal measurement of kidney function in the athletic population [5]. If 24-h urine collections could not be used, alternative measurements of kidney function and eGFR using cystatin C would be preferable in these populations than creatinine. We underline that none of the aforementioned studies included oversight from or collaboration with a nephrologist.

Baranauskas et al. found that athletes following a HPD (2.0–4.8 g/kg/day) had excessive endogenous acid production and significant acid–base imbalances promoting further pH lowering over that associated with exercise [117]. This negatively affects bone mineral metabolism, promotes kidney stones production, and may contribute to muscle mass

reduction [118]. In addition, these diets are also rich in phosphorus, sodium, and saturated fats, which may increase the risk of CKD [117]. It is critical to recognize that dietary recommendations should be individualized and accommodated to those at high risk, and it is dangerous to assume that all athletes are free of risk because they are fit. A study of people living in Central America who have developed CKD of unknown etiology suggests that a combination of extreme exertion, heat, and dehydration could contribute to repeated acute kidney injury and CKD, even without an underlying condition [119] (Fig. 3). It is important to stress that the use of other potentially nephrotoxic agents, including certain dietary supplements, ergogenic aids, nonsteroidal antiinflammatory drugs, and anabolic steroids, may also contribute to focal segmental glomerulosclerosis and CKD [120–122]. The combination of these substances with HPI is largely unstudied.

Despite these limitations, the ISSN has claimed that "a series of controlled investigations spanning up to one year in duration utilizing protein intakes of up to 2.5–3.3 g/kg/day in healthy resistance-trained individuals consistently indicate that increased intakes of protein exert no harmful effect on markers of kidney function" [14]. Consequently, fitness professionals and social media often cite these studies as evidence of a lack of harmful effects of HPD. As disclosed in Jäger et al. [14], we highlight that the ISSN is supported in part by grants from raw good suppliers and branded companies that sell dietary protein supplements. Furthermore, several of the authors of the ISSN Position Stand: Protein and Exercise have potential conflicts of interest with sports nutrition companies that sell protein-containing supplements [14].

6 Conclusion

Existing data suggest that glomerular hyperfiltration caused by HPD induces an initial, acute increase that can be followed by a long-term, subsequent decline in GFR, leading to CKD, if HPD intake is prolonged over time, even in individuals without preexisting kidney disease. Moreover, growing evidence highlights the association of HPI with a number of metabolic complications that may be injurious to renal function. Due to exponential popularity of HPD among athletes, bodybuilders, weekend warriors, and the general population seeking weight loss, further properly designed studies are needed to investigate and confirm its long-term effects on kidney function. Athletes choosing a HPD should be aware of the potential long-term risks and should discuss them with their physicians, following individualized recommendations according to their personal health status. CKD may not be the final destination for everyone, but it does represent a potential threat for some.

Declarations

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