

Creatine supplementation and muscles: From metabolism to medical practice

Romana VULTURAR^{1,2}, Bianca JURJIU^{3,4}, Marc DAMIAN⁵, Anca BOJAN^{6,7},
 Sebastian Romeo PINTILIE⁵, Claudia JURCA⁸, Adina CHIS^{1,2}, Simona GRAD^{9,10}

¹Department of Molecular Sciences, "Iuliu Hatieganu" University of Medicine and Pharmacy,
 Cluj-Napoca, Romania

²Cognitive Neuroscience Laboratory, "Babes-Bolyai" University, Cluj-Napoca, Romania

³Department of Rheumatology, Emergency Clinical County Hospital Cluj, Cluj-Napoca, Romania

⁴Discipline of Rheumatology, "Iuliu Hatieganu" University of Medicine and Pharmacy,
 Cluj-Napoca, Romania

⁵Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

⁶Hematology Department, "Iuliu Hatieganu" University of Medicine and Pharmacy,
 Cluj-Napoca, Romania

⁷Hematology Department, "Prof. Dr. Ioan Chiricuta" Oncological Institute, Cluj-Napoca, Romania

⁸Department of Genetics, University Oradea, Faculty of Medicine and Pharmacy Oradea, Romania

⁹Department of Internal Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy,
 Cluj-Napoca, Romania

¹⁰^{2nd} Department of Internal Medicine, Emergency Clinical County Hospital Cluj, Cluj-Napoca, Romania

ABSTRACT

Creatine has become the most popular dietary supplement in sport and exercise physiology. In humans creatine is synthesized by the kidneys, pancreas and liver and transported mainly into brain, skeletal and cardiac muscle. Phosphocreatine is a high-energy content molecule, essential for the ADP to ATP conversion during intensive physical activity. Creatine and phosphocreatine are crucial in the energy shuttle system of high-energy phosphates between the mitochondrial ATP production and the cytosolic ATP consumption.

Creatine supplementation increases lean body mass acting on myogenic regulatory factors. During muscular recovery, creatine supplementation regulates the regeneration process by reduction of muscle damage-induced inflammation and oxidative stress, activation and proliferation of satellite cells and regulation of calcium transport in muscle. The effects of creatine supplementation on muscle physiology are beneficial in anaerobic/aerobic exercises. In several muscle disorders (muscular dystrophies, in idiopathic inflammatory myopathies) creatine improved functional performance, but apparently not in metabolic myopathies; in McArdle diseases it may even have paradoxical effects.

More research is warranted to better understand the short and long-term effects and safety of creatine supplementation among adolescents or elderly, as well as in different types of muscle diseases; for the two enzymatic genetic defects of creatine biosynthesis – arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT), respectively – normal neurodevelopment has been achieved in early initiation of creatine therapy.

Keywords: creatine supplementation, creatine kinase, muscle injury, muscle regeneration process, genetic nerometabolic disorders, AGAT, GAMT

INTRODUCTION

The metabolic and physiological effects of creatine were extensively researched after Harris and collaborators discovered that exogenous creatine administration increases creatine (Cr) and phosphocreatine (PCr) content in muscle (1,2). Thus, Cr – an amino acid derivative component – has become the most popular dietary supplement in exercise physiology and sport. First taken in the Olympic Games in Barcelona by successful sprinters, Cr has been used afterwards to increase the physical performance in athletes and in healthy individuals (3). At present, a huge body of evidence supports the efficacy of Cr supplementation to enhance physiological function in many types of exercise of different duration and intensity, and to improve skeletal muscle mass, strength, and even bone mineral density in healthy individuals or in those with neuromuscular diseases (3-9). Recent studies showed that Cr also has antioxidant, anti-inflammatory and immunomodulatory effects (10), potentially promoting vascular protection (2). Besides, this compound has positive effects on thermoregulation, neural development, cognition and thus quality of life (11-16).

DIETARY SOURCES OF CREATINE AND METABOLISM

Studies have shown that red meat and seafood are some of the most creatine-dense foods (17). In table 1 is presented the creatine content of some common foods (creatine is metabolized to creatinine and the creatine content may decrease from the values in the table as a function of time cooking) (18).

TABLE 1. Creatine content of some common foods (18)

Food	Serving size	Creatine content (g)
Cod	225 g	1-1.67
Herring	225 g	2-4
Salmon	225 g	1.5-2.5
Beef (lean)	225 g	1.5-2.5
Pork	225 g	1.5-2.5
Milk	250 ml	0.05-0.1
Breast milk	250 ml	0.25-0.5

Creatine (Cr) is a guanidine compound with both exogenous and endogenous sources, being synthesized by the kidneys, pancreas, and liver. The creatine transporter (CRTR or SLC6A8) mediates the uptake of Cr primarily into skeletal muscle, but also into the cardiac muscle and brain. At the blood-brain barrier, the CRTR transporter is highly expressed. Part of the intracellular creatine is reversibly converted into the high-energy compound phosphocreatine (PCr) by the action of creatine kinase (CK). Three cytosolic isoforms of CK exist:

the brain type (BB-CK), the muscle type (MM-CK), and the heterodimer MB-CK; additionally, there are two mitochondrial isoforms. Creatine and phosphocreatine (PCr) are non-enzymatically converted into creatinine (which is mainly excreted in urine), with a constant daily turnover of 1.5% of body creatine. The daily creatinine excretion in urine is directly proportional to the total body creatine, and in particular to muscle mass (i.e. 20-25 mg/kg/24h in children and adults, and lower in infants younger than 2 years) (3,11).

In humans, the skeletal and cardiac muscle (the tissues containing the most Cr) are generally unable to synthesize this molecule, and only a small proportion of body creatine is synthesized in the brain. Cr transport may be modulated through acute mechanisms (influenced by the Cr concentration changes) and chronic mechanisms (regulated by CRTR transporter gene expression, translation, or post-translational mechanisms) (11).

After its synthesis, Cr is stored mainly in the skeletal and cardiac muscle and in the brain. To perform its physiological role, Cr is transformed into PCr by creatine kinase (CK). The phosphate group is provided by ATP (adenosine triphosphate), which is converted into ADP (adenosine diphosphate) in the reaction. PCr is a high-energy reserve molecule, available for the conversion of ADP to ATP, essential during intense physical activity and relative high-energy demands. Cr kinase catalyzes the reversible transfer of the N-phosphoryl group from phosphoryl Cr to ADP to regenerate ATP and restore Cr skeletal muscle content. Thus, Cr and PCr are molecules with fundamental roles in the *energy shuttle system* (ESS) of high-energy phosphates between the mitochondrial sites of ATP production and the cytosolic sites of ATP utilization (3). The involvement of ESS depends on different physiological muscle fiber demands, being important for ATP production in fast-twitch muscle fibers (with mainly anaerobic/glycolytic metabolism), and less significant in slow-twitch muscle fibers (with oxidative metabolism). When high-intensity exercise occurs, the ATP must be hydrolyzed very fast, both ADP molecules and the hydrogen ions being buffered – Figure 1 (19).

CREATINE SUPPLEMENTATION AND MUSCLE CHANGES

As an increase in muscle mass is often required to improve performance in strength and power or speed sports, different studies have investigated the hypertrophic effects of Cr supplementation (3). A typical Cr loading period (first 5-7 days) resulted in a 0.6-2.0 kg gain in lean body mass (3). Cr supplementation during a chronic resistance exercise (6-8 weeks) increased the lean body mass by about 3 kg. Cr supplementation in combination with glucose coupled with 4-8 weeks of

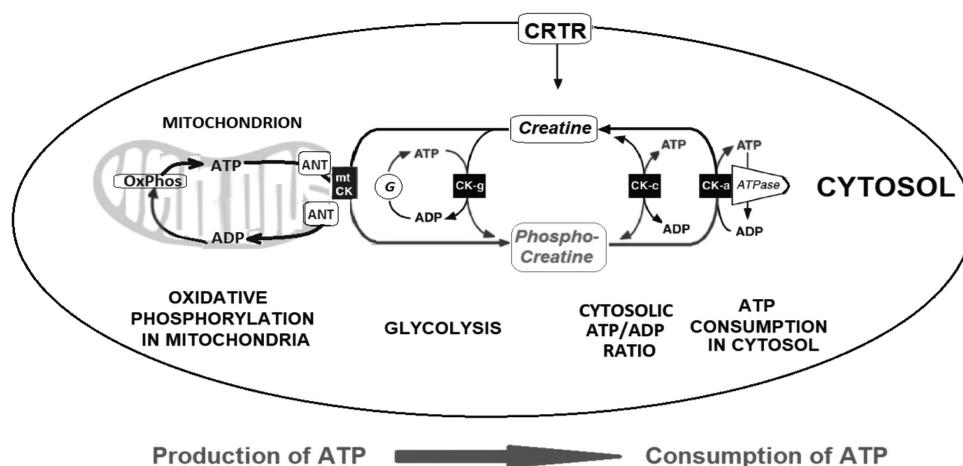


FIGURE 1. The creatine kinase/phosphocreatine system with compartment-specific isoenzymes of creatine kinase – adapted after (3,14). ADP – adenosine diphosphate; ATP – adenosine triphosphate; CRTR – creatine transporter; ANT – adenine nucleotide translocator; OxPhos – oxidative phosphorylation; G – enzymes involved in glycolysis; CK – creatine kinase; mtCK – mitochondrial CK isoforms; CK-g – glycolytic CK; CK-c – cytosolic CK; CK-a – ATPases CK (transporters, pumps and enzymes)

strength training stimulates greater gains in lean mass than Cr supplementation alone. Willoughby and Rosene discovered that increases in lean body mass are due to the effects of Cr supplementation on myogenic regulatory factors (i.e., MRF-4, Myf-5, Myo-D, and myogenin), which act on gene and myosin heavy-chain protein expression (3). Furthermore, Cr ingestion (load: 24 g/day, 6 g/serving, 4 servings/day, 7 days; maintenance: 6 g/day, 1 serving/day, 15 weeks) during resistance training promotes the proliferation of satellite cell (muscle stem cells) function and stimulates the myonuclei relative distribution in skeletal muscle (20).

As for sarcopenia, Cr long-term benefits to the elderly population need to be further evaluated before including its supplementation as an established recommended program. Despite contradictory results on its efficacy, the number of studies involving supplementary Cr in elderly population is increasing, and positive effects are being identified (21,22). Creatine supplementation may improve muscular mass and function in elderly when combined with physical exercise, and it can help maintain muscle mass without exercise, preventing aggravation of sarcopenia (23). In diabetes, 5 g/day Cr supplementation, with a normal or high-protein diet, proved to be safe for kidney function, but creatine supplementation should always be considered individually (24).

The administration of creatine supplements in adolescent populations is controversial, due to lack of clinical data and randomized controlled studies to support its safety. Creatine is still a popular dietary supplement of choice among adolescents (both in athletes and special populations) (25). Among pediatric populations, a strong rationale exists for creatine supplementation in several neuromuscular and metabolic disorders (23,25).

CREATINE SUPPLEMENTATION AND REGENERATION AFTER EXERCISE-INDUCED MUSCLE INJURY

It is known that high-intensity muscle work leads to damage of myofibrils, as seen primarily in athletes. During recovery, the muscle undergoes structural repair, and Cr supplementation has been demonstrated to regulate at least four important mechanisms involved in the regeneration process (Table 2).

TABLE 2. Potential mechanisms of creatine supplementation-induced muscle regeneration

Creatine supplementation potential mechanisms	References
Reduction of oxidative stress	(26,27)
Reduction of muscle damage-induced inflammation	(28,29)
Satellite cells activation and proliferation	(20,30)
Regulation of the transport of calcium in the muscle	(3,31)

CREATINE FOR TREATING MUSCLE AND NEUROMETABOLIC DISEASES

Many inherited or acquired muscle diseases evolve with progressive muscle weakness. In neuromuscular disorders endogenous stores of Cr and PCr are lower than in controls (32). In muscular dystrophies, supplementation of Cr resulted in muscle strength improvement, as has been shown in a meta-analysis of six trials on 192 subjects in the Cr-treated group versus placebo; besides, was identified an increased functional perfor-

mance in one trial on 37 patients and increased well-being in four trials (32). Nevertheless, in patients with myotonic dystrophy the response to creatine supplementation was not consistent, possibly due to creatine transport disturbances (18).

Regarding the metabolic myopathies, the Cr supplementation either had no effect (i.e. in mitochondrial myopathies) (32,33), or even induced deterioration of clinical parameters and increased muscle pain, as has been shown in a cross-over trial in glycogenosis type V (McArdle disease) (34); there are only modest benefits of creatine monohydrate supplementation in administration of low doses and possibly negative effects (cramping) at higher doses in this metabolic disease (18). Inflammatory idiopathic myopathies (polymyositis, dermatomyositis, inclusion body myositis) are acquired inflammatory diseases evolving with muscle inflammation, treated with immunosuppressive drugs. In the Cr-treated groups, functional parameters improved, and the tolerance was good (35).

Genetic disorders of creatine biosynthesis [guanidinoacetate methyltransferase (GAMT) deficiency and arginine:glycine amidinotransferase (AGAT) deficiency, respectively) are two neurometabolic disorders caused by enzymatic deficiencies which benefit from creatine therapy. Thus, in GAMT deficiency, the aim of therapy is to restore cerebral creatine levels; creatine supplementation (400 mg/kg/day in 3-6 doses) was associated with ornithine administration resulted in normal

neurodevelopment. In AGAT deficiency, the aim of treatment is to restore the concentration of cerebral and muscular creatine; the therapy with creatine monohydrate (100-800 mg/kg/d) lead to almost complete restoration of brain creatine and significant improvement of myopathy in most patients. Early diagnosis and treatment in these patients may prevent intellectual disability and myopathy (11,36).

CONCLUSIONS

There are important core references which underline how creatine supplementation in adults is safe and how it can lead to significant increase in muscle performance. The effects of creatine supplementation are beneficial in exercise, muscle hypertrophy programs, prevention of exercise-induced muscle damage and facilitation of recovery after injury. In muscle disorders creatine improved functional performance in muscular dystrophies and in idiopathic inflammatory myopathies, but apparently not in metabolic myopathies, and in McArdle diseases it may even have paradoxical effects. More research is warranted to better understand the short and long-term effects and safety of creatine among adolescents or elderly, as well as in different types of muscle diseases, excepting the two genetic defects of creatine synthesis (AGAT and GAMT deficiencies) for which normal neurodevelopment has been achieved in early initiation of creatine therapy.

Conflict of interest: none declared
Financial support: none declared

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