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CREATINE SUPPLEMENTATION AND RENAL SAFETY: THE NEPHRON RESERVE HYPOTHESIS

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Abstract

Purpose: This narrative review proposes the nephron reserve hypothesis as a framework for reconciling conflicting evidence on creatine supplementation and kidney health.

Materials and methods: Evidence was synthesized from meta-analyses, randomized controlled trials, animal models, and case reports identified through PubMed, Scopus, Web of Science, and Google Scholar through March 2025, with priority given to studies using creatinine-independent renal endpoints.

Results: In individuals with preserved renal functional reserve, creatine at standard doses (3–5 g/day) does not impair glomerular filtration rate. Meta-analyses confirm that observed creatinine elevations reflect altered metabolic turnover rather than nephron injury. Evidence in chronic kidney disease remains sparse. Case reports of interstitial nephritis, tubular necrosis, and cast nephropathy, together with animal data from reduced-nephron-mass models, suggest creatine may unmask renal vulnerability in high-risk settings.

Conclusions: Creatine safety should be assessed according to baseline renal reserve and clinical phenotype. Recommendations for compromised kidneys remain precautionary and are intended to guide risk assessment and future research.

Keywords: creatine supplementation, nephron reserve, renal functional reserve, glomerular filtration rate, chronic kidney disease, hyperfiltration, creatinine, kidney safety, sport supplementation

1. Introduction

Creatine monohydrate (α-methyl-guanidine-acetic acid; $C_4H_9N_3O_2$) has been used as an ergogenic dietary supplement for over three decades and is among the most studied performance-enhancing compounds in sports nutrition (Kreider et al. 2017). Beyond its role in replenishing intramuscular phosphocreatine stores and accelerating adenosine triphosphate (ATP) resynthesis during high-intensity exercise, growing evidence points to therapeutic applications in neurodegenerative disease, sarcopenia, traumatic brain injury, and metabolic disorders (Gualano et al. 2012; Roschel et al. 2021). Given how widely competitive and recreational athletes use it, a clear understanding of creatine's renal safety profile matters for sports medicine practitioners, coaches, and athletes alike.

Despite this, concerns about creatine's effects on renal function have persisted since the original case report by Pritchard and Kalra (1998), who described deterioration in glomerular filtration rate (GFR) in a young athlete supplementing with creatine. Subsequent case reports of acute interstitial nephritis (Koshy et al. 1999; Ardalan et al. 2012), acute kidney injury (Thorsteinsdottir et al. 2006), and cast nephropathy (Filler et al. 2025) have kept these concerns alive, even as controlled trial evidence has consistently shown no adverse renal effects in healthy populations.

The literature presents a paradox. Two independent systematic reviews with meta-analyses -- de Souza e Silva et al. (2019) analyzing 15 studies and Kabiri Naeini et al. (2025) analyzing 21 studies -- concluded that creatine supplementation does not adversely affect GFR, and that observed elevations in serum creatinine represent a predictable pharmacokinetic consequence of expanded creatine pools rather than nephrotoxicity. At the same time, position statements from the International Society of Sports Nutrition and narrative reviews consistently acknowledge that evidence for safety in populations with pre-existing kidney disease remains "very limited" and represents "a very important limitation in the literature" (Longobardi et al. 2023).

This review proposes the nephron reserve hypothesis as a provisional framework that may explain these seemingly contradictory findings. Drawing on the renal physiology of functional reserve first described by Bosch et al. (1983) and on the broader nephrology literature on hyperfiltration (Brenner et al. 1982; Brenner et al. 1996), we argue that creatine's renal safety depends not on the supplement itself but on the remaining compensatory capacity of the kidneys

receiving it. In organs with full nephron endowment, the additional creatinine load from creatine metabolism appears to be handled within physiological margins. In organs with diminished nephron mass or pre-existing compromise, the same load may narrow the available compensatory margin and increase susceptibility to injury. This causal pathway remains inferential rather than proven in humans and should be interpreted as a hypothesis to be tested rather than an established mechanism.

1.1. Search strategy

This narrative review was designed as a hypothesis-generating synthesis rather than a formal systematic review. To improve transparency, the literature base was assembled from PubMed, Scopus, Web of Science, Google Scholar, and reference lists of key reviews and primary studies published through March 2025. Search terms combined creatine-related concepts ("creatine supplementation," "creatine monohydrate," "serum creatinine") with renal outcomes and physiology terms ("kidney function," "renal function," "glomerular filtration rate," "cystatin C," "albuminuria," "renal functional reserve," "hyperfiltration," and "chronic kidney disease"). Priority was given to meta-analyses, randomized controlled trials, studies using creatinine-independent renal endpoints, mechanistic nephrology literature on hyperfiltration and renal functional reserve, and case reports or animal studies relevant to pre-existing renal compromise. Because the objective was interpretive rather than exhaustive, this review does not claim the comprehensiveness of a PRISMA-conducted systematic review; it instead aims to bring together the literature most relevant to the proposed nephron reserve framework while distinguishing direct evidence from mechanistic inference.

2. Creatine metabolism and renal handling: the creatinine confound

2.1. Endogenous creatine synthesis and supplementation pharmacokinetics

Creatine is synthesized endogenously at a rate of approximately 1–2 g/day through a two-step process involving the kidneys (arginine-glycine amidinotransferase, AGAT) and the liver (guanidinoacetate N-methyltransferase, GAMT), with S- adenosylmethionine as the methyl donor (Wyss and Kaddurah-Daouk 2000). Approximately 95% of the total body creatine pool (120–140 g in a 70-kg adult) resides in skeletal muscle, of which roughly two-thirds is stored as phosphocreatine (Balsom et al. 1994).

Oral creatine monohydrate supplementation has predictable pharmacokinetics. During a loading phase (typically 20 g/day for 5–7 days), intramuscular creatine stores increase by 20–

40%, approaching saturation. Maintenance dosing (3–5 g/day) sustains these elevated stores (Hultman et al. 1996). Creatine not taken up by tissues degrades non-enzymatically to creatinine at a relatively constant rate of approximately 1.7% of the total creatine pool per day (Persky and Brazeau 2001). This degradation is irreversible and proceeds spontaneously through cyclization and dehydration.

2.2. The creatinine measurement artifact

Creatinine is freely filtered at the glomerulus and undergoes substantial tubular secretion via organic cation transporters (OCT2 at the basolateral membrane, MATE1/MATE2K at the apical membrane of proximal tubular cells). Recent pharmacometric quantification by Chen and Taubert (2025) showed that net creatinine tubular secretion accounts for approximately 31% of total creatinine clearance, higher than earlier estimates suggested. This means creatinine clearance systematically overestimates true GFR by approximately 45%, and all standard eGFR equations (MDRD, CKD-EPI) are calibrated to account for this overshoot under steady-state conditions (Levey et al. 2009). The clinical utility of creatinine rests on the assumption that creatinine production is relatively stable and proportional to muscle mass, an assumption that creatine supplementation violates.

The fundamental confound is straightforward: increasing the total body creatine pool through supplementation predictably increases creatinine production, elevating serum creatinine independently of any change in GFR. The 2025 meta-analysis by Kabiri Naeini et al. reported a statistically significant but clinically modest increase in serum creatinine (reported mean difference: 0.07; 95% CI: 0.01–0.12; $p = 0.03$) with no parallel change in GFR. Subgroup analysis by duration suggested that this elevation was most pronounced during the first week (reported MD = 0.12; 95% CI: 0.03–0.21), was not significant during weeks 1–12, and became significant again beyond 12 weeks as the expanded creatine pool reached a new metabolic steady state. Because the published report presents these mean differences in a way that can be misread clinically, the key message for clinicians and sport medicine practitioners is the direction and modest size of the creatinine change rather than the exact absolute unit.

This dissociation between serum creatinine and GFR has direct clinical consequences. Creatinine-based estimated GFR (eGFR) equations, including the CKD-EPI 2021 equation (Inker et al. 2021), will systematically underestimate true GFR in creatine-supplemented individuals, potentially triggering false-positive diagnoses of kidney disease. The case reported by Williamson and New (2014) illustrates this: a middle-aged man taking creatine ethyl ester

was referred for suspected renal failure based on elevated creatinine and reduced eGFR, which normalized completely after supplement cessation. This matters most for athletes in routine screening, where creatine-driven creatinine elevation can prompt unnecessary concern or needless withdrawal from training.

2.3. Creatinine-independent markers of renal function

The recognition that creatinine is unreliable as a renal biomarker during creatine supplementation has driven interest in creatinine-independent assessments. Cystatin C, a low-molecular-weight protein freely filtered and completely catabolized by the proximal tubule, is not influenced by creatine intake or muscle mass and gives a more accurate picture of GFR in this context (Inker et al. 2012). Measured GFR (mGFR) using exogenous markers -- ^{5} ^{1}Cr-EDTA, iohexol, or inulin clearance -- is the reference standard.

Longobardi et al. (2023) noted that studies assessing creatine safety using these more reliable methods have consistently found no evidence of kidney impairment. Among the controlled trials employing mGFR, cystatin C, proteinuria, or albuminuria as endpoints, none showed renal injury attributable to creatine supplementation in healthy participants.

3. Evidence for safety in kidneys with intact nephron reserve

3.1. Meta-analytic evidence

Two systematic reviews with meta-analyses have directly addressed the question of creatine supplementation and renal function.

De Souza e Silva et al. (2019) conducted the first systematic review and meta-analysis, published in the *Journal of Renal Nutrition* . After screening 290 records, 15 studies were included in qualitative analysis and 6 in quantitative synthesis. The paper reported a standardized mean difference for serum creatinine of 0.48 (95% CI: 0.24–0.73; I^2 = 22%) and for plasma urea of 1.10 (95% CI: 0.34–1.85; I^2 = 28%), while concluding overall that creatine supplementation did not induce renal damage in the studied amounts and durations. The key point for this review is not that creatinine remains unchanged but that modest creatinine elevations can coexist with preserved global renal function and should not automatically be equated with nephrotoxicity.

Kabiri Naeini et al. (2025) published a substantially larger meta-analysis in *BMC Nephrology*, incorporating 21 studies in the systematic review (12 eligible for quantitative synthesis of

creatinine outcomes, 5 for GFR). With 177 participants in the creatine group and 263 controls, the pooled analysis showed a small, statistically significant increase in serum creatinine (reported MD = 0.07; 95% CI: 0.01–0.12; p = 0.03) but no statistically significant change in GFR. The authors' conclusion was unambiguous: "creatine supplementation is associated with a modest, transient increase in serum creatinine levels, likely due to metabolic turnover rather than renal impairment." Across pooled studies, creatinine moved slightly while GFR did not.

3.2. Randomized controlled trials with creatinine-independent endpoints

The strongest methodological evidence for renal safety comes from trials using creatinine-independent markers, either cystatin C or directly measured GFR with exogenous tracers, which bypass the creatinine artifact entirely.

Gualano et al. (2008) ran the first RCT to use cystatin C as the primary renal endpoint during creatine supplementation. In this double-blind, placebo-controlled trial of 18 healthy sedentary males receiving approximately 10 g/day creatine for 12 weeks alongside moderate aerobic training, cystatin C concentrations fell over time in both groups (creatine: 0.82 ± 0.09 to 0.71 ± 0.06 mg/L; placebo: 0.88 ± 0.07 to 0.75 ± 0.09 mg/L; p = 0.0001), indicating improved rather than impaired GFR with training. No between-group difference was observed, confirming that creatine supplementation did not compromise filtration capacity when assessed by a biomarker independent of creatine metabolism.

Bonfá et al. (2011) extended this evidence using the reference-standard method: ^{5} ^{1}Cr-EDTA clearance to directly measure GFR in postmenopausal women (mean age 58 ± 3 years) receiving 20 g/day loading for one week followed by 5 g/day maintenance for 11 weeks. Measured GFR was unchanged in both groups (creatine: 86.16 ± 14.36 to 87.25 ± 17.60 mL/min/1.73 m²; placebo: 85.15 ± 8.54 to 87.18 ± 9.64 mL/min/1.73 m²; p = 0.81). This is one of the clearest demonstrations that creatine does not alter true glomerular filtration.

3.3. Long-term supplementation studies

Several studies have examined creatine use over extended durations, addressing the concern that short-term trials may miss delayed nephrotoxicity.

Kreider et al. (2003) followed 98 Division IA college football players supplementing with creatine for up to 21 months (mean 9.3 ± 2.0 months in the intermediate group; 19.3 ± 2.4 months in the long-term group) and found no significant changes across a 69-item panel of serum, whole blood, and urinary markers, including renal function parameters. Poortmans and

Francaux (1999) reported that long-term oral creatine supplementation (10 months to 5 years) did not impair creatinine clearance, urea clearance, or albumin excretion in healthy athletes, establishing the foundational long-term safety dataset.

Garcia, Longobardi, Gualano et al. (2025) ran a 32-week real-world cohort study in 71 female football players receiving standard loading (20 g/day for 7 days) followed by maintenance (5 g/day for 31 weeks) across a full competitive season. While eGFR dipped transiently at mid-season (90.34 to 83.57 mL/min/1.73 m^2; $p < 0.0001$ vs. baseline), it returned fully to baseline by week 32 (91.58 mL/min/1.73 m^2; $p = 1.000$ vs. baseline). Albuminuria actually decreased over the supplementation period ($p < 0.001$), a finding inconsistent with kidney injury and suggestive that the eGFR dip reflected the creatinine measurement artifact during the loading and early maintenance phases.

Gualano et al. (2011) conducted a randomized, double-blind, placebo-controlled trial specifically in type 2 diabetic patients, a population with heightened renal vulnerability, and found that 12 weeks of creatine supplementation (5 g/day) did not impair kidney function, as assessed by ^{5} ^{1}Cr-EDTA GFR, proteinuria, and albuminuria. Measured GFR was virtually identical between groups post-intervention (creatine: 96.1 ± 15.0; placebo: 96.4 ± 26.8 mL/min/1.73 m^2; $p = 0.58$). This study is worth singling out because it extended the safety evidence beyond healthy athletes to a metabolically compromised but renally intact population.

3.4. Large-scale surveillance evidence

Kreider and Bonilla (2025) assembled the largest safety analysis to date, covering 685 human clinical trials involving approximately 13,452 placebo participants and 12,839 creatine participants, with an average dose of approximately 12.5 g/day over approximately 65 days and study durations extending up to 14 years. Side effects were reported in 13.2% of placebo studies versus 13.7% of creatine studies ($p = 0.776$), with no significant difference. No renal adverse events emerged as a significant signal across this sample. This dataset has the statistical power no individual trial can match for detecting rare nephrotoxic events.

3.5. Special populations with preserved renal function

Gualano et al. (2010) reported a relevant case study: a young man with a single kidney (congenital solitary kidney) who underwent short-term high-dose creatine supplementation (20 g/day for 5 days followed by 5 g/day for 30 days). Measured GFR by ^{5} ^{1}Cr-EDTA remained stable throughout supplementation, and no proteinuria or albuminuria developed. A single case

cannot establish safety, but it does show that even with reduced nephron mass, creatine did not cause detectable injury over a short supplementation period in the absence of other renal pathology.

3.6. Mendelian randomization evidence

Zhou et al. (2024) provided epidemiological evidence using Mendelian randomization (MR) analysis to assess the causal relationship between creatine levels and renal function. The MR analysis found no significant causal association between genetically predicted creatine levels and renal dysfunction, which supports the view that the observational association between creatine use and elevated creatinine does not reflect a causal pathway to kidney injury.

3.7. Position statements and expert consensus

The International Society of Sports Nutrition (ISSN) position stand on creatine supplementation (Kreider et al. 2017) concluded that creatine monohydrate is "the most effective ergogenic nutritional supplement currently available to athletes" and that "there is no scientific evidence that short- or long-term use of creatine monohydrate has any detrimental effects on otherwise healthy individuals." The ISSN specifically addressed kidney safety, stating that creatine does not adversely affect renal function in healthy persons using recommended dosages. Antonio et al. (2021) addressed the creatinine artifact directly in a dedicated misconceptions paper, stating that "transient increases in blood or urinary creatine or creatinine due to creatine supplementation are unlikely to reflect a decrease in kidney function" and identifying the 1998 Pritchard and Kalra case, confounded by pre-existing glomerulosclerosis and concurrent cyclosporine therapy, as the origin of the persistent safety myth.

Longobardi et al. (2025), in a safety review in *Frontiers in Nutrition*, reiterated that creatine is "safe for healthy individuals" and that kidney function assessment should use biomarkers independent of creatinine (e.g., direct GFR measurements, cystatin C, proteinuria, albuminuria, and urinary albumin-tocreatinine ratio) to avoid the creatinine confound.

4. Evidence for risk in kidneys with pre-existing compromise

4.1. Case reports of renal injury

While controlled trials have consistently shown safety in healthy populations, a series of case reports has documented renal complications temporally associated with creatine supplementation, mostly in individuals with identifiable risk factors.

Pritchard and Kalra (1998) published the seminal case in *The Lancet*, describing a 25-year-old man who developed reduced GFR and elevated creatinine after 8 weeks of creatine supplementation at recommended doses. As Poortmans and Francaux (1998) pointed out in their response, the patient had pre-existing glomerulosclerosis for several years, "which may explain the further impairment in renal function in this specific case." This original report thus supports, rather than contradicts, the nephron reserve hypothesis: the adverse outcome occurred in a kidney with pre-existing structural disease, not in a healthy organ.

Koshy et al. (1999) reported interstitial nephritis in a patient taking creatine supplements. The histopathological finding of interstitial inflammation raised the possibility of a direct immunologic or toxic reaction, though the mechanism was not established and confounders were present.

Ardalan et al. (2012) described a 32-year-old man who developed interstitial nephritis and renal failure after creatine monohydrate supplementation (loading dose followed by 1 g/day maintenance for three weeks). The patient had no prior history of renal disease. Serum creatinine rose to 4.3 mg/dL, and renal biopsy confirmed interstitial nephritis. Renal function improved after corticosteroid therapy and supplement cessation. While this case is often cited as evidence of direct nephrotoxicity, the immunologic pattern (interstitial nephritis responsive to steroids) suggests an idiosyncratic hypersensitivity reaction rather than a dose-dependent toxic mechanism.

Thorsteinsdottir et al. (2006) reported a 24-year-old weight lifter who developed acute renal failure (creatinine 3.8 mg/dL) and proteinuria while taking creatine and multiple other supplements. Renal biopsy showed acute interstitial nephritis. The concurrent use of multiple supplements complicates attribution, but the case illustrates the cumulative burden on kidneys exposed to multiple bioactive compounds.

Taner, Aysim, and Abdulkadir (2011) reported an 18-year-old male bodybuilder who developed acute renal failure after creatine monohydrate supplementation at recommended doses, with no prior history of kidney disease. Renal biopsy revealed acute tubular necrosis (ATN), the first reported case of creatineassociated ATN, distinct from the interstitial nephritis pattern described in earlier reports. Serum creatinine normalized (88.4 μmol/L) and proteinuria resolved (82 mg/day) within 25 days of supplement cessation. The finding of focal tubular injury with dilatation of tubular lumina and epithelial cell flattening suggests a direct tubular

toxic mechanism, potentially mediated by creatinine metabolite accumulation or osmotic stress at the tubular level.

Filler et al. (2025) described a 17-year-old male who developed acute kidney injury with cast nephropathy following a six-day high-dose creatine loading regimen. Cystatin C and creatinine rose in parallel, indicating true renal injury rather than a measurement artifact. Kidney biopsy confirmed cast nephropathy without light chain disease. This case matters because it showed genuine renal injury verified by a creatinine-independent marker and histopathology, occurring during a supraphysiological loading protocol in an adolescent, a population in whom nephron reserve has not been characterized.

4.2. Animal models of reduced nephron mass

Animal studies using subtotal nephrectomy models provide controlled evidence for differential renal responses to creatine based on nephron status.

Taes et al. (2003) investigated chronic creatine supplementation in two-thirds nephrectomized male Wistar rats and sham-operated controls. In both sham-operated animals and animals with moderate preexisting renal failure, creatine supplementation did not worsen inulin clearance, creatinine clearance, albumin excretion, or other renal injury indices over four weeks. This tempers any overly simple claim that reduced nephron mass alone is enough to make creatine harmful; susceptibility likely depends on the specific disease context, degree of reserve loss, dose, and concomitant stressors.

Edmunds et al. (2001) studied creatine supplementation in the Han:SPRD rat model of polycystic kidney disease and reported that creatine exacerbated cyst growth and accelerated renal functional decline compared with unsupplemented controls, consistent with creatine posing a specific risk to structurally compromised kidneys.

4.3. Populations at theoretical risk

Several populations have reduced nephron reserve and may therefore be more vulnerable to creatinine-related renal stress:

- **Chronic kidney disease (CKD) stages 3–5:** Progressive nephron loss is the defining feature of CKD. No randomized controlled trial has evaluated creatine supplementation in patients with eGFR < 60 mL/min/1.73 m², making this the most pressing evidence gap.

- **Solitary kidney (congenital or post-nephrectomy):** Kidney donors lose approximately 50% of nephron mass. Post-donation kidneys undergo compensatory hyperfiltration, increasing single nephron GFR (SNGFR) by approximately 35% (ter Wee et al. 1994). The remaining renal functional reserve is consequently diminished.
- **Diabetic nephropathy:** Glomerular hyperfiltration is an early hemodynamic hallmark of diabetic kidney disease, driven by tubuloglomerular feedback disruption via enhanced SGLT2 activity and sodium reabsorption (Cortinovis et al. 2022). Diabetic kidneys already operating in a hyperfiltration state have limited residual capacity to accommodate additional solute loads.
- **Low nephron endowment:** Low birth weight, prematurity, and intrauterine growth restriction are associated with reduced nephron number (Brenner and Mackenzie 1997; Luyckx and Brenner 2005). Individuals born with fewer nephrons may reach the threshold of adaptive hyperfiltration at lower provocation levels.
- **Autosomal dominant polycystic kidney disease (ADPKD):** The animal evidence from Edmunds et al. (2001) raises concern about creatine in ADPKD patients, whose progressive cyst expansion reduces functional parenchyma over time.

5. The nephron reserve hypothesis: a mechanistic framework

5.1. Renal functional reserve

The concept of renal functional reserve (RFR) was first described by Bosch et al. (1983), who showed that healthy kidneys increase their GFR by 10–40% (mean 26%) in response to a protein load. This increment reflects the recruitment of previously quiescent filtration capacity. Armenta, Madero, and Rodriguez-Iturbe (2022), in a review published in the Clinical Journal of the American Society of Nephrology, defined RFR as the difference between resting GFR and the maximal GFR achievable under physiological stimulation.

The kidney does not normally operate at maximal filtration capacity. Estimates suggest that baseline GFR represents approximately 75% of the kidney's total filtration potential (Ronco et al. 2017). This reserve is a physiological buffer, enabling the kidney to accommodate transient increases in solute load, whether from dietary protein, pregnancy, or creatine supplementation, without hemodynamic strain on individual nephrons. Martin, Armstrong, and Rodriguez (2005) characterized hyperfiltration as "a normal adaptive mechanism that occurs in response to several physiological conditions," and found no significant evidence for a detrimental effect of high solute loads on renal function in healthy individuals.

Nephron endowment varies widely across individuals. Human nephron number ranges from approximately 200,000 to over 2,500,000 per kidney, with a mean of approximately 900,000 (Luyckx, Shukha, and Brenner 2011). This means that individuals near the lower bound of normal endowment have inherently less functional reserve, even when baseline GFR is clinically normal. Low birth weight, prematurity, and intrauterine growth restriction are associated with 30–50% fewer nephrons and compensatory glomerular hypertrophy in remaining units (Zandi-Nejad, Luyckx, and Brenner 2006).

When nephron mass is reduced, whether congenitally or through acquired disease, remaining nephrons undergo compensatory hyperfiltration to maintain total GFR. This adaptive response preserves overall filtration at the cost of consuming the functional reserve. Glomerular volume varies inversely with nephron number, reflecting structural hypertrophy in the remaining units (Luyckx et al. 2011). As RFR declines, the kidney's capacity to tolerate additional hemodynamic demands diminishes. When remaining nephrons are operating near their maximum SNGFR, any additional stimulus, including the increased creatinine production from creatine supplementation, may push individual nephrons into a maladaptive range.

5.2. Disrupted creatine homeostasis in reduced GFR

Post et al. (2024) provided direct evidence linking nephron reserve to creatine metabolism. In a comparative study of 553 kidney transplant recipients (KTR) versus 168 healthy controls, KTR had significantly lower plasma creatine and 66% lower urinary guanidinoacetate excretion (both $p < 0.001$).

Since the kidney is the primary site of guanidinoacetate synthesis via AGAT, this finding shows that creatine homeostasis is disturbed in proportion to renal functional loss. Measured GFR correlated positively with endogenous creatine synthesis rate, with guanidinoacetate excretion mediating 93–95% of this association.

This observation supports the idea that declining renal reserve may alter creatine handling, but it does not by itself prove a specific injury pathway from supplementation to glomerulosclerosis. A more cautious reading is that exogenous creatine may interact differently with kidneys that have limited excretory reserve, thereby narrowing the physiologic margin available to buffer increases in creatinine generation.

A related finding comes from Bernales-Delmon and Basualto-Alarcon (2025), who ran an open-label pilot trial of creatine supplementation (5 g/day for 8 weeks) in chronic hemodialysis

patients with end-stage renal disease. In this population, where creatinine is cleared by dialysis rather than residual glomerular filtration, creatine supplementation improved skeletal muscle mass, physical performance, and body composition without reported renal adverse effects. This observation fits the nephron reserve hypothesis, but should be read as supportive context rather than definitive mechanistic proof.

5.3. Mechanistic interpretation: what is established and what remains inferential

Brenner, Meyer, and Hostetter (1982) proposed that high dietary protein intake can promote progressive glomerular sclerosis through hemodynamically mediated glomerular injury. The Brenner paradigm involves amino acid-driven changes in renal plasma flow, glomerular capillary pressure, and singlenephron filtration dynamics. That literature remains relevant to the concept of renal reserve, but it should not be transferred wholesale to creatine supplementation. Creatinine is a filtered waste solute rather than an amino acid stimulus, and current human evidence does not show directly that creatine-derived creatinine load reproduces the same afferent vasodilatory and capillary-pressure effects described in protein-loading models.

The nephron reserve hypothesis should therefore be framed as a synthesis of several partially overlapping mechanisms rather than as proof of a single Brenner-type pathway. First, creatine supplementation reliably raises serum creatinine through increased metabolic turnover, creating a measurement artifact in healthy kidneys. Second, in kidneys with reduced nephron mass or pre-existing disease, that same increase may narrow the available physiologic reserve and expose individuals to a smaller margin for handling additional metabolic or hemodynamic stress. Third, the injury patterns described in the literature are heterogeneous. Interstitial nephritis, acute tubular necrosis, and cast nephropathy are not interchangeable and do not all imply the same mechanism. The cast nephropathy case described by Filler et al. (2025) is most consistent with tubular precipitation during aggressive loading, whereas Ardalan et al. (2012) and Thorsteinsdottir et al. (2006) are more compatible with idiosyncratic or multifactorial tubulointerstitial injury.

The most defensible mechanistic conclusion at present is modest: in compromised kidneys, creatine supplementation may add stress to an already reduced reserve state, and aggressive loading may be less forgiving than maintenance dosing. Whether this occurs predominantly through altered tubular handling, cast formation, additive osmotic burden, or hyperfiltration-mediated injury remains uncertain and requires direct study.

5.4. The two-threshold model

We propose a two-threshold model to conceptualize creatine's renal effects (Figure 1), though we emphasize that this model is conceptual rather than quantitatively validated:

Threshold 1: The creatinine artifact threshold. In all individuals, creatine supplementation can increase serum creatinine through non-renal metabolic mechanisms. This elevation may cross laboratory reference ranges and trigger clinical concern, but by itself does not establish nephron injury. It is detectable by creatinine-based assays and eGFR equations but may be absent from cystatin C or measured GFR assessments.

Threshold 2: The renal vulnerability threshold. This threshold is hypothesized to exist only in kidneys with reduced nephron reserve. Here, the same supplementation-related increase in creatinine generation may coexist with limited adaptive capacity, pre-existing structural disease, or high-risk clinical states such that a previously compensated kidney becomes more vulnerable to true injury. The exact level at which this threshold is crossed is unknown; it should be understood as a biologically plausible but unvalidated construct rather than a measured clinical cutoff.

In kidneys with intact nephron reserve, current evidence suggests that only Threshold 1 is usually crossed: creatinine rises modestly, GFR remains stable, and no convincing evidence of injury is seen. In kidneys with compromised reserve, both thresholds may be crossed in selected circumstances, but available evidence comes mainly from case reports, animal models, and indirect clinical reasoning rather than direct human proof.

Figure 1. Conceptual schematic of the two-threshold model. The figure should depict renal reserve on one axis and supplementation-related creatinine generation or clinical stress on the other. Threshold 1 marks the point at which serum creatinine rises enough to affect creatinine-based eGFR without evidence of kidney injury. Threshold 2 marks the hypothesized transition from compensated vulnerability to true renal injury in susceptible kidneys. Because quantitative thresholds remain unknown, the schematic should label these transitions as conceptual and map them to the supporting evidence base: creatinine artifact data from meta-analyses and trials, and vulnerability data from case reports, reduced-nephronmass animal models, and indirect mechanistic nephrology literature.

6. Clinical implications and risk stratification

6.1. Assessment before supplementation

Given the evidence reviewed, safety assessment before creatine supplementation should be individualized according to readily identifiable clinical risk phenotypes rather than presumed nephron number alone. The recommendations below are precautionary and should be read as low-certainty guidance, because no randomized controlled trial has directly tested creatine supplementation in patients with established CKD or other clearly compromised renal states.

1. **Baseline evaluation:** Obtain serum creatinine, eGFR, blood pressure, and urinalysis or urinary albumin assessment before supplementation. In individuals with unusually high muscle mass, prior abnormal creatinine values, or specific concern about renal reserve, cystatin C-based estimation or direct nephrology evaluation may be more informative than creatinine-based eGFR alone.
2. **High-yield clinical risk factors:** Prioritize phenotypes that are identifiable in routine practice, including known CKD, persistent albuminuria or proteinuria, solitary kidney, kidney transplant status, structural kidney disease (including ADPKD), prior severe acute kidney injury, diabetes with kidney involvement, and concurrent exposure to nephrotoxic medications such as NSAIDs or calcineurin inhibitors. Low birth weight and prematurity remain biologically relevant but are usually supporting context rather than stand-alone screening tools in adult clinical care.
3. **Pragmatic risk framing:**
    - **Lower-risk phenotype:** Normal urinalysis or albuminuria assessment, preserved eGFR, no known kidney disease, and no major renal risk factors. In this group, standard-dose creatine appears unlikely to harm renal function, though a small creatinine rise may still occur.
    - **Intermediate-uncertainty phenotype:** Borderline renal indices, diabetes without documented nephropathy, prior kidney injury, solitary kidney with stable function, or other structural risk factors but no clear active kidney disease. In this group, supplementation should be approached cautiously, with counseling that evidence is indirect and that maintenance-only dosing is preferable to loading.

- **Higher-risk phenotype:** Established CKD, persistent albuminuria/proteinuria, kidney transplant recipients with unstable function, active glomerular disease, or recent clinically significant kidney injury. In this group, creatine use should generally be avoided outside specialist supervision or research settings because current evidence is not sufficient to support safety.

6.2. Monitoring during supplementation

For individuals who proceed with creatine supplementation:

- Reassess kidney-related biomarkers after approximately 4–6 weeks to establish the individual's new post-supplementation baseline.
- Interpret creatinine changes in context. A modest isolated creatinine rise can reflect altered creatine-creatinine turnover, especially when cystatin C, albuminuria, and clinical status remain stable.
- Escalate evaluation if the biomarker pattern suggests more than a simple creatinine artifact, particularly if cystatin C rises, albuminuria or proteinuria develops, blood pressure worsens, symptoms emerge, or kidney function declines persist after temporary discontinuation.
- When concern exists, cystatin C, urinary albumin-to-creatinine ratio, and direct clinical assessment are more informative than serial creatinine measurements alone.

6.3. Dosing considerations

The risk of adverse renal effects remains uncertain but is most plausible in settings of limited reserve and aggressive loading. The case of Filler et al. (2025) underscores that high-dose loading protocols may be less forgiving than standard maintenance dosing. A cautious approach would include:

- Favoring maintenance dosing (3–5 g/day) over loading protocols when any renal risk factor is present
- Avoiding concurrent dehydration, very high protein intake, or potentially nephrotoxic medications when possible
- Stopping supplementation promptly and reassessing if biomarker changes extend beyond an isolated creatinine increase
- Treating these measures as precautionary clinical judgment rather than validated guideline-level recommendations

6.4. Evidence level of clinical recommendations

Taken together, these recommendations are best understood as **conditional, low-certainty guidance** derived from strong safety data in healthy populations, but only indirect evidence in compromised kidneys. They should inform shared decision-making, not substitute for direct evidence in CKD or other high-risk groups.

7. Limitations and future directions

Several limitations should be noted. First, the controlled trial literature is heavily weighted toward healthy, young, male athletes. Generalizing to women, older adults, children, and individuals with comorbidities requires caution. The Kabiri Naeini et al. (2025) meta-analysis noted that risk-of-bias assessments were mostly at the level of some concern," with common methodological gaps including absent allocation concealment, small sample sizes, and limited follow-up duration.

Second, no randomized controlled trial has evaluated creatine supplementation in patients with established CKD (eGFR < 60 mL/min/1.73 m^2). This is the most pressing evidence gap in the field. Until such trials are conducted, with measured GFR and creatinine-independent biomarkers as primary endpoints and adequate follow-up duration, any recommendation to avoid creatine in CKD should be recognized as precautionary rather than directly evidence-based.

Third, variability in creatinine assay methodology across studies introduces measurement bias. Pre- and post-2009 standardization to SRM 967 produced material differences in reported creatinine values, and different assay platforms (compensated Jaffe, enzymatic, sarcosine oxidase) show variable susceptibility to interference from creatine itself (Kabiri Naeini et al. 2025). Standardizing assay reporting in future creatine trials is overdue.

Fourth, the case report literature is inherently limited by confounding (concurrent supplement use, preexisting unrecognized pathology, reporting bias) and cannot establish causation. The case of Ardalan et al. (2012), for example, may represent an idiosyncratic hypersensitivity rather than a generalizable dosedependent mechanism.

Future research priorities include:

1. **Randomized controlled trials of creatine supplementation in CKD stages 2–3,** using measured GFR and cystatin C as co-primary endpoints, with a minimum follow-up of 12 months.
2. **Renal functional reserve testing in creatine users,** comparing protein-stimulated GFR responses in supplemented versus unsupplemented individuals to directly quantify the impact on renal compensatory capacity.
3. **Prospective cohort studies** linking long-term creatine use (>5 years) with kidney outcomes using cystatin C-based GFR to avoid the creatinine artifact.
4. **Pharmacogenomic investigations** into individual susceptibility to creatine-related renal effects, including polymorphisms in creatine transporters (SLC6A8), organic cation transporters (OCT2/MATE), and AGAT.
5. **Standardization of creatinine assay reporting** in all future supplementation trials, including specification of assay platform, calibration standard, and known interferences.

8. Conclusions

The weight of evidence supports the conclusion that creatine monohydrate supplementation, when used at recommended doses in individuals with intact renal reserve, does not appear to impair kidney function. The modest elevation in serum creatinine observed during supplementation is better understood as a metabolic and interpretive confound than as a signal of nephron injury, particularly when cystatin C, measured GFR, albuminuria, and other renal endpoints remain stable.

That said, evidence in patients with pre-existing renal compromise remains limited and mixed. Case reports, reduced-nephron-mass animal models, and mechanistic nephrology literature together justify caution, but they do not prove a single causal pathway or identify a definitive clinical threshold for harm. The nephron reserve hypothesis should be understood as a useful organizing model that points to biologic plausibility and differential susceptibility, not as a settled explanation of creatine-associated renal injury.

In practice, the message for sports medicine practitioners and athletes is that creatine is not inherently nephrotoxic in healthy kidneys, but that things get more complicated in people with reduced renal reserve, structural kidney disease, or other high-risk phenotypes. Prospective studies in those populations are needed before precautionary guidance can be converted into evidence-based clinical recommendations.

Disclosure

Author's contribution

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