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CREATINE SUPPLEMENTATION: NEW INSIGHTS AND PERSPECTIVES ON BONE AND BRAIN HEALTH

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KEY POINTS

- Creatine is an effective dietary supplement to enhance muscle mass and performance (i.e., strength, endurance, power) when combined with a resistance training program.
- Creatine can increase the activity of osteoblasts (cells involved in the bone formation process), reduce bone resorption (loss), and when combined with resistance training can increase the muscle-to-bone interaction.
- There are some studies in clinical and aging populations that show positive effects from the combination of creatine and resistance training on measures of bone mineral and strength compared to placebo.
- Creatine supplementation may increase brain creatine levels, measures of cognitive function (e.g., memory, processing speed, and executive function), and sport skill execution. These effects appear to be stronger when the brain is stressed (e.g., sleep deprivation, mental fatigue, or hypoxia) and with higher doses of creatine (≥ 10 g/day).
- Preliminary data suggests that creatine has some ability to enhance recovery following traumatic brain injury in young adults (concussion) and decrease symptoms of depression in clinical populations.
- There are limited data evaluating the effects of creatine on neurological diseases. Some studies have shown beneficial effects in young males with muscular dystrophy and in stroke survivors, while there is currently no evidence to indicate that creatine significantly benefits those with Alzheimer's, Parkinsons', Multiple Sclerosis, or Amyotrophic Lateral Sclerosis disease.

INTRODUCTION

One of the most researched and effective dietary supplements is creatine monohydrate (Antonio et al., 2021). Creatine is a naturally derived nitrogen-containing molecule endogenously synthesized in the liver and brain from reactions involving the amino acids arginine, glycine and methionine (Wyss & Kaddurah-Daouk, 2000). Therefore, creatine is technically considered a non-essential nutrient (Persky et al., 2003). Beyond endogenous synthesis, creatine can be obtained in the diet from food products such as red meat and seafood (i.e., ~ 5 g of creatine per 1 kg of meat) (Persky et al., 2003) or through the ingestion of commercially manufactured products containing creatine (Kreider et al., 2022). Upon ingestion or release from the liver, creatine enters the systemic circulation and gains entry into energetically demanding tissues, primarily skeletal muscle, through a creatine-specific transporter (Persky et al., 2003). In the human body, almost the entirety of creatine (~ 95%) is stored within skeletal muscle (Kreider et al., 2017), with the remainder stored across other tissues such as bone and brain (Walker, 1979). Within the cell, approximately 66% of creatine is bound to phosphate and stored as phosphorylcreatine (PCr) (Persky et al., 2003), which can combine with adenosine diphosphate (ADP) to rapidly resynthesize adenosine triphosphate (ATP) during and following muscle contractions (McCall & Persky, 2007). Therefore, increasing intramuscular creatine stores would likely increase high-energy phosphate metabolism and exercise training capacity (Kaviani et al., 2020; Kreider et al., 2017). The total intramuscular creatine pool amounts to ~ 120 mmol/kg dry muscle mass for the average omnivore which is likely reduced in vegans or vegetarians (Kaviani et al., 2020) and older populations (Chilibeck et al., 2017; Kreider et al., 2022). Creatine supplementation further increases intramuscular creatine stores by ~ 20-40% (Harris et al., 1992; Hultman et al., 1996) and influences protein and calcium kinetics, myogenic regulatory factors, satellite cells, growth factors, oxidative stress and inflammation (Chilibeck et al., 2017). These mechanisms help explain the plethora of research showing improvements in measures of muscle mass and performance (i.e., strength, endurance, power) in young and older populations after supplementing with creatine (Burke et al., 2023; Candow et al., 2021a, b, 2022a; Forbes et al., 2021a, 2023; Kreider et al., 2017, 2022). Seminal studies in the 1990s by Dr. Roger Harris and Dr. Eric Hultman established effective creatine ingestion strategies to increase intramuscular creatine stores. Collectively, ingesting 20-30 g of creatine (i.e., creatine-loading; 4-6 x 5 g throughout the day) for ≥ 4 days (Harris et al., 1992) or 3 g/day of creatine for 28 days (Hultman et al., 1996) increased total muscle creatine stores by ~ 20%. Upon creatine cessation, elevated creatine stores took up to 30 days to return back to pre-supplementation levels (Harris et al., 1992; Hultman et al., 1996). It is important to note that the "responsiveness" to creatine supplementation is primarily dictated by initial intramuscular creatine levels (Harris et al., 1992; Syrotuik & Bell, 2004). Those with lower intramuscular creatine stores (i.e., vegans, vegetarians) will respond more favorably (i.e., greater increases in muscle levels) compared to those with higher initial creatine stores (i.e., omnivores) (Kaviani et al., 2020). Further, there are some evidence-based strategies that enhance creatine uptake into skeletal muscle. For example, creatine could be ingested with high-glycemic carbohydrates and/or protein (Steenge et al., 2000), both of which stimulate insulin release and augment muscle creatine retention (Green et al., 1996). In addition, creatine ingestion in close proximity to exercise appears to enhance creatine uptake, possibly through muscle-induced stimulation of creatine transport kinetics (Persky et al., 2003). However, there is no evidence that the timing of creatine supplementation influences the physiological adaptations from resistance training (Candow et al., 2022b; Forbes et al., 2021b).

In addition to the well-established effects of creatine supplementation on skeletal muscle, there is accumulating research showing that creatine may have some favorable effects on bone tissue and the brain. These findings could have clinical significance for populations at risk for accelerated bone loss, neurological diseases, and brain injury. The purpose of this Sports Science Exchange article is to highlight recent evidence examining the efficacy of creatine supplementation on bone biology, and brain health and function in various populations.

CREATINE AND BONE

There is a growing body of research showing some beneficial effects of creatine supplementation on measures of bone biology (both from bone preservation and formation perspectives) across a variety of human populations. In two studies involving young boys with muscular dystrophy (a condition that leads to accelerated bone loss), creatine supplementation (3-5 g/day) for 3-4 months decreased the urinary excretion of cross-linked n-telopeptides of Type I collagen (NTx), an indicator of bone resorption, by 19-33% compared to placebo (Louis et al., 2003; Tarnopolsky et al., 2004). There is additional evidence that creatine supplementation (~ 9 g/day) during 5-10 weeks of resistance training significantly reduced NTx release in healthy young (Cornish et al., 2009) and older adults (Candow et al., 2008). Mechanistically, creatine increases osteoblast cell activity (Gerber et al., 2005) which increases their production of osteoprotegerin, a cytokine that inhibits the differentiation of osteoclast cells involved in the bone resorption process (Yasuda et al., 1998). A few studies have shown that creatine supplementation (8-10 g/day) and resistance training (12-52 weeks) increases upper-limb bone mineral content (Chilibeck et al., 2005), lower-limb total bone area (Candow et al., 2021a) and femoral shaft subperiosteal width (an indicator of bone bending strength) and decreases the rate of bone mineral density loss in older adults (Chilibeck et al., 2015). These results may be exercise dependent as creatine supplementation alone (with no exercise stimulus) fails to produce similar bone benefits in older adults (Lobo et al., 2015; Sales et al., 2020). Potentially, greater muscle accretion from creatine supplementation and resistance training may act as a pulley and bone as a lever which over time, could stimulate bone formation (Kirk et al., 2020). Collectively, creatine supplementation has the potential to have favorable effects on bone tissue, possibly by influencing the bone remodeling process. These preliminary findings may have clinical applications for conditions associated with accelerated bone loss, such as muscular dystrophy, osteoporosis, and frailty.

CREATINE AND THE BRAIN

There is emerging research interest focused on the potential applications of creatine supplementation for improving brain health and function (Forbes et al., 2022). The brain is highly energetic (utilizes 20% of total energy expenditure at rest) and requires a constant supply of ATP. The importance of creatine for proper brain function is clearly demonstrated in individuals suffering from creatine deficiency syndromes, which are characterized by developmental delays, learning disabilities, seizures, and movement disorders (Stöckler et al., 1994). Further, several neurological disorders are associated with low brain creatine levels (Ostojic, 2022). The brain is unique in that it endogenously synthesizes creatine and permits entry of creatine from the circulation across the blood-brain barrier (Braissant et al., 2007). However, the brain appears to have a limited capacity for creatine uptake (Braissant et al., 2007) as creatine supplementation only increases brain creatine content by ~ 6% (Dolan et al., 2018; Fernandes-Pires & Braissant, 2022). Subsequently, speculation exists that high creatine dosages (e.g., 10-20 g/day) for extended periods of time (i.e., months) may be required to elevate brain creatine levels to produce meaningful brain benefits. However, large-scale dose-response studies involving creatine and measures of brain health and function have yet to be performed.

Cognitive Benefits

There is evidence that creatine supplementation can improve some measures of cognition (reviewed in Forbes et al., 2022). For instance, creatine has been shown to improve memory, particularly in older adults (Prokopidis et al., 2023a). Further, there are also sport-specific skill execution benefits following creatine supplementation. A recent study examined ten elite rugby players that completed 10 trials on a passing skill test following a night of normal sleep or when sleep deprived (3-5 hr of sleep) with and without creatine. Sleep deprivation significantly reduced passing accuracy, however, this reduction was abolished by creatine supplementation (acute doses of 4.5 and 9 g) (Cook et al., 2011). These results provide preliminary evidence that acute ingestion of creatine has the ability to maintain cognitive function when the brain is stressed, which may have implications for athletes who have difficulty sleeping prior to a competition or match or during the later/end stages of competition. For example, 7 days of creatine supplementation (20 g/day) prior to performing a 19.2 km time trial in mountain bikers significantly increased cognitive performance on several standardized computer cognitive tests, including a go-no-go reaction time test, Erikson Flanker task, and a Corsi block test when assessed immediately post-exercise (Borchio et al., 2020). However, two studies performed in soccer players found no greater effect from creatine (20 g/day for 6-7 days) on shooting accuracy, compared to placebo in a non-stressed situation (Cox et al., 2002; Mohebbi et al., 2012). While research is limited, these findings indicate that creatine has the ability to maintain or improve measures of cognition during stressful situations (e.g., after exercise or sleep deprivation). These results are further supported by non-sport research studies showing beneficial effects from creatine supplementation on cognitive function following mental fatigue (Van Cutsem et al., 2020), sleep deprivation (McMorris et al., 2006, 2007), hypoxia (Turner et al., 2015) and in older adults (Prokopidis et al., 2023b).

Traumatic Brain Injury

Another major focus area of creatine research involves traumatic brain injury (TBI). Following a TBI there is a significant reduction in brain creatine content (Vagnozzi et al., 2013) as evidenced by the negative correlation between cumulative head impacts and brain creatine levels in former professional football players (Alosco et al., 2020). It has been proposed that creatine supplementation could enhance recovery following a TBI (Dolan et al., 2019). In animal models, creatine supplementation attenuated or reduced brain damage following exposure to a TBI (Sullivan et al., 2000). Limited data exists in humans, with only two open-label studies, however, the results appear promising as creatine supplementation (0.4 grams/kg/day) for 6 months improved measures of cognition, communication, self-care, personality and behavior and decreased the incidence of headaches, dizziness, and fatigue in children and adolescents who were diagnosed with a concussion (Sakellaris et al., 2006; 2008). It is important to note that brain creatine levels were not measured in these studies. These positive findings may have application for other populations at high risk for TBI, such as athletes and military personnel. A recent systematic review concluded that creatine supplementation has the potential to provide service members or medics with an additional tool to bridge the gap between a poor or positive TBI prognosis (Newman et al., 2023).

Mood Disorders

Mood disorders, including generalized depression and anxiety, are prevalent in both the general population and athletes (Bär & Markser, 2013; Kessler et al., 2005). There is a growing body of research demonstrating an association between brain creatine content and mood disorders. For example, Kondo et al. (2016) and Faulkner et al. (2021) found negative correlations between creatine content in the prefrontal cortex and depressive symptoms in adolescents and adults. In a large study involving >20,000 adults who were categorized based on habitual dietary intake of creatine, the authors found that those who consumed the lowest amounts of creatine had the highest prevalence of depressive symptoms (10.23/100 persons) compared to those ingesting the highest amounts of creatine (5.98/100 persons) (Bakian et al., 2020). Creatine supplementation reduced symptoms of depression in small cohort populations of individuals diagnosed with major depressive disorder (Kious et al., 2019) and reduced symptoms of anxiety in individuals with methamphetamine dependence (Hellem et al., 2015). These beneficial effects may be related to creatine functioning as a neurotransmitter, increasing brain-derived neurotrophic factor (BDNF) and/or reducing oxidative stress which may have favorable effects on brain bioenergetics over time (Cunha et al., 2018; Kious et al., 2019).

Neurodegenerative Diseases

Since many neurological diseases are associated with reduced brain creatine content, supplementing with creatine may serve as an effective therapeutic countermeasure to various disease characteristics. However, research to date in human populations is mixed, with only a few studies showing some benefits (Forbes et al., 2022). Collectively, creatine supplementation has been shown to improve measures of muscle and bone mass, muscle performance and exercise tolerance in young boys with Duchenne and Becker's muscular dystrophy (Louis et al., 2003; Tarnopolsky et al., 2004). In stroke survivors, creatine supplementation (0.1 g/kg/day) during 10 weeks of supervised resistance training improved walking performance over time (Butchart et al., 2022). In contrast, creatine does not significantly improve disease characteristics in those with Alzheimer's or Parkinsons' disease, Multiple Sclerosis or Amyotrophic Lateral Sclerosis (Forbes et al., 2022). Large-scale randomized controlled trials are needed to determine with greater certainty whether creatine, with and without resistance training, has any beneficial effects on various neurological diseases.

SUMMARY AND PRACTICAL APPLICATIONS

Creatine is a well-established ergogenic aid that enhances resistance training adaptations, including gains in muscle mass and performance. Beyond skeletal muscle, the combination of creatine supplementation and resistance training has been shown to enhance markers of bone mineral and strength and reduce markers of bone resorption in clinical and older populations. Further, creatine supplementation can elevate brain creatine levels, thereby positively influencing cognitive function, particularly when the brain is stressed (i.e., sleep deprivation, mental fatigue, and hypoxia). Lastly, there is preliminary research that shows some beneficial effects from creatine in young males with Muscular Dystrophy and in stroke survivors but creatine fails to benefit those with Alzheimer's or Parkinson's disease, Multiple Sclerosis, or Amyotrophic Lateral Sclerosis. Overall, creatine appears to be one of the most effective and versatile supplements with emerging data that creatine can impact bone tissue and the brain.

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