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CREATINE USE IN SPORTS: SAFETY AND MECHANISMS OF ACTION

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ABSTRACT

Background: Creatine was first isolated from muscle in 1832 and now is a globally popular ergogenic supplement, valued at USD 1.11 billion in 2024 and projected to reach USD 4.21 billion by 2030. It functions as a rapidly mobilizable energy reserve via the phosphocreatine system and modulates Ca^{2+} handling in muscle cells.
Aim: This study present the current knowledge on creatine supplementation, its prevalence, mechanisms of action, effects on performance and muscle growth and safety profile.
Material and methods: A literature review of studies published in the PubMed and Google Scholar databases was conducted, analysing clinical trials, meta-analyses, and systematic reviews concerning creatine metabolism, dosing strategies, performance outcomes (anaerobic, strength, aerobic), hypertrophy and adverse effects.
Results: Creatine supplementation improves short-burst efforts and strength, however moderately enhances and even can decrease endurance. Creatine also has anabolic properties and can improve gains in muscle mass. Dosing regimens reliably elevate intramuscular stores within days (loading) or weeks (daily use). Side effects are generally conducted to transient water retention and gastrointestinal symptoms, with no evidence of renal or hepatic harm.
Conclusions: Creatine is a safe, well-researched supplement that can enhance anaerobic capacity, muscular strength, and hypertrophy when used in appropriate dosing protocols. Its benefits for prolonged aerobic exercise are modest, but users should expect temporary weight gain, that can decrease endurance.

KEYWORDS

Creatine, Ergogenic Supplement, Phosphocreatine, Anaerobic Performance, Muscle Strength

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1. Introduction

Creatine is one of the popular ergogenic supplements among athletes (Kreider et al., 2017). In 1832, French chemist Michel-Eugène Chevreul first discovered a new muscle-derived compound, which he named "creatine" (Balsom et al., 1994). Fifteen years later, Justus von Liebig, using more advanced analytical techniques, confirmed that creatine is a constant component of mammalian muscle and noted that wild animals can have up to ten times more creatine than domesticated animals, suggesting a link between its accumulation and muscle activity (Balsom et al., 1994). At the same time, Hermann von Heintz and Max von Pettenkofer detected a chemical substance related to creatine in urine; Liebig later named this "creatinine," and conducted research that showed a link between creatinine levels and muscle mass, supporting the idea that creatinine derives from the breakdown of muscle-stored creatine (Balsom et al., 1994). Creatine supplementation entered the mainstream after the 1992 Olympic Games in Barcelona, when several British gold medallists credited creatine with enhancing their performance (Butts et al., 2018). Since then, the global market for creatine supplements has developed rapidly, mainly due to increasing interest and the prevailing fashion for healthy lifestyles, sports, and supplementation; as a result, in 2024 this market was valued at approximately USD 1.11 billion, and it is assumed to reach USD 4.21 billion by 2030 (Creatine Supplements Market Size | Industry Report, 2030, n.d.). This study aims to outline the current understanding of creatine supplementation: its prevalence of intake, underlying physiological mechanisms, effects on physical performance, and potential adverse effects.

2. Research materials and methods

A review of the literature available in the PubMed and Google Scholar databases was carried out, focusing on clinical trials, meta-analyses, and systematic reviews related to creatine consumption, its physiological mechanisms, impact on physical performance, and potential adverse effects. To specifically evaluate the effect of creatine on exercise performance, the search strategy included keywords such as "creatine, metabolism, endurance, muscle growth, side effects, supplementation."

3. Research results

3.1. Creatine

3.1.1. Synthesis and mechanism of action

Creatine is an amino acid derivative, naturally occurring in the human body, that can be found in skeletal muscle but also in small quantities in the brain, liver, kidney, and testes (Greenhaff, 1997). Creatine synthesis consists of two stages that take place mainly in the kidney and liver. In the first stage, which occurs in the kidney, the AGAT enzyme transfers an amidino group from arginine to glycine; this reaction forms guanidinoacetate (GAA) as the main product and ornithine as a by-product (Figure 1). After the first stage, GAA is transported through the blood to the liver, where, during the second phase, the enzyme GAMT transforms GAA into creatine as the main product and S-adenosylhomocysteine as a by-product (Brosnan et al., 2011) (Figure 1).

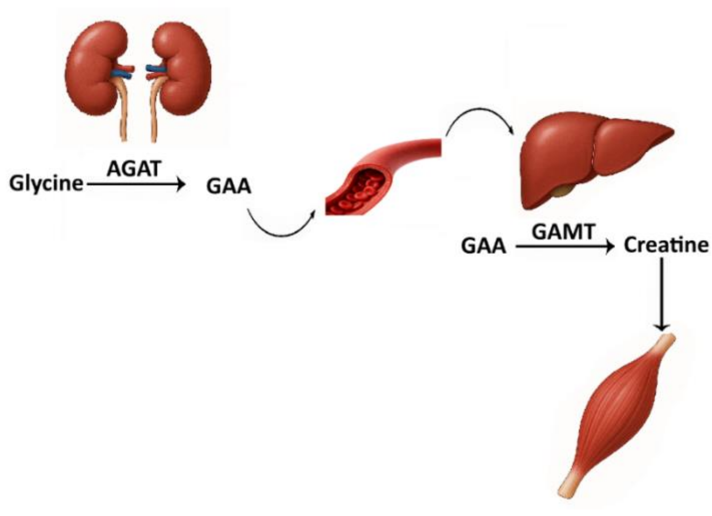

Fig. 1. *Creatine synthesis*

After creatine synthesis, it is mainly stored in the skeletal and heart muscle, and in smaller quantities in the brain and testes; to fulfill its role—serving as a storage for a quickly and easily accessible energy reserve capable of regenerating ATP—creatine has to be transformed into phosphocreatine (PCr) by the enzyme creatine kinase, which uses a phosphate group provided by adenosine triphosphate (ATP). During intense physical exertion, creatine kinase catalyses the reversible transfer of the phosphate group from PCr back to ADP to replenish ATP and restore creatine levels in skeletal muscle (Negro et al., 2019) (Figure 2).

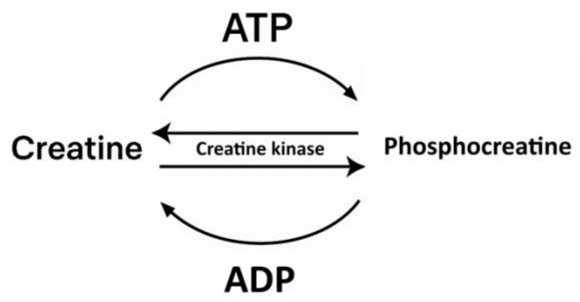

Fig. 2. *Phosphocreatine and creatine cycle*

3.1.2. Metabolism and excretion

Creatine and phosphocreatine nonenzymatically convert into creatinine at a rate of about 2 g per day and are primarily eliminated via renal excretion, and since virtually all creatinine originates from creatine, increasing muscle creatine stores leads to higher blood creatinine levels, indicating its site of formation. Creatine elimination thus occurs through three main mechanisms: irreversible transport into muscle tissue, conversion to creatinine, and renal excretion (Persky et al., 2003). The most significant of these is believed to be the transport into muscle, particularly into fast-twitch fibers (Demant & Rhodes, 1999). Although conversion to creatinine and renal excretion play a comparatively smaller role, creatine clearance is relatively low, mainly due to its reabsorption in the kidneys, but increases when high doses (around 20 g/day) are consumed, significantly enhancing urinary creatine excretion (Persky et al., 2003).

3.2. The effects of creatine on enhancing physical activity performance

Many studies have demonstrated that creatine supplementation has a positive effect on exercise performance (Kreider et al., 2017; Wu et al., 2022). These investigations illustrate the varied effects of creatine depending on the protocols employed, the metabolic differences inherent to each discipline and the different supplementation regimens applied (Cooper et al., 2012; Wu et al., 2022).

3.2.1. Impact of creatine supplementation on primarily anaerobic exercise performance

A meta-analysis has identified an enhancing effect of creatine supplementation on largely anaerobic performance (Mielgo-Ayuso et al., 2019). This advantage during physical exercise potentially stems from increased activity of the sarcoplasmic reticulum Ca^{2+}-ATPase, which intensifies calcium sequestration to the muscle cell calcium store and allows cells to enhance the rate of force production due to the release of actomyosin bonds (Cooper et al., 2012). In an animal research model, the involvement of phosphocreatine and creatine kinase in calcium management showed that ATP regenerated locally from phosphocreatine can sustain a high rate of Ca^{2+} uptake from the cytosol into the sarcoplasmic reticulum. Moreover, it was noticed that elimination of phosphocreatine markedly slows down the accumulation of Ca^{2+} within the sarcoplasmic reticulum, leading to a decrease in the peak of subsequent calcium release, resulting in weaker contractile force (Duke & Steele, 1999)

3.2.2. Performance benefits of creatine in the Wingate Anaerobic Test

The Wingate Anaerobic Test (WAT) assesses anaerobic performance by evaluating the capacity of the ATP–phosphocreatine system and anaerobic glycolysis by requiring the subject to perform a 30-second all-out sprint against a fixed, maximal resistance (Castañeda-Babarro, 2021). The energy demand of muscles during exercise lasting up to 30 seconds is considered to be met mainly by phosphocreatine, which is why the effect of supplementation should be noticeable (Branch, 2003). Main results are: Peak Power, which is the highest mechanical output; Mean Power, indicating the average power output over the 30 seconds; and the Fatigue Index, which reflects the decline in power throughout the effort. Since the introduction of WAT, it has become the gold standard for anaerobic performance assessment, giving rise to numerous variations of this test (Castañeda-Babarro, 2021). In the current meta-analysis, authors collected and reviewed randomized, double-blind trials examining the effects of creatine supplementation on the physical performance of soccer players; a total of 168 athletes (118 men and 50 women) aged between 15 and 30 years were included in the analysis. In most studies, creatine was implemented by a loading dose of 20–30 g of creatine per day (divided into 3–4 doses) for 6–7 days followed by a maintenance dose of 5 g per day for up to nine weeks, while alternative protocols used a daily dose of 3 mg of creatine per kilogram of body weight for 14 days (Mielgo-Ayuso et al., 2019). Compared to placebo, the creatine group elicited a substantial and statistically significant enhancement in anaerobic performance indicated by the Wingate test, with a pooled standardized mean difference of 2.26 (95 % CI, 1.40–3.11), indicating that participants receiving creatine increased their peak and mean anaerobic power by more than two standard deviations relative to placebo—and this large-magnitude effect remained highly significant ($p < 0.001$) despite moderate between-study heterogeneity ($I^2 = 72$ %) (Mielgo-Ayuso et al., 2019). Collectively, these results demonstrate that creatine supplementation augments short-burst anaerobic performance in Wingate cycling protocols.

3.2.3. Effects of Creatine on Lower-Limb Strength

In another meta-analysis examining the effects of creatine supplementation on lower-limb muscular performance during high-intensity efforts of up to three minutes, dependent (pre- vs. post-supplementation) data from the same participants were compared (Lanhers et al., 2015). It is considered that the energy demand of muscles during physical exercise lasting up to 150 seconds is met mainly by phosphocreatine and anaerobic glycolysis, which is why the effect of supplementation should be noticeable (Branch, 2003). Researchers indicate that creatine supplementation significantly improved muscle strength in pre- and post-supplementation comparisons of dependent data in the lower limbs, especially in the quadriceps, as evidenced by an increase in maximal squat load with an effect size of 0.390 (95 % CI: 0.099–0.682; $p = 0.009$) and improved performance in a squat jump test with an effect size of 0.455 (95 % CI: 0.146–0.765; $p = 0.004$) (Lanhers et al., 2015). Also in the same meta-analysis, creatine supplementation showed a small, but statistically significant, improvement in lower-limb strength compared with placebo, based on independent data (Lanhers et al., 2015). For the one-repetition maximum squat test, the standardized effect size was 0.336 (95 % CI 0.047–0.625; $p = 0.023$). In the leg press test, total weight lifted improved with an effect size of 0.297 (95 % CI 0.098–0.496; $p = 0.003$) (Lanhers et al., 2015). When pooling all assessments targeting the quadriceps—such as squat, leg press, countermovement jump, leg extension, and isokinetic measures—the overall effect size was 0.266 (95 % CI 0.150–0.381; $p < 0.0001$). Expanding to a global analysis of all lower-limb performance tests yielded an effect size of 0.235 (95 % CI 0.125–0.346; $p < 0.0001$), confirming a generalized benefit of creatine on lower-body strength (Lanhers et al., 2015). A stratified analysis within quadriceps-specific measures further demonstrated that creatine most strongly enhanced explosive concentric–eccentric performance: the effect size for squat was 0.319 (95 % CI 0.041–0.597; $p = 0.025$) and for vertical jump was 0.455 (95 % CI 0.146–0.765; $p = 0.004$) (Lanhers et al., 2015). The above results confirm that creatine supplementation has a positive effect on short-duration physical efforts.

3.3. Impact of creatine supplementation on primarily aerobic exercise performance

After the first one to two minutes of transition from rest to continuous work, the ATP necessary for muscle contraction is increasingly supplied by oxidative phosphorylation, while the relative contributions of phosphocreatine (PCr) breakdown and anaerobic glycolysis steadily decline (Branch, 2003; Hargreaves & Spriet, 2020). The proposed mechanism of improving aerobic performance is that creatine in the cytosol accepts ATP exported from the mitochondria and improves the resynthesis of phosphocreatine during recovery periods, potentially enhancing mitochondrial ATP production (Mujika & Padilla, 1997). Creatine is well established for its positive effects on short-duration resistance exercise; however, its influence on longer endurance efforts has also been the subject of investigation (Branch, 2003). Tasks lasting more than 150 seconds derive most of the energy required for their execution by oxidative phosphorylation, and a recent meta-analysis compared performance outcomes in exercises exceeding this threshold between creatine-supplemented and control groups (Branch, 2003). This analysis included various disciplines, including bicycle ergometry, kayaking, sprint running, rowing, and swimming (Branch, 2003). Across 69 effect sizes, the mean improvement was small but statistically significant (ES = 0.20 ± 0.07; 95 % CI 0.06–0.34), indicating an average increase of 2.7 ± 1.2 %, based on measures of heart rate (HR), exercise duration (time), total work performed (J), power output (W) and oxygen consumption (VO_2) (Branch, 2003). Heart rate responses also demonstrated a small but statistically significant reduction (ES = 0.65 ± 0.09; 95 % CI 0.41–0.90), about 4.5 ± 0.8 bpm (Branch, 2003). The proposed mechanism is that even a small enhancement in phosphocreatine stores may increase performance in the initial oxidative phase, particularly during steady-state activities such as cycle ergometry, where the workload is relatively constant (Hargreaves & Spriet, 2020). When exercise duration extends, ATP production shifts towards oxidative phosphorylation and the contribution of the ATP–PCr system decreases, causing the ergogenic effect of creatine to dissipate (Hargreaves & Spriet, 2020). However, creatine supplementation is not considered an optimal strategy for improving outcomes in mainly aerobic prolonged endurance disciplines, such as running or swimming (Branch, 2003). While it may offer a slight performance increase in stationary cycling—approximately a 2–5 % increase in power output—its practical significance in typical endurance training is very limited and often undetectable without specialized measurement in a controlled environment (Branch, 2003). In another meta-analysis, participants who underwent a 6-day creatine loading protocol presented a statistically significant gain in body weight (from 73.5 ± 2.3 kg to 74.4 ± 2.3 kg), while the placebo group did not show any significant change (73.6 ± 3.3 kg to 73.5 ± 3.2 kg). Potentially, increased body mass is associated with a substantial decrease in performance; their average 6 km run time increased significantly by 0.43 min (from 23.36 to 23.79 min), and their post-run blood lactate concentration also increased (from 15.3 to 17.2 mmol/L), indicating that the extra weight from creatine loading has a negative effect on running efficiency (BALSOM et al., 1993)

3.4. Muscle growth

In a study conducted among gym members, supplementation in sport was most frequently used to increase muscle mass, with 55.7 % of respondents citing this goal, and creatine was consumed by 49.5 % of the men attending the gym (Ruano & Teixeira, 2020). In a separate meta-analysis investigating the impact of creatine supplementation on muscle tissue assessed via direct imaging diagnostics capable of evaluating regional hypertrophy, researchers employed magnetic resonance imaging, computed tomography, and ultrasonography. Adults participated in at least six weeks of resistance training combined with either creatine or placebo, with muscle growth measured in predefined regions. The analysis showed that participants who underwent creatine supplementation achieved greater muscle gains in the elbow and knee flexor and extensor musacle groups than the control group without supplementation (pooled SMD = 0.11; 95 % CrI: −0.02 to 0.25; posterior P(SMD > 0) = 0.961), indicating a small but statistically significant anabolic effect on regional muscle hypertrophy (Burke et al., 2023). In another clinical trial, researchers examined the effect of creatine supplementation on hypertrophy in specific muscle groups via dual-energy X-ray absorptiometry (DXA) scans to detect changes in muscle mass (Nunes et al., 2017). Participants went through a seven-day loading phase, where they took four daily doses of 0.3 g/kg of creatine, which was followed by a seven-week maintenance phase with a single daily dose of 0.03 g/kg. During the supplementation period, they underwent eight weeks of resistance training (Nunes et al., 2017). Compared with placebo, the creatine-supplemented group experienced a statistically significant higher 7.1 ± 2.9 % increase in upper-limb lean mass (effect size = 0.61; $p < 0.001$), compared to a 3.2 ± 2.1 % increase in lower-limb lean mass (effect size = 0.34; $p < 0.001$); moreover, those increases in both regions were higher than in the placebo group (Nunes et al., 2017). Researchers propose that this effect is due to a higher accumulation of creatine in the muscles of the upper limbs, which are characterized by a higher proportion of fast-twitch fibers that absorb creatine more efficiently, resulting in increased creatine retention and a more pronounced anabolic effect in that muscle group (Nunes et al., 2017).

3.5. Safety of creatine supplementation

Creatine is considered a safe ergogenic; it has been extensively studied, as confirmed by numerous short- and long-term trials (Kreider et al., 2017). Historically, the main concerns regarding creatine use focused on its potential impact on liver and kidney function (Kreider et al., 2017; Poortmans & Francaux, 2000).

3.5.1. Impact on kidney function

In the past, concerns were raised about creatine supplementation primarily because studies reported increases in urinary creatinine excretion (Kreider et al., 2017). A review comparing numerous studies on the effects of creatine on renal function concluded that the observed increase in urinary creatine excretion is attributable to the muscles' inability to absorb approximately 40–60 % of the ingested dose, with the excess subsequently eliminated in the urine (Poortmans & Francaux, 2000). Furthermore, research has shown that main renal function parameters—such as creatinine clearance, urea clearance, and albumin clearance—do not differ significantly between creatine-supplemented and control groups (Poortmans & Francaux, 2000). Likewise, a meta-analysis found no impact of creatine supplementation on blood creatinine levels, creatinine clearance, or urea concentration (de Souza e Silva et al., 2019).

3.5.2. Impact on liver function

A clinical trial examining dietary creatine intake from regular foods found that the probability of developing liver fibrosis, cirrhosis, or hepatic steatosis in the U.S. population aged 12 and older was comparable between the creatine and placebo groups, indicating the safety of creatine supplementation (Todorovic et al., 2023).

3.5.3. Impact on body mass gain

The only consistently reported side effect of creatine supplementation described in the literature is weight gain (Kreider et al., 2017). In a clinical trial, a statistically significant increase was observed after four weeks of supplementation in total body weight (from 90.42 ± 14.74 to 92.12 ± 15.19 kg) and total body water content (from 53.77 ± 1.75 to 57.15 ± 2.01 L), while no significant changes were found in body fat percentage or daily caloric intake in that group, nor were any significant changes observed in the placebo group (Kutz & Gunter, 2003). Total body mass increase is mainly due to intracellular water retention, which is linked to creatine's osmotic properties and the main location where it is stored (Gualano et al., 2016; Kutz & Gunter, 2003; Negro et al., 2019). This effect occurs mainly during short- to mid-term creatine supplementation, especially the loading phase, whereas long-term use drives weight gain mainly through muscle tissue growth rather than fluid accumulation (Antonio et al., 2021).

3.6. What supplementation protocol should be used?

3.6.1. Loading phase

Creatine "loading" typically involves taking 20–25 g of creatine per day for 5–7 days; this dose should be split into several smaller doses (for example, four or five 5 g servings throughout the day). It is recommended to use single doses of less than 10 g during the loading phase in order to avoid gastrointestinal symptoms, such as diarrhoea. This initial phase is followed by a "maintenance" regimen, which involves taking about 3–5 g of creatine once daily (Kreider et al., 2017).

3.6.2. Daily supplementation without a loading phase

This involves daily use of a dose of 3–5 g per day; saturation is typically achieved after approximately four weeks, which helps reduce the likelihood of side effects such as diarrhoea or weight gain due to the loading phase (Kreider et al., 2017).

4. Discussion

This current literature review suggests that creatine supplementation reliably increases short-duration anaerobic efforts by serving as a storage for a quickly and easily accessible energy reserve capable of regenerating ATP, especially important during short-term exercise. Studies suggest that elevated phosphocreatine availability also optimizes sarcoplasmic-reticulum Ca^{2+} handling and augments contractile force. The positive ergogenic effect of creatine supplementation, however, depends on the discipline for which it is used. During long-term endurance exercise, creatine exhibits only modest enhancement in controlled environments or no influence at all. In other studies, creatine has even shown a negative influence on prolonged physical exercise, mainly due to increased total body mass, which in these disciplines is known to be undesirable. However creatine, due to its anabolic properties can significantly increase muscle mass gain, especially at upper limb. Taking into account that creatine is stored intracellularly (mainly in skeletal muscles) and its osmotic properties, at the beginning of supplementation it can increase water retention and, at the same time, body mass. Overall, creatine is considered a safe and well-researched supplement, but at high doses it can increase water retention and cause gastrointestinal symptoms, such as diarrhoea.

5. Conclusions

Creatine is considered as safe supplementation that can significantly enhances anaerobic capacity, muscular strength and muscle mass gains. During supplementation should be used appropriate protocols, depending on the symptoms experienced. Safety profiles show no adverse renal or hepatic outcomes; transient gastrointestinal symptoms and early water weight are the primary side effects related to hight doses. Further studies should elucidate long-term effects across diverse athletic populations, optimize dosing schedules for endurance disciplines, and investigate molecular responses in different muscle fiber types.

Disclosure

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Writing – review and editing: Adam Rafałowicz, Urszula Justyna Wojciechowska, Paweł Radkowski, Magdalena Rafałowicz, Łukasz Grabarczyk

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