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What do we know about creatine supplementation?

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Abstract

Creatine is one of the most often used supplements nowadays. Its popularity can be attributed to a wide variety of clinical implications.

The intent of this paper was to evaluate and review the latest publications about the usage and potential clinical effects on the human body of creatine supplementation and to bring attention to new findings in this subject.

Authors explored PubMed, CrossRef and Google Scholar using keywords: creatine, supplements, ergogenic aids, neuroprotection, bioenergetics. Furthermore, the references of selected articles were manually investigated for additional relevant articles. The bibliography focused mainly on systematic reviews, randomized controlled trials (RCTs) and case reports. The selection of individual articles was carried out in accordance with the determinants of general medicine readership.

There is still a lot to learn about creatine supplementation and its potentially beneficial effects. Further evidence-based studies are required, as the amount of reliable data and information is still not sufficient and lots of them have yet to be examined.

Keywords: creatine; supplementation; ergogenic aids; sport

Introduction

Creatine (methylguanidine-acetic acid) is an organic chemical compound that is endogenously formed in the kidneys, liver and to a lesser extent in the pancreas as a product of reactions involving arginine, glycine and methionine. Most of the exogenous supply of the creatine comes from meat consumption and/or dietary supplement.[1] Most of the creatine (95%) is found in skeletal muscles (type II, fast twitch muscle fibers) of which two-thirds are phosphorylated (PCr) and one-third is stored as free creatine (Cr).[2]

Due to increased popularity of creatine supplementation, the International Society of Sports Nutrition (ISSN) published an article in 2017 with position about safety and efficacy of creatine supplementation in exercise, sport and medicine.[3] It is estimated that over 400 million USD worth creatine is sold annually on the supplements market.[4]

Prevalence of the creatine supplements consumption is connected with its numerous clinical applications. Studies have shown its effectiveness in increasing muscle mass, enhancing post-workout recovery, preventing injuries, accelerating the rehabilitation process, body temperature regulation and also spinal cord neuroprotection.[3] In addition to these well-known benefits of using creatine, mostly by athletes or professional players, creatine supplementation may also serve as a complementary treatment to conventional medical interventions.[5] In recent years, researchers have studied prospects of creatine exploit in conditions such as diabetes[6,7], sarcopenia[8,9], cognitive functions[10,11,12], cardiovascular health (CVD)[13–16], Huntington's Disease (HD)[17,18], osteoporosis[19] and much more.

Metabolic basis

Synthetized Cr arrives at designated tissues through transport via the blood vessel route and intracellular transport moderated by a neurotransmitter called creatine transporter (CrT), which is dependent on chloride and sodium ions.[20] Even though, some of the previously mentioned tissues may synthesize Cr on their own, CRT is essential to carry endogenous and exogenous Cr to distant cells with high energy demands to maintain appropriate physiological function.[21]

Creatine and its phosphorylated form are crucial in preserving adenosine triphosphate (ATP) accumulation in cells with high-energy requirements e.g. myocytes, cardiomyocytes, hepatocytes, enterocytes, inner ear cells, kidney cells, spermatozoa, and photoreceptor cells.[22]

After reaching the intracellular territory, the enzyme - creatine kinase (CK) starts the reversible transphosphorylation reaction, leading to the creation of PCr. Phosphocreatine and creatine are smaller molecules and less negatively charged than the ATP and adenosine diphosphate (ADP) in cells expressing CK, what reflects a thermodynamic and functional evolution in energy metabolism.[23]

PCr is used as a substrate of reaction leading to produce ATP from ADP. Myocytes have storage of ATP and PCr for approximately 10 seconds of energetic exercising. Creatine supplementation effects in a total Cr concentration increase of 10% to 30%, followed by PCr accumulation increased by 10% to 40%.[2]

Creatine is involuntarily degraded to creatinine (Crn) in a nonenzymatic process depending on pH and temperature. Crn can propagate out of the cells to be further eliminated by the kidneys into the urine.[24]

Creatine dosing

Currently, there are no rigid rules regarding dosage and the period of supplementation needed to achieve a given effect. A recent researches show that the Cr doses are ranging from 0.03 g/kg/day up to 5 g/d.[25,26]

There is also a tendency, mostly among the athletes, to implement a loading dose of creatine before the introduction of a daily maintenance dose. A widely accepted loading dose ranges from 20 to 25 g/day, in 4 doses for a period of 5 to 7 days. The ISSN propose a loading dose of 0.3 g/kg/day in divided doses for at least 3 days.[2]

Safety concerns

Numerous published RCTs are providing evidence on safety of creatine supplementation. The studies have been performed in both athletic and general population groups, including supplementation for various periods of time (even up to 5 years) and not any inauspicious changes in clinical health markers were shown.[27,28]

In addition to this, the assessment of the side effects reports related to dietary supplementation, including adolescent populations, have exposed that the creatine was exceptionally recalled and was not linked with any substantial number or consistent pattern of deleterious incidents.[3,29] The literature has not provided any confirmation that creatine may promote renal dysfunction[30–32] or has long-term detrimental effects.[3,33,34]

Furthermore, as previously mentioned, the possible medical uses of creatine supplementation that lead to general health improvement, well-being and provide beneficial therapeutic effects in populations ranging from adolescents to elders has evolved without recognizing any significant risks or side effects.[3] Wallimann et al. endorsed that individuals ought to ingest 3 g/d of Cr throughout the lifespan in order to promote general health.[35]

Effects on sports

Creatine is a well-recognized supplement in the sports community considering mainly its effects in enhancing performance and endurance, increasing muscle mass, anti-catabolic effects, counteracting oxidative stress[36], as well as in preventing injuries and accelerating medical rehabilitation processes.[37]

Greydanus and Patel in their work from 2010 claim that Cr supplementation helps gain lean body mass. Authors state that it also helps improving power, strength and efficacy in short-duration, intense drills.[38]

Gaining body mass has been observed in individuals using a creatine supplement without regular exercising. On the other hand, taking creatine in combination with a resistance training program showed significantly larger increases in body mass.[39]

Moreover, the creatine helps in prevention of strength loss induced by concurrent exercise.[40]

Presently, the availability of scientific evidence indicates that creatine supplementation is useful in boosting performance in short-duration, high-intensity resistance training with significant results in gaining lean body mass. However, the unambiguous translation of these effects on the field of play remains unexplored.[2]

Effects on glycemic control

The beginnings of research in this direction were initiated by Alsever et al.[41] and Marco et al.[42] in the 1970s. Both groups of scientists proved, on in vitro models, that creatine is able to moderately increase insulin secretion.

Pinto et al. in their meta-analysis make conclusions that Cr supplementation, especially in conjunction with training, may possibly affect glucose uptake. Additionally, it is believed that creatine can reinforce capacity on glucose transporter and AMPK-α protein, increasing insulin sensitivity. However, authors point out that there are not sufficient evidence from clinical interventions testing the effects of creatine supplementation in glucose metabolism, hence the subject needs further research.[43]

Also Solis et al.[7] in their work indicates that argumentation supporting the impact of creatine on glucose metabolism remains hypothetical. The evidence is difficult to analyze as creatine responses are strongly dependent on the experimental model established.

Based on the available evidence, it can be legitimately assumed that Cr supplementation may help in healthy glucose management.[5]

Effects on vascular health

In 2001 Arciero et al.[44] tested positive impact of creatine supplementation on blood flow in the lower limb (calf) and forearm. The study was performed on 30 healthy, male volunteers who were divided into 3 groups (Cr + resistant training, Cr alone and placebo). Authors reported that statistically significant results were obtained only in the Cr + resistant training group. All things considered, we can assume that results of this experiment only indicate a synergistic or additive effect resulting from Cr ingestion.

Further studies by Van Bavel et al.[13] and Moraes et al.[45] in their studies focused on the influence of creatine supplementation on microvasculature. Systemic microcirculation, microvascular reactivity, and skin capillary density were evaluated.

The first group of researchers performed study on patients who were on strict vegan diet. Subjects were divided into 2 groups (5g/day of Cr for 3 weeks, and placebo control group). Results showed that the basal capillary density of the test group was found to be significantly higher comparing with the placebo group. Moreover, the authors reported notable increase, during post-occlusive reactive hyperemia, in capillary recruitment. Not any specific activity of Cr were assessed to these benefits. [13]

The second group of scientists claim that vascular reactivity presented significant improvement in response to Cr supplementation. Like previously, there wasn't any direct mechanism of Cr reported, but it is discussed by the authors that Cr may lead to an increased bioavailability of epoxyeicosatrienoic acid (EET) and hence improvement of EDHF stimulation and microvascular dilation. However, due to the lack of an adequate control group, the results of this study must be taken with a pinch of salt.[45]

Effects on cognitive functions

It is reported that the Cr supplementation may increase brain PCr concentration by 5 to 15%, thus improving brain bioenergetics.[46,47]

In 2002, an interesting discovery was made by Watanabe and collaborators, who have stated that Cr supplementation 8 g/day for 5 days caused increased oxygen utilization in the brain cells, what led to a reduction of mental fatigue in subjects.[48]

Evidence-based medicine have found that creatine supplementation may be a powerful tool in suppressing mental fatigue and/or improving cognitive and executive functions and/or memory.[5,10,49]

In 2009, Ling and associates have demonstrated that perception on some duties was improved after Cr supplementation.[50]

Given the currently available reports, it seems reasonable to conclude that creatine supplementation contributes to increasing brain creatine concentration and/or support cognitive function, especially as one ages.[5]

Effects on neurodegenerative diseases and muscular dystrophy

The usefulness of creatine has been the subject of many studies including its effects on neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS).[5,51]

Some of the studies, especially in vitro research, indicated improved fatigue tolerance and/or clinical outcomes. On the other hand, Bender et al. in their huge clinical trial, performed on 1687 patients, on influence of Cr on PD, HD, and ALS did not verified the optimistic thesis and didn't find any significant difference between the test and the control groups.[52]

The reason animal studies may have presented more optimistic outcomes may be dictated by the fact that humans usually don't show symptoms of neurodegenerative diseases unless they have lost 70% or more of their α-neurons.[5]

What attracts attention is that results of Cr supplementation in patients suffering from muscular dystrophies(MDs) have been more encouraging because the muscle is the main target. Kley et al. in their review mentioned that short- and medium-term Cr supplementation is improving muscle strength and enhancing overall performance in patients suffering from MDs and inflammatory myopathies, but no significant changes were reported from high-quality RCTs on patients suffering from metabolic myopathies.[53]

Hence, while Cr n have been proven to own neuroprotective abilities, improve muscle mass, strength and endurance in human population, the efficiency of its extended, high-dose supplementation is yet to be proven in neurodegenerative diseases, while promising results were obtained in patients with muscular dystrophy.

Summary

The potential benefits of creatine supplementation go far beyond increasing muscle Cr and PCr concentration and thus enhancing performance and training adaptations. Studies have clearly shown a few potential general health and therapeutic benefits, particularly as we age.

Despite the fact that additional research is necessary to explore further the health and potential therapeutic benefits of creatine supplementation

Further studies should focus on examining the potential medical benefits of creatine monohydrate and precursors like guanidinoacetic acid on sport, health and medicine.

Currently, creatine doesn't seem to replace any of standard treatment protocols, but can be a valuable tool in the treatment process, however more high-quality scientific evidence is needed to unequivocally determine its usefulness.

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