

# Effects of Creatine Supplementation on Renal Function: A Systematic Review and Meta-Analysis

Alexandre de Souza e Silva, PhD,<sup>\*</sup> Adriana Pertille, PhD,<sup>†</sup> Carolina Gabriela Reis Barbosa, MSc,<sup>‡</sup> Jasiele Aparecida de Oliveira Silva, MSc,<sup>\*,‡</sup> Diego Vilela de Jesus, PE,<sup>\*</sup> Anna Gabriela Silva Vilela Ribeiro, MSc,<sup>‡</sup> Ronaldo Júlio Baganha, PhD,<sup>\*</sup> and José Jonas de Oliveira, MSc<sup>\*,†</sup>

Creatine supplements are intended to improve performance, but there are indications that it can overwhelm liver and kidney functions, reduce the quality of life, and increase mortality. Therefore, this is the first systematic review and meta-analysis study that aimed to investigate creatine supplements and their possible renal function side effects. After evaluating 290 non-duplicated studies, 15 were included in the qualitative analysis and 6 in the quantitative analysis. The results of the meta-analysis suggest that creatine supplementation did not significantly alter serum creatinine levels (standardized mean difference = 0.48, 95% confidence interval 0.24-0.73,  $P = .001$ ,  $I^2 = 22\%$ ), and did not alter plasma urea values (standardized mean difference = 1.10, 95% confidence interval 0.34-1.85,  $P = .004$ ,  $I^2 = 28\%$ ). The findings indicate that creatine supplementation does not induce renal damage in the studied amounts and durations.

© 2019 by the National Kidney Foundation, Inc. All rights reserved.

## Introduction

CREATINE IS A compound formed by the amino acids methionine, glycine, and arginine obtained through diet and/or endogenously synthesized.<sup>1,2</sup> Creatine supplementation is a promising ergogenic resource capable of increasing athletic performance<sup>3</sup> during short duration and high intensity exercise,<sup>4</sup> and is usually consumed by professional and amateur athletes.<sup>5</sup>

In addition, creatine supplementation has consistently been reported as a strategy to increase muscle creatine and phosphocreatine,<sup>6-11</sup> which would allow an increase in the availability of phosphocreatine, thus promoting an increase in the cellular bioenergetics of the phosphogenic system as well as in the transport of high energy phosphates between the mitochondria and the cytosol through the circulation of creatine phosphate.<sup>12-14</sup>

There is also evidence of therapeutic benefits of creatine supplementation in patients with type 2 diabetes, such as improved insulin sensitivity, glucose tolerance, expression of Glucose Transporter Type 4 (GLUT-4) protein,<sup>15</sup> and aiding in the treatment of metabolic disorders and neuromuscular diseases such as accelerating recovery after immobilization.<sup>16</sup> However, the indiscriminate use of this supplement has raised concerns about its safety, especially in relation to liver and kidney changes.<sup>17</sup>

To the best of our knowledge, there has been no systematic review and meta-analysis study that has investigated creatine supplementation and its possible side effects on renal function. Therefore, we aimed to perform a systematic review and meta-analysis of randomized clinical trials to investigate whether creatine supplementation may induce renal damage.

## Methods

### Search Strategy

The review procedures followed the Preferred Reporting Items for Systematic reviews (PRISMA) statement guidelines.<sup>18</sup> The search was conducted in 4 electronic databases (PubMed, Web of Science, SciELO, and Cochrane) up to March 2018, with no language restrictions. The terms used for the search were (creatine supplementation) AND function renal, (creatine supplementation) AND kidney, (creatine supplementation) AND renal insufficiency. After the exclusion of duplicate studies, 2 investigators independently screened the titles and abstracts to select articles relevant to the study topic.

<sup>\*</sup>Centro Universitário de Itajubá - FEPI, Physical Education Department, Itajubá, Brazil.

<sup>†</sup>Universidade Metodista de Piracicaba, Post-graduate Program in Human Movement Sciences, São Paulo, Brazil.

<sup>‡</sup>Universidade São Francisco, Psychological Evaluation Department, Bragança Paulista, Brazil.

Support: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Financial Disclosure: The authors declare that there is no conflict of interest associated with this manuscript.

Address correspondence to: Alexandre de Souza e Silva, Centro Universitário de Itajubá - FEPI, Av. Dr. Antônio Braga Filho, 687 - Varginha, Itajubá, Minas Gerais 37501-002, Brazil. E-mail: alexprofms@yahoo.com.br

© 2019 by the National Kidney Foundation, Inc. All rights reserved.

1051-2276/\$36.00

<https://doi.org/10.1053/j.jrn.2019.05.004>

## Eligibility Criteria

Studies were eligible based on the following inclusion criteria: (1) randomized controlled trials; (2) published in peer-reviewed scientific journals; (3) case studies; and (4) studies assessing creatine supplements and kidney effects. Exclusion criteria were as follows: (1) animal studies; (2) review articles; (3) abstracts from conferences and unpublished studies; (4) lack of creatine supplementation; (5) no evaluation of renal damage after supplementation; and (6) prior renal damage before supplementation. According to the inclusion/exclusion criteria, 13 studies were excluded.<sup>19-31</sup> Full-text articles were assessed independently for eligibility by 2 reviewers. Disagreement on the inclusion or exclusion of studies was resolved by consensus, or, if necessary, by the participation of a third reviewer. In addition, the reference list of the eligible studies was also analyzed to identify potentially relevant studies.

## Data Extraction

The same 2 reviewers independently extracted the following data from each eligible study: the first author's name, publication year, search objective, type of supplement, daily and weekly frequency, supplementation program procedure, period of the supplementation program in weeks, completion of studies, used journals, and mean age (years). The studies that presented outcome values with a standard error (SE) with a known sample size (N) were converted to standard deviation (SD) according to the formula:  $SD = SE \times \sqrt{N}$ . Disagreement on the data extraction was resolved by consensus.

## Evaluation of the Methodological Quality of Studies

The analysis of the methodological quality of the eligible studies was carried out by 2 independent researchers. Disagreements were resolved by consensus. Randomized controlled trials were evaluated using the Physiotherapy Evidence Database<sup>32</sup> (PEDro) scale. Non-randomized, case, and cross-sectional studies were analyzed using criteria developed by the Joanna Briggs Institute (JBI) that has different assessment tools for each study design in question.<sup>33</sup> The PEDro scale is composed of 11 items; however, its score ranges from 0 to 10 since the first item is not computed in the final score.<sup>32</sup> The evaluation tool developed by the JBI has 9 items for the analysis of non-randomized studies and 8 items for cross-sectional studies and case reports.<sup>33</sup>

## Statistical Analysis

A quantitative meta-analysis was performed by 2 reviewers using Review Manager Software (version 5.2, The Nordic Cochrane Center, The Cochrane Collaboration, 2012, Copenhagen, Denmark). Biochemical data (creatinine, creatinine clearance, and urea) were analyzed in the meta-analysis. The standardized mean difference (SMD) with 95% confidence intervals (CIs) was calculated

with the following data entries: pre-mean, pre-SD, post-mean, post-SD, and sample size.

Heterogeneity was evaluated by the *P*-value and by the *I*<sup>2</sup> statistic in the combined analyses that represented the percentage of the total variation among the studies. If the *P*-value was <0.1 or the *I*<sup>2</sup> value was >50%, the summary estimate was analyzed in a random effects model. Otherwise, a fixed effects model was applied. A sensitivity analysis, excluding one study at a time, was performed with the outcome examined to ensure that the results were not simply due to one large study or a study with an extreme result. Studies were considered influential if removal resulted in a change in the SMD from significant (*P* < .05) to non-significant (*P* > .05).

Three meta-analyses were performed based on the biochemical profile: (1) creatinine level, (2) creatinine clearance, and (3) urea level. Results are presented as SMDs for absolute values between groups with a 95% CI. The level of significance was set at *P* < .05.

## Results

### Study Selection

The search strategy identified 509 records in the 4 electronic databases (PubMed, Web of Science, SciELO, and Cochrane). After a review of titles and abstracts, 28 studies were selected for full-text review and, according to the inclusion/exclusion criteria, 15 studies were considered eligible. Figure 1 provides an overview of the full selection process.

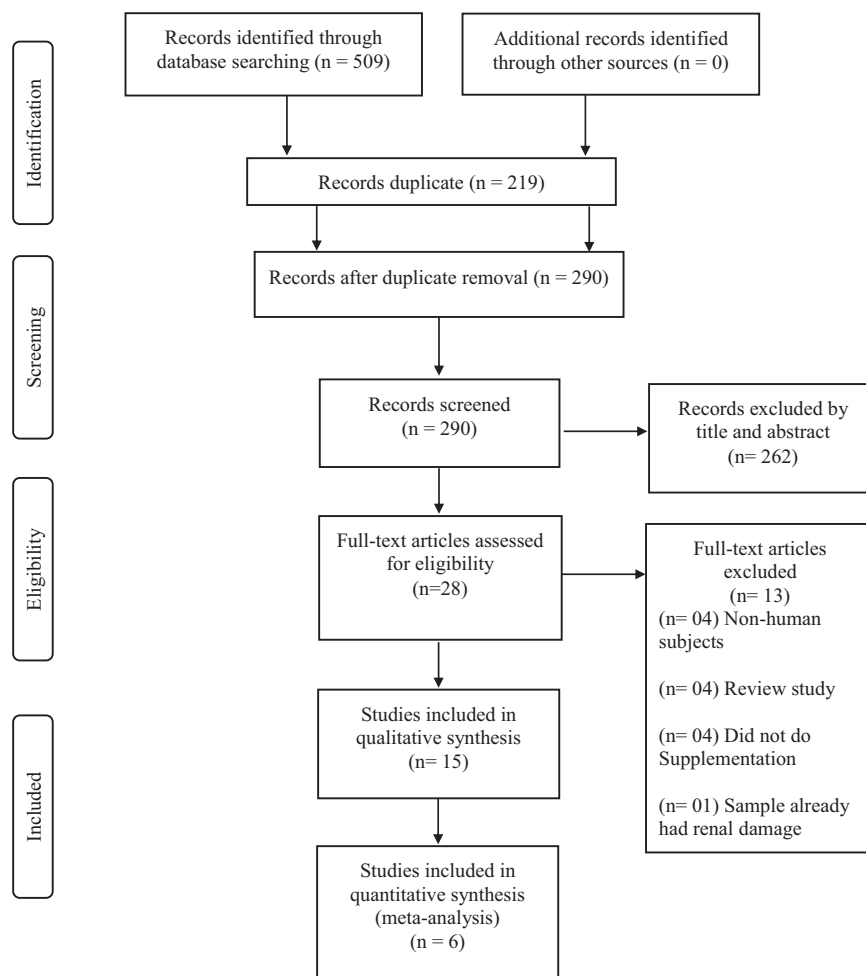
### Study Characteristics

The general characteristics and results for each eligible study are summarized in Tables 1 and 2. The studies (*n* = 15) were published from 1997 to 2013 and included a total of 497 subjects. These studies were conducted in Brazil,<sup>4,15,34-36</sup> England,<sup>37</sup> the United States,<sup>16,38,39</sup> the Netherlands,<sup>5</sup> Uruguay,<sup>40</sup> Belgium,<sup>41</sup> Turkey,<sup>42</sup> and Austria.<sup>43</sup> The studies indicated a creatine intake of 4–20 g/day in the creatine supplementation groups, which were compared to control groups (without creatine intake)<sup>16,38</sup> who were given placebo solutions composed of 500 mL of carbohydrates,<sup>15,37</sup> dextrose,<sup>34,35,44</sup> maltodextrin,<sup>4,40</sup> glucose polymer,<sup>5</sup> and gatorade powder.<sup>41</sup> The follow-up interval from the pre- to post-supplementation period ranged from 5 days to 132 weeks in the longitudinal studies and case studies ranged from 6 weeks to 112 weeks.

### Quality Assessment of Studies

Randomized trials, evaluated by the PEDro scale, presented an average score of 6 points. One study scored 4 points,<sup>4</sup> 4 studies scored 6 points,<sup>5,34,40,44</sup> 2 studies scored 7 points,<sup>35,37</sup> and 1 study scored 8 points<sup>44</sup> (Table 3).

The non-randomized studies, evaluated by the JBI's critical evaluation tool, obtained a score of 5 points<sup>41</sup> and 6 points<sup>16</sup> (Table 4). Item 6, which refers to the follow-up of subjects, did not apply to the study by Kreider et al.,<sup>16</sup>



**Figure 1.** Organization of articles reviewing the effects of creatine in renal function. PRISMA 2009 flow diagram. Adapted from Reference.<sup>18</sup>

since the study subjects were assigned to groups based on whether or not they received supplements.

The cross-sectional study by Mayhew et al.<sup>38</sup> obtained a score of 4 points (Table 5).

The case reports presented an average of 7 points, ranging from 6 points<sup>36,39</sup> to 7 points<sup>42,43</sup> (Table 6). Item 7 was not applicable because the focus of the studies, renal damage, was considered an adverse effect of creatine supplementation.

## Meta-Analysis

Five studies evaluating serum creatinine levels before and after subjects received either creatine supplementation or a placebo were included in the meta-analysis, resulting in 8 outcome measures in 220 subjects. The period of supplementation varied between 5 days<sup>41</sup> and 112 weeks.<sup>43</sup> In summary, meta-analysis using the fixed-effects model indicated that creatine supplementation did not significantly alter creatinine levels and did not induce renal damage (SMD = 0.48, 95% CI 0.24–0.73,  $P < .001$ ,  $I^2 = 22\%$ ). Sensitivity analyses showed that the creatinine

concentration results were not affected by any particular study. Figure 2 shows the forest plot of creatinine levels.

Three studies evaluating the glomerular filtration rate through creatinine clearance before and after creatine supplementation or placebo use were included in the meta-analysis, resulting in 5 outcome measures in 136 subjects. The study by Kreider et al.<sup>16</sup> presented data of 6, 12, and 21 months of creatine supplementation or placebo use. In general, creatine supplementation did not induce renal damage (SMD = 12.25, 95% CI –25.75 to 1.44,  $P = .08$ ,  $I^2 = 0\%$ ). Sensitivity analyses showed that the creatinine clearance results were not affected by any particular study. Figure 3 shows the forest plot of creatinine clearance.

Six studies that assessed plasma urea concentrations before and after creatine supplementation or placebo use were included in the meta-analysis, resulting in 14 outcome measures in 382 subjects. The study by Groeneveld et al.<sup>5</sup> presented data for 1, 2, 4, 8, and 12 months and any time when supplements were given. Carvalho et al.<sup>4</sup> evaluated the effect of creatine supplements in 2 distinct groups (CRE1 and CRE2) and in a placebo group (PLA) before

**Table 1.** Results of Studies of Creatine Supplementations' Effects (n = 11) on Renal Function in Longitudinal Studies

No	Author(s)	Title	Age (y)	Supplementation Program (Protocol)			Conclusion Regarding Creatine Supplementation	Journal
				Type of Supplement	Daily and Weekly Quantities	Period in Days and Weeks		
1	Robinson et al. <sup>37</sup>	Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function	26 ± 8	Creatine	5 g/d 4 times a day for 5 d, then 3 g/d for 8 wk	8 wk and 5 d	Do not affect kidney function	Br J Sports Med
2	Robinson et al. <sup>37</sup>	Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function	27 ± 6	Creatine	5 g/d 4 times a day for 5 d, then 3 g/d for 8 wk	8 wk and 5 d	Do not affect kidney function	Br J Sports Med
3	Lugaresi et al. <sup>34</sup>	Does long-term creatine supplementation impair kidney function in resistance-trained individuals consuming a high-protein diet?	27 ± 5* 24 ± 3	Creatine monohydrate	20 g/d for 5 d, divided into 4 times daily, followed by 5 g/d throughout the trial	12 wk	Do not affect kidney function	J Int Soc Sports Nutr
4	Gualano et al. <sup>15</sup>	Creatine supplementation does not impair kidney function in type 2 diabetic patients: a randomized, double-blind, placebo-controlled, clinical trial	56.4 ± 8.2* 57.5 ± 5.0	Creatine monohydrate	5 g/d once daily	12 wk	Do not affect kidney function	Eur J Appl Physiol
5	Mayhew et al. <sup>38</sup>	Effects of long-term creatine supplementation on liver and kidney functions in American college football players	20.1 ± 0.8* 20.5 ± 1.4	Creatine monohydrate	Between 5 and 20 g/d (13.9 ± 5.8 g) for 5 y and 6 mo	~132 wk	Do not affect kidney function	Int J Sport Nutr Exerc Metab
6	Cancela et al. <sup>40</sup>	Creatine supplementation does not affect clinical health markers in football players	19.6 ± 3.5	Creatine monohydrate	4.4 g of creatine 3 times a day for 7 d, then 2.6 g creatine each day for 49 d	12 wk and 1 d	Do not affect kidney function	Br J Sports Med

7	Kreider et al. <sup>16</sup>	Long-term creatine supplementation does not significantly affect clinical markers of health in athletes	19.2 ± 2	Creatine monohydrate with carbohydrate drink	15.75 g/d for 5 d and an average of 5 g/d thereafter in 5-10 g doses following supervised training sessions	0-6 mo 7-12 mo 12-21 mo	Do not affect kidney function	Mol Cell Biochem
8	Carvalho et al. <sup>4</sup>	Creatine supplementation associated with resistance training does not alter renal and hepatic functions	23.0 ± 3.2* 24.3 ± 4.9	Creatine monohydrate	20 g/d divided into 4 times daily for 7 d and 0.03 g/kg body weight/day of creatine monohydrate for 7 wk	8 wk	DO not affect kidney function	Rev Bras Med Esporte
9	Carvalho et al. <sup>4</sup>	Creatine supplementation associated with resistance training does not alter renal and hepatic functions	23.0 ± 3.2* 25.2 ± 7.4	Creatine monohydrate	20 g/d divided into 4 times daily for 7 d and 5 g/d for 7 wk	8 wk	Do not affect kidney function	Rev Bras Med Esporte
10	Groeneveld et al. <sup>5</sup>	Few adverse effects of long-term creatine supplementation in a placebo-controlled trial	58.4 ± 10.9* 57.7 ± 11.1	Creatine monohydrate	5 g/d 2 times daily	4 wk 8 wk 16 wk 32 wk 48 wk At any time	Do not affect kidney function	Int J Sports Med
11	Gualano et al. <sup>44</sup>	Effects of creatine supplementation on renal function: a randomized, double-blind, placebo-controlled clinical trial	24.6 ± 4.2* 24.2 ± 5.0	Creatine	0.3 g/d/kg of body weight for the first week, and 0.15 g/d/kg of body weight for the next 11 wk	12 wk	Do not affect kidney function	Eur J Appl Physiol
12	Neves et al. <sup>35</sup>	Effect of creatine supplementation on measured glomerular filtration rate in postmenopausal women	57 ± 3* 59 ± 3	Creatine monohydrate	20 g/day for 7 d divided into 4 equal doses, followed by single doses of 5 g/d for the next 11 wk	12 wk	Do not affect kidney function	Appl Physiol Nutr Metab
13	Poortmans et al. <sup>41</sup>	Effect of short-term creatine supplementation on renal responses in men	25.1 ± 2.7	Creatine monohydrate	20 g/d divided into 4 times daily for 5 d	5 d	Do not affect kidney function	Eur J Appl Physiol

\*Placebo group.

**Table 2.** Results of Studies of Creatine Supplementations' Effects ( $n = 4$ ) on Renal Function in Case Studies

No	Author(s)	Title	Supplementation Program (Protocol)			Period in Days and Weeks	Conclusion Regarding Creatine Supplementation	Journal
			Age (y)	Type of Supplement	Daily and Weekly Quantities			
1	Taner et al. <sup>42</sup>	The effects of the recommended dose of creatine monohydrate on kidney function: case report	18	Creatine monohydrate	20 g/d for 5 d and maintenance (1 g/d for the next 6 wk)	5 d and 6 wk	Affects kidney function	Nephrol Dial Transplant
2	Thorsteinsdottir et al. <sup>39</sup>	Acute renal failure in a young weight lifter taking multiple food supplements, including creatine monohydrate: case study	24	Creatine	5 g/d 3 times per week, totaling 15 g/wk	24 wk	Affects kidney function	J Ren Nutr
3	Gualano et al. <sup>36</sup>	Effect of short-term high dose creatine supplementation on measured GFR in a young man with a single kidney: case report	20	Creatine monohydrate	20 g/d for 5 d divided into 4 equal doses, followed by single doses of 5 g/d for the next 30 ds	5 d and 4 wk	Do not affect kidney function	Am J Kidney Dis
4	Barisic et al. <sup>43</sup>	Effects of oral creatine supplementation in a patient with MELAS phenotype and associated nephropathy: case report	18	Creatine monohydrate	20 g/d, given in 4 single dosages for 12 d, and followed by a maintenance dosage of 5 g/d	12 d and 112 wk	Affects kidney function	Neuropediatrics

and after 8 weeks. In the first stage, the groups were given 20 g supplements (creatine or a placebo) for 7 days. In the second stage, the CRE1 and PLA groups consumed 0.03 g/kg of creatine or maltodextrin, respectively, while the CRE2 group consumed 5 g/day of creatine. In general, creatine supplementation did not alter plasma urea levels (SMD = 1.10, 95% CI 0.34–1.85,  $P = .004$ ,  $I^2 = 28\%$ ). Sensitivity analyses showed that the urea concentration results were not affected by any particular study. [Figure 4](#) shows the forest plot of urea.

## Discussion

Our systematic review and meta-analysis investigated the effects of creatine supplementation on renal function. Creatine is synthesized in the liver and is not an essential nutrient,<sup>1,2</sup> but creatine supplementation has been shown to be detrimental to renal function.<sup>4,17</sup>

In the longitudinal studies analyzed, creatine supplementation did not lead to renal function damage.<sup>4,5,15,16,34,35,37,38,40,41,44</sup> In the study by Carvalho et al.,<sup>4</sup> some indicators of renal activity remained at baseline, even after creatine supplementation. These results agreed with that of the study by Davani-Davari et al.,<sup>45</sup> indicating that there are no data to prove that the use of creatine supplements causes renal damage. Thus, creatine supplementation for healthy individuals has been shown to be safe and does not alter renal function.

In this systematic review and meta-analysis, the values of creatinine levels, creatinine clearance, and urea were also evaluated. According to Carvalho et al.,<sup>4</sup> creatinine level is an indicator of renal function and elevated levels may be related to renal damage. Creatine supplementation may alter serum creatinine levels and may contribute to a false indicator of renal damage. In the meta-analysis performed in our study, serum creatinine levels did not indicate renal damage following creatine supplementation.

Creatinine levels did not change after creatine supplementation in healthy subjects,<sup>4</sup> bodybuilders,<sup>34</sup> athletes,<sup>16</sup> men and women with type 2 diabetes,<sup>15</sup> and postmenopausal women.<sup>35</sup>

Gualano et al.,<sup>15</sup> who studied individuals with type 2 diabetes, agreed with Neves et al.,<sup>35</sup> who studied postmenopausal women, that creatine supplementation does not impair kidney function. These findings are important since they may lead to new creatine treatment possibilities in the study population.

Creatinine clearance evaluates renal function by estimating the glomerular filtration rate. The studies included in this meta-analysis also demonstrated that the groups supplemented with creatine did not show renal damage since creatine supplementation did not induce a change in the glomerular filtration rate in these studies.<sup>15,16,35</sup>

In addition, urea is synthesized in the liver as a result of protein metabolism and filtered through the kidneys. With decreased renal filtration capacity, an increase in



**Table 3.** Assessment Study Quality Using the PEDro Scale for Randomized Clinical Trials

Items	Robinson et al. <sup>37</sup>	Groeneveld et al. <sup>5</sup>	Cancela et al. <sup>40</sup>	Gualano et al. <sup>44</sup>	Carvalho et al. <sup>4</sup>	Gualano et al. <sup>15</sup>	Neves et al. <sup>35</sup>	Lugaresi et al. <sup>34</sup>
1. Eligibility criteria*		Y		Y		Y	Y	Y
2. Random allocation	Y	Y	Y	Y	Y	Y	Y	Y
3. Concealed allocation						Y		
4. Similar at baseline				Y		Y	Y	Y
5. Blinding subjects	Y	Y	Y	Y	Y	Y	Y	Y
6. Blinding therapists	Y	Y	Y	Y	Y	Y	Y	Y
7. Blinding assessors								
8. Adequate follow-up	Y	Y	Y			Y	Y	
9. Intention to treat analysis	Y		Y					
10. Between-group statistical comparison	Y	Y	Y	Y	Y	Y	Y	Y
11. Point estimate/measure of variability	Y	Y		Y	Y	Y	Y	Y
Score total	7/10	6/10	6/10	6/10	5/10	8/10	7/10	6/10

Y, contemplated item.

\*Item 1 does not contribute to the total score.

**Table 4.** Assessment Study Quality Using the JBI Critical Appraisal for Non-Randomized Experimental Studies

Items	Poortmans et al. <sup>41</sup>	Kreider et al. <sup>16</sup>
1. Is it clear what is the “cause” and what is the “effect”	Y	Y
2. Similar groups		
3. Similar groups in terms of treatments received, other than the intervention	Y	Y
4. Control group	Y	Y
5. Measurements pre and post the intervention/exposure		Y
6. Follow-up complete or differences between groups described and analyzed	Y	N/A
7. Outcomes measured in the same way	Y	Y
8. Outcomes measured in a reliable		Y
9. Appropriate statistical analysis		
Score total	5/9	6/8

JBI, Joanna Briggs Institute; N/A, not applicable; Y, contemplated item.

**Table 5.** Assessment Study Quality Using the JBI Critical Appraisal for Cross-Sectional Studies

Items	Mayhew et al. <sup>38</sup>
1. Eligibility criteria	
2. Subjects and setting characteristics	Y
3. Exposure measured in a valid and reliable	
4. Patients were included based on either a specified diagnosis/definition	Y
5. Confounding factors identified	Y
6. Strategies to deal with confounding factors	Y
7. Outcomes measured in a valid and reliable	
8. Appropriate statistical analysis	
Score total	4/8

JBI, Joanna Briggs Institute; Y, contemplated item.

blood urea may occur. Carvalho et al.<sup>4</sup> did not show changes in urea levels with creatine supplementation and the results of this meta-analysis demonstrated that this indicator of renal damage did not change after the supplementation protocols.<sup>4,5,15,16,34,35</sup>

Creatine supplementation was associated with renal function impairment in the case studies analyzed,<sup>39,42,43</sup> but only the study by Gualano et al.<sup>36</sup> showed no alterations

in renal function. In the study by Taner et al.,<sup>42</sup> the subject was hospitalized with acute renal failure. In this case, the subject was a bodybuilder and supplemented creatine at 20 g/day for 5 days and maintained 1 g/day for the next 6 weeks. The authors concluded that the renal impairment was caused by creatine supplementation, since the subject did not use any other drugs that could have impaired the renal function; however, as there was only 1 patient in this report with no evaluation of the patient's condition prior to the supplementation, the conclusions drawn in this article should be interpreted with caution.

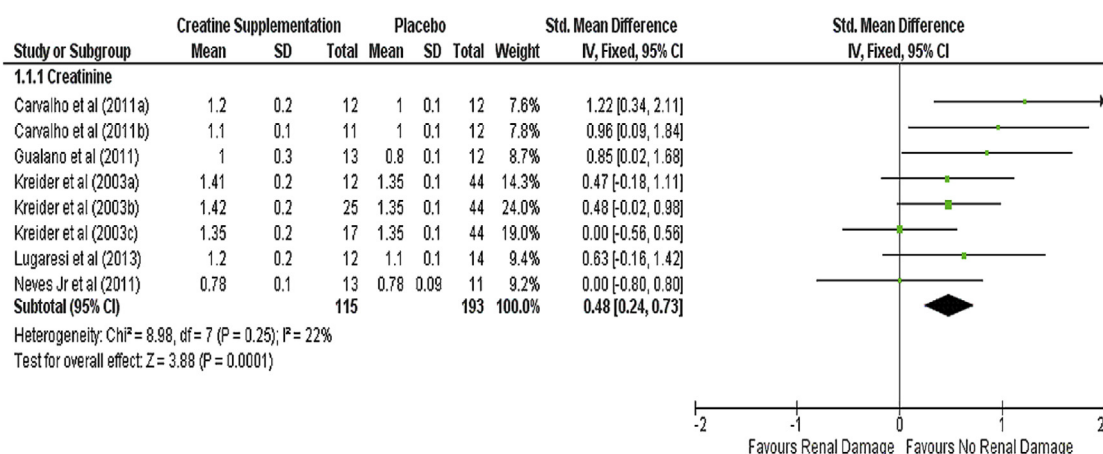
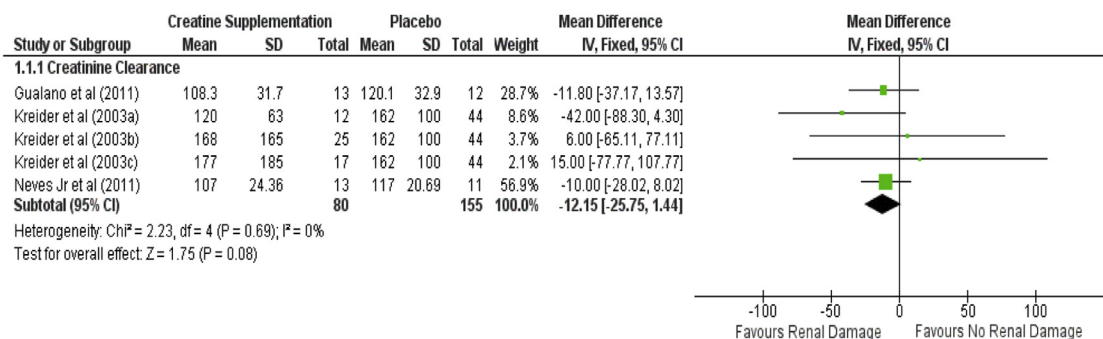
Thorsteinsdottir et al.<sup>39</sup> also reported a case of renal failure in a bodybuilder; however, in addition to creatine supplementation the individual used other types of supplements, which may have contributed to kidney damage. Barisic et al.<sup>43</sup> presented a case study with creatine supplementation in an individual who already had a history of renal damage. However, the use of creatine, despite inducing an increase in creatinine levels, has been shown to be beneficial in such instances. Thus, it is evident that renal damage may not have been caused by creatine.

In the case described by Gualano et al.,<sup>36</sup> the effects of creatine supplementation on renal function were analyzed in a young man with a single kidney and a decreased

**Table 6.** Assessment Study Quality Using the JBI Critical Appraisal Case Reports

Items	Barisic et al. <sup>43</sup>	Thorsteinsdottir et al. <sup>39</sup>	Gualano et al. <sup>36</sup>	Taner et al. <sup>42</sup>
1. Demographic characteristics described	Y	Y	Y	Y
2. Subject history described	Y	Y	Y	Y
3. Pre-intervention clinical condition described	Y	Y	Y	Y
4. Diagnostic tests or assessment methods and results	Y	Y	Y	Y
5. Intervention/treatment described	Y		Y	Y
6. Post-intervention clinical condition described	Y	Y	Y	Y
7. Adverse events	N/A	N/A	N/A	N/A
8. Takeaway lessons	Y	Y	Y	Y
Score total	7/7	6/7	7/7	7/7

JBI, Joanna Briggs Institute; N/A, not applicable; Y, contemplated item.

**Figure 2.** Effects of creatine supplementation on creatinine.**Figure 3.** Effects of creatine supplementation on creatinine clearance.

glomerular filtration rate. No damage was observed in the kidney. Therefore, creatine supplementation has been shown to have no adverse effect on renal function, in this case study. The results of this case agree with that of another study that used creatine supplementation in patients with renal problems.<sup>29</sup>

Other important aspects related to creatine supplementation to consider are the positive health aspects. Creatine appears to contribute to increased strength, maintenance of lean mass, proliferation and differentiation of satellite cells, and induces an increase in the gene expression of

insulin-like growth factor-1. Insulin-like growth factor-1 stimulates the phosphoinositide 3-kinase (PI3K) - Protein Kinase B (AKT) - Mammalian Target of Rapamycin (mTOR) pathway, which is important for protein synthesis.<sup>17</sup>

Based on the above studies, we propose that creatine supplementation is safe, even for long periods of time.

The present review (limited to full-text studies and reliable results) highlights the evaluation and inclusion of high quality studies. Limitations of the study include a lack of inclusion of additional variables related



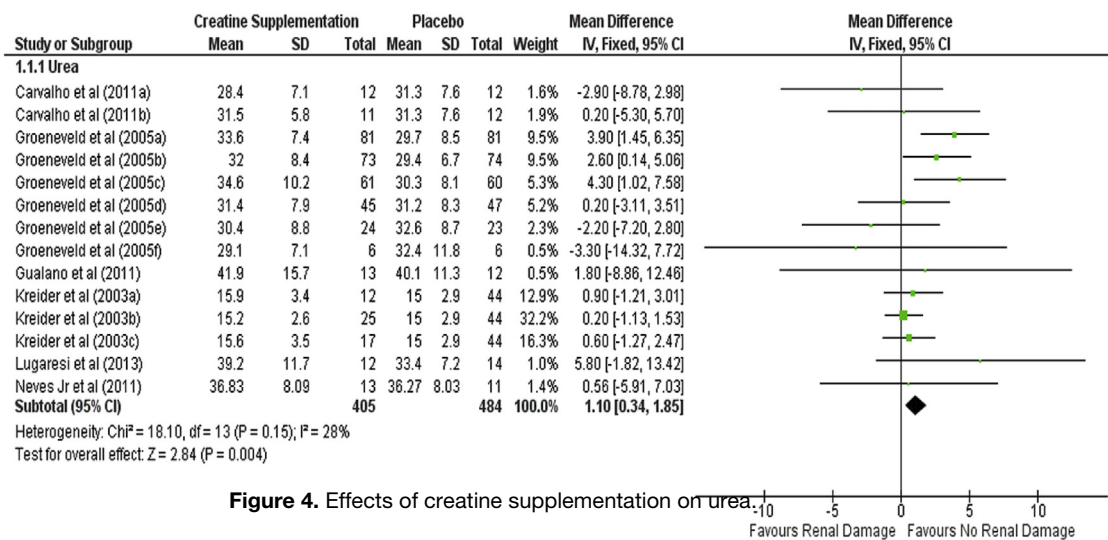


Figure 4. Effects of creatine supplementation on urea.

to renal damage for meta-analysis such as total protein, albumin, and globulin; however, the homogeneity of the data included could not be guaranteed. Therefore, we chose to include only variables with robust and reliable results. Another limitation was the inclusion of studies only published in English and Portuguese; however, the studies were from the most reliable databases.

The objective of this systematic review and meta-analysis is to analyze the studies that verified the effects of creatine supplementation on renal function. We conclude that most of the studies did not demonstrate renal damage with creatine supplementation; therefore, we are of the opinion that creatine supplements are safe for young adults and patients with chronic renal diseases. We suggest that further studies are needed that analyze the effects of creatine supplements in elderly patients with chronic renal failure and/or individuals with other pathologies. In addition, we emphasize the importance of more studies about quality control standards for dietary supplements.

### Practical Application

The findings indicate that creatine supplementation does not induce renal damage. Thus, the creatine supplementation is relevant to clinicians in renal nutrition and/or working with population interested as athletes of strength and bodybuilding.

### Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1053/j.jrn.2019.05.004>.

### References

- Williams MH, Branch JD. Creatine supplementation and exercise performance: an update. *J Am Coll Nutr*. 1998;17:216-234.
- Kreider R. Creatine supplementation: analysis of ergogenic value, medical safety, and concerns. *J Exerc Physiol Online*. 1998;1:7-18.
- Naderi A, Earnest CPR, Wilson MJ, et al. Co-ingestion of nutritional ergogenic aids and high-intensity exercise performance. *Sports Med*. 2016;46:1407-1418.
- Carvalho APPE, Molina GE, Fontana KE. Creatine supplementation associated with resistance training does not alter renal and hepatic functions. *Rev Bras Med Esporte*. 2011;17:237-241.
- Groeneveld GJ, Beijer C, Veldink JH, et al. Few adverse effects of long-term creatine supplementation in a placebo-controlled trial. *Int J Sports Med*. 2005;26:307-313.
- Branch JD. Effect of creatine supplementation on body composition and performance: a meta-analysis. *Int J Sport Nutr Exerc Metab*. 2003;13:198-226.
- Gualano B, Roschel H, Lancha AH Jr, et al. In sickness and in health: the widespread application of creatine supplementation. *Amino Acids*. 2012;43:519-529.
- Gualano B, Rawson ES, Candow DG. Creatine supplementation in the aging population: effects on skeletal muscle, bone and brain. *Amino Acids*. 2016;48:1793-1805.
- Bender A, Klopstock T. Creatine for neuroprotection in neurodegenerative disease: end of story? *Amino Acids*. 2016;48:1929-1940.
- Chilibeck PD, Kaviani M, Candow DG, et al. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. *Open Access J Sports Med*. 2017;8:213-226.
- Heaton LE, Davis JK, Rawson ES, et al. Selected in-season nutritional strategies to enhance recovery for team sport athletes: a practical overview. *Sports Med*. 2017;47:2201-2218.
- Greenhaff P. The nutritional biochemistry of creatine. *J Nutr Biochem*. 1997;11:610-618.
- Kraemer WJ, Volek JS. Creatine supplementation. Its role in human performance. *Clin Sports Med*. 1999;18:651-666.
- Wallimann T, Dolder M, Schlattner U, et al. Some new aspects of creatine kinase (CK): compartmentation, structure, function and regulation for cellular and mitochondrial bioenergetics and physiology. *Biofactors*. 1998;8:229-234.

15. Gualano B, De Salles Painelli V, Roschel H, et al. Creatine supplementation does not impair kidney function in type 2 diabetic patients: a randomized, double-blind, placebo-controlled, clinical trial. *Eur J Appl Physiol*. 2011;111:749-756.
16. Kreider RB, Melton C, Rasmussen CJ, et al. Long-term creatine supplementation does not significantly affect clinical markers of health in athletes. *Mol Cell Biochem*. 2003;244:95-104.
17. Gualano B, Aquesta FM, Ugrinowitsch C, et al. Efeitos da suplementação de creatina sobre força e hipertrofia muscular: atualizações. *Rev Bras Med Esporte*. 2010;16:219-223.
18. Moher D, Liberati A, Tetzlaff J. Preferred reporting items for systematic review and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
19. Baracho NCV, Castro LP, Borges NC, et al. Study of renal and hepatic toxicity in rats supplemented with creatine. *Acta Cir Bras*. 2015;30:313-318.
20. Ellery SJ, Larosa DA, Kett MM, et al. Dietary creatine supplementation during pregnancy: a study on the effects of creatine supplementation on creatine homeostasis and renal excretory function in spiny mice. *Amino Acids*. 2016;48:1819-1830.
21. Farquhar WB, Zamburski EJ. Effects of creatine use on the athlete's kidney. *Curr Sports Med Rep*. 2002;1:103-106.
22. Genc G, Okuyucu A, Meydan BC, et al. Effect of free creatine therapy on cisplatin-induced renal damage. *Ren Fail*. 2014;36:1108-1113.
23. Pritchard NR, Kalra PA. Renal dysfunction accompanying oral creatine supplements. *Lancet*. 1998;351:1252-1253.
24. Gualano B, Ugrinowitsch C, Seguro AC, et al. A suplementação de creatina prejudica a função renal? *Rev Bras Med Esporte*. 2008;14:68-73.
25. Jeremias A, Albirini A, Ziada KM, et al. Prognostic significance of creatine kinase-MB elevation after percutaneous coronary intervention in patients with chronic renal dysfunction. *Am Heart J*. 2002;143:1040-1045.
26. McLaurin MD, Apple FS, Falahati A, et al. Cardiac troponin I and creatine kinase-MB mass to rule out myocardial injury in hospitalized patients with renal insufficiency. *Am J Cardiol*. 1998;82:973-975.
27. Pline KA, Smith CL. The effect of creatine intake on renal function. *Ann Pharmacother*. 2005;39:1093-1096.
28. Taes YE, Delanghe JR, De Vriese AS, et al. Creatine supplementation decreases homocysteine in an animal model of uremia. *Kidney Int*. 2003;64:1331-1337.
29. Taes YE, Delanghe JR, De Bacquer D, et al. Creatine supplementation does not decrease total plasma homocysteine in chronic hemodialysis patients. *Kidney Int*. 2004;66:2422-2428.
30. Taes YE, Marescau B, De Vriese A, et al. Guanidino compounds after creatine supplementation in renal failure patients and their relation to inflammatory status. *Nephrol Dial Transpl*. 2008;23:1330-1335.
31. Williamson L, New D. How the use of creatine supplements can elevate serum creatinine in the absence of underlying kidney pathology. *BMJ Case Rep*. 2014;2014:1-4.
32. Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther*. 2003;83:713-721.
33. Aromataris E, Munn Z, eds. *Joanna Briggs Institute reviewer's manual*. The Joanna Briggs Institute. <https://reviewersmanual.joannabriggs.org/>. Accessed October 1, 2018.
34. Lugaesi R, Leme M, Painelli VS, et al. Does long-term creatine supplementation impair kidney function in resistance-trained individuals consuming a high-protein diet? *J Int Soc Sports Nutr*. 2013;10:1-6.
35. Neves MJr, Gualano B, Roschel H, et al. Effect of creatine supplementation on measured glomerular filtration rate in postmenopausal women. *Appl Physiol Nutr Metab*. 2011;36:419-422.
36. Gualano B, Ferreira DC, Sapienza MT, et al. Effect of short-term high dose creatine supplementation on measured GFR in a young man with a single kidney: case report. *Am J Kidney Dis*. 2010;55:e7-e9.
37. Robinson TM, Sewell DA, Casey A. Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function. *Br J Sports Med*. 2000;34:284-288.
38. Mayhew DL, Mayhew JL, Ware JS. Effects of long-term creatine supplementation on liver and kidney functions in American college football players. *Int J Sport Nutr Exerc Metab*. 2002;12:453-460.
39. Thorsteinsdottir B, Grande JP, Garovic VD. Acute renal failure in a young weight lifter taking multiple food supplements, including creatine monohydrate. *J Ren Nutr*. 2006;16:341-345.
40. Cancela P, Ohanian C, Cuitiño E, et al. Creatine supplementation does not affect clinical health markers in football players. *Br J Sports Med*. 2008;42:731-735.
41. Poortmans JR, Auquier H, Renaut V, et al. Effect of short-term creatine supplementation on renal responses in men. *Eur J Appl Physiol Occup Physiol*. 1997;76:566-567.
42. Taner B, Aysim O, Abdulkadir U. The effects of the recommended dose of creatine monohydrate on kidney function: case report. *NDT Plus*. 2011;4:23-24.
43. Barisic N, Bernert G, Ipsiroglu O, et al. Effects of oral creatine supplementation in a patient with MELAS phenotype and associated nephropathy. *Neuropediatrics*. 2002;33:157-161.
44. Gualano B, Ugrinowitsch C, Novaes RB, et al. Effects of creatine supplementation on renal function: a randomized, double-blind, placebo-controlled clinical trial. *Eur J Appl Physiol*. 2008;103:33-40.
45. Davani-Davari D, Karimzadeh I, Ezzatzadegan-Jahromi S, et al. Potential adverse effects of creatine supplement on the kidney in athletes and body-builders. *Iran J Kidney Dis*. 2018;12:253-260.