INTEGRATED HEALTHCARE
PRACTITIONERS
Integrated Healthcare Practitioners' Dietary and Nutritional Supplement, and Herbal Remedies Management Program

Author: Philip Rouchotas MSc, ND and Heidi Fritz, MA, ND

SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 0.5 CREDIT NUTRITIONAL MEDICINE, 0.5 CREDIT PHARMACOLOGY AND BY THE CNPBC; ONE CE HOUR.

Creatine

Clinical applications.

INTRODUCTION

Creatine is a compound derived from the amino acids glyine, arginine, plus a methyl group from methionine, and is involved in the cellular generation of ATP as phosphocreatine (PCr) (Baker 2003). Commonly available as creatine monohydrate, creatine is best known in the world of sports nutrition and bodybuilding for its putative ability to increase protein synthesis and augment muscle development. What is less widely known is that creatine has also been used to treat sarcopenia in the elderly, immobilization atrophy, and various muscular dystrophies with documented efficacy. This article reviews the evidence for use of creatine for performance enhancement as well as these additional areas.

PHYSIOLOGY

Creatine exists in two forms within the body: phosphocreatine (PCr) and free creatine (Cr). Body stores are synthesized endogenously by the liver and derived from the diet; after release into the blood, creatine is actively concentrated in tissues with high creatine kinase (CK) activity, which also seem to be those with highest energy requirements: retinal photoreceptors, and skeletal and cardiac muscle (Baker 2003). Intermediate levels concentrate in the brain (Baker 2003).

Inside the muscle cell, creatine acts as an "energy buffer" (Baker 2003) or alternate anaerobic source of ATP under conditions of high energy demand. It allows for rapid re-phosphorylation of ADP according to the following reaction:

PCr + ADP + H ⟷ Cr + ATP (catalyzed by CK)

According to Baker, PCr accounts for ~50% of energy used during the first ten seconds of muscle contraction (2003). Decreased muscle creatine results in slower contraction and lower peak force, and Cr supplementation can reverse this (Baker 2003). In addition to direct generation of ATP, creatine also:

- transports ATP from the mitochonridal matrix into the cytosol (Pearlman 2006)
- protects mitochondrial CK from inactivation, which may occur through reactive oxygen species (ROS) generated by the electron transport chain (Baker 2003)
- protects against acidosis during exercise through consumption of H+ in the reaction above (Terjung 2000)
- upregulates the GLUT4 glucose transporter, thereby increasing cellular uptake of glucose (Pearlman 2000)
- contributes to activation of other energy producing pathways such as glycolysis and glycogenolysis (Pearlman 2006, Terjung 2000)
- increases calcium uptake from the cytosol to the sarcoplasmic reticulum (SR) in certain musculoskeletal disorders, allowing muscle relaxation (Pearlman 2006).

Heidi Fritz, ND, MA (CAND)
Research Fellow
Canadian College of Naturopathic Medicine

Bronte Naturopathic Clinic
1255 Sheppard Avenue East
Toronto, Ontario, Canada M2K 1E2
905-876-3047 ext 204
hfritz@ccnm.edu

Philip Rouchotas, MSc, ND
Editor-in-Chief,
Integrated Healthcare Practitioners
Associate Professor, Clinical Nutrition,
Canadian College of Naturopathic Medicine

60 Bloor Street West, Suite 1106
Toronto, Ontario, Canada M4W 3B8
philip@ihpmagazine.com

PERFORMANCE ENHANCEMENT

It is not within the scope of this review to highlight all available evidence of creatine supplementation in performance enhancement. Several excellent reviews have addressed the topic in considerable detail (Juhn 1998a, Persky 2001, Wyss 2000). We attempt to address the questions; what activities appear to benefit most from creatine supplementation? What activities have predominantly failed to demonstrate benefit from creatine supplementation? What is an appropriate strategy for advising athletes on the use of creatine for performance enhancement?

The most consistent area in which creatine supplementation has been shown to benefit performance enhancement is repeated activities of short duration (six to 60 seconds), high intensity. Creatine most specifically improves performance in resistance training, and in short duration maximal intensity sprint intervals on a stationary bike (cycle ergometry). In these settings, the following outcomes are consistent findings, although not demonstrated by all intervention trials; increased lean muscle mass, muscle fibre diameter, one repetition maximum (1RM) performance, total strength, total work, and total power output (Juhn 1998a, Wyss 2000).

It is important to note that the above- outlined benefits are not readily reproducible for events in which the athletes body mass is under their control (Juhn 1998a). While weight lifting and stationary cycling demonstrate consistent improvement, repeat short duration high intensity sprints of swimming or running do not appear to benefit from creatine supplementation (Juhn 1998a, Wyss 2000). The proposed basis relates to body mass increases associated with water retention among creatine supplementing individuals impairing performance of activities in which the athlete must control their own body weight (Juhn 1998a).

Activities of longer duration (>60s) likewise do not appear to benefit from creatine supplementation. The basis becomes a function of both water retention- related increased body mass (Juhn 1998a) and the minimal contribution of the phosphocreatine energy system to total ATP production for activities of longer than 10-30s in duration (Juhn 1998a, Wyss 2000).

We identify an important limitation of existing trials of creatine for performance enhancement inadequately addressed in the literature; studies appear most interested in elucidating if while in a creatine loaded state, can the athlete perform at an elevated level? A far more appropriate application of creatine is as follows; athletes are instructed to utilize creatine during the off season of their respective sport. Most athletes attempt to gain muscle mass during their off season, while attempting to maintain or minimally lose mass during their active season. We advise athletes to utilize creatine during their off season, to maximally benefit from their resistance training regime. Muscle creatine content and water-weight gain return to pre- supplementation levels within 28 days of discontinuation (Juhn 1998a, Perskey 2001, Wyss 2000). Athletes are instructed to discontinue creatine one month prior to reporting for their training camp. Dosing is discussed below.

INJURY AND IMMOBILIZATION

Creatine has been shown to attenuate loss of muscle mass and strength induced by immobilization. Three RCTs listed in Table 1 have demonstrated creatine's ability to decrease loss of lean tissue, increase muscle strength and endurance, and prevent GLUT4 downregulation thereby increasing insulin sensitivity caused by disuse. It is thought that this effect is mediated by increased production of myosin, potentiation of satellite cell mitotic activity, and by effects on myocyte osmolarity that lead to increased expression of muscle protein transcription factors such as MRF-4 and myogenin (Candow 2008, Johnston 2009, Hespel 2001). Anabolic effects may also be mediated by creatine's insulinotropic effects.

SARCOPENIA

According to the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is an age associated syndrome "characterised by progressive and generalised loss of skeletal muscle mass and strength" (Cruz-Jentoft 2010). Sarcopenia occurs in up to 40% of adults over sixty, and results in reduced strength and mobility, decreased physical function, and increased risk of injury (Abellan van Kan 2009). Through the mechanisms described above, creatine has been shown to increase lean body mass in the elderly. In a selection of human trails (Brose 2003, Candow 2008, Chrusch 2001, Gotshalk 2008, Gotshalk 2002, Stout 2007 [Abstr]), creatine has been shown to increase muscle strength and endurance, increase muscle fiber thickness, reduce total body protein breakdown, decrease fatigue when used alone or in conjunction with resistance training. Because sarcopenia is so closely associated with decreased physical function (Landers 2001) and increased mortality in the elderly (Gale 2007, Rantanen 2000), creatine supplementation may be an effective strategy to preserve quality of life and longevity in this population.

Table 1. Clinical trials of creatine for immobilization atrophy

Design	Outcomes	Reference
Randomized single blind, placebo controlled cross over trial; N=7 men had arms immobilized by casting; Creatine 20g per day x 7d	Lean tissue mass better maintained on creatine: 0.9% improvement vs 23.7% loss on placebo, p<0.05	Johnston 2009
N=22 healthy subjects with legs first immobilized by a cast x2wk, then given rehab therapy x6wk; Creatine 15g/d during immobilization, then 2.5g/d during rehab.	Creatine did not affect muscle expression or phosphorylation of 5 -AMP-activated protein kinase (AMPK) or its subunits during immobilization and rehabilitation.	Eijnde 2005
N=22 healthy subjects with legs immobilized x2wk then given rehab x10wk; Creatine 20g/d during immobilization, then 5g/d during rehab.	During immobilization, quadriceps cross sectional area (CSA) and maximal knee-extension power (Wmax) ↓10% and 25% respectively in both groups. During rehab, both CSA and Wmax improved more quickly in the creatine group, p<0.05 compared to placebo. MRF4 protein expression ↑in the creatine group only and this was correlated with mean muscle fibre diameter.	Hespel 2001
N=22 healthy subjects with legs immobilized x2wk then given rehab x10wk; Creatine 20g/d during immobilization, 15g/d x first 3wk of rehab, then 5g/d x last 7wk of rehab.	Immobilization ↓GLUT4 in the placebo group by 20%, p<0.05 compared to baseline, but not in the creatine group where it ↑by 9%. During the rehab phase, GLUT4 increased by 40% compared to baseline (p<0.05) in the Cr group, while levels in the placebo group simply normalized. ↑muscle glycogen at 3wk but not at 10wk in Cr vs P.	Op't Eijnde 2001
Key Cr creatine; P placebo Note All studies are randomized double blind placebo controlled trials unless otherwise stated.		

MUSCULAR DYSTROPHY

There are eight human trials examining the effect of creatine for muscular dystrophies (MD), seven RCTs (Escolar 2005, Louis 2003, Schneider-Gold 2003, Tarnopolsky 2004a, Tarnopolsky 2004b, Walter 2002, Walter 2000) and one open trial (Matsumura 2004). Of these, five found significant improvements between groups in parameters related to muscle strength and endurance or subjective improvement; two found no significant effects but found trends suggestive of benefit; and one trial found no benefits with creatine for MD. It should be noted that in the two trials finding trends toward improvement there was indication of a strong placebo effect in the control groups that could have offset any benefits observed with creatine treatment: Escolar et al (1999) reported that during the course of the study, the placebo group unexpectedly showed no deterioration over time. Walter (2002) reported that during the first phase of their crossover study, the strength of the placebo effect obscured any benefits observed in the overall study; conversely, when only the second crossover phase was analyzed, there was a significant difference in muscle strength between groups. None of the studies found benefits on cardiopulmonary function.

A 2007 Cochrane meta analysis of creatine for muscle disorders included the seven RCTs and reported that there was a significant increase in maximum voluntary contraction compared to placebo, with a weighted mean difference of 8.47% (95%CI 3.55-13.38), as well as a significant increase in lean body mass compared to placebo (weighted mean difference 0.63 kg, 95%CI 0.02-1.25) (Kley 2007).

In addition, a RCT investigating creatine for idiopathic inflammatory myopathies found significant improvements in functional performance time as measured by ability to perform a series of exercises such as walking and rising from sitting to standing, functional index of myositis, and muscle bioenergetics as measured by proton magnetic resonance spectroscopy (pMRS) after six months (Chung 2007).

NEUROMUSCULAR CONDITIONS

Fourteen human trials have investigated creatine in patients with neuromuscular conditions. Evidence for creatine in these conditions, which include ALS (Drory 2002 [Abstr], Gordon 2008, Groeneveld 2003, Mazzini

2001, Rosenfeld 2008, Shefner 2004) , Huntington disease (HD) (Bender 2005, Hersch 2006, Tabrizi 2003 and 2005, Verbessem 2003), and Parkinson's disease (PD) (Bender 2006, Bender 2008, Hass 2007, NINDS NET-PD Investigators 2008 and 2006), is less compelling than that for muscular dystrophy, however a few trials exist reporting benefit.

Mazzini et al (2001) report temporary improvement in muscle strength and Rosenfeld (2008) found a non-significant trend to improved survival with use in ALS; in HD creatine has been shown to decrease markers of DNA damage (Hersch 2006) and brain glutamate (Bender 2005); in PD creatine has been shown to increase muscle strength and endurance (Hass 2007) and may decrease the amount of dopaminergic therapy required over time (Bender 2006).

PHARMACOLOGY AND DOSING: CREATINE LOADING

Normal muscle creatine content is approximated at 125mmol/kg dry mass. There is a wide variance in muscle creatine content. Creatine supplementation achieves increases in muscle creatine content to a maximum ceiling of 155- 160mmol/ kg dry mass, although a selection of cases have been observed with levels as high as 180mmol/kg dry mass achieved under certain experimental conditions (Persky 2001, Juhn 1998a, Wyss 2000). An individual's baseline muscle creatine content determines whether an individual will be a "responder" to creatine supplementation. An individual with a baseline muscle creatine content approaching 150mmol/kg dry mass will not experience the impact to muscle creatine content through supplementation that an individual with a baseline muscle creatine content of 100mmol/kg dry mass would be anticipated to experience (Persky 2001, Juhn 1998a, Wyss 2000).

Muscle creatine content increases rapidly following oral supplementation. While a variety of dosing schedules have been implemented in controlled human trials, the most standard dosing regime calls for 20g of creatine administered per day for the first 5-7 days (the loading phase), followed by a maintenance dose of 3-5g per day thereafter. This dosing regime achieves maximal muscle creatine concentration within two days for most individuals (Persky 2001, Juhn 1998a, Wyss 2000).

A selection of factors have been demonstrated to accelerate the rate of uptake of supplemental creatine into skeletal muscle. Coadministration of carbohydrate with creatine appears to enhance creatine absorption, suggested to occur as a result of the insulin response to the carbohydrate which then upregulates transport of creatine into muscle. Exercise also appears to enhance muscle uptake of creatine. This effect may account for the discrepancy among studies of creatine for performance enhancement; a greater proportion of athletes are likely to have higher baseline muscle creatine content (Juhn 1998a, Wyss 2000).

The dosing schedule outlined above has been questioned by several authorities. Creatine supplementation at 3g per day was demonstrated to achieve maximal muscle creatine content within 30 days of supplementation; maximal muscle creatine content may have been achieved with this dosing schedule even sooner, but follow- up biopsy was not performed until day 30 (Hultman 1996). Large doses of creatine (20g per day) or greater have been shown to increase urinary excretion of formaldehyde, a safety concern of creatine supplementation, reviewed below (Poortmans 2005, Yu 2000). A dosing regime of 7g per day failed to increased formaldehyde production, also reviewed below (Candow 2008).

Given the potential concern of supplementation with large doses of creatine, and the ability of more physiological dosages to achieve identical muscle creatine content, the basis for recommendation of the "standard" dosing regime deserves scrutiny. We recommend a dosing schedule of 3g per day, delivered in juice, for use of creatine among athletes, or for prevention of immobilization- induced atrophy. In settings of neuromuscular/ neurodegenerative diseases and/ or prevention of sarcopenia in the elderly, a long-term daily dose of between 1-2g is recommended, with a 14-30 day "loading phase" of 3g per day.

SAFETY

Creatine has been well tolerated with no serious adverse effects in the studies reviewed above. Additional trials of creatine supplementation have shown it to be safe for long term use, up to five years of supplementation (Baker 2003, Poortmans 1999). Trials have shown no effect on liver enzymes, renal function, or blood pressure (Kamber 1999, Persky 2001, Poortmans 1999). Baker and Tarnopolsky note that although creatine use in the elderly with mild chronic renal insufficiency may lead to slight increases in serum creatinine, the breakdown product of creatine, this is not to be equated with renal failure; instead, the supplemented creatine is acting as " 'virtual' muscle mass for which a new set point must be reached" (2003). Two cases of kidney dysfunction have been reported, however, these effects have not been replicated in prospective studies (Baker

2003, Persky 2001). Mild side effects that have been reported anecdotally include weight gain between one to two kg due to increased water content within muscle mass; mild gastrointestinal distress; and muscle cramps (Persky 2001). There is some concern that fluid concentration within the muscle cells may potentially lead to dehydration (Juhn 1998). Doses >50g/d are not recommended. For further discussion of safety, see the review by Juhn and Tarnopolsky (1998b).

There have been concerns raised about observations that creatine supplementation leads to increased urinary formaldehyde levels (Yu 2000). Poortmans et al (2005) examined this in a short-term, high dose feeding trial in humans. After ingesting 21g creatine monohydrate for 14 days, serum creatine increased 7.2 fold, urinary creatine increased 141 fold, there was no change in creatinine levels, and 24hr urine excretion of methylamine and formaldehyde increased 9.2-fold and 4.5-fold respectively. However increases were still within normal limits for healthy humans, and there was no increase in urinary albumin output, indicating integrity of renal permeability (Poortmans 2005). Candow et al (2008) administered creatine to older men at a dose of 0.1g/kg body weight (7g per day for the "standard" 70kg male) for 10 weeks. There was no impact from the intervention on formaldehyde production, and the intervention successfully improved lean tissue mass and bench press strength relative to placebo.

PRESCRIPTION

We consider creatine to be a valuable medicine for application in an incredibly wide array of clinical settings. Evidence in specific settings of athletic performance, neuromuscular diseases, neurodegenerative diseases, sarcopenia prevention, and immobilization injury clearly identify a role for creatine in enhancing and/ or preserving lean muscle mass. It is not surprising that evidence has also begun to emerge for similar applications among patients with cancer (Bourgeois 2008, Norman 2006). Administration of near-physiological dosages (1-3g per day) is accompanied with an impeccable safety profile. It is important to inform patients of the 0.5-1.6kg increase in body weight that will occur as a result of water retention during the loading phase (Juhn 1998a). With the 1-3g per day dosing regime proposed, this increase in body weight caused by water retention typically goes unnoticed. ■

References

Abellan van Kan G. Epidemiology and consequences of sarcopenia. J Nutr Health Aging. 2009 Oct;13(8):708-12.

Baker SK, Tarnopolsky MA. Targeting cellular energy production in neurological disorders. Expert Opin Investig Drugs. 2003 Oct;12(10):1655-79.

Bender A, Samtleben W, Elstner M, Klopstock T. Long-term creatine supplementation is safe in aged patients with Parkinson disease. Nutr Res. 2008 Mar;28(3):172-8.

Bender A, Koch W, Elstner M, Schombacher Y, Bender J, Moeschl M, Gekeler F, Müller-Myhsok B, Gasser T, Tatsch K, Klopstock T. Creatine supplementation in Parkinson disease: a placebo-controlled randomized pilot trial. Neurology. 2006 Oct 10;67(7):1262-4.

Bender A, Auer DP, Merl T, Reilmann R, Saemann P, Yassouridis A, Bender J, Weindl A, Dose M, Gasser T, Klopstock T. Creatine supplementation lowers brain glutamate levels in Huntington's disease. J Neurol. 2005 Jan;252(1):36-41.

Bourgeois JM, Nagel K, Pearce E, Wright M, Barr RD, Tarnopolsky MA. Creatine monohydrate attenuates body fat accumulation in children with acute lymphoblastic leukemia during maintenance chemotherapy. Pediatr Blood Cancer. 2008 Aug;51(2):183-7.

Brose A, Parise G, Tarnopolsky MA. Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. J Gerontol A Biol Sci Med Sci. 2003 Jan;58(1):11-9.

Candow DG, Little JP, Chilibeck PD, Abeysekara S, Zello GA, Kazachkov M, Cornish SM, Yu PH. Low-dose creatine combined with protein during resistance training in older men. Med Sci Sports Exerc. 2008 Sep;40(9):1645-52.

Chrusch MJ, Chilibeck PD, Chad KE, Davison KS, Burke DG. Creatine supplementation combined with resistance training in older men. Med Sci Sports Exerc. 2001 Dec;33(12):2111-7.

Chung YL, Alexanderson H, Pipitone N, Morrison C, Dastmalchi M, Ståhl-Hallengren C, Richards S, Thomas EL, Hamilton G, Bell JD, Lundberg IE, Scott DL. Creatine supplements in patients with idiopathic inflammatory myopathies who are clinically weak after conventional pharmacologic treatment: Six-month, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2007 May 15;57(4):694-702.

Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010 Jul;39(4):412-23.

Drory VE, Gross D. No effect of creatine on respiratory distress in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2002 Mar;3(1):43-6.

Eijnde BO, Derave W, Wojtaszewski JF, Richter EA, Hespel P. AMP kinase expression and activity in human skeletal muscle: effects of immobilization, retraining, and creatine supplementation. J Appl Physiol. 2005 Apr;98(4):1228-33

Escolar DM, Buyse G, Henricson E, Leshner R, Florence J, Mayhew J, Tesi-Rocha C, Gorni K, Pasquali L, Patel KM, McCarter R, Huang J, Mayhew T, Bertorini T, Carlo J, Connolly AM, Clemens PR, Goemans N, Iannaccone ST, Igarashi M, Nevo Y, Pestronk A, Subramony SH, Vedanarayanan VV, Wessel H; CINRG Group. CINRG randomized controlled trial of creatine and glutamine in Duchenne muscular dystrophy. Ann Neurol. 2005 Jul;58(1):151-5.

Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. Int J Epidemiol. 2007 Feb;36(1):228-35.

Gordon PH, Cheung YK, Levin B, Andrews H, Doorish C, Macarthur RB, Montes J, Bednarz K, Florence J, Rowin J, Boylan K, Mozaffar T, Tandan R, Mitsumoto H, Kelvin EA, Chapin J, Bedlack R, Rivner M, McCluskey LF, Pestronk A, Graves M, Sorenson EJ, Barohn RJ, Belsh JM, Lou JS, Levine T, Saperstein D, Miller RG, Scelsa SN; Combination Drug Selection Trial Study Group. A novel, efficient, randomized selection trial comparing combinations of drug therapy for ALS. Amyotroph Lateral Scler. 2008 Aug;9(4):212-22.

Gotshalk LA, Volek JS, Staron RS, Denegar CR, Hagerman FC, Kraemer WJ. Creatine supplementation improves muscular performance in older men. Med Sci Sports Exerc. 2002 Mar;34(3):537-43.

Gotshalk LA, Kraemer WJ, Mendonca MA, Vingren JL, Kenny AM, Spiering BA, Hatfield DL, Fragala MS, Volek JS. Creatine supplementation improves muscular performance in older women. Eur J Appl Physiol. 2008 Jan;102(2):223-31.

Groeneveld GJ, Veldink JH, van der Tweel I, Kalmijn S, Beijer C, de Visser M, Wokke JH, Franssen H, van den Berg LH. A randomized sequential trial of creatine in amyotrophic lateral sclerosis. Ann Neurol. 2003 Apr;53(4):437-45.

Hass CJ, Collins MA, Juncos JL. Resistance training with creatine monohydrate improves upper-body strength in patients with Parkinson disease: a randomized trial. Neurorehabil Neural Repair. 2007 Mar-Apr;21(2):107-15.

Hersch SM, Gevorkian S, Marder K, Moskowitz C, Feigin A, Cox M, Como P, Zimmerman C, Lin M, Zhang L, Ulug AM, Beal MF, Matson W, Bogdanov M, Ebbel E, Zaleta A, Kaneko Y, Jenkins B, Hevelone N, Zhang H, Yu H, Schoenfeld D, Ferrante R, Rosas HD. Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. Neurology. 2006 Jan 24;66(2):250-2.

Hespel P, Op't Eijnde B, Van Leemputte M, Ursø B, Greenhaff PL, Labarque V, Dymarkowski S, Van Hecke P, Richter EA. Oral creatine supplementation facilitates the rehabilitation of disuse atrophy and alters the expression of muscle myogenic factors in humans. J Physiol. 2001 Oct 15;536(Pt 2):625-33.

Hultman E, Söderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in men. J Appl Physiol. 1996 Jul;81(1):232-7.

Johnston AP, Burke DG, MacNeil LG, Candow DG. Effect of creatine supplementation during cast-induced immobilization on the preservation of muscle mass, strength, and endurance. J Strength Cond Res. 2009 Jan;23(1):116-20

Juhn MS, Tarnopolsky M. Oral creatine supplementation and athletic performance: a critical review. Clin J Sport Med. 1998a Oct;8(4):286-97.

Juhn MS, Tarnopolsky M. Potential side effects of oral creatine supplementation: a critical review. Clin J Sport Med. 1998b Oct;8(4):298-304.

Kamber M, Koster M, Kreis R, Walker G, Boesch C, Hoppeler H. Creatine supplementation--part I: performance, clinical chemistry, and muscle volume. Med Sci Sports Exerc. 1999 Dec;31(12):1763-9.

Kley RA, Vorgerd M, Tarnopolsky MA. Creatine for treating muscle disorders. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004760.

Landers KA, Hunter GR, Wetzstein CJ, Bamman MM, Weinsier RL. The interrelationship among muscle mass, strength, and the ability to perform physical tasks of daily living in younger and older women. J Gerontol A Biol Sci Med Sci. 2001 Oct;56(10):B443-8.

Louis M, Lebacq J, Poortmans JR, Belpaire-Dethiou MC, Devogelaer JP, Van Hecke P, Goubel F, Francaux M. Beneficial effects of creatine supplementation in dystrophic patients. Muscle Nerve. 2003 May;27(5):604-10.

Matsumura T, Yokoe M, Nakamori M, Hattori N, Saito T, Nozaki S, Fujimura H, Shinno S. [A clinical trial of creatine monohydrate in muscular dystrophy patients]. Rinsho Shinkeigaku. 2004 Oct;44(10):661-6.

Mazzini L, Balzarini C, Colombo R, Mora G, Pastore I, De Ambrogio R, Caligari M. Effects of creatine supplementation on exercise performance and muscular strength in amyotrophic lateral sclerosis: preliminary results. J Neurol Sci. 2001 Oct 15;191(1-2):139-44.

NINDS NET-PD Investigators. A pilot clinical trial of creatine and minocycline in early Parkinson disease: 18-month results. Clin Neuropharmacol. 2008 May-Jun;31(3):141-50.

NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology. 2006 Mar 14;66(5):664-71.

Norman K, Stübler D, Baier P, Schütz T, Ocran K, Holm E, Lochs H, Pirlich M. Effects of creatine supplementation on nutritional status, muscle function and quality of life in patients with colorectal cancer--a double blind randomised controlled trial. Clin Nutr. 2006 Aug;25(4):596-605.

Op 't Eijnde B, Ursø B, Richter EA, Greenhaff PL, Hespel P. Effect of oral creatine supplementation on human muscle GLUT4 protein content after immobilization. Diabetes. 2001 Jan;50(1):18-23

Pearlman JP, Fielding RA. Creatine monohydrate as a therapeutic aid in muscular dystrophy. Nutr Rev. 2006 Feb;64(2 Pt 1):80-8.

Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. Pharmacol Rev. 2001 Jun;53(2):161-76.

Poortmans JR, Kumps A, Duez P, Fofonka A, Carpentier A, Francaux M. Effect of oral creatine supplementation on urinary methylamine, formaldehyde, and formate. Med Sci Sports Exerc. 2005 Oct;37(10):1717-20.

Poortmans JR, Francaux M. Long-term oral creatine supplementation does not impair renal function in healthy athletes. Med Sci Sports Exerc. 1999 Aug;31(8):1108-10.

Rantanen T, Harris T, Leveille SG, Visser M, Foley D, Masaki K, Guralnik JM. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. J Gerontol A Biol Sci Med Sci. 2000 Mar;55(3):M168-73.

Rosenfeld J, King RM, Jackson CE, Bedlack RS, Barohn RJ, Dick A, Phillips LH, Chapin J, Gelinas DF, Lou JS. Creatine monohydrate in ALS: effects on strength, fatigue, respiratory status and ALSFRS. Amyotroph Lateral Scler. 2008 Oct;9(5):266-72.

Shefner JM, Cudkowicz ME, Schoenfeld D, Conrad T, Taft J, Chilton M, Urbinelli L, Qureshi M, Zhang H, Pestronk A, Caress J, Donofrio P, Sorenson E, Bradley W, Lomen-Hoerth C, Pioro E, Rezania K, Ross M, Pascuzzi R, Heiman-Patterson T, Tandan R, Mitsumoto H, Rothstein J, Smith-Palmer T, MacDonald D, Burke D; NEALS Consortium. A clinical trial of creatine in ALS. Neurology. 2004 Nov 9;63(9):1656-61.

Schneider-Gold C, Beck M, Wessig C, George A, Kele H, Reiners K, Toyka KV. Creatine monohydrate in DM2/PROMM: a double-blind placebo-controlled clinical study. Proximal myotonic myopathy. Neurology. 2003 Feb 11;60(3):500-2.

Stout JR, Sue Graves B, Cramer JT, Goldstein ER, Costa PB, Smith AE, Walter AA. Effects of creatine supplementation on the onset of neuromuscular fatigue threshold and muscle strength in elderly men and women (64 - 86 years). J Nutr Health Aging. 2007 Nov-Dec;11(6):459-64.

Tarnopolsky MA, Mahoney DJ, Vajsar J, Rodriguez C, Doherty TJ, Roy BD, Biggar D. Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. Neurology. 2004 May 25;62(10):1771-7. a.

Tarnopolsky M, Mahoney D, Thompson T, Naylor H, Doherty TJ. Creatine monohydrate supplementation does not increase muscle strength, lean body mass, or muscle phosphocreatine in patients with myotonic dystrophy type 1. Muscle Nerve. 2004 Jan;29(1):51-8. b.

Tabrizi SJ, Blamire AM, Manners DN, Rajagopalan B, Styles P, Schapira AH, Warner TT. High-dose creatine therapy for Huntington disease: a 2-year clinical and MRS study. Neurology. 2005 May 10;64(9):1655-6.

Tabrizi SJ, Blamire AM, Manners DN, Rajagopalan B, Styles P, Schapira AH, Warner TT. Creatine therapy for Huntington's disease: clinical and MRS findings in a 1-year pilot study. Neurology. 2003 Jul 8;61(1):141-2.

Terjung RL, Clarkson P, Eichner ER, Greenhaff PL, Hespel PJ, Israel RG, Kraemer WJ, Meyer RA, Spriet LL, Tarnopolsky MA, Wagenmakers AJ, Williams MH. American College of Sports Medicine roundtable. The physiological and health effects of oral creatine supplementation. Med Sci Sports Exerc. 2000 Mar;32(3):706-17.

Verbessem P, Lemiere J, Eijnde BO, Swinnen S, Vanhees L, Van Leemputte M, Hespel P, Dom R. Creatine supplementation in Huntington's disease: a placebo-controlled pilot trial. Neurology. 2003 Oct 14;61(7):925-30.

Walter MC, Lochmüller H, Reilich P, Klopstock T, Huber R, Hartard M, Hennig M, Pongratz D, Müller-Felber W. Creatine monohydrate in muscular dystrophies: A double-blind, placebo-controlled clinical study. Neurology. 2000 May 9;54(9):1848-50.

Walter MC, Reilich P, Lochmuller H, Kohnen R, Schlotter B, Hautmann H, Dunkl E, Pongratz D, Muller-Felber W. Creatine monohydrate in myotonic dystrophy: a double-blind, placebo-controlled clinical study. J Neurol. 2002 Dec;249(12):1717-22.

Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev. 2000 Jul;80(3):1107-213.

Yu PH, Deng Y. Potential cytotoxic effect of chronic administration of creatine, a nutrition supplement to augment athletic performance. Med Hypotheses. 2000 May;54(5):726-8.

Questions

1. Creatine acts as a quick source of ATP during conditions of high energy demand. As such, it exists as free creatine and phosphocreatine.
A. True
B. False

2. Creatine has been shown to upregulate the GLUT6 transporter in muscle, thereby increasing glucose uptake into muscle fibres.
A. True
B. False

3. In the area of performance enhancement, creatine is most useful for which of the following?
A. Short duration, high intensity exercise
B. Marathon running
C. Resistance training
D. Short duration maximal intensity sprints on a stationary bike
E. A, C, & D

4. Creatine has been shown to have the following effects on muscle tissue:
A. Increased lean muscle mass
B. Increased muscle fibre diameter
C. Increased one repetition maximum (1RM) performance
D. Increased total strength, total work, and total power output
E. All of the above

5. Activities of duration over 60 seconds are highly benefited by use of creatine
A. True
B. False

6. Creatine has the ability to benefit athletes by augmenting the amount of lean muscle mass gained during off-season resistance training, thereby indirectly enhancing performance in their sport of choice.
A. True
B. False

7. Which of the following is true?
A. Creatine has been shown to offset immobilization atrophy of muscle mass by close to 25%
B. In the elderly, creatine has been shown to increase maximal isometric strength, maximal dynamic strength, and lower extremity functional capacity
C. Creatine has been shown to improve cardiopulmonary function in muscular dystrophies.
D. A & B
E. A & C

8. Bender 2006 found that Parkinson's disease patients who received creatine required a significantly smaller dose increase of dopaminergic therapy compared to patients in the control group after two years.
A. True
B. False

9. Which of the following is true about creatine loading?
A. Creatine supplementation increases muscle creatine content to a maximum of 155- 160mmol/ kg dry mass
B. Baseline muscle creatine content determines the magnitude of benefit that an individual will experience from creatine
C. The traditional 20g loading doses of creatine given for the first few days of supplementation have been shown to increase urinary formaldehyde undermining the safety of this dose
D. Lower doses have not demonstrated this effect, therefore a dose of 1-3g per day depending on the context is a safe yet effective dose for creatine administration
E. All of the above

10. A trial investigating creatine for use in idiopathic inflammatory myopathies found significant improvements in:
A. Walking and rising from sitting to standing,
B. Functional index of myositis, and
C. Muscle bioenergetics as measured pMRS
D. None of the above
E. All of the above

FAX OR EMAIL ANSWERS TO:
416.703.6392
philip@ihpmagazine.com