



THE SAFETY AND EFFICACY OF CREATINE MONOHYDRATE SUPPLEMENTATION: WHAT WE HAVE LEARNED FROM THE PAST 25 YEARS OF RESEARCH

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- Many studies have demonstrated that the ingestion of ~20 g/d of creatine monohydrate for 5 d is effective at maximally increasing muscle creatine. The ingestion of 3-5 g/d for about 4 wk appears to be equally as effective, but there are fewer data. Increased muscle creatine levels can be maintained with low-dose supplementation (3-5 g/d), dietary sources (most meats contain about 0.7 g/6 oz serving) or a combination.
- If muscle creatine and phosphocreatine are increased by creatine monohydrate supplementation, the performance of brief (< 30 s), intense exercise can be improved, especially if there are repeated bouts. Creatine supplements most consistently improve the performance of resistance exercise/training programs. The performance of longer-duration exercise (> 30 s) and sprints embedded during or at the end of endurance exercise may also be enhanced with creatine monohydrate supplementation, possibly because supplementation increases glycogen synthesis.
- Creatine monohydrate supplementation enhances a variety of factors and processes involved in adaptation to exercise, including increased gene/growth factor expression, satellite cell number and intracellular water content. Therefore, in addition to improving the quality of strength and conditioning workouts, increased muscle creatine may improve adaptation to intense training.
- Brain creatine levels can also be increased with creatine monohydrate supplementation, and several studies have shown improved cognitive processing, which could be valuable for athletes, especially when fatigued. There is the potential that creatine monohydrate supplementation may reduce the severity or decrease the duration of mild traumatic brain injury (mTBI, concussion), although there are few data.
- After 25 yr of research on the effects of creatine monohydrate supplementation across multiple body systems and processes, in healthy adults taking recommended doses, clinical trials have not revealed adverse effects. A small number of case studies reporting adverse effects have been published, but these are confounded by pre-existing disease, concomitant medication, other supplement use or extreme unaccustomed exercise. Available data indicate that creatine monohydrate supplementation, when used properly, poses no threat to the renal, muscular and thermoregulatory systems.

INTRODUCTION

History and Background

Creatine is a naturally occurring compound that is consumed in the diet, mostly through meat and fish (3-5 g/kg raw meat), and is also produced in the liver, pancreas and kidneys. Chevreul discovered creatine in 1832, and, nearly 100 years later, it was determined that creatine plays a central role in energy production during muscle contraction. In humans, the majority of creatine is stored in skeletal muscle where creatine, phosphocreatine (PCr) and the enzyme creatine kinase, react with adenosine diphosphate (ADP), to resynthesize adenosine triphosphate (ATP) (Sahlin, 2014). During brief, maximal exercise, such as sprinting, as much as 80% of ATP is produced via the creatine kinase reaction.

Normal muscle creatine levels are about 124 mmol/kg dry muscle (Harris et al., 1974), but this varies based on the diet, and possibly with aging and physical activity. Vegan vegetarians have less body creatine, but this does not imply deficiency per se, only lower levels in muscle and blood. Some, but not all studies show that muscle creatine decreases with age, although it is unclear if this is a result of low levels of physical activity or aging itself (Rawson & Venezia, 2011). Muscle creatine decreases during extreme inactivity, such as in immobilization, but does not appear to increase in response to sprint exercise training.

Creatine supplementation (i.e., feeding) studies conducted nearly 100 years ago indicated that ingested creatine was retained by the body, but without muscle biopsies, the important connection to exercise performance was not pursued. The seminal work by Harris et al. (1992) using muscle biopsies showed that oral ingestion of creatine monohydrate increased muscle creatine (~20%). Following that study, numerous investigations on creatine monohydrate supplementation were published, including studies on: optimizing uptake, ergogenic effects, safety, mechanisms supporting a performance enhancing effect, and clinical studies in aging and patient populations (reviewed in Gualano et al., 2012; Heaton et al., 2017; Persky & Rawson 2007; Rawson & Persky 2007; Rawson & Venezia 2011; Rawson et al., 2018).

The majority of the research on creatine supplementation has focused on creatine monohydrate, and so, the most data on safety (Persky & Rawson 2007; Rawson et al., 2017) and efficacy (Branch, 2003; Gualano et al., 2012; Lanhers et al., 2015; 2017; Rawson & Volek, 2003) are available for creatine monohydrate. No advantage has been shown using a different formulation of creatine, and these alternative products typically contain less creatine and can be more expensive (Jäger et al., 2011). Thus, unless otherwise specified, in this Sports Science Exchange article, creatine supplementation will refer to creatine monohydrate supplementation.

SUPPLEMENTATION

The exact dose of creatine to maximally increase muscle creatine is not known, but most studies have followed a high-dose, short-term protocol (~20 g/d for 5 d) or a lower-dose, longer-term protocol (3-5 g/d for ~30 d) to reach muscle creatine saturation (Hultman et al., 1996). Only small amounts of dietary/supplemental creatine (3-5 g/d) appear necessary to maintain elevated muscle creatine levels as long as desirable. Because muscle creatine uptake is insulin mediated, muscle creatine uptake can be further increased by ingesting creatine supplements with insulinogenic nutrients such as carbohydrate, carbohydrate/protein combinations or with exercise which has insulin-like effects (reviewed in Snow & Murphy, 2003). Excess supplemental creatine, which is not taken up by the tissues, is excreted in the urine (Rawson et al., 2002). The factor that determines the magnitude of muscle creatine increase in response to supplementation appears to be initial muscle creatine; those with low basal levels will have the largest increases with supplementation (Harris et al., 1992).

ERGOGENIC EFFECTS

Exercise and Sports Performance

The performance of high-intensity exercises lasting less than 30 s is typically improved following creatine supplementation. This beneficial effect appears to be most evident when there are repeated bouts of intense exercise (Branch, 2003; Gualano et al., 2012). With the exceptions of running, cycling and swimming, it is difficult to translate laboratory exercise performance tests to sports-specific performance, especially for team sports. One research team showed that elite soccer players had no improvement in shooting accuracy, but completed sprints faster following creatine ingestion. This sprint improvement translated into gaining nearly a full step on a competitor not ingesting creatine (Cox et al., 2002). Clearly, this could be beneficial during a competitive sporting event.

The longer exercise duration lasts beyond 30 s, the less likely creatine supplements will have an ergogenic effect, or possibly a statistically measurable effect. For instance, van Loon et al. (2003) showed no effect of creatine supplements on a cycling time trial. Conversely, Nelson and colleagues (2000) showed a decreased oxygen cost of submaximal cycling exercise following creatine supplementation. It appears that sprints imbedded during or at the end of endurance exercise are improved with creatine supplementation (Engelhardt et al., 1998; Tomcik et al., 2018; Vandebuerie et al., 1998). If creatine supplementation enhances performance beyond 30 s of exercise, it could be due to increased muscle glycogen content, consequent to creatine loading (Nelson et al., 2001; Roberts et al., 2016; Volek & Rawson, 2004) (Table 1).

Resistance Training Performance

One of the most consistent findings in the literature is improved resistance training performance following creatine supplementation. In a narrative review, Rawson and Volek (2003) showed that creatine supplementation markedly increases strength and muscle endurance.

Performance	Time/ Nature of Activity	Potential Benefit	Comments	Relevant Research
High intensity exercise - Laboratory tests	< 30 s	Increased peak/ mean power, decreased fatigue	Many supportive studies; more effective over repeated bouts of exercise	(reviewed in Branch, 2003; Gualano et al., 2012)
High intensity exercise - Field tests	< 30 s	Increased speed/ decreased time to complete a fixed distance	Supportive studies, fewer studies overall, theoretically the increase in body mass may reduce ergogenic effect in weight- bearing sports (e.g., running), but not known	
Swimming		Increased power/ decreased time to complete a fixed distance	Supportive studies for improved performance over repeated sprint intervals; probably not effective in single sprints	(reviewed in Hopwood et al., 2006)
Medium duration tasks	30 s to 5 min	Increased power output, speed / decreased time to complete a fixed distance	Some studies show enhanced performance, possibly due to increased muscle glycogen subsequent to creatine supplementation	(reviewed in Branch, 2003; Gualano et al., 2012)
Sprinting within or after endurance exercise		Increased power output, speed; decreased fatigue, time to complete a fixed distance	Supportive studies, but fewer studies overall	(Engelhardt et al., 1998; Vandebuerie et al., 1998; Tomcik et al., 2018)
Endurance exercise	> 5 min	Decreased oxygen cost of exercise	Most studies show no improvement in endurance performance	(Nelson et al., 2001; van Loon et al., 2003)
Strength and conditioning workouts	Intermittent	Spontaneous increase in total lifting volume, increased number of repetitions at a given weight, increased strength, increased lean body mass	Many supportive studies	(reviewed in Rawson & Volek 2003; Lanthers et al., 2017)

Table 1. Effects of Creatine Monohydrate Supplementation on Exercise Performance

In meta-analysis reviews, Lahners and colleagues (2015; 2017) also showed that creatine ingestion increases muscle strength, and Branch (2003) showed increased lean body mass. Thus, even if creatine supplements do not directly improve performance of a particular sport per se, increased strength, muscular endurance and lean mass, because of higher-quality strength and conditioning training, may translate into improved sports performance.

Muscular Adaptations

Although creatine supplementation does not appear to increase muscle protein synthesis (MPS) or muscle protein breakdown (MPB), it may improve the adaptive response to exercise training in other ways. For example, creatine supplementation plus resistance training increase fat-free mass and strength and also myofibrillar protein, Type I, IIa and IIx myosin heavy chain messenger RNA (mRNA) expression, Type I and Type IIx myosin heavy chain protein expression, creatine kinase, myogenin and myogenic regulatory factor 4 (MRF-4) mRNA expression, and myogenin and MRF-4 protein expression compared with resistance training and placebo ingestion (Willoughby & Rosene 2001; 2003). Olsen and colleagues (2006) reported increased satellite cell number and myonuclei concentration in individuals ingesting creatine supplements while participating in a resistance training program. In addition to augmenting the effects of resistance training, creatine supplements may have direct effects on skeletal muscle. As examples, Deldicque et al. (2005) reported increased insulin-like growth factor I and II (IGF-I and IGF-II) mRNA and Safdar et al. (2008) described increased expression of genes involved with osmosensing, cytoskeleton remodeling, glucose transporter 4 (GLUT 4) translocation, glycogen and protein synthesis, satellite cell proliferation and differentiation, DNA replication and repair, mRNA processing and transcription, and cell survival. These adaptations may be in response to increased intracellular water resulting from creatine supplementation (Deminice et al., 2016). Previous studies have shown that hyper-hydrating a muscle cell decreases protein breakdown and RNA degradation, and increases glycogen content (Low et al., 1996), and protein, DNA and RNA synthesis (Berneis et al., 1999; Häussinger et al., 1993). The muscular adaptations associated with creatine supplementation can improve training responses and enhance recovery from a period of inactivity such as during rehabilitation from an injury (Rawson et al., 2018) (Table 2).

Brain Adaptations

Several groups have demonstrated improved cognitive processing subsequent to creatine supplementation (reviewed in Dolan et al., 2018; Gualano et al., 2016; Rawson & Venezia, 2011). These effects have not been well explored in athletes, but faster processing or reaction time could benefit an athlete's performance. For instance, the decline in cognitive processing caused by sleep deprivation and exercise is attenuated by creatine supplementation as Cook et al. (2011) showed that following sleep deprivation, acute creatine or caffeine ingestion maintained performance on a rugby passing skill test, while performance worsened following placebo ingestion. Turner and colleagues (2015) reported that creatine supplementation attenuated the decline in cognitive processing caused by breathing hypoxic gases for 90 min. Collectively, these studies indicate that creatine supplementation may be useful in improving certain aspects of cognitive processing, and that these benefits may be most evident under stressful conditions such as sleep deprivation, exercise and hypoxia.

Effect	Underlying Mechanism	Sample Supportive References	Relevant Reviews
Improved performance in a single intense exercise bout	Increased muscle creatine availability prior to exercise	(Harris et al., 1992; Hultman et al., 1996)	(Sahlin, 2014)
Improved performance during repeated bouts of intense exercise/improved recovery between bouts of exercise (min)	Increased phosphorylcreatine resynthesis	(Greenhaff et al., 1994; Yquel et al., 2002)	(Branch, 2003; Gualano et al., 2012)
Improved recovery between bouts of exercise (hr to d) or improved training adaptations Swimming	Increased glycogen resynthesis	(Nelson et al., 2001; Roberts et al., 2016; Tomcik et al., 2018)	(Volek & Rawson, 2004)
	Increased growth factor and gene expression	(Burke et al., 2008; Deldicque et al., 2005; Safdar et al., 2008; Willoughby & Rosene, 2001; 2003)	(Heaton et al., 2017; Rawson & Persky, 2007; Rawson et al., 2018)
	Increased satellite cell number/activity	(Olsen et al., 2006)	Supportive studies, but fewer studies overall
	Cellular hyperhydration	(Berneis et al., 1999; Häussinger et al., 1993)	
	Decreased post-exercise inflammation	(Bassit et al., 2008; 2010; Deminice et al., 2013; Santos et al., 2004)	(Rawson et al., 2017)
	Decreased post-exercise muscle damage	(Cooke et al., 2009; Veggi et al., 2013)	
	Increased post-exercise strength recovery	(Cooke et al., 2009; Rosene et al., 2009)	
Improved training efficiency/increased training volume	Increased muscle creatine availability prior to training	(Harris et al., 1992; Hultman et al., 1996)	(Rawson & Volek, 2003)
	Increased phosphorylcreatine resynthesis during training workouts	(Greenhaff et al., 1994; Yquel et al., 2002)	
	Increased glycogen availability before training and increased resynthesis following training	(Nelson et al., 2001; Roberts et al., 2016; Tomcik et al., 2018)	(Volek & Rawson, 2004)

Table 2. Potential Mechanisms for Improved Exercise Performance and Exercise Adaptations with Creatine Monohydrate Supplementation

Importantly, given the focus on prevention of mild traumatic brain injuries (mTBI), or concussion, in sports, creatine monohydrate also shows promise as a nutrient that may decrease the severity of or enhance recovery from mTBI. Decreased brain creatine has been reported following mTBI (Vagnozzi et al., 2013), and creatine supplementation reduces damage in animals exposed to TBI (Sullivan et al., 2000). In two open label studies in humans, creatine supplementation improved cognition, communication, self-care, personality and behavior, and decreased headaches, dizziness and fatigue in patients with TBI (Sakellaris et al., 2006; 2008). More research on the beneficial effects of creatine on mTBI is needed, but athletes who are already ingesting creatine supplements to improve sports performance or improve response to training may receive additional protective effects on the brain (reviewed in Dolan et al., 2018; Rawson et al., 2018).

SAFETY

The safety of creatine monohydrate supplementation has been well investigated and extensively reviewed (Gualano et al., 2012; Persky & Rawson, 2007; Rawson et al., 2017). Concern about the safety of creatine can be placed into categories of impaired renal function, muscle dysfunction or impaired thermoregulation (Table 3). It appears as if these concerns are unfounded and were in part created by an uninformed media in response to the unfortunate 1997 deaths of three collegiate wrestlers who were taking extreme measures to lose body mass, and a single 1998 case study of a man with prior kidney disease who was taking a nephrotoxic drug and began creatine supplementation. Based on clinical trial data, there is no evidence that ingesting creatine supplements at recommended doses impairs renal, muscular or thermoregulatory processes. In fact, some data indicate that creatine supplements may enhance muscle function (e.g., decreased muscle damage and inflammation following intense exercise, Rawson et al., 2017) or thermoregulatory response to exercise (e.g., decreased exercise body temperature, Lopez et al., 2009). It is noteworthy, given the number of athletes who ingest creatine, that post-marketing reports along with clinical studies over the past 25 years have not revealed a high prevalence of adverse effects (Table 3).

SUMMARY AND PRACTICAL APPLICATIONS

Creatine is one of the most well-studied dietary supplements of all time, including efficacy and safety research on healthy, athlete, elderly and patient populations. Performance-enhancing effects during brief, intense exercise and resistance training have been well documented. Some studies indicate that creatine supplementation can improve the performance of sprints that occur during or following endurance exercise. New data indicate a role for creatine in improving brain health and metabolism. Creatine is well-tolerated, inexpensive, has a very good safety profile and can offer muscular and brain benefits to a variety of individuals.

- Based on the best available evidence, the ingestion of 20 g/d of creatine monohydrate for 5 d or 3-5 g/d for about 30 d will maximally increase muscle creatine. The exact dose needed to increase brain creatine is unknown, but standard loading doses have been effective at increasing brain creatine in some studies.
- Creatine monohydrate is the form of creatine that has been most studied, and therefore the greatest amount of efficacy and safety data are available for this form. There are no data indicating that other available forms of creatine are more effective, and there are few safety data on other types of creatine supplements. Based on this information, there appears to be no rationale for recommending another form of creatine as a supplement.
- To optimize creatine uptake, ingest supplements following a carbohydrate or carbohydrate/protein-containing meal or following exercise.
- The performance of brief (< 30 s), high-intensity sprint-type exercise should improve with creatine supplementation, and

Potential Concern	Evidence of Reduced Function	Evidence of Improved Function	Evidence of No Detrimental Effect	Relevant Reviews
Renal stress	Case studies, confounded by drugs/medication, prior disease, other supplements	No trials show improved renal function	Multiple trials (> 20) using various methods, show no effect on renal function	(Gualano et al., 2012)
Muscle dysfunction	Case studies of exertional rhabdomyolysis, confounded by unaccustomed/extreme exercise, drugs/medication, dehydration, traumatic injury, other supplements	Several trials show decreased muscle cramps, tightness, strains and total injuries in habitual creatine users. Several studies show decreased post-exercise inflammation, increased strength recovery, decreased delayed onset muscle soreness (DOMS)	Several trials show no evidence of improved or reduced muscle function	(Rawson et al., 2017)
Thermo-regulatory strain	None	Some trials show decreased exercise body temperature	Several trials show no evidence of improved or reduced thermoregulatory function	(Lopez et al., 2009)
Other organ strain	None	None	Several trials show no change in markers of cardiac or liver function	

Table 3. Potential Safety Concerns with Creatine Monohydrate Supplementation

these sprints could occur alone, in repeated bouts or during/after endurance exercise.

- In theory, the small body mass gain associated with creatine supplementation could negate the beneficial effects on performance during weight-bearing exercise, or even be ergolytic. This has not been proven, and performance improvements have been shown in weight-bearing activities such as running.
- Overall, creatine monohydrate supplements could benefit a number of athletes across a variety of sporting activities or in strength and conditioning training. As with all dietary supplements, experimentation in practice, prior to competition, is recommended.

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