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Review

The Effects of Creatine Supplementation on Markers of Muscle Damage and Inflammation Following Exercise in Older Adults: A Brief Narrative Review

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Abstract

Exercise induced muscle damage occurs following strenuous and unfamiliar exercise and results in biomarkers of muscle damage and inflammation in the circulation. Creatine (Cr) is a commonly utilized nutritional supplement which has been proposed to enhance post-exercise recovery and has been suggested to decrease exercise induced inflammation. Exercise is well recognized to be beneficial for older adults to maintain skeletal muscle mass and strength as well as promote health for other biological systems. However, older adults can experience chronic low-grade inflammation, sometimes referred to as 'inflammaging'. Therefore, it may be prudent to limit post-exercise induced skeletal muscle damage and inflammation for the older adult population who may already be in a pro-inflammatory state and at risk of age-related muscle loss (sarcopenia). The purpose of this brief narrative review is to outline the current research on Cr and its effects on biomarkers of muscle damage and inflammation in

older adults. Further, the review will suggest areas of research that are required to fully understand how Cr supplementation may affect muscle damage and inflammatory biomarkers in older adults who exercise.

Keywords
Creatine; creatine kinase; aging; anti-inflammatory

1. Introduction

Exercise-induced muscle damage (EIMD) occurs to varying degrees following a bout of exercise to a magnitude dependent on factors such as exercise intensity, volume, mode of exercise, muscle group being contracted and genetic variables [1]. EIMD is often characterized by delayed onset muscle soreness (DOMS), periods of decreased strength and functionality as well as increased circulating biomarkers of inflammation, muscle proteins and oxidative stress [2, 3]. EIMD can result in decreased training ability (due to the decrease in strength performance) [4, 5] and possibly result in decreased exercise induced biological adaptations [6].

Creatine monohydrate (Cr) is a highly researched nutritional supplement with many known benefits including increasing lean tissue mass in younger and older adults [7, 8]. Recent evidence suggests that although Cr supplementation may not increase the rate of recovery of muscle strength or delayed onset muscle soreness, it may result in lower creatine kinase (CK) levels [9] and inflammation [10] 48-hours post-exercise suggesting a possible effect on EIMD. The mechanisms through which Cr may benefit EIMD are not clear. Oral Cr supplementation results in higher muscle phosphocreatine (PCr) concentrations [11] which may stabilize the membrane of muscle cells and decrease membrane fluidity [12]. Therefore, the increase in phosphocreatine as a result of Cr supplementation may be protective from hard exercise and maintain intramuscular structure [13].

Older adults can experience age-related loss of skeletal muscle mass and strength, and loss of physical functioning which is referred to as sarcopenia. Individuals with sarcopenia may be at increased risk of all-cause mortality and disability [14]. It has been postulated that combining Cr supplementation with resistance exercise training can slow the rate of muscle and bone loss, decrease fat mass, and improve physical performance and daily functioning in older adults [15, 16]. However, the effects of Cr supplementation along with exercise training on biomarkers of inflammation and muscle damage has not been extensively studied in the older adult population. Older adults are at increased risk of a heightened pro-inflammatory state known as ‘inflammaging’ and thus, may respond differently to acute or chronic bouts of exercise when supplementing with Cr. Thus, the purpose of this brief review is to outline the current studies which have evaluated the effects of Cr supplementation on markers of muscle damage and inflammation following exercise in older adults.

2. Discussion

2.1 Markers of Muscle Damage

The literature evaluating the effects of creatine supplementation on markers of muscle damage in older adults is limited [17, 18]. One study aimed to determine if supplementing with Cr would enhance muscle strength and fat free mass to a greater extent than placebo following a resistance training protocol, but as part of their investigation the researchers also evaluated systemic blood concentrations of CK as an indirect biomarker of skeletal muscle damage [17]. Twenty-eight older adults (male: n = 15, age = 67.8 ± 4.0 yrs.; female: n = 13, age = 69.3 ± 6.3 yrs.) were randomized and received either Cr (5 g Cr + 2 g dextrose per day) or placebo (7 g dextrose per day) for 14-weeks and simultaneously completed resistance training 3-days per week over that time. Participants underwent a medical evaluation and screening with an electrocardiogram before and after a graded cycle test up to 6 metabolic equivalents (METs). Participants were excluded if they smoked or there was evidence of coronary or congestive heart disease, uncontrolled hypertension, chronic obstructive pulmonary disease, diabetes mellitus, renal failure, or major orthopedic disability. The resistance training consisted of both upper and lower body muscle groups performed in a circuit format. Upper body exercises were performed for 10 repetitions while remaining exercises were completed for 12 repetitions progressing from 1 set at 50% of the participants one-repetition maximum (1RM) to 3 sets of 80% 1RM by the end of the training period. The resistance training protocol resulted in greater muscle strength, functional performance, and muscle fiber area regardless of treatment group. However, Cr supplementation resulted in increased plasma CK levels (male: before training = 53.3 ± 31.5 U/L vs. after training = 107.4 ± 76.4 U/L; female: before training = 83.3 ± 85.0 U/L vs. after training = 112.3 ± 98.2 U/L) compared to the placebo group (male: before training = 83.7 ± 50.0 U/L vs. after training = 81.9 ± 43.8 U/L; female: before training = 67.6 ± 40.9 U/L vs. after training = 47.0 ± 22.1 U/L). Although it appears that Cr supplementation may increase muscle damage with resistance training, the authors note that these CK values were still within the normal range for older adults. The older adults in this study were healthy; however, the response of CK values to older adults that are not healthy or have chronic low-grade inflammation requires further research.

A pilot study investigated the effects of Cr supplementation on muscle damage following eccentric exercise in older adults using statins [18]. Statin medication is known to cause myalgia and may influence muscle damage biomarkers as well [19, 20]. Older men and women were randomized to receive either Cr and statins (n = 10; age = 60 ± 7 yrs.; 10 g/d Cr + 80 mg/d atorvastatin) or placebo and statins (n = 9; age = 52.6 ± 6 yrs.; ~10 g/d lactose + 80 mg/d atorvastatin) for 4-weeks. Participants were considered healthy, non-smoking, post-menopausal, did not exercise regularly (<3 days/week), were not currently dieting, consumed limited alcohol (<2 beverages/day), were not consuming dietary (i.e., Cr, coenzyme Q10, protein) or anabolic supplements, and were not consuming other substances associated with an increased risk of statin-associated muscle symptoms when consumed with statins. At the time of recruitment, participants were not currently taking statins or other cholesterol lowering drugs, but 5 participants had previously used statins. Following the supplementation protocol, participants completed a maximal treadmill test (Bruce protocol) and after a 30-minute break completed eccentric walking exercise where they walked down a -15% grade for 45 minutes (3 bouts of 15-minutes with a 5-minute break between) at a

speed to elicit 65% of the participants maximal heart rate. The results showed that there was no difference between treatment groups for serum CK levels, muscle soreness, pain severity, or the interference of pain with the structured exercise bout. These results suggest that Cr supplementation combined with a statin medication does not negatively influence the development of muscle damage biomarkers and soreness in a cohort of older adults who complete stressful eccentric downhill walking exercise.

Taken together, the current limited evidence does not support the hypothesis that Cr supplementation can beneficially prevent or mediate muscle damage from exercise in older adults. However, the partial research also points out that there is no negative effect of Cr supplementation on muscle damage biomarkers nor muscle soreness (DOMS) after acute bouts of exercise. Future research should evaluate the effects of Cr supplementation with exercise in different diseased populations, particularly in older adults. This will help to gain a better understanding on how systemic muscle damage biomarkers, such as CK, lactate dehydrogenase, and myoglobin, will respond to acute bouts of exercise when taking Cr as a nutritional supplement. Also, future research should evaluate exercise that predominantly stresses the phosphagen energy system, such as resistance-exercise, as it is the primary energy system whereby Cr supplementation is thought to enhance performance outcomes. Although there is an abundance of research on Cr supplementation, minimal research has investigated the effects of this supplement on biomarkers of muscle damage in older adults. Furthermore, to our knowledge, there has been no research looking at how Cr supplementation with acute bouts of eccentric based resistance-exercise may influence muscle damage by directly evaluating cytoskeleton, sarcomere, and membrane damage to the sarcolemma of muscle cells via muscle tissue biopsies in older adults. It is suggested that more research evaluating this is required to fully elucidate the effects of Cr supplementation during exercise. A recent systematic review and meta-analysis demonstrated that there was a paradoxical effect of Cr supplementation whereby acute exercise with Cr supplementation lowered the EIMD response; nevertheless, this tendency was reversed with chronic exercise training [21].

2.2 Markers of Inflammation

A recent pilot study investigated whether Cr supplementation combined with a resistance training program can improve markers of inflammation in healthy older adults (n = 27; age = 67 ± 6 yrs.) [22]. Participants were excluded if they had consumed ergogenic supplements within 6-months of study participation, were taking medications which affected muscle growth or function (e.g., statins and anti-inflammatory drugs), had kidney, liver, or heart disease, followed a vegetarian/vegan or restrictive diet, or performed structured physical activity. Participants completed a 12-week resistance training program and were randomized (stratified randomization based on sex) to receive either Cr (5 g/d) or placebo (5 g/d maltodextrin). Blood samples were collected at rest prior to the resistance training and supplementation protocols and again 2-days following the completion of the training program, and were analyzed for glucose, insulin, adiponectin, leptin, interleukin-6 (IL-6), IL-10, monocyte chemo-attractant protein-1 (MCP-1) and C-reactive protein (CRP). No differences were observed between treatment groups for any outcome measure, and only MCP-1 changed in both groups (placebo, pre-treatment = 72.1 ± 68.4 pg/mL vs. post-treatment = 25.6 ± 17.5 pg/mL, $p < 0.001$; Cr, pre-treatment = 78.8 ± 43.7 pg/mL vs. post-treatment = 23.1 ± 18.6 pg/mL, $p < 0.001$) in response to the resistance training program. MCP-1 is

a chemokine which helps regulate the migration and infiltration of monocytes and macrophages [23] and thus, lowering MCP-1 may positively influence the inflammatory profile of older adults. These results suggest that Cr combined with resistance training does not have a synergistic interaction as Cr was no more beneficial than resistance training alone in modifying several biomarkers of inflammation and metabolic function.

Another study investigated the effects of Cr, as part of a multi-ingredient supplement (30 g whey protein, 2.5 g Cr, 400 mg calcium, 500 IU vitamin D and 1500 mg omega-3 polyunsaturated fatty acids), on systemic inflammation alone and in combination with exercise training (resistance exercise and high-intensity interval training) [24]. A total of 49 healthy older men (65 years of age or older) were randomized to consume either the multi-ingredient supplement or placebo (22 g carbohydrates (56 kcal)) twice daily for 18-weeks (6-weeks of treatment alone followed by 12-weeks of treatment combined with exercise training). All participants were non-smokers over the age of 60 years old, had a BMI within the normal – overweight range, blood pressure within the normal – stage I hypertension, were not participating in structured exercise programs within the 6-months of study participation, and completed an oral glucose tolerance test and exercise stress test to confirm eligibility. Participants were excluded if they had significant weight gain or loss within 6-months of study participation, were consuming non-steroidal anti-inflammatories, statins or anticoagulants, had an injury preventing safe exercise participation, had diabetes mellitus, cancer, unstable cardiac or gastrointestinal disease, or had an infectious disease. The resistance training protocol utilized two whole body resistance training sessions per week and one high intensity interval training session per week. Resistance training sessions on Mondays included chest press, horizontal row, leg press and leg extension, while Fridays consisted of lateral pulldown, shoulder press, leg press and leg extension. All exercises were performed at 80% of the participants 1 repetition maximum (resulting in 6-8 repetitions) for 3 sets, with the last set performed until participants reached volitional exhaustion. The high intensity interval training consisted of participants completing 10, 60 second intervals at a workload resulting in ~90% maximal heart rate at a cadence above 90 rpm. The work intervals were broken up with 60 seconds of cycling at 25 watts at a self-selected pace. Blood samples were collected during weeks 1 (baseline), week 6, and week 19 (at least 72 hours after the last exercise session). The multi-ingredient supplement on its own resulted in an ~1-3% decrease in IL-6 and tumour necrosis factor-alpha (TNF-α) but no change in CRP. In combination with exercise training, the multi-ingredient supplement resulted in a further ~11-12% decrease in systemic IL-6 and TNF-α and 10% decrease in CRP. The design of this study, with a multi-ingredient supplement, does not allow us to determine if Cr contributed to the anti-inflammatory response or not, especially considering that there were other ingredients with known anti-inflammatory properties (i.e., omega-3 fatty acid and vitamin D). Additionally, the studies evaluated systemic inflammatory markers following an exercise training program, but not acutely following exercise. Chronic exercise training is known to be anti-inflammatory [25]; however, acute bouts of exercise result in acute pro-inflammatory responses locally in skeletal muscle tissue [2].

Delineating how Cr supplementation, by itself, may influence the inflammatory response to exercise requires further research. Our research has shown that 12-weeks of Cr supplementation (20 g/d for the first week and 5 g/d for the following 11-weeks) in aging adults with knee osteoarthritis (OA; considered a low-grade inflammatory disease) had no effect on reducing inflammatory biomarkers at rest including CRP, IL-1β, IL-6, s100 A8/A9, and TNF-α [26]. Participants were included if they were between the ages of 45 -65 years old, had a body mass index >25 kg/m^2,

had knee pain during activities of daily living, and had radiographic evidence of mild – moderate knee OA (Kellgren & Lawrence grades II & III). Participants were excluded if they had severe knee OA (based on radiographic evidence), previous surgery or traumatic injury of the hip, knee, or ankle, utilized a walking aid during ambulation, were unable to perform physical activity due to medical reasons, were unable to provide consent, or had a history of one of the following: diabetes; cardiovascular disease; ankylosing spondylitis; other forms of arthritis; renal problems requiring dialysis or hemodialysis. We did not evaluate the response of the participants to an acute bout of exercise but, previous research has demonstrated that in young, healthy athletes, that Cr supplementation may decrease the acute inflammatory response to exercise [10, 27-29]. It would be interesting to evaluate how Cr supplementation may influence the inflammatory response to exercise in a variety of pathological conditions that have heightened inflammatory milieu. Future research will enhance our understanding of this topic area.

3. Conclusions

The current evidence does not support the hypothesis that Cr supplementation can alter markers of muscle damage or inflammation in response to exercise in older adults. However, due to the minimal available research, strong conclusions cannot be drawn. In younger adults, the pro-inflammatory response to exercise is important for signaling muscle adaptations and therefore the use of anti-inflammatories may be detrimental to muscle adaptations [30]; however, it is unclear if anti-inflammatory measures are counterproductive in a state of chronic low-grade inflammation, such as with aging. One study suggests that anti-inflammatories may result in greater adaptations to resistance training in older adults [31] thus, if Cr elicits anti-inflammatory properties in response to exercise, it may be beneficial for older adults. More research is required to identify if Cr can moderate exercise induced muscle damage and the pro-inflammatory milieu.

Author Contributions

SMC and DMC conceptualized and contributed to writing of the original manuscript and have reviewed and agreed to the published version of the manuscript.

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Competing Interests

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