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THE IMPACT OF CREATINE SUPPLEMENTATION AND HIGH-PROTEIN DIET ON KIDNEY FUNCTION IN PHYSICALLY ACTIVE INDIVIDUALS: A NARRATIVE REVIEW

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ABSTRACT

The safety of high-protein diets (HPD) and creatine supplementation remains a central topic of debate between the sports nutrition and nephrology communities. While athletes utilize these strategies to optimize body composition and performance, concerns regarding renal health, specifically glomerular hyperfiltration and the interpretation of creatinine-based biomarkers, persist. This narrative review synthesizes evidence from randomized controlled trials, systematic reviews and meta-analyses, observational studies, mechanistic studies, and clinical guidelines. Current evidence suggests that in healthy, physically active individuals, neither creatine supplementation at recommended doses nor high protein diet (up to 3.4 g/kg/d) negatively affect renal function. However, the interpretation of serum creatinine in active populations is often harder to interpret accurately by higher muscle metabolism and creatine supplementation. While nephrology literature highlights potential risks of high protein diet in individuals with pre-existing chronic kidney disease, these findings may not be directly generalizable to the healthy population. Studies regarding both creatine supplementation and HPD in healthy individuals at the same time are limited and need further research.

KEYWORDS

Creatine, High-Protein Diet, Renal Function, Athletes, Kidney Health

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Introduction

The field of sports nutrition and exercise medicine has experienced a growing interest in dietary strategies aimed at optimizing training adaptations, improving body composition, and enhancing athletic performance. Creatine monohydrate remains one of the most thoroughly researched and popular ergogenic aids worldwide, used by both professional athletes and occasional fitness enthusiasts to improve muscle mass, strength, and recovery (Costa i in., 2023).

Concurrently, high-protein diets (HPD), often defined as an intake exceeding 1.5 g/kg/day or significantly surpassing the United States Recommended Dietary Allowance (RDA) of 0.8 g/kg/day, have become a staple for individuals seeking to optimize body composition and mitigate sarcopenia (Van Elswyk i in., 2018a).While these strategies are widely recognized for their efficacy, their long-term impact on renal health remains a subject of persistent debate within the scientific community.

The physiological justification underlying these strategies is closely linked to skeletal muscle metabolism, energy homeostasis, and the regulation of muscle protein synthesis. Creatine serves as a critical energy buffer, existing primarily as phosphocreatine (PCr) in skeletal muscle where it facilitates the rapid resynthesis of adenosine triphosphate (ATP) via the creatine kinase reaction during high-intensity anaerobic efforts (Kreider i in., 2017). Thus supplementation of this nutrient even at low doses is effective for increasing maximal strength and endurance (De Oliveira Vilar Neto i in., 2020). In addition to its role in bioenergetics, creatine may influence cellular hydration, glycogen content, satellite cell proliferation, and growth factor expression (Mills i in., 2020). Complementary to this following high-protein diets provide essential amino acids required to stimulate muscle protein synthesis (MPS), a fundamental anabolic process crucial for skeletal muscle hypertrophy, maintenance, and repair following resistance training (Morton i in., 2018).

Current evidence suggests that the combined use of creatine and protein supplementation may enhance gains in muscular strength and lean tissue mass more effectively than protein supplementation alone, although findings across studies remain somewhat inconsistent (Forbes, 2026). Assessing the safety of these practices requires a precise evaluation of kidney function, typically measured by the glomerular filtration rate (GFR) and its common clinical proxy, serum creatinine (Van Elswyk i in., 2018b)**.** However, the interpretation of

these biomarkers is frequently confounded in athletic populations. Serum creatinine is a byproduct of the non-enzymatic degradation of creatine, and its levels are heavily influenced by muscle mass and exogenous intake of meat or creatine supplements (Antonio i in., 2021). Consequently, physically active individuals often exhibit elevated serum creatinine levels, which can lead to false-positive indications of kidney injury and inaccurate estimated GFR (eGFR) calculations, despite preserved renal health (Medeiros i in., 2025).

A central controversy exists between the sports nutrition literature and the nephrology literature regarding the long-term safety of high protein diet. The nephrology perspective often emphasizes that a high protein intake increases renal blood flow and intraglomerular pressure leading to higher glomerular filtration rate (GFR)(Esmeijer i in., 2020).While this "glomerular hyperfiltration" is an adaptive mechanism to clear nitrogenous waste, nephrologists argue that prolonged exposure may eventually exhaust the renal functional reserve, leading to progressive glomerular damage and potential chronic kidney disease (CKD) (De Lorenzo i in., 2024), (G.-J. Ko i in., 2020). Despite the volume of research supporting the short-term safety of these interventions, significant gaps remain. The majority of available studies are limited by short follow-up durations (often <12 weeks), small sample sizes, and a lack of control groups consuming standard protein intake (Van Elswyk i in., 2018b). Furthermore, there is a notable paucity of longitudinal data evaluating chronic high-protein dieting in healthy athletes over many years (Kamper & Strandgaard, 2017). Given the rising global prevalence of CKD and the high popularity of these nutritional aids, a comprehensive synthesis of the current evidence is required to distinguish between normal physiological adaptation and pathological risk (G.-J. Ko i in., 2020).

The objective of this narrative review is to synthesize the current scientific evidence regarding the effects of creatine supplementation and high-protein diets on kidney function in physically active individuals. By integrating findings from randomized controlled trials, meta-analyses, and epidemiological data, this review aims to clarify the difference between adaptive and maladaptive renal responses, address the clinical interpretation of biomarkers in athletes, and identify critical areas for future long-term research.

Methodology

This article is a structured narrative review designed to synthesize current scientific evidence regarding the effects of creatine supplementation and high-protein diets on renal health in physically active individuals. The methodology follows a qualitative synthesis of multidisciplinary data to distinguish between benign physiological adaptations and pathological risks. Findings were organized into four thematic categories to facilitate a structured analysis: (1) creatine supplementation and renal function, (2) high-protein diets and kidney function, (3) combined effects, and (4) biomarkers and diagnostic challenges.

Search strategy

The literature search strategy focused on identifying relevant peer-reviewed publications within major electronic databases, including PubMed, Scopus and Google Scholar.

Inclusion Criteria

Studies were included in this review if they were published in the English language and involved human participants. A strong preference was placed on literature published after 2017 to ensure the synthesis reflects contemporary clinical standards and analytical techniques. The primary population of interest consisted of healthy, athletic, resistance-trained, or physically active individuals. Eligible investigations were required to assess renal function (e.g., measured or estimated GFR) or kidney-specific biomarkers in the context of exogenous creatine or high-protein intake. The review incorporated the following source types:

- Randomized controlled trials (RCTs) and crossover designs.
- Systematic reviews and meta-analyses, which represent the highest levels of evidence.
- Observational and cohort studies to provide long-term populational perspectives.
- Mechanistic studies to clarify renal hemodynamic responses.
- Clinical guidelines and position stands from professional academic societies, such as the International Society of Sports Nutrition (ISSN)

Exclusion Criteria

Studies were excluded if they were unrelated to renal outcomes or lacked relevance to sports nutrition and physically active populations. While clinical data from nephrology were used for comparative purposes, studies focused exclusively on severe chronic kidney disease (CKD), end-stage renal disease, or unrelated pathologies (e.g., cancer or organ transplantation) were excluded when findings were not considered generalizable to healthy athletes. Additionally, duplicate publications, non-English articles, and studies provided only in abstract form were omitted from the main synthesis to maintain data integrity.

Results

Creatine supplementation and renal function

The scientific consensus, supported by extensive meta-analyses and longitudinal investigations, indicates that creatine supplementation does not adversely impact kidney function in healthy, physically active individuals (De Souza E Silva i in., 2019; Naeini i in., 2025). Recent systematic reviews and meta-analyses of randomized controlled trials (RCTs) demonstrate that while creatine intake may be associated with a modest, statistically significant increase in serum creatinine levels (mean difference: 0.07 μmol/L), it has no statistically significant effect on the glomerular filtration rate (GFR) (Naeini i in., 2025). This dissociation between creatinine levels and GFR is a critical clinical distinction; it suggests that observed fluctuations in blood markers are a predictable byproduct of metabolic turnover and saturated muscle stores rather than an indicator of renal impairment or nephrotoxicity (De Souza E Silva i in., 2019).

The primary challenge in evaluating renal safety in athletic and physically active populations is the inherent limitation of serum creatinine as an indirect marker of kidney health. (De Oliveira Vilar Neto i in., 2020). Creatine and phosphocreatine undergo continuous, low-grade, non-enzymatic degradation into creatinine, which is then exported to the blood for renal excretion (Medeiros i in., 2025). Because serum creatinine concentrations are heavily influenced by muscle mass, physical activity, and exogenous intake, physically active individuals often exhibit baseline levels at the upper end of the normal range (De Oliveira Vilar Neto i in., 2020). Supplementation further elevates these levels through the spontaneous conversion of the supplement itself, often leading to "false-positive" indications of kidney injury when using traditional creatinine-based estimated GFR (eGFR) equations (Medeiros i in., 2025). Consequently, relying solely on serum creatinine to assess renal function in athletes supplementing with creatine is considered clinically misleading (Antonio i in., 2021)

To address the diagnostic limitations of traditional markers, recent high-quality RCTs have utilized more sensitive renal injury biomarkers, such as Kidney Injury Molecule-1 (KIM-1) and Monocyte Chemoattractant Protein-1 (MCP-1)(De Oliveira Vilar Neto i in., 2020). KIM-1 is a highly specific marker for proximal tubular damage, while MCP-1 identifies early glomerular and tubulointerstitial inflammation. A 35-day double-blind, placebo-controlled trial in healthy active males found that while the supplemented groups (3 g/day and 5 g/day) experienced the expected rise in serum creatinine, there were no significant differences in KIM-1 or MCP-1 levels compared to placebo (De Oliveira Vilar Neto i in., 2020).

These findings provide objective evidence that recommended dosages of creatine do not induce subclinical or structural renal damage (De Oliveira Vilar Neto i in., 2020). Long-term safety is further supported by both cohort studies and expert position stands. Large-scale epidemiological data from the NHANES 2017–2018 survey found no significant association between dietary creatine intake and the risk of kidney failure at the population level. (Ostojic, 2021). Controlled trials in athletes have mirrored these results; for instance, American collegiate football players consuming up to 10 g/day for 21 months showed no clinically significant changes in markers of renal function or clinical urinalysis. The International Society of Sports Nutrition (ISSN) maintains in its official position stand that there is no compelling scientific evidence that short- or long-term use (up to 30 g/day for 5 years) has any detrimental effects on the kidney health of healthy individuals (Kreider i in., 2017).

Despite the robust evidence for safety, early concerns often stem from individual case reports where renal dysfunction was confounded by pre-existing disease, inappropriate dosages, or the co-ingestion of potentially nephrotoxic substances like anabolic steroids (Antonio i in., 2021). Clinical trials—including those involving type 2 diabetics and postmenopausal women—consistently report no impairment of renal function when standard protocols (e.g., 3–5 g/day) are followed (Msc in Biochemistry, PhD in Candidate, Baghdad iraq & Chillab, 2025).

In conclusion, current evidence from systematic reviews and RCTs demonstrates that creatine supplementation is safe for renal function in healthy, physically active individuals. While it predictably elevates serum creatinine due to increased metabolic turnover, it does not impair the kidneys nor renal function, as confirmed by both traditional markers and novel subclinical injury biomarkers (De Oliveira Vilar Neto i in., 2020; Naeini i in., 2025)

High-protein diets and kidney function

Current scientific evidence, particularly large-scale systematic reviews and meta-analyses, suggests that high-protein diets (HPD) do not adversely affect kidney function in healthy, physically active individuals (Van Elswyk i in., 2018a). A definitive meta-analysis of randomized controlled trials (RCTs) involving 1,358 participants found that while HPDs (defined as ≥ 1.5 g/kg/day or ≥ 20% of energy intake) may result in higher post-intervention glomerular filtration rates (GFR), the actual absolute change in GFR from baseline does not differ between high and normal protein intakes (Devries i in., 2018). These findings indicate that elevated protein consumption does not induce clinically significant renal impairment in adults without pre-existing kidney disease. (Van Elswyk i in., 2018a).

The physiological mechanism underpinning the renal response to increased protein intake is "glomerular hyperfiltration," characterized by an increase in renal blood flow and intraglomerular pressure (De Lorenzo i in., 2024).This process facilitates the efficient excretion of protein-derived nitrogenous waste products, such as urea. (G.-J. Ko i in., 2020). In healthy individuals, this is recognized as an adaptive whole-kidney response utilizing the "kidney functional reserve," similar to the benign hyperfiltration observed during pregnancy or following unilateral nephrectomy (Devries i in., 2018). Importantly, these transient increases in GFR represent a normal adjustment to increased metabolic workload rather than a precursor to pathological damage.(Van Elswyk i in., 2018b).

In contrast, the nephrology literature often emphasizes the "hyperfiltration theory," which suggests that prolonged increases in intraglomerular pressure can lead to progressive glomerular damage, sclerosis, and the eventual development of chronic kidney disease (CKD)(Ortega i in., 2024). This "vicious cycle" is particularly relevant in clinical populations with reduced nephron mass, where hyperfiltration is a maladaptive compensatory mechanism occurring at the single-nephron level rather than a whole-organ adaptation (G.-J. Ko i in., 2020). Consequently, clinical guidelines from organizations such as KDOQI recommend protein restriction (0.55–0.60 g/kg/day) only for individuals with established CKD to slow disease progression and reduce uremic toxins (Ikizler i in., 2020). However, several researchers argue that these clinical risks are often inappropriately extrapolated to healthy athletes with fully intact renal function (Devries i in., 2018).

The distinction between adaptive physiological hyperfiltration and maladaptive pathological hyperfiltration is summarized in Figure 1.

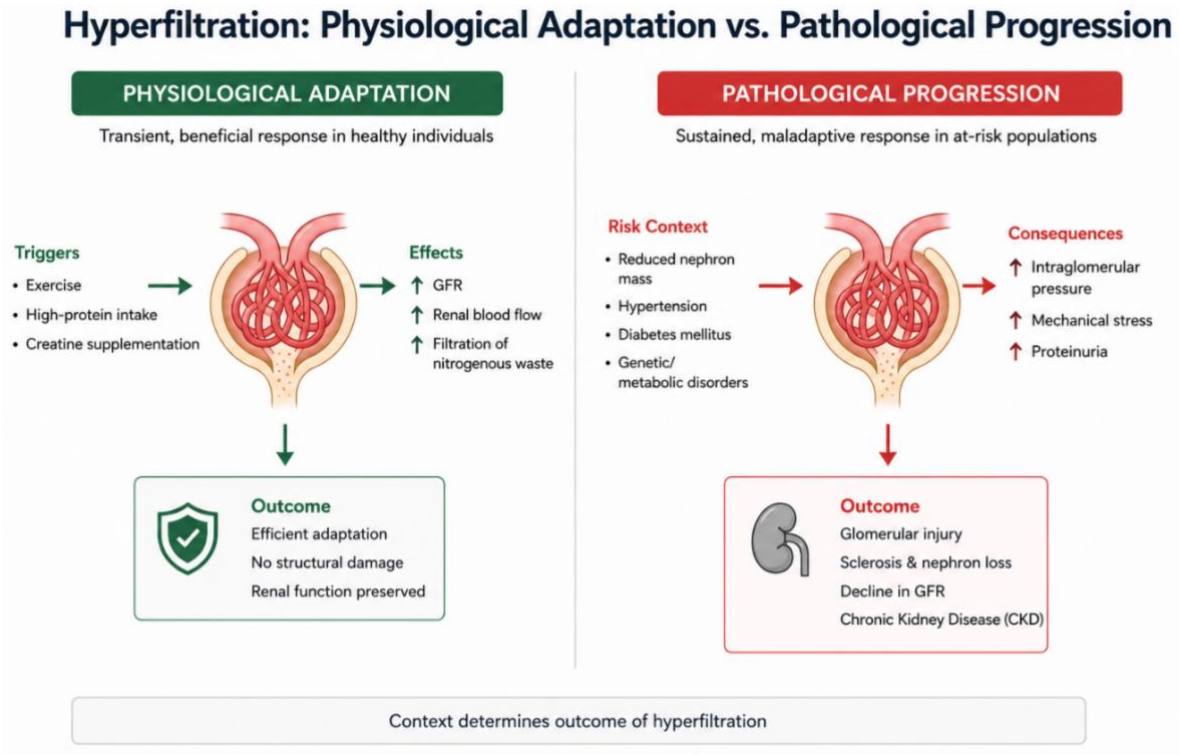

Fig. 1. *Comparison of physiological and pathological renal hyperfiltration. In healthy individuals, transient increases in GFR represent a benign adaptive response to increased metabolic demand, whereas sustained hyperfiltration in at-risk populations may contribute to glomerular injury and chronic kidney disease progression.*

Created by the authors based on concepts described by G.-J. Ko et al., De Lorenzo et al. and Ortega et al.

Observational and cohort studies have provided mixed results, often influenced by the source of dietary protein. Large-scale data, such as the Singapore Chinese Health Study and the Alpha Omega Cohort, have associated high intakes of red and processed meats with an increased risk of end-stage renal disease (ESRD) and accelerated eGFR decline in older adults or those with pre-existing risk factors (G.-J. Ko i in., 2020). These risks may be mediated by a higher dietary acid load, high phosphorus content, and gut microbiome dysbiosis associated with animal-based proteins (De Lorenzo i in., 2024). In contrast, plant-based protein sources appear to be renoprotective and are associated with a slower decline in renal function (Ajjarapu i in., 2019).

Controlled investigations specifically focusing on resistance-trained individuals have reported safety at even higher protein thresholds. RCTs in athletes utilizing protein intakes of 2.5 to 3.4 g/kg/day for up to one year consistently show no detrimental changes in serum creatinine, urea, or markers of renal health (Antonio, 2019). Despite these positive results, the current literature is limited by several factors: the majority of trials are short-term (often <12 weeks), utilize relatively small sample sizes, and rely on creatinine-based estimated GFR (eGFR), which can be imprecise in populations with high muscle mass or fluctuating dietary protein. Furthermore, there is a lack of multidisciplinary oversight from nephrologists in sports nutrition studies to detect early subclinical markers of renal stress (De Lorenzo i in., 2024).

In conclusion, for healthy, physically active individuals, high-protein diets are not associated with impaired kidney function, and the associated renal adaptations are considered physiological rather than pathological. While nephrology perspectives provide a necessary caution for at-risk populations, current evidence supports the safety of protein intakes well above the RDA for athletic purposes, provided there is no pre-existing renal dysfunction (Van Elswyk i in., 2018a).

Combined effects

Creatine supplementation and high-protein diets (HPD) are frequently co-administered by resistance-trained and athletic populations to synergistically support muscle hypertrophy, recovery, and strength adaptations (Costa i in., 2023). Systematic reviews and meta-analyses confirm that both dietary protein supplementation and creatine monohydrate independently augment gains in one-repetition maximum (1RM) strength and fat-free mass (FFM) during prolonged resistance exercise training (Van Elswyk i in., 2018a).

Evidence from randomized controlled trials (RCTs) suggests that combining these strategies may provide additive physiological benefits, such as increased training volume, enhanced satellite cell proliferation, and improved intramuscular energy buffering (Kreider i in., 2017). For example, low-dose creatine combined with protein supplementation has been shown to increase lean tissue mass and upper body strength while potentially mitigating muscle protein degradation (Kreider i in., 2017).

Despite their widespread simultaneous use, scientific investigations specifically designed to evaluate the cumulative long-term renal impact of combined creatine supplementation and chronic HPD remain limited (Antonio, 2019). Current evidence, including 12-week randomized trials in resistance-trained individuals and cross-sectional analyses of bodybuilders, does not demonstrate clinically meaningful kidney dysfunction or impaired glomerular filtration rates (GFR) when both strategies are utilized within established recommended ranges (Marta Korchowiec i in., 2025). However, the current literature is constrained by a small number of studies directly investigating the interaction between high nitrogen loads and exogenous creatine, with most interventions characterized by short follow-up durations of less than six months. (Van Elswyk i in., 2018a).

Furthermore, the field's heavy reliance on serum creatinine-based biomarkers remains a significant limitation, as these markers are confounded by high muscle mass and exogenous intake, potentially yielding false-positive indications of renal stress (Antonio i in., 2021). Consequently, there is a clear need for further long-term, longitudinal research utilizing more sensitive injury markers to definitively establish the safety of these combined dietary strategies on renal outcomes.(G.-J. Ko i in., 2020; Msc in Biochemistry, PhD in Candidate, Baghdad iraq & Chillab, 2025).

Biomarkers and diagnostic challenges

The assessment of renal health in physically active populations presents significant diagnostic challenges due to the inherent limitations of traditional renal biomarkers. Serum creatinine, the most widely utilized proxy for kidney function, is considered a crude index in athletes because its concentration is heavily influenced by non-renal factors such as total muscle mass, body size, and exercise-induced metabolic turnover (De Lorenzo i in., 2024). In resistance-trained individuals who possess high lean body mass, baseline creatinine levels often reside at the upper limit of the clinical reference range (Antonio i in., 2021).

Furthermore, traditional estimated glomerular filtration rate (eGFR) equations, such as the MDRD and CKD-EPI creatinine formulas, were derived from populations that do not reflect the unique physiology of athletes. These equations often lose accuracy in individuals with extremes of muscle mass, potentially yielding "false-positive" indications of kidney injury and imprecise GFR estimations when filtration is actually preserved (De Lorenzo i in., 2024).

Diagnostic interpretation is further complicated by the fact that creatinine is not only filtered by the glomeruli but also actively secreted by the proximal tubules, which may lead to an overestimation of glomerular filtration rate when creatinine-based measurements are used (Kamper & Strandgaard, 2017). While 24-hour urine collection for creatinine clearance provides a more integrated assessment than single blood draws, it remains subject to errors in collection timing and the influence of high dietary protein or meat intake, which acutely raises serum levels (Kamper & Strandgaard, 2017).

Because renal disease is often only clinically detectable once functional capacity has declined by at least 50%, standard biomarkers frequently fail to identify subclinical or early-stage renal stress in healthy athletic cohorts (De Oliveira Vilar Neto i in., 2020).

This necessity for earlier detection has shifted research interest toward biomarkers that are independent of musculoskeletal factors. Alternative and emerging biomarkers offer a potential solution to these diagnostic challenges. Cystatin C, a low-molecular-weight protein produced by all nucleated cells, is freely filtered by the glomeruli and is less influenced by muscle mass, exercise, and dietary protein intake than serum creatinine(Kamper & Strandgaard, 2017). This makes it a superior filtration marker for athletes and bodybuilders, as evidenced by its use in refined CKD-EPI equations to provide more precise eGFR calculations in studies where creatinine-based results were confounded(Kamper & Strandgaard, 2017).

Additionally, emerging biomarkers such as Kidney Injury Molecule-1 (KIM-1) and Monocyte Chemoattractant Protein-1 (MCP-1) may improve the early detection of structural renal injury. KIM-1 is considered a sensitive marker of proximal tubular damage and may increase before measurable changes in traditional renal function parameters such as eGFR become apparent, whereas MCP-1 has been associated with glomerular and tubulointerstitial inflammatory processes(De Oliveira Vilar Neto i in., 2020). Although other candidates like neutrophil gelatinase-associated lipocalin (NGAL) show promise for early detection, they have yet to be fully verified for routine clinical use in sports medicine (Haase-Fielitz i in., 2014).

Ultimately, the complexity of metabolic turnover in active individuals necessitates a cautious, multi-marker approach, prioritizing muscle-independent and structural injury markers to ensure accurate assessment of renal health (Kamper & Strandgaard, 2017).

A comparison of traditional and emerging renal biomarkers relevant to athletic populations is presented in Table 1.

Comparison of renal biomarkers.

Table 1. Comparison of traditional and emerging renal biomarkers used in physically active individuals. The table was developed based on findings from the included literature sources.

BIOMARKER	PRIMARY PHYSIOLOGICAL ROLE	INFLUENCE OF MUSCLE MASS/DIET/EXERCISE	CLINICAL RELEVANCE	ADVANTAGES AND DISADVANTAGES
SERUM CREATININE	End product of the non-enzymatic degradation of muscle creatine and phosphocreatine	Strongly influenced by high muscle mass, intense exercise, meat consumption, and creatine supplements	Standard screening tool; elevated levels often lead to "false-positives" for kidney injury in athletes	Advantage: Inexpensive and widely available Disadvantage: Low specificity in athletes
BLOOD UREA NITROGEN (BUN)	Primary nitrogenous waste product formed from the catabolism of dietary and tissue protein	Significantly increased by high-protein diets independent of actual kidney damage	Used to monitor nitrogen load; high levels may theoretically contribute to oxidative stress	Advantage: Widely available. Disadvantage: Highly sensitive to recent protein intake
CYSTATIN C	Endogenous filtration marker produced at a constant rate by all nucleated cells	Independent of total muscle mass and dietary protein intake. Can be influenced by age, high body mass, smoking, high plasma CRP, high-dose corticosteroid use.	Recognized as a superior filtration marker for athletes and those on high-protein diets	Advantage: High diagnostic accuracy in athletes. Disadvantage: More expensive than creatinine.
KIM-1 (KIDNEY INJURY MOLECULE-1)	Highly specific marker for proximal renal tubular damage	Investigational biomarker without reference ranges. Not significantly affected by short-term creatine supplementation.	Provides early detection of subclinical structural tubular injury before GFR changes occur	Advantage: High specificity for tubular stress. Disadvantage: Limited availability for routine clinical use
MCP-1 (MONOCYTE CHEMOATTRACTANT PROTEIN-1)	Pro-inflammatory chemokine marking glomerular and tubulointerstitial inflammation	Investigational biomarker; lacks standardized reference values. Levels remain stable during creatine supplementation.	Identifies subclinical glomerular inflammation and disease progression	Advantage: Sensitive to early renal inflammation. Disadvantage: Needs more longitudinal human validation
NGAL (NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN)	Protein produced by injured nephron epithelia	Sensitivity to exercise-induced stress has not been fully verified in athletic cohorts	Used primarily to detect acute kidney injury (AKI) earlier than traditional markers	Advantage: Detects injury before functional decline. Disadvantage: Not yet verified for routine CKD monitoring

Discussion

Interpretation of Findings

The synthesis of contemporary high-level evidence indicates that creatine supplementation and high-protein diets (HPD) do not demonstrate clinically meaningful renal dysfunction in healthy, physically active individuals when utilized within established recommended ranges (Naeini i in., 2025).

Meta-analyses of randomized controlled trials (RCTs) confirm that while these nutritional strategies may alter biochemical proxies, specifically by inducing a modest, transient increase in serum creatinine, actual glomerular filtration rate (GFR) remains stable, suggesting preserved renal health across diverse athletic cohorts (De Souza E Silva i in., 2019; Devries i in., 2018; Naeini i in., 2025). For instance, a 2025 meta-analysis showed that while creatine is associated with a modest increase in serum creatinine, actual GFR remains stable, suggesting preserved filtration capacity.(Naeini i in., 2025) Similarly, systematic reviews of

HPDs (up to 3.4 g/kg/d) report that absolute changes in GFR from baseline do not differ significantly between high and normal protein intakes in healthy adults (Devries i in., 2018).

Despite these reassuring findings, long-term prospective evidence remains limited, as most controlled trials do not extend beyond six months. As a result, a significant knowledge gap persists regarding the cumulative renal effects of prolonged co-administration of creatine supplementation and high-protein diets over many years or decades (Van Elswyk i in., 2018a).

Physiological and Clinical Significance

A fundamental distinction must be made between physiological renal adaptation and pathological kidney injury. In clinical nephrology, the "hyperfiltration theory" suggests that chronic increases in intraglomerular pressure lead to sclerosis and nephron loss.(De Lorenzo i in., 2024). However, in healthy athletes, the hyperfiltration observed after protein ingestion represents a benign utilization of the “kidney functional reserve,” an adaptive response to facilitate the excretion of increased nitrogenous waste products like urea (Devries i in., 2018; G. J. Ko i in., 2017). This response is comparable to other physiological states, such as pregnancy, characterized by adaptive hyperfiltration that are not inherently associated with long-term renal damage (Devries i in., 2018).

Furthermore, the rise in creatinine production associated with creatine use is not a marker of damage but a predictable pharmacokinetic event, as approximately 1–2% of intramuscular creatine spontaneously degrades into creatinine daily (De Oliveira Vilar Neto i in., 2020). Coupled with intense exercise-induced metabolic turnover, these biochemical shifts reflect an adjustment to a higher solute load rather than structural injury (Antonio i in., 2021).

In sports medicine practice, serum creatinine and creatinine-based eGFR (e.g., MDRD, CKD-EPI) frequently overestimate renal dysfunction because they were derived from populations that do not reflect the unique physiology of athletes(De Lorenzo i in., 2024). In resistance-trained individuals with high lean body mass, baseline creatinine levels often reside at the upper limit of clinical reference ranges, leading to potential "false-positive" indications of kidney injury (De Lorenzo i in., 2024).

Consequently, clinicians must provide a contextual interpretation of renal biomarkers that accounts for muscle mass, training volume, and supplement use. When diagnostic clarity is required, muscle-independent markers such as Cystatin C are superior, as they are not influenced by dietary protein or muscle mass (Kamper & Strandgaard, 2017). Additionally, novel injury markers like Kidney Injury Molecule-1 (KIM-1) for tubular damage and Monocyte Chemoattractant Protein-1 (MCP-1) for glomerular inflammation offer greater sensitivity for detecting subclinical renal stress (De Oliveira Vilar Neto i in., 2020).

Comparison of Perspectives and Limitations

A fundamental tension persists between the perspectives of the sports nutrition and nephrology communities. Nephrology literature frequently reports caution regarding HPDs based on the potential for long-term exhaustion of the renal reserve (Kalantar-Zadeh i in., 2020). However, findings from chronic kidney disease (CKD) populations, where protein restriction (0.6–0.8 g/kg/d) is necessary due to reduced nephron mass, are not directly generalizable to healthy athletes with fully intact renal capacity(Devries i in., 2018). Most studies suggesting risk are observational and subject to confounding, while athletic safety studies often lack control groups consuming normal protein intakes (De Lorenzo i in., 2024).

The current literature is constrained by several methodological limitations:

- Small sample sizes (often $n < 20$ per group) and short follow-up durations (typically 1–12 weeks) limit the ability to detect rare adverse events or slow, progressive decline (Mills i in., 2020).
- There is a paucity of combined-intervention studies directly evaluating the cumulative renal impact of simultaneous high-dose creatine and chronic HPD.
- Heterogeneity in HPD definitions (ranging from 1.2 to >3.4 g/kg/d) and continued reliance on indirect, creatinine-based biomarkers persist (De Lorenzo i in., 2024; Whittaker, 2023).
- There is a notable lack of representation for females and elite athletic populations in safety data.

Conclusions

The synthesis of contemporary high-level evidence indicates that creatine supplementation and high-protein diets (HPD) do not demonstrate clinically meaningful renal dysfunction in healthy, physically active individuals when utilized within established recommended ranges (Msc in Biochemistry, PhD in Candidate, Baghdad iraq & Chillab, 2025).

Current scientific evidence suggests that although these nutritional strategies may influence biochemical markers—particularly through modest and transient increases in serum creatinine—measured glomerular filtration rate (GFR) generally remains stable, supporting preserved renal function in healthy physically active individuals (Naeini i in., 2025).

It is important to differentiate between physiological renal adaptation, such as the benign hyperfiltration used to clear an increased nitrogenous solute load, and pathological kidney injury, which is primarily characterized by structural damage and progressive functional loss in at-risk clinical populations (Esmeijer i in., 2020).

Furthermore, this review highlights that traditional renal biomarkers, such as serum creatinine and creatinine-based eGFR, are limited in their diagnostic accuracy for athletes due to the substantial influences of high muscle mass, intense exercise, and supplemental creatine turnover (De Oliveira Vilar Neto i in., 2020).

Future Research Directions

Despite the current consensus on short-to-medium-term safety, significant gaps remain in the longitudinal literature, particularly regarding the cumulative effects of these dietary strategies co-administered over decades of an athletic career (Van Elswyk i in., 2018a).

There is an urgent need for large-scale, long-term randomized controlled trials (exceeding two years) that evaluate the safety of chronic high-solute loads and investigate protein intakes exceeding 2.0 g/kg/day in combined-intervention designs (De Lorenzo i in., 2024; Kreider, Jagim, i in., 2025). Future research must also address the underrepresentation of female and elite athletic populations to establish evidence-based safety guidelines for these specific demographics (Kreider, Gonzalez, i in., 2025).

To enhance diagnostic precision, upcoming trials should prioritize the use of direct GFR measurements alongside emerging, muscle-independent biomarkers such as Cystatin C, and sensitive injury markers like KIM-1, NGAL, and MCP-1(De Oliveira Vilar Neto i in., 2020). Ultimately, the contextual interpretation of renal biomarkers remains vital for clinical practice, ensuring that benign physiological adaptations in athletes are not misidentified as pathological renal impairment (De Lorenzo i in., 2024).

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