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Creatine Supplementation - therapeutic use and benefits for athletes: A Review

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ABSTRACT

Introduction: Creatine has become one of the most popular dietary supplements and is a very important substance in cellular metabolism. The human body can produce creatine endogenously; however, it is not enough, and the rest should come from diet. Supplementation of creatine can increase lean body mass, muscle mass, and performance in high-intensity sports. Creatine can help not only in sports, but also in medical disorders, such as sarcopenia, type 2 diabetes, or neurodegenerative diseases. **Aim of the study:** This review aims to describe the mechanism and metabolism of creatine, discuss its therapeutic use, and identify the benefits of creatine supplementation for athletes. **Materials and methods:** To write this review, we used PubMed databases with the following search terms: "Creatine", "Creatine supplementation", "Creatine health", "Creatine brain", "Creatine sport", "Creatine diseases". Articles that were not written in English were not used in this review. **Conclusion:** Creatine is a very popular dietary supplement and is also essential to cellular function and metabolism. Supplementation of creatine leads to an increase in lean body mass and muscle mass. Creatine not only offers benefits in sport but can also be helpful as a therapeutic substance. The positive effects of creatine supplementation can be applied to diseases such as cerebral creatine deficiency syndrome and type 2 diabetes. Supplementation should be considered in older adults to help protect against muscle mass loss and sarcopenia.

Keywords: Creatine, Creatine supplementation, Creatine diseases, Creatine health.

1. INTRODUCTION

Creatine (Cr), also known as methylguanidine-acetic acid, has recently become a more popular dietary supplement, especially among athletes. It may be produced endogenously from three amino acids (glycine (Gly), methionine, and arginine (Arg)). This process occurs in the kidneys, liver, and pancreas (Wyss and Kaddurah-Daouk, 2000). To acquire Cr exogenously, we have to consume mostly red meat, seafood (Kreider et al., 2017), or dietary supplements. However, it is hard to saturate Cr stores in muscles only through diet (Forbes et al., 2023).

Plants contain almost no Cr (Balsom et al., 1994). People who eat only plant-based foods acquire Cr from the endogenous synthesis pathway; therefore, the concentrations of Cr in their muscles are lower. This means that these people should

consume Cr exogenously, for example, by taking supplements (Ostojic & Forbes, 2022).

When the Cr enters the blood, almost 95% is stored in skeletal muscles, and the rest may be found in the brain or testes (Buford et al., 2007). 67% of Cr that is stored in skeletal muscles is transformed to phosphocreatine (PCr), and the rest of it remains as a free Cr (Wyss et al., 2000). Every day, almost 2% of stored Cr can be lost due to the non-enzymatic process of degradation in which Cr is metabolized to creatinine. That's why an average person needs around 2 grams of Cr per day. Half of it is synthesized endogenously via metabolic pathways, and the rest should be obtained from the diet (Forbes et al., 2023; Ostojic & Forbes, 2022).

Cr supplementation may be considered one of the options supporting the therapeutic processes in diseases and disorders, such as sarcopenia and neurodegenerative diseases (Candow et al., 2019; Post et al., 2019). Recent studies have shown that Cr is an essential nutrient, and a low dietary intake of Cr can increase the risk of short stature in children (Korovljev et al., 2021) or depression and worse cognitive function in adults (Kreider & Stout, 2021).

Taking into account the body's ability to metabolize Cr, people can be divided into two groups - "responders" and "non-responders". The first group is the beneficiaries of Cr supplementation. They can achieve better results and greater benefits from supplementation than individuals in the second group. Lower levels of Cr and PCr in muscles at the beginning of supplementation, a higher percentage of muscle type II fibers, and higher fat-free mass are associated with a better response (Syrotuik & Bell, 2004). Varillas-Delgados, (2024) cohort study of professional football players, was the first to show that individuals with the CC genotype and the C allele of the AMPD1 gene polymorphism have a higher probability of a better response to increases in muscle mass and BMI.

Harris et al., (1992) was the first to document a 20% increase in Cr levels in muscles during Cr monohydrate supplementation. In Brooks et al., (2023) analysis, it was shown that after a Cr supplementation trial, participants had a significant increase in total body water and lean mass.

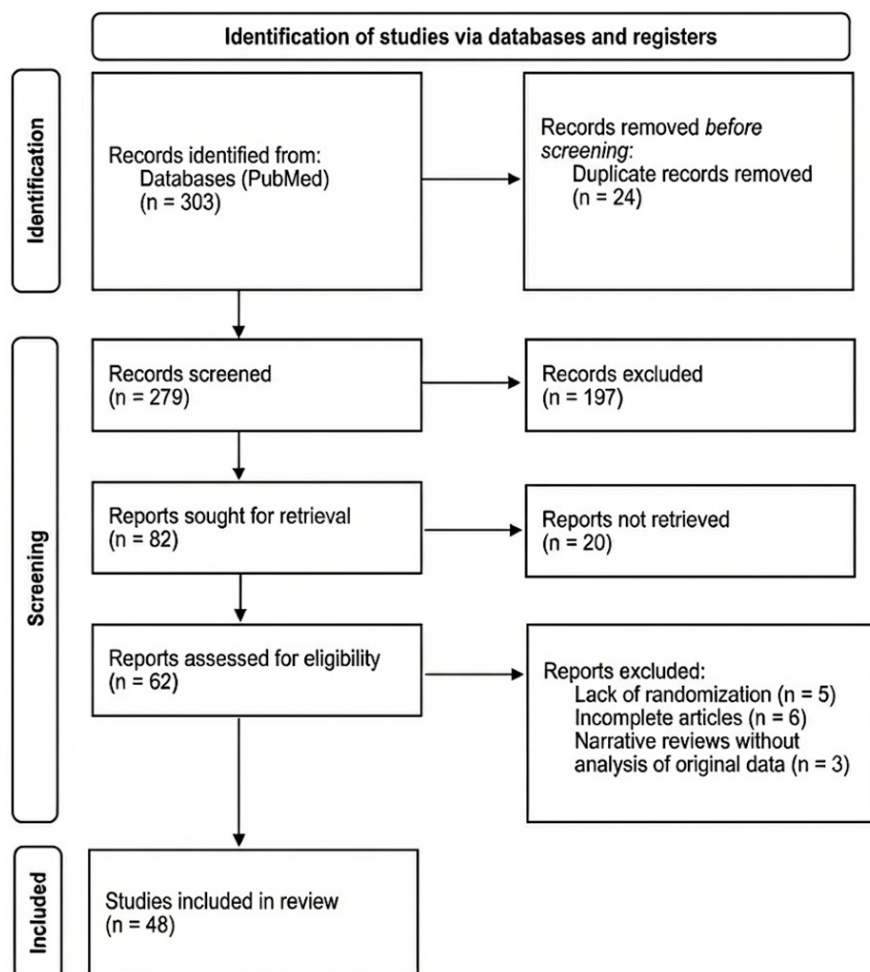


Figure 1. Flow chart

2. REVIEW METHODS

To write this review, we used the scientific database PubMed. We focused on the newest articles and researches, which should be written in English. Our research concentrates on studies about Cr influence in sport, and therapeutic use in diseases like diabetes, Duchenne muscular dystrophy, etc. Keywords that we used for searching were: “Creatine”, “Creatine supplementation”, “Creatine diseases”, “Creatine health”. To prepare articles for this study we’ve been doing research from June to August 2025. The selection procedures are shown in Figure 1.

3. RESULTS & DISCUSSION

What does creatine do in a cell?

Cr is one of the most essential substances in cellular energy metabolism. Cr and adenosine triphosphate (ATP) are the substrates of the creatine kinase enzyme reaction that phosphorylates them to PCr. This process can be reversed by the same enzyme. When PCr is converted back to Cr, the phosphate bond breaks, releasing enough energy to phosphorylate an ADP molecule to ATP. Based on these metabolic pathways, it can be concluded that PCr can store energy to synthesize ATP without using oxygen.

Creatine biosynthesis and metabolism

Primary production of Cr takes place in the liver, kidneys, and pancreas (Wyss et al., 2000); however, it can also be produced in organs like the brain (Béard & Braissant, 2010) or testes (Moore, 2000). To produce Cr, the human body needs three amino acids: Arg, Gly, and methionine, and also three enzymes: L-arginine: glycine aminotransferase (AGAT), guanidinoacetate methyltransferase, and methionine adenosyltransferase (Brosnan et al., 2011). The first process of endogenous synthesis is the transfer of the amidino group of arginine to the N-amine group of glycine, which is catalyzed by AGAT and can be reversed by the same enzyme. The products of this reaction are L-ornithine and guanidinoacetate (GAA). Then GAA is methylated to Cr by Guanidinoacetate N-Methyltransferase using the methyl group from S-adenosyl-L-methionine. After that, Cr gets into the bloodstream to finally reach the target tissues. Intracellular transport of Cr is carried out by the sodium-dependent creatine transporter (Balestrino et al., 2009). After that, Cr undergoes the exact process described in subsection 3. At the end, Cr is spontaneously degraded to creatinine by a non-enzymatic process, which is dependent on pH and temperature (Uzzan et al., 2009). Creatinine may diffuse out of the cell, and then it is excreted by the kidneys in the urine.

What are the benefits of supplementation of creatine for athletes?

Cr is one of the most popular substances taken by athletes. It is not banned in any sport, nor is it considered as doping (Kreider et al., 2017). It has been documented that Cr can improve various parameters of exercise performance (Wax et al., 2021). As mentioned earlier, the storage of Cr can produce loads of ATP. That is why Cr supplementation can help in sports that require high-intensity effort. Cr supplementation increases lean body mass, power, strength, and efficiency during high-intensity short exercises (Greydanus & Patel, 2010).

Mielgo-Ayuso et al., (2019) conducted a systematic review and meta-analysis describing the effects of Cr supplementation on athletic performance in a group of soccer athletes. They investigated three performances: aerobic, phosphagen metabolism, and anaerobic. On the aerobic performance, Cr did not bring any significant effects. Improvements in submaximal treadmill interspersed with high-intensity (Bower et al., 2003) and ball-sport endurance in speed tests with mean circuit time (Williams et al., 2014) were reported in only two studies. It turned out that, in phosphagen metabolism, Cr increases physical performance, but not significantly. The results showed that the improvement in strength performance with Cr supplementation is moderate, but not significant. It was also found that Cr may have a potentially significant ergogenic effect on anaerobic performance. The improvement was most visible in the Wingate test. The authors concluded that Cr supplementation can improve performance in physical tests that utilize anaerobic metabolism. To obtain better results of Cr supplementation, the dosage regimen should include a load dose of 20-30 g/d divided into 3 to 4 portions for 6 to 7 days, followed by 5 g/d for 9 weeks or 3 mg/kg/d for 2 weeks or more (Mielgo-Ayuso et al., 2019).

Interestingly, Cr absorption by tissues is affected by insulin and glucose (Rooney et al., 2002). It has been reported that reduced concentration of GLUT-4 during immobilization can be restored by a standard protocol of 20 grams per day of Cr, also in addition to Cr 15 g/d for 21 days, then 7 days of 5 g/d Cr can highly increase concentration of GLUT-4, glycogen, and Cr storage in muscles (Op 'T Eijnde et al., 2001).

Burke et al., (2008) conducted a randomized controlled trial comparing vegetarians and non-vegetarians with a placebo group during an 8-week heavy resistance training protocol and 1 week of Cr protocol. After that, they conducted a 49-day maintenance phase. In the research group, a higher increase of muscle insulin-like growth factor (IGF-1) was observed, compared to the placebo group. Based on the authors' conclusions, the addition of Cr, which increases total Cr levels and PCr storage, may stimulate IGF-1 production and protein synthesis, leading to muscle hypertrophy.

Consuming Cr during training can improve faster recovery and may reduce the risk of injury (Kreider et al., 2017). Cr supplementation increased recovery during intermittent activities, like interval training or sprints (Wax et al., 2021). Lactate dehydrogenase and plasma creatine kinase are the blood markers of muscle damage, which may occur after training. The literature shows that athletes who supplement Cr have less concentration of kinase creatine in blood than people who don't consume this dietary nutrient (Cooke et al., 2009; Wang et al., 2018). Cooke et al., (2009) showed that participants in their study who had been taking Cr supplements had 10% higher isokinetic and 21% higher isometric knee extension during recovery from muscle damage after exercise.

Medical use of creatine

Besides the benefits in sports, Cr has also been shown to play a therapeutic role in various populations. Gualano et al., (2011) conducted a trial assessing the impact of Cr supplementation on glycemic control in patients with type 2 diabetes. During the 12-week trial, patients received 5g/d of Cr or a placebo. Then they joined the training program. Glycosylated hemoglobin, glucose curve, insulin, GLUT-4 expression, and other factors were compared between the two groups. It turned out that the group with Cr supplementation had significantly lower glycosylated hemoglobin, lower glucose concentration under the delta, decreased glycemia during the meal tolerance test, and increased GLUT-4 translocation compared to the placebo group.

Sarcopenia is an age-related muscle disorder characterized by the loss of skeletal muscles. It affects 8-13% of the population after 60 years old (Shafiee et al., 2017). Consequently, not only does it lead to loss of muscle mass, but it also makes people weaker, more cachectic, and susceptible to other diseases. In Devries & Phillips (2014) meta-analysis, older people during resistance training (RT) who also took Cr increased their total body mass and fat-free mass compared to the group that did not take Cr. Also, the first group had better results on the bench chest press and leg press, and performed better on the 30-second chair stand test. Candow et al., (2019) stated that combining Cr intake with RT in the healthy aging population can increase muscle mass, physical performance, strength, bone, and fat mass. However, it depends on variables such as PCr concentration, muscle fiber type, individual diet, etc. Effects of Cr supplementation with or without RT have not been shown to have a positive impact on bone measurements in the older female population. However, the influence of Cr alone on bone measurements in older males is unknown (Candow et al., 2021).

Dolan et al., (2019) analyzed articles on the increase in Cr concentration in the brain during supplementation in adolescents and adults. Most of the studies that were analyzed have shown an increase of 3-10% of Cr in the brain. On the other hand, Merege-Filho et al., (2017) conducted a trial of 7-day Cr supplementation in a healthy youth population, and the results showed no increase in Cr concentration in the brain. This outcome suggests that brain Cr in this young population does not originate primarily from exogenous sources. However, it cannot be ruled out that changing the Cr supplementation protocols might have yielded different results. The fact that the brain has the ability to create Cr (Andres et al., 2008) on its own means it could be more resistant to the intake of exogenous Cr. People with reduced SLC6A8 expression in astrocytes may have less demand for exogenous Cr (Béard & Braissant, 2010).

Cerebral creatine deficiency syndromes (CCDS) are a small group of hereditary neurometabolic disorders characterized by low brain Cr levels, resulting from biosynthetic disorders or transport deficiencies. The symptoms of CCDS, such as development and mental disorders, for example, difficulties in learning, can be reversed in part by Cr supplementation. Sun et al., (2023) performed a cohort study in which they researched the group of children with CCDS. Patients received different diets depending on the type of disorder they had. Some children were getting Cr monotherapy, and the rest, in addition to Cr, had received various amino acids. Children with CCDS type 2, after 2-3 weeks of treatment, the Cr level had returned to the normal range, and the brain Cr levels had returned to 50-80% of the normal range after 6-9 months of treatment. One patient, after 10 years of treatment, started school and performed intellectual functions like normal children. Four patients, after 4-8 months of treatment, improved cognitive and motor skills (running, walking, climbing stairs, communicating, reading, speaking, etc.). However, they had slow speech. Unfortunately, patients with CCDS type 1 who received Cr monotherapy for 6 months did not improve in any clinical manifestations. One patient who received Arg and Gly instead of Cr for 2 months showed some improvement in walking and learning. Based on these data, early treatment of patients with CCDS type 2 using Cr, ornithine, and a low-protein diet may lead to improved clinical outcomes. Patients with CCDS type 3 can demonstrate Cr treatment effects when the intervention is undertaken early (Sun et al., 2023).

Parkinson's disease (PD) is the second most common neurodegenerative disorder and affects 2-3% of the population over 65 years of age (Poewe et al., 2017). This disease is associated with a progressive loss of dopaminergic neurons, which affects motor (stiffness, slowness, etc.) and cognitive aspects (cognition, sleep, autonomic function, etc.) (Mo et al., 2017; Olanow et al., 2009). In trials using Coenzyme Q10 and Cr supplementation in mice as a therapeutic approach, this combination has been shown to be effective in treating PD (Yang et al., 2009). Li et al., (2015) conducted a trial to investigate the effects of Coenzyme Q10 and Cr supplementation therapy on mild cognitive impairment in PD and their influence on plasma phospholipid levels (PL). The patients were rated using the Montreal Cognitive Assessment (MoCA) and the Unified Parkinson's Disease Rating Scale III (UPDRS). After 12 and 18 months of treatment, patients receiving combination therapy had significantly higher MoCA scores, and PL levels were substantially lower compared to the control group. However, the UPDRS III score had no significant differences. It can be concluded that combined therapy of Cr and Coenzyme Q10 may delay the deterioration of cognitive functions in PD with mild cognitive impairment. Mo et al., (2017) conducted a meta-analysis comparing Cr treatment with placebo in PD. The results showed that the group receiving Cr treatment, compared with placebo, did not have a greater improvement in the UPDRS mental score, the UPDRS activities of daily living score, the UPDRS motor score, or the UPDRS total score. However, in two studies, patients who received Cr had higher Schwab & England Scale scores. They concluded that there is no significant evidence that Cr supplementation influences PD. They emphasize that more clinical trials are needed.

Duchenne muscular dystrophy (DMD) is a lethal inherited disorder caused by a mutation in the dystrophin gene located on the X chromosome and occurring with a frequency of 1/5000 live male births (Kolwicz et al., 2019; Verhaart & Aartsma-Rus, 2019). DMD results in the destruction of muscles, and for this reason, patients die mostly due to respiratory and cardiac muscle failure (Kolwicz et al., 2019). Banerjee et al., (2010) conducted a randomized, placebo-controlled study to assess the effects of Cr monohydrate supplementation on cellular energetics and muscle strength in DMD. Eighteen boys were receiving 5 grams of Cr for 8 weeks. At the beginning, all patients had lower PCr/inorganic phosphate and PCr/ATP and higher phosphodiester/PCr ratios. After treatment, boys who received Cr supplementation had higher PCr levels than those in the placebo group. Significant differences were observed in PCr/inorganic phosphate, PCr/ATP, and phosphodiester/PCr ratios between these two groups. Patients under 7 years old had better treatment outcomes than those in other age groups. Parents of these patients also observed subjective improvement after Cr supplementation. However, this study did not provide evidence that Cr can give any clinical benefits in long-term treatment or extend lifespan.

Research on Cr's influence on cognitive function has been carried out for many years. Nowadays, opinions about its positive effect, or zero impact on the increase of cognitive functions, are divided. In one of the latest reviews on Cr's impact on brain health, Roschel et al., (2021) analyzed multiple trials. Researchers emphasize that some studies may have yielded false results depending on the study population, supplementation dosing, or duration of the process. However, they made some positive conclusions. There is a possibility that Cr supplementation may improve cognitive function, especially when Cr levels are low in the brain. Stressors induce this condition, for example: lack of sleep, exercise, and pathological disorders like Alzheimer's disease, CCDS, and aging. Roschel et al. stated that there is a need to explore Cr's impact on the brain further. We also need to optimize the Cr supplementation protocol and perform more research on Cr levels and their effects on cognitive function. The summaries are presented in table 1.

Table 1. summarizes the presented study about medical use of creatine

Author(s) & Year	Condition/Population	Protocol/Intervention	Findings & Conclusions
Gualano et al., 2011	Type 2 Diabetes	5g/d Cr + training (12 weeks)	Significantly lower HbA1c, lower glucose concentration under the delta, and increased GLUT-4 translocation compared to placebo.
Devries & Phillips, 2014	Older adults (Sarcopenia)	Cr + Resistance Training	Increased total body mass and fat-free mass; better performance in chest/leg press and chair stand test compared to resistance training alone.
Candow et al., 2019, 2021	Healthy aging population	Cr + Resistance Training	Increase in muscle mass, strength, and physical performance.
Dolan et al., 2019	Adolescents and adults	Cr Supplementation	Most studies showed a 3-10% increase in

			brain Cr concentration.
Merege-Filho et al., 2017	Healthy youth	7-day Cr supplementation	No increase in brain CR concentration, probably the brain is resistant to exogenous Cr in this population or relies on endogenous synthesis.
Sun et al., 2023	Cerebral Creatine Deficiency Syndrome (CCDS)	Therapies with Cr + aminoacids, or Cr alone	CCDS Type 1: No clinical improvement with Cr monotherapy. CCDS Type 2: Cr levels normalized, cognitive and motor skills improved. CCDS Type 3: Effective with early intervention.
Li et al., 2015	Parkinson's Disease (PD) with mild cognitive impairment	Cr + Coenzyme Q10 (12–18 months)	Higher MoCA scores (improved cognition) and lower plasma phospholipid levels. No significant difference in UPDRS III (motor score).
Mo et al., 2017	Parkinson's Disease (PD)	Cr versus Placebo	No significant evidence that Cr improves UPDRS scores (mental, motor, ADL). More clinical trials needed.
Banerjee et al., 2010	Duchenne Muscular Dystrophy (DMD)	5g/d Cr (8 weeks)	Higher PCr/inorganic phosphate, PCr/ATP, phosphodiester/PCr ratios compared to placebo. Subjective improvement reported, but no evidence of extended lifespan or long-term clinical benefit.
Roschel et al., 2021	Cognitive Function	Cr Supplementation	Cr supplementation may improve cognitive function, especially when Cr levels are low in the brain. More research on Cr levels and their effects on cognitive function are needed.

4. CONCLUSION

Cr is becoming a very popular dietary supplement. This substance is the foundation of cell function and metabolism. Except for endogenous production of Cr, people should obtain the rest from diet or as supplements. Cr supplementation can increase lean body mass and muscle mass. In the athletic population, it enhances power, strength, and performance in anaerobic and high-intensity sports. It also protects from injuries and provides faster recovery. Cr not only brings benefits in sport, but it can also be helpful as a therapeutic substance. Positive effects of Cr supplementation can be used in diseases like CCDS or type 2 diabetes. Supplementation should be considered in the older population to help protect against muscle mass loss or sarcopenia. The opinions on the influence of Cr supplementation on cognitive functions are divided; more research about this process should be carried out.

Abbreviations

AGAT - L-arginine: glycine aminotransferase

Arg – Arginine

ATP - Adenosine triphosphate

Cr – Creatine

CCDS – Cerebral creatine deficiency syndrome

DMD - Duchenne muscular dystrophy

GAA – Guanidinoacetate

Gly – Glycine

IGF-1 – Insulin-like growth factor

MoCA - Montreal Cognitive Assessment

PCr - Phosphocreatine

PD - Parkinson's disease

PL - Plasma phospholipid levels

UPDRS - Unified Parkinson's Disease Rating Scale III

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Authors' Contributions

Conceptualization and Methodology: Jakub Szmit, Marta Wolszczak, Hanna Wołodkiewicz

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Writing review and editing: Jakub Szmit, Marta Wolszczak, Hanna Wołodkiewicz

Visualization, Supervision & Project administration: Jakub Szmit

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Ethical approval

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Conflict of interest

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Data and materials availability

All data associated with this study will be available based on reasonable request to the corresponding author.

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