Creatine Supplementation

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Abstract
Creatine monohydrate is a dietary supplement that increases muscle performance in short-duration, high-intensity resistance exercises, which rely on the phosphocreatine shuttle for adenosine triphosphate. The effective dosing for creatine supplementation includes loading with 0.3 g·kg^{-1}·d^{-1} for 5 to 7 days, followed by maintenance dosing at 0.03 g·kg^{-1}·d^{-1} most commonly for 4 to 6 wk. However loading doses are not necessary to increase the intramuscular stores of creatine. Creatine monohydrate is the most studied; other forms such as creatine ethyl ester have not shown added benefits. Creatine is a relatively safe supplement with few adverse effects reported. The most common adverse effect is transient water retention in the early stages of supplementation. When combined with other supplements or taken at higher than recommended doses for several months, there have been cases of liver and renal complications with creatine. Further studies are needed to evaluate the remote and potential future adverse effects from prolonged creatine supplementation.

Introduction

Creatine is an ergogenic supplement that has been used by athletes with the goal of increasing strength gains in the weight room. In the 1990s, creatine became a popular supplement used by athletes to augment resistance training. The popularity of creatine grew as studies began to show some benefits with strength training, particularly with short, high-intensity exercises (67,73). A survey of division 1 athletes in 1999 found that 48% of male athletes reported current or prior use of creatine (41). Creatine also was found to be the most popular supplement used by a cohort of high school athletes in a survey completed in Iowa in 2001 (44). Metzl *et al.* (45) found that usage increased in high school by grade, and in the 11th and 12th grade, the usage was about 12%. The recent surveys have shown a decrease in popularity of creatine with whey protein being the most popular (17,50).

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Creatine has been one of the more extensively studied dietary supplements (78). There have been upward of 300 studies evaluating the effects of creatine on resistance training, with 70% reporting increases in strength (39). Several forms of creatine exist; however creatine monohydrate has been the most extensively studied, and its formulation has shown benefits in short-duration, high-intensity weightlifting and cycling (10).

Many situations within athletics and during training for sport require fast and intense muscle contractions. Intense sport activities less than 10 s in duration are dependent on intramuscular stores of adenosine triphosphate (ATP) and phosphocreatine (78,81). Several studies have shown increases in intramuscular stores of creatine and phosphocreatine with creatine monohydrate supplementation, and the increases range from 10% to 40% (7,39). However there is an upper limit of creatine stores that are possible in human muscle (23), which has been reported as high as 160 g in the human body (10). Therefore athletes with full stores of creatine in their muscles will not receive benefit from supplementation. People with lower creatine stores in their muscles receive the greatest effect on intramuscular creatine stores when supplemented with oral creatine (11,26). Therefore the theory behind creatine supplementation is to increase stores in the muscle to facilitate ATP and phosphocreatine production, delaying the onset of muscle fatigue (81).

Biochemistry

Creatine is a nitrogenous amine that was discovered in 1832 (5). It is found primarily in skeletal muscle, with 95% of the body's creatine stores found within skeletal muscle (49,78). The total amount of creatine in the body is equal to the free creatine plus the phosphocreatine (11), which equals approximately 120 g in a 70-kg person (74). The exogenous sources of creatine are animal products such as red meat and fish. The normal dietary intake of creatine in an omnivorous diet is around 1 g per day (49,78). The liver, kidney, and pancreas form endogenous stores of creatine (49,78). The endogenous production of creatine is downregulated during exogenous creatine supplementation; however

the endogenous production returns to baseline after supplementation is discontinued (14).

The first step in endogenous synthesis of creatine occurs in the kidney and starts with the amino acids glycine and arginine (49). The product is then transferred to the liver where a methyl group from methionine is added forming creatine (49,78). Circulating creatine is brought into skeletal muscle via transporters in the cell membrane. The rate of creatine uptake has been shown to be influenced by exercise, catecholamines, and insulin-like growth factor (26,49,59). Once within the cell, creatine can be phosphorylated to form phosphocreatine in a reversible enzymatic reaction facilitated by creatine kinase. The phosphate group comes from ATP forming adenosine diphosphate (ADP). The reverse reaction occurs when ATP is being used by the cell, and phosphocreatine can shuttle a phosphate group to ADP (49,78).

During short-duration, high-intensity exercises, ATP needs are met by both anaerobic glycolysis and phosphocreatine shuttle (49,81). Anaerobic glycolysis is the dominant form of ATP production between 10 and 30 s when at maximal effort, while the phosphocreatine shuttle predominates as an ATP source during maximal effort exercises less than 10 s (5,72,81). By increasing stores of phosphocreatine with creatine supplementation, the belief is one can decrease muscle fatigue and increase performance by prolonging the phosphocreatine shuttle (42,78).

In addition to increasing phosphocreatine stores, there are other proposed mechanisms by which creatine supplementation can improve performance during these exercises. One proposed mechanism is faster resynthesis of phosphocreatine during rest and recovery between bouts of maximal exercises; more creatine in the muscles would equate to more potential phosphocreatine (42,73). Conflicting data exist regarding creatine supplementation improving phosphocreatine resynthesis (24,68). Other mechanisms include aiding ATP production via glycolysis by increasing phosphofructokinase activity or by buffering hydrogen ions (42,81).

Dosing of Creatinine

Studies have shown that intramuscular stores of total creatine and phosphocreatine can be increased by supplementing with oral creatine monohydrate for 5 to 7 d with a dose of 20 to 25 $g \cdot d^{-1}$ (10,11,13,24,26,30,68). The greatest increase of creatine and phosphocreatine is reported to be in the first 2 d of supplementation (26). The typical dosing in studies that have shown increases in strength performance includes both a loading and maintenance phase. Depending on the study, the loading phase varies from 5 to 7 d at 0.3 $g \cdot kg^{-1} \cdot d^{-1}$ (30). During the loading phase, the daily dose is divided into four equal doses throughout the day dissolved in a liquid. After the 5- to 7-d loading phase, the athlete continues with the maintenance phase at 0.03 $g \cdot kg^{-1} \cdot d^{-1}$ (30). The length of the maintenance phase varies in studies from 28 d to 10 wk (30,67). When a carbohydrate or protein is added to creatine supplementation, there may be an increase in muscle retention of creatine (10), particularly in the first few days, resulting in a decreased need for loading. However alternative dosing methods also have been shown to effectively increase creatine stores and have effects on strength gains. Regimens without the creatine loading phase, 3 to 6 $g \cdot d^{-1}$ for 28 d and 6 $g \cdot d^{-1}$ for 12 wk, also have been shown to be effective in increasing creatine stores (10). The increase in creatine stores occurs more slowly and therefore may take longer to see the strength training effects.

Creatine ethyl ester has received recent attention (33,54, 62,70). In order to increase the intramuscular creatine levels, one of the latest creatine variations is creatine ethyl ester. Creatine ethyl ester is alleged to increase creatine bioavailability (62). Esterification of creatine decreases its hydrophilicity, and manufacturers of creatine ethyl ester claim that this allows it to bypass the creatine transporter due to enhanced sarcolemmal permeability toward creatine (62). Studies have shown that creatine ethyl ester is a substrate for creatine kinase (54). Yet recent studies show that creatine ethyl ester is converted to creatinine, not creatine (22,70). Increases in plasma creatinine were found with creatine ethyl ester. In addition, nonenzymatic cleavage of creatine ethyl ester was reported (33), leading them to report that creatine ethyl ester is a pronutrient for creatinine rather than creatine under all physiological conditions encountered during transit through the various tissues; thus no ergogenic effect is to be expected from supplementation. Other forms of creatine, such as a buffered form of creatine, to increase hydrophilic nature of the molecule is a more efficacious and/or safer form of creatine to consume than creatine monohydrate (31).

Adding other supplements to creatine has been investigated to find a mixture that may produce additional benefit; these include conjugated linoleic acid (15,65), whey protein (16,34), dextrose (66), betaine (19), beta-alanine (29,64,80), and D-pinitol (35). Of these supplements, whey protein, dextrose, and beta-alanine appear to be beneficial in addition to creatine. Further research is needed to ensure that increased efficacy comes along with continued safety.

Effects of Creatinine on Performance

Creatine monohydrate's effect on resistance training exercises has been extensively researched. There are numerous controlled studies that have reported increases in performance and muscle strength in short-duration, maximum-intensity exercises (1,7,8,13,18,20,36,47,63,67,73,78,79). Resistance training has been measured in many ways in the literature, including exercises such as bench press, leg press, biceps curls, leg extensions, jump squats, and bicycle ergometry (1,7,8,13,18,20,36,47,63,67,73,78,79). The method of measurement of strength and performance in creatine studies includes one repetition maximum, mean power, total force, and number of repetitions. The results regarding creatine supplementation's ergogenic effect are not unanimous. However, there is a significant body of evidence that creatine increases performance in short-duration, maximum-intensity resistance training.

Conflicting evidence exists regarding studies of the effect of creatine supplementation on anaerobic performance (7,8,73,81). Currently, studies consistently have observed no effect on aerobic performance with creatine supplementation (4,55,61,73).

In addition to performance measurements, evidence has supported increases in fat-free mass (7,47,67) and Type II muscle fiber area (11,27,71). Muscle glycogen levels may

also be affected by creatine supplementation, likely as a result of increased cellular water content (48,69,73). Increases in body mass with creatine supplementation have been reported as far back as 1928. However current evidence suggests that the increase in body mass observed with creatine is due to the decreased urine output and water retention during the initial stages of creatine loading (7,21,30,79). There is no evidence that creatine supplementation affects protein synthesis (73).

Sport-specific performance also has been studied quite extensively to see if the effect of creatine supplementation extended from the weight room to the field of play. Multiple studies have investigated creatine supplementation effect on sprinting, swimming, and agility training and have failed to show an effect (9,12,46,56,75).

Side Effects of Creatinine

The International Society of Sports Nutrition's position statement on creatine monohydrate states that there is no scientific evidence of side effects or adverse effects when creatine is used appropriately (10). They therefore conclude that if used properly, creatine is an acceptable nutritional supplement and ergogenic aid for young athletes to use (10). No adverse effects were reported in a study of young healthy individuals after supplementation with creatine from 7 d to 10 wk (2,67).

Creatine is excreted by the kidney, which led to the hypothesis that creatine supplementation may be detrimental to renal function. Several studies have looked at serum creatinine levels during creatine loading but have not reported significant increases in serum creatinine in younger healthy populations (40,51,52,58). Slight increases in serum creatinine levels have been reported with larger doses of creatine during the loading phase, although not statistically significant. However increases in urinary creatinine excretion and decreases in total urine volume output have been reported during creatine loading (30,67). The decrease in urinary output is thought to result in fluid retention and weight gain during the initial phases of creatine supplementation. Creatine has been reported to result in weight gain and water retention during short-term use (32,78). In the literature, there is a case report of a 20-year-old man with interstitial nephritis as a result of creatine supplementation (38). However the individual in the case was taking loading doses of creatine ($20 \text{ g} \cdot \text{d}^{-1}$) over a 4-wk period instead of the recommended and well-studied loading phase of 5 to 7 d. A longer study of creatine supplementation in nonathletes with other medical comorbidities also did not show evidence of renal problems.

Although there have not been significant increases in serum creatinine with creatine supplementation, there have been other concerns about the effects of creatine loading on the kidney. Creatine can be metabolized to methylamine and subsequently formaldehyde during urinary excretion. Both methylamine and formaldehyde are known cytotoxic substances raising concerns about potential harmful effects to the kidney with long-term use. Studies have shown significant increases in both methylamine and formaldehyde after short-term creatine supplementation at loading doses (37,53,60). Further studies are needed to further evaluate the potential harm to the kidney related to the increases in urinary methylamine and formaldehyde levels, particularly with longer term use and high loading doses of creatine.

In the literature, there are case reports of young healthy individuals developing acute liver failure when one of the dietary supplements they were ingesting was creatine (3,77). However in these cases, the individuals were taking large doses of creatine in addition to several other dietary supplements for weight training. When creatine has been studied in isolation and at acceptable doses, there have been no significant adverse effects to the liver (40,58).

Since creatine does result in a decrease in urinary volume and water retention during supplementation, concerns arose that athletes could develop problems staying hydrated and regulating body temperature. Creatine supplementation increases intracellular volume with increased cellular water volume. A study evaluated lower extremity anterior compartment pressures after heat-stressed exercise, and it did find transient asymptomatic increases in compartment pressures with creatine supplementation compared to placebo (28). There is a case report of compartment syndrome occurring with large doses of creatine (57), with subsequent resolution with cessation. In 1998, the University of Tennessee football team had many of their football players develop cramping during a game, after the team instituted a creatine supplementation program. The number of athletes was disproportional to historic values of athletes cramping, which caused the linkage to creatine usage. Further studies have since shown no increase in the incidence of cramping in college football players taking creatine (25). Several studies also have reported no issues with heat tolerance or hydration status with creatine supplementation (43,76).

The safety of creatine in the pediatric and adolescent population is lacking appropriate research. In addition, studies that have shown benefit in resistance training have not included subjects less than 18 years of age. Therefore creatine supplementation in athletes less than 18 years old needs further research before it should be recommended (10).

Creatine Purity

Creatine is an unregulated dietary supplement that is readily available to consumers and legal for use in athletic training. The supplement is not banned by The National Collegiate Athletic Association (NCAA) or by the International Olympic Committee (IOC) (10). The NCAA does prohibit individual institutions from distributing creatine supplements. The IOC ruled to allow creatine given the substance is readily found in animal proteins (10). However creatine is a dietary supplement that falls under the Dietary Supplement Health and Education Act, and is not directly regulated by the Food and Drug Administration. In general, those who participate in athletics under the supervision of institutions such as the NCAA and IOC should use caution when using any dietary supplement due to reported contamination of creatine (6).

Conclusions

Creatine monohydrate is a dietary supplement that increases muscle performance in short-duration, high-intensity resistance exercises that predominantly rely on the phosphocreatine shuttle for ATP. Creatine does not seem to have a positive effect on sport-specific activities such as sprinting or

swimming. The effective dosing for creatine supplementation includes loading with 0.3 g·kg^{-1}·d^{-1} for 5 to 7 d, followed by maintenance dosing at 0.03 g·kg^{-1}·d^{-1} most commonly for 4 to 6 wk. However loading doses are not necessary to increase the intramuscular stores of creatine or effect resistance training performance. Creatine is a relatively safe supplement with few adverse effects reported. The most common adverse effect is transient water retention in the early stages of supplementation. When combined with other supplements or taken at higher than recommended doses for several months, there have been cases of liver and renal complications with creatine. Creatine loading increases urinary concentrations of the cytotoxic substances methylamine and formaldehyde, and athletes should be warned about the unknown affect on the kidney with long-term use. Further studies are needed to evaluate the remote and potential future adverse effects from prolonged creatine supplementation. Creatine is an ergogenic supplement with few adverse effects, and when used short term at appropriate dose, it can augment short-duration, maximum-intensity resistance training.

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