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The impact of creatine supplementation on the development of kidney disease – literature review

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Abstract

Introduction: Creatine, a widely studied dietary supplement, is known for enhancing athletic performance and muscle strength. Concerns persist regarding its impact on kidney health, as it raises serum creatinine levels, potentially confounding renal function assessments. This review examines creatine's role in sports and clinical contexts, emphasizing safety and kidney health implications.

Aim of the study: To assess the effects of creatine supplementation on kidney function by summarizing evidence from case studies, clinical trials, and long-term research, addressing safety concerns in healthy and at-risk individuals.

State of knowledge: Research supports creatine's efficacy in improving athletic performance, recovery, and muscle strength, with therapeutic benefits in neurodegenerative diseases, type 2 diabetes, aging, and chronic conditions. Robust trials show no adverse renal effects in healthy individuals, even with long-term or high-dose use. However, case reports highlight potential risks for individuals with pre-existing kidney conditions, especially without monitoring. Elevated serum creatinine levels caused by creatine can mislead eGFR-based renal function tests, warranting cautious interpretation.

Conclusions: When used as recommended, creatine is safe and effective for improving athletic and clinical outcomes in healthy individuals. While no direct renal impairment has been observed, caution is essential for those with kidney conditions. Pre-supplementation renal assessments, individualized dosing, and regular monitoring are advised to minimize risks. Creatine remains a valuable supplement, and further research is needed to confirm its long-term safety across various populations.

Key words: creatine; supplementation; kidney; kidney disease; sport

Abbreviation:

ISSN - International Society of Sports Nutrition

GFR - Glomerular Filtration Rate

eGFR - Estimated Glomerular Filtration Rate

MDRD - Modification of Diet in Renal Disease

CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration

MELAS - Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes

AQCS - Acute Quadriceps Compartment Syndrome

1. Introduction

Creatine (alpha-methyl-guanidine-acetic acid) supplementation is common among both professional and amateur athletes [1]. In the realm of sports and athletic performance, the pursuit of excellence often drives individuals to explore various methods to enhance their physical capabilities. Among the myriad of supplements available, creatine stands out as one of the most extensively studied and widely utilized. While creatine supplementation has garnered attention for its potential to improve muscle strength and power, concerns about its impact on kidney health have also emerged [1]. Some studies suggest that creatine may increase serum creatinine levels, potentially indicating kidney dysfunction, although this does not necessarily translate to actual kidney damage [1]. As athletes strive to gain a competitive edge, understanding the science, benefits, and potential risks of creatine supplementation, including its potential implications for kidney health, becomes paramount [1]. This review delves into the role of creatine in athletic performance, examining its biochemical impact, effectiveness, with a particular focus on its potential effects on kidney function. Due to the widespread use of creatine supplements, the International Society of Sports Nutrition (ISSN) released an updated position statement in 2017, addressing the safety and effectiveness of creatine supplementation in the contexts of exercise, sports, and medicine [2]. Studies indicate that creatine supplementation may improve post-exercise recovery, aid in injury prevention, assist in thermoregulation, support rehabilitation, and provide neuroprotection for concussions and spinal cord injuries. Moreover, research has explored various clinical applications of creatine

supplementation, including its potential benefits for neurodegenerative diseases like muscular dystrophy, Parkinson's, and Huntington's disease, as well as for conditions such as diabetes, osteoarthritis, fibromyalgia, aging, brain and heart ischemia, adolescent depression, and during pregnancy [2].

Nonetheless, it is still considered if the creatine supplementation has no negative effect on kidney function. Series of case reports show that there could be a link between kidney failure and oral creatine uptake [3-9]. On the other hand, there are overwhelming number of randomized control trials have not found any negative adverse effect [20, 24-50]. It should be mentioned that most of the studies involve healthy individuals.

2. Kidney physiology and creatine metabolism

The kidneys are essential organs responsible for maintaining homeostasis within the body. Each kidney contains approximately one million nephrons, which are the functional units that filter blood and produce urine. Filtration begins in the glomerulus, where blood plasma is filtered, and essential substances such as water, electrolytes (e.g., Na+, Ca2+, Cl-) and nutrients are reabsorbed in the tubules, while waste products and excess fluids are excreted. The kidneys also regulate blood pressure, red blood cell production, and electrolyte balance through hormone secretion and other mechanisms. Additionally, they maintain the body's acid-base balance by selectively excreting hydrogen ions and reabsorbing bicarbonate [10-13]. It is estimated that a loss of at least 75% of the kidneys' functional capacity is required before homeostasis is significantly impaired [14].

The glomerular filtration rate (GFR), which refers to the volume of fluid filtering into Bowman's capsule per unit time, is a key indicator in assessing kidney function [11]. Although it cannot be measured directly, GFR can be estimated from the clearance rates of certain filtered solutes. The estimated Glomerular Filtration Rate (eGFR) is a critical measure of kidney function, reflecting the rate at which the kidneys filter blood. In a normally functioning kidney, eGFR values typically range from 90 to 120 mL/min/1.73 m^2, indicating healthy kidney performance [10]. This measure is essential for assessing renal health, as it helps detect early signs of kidney dysfunction and monitor disease progression [15]. Maintaining a normal eGFR is crucial for overall health, as it ensures the efficient removal of toxins and maintenance of fluid and electrolyte balance [10].

eGFR is derived from mathematical formulas that incorporate most often serum creatinine levels, along with variables such as age, sex, and race [16,17]. Prominent equations used for

this purpose include the Modification of Diet in Renal Disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Serum creatinine, a metabolic byproduct of muscle activity, is excreted by the kidneys, and its concentration in the bloodstream offers an indirect assessment of kidney filtration efficacy [16,17]. Regular eGFR monitoring is vital for the early detection of kidney dysfunction, supporting clinical decision-making, and managing patients with chronic kidney disease or other conditions that impact renal function [16-18]. Although, the estimated glomerular filtration rate (eGFR) is influenced by the rate at which biochemical markers are generated through metabolic processes, as well as their tubular secretion, reabsorption, and excretion [16-18]. As a creatine's end metabolic product is creatinine, creatinine clearance may be elevated among those intaking creatine supplementation [19]. Since the most common equations use serum level of creatinine to calculate eGFR, thus eGFR can be inadequate due to creatine supplementation [20]. Some physicians ignore this bias, which can result in the misinterpretation of test results and lead to incorrect diagnosis of kidney failure. The key takeaway is that any serum biomarker affected by creatine metabolism might not provide an accurate assessment of kidney function in individuals using creatine supplements [16-20].

3. Creatine supplementation and kidney function – literature review

There are numerous case studies and controlled studies that are associated to oral creatine supplementation and its effect on kidney function.

Pritchard et al. were the first who described cases of renal dysfunction linked to oral creatine supplementation [3]. This work highlights that creatine may contribute to compromised kidney function, especially in individuals with pre-existing risk factors, such as focal segmental glomerulosclerosis with frequently relapsing nephrotic syndrome, as the 25-year-old patient in this case. The case underscore the need for:

- pre-supplementation assessment: evaluation of baseline renal function is recommended, particularly in populations with risk factors such as hypertension, diabetes, or a history of kidney disease;
- monitoring during use: regular monitoring of serum creatinine and renal function parameters is essential, especially during prolonged or high-dose supplementation;
- individualized dosage: adhering to recommended dosages is critical to minimizing potential renal strain [3].

The authors acknowledge the limitations of their report, including the lack of long-term follow-up.

Barisic et al. explored the effects of oral creatine supplementation in an 18-year-old patient with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes phenotype (MELAS) and associated nephropathy [4]. Creatine supplementation showed potential therapeutic benefits in terms of symptom management including neurological improvements (reduction in stroke-like episodes and an improvement in muscle strength and fatigue, which are hallmark symptoms of MELAS), metabolic effects (stabilization of lactate levels, indicating improved mitochondrial efficiency and reduced metabolic stress) [4]. There were no significant increases in serum creatinine or other markers of renal dysfunction, suggesting that creatine did not acutely worsen kidney function [4].

The case report described by Koshy et al. investigates a potential link between oral creatine supplementation and the development of interstitial nephritis, an inflammatory condition of the kidney interstitium, in an otherwise healthy 20-year-old individual [5]. While the exact mechanism of creatine-induced interstitial nephritis is unclear, the authors hypothesize that metabolites of creatine or impurities in the supplement may have acted as triggers for the immune-mediated inflammation [5]. The absence of pre-existing kidney conditions in this case suggests that even healthy individuals might be at risk of renal complications from creatine, particularly with prolonged or high-dose use [5]. This case raises concerns about the safety of unregulated dietary supplements and highlights the importance of evaluating kidney function in individuals using creatine.

Robinson et al. reported the development of acute quadriceps compartment syndrome (AQCS) and rhabdomyolysis in a 25-year-old male weightlifter, highlighting a potential association with the use of high-dose creatine supplementation and intense physical activity [6]. While Revai et al. described a case of severe nephrotic syndrome in a 22-year-old bodybuilder with long-term use of anabolic steroids and creatine. The findings suggest a synergistic detrimental effect of these substances on renal health, raising concerns about their combined use [7]. Taner et al. claimed that the standard doses of creatine monohydrate do not significantly impair renal function in healthy individuals. The study emphasizes that adverse effects are more likely at high doses or, as shown above, in individuals with pre-existing renal conditions [8]. Thorsteinsdottir et al. described a case of acute renal failure in a 24-year-old weightlifter who consumed multiple food supplements, including creatine monohydrate. The report raises

awareness about the potential cumulative risk of renal impairment due to the combination of creatine and other dietary supplements [9].

Interestingly, Gualano et al. examines the effects of short-term, high-dose creatine supplementation on glomerular filtration rate (GFR) in a 20-year-old man with a single kidney. The primary aim was to determine whether high-dose creatine adversely impacts renal function in an individual with reduced renal reserve [21]. The patient was administered 20 g/day of creatine monohydrate for 5 days [21]. GFR was measured using the method of inulin clearance both before and after the supplementation period. Serum creatinine levels and urinary markers were monitored to detect any signs of renal dysfunction. No significant changes in measured GFR were observed following the supplementation period [21]. Pre- and post-supplementation GFR values remained within the normal range, suggesting preserved renal filtration capacity. While serum creatinine levels showed a mild increase post-supplementation, attributed to the conversion of supplemented creatine into creatinine, rather than an actual decline in kidney function [21]. The findings suggest that short-term, high-dose creatine supplementation does not adversely affect renal function, even in an individual with reduced renal reserve (a single kidney). The mild increase in serum creatinine is a predictable physiological response due to the metabolic conversion of creatine to creatinine and does not reflect true renal dysfunction. The study emphasizes the importance of differentiating between true renal impairment and pseudo-elevation of creatinine levels in individuals supplementing with creatine. While these results are reassuring, they are limited to short-term use and may not extrapolate to long-term supplementation or higher-risk populations.

Not only case reports, but also experimental studies investigating the effects of creatine supplementation on kidney function were made.

The researches by Poortmans et al. consistently explored the effects of creatine supplementation on kidney function and other health markers. In their 1997 study, Poortmans et al. observed the short-term renal responses to creatine supplementation, finding no harmful effects on renal function in men [20]. The 1998 study highlighted a potential concern regarding renal dysfunction with creatine use [24]. However, in 1999, Poortmans and Francaux reassured that long-term creatine supplementation did not impair kidney function in healthy athletes [25]. Further studies, including the 2005 investigations, continued to show that creatine did not adversely affect kidney health, as evidenced by a lack of impact on urinary markers like methylamine, formaldehyde, and formate [26]. Additionally, their 2005 study showed minimal

side effects, reaffirming creatine's safety over long-term use [26]. These findings provide strong evidence that creatine supplementation, when used appropriately, does not negatively affect renal health, even in long-term use by athletes and non-athletes alike.

Moreover, the study of Mihic et al. proved that acute creatine loading has been shown to increase fat-free mass without adversely affecting blood pressure, plasma creatinine levels, or creatine kinase activity in both men and women, highlighting its immediate tolerability [27]. Similarly, dietary creatine supplementation does not alter hematological indices, markers of muscle damage, or hepatic and renal function in healthy individuals [28]. Long-term studies on athletes, including football players and resistance-trained individuals, also reveal no significant adverse effects on liver and kidney function, even under high-protein diets [29,31,34,41]. In older adults, creatine supplementation combined with resistance training improves muscle strength, body composition, and physical fitness without impairing health markers, making it a valuable tool for addressing age-related muscle decline [30,31,45].

Studies in clinical populations further support the safety of creatine. In patients with Parkinson's disease, long-term supplementation was found to be safe, with no significant effects on clinical progression or adverse events reported [35,44,]. Trials in patients with type 2 diabetes, systemic lupus erythematosus, and peripheral artery disease demonstrated no impairment in renal function or other health markers, suggesting creatine's suitability in managing chronic conditions [38,42,48]. Furthermore, research in postmenopausal women indicated that creatine supplementation, often in combination with resistance training, supports bone health and does not affect kidney function [39,43,49].

Additional investigations have explored unique contexts of creatine use. For instance, studies found that creatine does not form carcinogenic heterocyclic amines under physiological conditions, alleviating concerns about long-term safety [46]. Changing to a vegetarian diet reduces body creatine stores, but supplementation effectively restores levels without disrupting carnitine and carnosine homeostasis [47]. Creatine ethyl ester supplementation has also been shown to enhance body composition and muscle performance when combined with heavy resistance training [37].

Across the spectrum of studies, from healthy athletes to clinical populations and older adults, creatine supplementation has demonstrated a safety profile and efficacy in improving various health and performance outcomes.

4. Conclusions

The comprehensive review of creatine supplementation highlights its well-established efficacy in enhancing athletic performance, improving muscle strength, and offering therapeutic benefits in various clinical contexts [1,2,20,24-50]. While initial case reports raised concerns about potential adverse effects on kidney function, robust evidence from randomized controlled trials and long-term studies consistently demonstrates that creatine supplementation does not impair renal health in healthy individuals [20,24-29,31,34,41,45]. Notably, short-term high-dose creatine usage, even in individuals with reduced renal reserve, shows no significant impact on glomerular filtration rate or other markers of renal dysfunction [21].

However, caution is warranted for populations with pre-existing kidney conditions, emphasizing the importance of pre-supplementation renal function assessment, individualized dosing, and regular monitoring to mitigate potential risks [3-9]. The influence of creatine supplementation on serum creatinine levels, which can confound eGFR calculations, underscores the need for careful interpretation of renal function tests in creatine users [16-20].

Overall, when used within recommended guidelines, creatine supplementation is both safe and effective for athletes, older adults, and clinical populations, providing significant health and performance benefits without compromising kidney function [2,30,35,38,39,42,44,49]. Further research into its long-term safety in at-risk populations and its impact in diverse clinical settings is encouraged to reinforce these findings [46,47].

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