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Creatine as a Compound and Supplement: Metabolism, Mechanism of Action, Effects, and Adverse Effects - A Review

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ABSTRACT

Introduction: In a world of ever-evolving athletic competition and scientific advancement, the pursuit of optimal supplement applications to achieve peak performance should come as no surprise. One of the most popular and extensively researched supplements is creatine, for which numerous studies over many years have supported its positive impact on athletic and strength performance, as well as muscle and strength gains. Over time, attention has also shifted toward exploring creatine's potential applications in other areas of medicine, as well as its use across various populations and age groups. Currently, the significance and importance of creatine are being highlighted not only in the context of its use across various sports disciplines, but also for its demonstrated beneficial effects in a range of medical conditions. These include improved prognosis in osteoporosis, osteopenia, and age-related sarcopenia, as well as its neuroprotective effects—for example, in brain injuries, ischemic diseases, diabetes, and other related conditions. Creatine, a compound naturally present in the human body—both endogenously synthesized and obtained through dietary intake—can also be effectively consumed as a supplement, exhibiting excellent bioavailability that results in tissue saturation, primarily within muscle tissue. Due to its well-documented positive effects, and being recognized as a safe supplement with virtually no significant adverse or health-compromising effects, creatine continues to grow in popularity. Given its approval for use by organizations such as the International Olympic Committee and the endorsement of the International Society of Sports Nutrition (ISSN), it is well on its way to becoming a leading supplement on the market. It is increasingly used not only by professional and amateur athletes, but also by a wide range of other populations across various age groups. Additionally, the concept of lifelong creatine supplementation is being increasingly discussed as a potentially beneficial strategy.

Materials and methods: The analysis is based on a review on studies found in PubMed and Scholarship. Keywords used were: „creatine supplementation", „creatine monohydrate", „creatine supplementation muscle", creatine neurodegenerative", „creatine absorption", „creatine kinase".

Aim of the study: The aim of this paper is to review the available medical literature and the current state of knowledge regarding creatine as a compound, its metabolism, as well as its significance as a supplement in enhancing performance and athletic achievements. Additionally, the paper explores its non-athletic applications and potential uses, taking into account the risks associated with supplementation, possible adverse effects, and optimal strategies for selecting appropriate dosages.

Conclusions: Creatine is a health-safe supplement, with studies demonstrating a near absence of significant adverse effects regardless of age group. It undergoes non-enzymatic conversion into creatinine, which is excreted in the urine via the kidneys without causing renal damage. The positive effects of creatine on athletic performance, endurance, muscle hypertrophy, strength gains, improved recovery between training sets, and increases in lean body mass are well-established and indisputable based on decades of research. In addition to its applications in sports, there is growing literature indicating creatine's beneficial effects in various medical conditions, including diabetes, ischemic heart disease, cerebral ischemia, traumatic brain injury, osteopenia, osteoporosis, and age-related sarcopenia (particularly when combined with resistance training). It is legal, considered safe by all available evidence, and according to some experts—even recommended.

Keywords: creatine, creatine supplementation, creatine monohydrate, creatine supplementation in eldery patients, creatine supplementation in children and adolescents, creatine adverse effects, creatine renal failure, creatine metabolysm, creatine in sport

Introduction

The approach to resistance training has evolved over the years and is still evolving day after day. With the new discoveries, scientific knowledge, and the pursuit of maximizing results, individuals are increasingly modifying their strength training based on evidence-based sources to achieve optimal outcomes. A crucial component of training is often appropriate supplementation, which plays a significant role in enhancing post-exercise recovery, promoting muscle hypertrophy, and increasing muscular strength. Among the most commonly used supplements in resistance training with scientifically proven efficacy are creatine, protein, caffeine, beta-alanine, and nitric oxide (NO) precursors (1). In this review paper, we will focus exclusively on one of the aforementioned supplements—creatine. Among individuals engaged in sports, whether recreational or professional athletes, creatine supplementation has been reported by a significant percentage of respondents, ranging from approximately 9% to 46% (2). This indicates that, on average, every fourth or third athlete has used this supplement, either for a short or extended duration. This observation highlights the necessity and importance of systematic, evidence-based knowledge regarding the safety and efficacy of creatine—not only in enhancing strength performance and athletic achievements but also in its potential applications in various medical conditions. The following review paper discusses the current and past state of knowledge regarding the effects of creatine supplementation on the human body. It will examine its reported impacts in the literature, including its role in muscle hypertrophy, recovery, and strength performance enhancement. Additionally, we will explore less frequently addressed but equally relevant topics, such as its effects on brain function and memory improvement, its potential applications in neurodegenerative diseases, ischaemia, aging and aging-related conditions.

Metabolic role, synthesis, degradation

Creatine (α-methyl-guanidine-acetic acid) is a naturally occurring compound in the human body, synthesized from the amino acids methionine, arginine, and glycine. This process takes place in the kidneys, liver, and pancreas and may be less intensive depending on creatine intake, particularly when exogenous supplementation is introduced (3). The amount of creatine produced and stored in the human body is also influenced by dietary intake (4). Creatine is primarily found in animal-derived foods, such as fish and meat, particularly red meat (5). The vast majority of creatine in the human body—approximately 95%—is localized in skeletal muscles (6). In addition to skeletal muscles, tissues with the highest levels of creatine and creatinine include the heart, sperm cells, and retinal photoreceptor cells. Lower concentrations are found in macrophages, endothelial cells, the brain, adipose tissue, intestines, seminal vesicles, spleen, kidneys, liver, lungs, red blood cells, and serum (7–13). Increased oral creatine intake, whether through supplementation or dietary sources, leads to a higher accumulation of creatine in muscle tissue (4). In tissues where creatine is present, creatine kinase (CK) is also found, specifically in the form of tissue-specific isoenzymes, such as MM-CK in muscles and BB-CK in the brain. Creatine kinase isoenzymes are composed of dimers of cytosolic enzyme subunits that are tissue-, species-, and development-specific. Regardless of the tissue in which it is expressed, creatine kinase consistently catalyzes the transfer of the γ-phosphate group from ATP to the guanidine group of creatine (Cr), resulting in the formation of phosphocreatine (PCr) and ADP (14).

Approximately two-thirds of the creatine present in muscles is stored in the form of phosphocreatine (PCr), while the remaining portion exists as free creatine (Cr) (2). Due to the reversible nature of the reaction catalyzed by creatine kinase, phosphocreatine plays a crucial role in tissues with high and fluctuating energy demands, where it serves as a key compound in maintaining ATP availability by acting as a donor of high-energy phosphate groups, thereby supporting rapid ATP regeneration. This mechanism enables ATP regeneration in tissues such as fast-twitch skeletal muscles, where ATP is rapidly consumed through hydrolysis during short-term, high-intensity exertion. Fast-twitch skeletal muscles contain creatine kinase (CK) with significant enzymatic activity, allowing ADP and ATP levels to remain nearly constant. In other words, the reaction catalyzed by creatine kinase operates in a state close to enzymatic equilibrium. In contrast, cardiac striated muscles, slow-twitch skeletal muscles, sperm cells, and other energy-demanding tissues require a continuous supply of high-energy phosphate groups, such as those derived from phosphocreatine, to maintain proper function. It is postulated that the energy supply to these tissues occurs in a cyclic, shuttle-like manner. Phosphate groups from ATP are transferred from the mitochondrial matrix to the intermembrane space via mitochondrial creatine kinase (Mi-CK), resulting in the formation of phosphocreatine (PCr) and ADP. ADP is then transported back into the mitochondrial matrix, where it undergoes rephosphorylation to ATP. Meanwhile, phosphocreatine can diffuse to sites of active ATP consumption within the cell. In these locations, tissue-specific cytosolic isoenzymes of creatine kinase regenerate ATP from phosphocreatine. The creatine (Cr) produced in this reaction subsequently diffuses back into the mitochondria, completing the cycle and ensuring a continuous supply of energy in the form of high-energy phosphate groups.(14).

The pool of creatine and phosphocreatine in the body is not constant. According to in vitro studies, the daily turnover of creatine and phosphocreatine represents a nearly fixed fraction of the total stored in the body. Specifically, approximately 1.1% of creatine and 2.6% of phosphocreatine undergo transformation per day. As a model example to illustrate this process, a 70 kg male with a total body creatine pool of approximately 120 g would undergo a daily conversion of around 2 grams of creatine into creatinine (Crn) (5,15). Since both the hydrolytic breakdown of phosphocreatine and the cyclization of creatine into creatinine occur through non-enzymatic processes, and their common end product is creatinine (Crn), these transformations can be considered as a combined pool undergoing conversion and subsequent excretion in the urine (4,16,17). As a result of these non-enzymatic transformations leading to the excretion of creatinine in the urine, the body's creatine levels would gradually decrease without dietary intake and endogenous synthesis, which occurs primarily in the liver and kidneys. The synthesis of creatine involves the conversion of arginine and glycine into guanidinoacetate (GAA) by the enzyme arginine:glycine amidinotransferase (AGAT), which subsequently undergoes methylation with the use of S-adenosylmethionine (SAM) by guanidinoacetate N-methyltransferase (GAMT) to form creatine (18).

Since the most common dietary sources of creatine are animal-derived products, such as meat—particularly red meat—and fish, and the average diet of a meat-consuming individual provides approximately 1 g of creatine per day (5), it is not surprising that individuals following a vegetarian or vegan diet tend to have lower intramuscular creatine stores. Vegetarians and vegans also exhibit greater increases in intramuscular creatine concentrations in response to exogenous creatine supplementation (19–21). Exogenous creatine supplementation reduces the body's endogenous creatine synthesis; however, after discontinuation of supplementation, endogenous synthesis returns to its baseline level observed prior to supplementation (3). Since the rate of the non-enzymatic conversion of creatine to creatinine is nearly constant, and more than 90% of the body's creatine pool is located in muscle tissue, the measurement of daily urinary creatinine (Crn) excretion can be used as an indicator of total muscle mass in humans (22,23). For this reason, athletes and individuals who exercise regularly, possessing greater muscle mass—and consequently higher creatine concentrations in muscle tissue—also experience a higher absolute rate of creatine breakdown and conversion (approximately 2% per day, a nearly constant fraction). As a result, they may require a higher dietary intake or supplementation of creatine, ranging from 5 to 10 grams per day, to maintain optimal and adequate creatine stores in the body (24).

The role in sport

In the context of global sports competition, success or failure is increasingly determined by fractions of a second, daily physical condition, overall athlete well-being, as well as endurance and physiological capabilities. It is therefore unsurprising that athletes seeking peak performance focus on enhancing endurance and maximizing physical potential through all available and legal means. Currently, creatine supplementation enjoys widespread enthusiasm among athletes. This section of the review aims to evaluate the impact of creatine supplementation on athletic performance, its various aspects, and the outcomes achieved.

During high-intensity exercise, particularly of short duration, the muscle's demand for ATP is met by two primary energy sources: first, phosphocreatine, and second, the process of glycolysis. Phosphocreatine serves as the primary source of ATP during exertion lasting approximately the first 10 seconds or less and is subsequently replaced by anaerobic glycolysis, which generates ATP for efforts lasting between approximately 10 and 30 seconds (25). Since prolonged, aerobic physical activities, such as long-distance running, primarily rely on oxidative phosphorylation as the dominant energy-producing process—one that does not directly utilize creatine—no significant improvements in endurance or performance have been observed in such disciplines with creatine supplementation. It appears that the benefits of creatine supplementation diminish as the duration of physical activity increases. (26,27). It is therefore unsurprising that the greatest benefits of creatine supplementation have been observed in athletes engaged in sports that primarily, or at least partially, rely on short, explosive physical efforts, including those performed repeatedly over time or in series—such as intermittent sprints or exertion followed by periods of rest, examples of such disciplines include bodybuilding, basketball, soccer, ski jumping, tennis (studies have shown performance improvements specifically in sprints, which are an integral part of this sport, but not in strength or power output related to racket strokes (28–30)., American football (31) (32), baseball, weightlifting, cycling (studies have demonstrated performance improvements and enhanced outcomes in sprints and acceleration phases.(33,34)) sprinting.and more (35,36). Due to the increase in creatine concentration resulting from supplementation and the subsequent rise in phosphocreatine availability—serving as a source of high-energy phosphate groups for ATP regeneration—there is a reduced reliance on glycolysis during physical exertion.(26) Creatine supplementation enhances performance and power output in repeated sprinting efforts by approximately 5–15%, as well as in single sprint efforts by 1–5%. It also increases power output, total work performed, and muscle contraction strength by approximately 5–15% during resistance training.

Additionally, it promotes strength gains, particularly in high-intensity exercises, and contributes to the increase in lean body mass.(37).

Creatine (Cr) supplementation, leading to an increase in phosphocreatine (PCr) concentration and availability in muscles, may enhance strength performance and athletic achievements across different age groups, including adults, adolescents, and older individuals.(38–40) The benefits of creatine supplementation are observed in both men and women. However, since most available studies on this topic have been conducted predominantly or exclusively on male participants, the precise quantitative and statistical effects of creatine supplementation in women remain an area for further research. Nonetheless, existing studies suggest that, compared to the benefits observed in men, the increase in muscle mass, strength, and hypertrophy in women is not as pronounced.(41–43) One of the proposed reasons for this difference may be that the majority of muscle creatine in the human body is stored in type 2 muscle fibers. Since individuals with a greater proportion (or mass) of these fast-twitch fibers are likely to experience more significant benefits from creatine supplementation—such as improved strength gains and training performance—men, who generally have a higher muscle mass than women, may derive greater benefits from creatine use.(44,45)

Regarding the impact of creatine supplementation on the efficacy of resistance training, available studies indicate that its use in conjunction with strength training results in significantly greater increases in strength parameters and muscle mass compared to training without additional creatine intake (placebo). For example, a meta-analysis conducted by Chilibeck et al. demonstrated that creatine supplementation led to a statistically significant increase in lean body mass and enhanced muscular strength in both the lower and upper limbs, as assessed by leg press and bench press performance tests. (46) Already in 1998, Kreider et al. published a study demonstrating that creatine supplementation (specifically in this 28-day study) resulted in an increase in lean body mass, training volume, and the total weight lifted during bench press, squats, and power cleans.(38)

A similar effect and conclusions were reported in a 2023 systematic review with meta-analysis published by Burke et al. This study also demonstrated superior muscle hypertrophy outcomes (measured using imaging techniques such as magnetic resonance imaging, computed tomography, or ultrasound) in comparison to the placebo group. (47) The aforementioned meta-analysis also highlights that the effects of creatine supplementation are more pronounced in young adults compared to older individuals.(47). This is consistent with the review of randomized trials from 2012 to 2021 published by Shih-Hao Wu et al. Based on an analysis of 16 randomized controlled trials, they concluded that creatine supplementation is most effective for muscle growth in the population of young adults. However, it is essential to emphasize the fundamental role of training in achieving this goal.(48) Creatine supplementation combined with resistance training enhances lean muscle mass growth regardless of the supplementation protocol. Specifically, lean mass gains were greater in the creatine-supplemented groups compared to placebo groups, regardless of whether supplementation was implemented only on training days or as a daily regimen with either lower doses (<5 g/day) or higher doses (>5 g/day). The benefits were observed both with and without a creatine loading phase. The loading phase refers to the short-term intake of high doses of creatine (e.g., >20 g/day for approximately 5–7 days) to rapidly saturate muscle tissue with creatine. A similar supplementation protocol, based on a creatine loading phase followed by maintenance dosing of 0.03–0.06 g/kg/day, was utilized in scientific studies, which observed that the addition of creatine to resistance training resulted in greater improvements in muscle strength, lean body mass, and muscle hypertrophy.(49) Furthermore, they reported a higher increase in intramuscular IGF-1 levels and muscle protein synthesis in the creatine-supplemented group compared to the placebo group. (50) Further details on the most optimal creatine supplementation strategies, including loading phases, will be discussed in later sections of this work. (51) Furthermore, the medical literature includes studies suggesting that creatine not only enhances athletic performance but also reduces muscle damage during training. Chia-Chi Wang et al. published findings indicating that creatine supplementation significantly increased one-repetition maximum (1RM) strength compared to the placebo group ($p < 0.05$). Additionally, post-exercise creatine kinase (CK) activity was significantly lower in the creatine-supplemented group compared to the placebo group ($p < 0.05$), suggesting a protective effect against muscle damage.(52) A study conducted by Volek et al. yielded similar conclusions. Muscle strength and the number of repetitions were greater in the creatine-supplemented group compared to the placebo group, as demonstrated in two exercises: bench press (assessing upper-body muscle strength) and squat jumps (assessing lower-body muscle strength). Additionally, an increase in body mass was observed, with an average gain of 1.4 kg. Furthermore, post-exercise lactate levels were elevated in the creatine-supplemented group, suggesting an enhanced anaerobic metabolic response to training.(53) Creatine supplementation leads to an increase in the total creatine pool, which facilitates the maintenance of high-intensity training by enabling faster ATP regeneration between sets. This, in turn, contributes to improvements in lean body mass, muscular strength, and muscle hypertrophy.(27,54) It is also worth mentioning the findings reported by Saremi et al. in their published study regarding the impact of resistance training combined with creatine supplementation on the levels of myostatin and Growth and Differentiation Factor-Associated

Serum Protein-1 (GASP-1), a regulator that promotes muscle growth. Resistance training alone resulted in an increase in GASP-1 levels and a significant decrease in circulating myostatin. However, when creatine supplementation was combined with training, the reduction in serum myostatin levels was even more pronounced ($p < 0.05$), though no further significant increase in GASP-1 levels was observed.(55) The conclusions drawn in this study, in conjunction with the current understanding of creatine's effects on performance, resistance training quality, and hypertrophy, open avenues for exploring additional mechanisms through which creatine contributes to muscle growth beyond merely enhancing ATP regeneration. The observed effect of creatine supplementation in reducing myostatin levels – a protein responsible for limiting muscle growth—suggests a potential additional pathway by which creatine facilitates greater muscle mass accrual. Confirming this alternative mechanism could further solidify creatine's role as a potent ergogenic aid in muscle hypertrophy.

Bioavailability, absorption, effect on body composition and selection of the most optimal supplementation strategy

When considering the optimal method of creatine supplementation, it is essential to examine the most commonly used supplementation protocols. The loading-phase protocol involves supplementing with 20–25 g of creatine per day for 5–7 days (approximately 0.3 g/kg/day), typically divided into several smaller doses, such as 5 g per serving. (4) A study conducted by Sale et al. concluded that consuming 20 g of creatine daily in smaller doses of 1 g per serving, taken 20 times a day at 30-minute intervals, resulted in lower urinary excretion of creatinine and its metabolites compared to the traditional loading method (e.g., four doses of 5 g per serving). This led to better creatine absorption, greater muscle saturation, and consequently, enhanced supplementation effects. (56) On the other hand, the supplementation protocol without an initial loading phase, involving daily intake of 3-5 g/day, has also been proven effective in studies. However, it should be noted that to achieve similar tissue saturation of creatine as in the loading protocol, a longer supplementation period (over 4 weeks) is required compared to the loading phase. (2,16,57) The choice of an appropriate supplementation strategy may depend on personal preferences, training goals, the time frame for achieving those goals, convenience, or potential side effects associated with each strategy. After discontinuing supplementation, creatine levels return to baseline within approximately 4–6 weeks. (16,58) However, no evidence suggests that they drop below pre-supplementation levels, indicating that creatine supplementation does not irreversibly disrupt endogenous creatine synthesis. (24)

After ingestion, creatine is absorbed from the gastrointestinal tract into the bloodstream and then taken up by tissues, with the largest amount being absorbed by muscle tissue.(59) The peak plasma creatine concentration following oral supplementation occurs approximately 60 minutes after intake.(16) The absorption process into the bloodstream is highly efficient, with an absorption rate of nearly 100%.(4,60,61) Due to creatine's greater stability in environments with a pH lower than 2.5, the gastrointestinal tract provides favorable conditions for maintaining creatine in its unchanged form, ensuring efficient absorption. (59) Creatine is removed from the bloodstream either through its transport to organs or via glomerular filtration in the kidneys.(62) The transport and uptake of creatine into organs are mediated by the creatine transporter type 1 (T1), a protein whose activity is dependent on creatine levels—its activity increases as intracellular creatine concentration decreases. (63)

When it comes to choosing a form of creatine for supplementation, several options are available. The most popular and well-researched form is creatine monohydrate (CM). Other forms include creatine salts such as citrate, phosphate, malate, pyruvate, magnesium creatine, creatine with sodium bicarbonate, anhydrous creatine, effervescent creatine, and ester forms like creatine ethyl ester. (27) Comparative studies of creatine monohydrate, creatine citrate, and creatine pyruvate have shown that pyruvate induces a higher peak creatine concentration than monohydrate and citrate, while maintaining the same absorption rate, elimination time, and time to peak serum concentration. However, this finding is not conclusive, as it remains uncertain whether the observed differences translate into greater muscle creatine saturation and, consequently, enhanced supplementation effects.(64) Additionally, it is worth noting that creatine monohydrate exhibits greater stability compared to its salt forms. (59) Creatine monohydrate, while highly stable in its solid powder form, loses stability in aqueous solutions due to an increased rate of cyclization, converting creatine into creatinine. However, current evidence does not support the notion that other forms of creatine, despite their improved solubility and stability in solutions, provide better tissue saturation, efficiency, or overall effectiveness.(59,65)

Changes in body composition during creatine supplementation most commonly involve an increase in lean body mass and overall body mass.(26) As previously discussed, the increase in lean body mass may be linked to creatine supplementation through several mechanisms. In contrast, the increase in overall body mass may as well be attributed to creatine's hydrophilic nature and osmotic properties, which can lead to an increase in water content, specifically intracellular water. This may explain the observed rise in total body mass during supplementation. (16) However, the medical literature presents varying findings on this matter.

Some studies conclude that creatine increases both total body mass and intracellular water content,(66) while others suggest that it does not significantly affect total body water. (67,68) Additionally, some research indicates that although creatine increases total body water, it does not alter its distribution between intracellular and extracellular compartments. (69) Given these conflicting results, drawing a definitive conclusion remains challenging. However, there is evidence suggesting that creatine supplementation may contribute to an increase in total body mass, overall body water content, and intracellular fluid volume.

Effects, Potential Applications, and Safety of Supplementation in Less Frequently Studied Age Groups: Children, Adolescents, and Older Adults

With the passage of time, an increasing number of scientific studies have examined the effects of creatine supplementation in adolescents. A significant portion of these studies supports its efficacy in this population, reporting minimal or no adverse effects.(70) Tarnopolsky et al. demonstrated that creatine supplementation led to increased lean body mass and grip strength in patients with Duchenne muscular dystrophy.(71) Additionally, Sakellaris et al. found that creatine improved prognosis in pediatric and adolescent patients with traumatic brain injury.(72) It is important to note that all these studies involved rigorous monitoring of participants for potential organ dysfunction, including liver and kidney function and inflammatory markers. No adverse effects of supplementation were reported, nor was there a need to discontinue supplementation due to creatine-related complications. These findings support the safety of creatine use in children and adolescents, particularly those engaged in high-level sports to enhance performance. (65)

In the older adult population, the most promising condition in which creatine supplementation may have a beneficial impact is age-related sarcopenia. This condition increases the risk of falls, injuries, and even mortality.(73) Creatine supplementation may have a beneficial effect in limiting the reduce of muscle mass and improving muscle function and daily performance in older adults. However, it is crucial to emphasize that these effects are not solely due to creatine supplementation but rather its combination with resistance training, which remains the fundamental factor in achieving these outcomes.(74–76) The validity of this theory is supported by research findings. For example, Candow et al. demonstrated that creatine supplementation combined with resistance training reduces muscle and bone mass loss as well as bone mineral resorption.(77) Similarly, studies by Chilibeck et al. indicate that creatine, when paired with resistance training, improves bone mineral density (78); also it decreases bone resorption, and strengthens bones in postmenopausal women (79). A positive effect on increasing lean body mass was not observed in postmenopausal women supplementing with creatine who did not engage in resistance training. Therefore, it cannot be concluded that creatine supplementation alone leads to lean mass gains; rather, its combination with exercise provides the potential for greater increases in lean body mass.(80) As a general conclusion on this matter, it can be stated that, similar to the adult population, older individuals also experience positive effects of creatine supplementation on muscle hypertrophy, increased muscle strength, and lean body mass when combined with regular resistance training. (26,81) There are also studies in the literature suggesting that creatine supplementation may enhance fatigue resistance, neuropsychological performance, and cognitive abilities. (82) A conclusion that can surely be drawn is that the topic of creatine supplementation in younger individuals, including children and adolescents, and older adults, warrants further investigation. Moreover, supplementation itself is at least worth considering in these populations, depending on our targets.

Non-Muscular and Non-Sports Applications and Effects on Other Organs

One of the frequently discussed topics regarding creatine supplementation—beyond its effects on training efficiency, performance, muscle hypertrophy, athletic results etc.—is its impact on brain function. While creatine presence in the brain is primarily determined by its endogenous synthesis, supplementation can increase its storage in this region. (83) However, brain creatine uptake is lower compared to muscle tissue. Studies have reported an average increase of 8.7% in brain creatine levels after four weeks of supplementation with 20 g/day, whereas in muscle tissue, creatine concentrations can rise by approximately 20–40% within 5–7 days with a similar supplementation regimen. (4,84,85) It therefore appears that achieving a significant increase in brain creatine concentration requires a longer supplementation period and/or a higher dosage compared to muscle tissue. (86) Regarding its effects on the nervous system, studies have reported that creatine may help reduce feelings of fatigue (87), including mental fatigue , even in conditions of sleep deprivation (88). Additionally, it has been suggested that creatine supplementation can improve memory (21) and cognitive function (89).

Evidence suggests that traumatic brain injuries (TBI) lead to a decrease in creatine concentration in brain (90), prompting the hypothesis that creatine supplementation may have beneficial effects in rehabilitation and recovery following such injuries. This theory is supported by animal studies demonstrating creatine’s neuroprotective properties and reduced neurological deficits post-injury.(91,92) Additionally, findings from Sakellaris et al. indicate positive effects in this context, showing improvements in headache, dizziness, and fatigue in children with TBI who supplemented with creatine for six months post-injury. Improvements were also observed in the duration of post-traumatic amnesia, the length of intubation and stay in the intensive care unit, the rate of recovery, and cognitive functions.(72,93) These results further support its potential neuroprotective role.

Regarding the use of creatine in neurodegenerative and neuromuscular diseases such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and Duchenne muscular dystrophy, the current literature primarily highlights its known benefits, such as improved muscle performance when combined with exercise. However, the only notable finding beyond these effects is a slight slowing of brain atrophy in pre-symptomatic individuals with Huntington's disease. No significant impact of creatine supplementation on disease progression or prognosis has been demonstrated in these conditions. (71,94,95)

With the increasing number of studies on creatine and its demonstrated benefits primarily in energy-demanding processes, conditions associated with energy deficits, or hypoxic environments, interest has also shifted toward its potential application in ischemic heart disease and stroke. (96–98) In their research, Balestrino et al. suggest that creatine supplementation may have beneficial effects in ischemic stroke, myocardial ischemia, and arrhythmia prevention. (96) However, further studies are needed to draw definitive conclusions on this matter.

In the elderly population, creatine supplementation has also been proposed to influence various health issues. Some of these, such as improvements in cognitive function and memory, as well as its role in sarcopenia and osteopenia, have already been discussed in previous sections. Therefore, they will only be left mentioned again here without further elaboration. In addition to the previously mentioned effects, other existing research suggest potential benefits affecting not only eldery groups, but the whole population, especially adults, including a possible role in reducing liver steatosis, lowering triglyceride and cholesterol levels (38,99,100), potential applications in depression (101,102) and diabetes management. In their study, Gualano et al. (103) observed a reduction in glycated hemoglobin levels and an increase in GLUT-4 translocation, suggesting that creatine supplementation (when combined with exercise) may have an additional positive effect on better glycemic control in individuals with diabetes.

Safety of Supplementation and Related Adverse Effects

One of the most frequently discussed topics regarding the side effects of creatine supplementation is it's potential impact on kidney function. Most cases of kidney damage reported in studies during supplementation involved massively excessive doses taken over prolonged periods, coexisting kidney disease or pre-existing renal insufficiency, and concurrent use of other nephrotoxic compounds or medications. (104,105) However, there is no confirmed evidence that creatine supplementation has a negative effect on kidney function (106,107), even in extreme age populations, such as children and the elderly. (3,108,109), and also in populations with higher risk of kidney problems or failure such as diabetic patients (DM2) (110) No negative effects have been demonstrated for long-term supplementation (studies have included individuals with a supplementation history of up to five years). (111,112) It should also be noted that plasma creatinine levels can be used to assess renal filtration function; however, its concentration may depend on various factors such as muscle mass, gender, and dietary creatine intake—whether from supplementation or sources like meat. (16) This leads to several conclusions. Firstly, serum creatinine levels may be elevated, even above the normal range, during creatine supplementation.(113) Secondly, serum creatinine measurement is not a reliable method for assessing renal filtration function during the creatine supplementation period, as elevated creatinine levels in this context may not be associated with kidney damage at all.

Creatine is rarely reported as a cause of adverse effects (114), and the only consistently observed effect that could be considered a side effect is weight gain, (37,115,116) which can also be regarded as a natural consequence of its structure and mechanism of action. It also does not cause an increased frequency of injuries and muscle cramps (24,117,118), dehydration (119,120), or gastrointestinal disturbances (24,117,118). However, there have been reports suggesting that the intake of large amounts (10 grams or more in a single dose) may increase the risk of diarrhea. (57) In light of the vast body of research demonstrating the potential benefits of creatine use, as well as numerous studies indicating minimal adverse effects and good tolerance of supplementation, recommendations and proposals have emerged supporting the potential benefits of lifelong chronic creatine supplementation at a low daily dose (3 g per day). (121)

In summary, regarding the safety of creatine supplementation, it is worth noting that creatine is not prohibited by the International Olympic Committee (IOC), the World Anti-Doping Agency (WADA), or the National Collegiate Athletic Association (NCAA). (122–124) According to the position of the International Society of Sports Nutrition (ISSN), creatine monohydrate—the most extensively and thoroughly researched form of creatine—is the most effective legal supplement for increasing lean body mass and enhancing performance during physical training. It has not been demonstrated that creatine use, even at higher doses and over extended periods, including many years, causes significant adverse effects. It is considered safe even for children and older adults. (2)

Conclusions

The scientific community is continuously evolving, and new research studies are constantly emerging. In light of current scientific evidence, creatine is gaining increasing recognition due to its wide range of effects. Its applications and well-documented benefits are particularly relevant in high-intensity sports, sprinting, and other, mostly short-duration activities that require substantial energy output. According to current research, regular creatine use combined with resistance training yields benefits such as improved gains in lean body mass, strength, and muscle hypertrophy. Moreover, it has been shown to positively influence prognosis and disease progression in conditions such as sarcopenia, osteopenia, and osteoporosis. Increasing attention is being given to its potential protective role against severe complications of myocardial or cerebral ischemia, particularly in traumatic contexts, as well as its neuroprotective effects, its role in enhancing memory and cognitive function, and in glycemic control among patients with diabetes. The medical literature already contains studies supporting the validity of these beneficial effects. While there have been high hopes regarding its potential positive impact on the prognosis of neurodegenerative and neuromuscular diseases, no conclusive evidence has yet demonstrated any relevant effect of creatine on outcomes in these conditions. Regardless of the chosen supplementation protocol—whether it includes a loading phase (20–25 g of creatine daily for the first 5–7 days followed by a maintenance dose of 3–5 g per day), or omits the loading phase (e.g., approximately 5 g daily, which is ultimately equally effective but achieves similar muscle creatine saturation more gradually, after about four weeks)—creatine appears, in light of current research, to be a health-safe supplement across all age groups, including children and older adults, with virtually no significant adverse effects. It is one of the most thoroughly studied supplements with proven efficacy and, moreover, is not prohibited by the International Olympic Committee, the World Anti-Doping Agency, or the National Collegiate Athletic Association

Authors' contribution

Conceptualization – Szymon Szypulski and Jakub Skiba; methodology – Sebastian Iwaniuk; software- Kinga Kowalik and Maria Michalska; check –Kinga Tylczyńska, Jakub Skiba and Zuzanna Skiba; formal analysis Aleksandra Zielińska and Sebastian Iwaniuk; investigation – Kinga Tylczyńska; resources – Szymon Szypulski; data curation – Zuzanna Skiba and Natalia

Tylczyńska; writing- Szymon Szypulski - rough preparation – Ignacy Maciejewski and Aleksandra Zielińska; - review and editing, Kinga Kowalik and Natalia Tylczyńska; visualization- Ignacy Maciejewski and Maria Michalska ; supervision – Aleksandra Zielińska; project administration – Szymon Szypulski; receiving funding not applicable. All authors have read and agreed with the published version of the manuscript.

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