

Potential Adverse Effects of Creatine Supplement on the Kidney in Athletes and Bodybuilders

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Introduction. Nowadays, creatine is one of the most common oral supplements used by professional athletes for boosting their strength and muscle mass. In this review, we collect available experimental and clinical data about renal safety of both short-term and long-term use of creatine.

Materials and Methods. Scientific literature was critically searched by keywords “creatine,” “renal insufficiency,” and “renal dysfunction” and their synonyms in medical databases (Scopus, MEDLINE, EMBase, and ISI Web of Knowledge). Overall, 19 relevant clinical and experimental articles were selected for this review.

Results. Short- and long-term creatine supplementations (range, 5 days to 5 years) with different doses (range, 5 g/d to 30 g/d) had no known significant effects on different studied indexes of kidney function such as glomerular filtration rate at least in healthy athletes and bodybuilders with no underlying kidney diseases. In addition, although short-term (range, 5 days to 2 weeks) high-dose oral creatine supplementation (range, 20 g/d to 0.3 g/kg/d) stimulated the production of methylamine and formaldehyde (as potential cytotoxic metabolites of creatine) in the urine of healthy humans, there was currently no definite clinical evidence about their adverse effects on the kidney function.

Conclusions. Although creatine supplementation appears to have no detrimental effects on kidney function of individuals without underlying kidney diseases, it seems more advisable to suggest that creatine supplementation not to be used by sportsmen or women with pre-existing kidney disease or those with a potential risk for kidney dysfunction.

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INTRODUCTION

It was at international consensus conference in 1991 that for the first time, the statement of effect of diet on exercise performance became bold: “Diet significantly influences exercise performance.¹” Since then, many supplements have been used by athletes and sportsmen as well as women to improve body performance.

Creatine is one of the most popular substances

in the athletes and bodybuilders worldwide. It has been declared that over 4 million kg and \$200 million of dietary supplementation industry is allocated for creatine annually.² Statistics in 2014 indicated that 14% of the United States college athletes were creatine consumers.³

Creatine is not an essential nutrient. It is naturally produced in the liver from 2 amino acids, glycine and arginine (N-[aminoiminomethyl]- N-methyl

a piturglycine). Creatine can be also originated from meat and fish.⁴ Muscles take creatine from the blood circulation and convert it to a compound named phosphocreatine by the means of creatine kinase. Phosphocreatine can produce energy by releasing adenosine triphosphate (ATP). Creatine supplementation causes its storage in muscles and as a result, more phosphocreatine and ATP formation. High loads of ATP can improve performance and muscle mass particularly in extensive exercise.⁴

The kidney plays an important role in body hemostasis, metabolizing, and excretion of exogenous compounds such as creatine. This review tries to collect available experimental and clinical data about kidney safety of both short-term and long-term usage of creatine in athletes and bodybuilders.

METHODS AND MATERIALS

Related articles were identified, using relevant keywords including “creatine,” “creatine monohydrate,” “creatine supplements,” “acute kidney injury,” “chronic kidney disease,” “renal dysfunction,” “renal impairment,” “renal damage,” and “renal insufficiency” in databases including the Scopus, MEDLINE, EMBase, ISI Web of Knowledge, Cochrane Central Registry of Controlled Trials, and Cochrane Database of Systematic Reviews. Inclusion criteria for selecting articles were as follows: (1) randomized clinical trials, (2) prospective or retrospective human studies, (3) case series or case reports, (4) and experimental studies. All aspects of renal impairment and dysfunction (both tubular and glomerular indexes) were considered, including urine volume, urinary creatinine concentration, creatinine clearance, urine electrolytes (sodium and potassium), serum electrolytes (sodium and potassium), serum creatinine, serum urea, serum uric acid, proteinuria, urinary excretion rate of creatinine potential toxic metabolites (eg, methylamine and formaldehyde), and relevant pathologic findings.

Exclusion criteria were non-English language articles, congress abstracts, and in vitro studies. Overall, 19 articles were taken into account for this review. They included 1 experimental study, 3 case reports, 3 clinical pilot studies, 2 retrospective studies, 1 randomized placebo-controlled cross-over trial, 1 randomized cross-over trial, 2 placebo-controlled clinical trials with no defined randomization and blinding, and 6 randomized double-blinded

placebo-controlled trials. The quality of clinical trial studies (n = 10) was assessed using the Jadad score system. The mean \pm standard deviation and range of calculated Jadad score were 2.9 ± 1.5 and zero to 5, respectively. Seven out of 10 clinical trials had Jadad scores equal or greater than 3.

RESULTS

Creatine Supplementation Effects on Kidney Function

About 30 years ago, the first papers about the effect of creatine consumption on healthy human kidney functions were published in the literature.⁵⁻⁷ Accordingly, for example in 1998, nephrologists reported a 25-year-old man who had been suffering from focal segmental glomerulosclerosis with frequent nephrotic relapses for 8 years. He was on cyclosporine treatment for 5 years with nearly normal kidney function and no relapse of proteinuria. As a soccer player, he initiated creatine consumption. Creatine dosing regimen included 5 g, 3 times a day for 7 consecutive days as a loading dose; after that, he consumed 2 g/d of creatine for 7 weeks as a maintenance dose. The patient's creatinine clearance decreased up to 60% after taking creatine for 7 weeks. His creatinine clearances recovered within 1 month of creatine supplement discontinuing. This report was considered as the first safety concern of oral creatine consumption published in the Lancet.⁸

Short-term Creatine Loading on Kidney Function

Creatine can convert to creatinine in the skeletal muscles and liver by a nonenzymatic hydrolysis.^{9,10} Serum creatinine has been considered by nephrologists as a classic marker of kidney function. However, many nonkidney factors such as protein intake and muscle mass may potentially alter its level.¹¹ Serum creatinine concentrations may rise as much as 50% within 2 hours of a meat meal and remain elevated up to 24 hours.¹² Short-term creatine supplementation is described as using this agent for less than 1 month.

Experimental studies. The issue of probable adverse effects of short-term creatine on kidney function has been studied in at least 1 experimental study conducted by Edmunds and colleagues. They demonstrated that creatine supplementation (loading dose of 2.0 g/kg for 1 week followed by

one-fifth of loading dose for 5 weeks) exacerbated disease progression indexes (eg, serum urea concentration and creatinine clearance) in an animal model of cystic renal disease.¹³

Clinical studies. Low-dose regimen is considered as daily creatine supplementation less than 20 g. Although short-time creatine ingestion appears to have no significant adverse effects on kidney functions in clinical studies that have been performed so far, its real effects on the body content of creatinine is equivocal. Poortmans and Francaux observed that 20 g/d creatine supplementation for 5 days in healthy men did not significantly change the amount of creatinine in both the urine and serum and also creatinine excretion rate or creatinine clearance.⁵ Similarly, a placebo-controlled study on healthy men students indicated that 5 days of oral creatine consumption (20 g/d) significantly increased in creatine concentration in plasma as well as urine but no significant change in urine creatinine, nor in creatinine clearance and albumin excretion rate.⁶ Similar findings were observed with the same creatine daily dose and duration in male physical education students.¹⁴ In line with these findings, in a randomized, double-blinded placebo-controlled trial on both sexes in 2000, this recent creatine supplementation regimen did not either affect plasma creatinine or creatinine clearance, but it increased total body mass and free fat mass.¹⁵

In contrast to the aforementioned results, some other clinical studies demonstrated that short-time creatine administration could affect the concentration of creatinine level or creatinine clearance. For example, 20 g/d of creatine supplementation for 6 days increased total creatine concentration in the muscle. This elevation in muscle creatine content continued after continuing creatine administration for a further 30 days with the maintenance dose of 2 g/d. Serum creatinine and its urinary excretion were also increased.⁴ In accordance to these results, Kreidar and colleagues demonstrated in a randomized double-blinded trial that 28 days of creatine administration (15.75 g/d) in football players increased not only total body weight and fat and bone free mass, but also serum creatinine content.¹⁶ Finally, the ingestion of 20 g/d of creatine for either 5 days or 9 weeks resulted in an increase in serum creatinine concentration by 25% and 40%, respectively.¹⁷

Creatine can also be detrimental for the kidney in other pathways. Creatine may convert to sarcosine which in turn, it can form other cytotoxic agents including methylamine.¹⁸ Formaldehyde as another cytotoxic agent can be produced from methylamine by the means of semicarbazide-sensitive amine oxidase.¹⁹ Methylamine and formaldehyde can potentially damage the integrity of the intestinal epithelium, endothelial cells, and also the kidney.^{19,20} In this regard, Poortmans and coworkers demonstrated that the consumption of 21 g of creatine monohydrate daily for 14 days in healthy volunteers elevated the content of plasma creatine by about 7.2 fold and creatine urine excretion rate by about 141 fold with no alteration on the plasma creatinine level as well as creatinine output. This investigation also implicated that creatine supplementation significantly increases the 24-hour urine level of methylamine and formaldehyde by about 9.2 and 4.5 fold, respectively. However, there was no significant correlation between plasma creatine and urine methylamine or formaldehyde.²¹ Sale and colleagues studied the consumption of 20 g/d of creatine for 5 days in 2 different dosage patterns. One group consumed creatine as a single dose of 20 g/d and the other one, ingested dose of 5 g of creatine 4 times a day. Single-dose regimen caused lower excretion of creatine leading to a greater creatine retention in the body and probably in the muscles. In addition, by lowering the peak plasma creatine concentration through spreading its dose evenly throughout the day, the urinary output of methylamine was significantly decreased.²² Finally, according to a double-blinded randomized trial, creatine ingestion with the dose 0.3 g/kg/d for 7 days increased the rate of urinary formaldehyde in both groups of individuals with or without resistance training by 30.4% and 63.4%, respectively. This result suggested that resistance exercise can significantly lower the increase of urinary formaldehyde excretion caused by creatine supplementation.²³

Daily creatine supplementation more than 20 g is considered as a high-dose regimen. In the only relevant clinical trial, Volek and colleagues reported an elevation in the content of serum creatinine after 7 days of creatine supplementation (0.3 g/kg of individual body weight per day) in 20 healthy men. However, no significant changes were observed in the urinary sodium, potassium, and creatinine excretion rates.²⁴

Long-term Creatine Loading on Kidney Function

Clinical studies. Creatine use for months to years is described as long-term supplementation with this agent. The effects of long-term creatine use have not been well-defined yet. The result of a randomized placebo-controlled study showed that long-term creatine use (induction dose of 21 g daily for 5 days and maintenance dose of 3 g/d for 58 additional days) in healthy men had no significant effect on creatinine clearance, urea clearance, and albumin excretion rate compared to the control group.⁵ In another investigation, different creatine doses taken for 10 months to 5 years did not alter urine output, urea clearance, urine albumin, and creatinine clearance in healthy athletes.⁷ Similarly, Mayhew and colleagues demonstrated that consumption of 5 g/d to 20 g/d of creatine for 0.25 to 5.6 years had no long-term detrimental effects on studied indexes of kidney function including serum urea as well as creatinine and creatinine clearance in the American College of Football Players.²⁵ In line with the aforementioned investigations, a literature review on 9 studies published between 1966 and September 2004 by Pline and Smith implicated that acute ingestion (4 to 5 days) of large amounts of creatine as well as longer creatine supplementation (up to 5.6 years) minimally affected creatinine concentrations and kidney function in young healthy adults.²⁶ Finally, the most relevant recent randomized double-blinded placebo-controlled trial supported this idea that high-dose creatine supplementation (about 10 g/d) over 3 months had no adverse effects on kidney function in the healthy males undergoing aerobic training.²⁷

In contrast to most studies that reported no direct association between long-term creatine supplementation and kidney dysfunction, few investigations revealed a slight but not clinically significant elevation in serum creatinine.^{16,27,28} For example, Schilling and coworkers demonstrated that long-term creatine consumption (0.8 to 4 years) with the mean loading of 13.7 ± 10.0 g/d and maintenance dose of 9.7 ± 5.7 g/d could only elevate the serum creatinine concentration within its normal range.²⁸

Apart from randomized or retrospective studies,^{16,29} there is at least 1 case report suggesting a possible association between kidney dysfunction and creatine supplementation. Taner and colleagues

reported an 18-year-old man referred to the hospital with the chief complaint of nausea, vomiting, and gastric pain. As a body builder, he had been using creatine supplementation with the initial dose of 20 g/d for 5 days followed by 1 g/d for the next 6 weeks. His blood pressure was 150/90 mm Hg. Regarding laboratory data of the patient at admission, serum urea (39.98 mmol/L), serum creatinine (201.55 mmol/L), and serum uric acid (0.37 mmol/L) values were high. Other biochemical parameters and blood count were normal. Urinalysis revealed only proteinuria and 24-hour protein excretion in the urine was 284 mg. Although there was no abnormality in kidneys ultrasonography, renal biopsy was suggestive of acute tubular necrosis. During hospitalization, creatine was discontinued and fluids were administered intravenously. Twenty-five days after discontinuing creatine supplement, blood pressure, serum creatinine, and proteinuria of the patient became normal.²⁹ In contrast, there were 4 cases referred with questionable abnormalities in their kidney function including high serum creatinine level and low estimated glomerular filtration rate. All of them were positive for human immunodeficiency virus and different antiretroviral agents were administered for them. They consumed creatine supplementation and whey protein to enhance their muscle profile. One of them took 5 g to 10 g of creatine monohydrate and 24 g to 30 g whey protein daily for undefined time period. By stopping the supplements and monitoring the patients, their serum creatinine levels were dropped. The authors believed that creatine and concentrated protein supplements misleadingly led to a high serum creatinine concentration and low estimated glomerular filtration rate, misdiagnosed as kidney disease in these patients. Patients with human immunodeficiency virus may particularly at risk of these misinterpretations because of human immunodeficiency virus itself or changes in muscle and fat distribution caused by certain medications.³⁰ Characteristics of experimental and clinical studies about effects of creatine supplementation on the kidney are listed in the order of study type (first experimental and in the following, clinical) and publication year in the Table.

CONCLUSIONS

Among included articles in this review, all

Summary of Experimental and Clinical Studies on Renal Safety of Different Dosage Regimens and Durations of Creatine Supplementation

Study	Dose and Duration	Regimen Dosage*	Regimen Duration†	Subjects	Type of Study	Main Results
Edmunds et al 2001 ¹³	Loading: 2 g/kg for 1 week Maintenance: One-fifth of loading for 5 weeks	Not defined	Short term	Rats with cystic kidney disease	Experimental	Exacerbation of disease progression indexes including elevation in serum urea concentration and reduction in creatinine clearance
Hultman et al 1985 ⁴	Loading: 20 g/d for 6 days Maintenance: 2 g/d for 30 day	Low dose	Short term	Men	Pilot clinical study	Increase in serum creatinine and urinary creatinine excretion
Poortmans et al 1997 ⁶	20 g/d for 5 days	Low dose	Short term	Healthy men	Placebo-controlled trial (Randomization and blinding were not defined)	No significant change in the amount of serum and urine creatinine No significant change in the total urinary protein and albumin excretion rates
Pritchard and Kalra 1998 ⁵	Loading: 5 g 3 times a day for 7 days Maintenance: 2 g/d for 7 weeks	Low dose	Loading dose: Short term Maintenance dose: Long term	Soccer player with the history of focal segmental glomerulosclerosis	Case report	Decrease in creatinine clearance
Kreider et al 1998 ¹⁶	15.75 g/d for 28 days	Low dose	Short term	Football players	Randomized double-blinded placebo-controlled trial	Increase in serum creatinine content
Poortmans and Francaux 1998 ⁵	Loading: 21g/d for 5 days Maintenance: 3 g/d for 58 days	Loading: high dose Maintenance: low dose	Loading dose: Short term Maintenance dose: Long term	Healthy men	Placebo-controlled trial (Randomization and blinding were not defined)	No significant effect on creatinine clearance, urea clearance, and albumin excretion rate
Kamber et al 1999 ¹⁴	20 g/d for 5 days	Low dose	Short term	Male physical education students	Randomized placebo-controlled cross-over trial	Significant increase in urine and serum creatinine Significant increase in serum creatinine No significant change in urine creatinine and creatinine clearance
Poortmans and Francaux 1999 ⁷	2-30 g/d for 10 months to 5 years	Both low and high doses	Long term	Healthy athletes	Pilot clinical with the control group	No significant alteration in glomerular filtration rate, tubular reabsorption, and glomerular membrane permeability No significant alteration in creatinine, urea, and albumin excretion rates
Mihic et al 2000 ¹⁵	20 g/d for 5 days	Low dose	Short term	Healthy men and women	Randomized double-blinded placebo-controlled trial	No significant change in blood pressure, plasma creatinine, and estimated creatinine clearance
Robinson et al 2000 ¹⁷	Loading: 20 g/d for 5 days Maintenance: 20 g/d for 5 days and then 3 g/d for 8 weeks	Low dose	Loading regimen: Short term Maintenance regimen: Long term	Healthy volunteers	Randomized double-blind placebo-controlled trial	Loading regimen: Reversible increase in serum creatinine concentration unrelated to renal dysfunction Maintenance regimen: Reversible increase in serum creatinine concentration unrelated to renal dysfunction

Continued

Study	Dose and Duration	Regimen Dosage*	Regimen Duration†	Subjects	Type of Study	Main Results
Volek et al 2001 ²⁴	0.3 g/kg/d for 7 days	High dose	Short term	Healthy men	Randomized double-blinded placebo-controlled trial	Increase in serum creatinine content but within normal ranges No significant changes in the urinary sodium, potassium, and creatinine excretion rates
Schilling et al 2001 ²⁸	Loading: 13.7 ± 10.0 g/d Maintenance: 9.7 ± 5.7 g/d for 0.8 to 4 years	Loading dose: High dose Maintenance dose: Low dose	Long term	Athletes of various sports	Retrospective	Increase in serum creatinine concentration within its normal range
Mayhew et al 2002 ²⁵	5 g/d to 20 g/d for 0.25 to 5.6 years	Both low and high doses	Long term	Football players	Retrospective	No significant effect on serum urea, creatinine and creatinine clearance
Poortmans et al 2005 ²¹	21 g/d for 14 days	High dose	Short term	Healthy men	Pilot clinical	Increase in plasma creatinine level and urine excretion of creatine Increase in the urine excretion of methylamine and formaldehyde No significant change in plasma creatinine level and creatinine output No significant correlation between plasma creatine and urine methylamine or formaldehyde
Gualano et al 2008 ²⁷	About 10 g/d for 3 months	Low dose	Long term	Healthy males undergoing moderate intensity aerobic training	Randomized double-blinded placebo-controlled trial	No significant effects on serum creatinine, serum as well as urinary sodium and potassium Decreased in serum cystatin C levels over time, suggesting an increase in glomerular filtration rate
Sale et al 2009 ²²	Group 1: 20 g/d for 5 days Group 2: 4 × 5 g/d for 5 days	Low dose	Short term	Healthy men	Randomized cross-over trial (Probably single blinded)	By lowering the peak plasma creatine concentration, the urinary output of methylamine significantly decreased
Willis et al 2010 ³⁰	5 g to 10 g daily for undefined time period in one case	Low dose	Not defined	4 HIV-positive men aged 25 to 46 years	Case report	High serum creatinine level and low estimated glomerular filtration rate resolved by stopping the supplements
Taner et al 2011 ²⁹	Loading: 20 g/d for 5 days Maintenance: 1 g/d for 6 weeks	Low dose	Loading: short term Maintenance: Long term	18-year-old man	Case report	Hypertension, proteinuria, and increased serum urea, serum creatinine, as well as serum uric acid Acute tubular necrosis
Nasser et al 2016 ²³	0.3 g/kg/d for 7 days	Both low and high doses	Short term	Male wrestlers	Randomized double-blinded placebo-controlled trial	Increase in the urinary excretion rate of formaldehyde Resistance exercise lowers the increase of urinary formaldehyde excretion caused by creatine supplementation

*Low- and high-dose regimens are defined as daily creatine supplementation less and more than 20 g, respectively.

†Short- and long-term regimens are defined as creatine duration of supplementation for less than and more than 1 month, respectively.

except 1 were human studies. In addition, more than half (55.6%) of clinical studies were clinical trials, mostly double-blinded and placebo-controlled. Seventy percent of relevant clinical trials were graded as high quality. As stated by the International Society of Sports Nutrition, creatine supplementation has no clinically significant side effects or adverse effects when given appropriately. In addition, although short-term (from 5 days to 2 weeks), high-dose oral creatine supplementation (from 20 g/d up to 0.3 g/kg/d) stimulates the production of methylamine and formaldehyde (as potential cytotoxic metabolites of creatine) in the urine of healthy humans, there is currently no definite clinical evidence about their adverse effects on the kidney function. It appears to be no major clinical concern about detrimental effects or sequel of both short- and long-term (ranged from 5 days to 5 years) with different doses creatine supplementations (ranged from 5 g/d to 30 g/d) on different studied indexes of kidney function at least in healthy athletes and bodybuilders with no underlying renal diseases. However, it seems prudent to consider and ask them about dietary intake or oral supplementation of creatine for at least 24 hours before the estimation of creatinine clearance by formula such as the Cockcroft-Gault equation. Measuring urinary albumin-excretion rate ($< 20 \mu\text{g}/\text{min}$) appears to be an alternate and practical test to assess any probable kidney injury in creatine supplement recipients. Finally, there is insufficient data about the effects of creatine on renal function and serum creatinine concentrations in elderly patients, those with chronic renal insufficiency, or individuals with other comorbidities. Until that time, it seems more advisable to suggest that creatine supplementation not to be used by sportsmen or women with pre-existing renal disease or those with a potential risk for kidney dysfunction such as diabetes mellitus, hypertension, and proteinuria.

CONFLICT OF INTEREST

None declared.

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