Creatine supplementation and muscles: From metabolism to medical practice

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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 neurometabolic 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).

| Food   | Serving size | Creatine content (g) |
|--------|--------------|----------------------|
| Cod    | 225 g        | 1.1-1.67             |
| 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 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
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 repARATION, 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 create- 
tine transport disturbances (18).

Regarding the metabolic myopathies, the Cr supple-
mentation 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 administra-
tion of low doses and possibly negative effects 
(cramping) at higher doses in this metabolic disease 
(18). Inflammatory idiopathic myopathies (polymyosi-
tis, dermatomyositis, inclusion body myositis) are ac-
quired inflammatory diseases evolving with muscle in-
flammation, treated with immunosuppressive drugs. In 
the Cr-treated groups, functional parameters im-
proved, and the tolerance was good (35).

Genetic disorders of creatine biosynthesis [guanidi-
noacetate 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 supple-
mentation (400 mg/kg/day in 3-6 doses) was associat-
ed 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 com-
plete restoration of brain creatine and significant im-
provement of myopathy in most patients. Early diagno-
sis and treatment in these patients may prevent intel-
tlectual disability and myopathy (11,36).

CONCLUSIONS

There are important core references which under-
line how creatine supplementation in adults is safe and 
how it can lead to significant increase in muscle perfor-
ance. The effects of creatine supplementation are 
beneficial in exercise, muscle hypertrophy programs, 
prevention of exercise-induced muscle damage and fa-
cilitation of recovery after injury. In muscle disorders 
creatine improved functional performance in muscular 
dystrophies and in idiopathic inflammatory myopa-
thies, but apparently not in metabolic myopathies, and 
in McArdle diseases it may even have paradoxical ef-
fects. 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 de-
fects of creatine synthesis (AGAT and GAMT deficien-
cies) for which normal neurodevelopment has been 
achieved in early initiation of creatine therapy.

REFERENCES

1. Harris RC, Söderlund K, Hultman E. 
Elevation of creatine in resting and exercised 
muscle of normal subjects by creatine 
supplementation. Clin Sci (Lond). 
1992;83(3):367-74.
2. Clarke H, Hickner RC, Ormsbee JM. The 
Potential Role of Creatine in Vascular 
Health. Nutrients. 2021;13:857.
3. Negro IA, D’Antona G. Creatine in Skeletal 
Muscle Physiology. In: Nonvitamin and 
Nonmineral Nutritional Supplements. 
Academic Press, Elsevier, 2019:59-68.
4. Gualano B, Macedo AR, Alves CRR, 
Roschel H, et al. Creatine supplementation and 
resistance training in vulnerable older 
woman: a randomised double-blind 
placebo-controlled clinical trial. Exp 
Gerontol. 2014;53:1-15.
5. Devries MC, Phillips SM. Creatine 
supplementation during resistance training in 
older adults – a meta-analysis. Med Sci 
Sports Exerc. 2014;46:1193-1203.
6. D’Antona G, Nabavi SM, Micheletti P, Di 
Lorenzo A, Aquilani R, Nisoli R, Rondanelli 
M, Daglia M. Creatine, L-carnitine, and ω3 
polyunsaturated fatty acid supplementation from healthy to diseased skeletal muscle. 
Biomed Res Int. 2014;613890.
7. Candow DG, Vogt E, Johannsmeyer S, 
Forbes SC, Farthing SC, Farthing JP. 
Strategic creatine supplementation and 
resistance training in healthy older adults. 
Appl Physiol Nutr Metab. 2015;40:689-694.
8. Ramirez-Campillo R, Gonzales-Jurado JA, 
Martinez C, et al. Effects of plyometric 
training and creatine supplementation on 
maximal intensity exercise and endurance in 
female soccer players. J Sci Med Sport. 
2015;6:S1440-S2440.
9. Wilkinson TJ, Lemmy AB, Jones JG, 
Sheikh F, et al. Can creatine 
supplementation improve body composition 
and objective physical function in rheumatoid 
arthritis patients? A randomised controlled 
trial. Arthritis Care Res. 2016;68(6):729-737.
10. Riesberg LA, Weed SA, Mc Donald TL, 
Eckerson JM, Drescher KM. Beyond 
muscles: the untapped potential of creatine. 
Int. Immunopharmacol. 2018;37:31-42.
11. Stockler-Ipsiroglu S, Mercimek-Mahmutoglu 
S, Salomonos GS. Creatine Deficiency 
syndrome. In: Saudubray JM, Baumgartner 
M, Waler J. Inherited Metabolic Diseases, 
Diagnostic and Treatment. Springer-Verlag, 
2016:243-250.
12. Ndika JD, Johnston K, Barkovich JA, Wirt 
MD, et al. Developmental progress and 
creatine restoration upon long-term creatine 
supplementation of a patient with 
arginine:glycine amidinotransferase 
deficiency. Mol Genet Metab. 2012; 
106:48-54.
13. Clark JF, Cecil KM. Diagnostic methods and 
recommendations for the cerebral creatine 
deficiency syndromes. Pediatr Res. 
2015;77:398-405.
14. Van de Kamp JM, Pouvels PJ, Aarsen FK, 
et al. Long-term follow-up and treatment in 
nine boys with X-linked creatine transporter 
defect. J Inherit Metab Dis. 2012; 
35:141-149.
15. Twycross-Lewis R, Kilduff LP, Wang G, Pitsiladis YP. The effects of creatine supplementation on thermoregulation and physical (cognitive) performance: a review and future prospects. *Amino Acids*. 2016;48(6):1843-1855.

16. Hall M, Manetta E, Tupper K. Creatine Supplementation: An Update. *Curr Sports Med Rep*. 2021;20(7):338-344.

17. Kreider RB, Kalman DS, Antonio J, et al. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *J Int Soc Sports Nutr*. 2017;14:18.

18. Tamopolsky MA. Creatine as a therapeutic strategy for myopathies. *Amino Acids*. 2011;40(5):1397-407.

19. Brosnan JT, Brosnan ME. Creatine: endogenous metabolite, dietary, and therapeutic supplement. *Annu Rev Nutr*. 2007;27:241-261.

20. Olsen S, Aagaard P, Kadi F, Tufekovic G, Verney JL, Olesen JL, Suetta C, Kjaer M. Creatine supplementation augments the increase in satellite cell and myonuclei number in human skeletal muscle induced by strength training. *J Physiol*. 2006;573:525-534.

21. Sestili P, Barbieri E, Stocchi V. Effects of Creatine in Skeletal Muscle Cells and in Myoblasts Differentiating Under Normal or Oxidatively Stressing Conditions. *Mini Rev Med Chem*. 2016;16(1):4-11.

22. Gualano B, Macedo AR, Alves CR, Roschel H, et al. Creatine Supplementation: An Update. *Curr Sports Med Rep*. 2021;20(7):338-344.

23. Dolan E, Gualano B, Rawson ES. Beyond muscle: The effects of creatine supplementation on brain creatine, cognitive processing, and traumatic brain injury. *Eur J Sport Sci*. 2019;19(1):1-14.

24. Rusu ME Popa DS. Protein food and amino acid supplements in athletes’ diet. *Palestina of the third millennium – Civilization and Sport*. 2016;17(2):146-152.

25. Jagim AR, Kerkvick CM. Creatine Supplementation in Children and Adolescents. *Nutrients*. 2021;13(2):664.

26. Rahimi R. Creatine supplementation decreases oxidative DNA damage and lipid peroxidation induced by a single bout of resistance exercise. *J Strength Cond Res*. 2011 Dec;25(12):3448-55.

27. Kim J, Lee J, Kim S, Yoon D, Kim J, Sung DJ. Role of creatine supplementation in exercise-induced muscle damage: a mini review. *J Exerc Rehabil*. 2015;11(5):244-250.

28. Bassit RA, Curi R, Costa Rosa LF. Creatine supplementation reduces plasma levels of pro-inflammatory cytokines and PGE2 after a halfironman competition. *Amino Acids*. 2008;35:425-431.

29. Deminice R, Rosa FT, Franco GS, Jordao AA, de Freitas EC. Effects of creatine supplementation on oxidative stress and inflammatory markers after repeated-sprint exercise in humans. *Nutrition*. 2013;29:1127-1132.

30. Safdar A, Yardley NJ, Snow R, Melov S, Tamopolsky MA. Global and targeted gene expression and protein content in skeletal muscle of young men following short-term creatine monohydrate supplementation. *Physiol Genomics*. 2008;32(2):219-228.

31. Cooke MB, Rybalka E, Williams AD, Cribb PJ, Hayes A. Creatine supplementation enhances muscle force recovery after eccentrically induced muscle damage in healthy individuals. *J Int Soc Sports Nutr*. 2009;6:13.

32. Kley RA, Tamopolsky MA, Vorgerd M, Cochrane Neuromuscular Group. Creatine for treating muscle disorders. *Cochrane Database Syst Rev*. 2013;2013(6):CD004760.

33. Kloppstock T, Querner V, Schmidt F, et al. A placebo-controlled crossover trial of creatine in mitochondrial diseases. *Neurology* 2000;55(11):1748-51.

34. Vorgerd M, Zange J, Kley R, Greth T, Hüsing A. Effect of high-dose creatine therapy on symptoms of exercise intolerance in McArdle disease: double-blind, placebo-controlled crossover study. *Arch Neurol*. 2002;59(1):97-101.

35. Chung YL, Alexanderson H, Pipitone N, Morrison C, et al. Creatine supplements in patients with idiopathic inflammatory myopathies who are clinically weak after conventional pharmacologic treatment: Six-month, double-blind, randomised, placebo-controlled trial. *Arthritis Rheum*. 2007;57(4):694-702.

36. Zschocke J, Hoffmann G. Vademecum metabolicum – Diagnosis and Treatment of Inherited Metabolic Disorders, Thieme Verlag, 2020.