Creatine in Health and Disease

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Contributor: Jeffrey Stout , Richard Kreider

Creatine has been mostly studied as an ergogenic aid for exercise, training, and sport, several health and potential therapeutic benefits have been reported. This is because creatine plays a critical role in cellular metabolism, particularly during metabolically stressed states, and limitations in the ability to transport and/or store creatine can impair metabolism.

ergogenic aids cellular metabolism phosphagens sarcopenia cognition diabetes creatine synthesis deficiencies concussion traumatic brain injury spinal cord injury muscle atrophy rehabilitation pregnancy immunity anti-inflammatory antioxidant anticancer

1. Introduction

Creatine supplementation is one of the most studied and effective ergogenic aids for athletes [1]. The multifaceted mechanisms by which creatine exerts its beneficial effect include increasing anaerobic energy capacity, decreasing protein breakdown, leading to increased muscle mass and physical performance [1]. While these well-recognized creatine effects benefit the athlete, creatine may also serve as a potential clinical and therapeutic supplementary treatment to conventional medical interventions [2][3][4][5][6][7][8][9][10]. In this regard, over recent years, researchers have been investigating the potential therapeutic role of creatine supplementation on health-related conditions such as diabetes [11], sarcopenia [4][6][12][13], osteoporosis [2][14], cancer [10][15][16][17][18], rehabilitation [4][19][20][21][22][23][24][25][26], cognition [3][27][28][29], and cardiovascular health [5][6][8][30][31][32], among others.

2. Role of Creatine in Aging Populations

Several studies have evaluated the effects of creatine supplementation in older populations in an attempt to prevent sarcopenia, maintain strength, and/or reduce the risk of chronic disease. The following discusses some of these potential applications.

2.1. Muscle Mass, Strength, Bone and Body Composition

Sarcopenia is an age-related muscle condition characterized by a reduction in muscle quantity, muscle strength, and functional capacity. Although multifactorial, sarcopenia may be caused by changes in muscle protein kinetics (synthesis and breakdown), neuromuscular function, inflammation, physical activity, and nutrition [12][14]. We also generally lose strength, muscle mass, bone mass, balance while increasing body fat as we age, whether clinically diagnosed with sarcopenia or not [3][33][34]. A number of nutritional and exercise interventions have been suggested to counteract sarcopenia in older individuals, including creatine supplementation during resistance training [12][14]. For example, Brose and colleagues [35] were among the first to report that creatine supplementation (5 g/day for 14 weeks) during heavy resistance training promoted greater gains in muscle mass and isometric muscle strength in older adults (>65 years). Chrusch and coworkers [36] reported that older participants (60–84 years) who supplemented their diet with creatine (0.3 g/kg/day for 5 days and 0.07 g/kg/day for 79 days) during supervised resistance training (3 days/week for 12 weeks) experienced greater gains in lean tissue mass, lower-body maximal strength, and endurance, and isokinetic knee flexion/extension power compared to controls. Candow and colleagues [37] reported that creatine (0.1 g/kg/day) and protein (0.3 g/kg/day) supplementation increased muscle mass and strength while decreasing protein degradation and bone resorption markers in older men. Chilibeck and associates [38] found that creatine supplementation (0.1 g/kg/day) during 12 months of resistance training increased strength and bone density in postmenopausal women. Gualano and coworkers [39] reported that creatine supplementation (20 g/day for 5 days; 5 g/day for 161 days) during resistance training improved appendicular lean mass and muscle function in older vulnerable women and that creatine supplementation alone resulted in similar gains in muscle mass compared to those engaged in resistance training alone. Aguiar and coworkers [40] also found that creatine supplementation (5 g/day for 12 weeks) combined with resistance training improved muscle endurance, ability to perform functional tasks, maximal strength, and muscle mass in older women.

Additionally, McMorris et al. [41] reported that creatine supplementation (20 g/day for 7 days) after sleep deprivation improved balance measures. Bernat and colleagues [42] reported that creatine supplementation (0.1 g/kg/day) during 8 weeks of high-velocity resistance training in untrained healthy aging men promoted significantly greater gains in leg press and total lower-body strength, muscle thickness, and some measures of peak torque and physical performance. Moreover, a meta-analysis revealed that older individuals participating in resistance training experienced greater gains in muscle mass, strength, and functional capacity when supplementing their diet with creatine [43]. A similar meta-analysis conducted by Candow and colleagues [9] found that older individuals who took creatine during resistance training experienced significantly greater gains in muscle mass and upper body. While not all studies report statistically significant effects, the preponderance of available research supports contentions that creatine supplementation, when combined with resistance exercise, can help maintain or increase muscle mass, strength, and balance in older individuals and therefore serve as an effective countermeasure to attenuate sarcopenia. The role of creatine supplementation during resistance training in sarcopenic populations will be discussed in more detail in this paper series on aging, sarcopenia, and bone health.

In addition, people often experience adult-onset obesity as they age, prompting them to diet to promote weight loss. Unfortunately, this often leads to loss of muscle mass and strength, which would be counterproductive in older individuals. Creatine supplementation while following an energy-restricted diet may be an effective strategy to maintain muscle mass, promote fat loss, and help manage adult-onset obesity. In support of this contention, Forbes and colleagues [44] recently conducted a meta-analysis on the effects of creatine on body composition and found that creatine supplementation may not only help maintain muscle mass but also promote fat mass loss. This strategy could be helpful in preventing or managing adult-onset obesity. Thus, although more research is needed, it can be reasonably concluded based on available literature that creatine supplementation, particularly when combined with resistance training, can promote gains in strength and help maintain or increase muscle mass and bone density in older individuals. Further, creatine supplementation during energy-restriction-induced weight loss interventions may be an effective way to preserve muscle mass, promote fat loss, and thereby help manage adult-onset obesity.

2.2. Cognitive Function

Creatine supplementation has been reported to increase brain PCr content by 5–15% and thereby enhance brain bioenergetics [21][45][33][34][46]. Consequently, research has examined whether creatine supplementation affects cognition, memory, and/or executive function in older individuals as well as patients with mild cognitive impairment [47][48][41][49][50]. Several studies have found that creatine supplementation attenuates mental fatigue [27][28][51] and/or can improve cognition, executive function, and/or memory [28][47][51][48][49][52]. For example, Watanabe and associates [53] found that creatine supplementation (8 g/day for 5 days) increased oxygen utilization in the brain and reduced mental fatigue in participants performing repetitive mathematical calculations. Rae et al. [49] found that working memory and processing speed increased with creatine supplementation (5 g/day for 6 weeks). McMorris and colleagues [41] reported that sleep-deprived participants better maintained random movement generation, time to react to choices, mood state, and balance when supplemented with creatine (20 g/day for 7 days). These researchers also reported that random number generation, forward spatial recall, and long-term memory tasks were significantly improved in elderly participants when supplemented with creatine. Ling et al. [50] also reported that cognition on some tasks was improved with creatine ethyl ester supplementation (5 g/day for 15 days). More recently, VAN Cutsem and coworkers [27] reported that creatine supplementation (20 g/day for 7 days) prior to performing a simulated soccer match improved muscular endurance and prolonged cognitive performance. While more research is needed and not all studies show benefit [51][54], it can be reasonably concluded based on current scientific evidence that creatine supplementation may increase brain creatine content and/or support cognitive function, particularly as one ages.

2.3. Glucose Management and Diabetes

Creatine uptake into tissue is influenced by glucose and insulin [55][56][57]. Creatine supplementation has also been reported to prevent declines in the GLUT-4 transporter during immobilization while increasing GLUT-4 by 40% during rehabilitation after atrophy [58]. Moreover, co-ingestion of creatine with carbohydrate [59][60] or creatine with carbohydrate and protein [61] has been reported to increase creatine uptake and/or muscle glycogen levels [59][61][62]. Consequently, research has evaluated whether creatine supplementation may influence glucose management [10][11][58][63][55][64]. For example, Gualano et al. [63] evaluated the effects of creatine supplementation (5 g/day for 12 weeks) during training in participants with type 2 diabetes. The researchers found that creatine supplementation improved glucose tolerance to ingesting a standard meal, increased GLUT-4 translocation, and promoted a significant reduction in HbA1c levels. Moreover, the AMPK-alpha protein content tended to be higher after Cr supplementation and was significantly related to the changes in GLUT-4 translocation and Hb1Ac levels, suggesting that AMPK signaling may be implicated in the effects of supplementation on glucose uptake in type 2 diabetes [64]. Thus, there is evidence to suggest that creatine supplementation enhances glucose uptake and insulin sensitivity and, therefore, can help individuals manage glucose and HbA1c levels, particularly when initiating an exercise program [10][11][65]. Based on this literature, it can be reasonably concluded that **c**reatine supplementation may support healthy glucose management.

2.4. Heart Disease

Coronary artery disease limits blood supply to the heart, thereby increasing susceptibility to ischemic events, arrhythmias, and/or heart failure. Creatine and PCr play an important role in maintaining myocardial bioenergetics during ischemic events [21]. For this reason, there has been interest in assessing the role of creatine or PCr administration in reducing arrhythmias, ischemia-related damage, and/or heart function in individuals with chronic heart failure [66][67][68][69][70][71][72][73][74][75][76]. For example, Anyukhovsky et al. [74] reported that intravenous administration of PCr and phosphocreatinine (300 mg/kg) in canines prevented the accumulation of lysophosphoglycerides in the ischemic zone of the heart, which is associated with an increased prevalence of arrhythmias. The researchers concluded that this might explain the antiarrhythmic action of PCr and phosphocreatinine in acute myocardial ischemia. Sharov and coworkers [73] reported that exogenous PCr administration protected against ischemia in the heart. Likewise, Balestrino and coworkers [21] evaluated the effects of adding PCr to cardioplegic solutions on energy availability during myocardial ischemia. The researchers found that PCr administration improved energy availability to the heart, reduced the incidence of arrhythmias, and improved myocardial function. As noted below, there is also evidence that creatine supplementation may maintain energy availability during brain ischemia and reduce stroke-related damage. Moreover, several studies have reported some benefit of oral creatine supplementation in heart failure patients participating in rehabilitation programs [77][78][79][80]. While not all studies report benefit from oral creatine supplementation [23][81] and more research is needed, current evidence suggests that phospho**c**reatine administration and possibly creatine supplementation support heart metabolism and health, particularly during ischemic challenges.

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