

Creatine Supplementation

Matthew Hall, DO and Thomas H. Trojian, MD, FACSM

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 $0.3 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for 5 to 7 days, followed by maintenance dosing at $0.03 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ 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). Metzler *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).

Department of Family Medicine, University of Connecticut, San Francisco Hospital, Hartford; and Department of Orthopedics, University of Connecticut Health Center, Farmington, CT

Address for correspondence: Thomas H. Trojian, MD, FACSM, University of Connecticut, 99 Woodland Street, Hartford, CT 06105; E-mail: ttrojian@stfranciscare.org.

1537-890X/1204/240-244
 Current Sports Medicine Reports
 Copyright © 2013 by the American College of Sports Medicine

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 down-regulated 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·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·kg⁻¹·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·kg⁻¹·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 crea-

tine loading phase, 3 to 6 g·d⁻¹ for 28 d and 6 g·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 phospho-creatine 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 $0.3 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for 5 to 7 d, followed by maintenance dosing at $0.03 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ 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.**

The authors declare no conflicts of interest and do not have any financial disclosures.

References

- Arciero PJ, Hannibal NS 3rd, Nindl BC, et al. Comparison of creatine ingestion and resistance training on energy expenditure and limb blood flow. *Metabolism*. 2001; 50:1429–34.
- Armentano MJ, Brenner AK, Hedman TL, et al. The effect and safety of short-term creatine supplementation on performance of push-ups. *Mil. Med.* 2007; 172:312–7.
- Avelar-Escobar G, Mendez-Navarro J, Ortiz-Olvera NX, et al. Hepatotoxicity associated with dietary energy supplements: use and abuse by young athletes. *Ann. Hepatol.* 2012; 11:564–9.
- Balsom PD, Harridge SD, Soderlund K, et al. Creatine supplementation per se does not enhance endurance exercise performance. *Acta Physiol. Scand.* 1993; 149:521–3.
- Balsom PD, Soderlund K, Ekblom B. Creatine in humans with special reference to creatine supplementation. *Sports Med.* 1994; 18:268–80.
- Baume N, Mahler N, Kamber M, et al. Research of stimulants and anabolic steroids in dietary supplements. *Scand J Med Sci Sports*. 2006; 16:41–8.
- Becque MD, Lochmann JD, Melrose DR. Effects of oral creatine supplementation on muscular strength and body composition. *Med. Sci. Sports Exerc.* 2000; 32:654–8.
- Birch R, Noble D, Greenhaff PL. The influence of dietary creatine supplementation on performance during repeated bouts of maximal isokinetic cycling in man. *Eur. J. Appl. Physiol. Occup. Physiol.* 1994; 69:268–76.
- Branch JD. Effect of creatine supplementation on body composition and performance: a meta-analysis. *Int. J. Sport Nutr. Exerc. Metab.* 2003; 13: 198–226.
- Buford TW, Kreider RB, Stout JR, et al. International Society of Sports Nutrition Position Stand: creatine supplementation and exercise. *J. Int. Soc. Sports Nutr.* 2007; 4:6.
- Burke DG, Chilibeck PD, Parise G, et al. Effect of creatine and weight training on muscle creatine and performance in vegetarians. *Med. Sci. Sports Exerc.* 2003; 35:1946–55.
- Burke LM, Pyne DB, Telford RD. Effect of oral creatine supplementation on single-effort sprint performance in elite swimmers. *Int. J. Sport Nutr.* 1996; 6:222–33.
- Casey A, Constantin-Teodosiu D, Howell S, et al. Creatine ingestion favorably affects performance and muscle metabolism during maximal exercise in humans. *Am. J. Physiol.* 1996; 271:E31–7.
- Cooper R, Naclerio F, Allgrove J, Jimenez A. Creatine supplementation with specific view to exercise/sports performance: an update. *J. Int. Soc. Sports Nutr.* 2012; 9:33.
- Cornish SM, Candow DG, Jantz NT, et al. Conjugated linoleic acid combined with creatine monohydrate and whey protein supplementation during strength training. *Int. J. Sport Nutr. Exerc. Metab.* 2009; 19:79–96.
- Cribb PJ, Williams AD, Stathis CG, et al. Effects of whey isolate, creatine, and resistance training on muscle hypertrophy. *Med. Sci. Sports Exerc.* 2007; 39:298–307.
- Dascombe BJ, Karunaratna M, Cartoon J, et al. Nutritional supplementation habits and perceptions of elite athletes within a state-based sporting institute. *J. Sci. Med. Sport.* 2010; 13:274–80.
- Dawson B, Cutler M, Moody A, et al. Effects of oral creatine loading on single and repeated maximal short sprints. *Aust. J. Sci. Med. Sport.* 1995; 27:56–61.
- del Favero S, Roschel H, Artioli G, et al. Creatine but not betaine supplementation increases muscle phosphorylcreatine content and strength performance. *Amino Acids.* 2012; 42:2299–305.
- Earnest CP, Snell PG, Rodriguez R, et al. The effect of creatine monohydrate ingestion on anaerobic power indices, muscular strength and body composition. *Acta Physiol. Scand.* 1995; 153:207–9.
- Francaux M, Poortmans JR. Effects of training and creatine supplement on muscle strength and body mass. *Eur. J. Appl. Physiol. Occup. Physiol.* 1999; 80:165–8.
- Giese MW, Lecher CS. Non-enzymatic cyclization of creatine ethyl ester to creatinine. *Biochem. Biophys. Res. Commun.* 2009; 388:252–5.
- Greenhaff PL. Creatine and its application as an ergogenic aid. *Int. J. Sport Nutr.* 1995; (5 suppl):S100–10.
- Greenhaff PL, Bodin K, Soderlund K, Hultman E. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. *Am. J. Physiol.* 1994; 266:E725–30.
- Greenwood M, Kreider RB, Greenwood L, Byars A. Cramping and injury incidence in collegiate football players are reduced by creatine supplementation. *J. Athl. Train.* 2003; 38:216–9.
- Harris RC, Soderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin. Sci.* 1992; 83:367–74.
- Hespe P, Op't Eijnde B, Van Leemputte M, et al. Oral creatine supplementation facilitates the rehabilitation of disuse atrophy and alters the expression of muscle myogenic factors in humans. *J. Physiol.* 2001; 536:625–33.
- Hile AM, Anderson JM, Fiala KA, et al. Creatine supplementation and anterior compartment pressure during exercise in the heat in dehydrated men. *J. Athl. Train.* 2006; 41:30–5.
- Hoffman J, Ratamess N, Kang J, et al. Effect of creatine and beta-alanine supplementation on performance and endocrine responses in strength/power athletes. *Int. J. Sport Nutr. Exerc. Metab.* 2006; 16:430–46.
- Hultman E, Soderlund K, Timmons JA, et al. Muscle creatine loading in men. *J. Appl. Physiol.* 1996; 81:232–7.
- Jagim AR, Oliver JM, Sanchez A, et al. A buffered form of creatine does not promote greater changes in muscle creatine content, body composition, or training adaptations than creatine monohydrate. *J. Int. Soc. Sports Nutr.* 2012; 9:43.
- Juhn MS, O'Kane JW, Vinci DM. Oral creatine supplementation in male collegiate athletes: a survey of dosing habits and side effects. *J. Am. Diet Assoc.* 1999; 99:593–5.
- Katseros NS, Reading DW, Shayya L, et al. Non-enzymatic hydrolysis of creatine ethyl ester. *Biochem. Biophys. Res. Commun.* 2009; 386:363–7.
- Kerksick CM, Rasmussen C, Lancaster S, et al. Impact of differing protein sources and a creatine containing nutritional formula after 12 weeks of resistance training. *Nutrition.* 2007; 23:647–56.
- Kerksick CM, Wilborn CD, Campbell WI, et al. The effects of creatine monohydrate supplementation with and without D-pinitol on resistance training adaptations. *J. Strength Cond. Res.* 2009; 23:2673–82.
- Kilduff LP, Vidakovic P, Cooney G, et al. Effects of creatine on isometric bench-press performance in resistance-trained humans. *Med. Sci. Sports Exerc.* 2002; 34:1176–83.
- Kim HJ, Kim CK, Carpentier A, Poortmans JR. Studies on the safety of creatine supplementation. *Amino Acids.* 2011; 40:1409–18.
- Koshy KM, Griswold E, Schneberger EE. Interstitial nephritis in a patient taking creatine. *N. Engl. J. Med.* 1999; 340:814–5.
- Kreider RB. Effects of creatine supplementation on performance and training adaptations. *Mol. Cell. Biochem.* 2003; 244:89–94.
- Kreider RB, Melton C, Rasmussen CJ, et al. Long-term creatine supplementation does not significantly affect clinical markers of health in athletes. *Mol. Cell. Biochem.* 2003; 244:95–104.
- LaBotz M, Smith BW. Creatine supplement use in an NCAA Division I athletic program. *Clin. J. Sport Med.* 1999; 9:167–9.

42. Lemon PW. Dietary creatine supplementation and exercise performance: why inconsistent results? *Can. J. Appl. Physiol.* 2002; 27:663–81.
43. Lopez RM, Casa DJ, McDermott BP, *et al.* Does creatine supplementation hinder exercise heat tolerance or hydration status? A systematic review with meta-analyses. *J. Athl. Train.* 2009; 44:215–23.
44. Mason MA, Giza M, Clayton L, *et al.* Use of nutritional supplements by high school football and volleyball players. *Iowa Orthop. J.* 2001; 21:43–8.
45. Metz JD, Small E, Levine SR, Gershel JC. Creatine use among young athletes. *Pediatrics.* 2001; 108:421–5.
46. Mujika I, Chatard JC, Lacoste L, *et al.* Creatine supplementation does not improve sprint performance in competitive swimmers. *Med. Sci. Sports Exerc.* 1996; 28:1435–41.
47. Nissen SL, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J. Appl. Physiol.* 2003; 94:651–9.
48. Op't Eijnde B, Urso B, Richter EA, *et al.* Effect of oral creatine supplementation on human muscle GLUT4 protein content after immobilization. *Diabetes.* 2001; 50:18–23.
49. Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. *Pharmacol. Rev.* 2001; 53:161–76.
50. Petroczi A, Naughton DP, Pearce G, *et al.* Nutritional supplement use by elite young UK athletes: fallacies of advice regarding efficacy. *J. Int. Soc. Sports Nutr.* 2008; 5:22.
51. Pline KA, Smith CL. The effect of creatine intake on renal function. *Annals Pharmacother.* 2005; 39:1093–6.
52. Poortmans JR, Francaux M. Long-term oral creatine supplementation does not impair renal function in healthy athletes. *Med. Sci. Sports Exerc.* 1999; 31:1108–10.
53. Poortmans JR, Kumps A, Duez P, *et al.* Effect of oral creatine supplementation on urinary methylamine, formaldehyde, and formate. *Med. Sci. Sports Exerc.* 2005; 37:1717–20.
54. Ravera S, Adriano E, Balestrino M, Panfoli I. Creatine ethyl ester: a new substrate for creatine kinase. *Mol. Biol. (Mosk).* 2012; 46:162–5.
55. Reardon TF, Ruell PA, Fiatarone Singh MA, *et al.* Creatine supplementation does not enhance submaximal aerobic training adaptations in healthy young men and women. *Eur. J. Appl. Physiol.* 2006; 98:234–41.
56. Redondo DR, Dowling EA, Graham BL, *et al.* The effect of oral creatine monohydrate supplementation on running velocity. *Int. J. Sport Nutr.* 1996; 6:213–21.
57. Robinson SJ. Acute quadriceps compartment syndrome and rhabdomyolysis in a weight lifter using high-dose creatine supplementation. *J. Am. Board Fam. Pract.* 2000; 13:134–7.
58. Robinson TM, Sewell DA, Casey A, *et al.* Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function. *Br. J. Sports Med.* 2000; 34:284–8.
59. Robinson TM, Sewell DA, Hultman E, Greenhaff PL. Role of submaximal exercise in promoting creatine and glycogen accumulation in human skeletal muscle. *J. Appl. Physiol.* 1999; 87:598–604.
60. Sale C, Harris RC, Florance J, *et al.* Urinary creatine and methylamine excretion following $4 \times 5 \times \text{day}(-1)$ or $20 \times 1 \text{ g} \times \text{day}(-1)$ of creatine monohydrate for 5 days. *J. Sports Sci.* 2009; 27(7):759–66.
61. Smith AE, Fukuda DH, Ryan ED, *et al.* Ergolytic/ergogenic effects of creatine on aerobic power. *Int. J. Sports Med.* 2011; 32:975–81.
62. Spillane M, Schoch R, Cooke M, *et al.* The effects of creatine ethyl ester supplementation combined with heavy resistance training on body composition, muscle performance, and serum and muscle creatine levels. *J. Int. Soc. Sports Nutr.* 2009; 6:6.
63. Stout J, Eckerson J, Ebersole K, *et al.* Effect of creatine loading on neuromuscular fatigue threshold. *J. Appl. Physiol.* 2000; 88:109–12.
64. Stout JR, Cramer JT, Mielke M, *et al.* Effects of twenty-eight days of beta-alanine and creatine monohydrate supplementation on the physical working capacity at neuromuscular fatigue threshold. *J. Strength Cond. Res.* 2006; 20:928–31.
65. Tarnopolsky M, Zimmer A, Paikin J, *et al.* Creatine monohydrate and conjugated linoleic acid improve strength and body composition following resistance exercise in older adults. *PLoS One.* 2007; 2:e991.
66. Tarnopolsky MA, Parise G, Yardley NJ, *et al.* Creatine-dextrose and protein-dextrose induce similar strength gains during training. *Med. Sci. Sports Exerc.* 2001; 33:2044–52.
67. Vandenberghe K, Goris M, Van Hecke P, *et al.* Long-term creatine intake is beneficial to muscle performance during resistance training. *J. Appl. Physiol.* 1997; 83:2055–63.
68. Vandenberghe K, Van Hecke P, Van Leemputte M, *et al.* Phosphocreatine resynthesis is not affected by creatine loading. *Med. Sci. Sports Exerc.* 1999; 31:236–42.
69. van Loon LJ, Murphy R, Oosterlaar AM, *et al.* Creatine supplementation increases glycogen storage but not GLUT4 expression in human skeletal muscle. *Clin. Sci.* 2004; 106:99–106.
70. Velema MS, de Ronde W. Elevated plasma creatinine due to creatine ethyl ester use. *Neth. J. Med.* 2011; 69:79–81.
71. Volek JS, Duncan ND, Mazzetti SA, *et al.* Performance and muscle fiber adaptations to creatine supplementation and heavy resistance training. *Med. Sci. Sports Exerc.* 1999; 31:1147–56.
72. Volek JS, Kraemer WJ, Bush JA, *et al.* Creatine supplementation enhances muscular performance during high-intensity resistance exercise. *J. Am. Diet Assoc.* 1997; 97:765–70.
73. Volek JS, Rawson ES. Scientific basis and practical aspects of creatine supplementation for athletes. *Nutrition.* 2004; 20:609–14.
74. Walker JB. Creatine: biosynthesis, regulation, and function. *Adv. Enzymol. Relat. Areas Mol. Biol.* 1979; 50:177–242.
75. Warber JP, Tharion WJ, Patton JF, *et al.* The effect of creatine monohydrate supplementation on obstacle course and multiple bench press performance. *J. Strength Cond. Res.* 2002; 16:500–8.
76. Watson G, Casa DJ, Fiala KA, *et al.* Creatine use and exercise heat tolerance in dehydrated men. *J. Athl. Train.* 2006; 41:18–29.
77. Whitt KN, Ward SC, Deniz K, *et al.* Cholestatic liver injury associated with whey protein and creatine supplements. *Semin. Liver Dis.* 2008; 28:226–31.
78. Williams MH, Branch JD. Creatine supplementation and exercise performance: an update. *J. Am. Coll. Nutr.* 1998; 17:216–34.
79. Ziegenfuss TN, Rogers M, Lowery L, *et al.* Effect of creatine loading on anaerobic performance and skeletal muscle volume in NCAA Division I athletes. *Nutrition.* 2002; 18:397–402.
80. Zoeller RF, Stout JR, O'Kroy JA, *et al.* Effects of 28 days of beta-alanine and creatine monohydrate supplementation on aerobic power, ventilatory and lactate thresholds, and time to exhaustion. *Amino Acids.* 2007; 33:505–10.
81. Zuniga JM, Housh TJ, Camic CL, *et al.* The effects of creatine monohydrate loading on anaerobic performance and one-repetition maximum strength. *J. Strength Cond. Res.* 2012; 26:1651–6.