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REVIEW ARTICLE

Creatine as a therapeutic strategy for myopathies

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Abstract Myopathies are genetic or acquired disorders of skeletal muscle that lead to varying degrees of weakness, atrophy, and exercise intolerance. In theory, creatine supplementation could have a number of beneficial effects that could enhance function in myopathy patients, including muscle mass, strength and endurance enhancement, lower calcium levels, anti-oxidant effects, and reduced apoptosis. Patients with muscular dystrophy respond to several months of creatine monohydrate supplementation (~0.075–0.1 g/kg/day) with greater strength (~9%) and fat-free mass (~0.63 kg). Patients with myotonic dystrophy do not show as consistent an effect, possibly due to creatine transport issues. Creatine monohydrate supplementation shows modest benefits only at lower doses and possibly negative effects (cramping) at higher doses in McArdle's disease patients. Patients with MELAS syndrome show some evidence of benefit from creatine supplementation in exercise capacity, with the effects in patients with CPEO being less robust, again, possibly due to limited muscle creatine uptake. The evidence for side effects or negative impact upon serological metrics from creatine supplementation in all groups of myopathy patients is almost non-existent and pale in comparison to the very substantial and well-known side effects from our current chemotherapeutic interventions for some myopathies (i.e., corticosteroids).

Dr. Tarnopolsky is the Co-founder and chief scientific officer for Life Sciences Nutritionals (we do not make any products containing creatine).

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Introduction

The term, myopathy refers to a primary disorder of skeletal muscle, and these are classified a primary (genetic) or acquired, with many subdivisions (Table 1). Myopathies lead to disability either by altering the contractile apparatus and leading to progressive weakness (i.e., muscular dystrophy, congenital myopathy) or by interfering with energy pathways and leading to contractile failure (i.e., mitochondrial myopathy, McArdle's disease). For a complete review of the myopathies, the reader is referred to a recent review article (van Adel and Tarnopolsky 2009). Conceptually, creatine supplementation could be a therapeutic strategy for metabolic myopathies given its role in anaerobic muscle energy delivery and link to control of mitochondrial respiration. Furthermore, the weakness and muscle atrophy seen in many forms of muscular dystrophy (i.e., fascioscapulohumeral dystrophy, myotonic dystrophy), could show a therapeutic benefit from creatine supplementation through strength, power, and fat-free mass, increases, as shown in older adults (Brose et al. 2003; Chrusch et al. 2001; Tarnopolsky et al. 2007). Creatine has a number of other potentially therapeutic effects including an anti-oxidant effect (Lawler et al. 2002), enhancement of satellite cell activation (Olsen et al. 2006), and neuroprotection (Yang et al. 2009, see also the paper by Beal). Specific to the pathogenesis of the dystrophinopathies is an increase in intra-cellular calcium that can activate proteases, and creatine is known to lower intra-cellular calcium by activating the SERCA Ca-ATPase pumps (Hespel et al.

Table 1 Examples of more common myopathies

Primary/genetic
Muscular dystrophy
Dystrophinopathy—Becker's, Duchenne (dystrophin)
Limb girdle—recessive (sarcoglycans, calpain 3, dysferlinopathy); dominant (collagen 6, caveolin-3)
Emery-Driefuss—X-linked (emerin); dominant (lamin A/C)
Congenital—Merosin, fukutin, FKRP, α-7 integrin
Fascioscapulohumeral—Type 1 (4q33 deletion); type 2 (methylation defect)
Occulopharngeal—Trinucleotide repeat expansion (CAG) in PABPN1
Myotonic—Type 1 (CTG repeat expansion 3′ of DMPK); type 2 (CCTG repeat expansion in CNBP)
Congenital myopathy
Nemaline rod (ACTA 1, nebulin), central core (ryanodine)
Metabolic myopathies
Fat oxidation defects—Carnitine palmitoyl transferase 2, trifunctional protein, very long chain acyl-CoA dehydrogenase
Glycogen storage disease—McArdle's disease (phosphorylase), Tarui's disease (phopshofructokinase)
Mitochondrial—chronic progressive external ophthalmoplegia (CPEO), mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
Secondary/acquired
Inflammatory
Polymyositis, dermatomyositis, inclusion body myositis, overlap myositis
Drug/Toxin
Statins, acute ethanol, anti-psychotic drugs, corticosteroids
Endocrine
Cushing's (corticosteroid excess), hypothyroid and hyperthyroid myopathy

The specific protein implicated in the dystrophies is indicated in the brackets. A more comprehensive list and description can be found in a recent review article (van Adel and Tarnopolsky 2009)

2002). Others have reviewed the theoretical data supporting a role of creatine in myopathy patients (Pearlman and Fielding 2006).

In addition to having a potential therapeutic effect in the myopathies as a supplement, creatine may also replace a deficiency state specific to certain myopathies. In fact, creatine deficiency was thought to be a cause of muscular dystrophy many decades ago based upon the observation that large amounts of creatine were excreted in the urine in such patients (Milhorat and Wolff 1938). Of interest, the secondary creatine deficiency syndrome called gyrate atrophy of the choroid leads to type II muscle fiber atrophy and weakness (Sipila et al. 1981). We have used direct measurements of total and phosphocreatine in patients with inflammatory myopathies, muscular dystrophy, congenital myopathy and mitochondrial myopathies and found low concentrations (Tarnopolsky and Parise 1999). Furthermore, we have also found that creatine transporter mRNA and possibly protein are lower in such patients (Tarnopolsky et al. 2001), possibly due to plasma membrane disruption. Others have reported lower phosphocreatine in muscle of patients with inflammatory myopathies (Park et al. 1994) and mitochondrial myopathies (Argov and Bank 1991).

A final very important consideration is that creatine monohydrate therapy may be a countermeasure to the negative effects of corticosteroids on bone and muscle. Corticosteroid therapy is the primary therapy for Duchenne muscular dystrophy (DMD), dermatomyositis, polymyositis, and overlap myositis, and the neuromuscular junction defect, myasthenia gravis. Corticosteroids are well known to cause muscle weakness associated with type II muscle fiber atrophy, osteopenia/osteoporosis, and attenuate linear growth in children. We gave methylprednisolone (7 mg/week, similar to the dose in boys with DMD) to growing rats for 6 weeks with and without creatine monohydrate (2% w/w in chow) (Roy et al. 2002). The creatine-treated rats with and without corticosteroids had larger type II muscle fibers and total creatine content in fast muscle as compared to those given corticosteroids and the control animals (Roy et al. 2002). Furthermore, the attenuation of linear growth induced by the steroids was not seen when the animals were co-administered the creatine (Roy et al. 2002). Importantly, we have also found evidence of bone protection in corticosteroid treated rats also on the creatine supplementation (Antolic et al. 2007). Other groups have found that creatine monohydrate supplementation prevented dexamethasone-induced reductions in voluntary

running in hamsters (Campos et al. 2006), and dexamethasone induced type II fiber atrophy and muscle mass loss in rats (Menezes et al. 2007).

Muscular dystrophies

Dystrophinopathies

Most of the studies completed to date have evaluated the role of creatine in the dystrophinopathies (Becker's and Duchenne) (Louis et al. 2003; Tarnopolsky et al. 2004; Walter et al. 2000), and myotonic dystrophy (type I and II) (Schneider-Gold et al. 2003; Tarnopolsky et al. 2004; Walter et al. 2002); however, the theoretical rationale for therapy should translate to other forms of muscular dystrophy, as positive effects were seen in one study using a mixed myopathy population (Walter et al. 2000). Given the potential alterations in the creatine transporter in patients with muscular dystrophy, there was concern that patients with myopathy may not "load" muscle in response to creatine supplementation. One study used magnetic resonance spectroscopy (MRS) and found a strong trend (8%, sample size estimate = 12 subjects) towards higher phosphocreatine/β-ATP muscle content in a sub-group of only six subjects and a relatively low dose of creatine (3 g/day) (Louis et al. 2003); we have found an increase in total creatine in *mdx* mice with supplementation (Payne et al. 2006); others have shown loading in patients with dystrophy (Banerjee et al. 2010). Finally, the beneficial effects seen in muscle-related outcomes of strength and muscle mass are consistent in myopathy patients and would be difficult to reconcile these findings if there was no entry of creatine into muscle.

The dystrophinopathies are X-linked recessive forms of muscular dystrophy due to mutations in the dystrophin gene. Dystrophin is a large cytoskeletal protein that links actin to the extra-cellular matrix through the dystroglycan and sarcoglycan complex. Complete (Duchenne) or partial (Becker's) loss of dystrophin protein leads to disruption of the plasma membrane and multi-faceted pathology, including calcium overload/calpain activation, ischemia (via loss of nitric oxide mediated dilatation), oxidative stress, and necrosis. Ultimately, the muscle is replaced with fibro-fatty tissue and progressive weakness ensues. Duchenne muscular dystrophy (DMD) affects ~1/3,500 live male births, and Becker's muscular dystrophy or manifesting female carriers of DMD likely affect ~1/10,000 people. DMD results in strength loss that leads to wheelchair confinement by ~12 years of age and respiratory failure in the early twenties often with cardiomyopathy. Treatment of DMD with prednisone (0.75 mg/kg/day) (Fenichel et al. 1991), or Deflazacort (0.9 mg/kg/day) (Biggar et al. 2001), increased muscle strength by 5–8% and slowed the progression of the disease (delay wheelchair confinement by ~2 years); however, the exact mechanism of action is unknown. The side effects of corticosteroid use are significant and well-known in these disorders (Hawker et al. 2005; Schara and Mortier 2001).

The first evidence for a potential role for creatine therapy in the dystrophinopathies came from in vitro experiments with primary myotubes (derived from satellite cells) from boys with DMD and the animal model of DMD (*mdx* mice) (Pulido et al. 1998). The myotubes cultured in 20 mM creatine showed better myotube formation and survival associated with a lower intra-cellular calcium concentration and higher Ca^{2+} ATPase pump activity (Pulido et al. 1998). Improved strength was reported by another group in the *mdx* mice model; however, they referred to creatine as creatinine in the text (Granchelli et al. 2000). Another study found improvements in mitochondrial function with creatine supplementation in *mdx* mice (Passaquin et al. 2002). In addition, an independent group also showed improvement in some, but not all, pathological muscle changes in *mdx* mice with creatine supplementation (Louis et al. 2004). Of interest, the *mdx* mice also show evidence for an increase in endogenous creatine synthesis, perhaps to compensate for the deficit (McClure et al. 2007). Finally, our group found that creatine showed evidence of potential therapeutic benefit in several outcome metrics (strength fatigue, Rotorod running, internal nuclei) (Payne et al. 2006). Together, the animal data provided a strong theoretical basis for proceeding with clinical trials in patient populations.

We completed an open trial of creatine monohydrate supplementation for 2 weeks in men and women with a variety of myopathies ($N = 81$), including several types of muscular dystrophy, and found an increase in peak strength, body mass and repetitive high-intensity strength of ~11% with no reported side effects (Tarnopolsky and Martin 1999). The first randomized, clinical trial was reported in 2001 with 36 children and adults with a variety of muscular dystrophies randomized (double-blinded, cross-over design) to creatine monohydrate (5 g/day pediatric; 10 g/day adult) or placebo for 2 months with a washout period (Walter et al. 2000). The creatine-treated group showed an increase in the sum of the muscle strength rating scale (Medical Research Council) and improvements in the Neuromuscular Symptom Scale, with no evidence of a change in plasma creatine kinase (CK) activity or other side effects (Walter et al. 2000). Shortly thereafter, another group reported on the results of creatine monohydrate (3 g/day) supplementation using a 12-week randomized, double-blind study in 15 boys and men with DMD and BMD (Louis et al. 2003). They reported an increase in strength and endurance, fat-free mass, and maintenance of

joint contracture score (the norm is to worsen over time) after treatment (Louis et al. 2003). Of interest, they also reported a small, but significant increase in bone mineral density and a lowering of *N*-telopeptides in the urine (a marker of bone breakdown) in the subjects taking creatine (Louis et al. 2003). In the latter study, a sub-group ($N = 6$) had muscle phosphocreatine content measured in muscle with only a trend towards an increase (Louis et al. 2003).

We initiated a randomized, double-blind, cross-over study in 30 boys with DMD (50% taking corticosteroids) with a 4-month active or placebo → 2-month wash-out → 4-month alternate treatment design, with a dose of 5 g/day (~0.1 g/kg/day)(Tarnopolsky et al. 2004). We found a significant increase in fat-free mass while on creatine, an increase in dominant hand-grip strength, and a strong trend towards an attenuation of the loss of strength in the MRC sum score, and the results were the same for boys taking corticosteroids (Tarnopolsky et al. 2004). Importantly, we also confirmed the results of Louis et al. (2003), by showing a ~50% reduction in *N*-telopeptide excretion in urine (suggesting lower bone breakdown) (Tarnopolsky et al. 2004). Although we did not find an effect on bone mass, it is likely that the duration of therapy (4 months) was too short to detect a significant effect on bone, and at the time when the study was initiated, we complete whole body dual X-ray absorptiometry scans primarily for total fat-free mass (primarily muscle) and did not use a femur- and spine-specific protocol that is more sensitive for bone mineral density measurements. Finally, creatine (5 g/day) and glutamine were compared to placebo in 50 ambulant boys with DMD over a 6-month trial using a randomized, double-blind, parallel group design (Escolar et al. 2005). The study was limited by not showing the expected decline in function in the boys allocated to placebo, but they found "strong, consistent non-significant trends" for all outcomes except manual muscle testing to show less deterioration on the two treatment arms versus placebo. Furthermore, the creatine group showed less deterioration ($P = 0.07$) for quantitative muscle testing and stair climbing ($P = 0.015$), and those who were age over 7 years in the creatine group ($N = 7$) "consistently showed less deterioration compared with other groups in the quantitative muscle testing arm and leg scores…" (Escolar et al. 2005). The latter study found no side effects from either intervention (Escolar et al. 2005).

Myotonic muscular dystrophy

Myotonic muscular dystrophy was initially named for the characteristic myotonia (slow muscle relaxation after contraction); it is a multi-systemic disorder with variable severity of cataracts, somnolence, hair loss, swallowing difficulties, cardiac conduction block, muscle atrophy and weakness, dysglycemia, gastrointestinal disturbance, and cognitive impairment (in the more severe cases). There are two main types of myotonic muscular dystrophy: type 1 (DM1) due to a CTG expansion in the 3′ intronic region of DMPK and type 2 (DM2) due to a CCTG expansion in intron 1 of the CNBP (formerly ZFN9) gene. The clinical differences are that DM1 primarily affects distal muscles while DM2 affects proximal muscles; there is no congenital form of DM2 and no appreciable cognitive impairment, and nearly 50% of patients with DM2 develop myalgias. In general, both disorders show more severe clinical consequences and earlier onset with larger tri- and tetra- nucleotide expansions, and the pathogenesis is primarily due to intra-nuclear mRNA inclusions that interfere with nuclear export of key mRNA species (Mankodi et al. 2003). It will be of interest to see if the creatine transporter is one of the mRNA species that gets retained in the nucleus and is responsible for the apparent lack of creatine loading in the two DM1 studies described below (Tarnopolsky et al. 2004; Walter et al. 2002).

We evaluated the potential benefits of creatine supplementation (5 g/day) in adult men and women with DM1 using a 4-month, double-blind, cross-over study design, identical in design to our DMD study described above (Tarnopolsky et al. 2004). We also used ^{31}Phosphorus-magnetic resonance spectroscopy to determine muscle phosphocreatine at the end of each trial and found no evidence of loading (Tarnopolsky et al. 2004). Likely as a consequence of the lack of creatine loading, we found no evidence of clinical benefit based upon the functional, strength, spirometry, or fat-free mass outcomes measured (Tarnopolsky et al. 2004). Given the high frequency of gastrointestinal complaints in patients with DM1, we did not see a greater incidence of such issues while the patients were on the creatine monohydrate arm of the study, and there were no adverse effects on liver function or creatine kinase activity (Tarnopolsky et al. 2004). We did find a slightly higher serum creatinine level, but creatinine clearance was not altered by treatment (Tarnopolsky et al. 2004). Another study evaluated the effect of creatine monohydrate (10.6 g/day × 10 days, 5.3 g/day × 46 -days) in 34 DM1 patients using a randomized double-blind, cross-over design (Walter et al. 2002). They found trends towards greater MRC scores ($P = 0.11$ overall, $P = 0.005$ s arm), improved neuromuscular symptom scores ($P = 0.15$ overall, $P = 0.06$ s arm), and quantitative muscle strength of the biceps ($P = 0.067$) for the creatine arm versus placebo, with no reported side effects and no alterations of liver or renal function or creatine kinase activity (Walter et al. 2002).

To date, there has only been one reported study of creatine supplementation in patients with DM2 (Schneider-Gold

et al. 2003). In this study, 20 patients were randomized to 10 g/day of creatine monohydrate ($N = 10$) or placebo ($N = 10$) for 3 months (Schneider-Gold et al. 2003). There was a significantly greater subjective improvement ($P < 0.01$) and higher scores for activity of daily living ($P < 0.05$) in those patients in the creatine group (Schneider-Gold et al. 2003), with no differences in MRC strength or leg strength. Interestingly, the increase in dominant hand strength was 9.8% for the creatine group and 1.0% in the placebo group (difference = 8.8%), which was not significant, but similar in magnitude to the overall effect seen in the Cochrane review (Kley et al. 2011), and similar to our DMD study in that the dominant hand (? more exercise) showed some evidence of improvement (Tarnopolsky et al. 2004).

Overall, patients with myotonic muscular dystrophy patients show similar directional and quantitative trends towards improvement as seen in the dystrophinopathies and likely other forms of muscular dystrophy. The magnitude and consistency of the effects are less apparent in myotonic patients, and this could be due to intra-nuclear CUG inclusions limiting export of the creatine transporter, thus limiting the ability to respond to creatine supplementation. In addition to evaluating this interesting scientific concept, it would be of interest to see if these patients can increase intra-muscular concentrations of total- or phosphocreatine with higher creatine doses, exercise, alpha-lipoic acid (Burke et al. 2003), or co-administration of carbohydrate and amino acids (Pittas et al. 2010).

Summary

The balance of evidence suggests that creatine monohydrate supplementation is well tolerated and safe in children and adults with muscular dystrophy. The data suggest that strength, overall function and fat-free mass all increase after several months of creatine monohydrate therapy. Importantly, there appears to be beneficial effects in myopathy patients who are also being treated with corticosteroids (Tarnopolsky et al. 2004). The data published to date on the topic have been incorporated into a meta-analysis by the Cochrane review group, and the results confirm this impression by showing a mean increase of 0.63 kg in fat-free mass and 8.5% in quantitative muscle strength with creatine monohydrate supplementation (total = 192 participants) (Kley et al. 2011). Future studies will need to determine whether the beneficial effects are maintained in the longer term (years), and whether there are unique aspects of therapy in other major categories of these disorders, such as fascioscapulohumeral dystrophy, limb girdle, and congenital dystrophy/myopathy.

Metabolic myopathies

The metabolic myopathies are genetic disorders with alterations in the pathways of intermediary metabolism. Disorders of amino acid metabolism and the urea cycle often present in the infant period as recurrent bouts of encephalopathy with no clinical evidence of primary myopathy. Disorders of glycolysis (i.e., phosphofructokinase deficiency, GSD 7) and glycogenolysis (i.e., myophosphorylase deficiency, GSD 5, McArdle's disease) are considered glycogen storage diseases (GSDs) due to the fact that glycogen usually accumulates in the muscle. The breakdown of muscle glycogen and subsequent metabolism through glycolysis are essential for anaerobic and aerobic exercise. As a consequence, patients with primary glycogenolytic or glycolytic defects usually present with muscle cramps in the early rest to exercise transition or with high-intensity exercise. Although maximal oxygen consumption (VO_{2peak}) is low in such patients (reflecting the need for carbohydrate-derived carbon sources for optimal aerobic metabolism), most patients with these types of metabolic myopathy are limited by the early exercise intolerance. The rate of ATP production from free fatty acids is less than carbohydrate, and fat becomes a more quantitatively more important fuel with longer duration and lower intensity exercise. Fatty acid oxidation defects (FAODs) can occur at any one of the many steps in fat oxidation from sarcolemmal transport to mitochondrial transport via the carnitine acyl-CoA tanslocase system to the four major steps in β-oxidation. Adult patients with FAODs usually present with exercise intolerance/myalgia during long duration exercise or with superimposed fasting or illness (when the demand for FFA oxidation is already high). The mitochondrial electron transport chain (ETC) is the final common pathway for aerobic energy transduction, and most patients with mitochondrial myopathies report exercise intolerance usually under similar stressors as the FAODs.

Mitochondrial disorders

Mitochondrial myopathies represent a sub-group of a larger group of mitochondrial disorders (mitochondrial cytopathies), where muscle is the primary tissue affected. Given that skeletal muscle is heavily dependent on mitochondrial derived aerobic respiration and mitochondrial dysfunction can lead to muscle atrophy, muscle fatigue, decreased endurance and muscle weakness are commonly seen in the mitochondrial myopathies (Tarnopolsky and Raha 2005). Skeletal muscle manifestations are also very prominent features in the general group of mitochondrial "cytopathies" even though other clinical features such as strokes, seizures, developmental regression, and optic atrophy with blindness often predominate the clinical picture. A primary

defect in the structure or function of the mitochondrial electron transport chin (ETC) is the fundamental pathology defining the mitochondrial disorders. The ETC is the final common pathway for the aerobic oxidation of energy from fat, protein, and carbohydrate and is composed of proteins that are encoded by both the nuclear and mitochondrial genome. The mitochondrial genome encodes for two ribosomal RNAs, 22 transfer RNAs, and 13 components of the electron transport chain (complex I, III, IV, and V). The protein subunits are assembled into holoenzyme complexes with nuclear and mitochondrial encoded subunits (except complex II which has only nuclear encoded subunits). Complexes I, III, and IV are involved in proton pumping from reduced NADH + H^+ and $FADH_2$ to form ATP in the presence of oxygen. The composition, assembly, and maintenance of electron transport chain require nearly 1,500 proteins and defects, and at least 200 of these have been documented to cause human disease (for review, see Tarnopolsky and Raha 2005).

By tradition, most of the mitochondrial cytopathies are described by acronyms that represent phenotypic characteristics. For example, MELAS syndrome stands for Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like episodes. As with many of the mitochondrial cytopathies, there are a wide variety of gene mutations that can lead to the same phenotype, and the same gene mutation can lead to a variety of different phenotypes. Given the multi-systemic involvement including brain, heart, liver and skeletal muscle, it is clear that there is a potential role for creatine monohydrate therapy in such disorders given that there is evidence of possible therapeutic benefit in each of these tissues and organs (Table 2). The ETC is the main source of free radical generation in the body, and disruption of the ETC leads to an increase in reactive oxygen species (ROS) production. Consequently, the potential role of creatine as an antioxidant (Lawler et al. 2002) has relevance to these disorders. Furthermore, by activation of the creatine/phosphocreatine shuttle, creatine supplementation could also lead to potential therapeutic benefit. The creatine/phosphocreatine system also has a role as a proton buffer, and the high lactic acid seen in most mitochondrial cytopathies could be favorably affected by creatine supplementation. Mitochondrial myopathies have also been associated with an increase in apoptosis, and the anti-apoptotic effects of creatine supplementation have been described (Baker and Tarnopolsky 2003). We have also shown a reversal of paracrystalline inclusions in a patient with a cytochrome *b* mutation with creatine monohydrate supplementation and less apoptosis of cybrid cells in vitro (Tarnopolsky et al. 2004). Finally, disruption of the electron transport chain leads to an increase in anaerobic energy transduction; higher levels of phosphocreatine could be of benefit as an alternative energy source.

We evaluated the effects of creatine monohydrate supplementation (10 g/day × 14 days → 3 g/day × 7 days) in seven patients with MELAS syndrome and severe exercise intolerance (VO_{2peak} = 9.7 mL/kg/min) using a randomized, double-blind, cross-over design (Tarnopolsky et al. 1997). We found higher dorsi-flexion and handgrip strength with a repeated bout high-intensity exercise test, with no increase in VO_{2peak}, and a non-significant increase in fat-free mass (+0.6 kg) (Tarnopolsky et al. 1997). Several other case reports and small series with MELAS patients have been reported (Tarnopolsky et al. 2004). We also reported a case study of a patient with a novel cytochrome *b* mutation who showed a reduction in sub-maximal exercise respiratory exchange ratio during sub-maximal exercise after 2 months of creatine monohydrate supplementation at 10 g/day (Tarnopolsky et al. 2004). A case study reported improvements in behavior, cognition, and brain creatine in a 18 year old with MELAS after 28 months of therapy with a mean intake of 5 g/day (Barisic et al. 2002). The patient had pre-existing renal failure, and the creatinine clearance deteriorated over time, but it was not clear whether that was part of the natural progression of the disorder (Barisic et al. 2002). A retrospective study in four patients with fairly severe mitochondrial cytopathy (MELAS, NARP, and Kearn-Sayre Syndrome) found a 12% improvement in steady state cycle ergometer power output with variable doses of creatine (0.1–0.35 g/kg/day) taken for between 9 months and 3 years (Komura et al. 2003). Similarly, another report in four patients with similar phenotypes (MELAS, KSS and NARP) found greater maximal power (range 8–17%) and endurance time (range = 30–57%) after 3 months of creatine supplementation (0.1–0.2 g/kg/day) (Borchert et al. 1999). Together, the above data suggest that sub-maximal endurance capacity is enhanced by creatine supplementation but not maximal capacity (VO_{2peak}). These data are consistent with the biological logic that would suggest that creatine could enhance mitochondrial respiratory function (energy shuttle) and improve sub-maximal exercise capacity but would not be expected to enhance mitochondrial biogenesis and influence VO_{2peak}.

There have been two prospective randomized trials in patients with mitochondrial DNA deletions and predominantly a chronic progressive external ophthalmoplegia (CPEO) phenotype (Klopstock et al. 2000; Kornblum et al. 2005). The first study evaluated the effects of creatine (20 g/day) on strength and clinical outcomes in 16 patients with CPEO or isolated myopathy with a 4-week, randomized, double-blind, cross-over design (Klopstock et al. 2000). There were no treatment effects on neuromuscular symptom or ataxia scores, functional tasks or peak biceps strength; however, the MRC muscle strength score (P = 0.14) and isokinetic biceps muscle strength

Table 2 Potential benefits of creatine monohydrate supplementation in patients with neuromuscular disorders

Potential benefit	Specific diseases	References
Increased fat-free mass	Muscular dystrophy, some mitochondrial myopathies, end-stage glycogen storage disease	Vandenberghe et al. (1997), Brose et al. (2003), Chrusch et al. (2001), Mihic et al. (2000), Kley et al. (2011)
Increased strength	Muscular dystrophy, some mitochondrial myopathies, end-stage glycogen storage disease	Kley et al. (2011), Tarnopolsky and Martin (1999), Tarnopolsky et al. (1997), Tarnopolsky and MacLennan (2000)
Increased high-intensity repetitive activity	Muscular dystrophy, glycogen storage disease	Tarnopolsky and MacLennan (2000), Tarnopolsky et al. (1997), Casey et al. (1996)
Satellite cell activation	Muscular dystrophy (especially DMD)	Dangott et al. (2000), Olsen et al. (2006)
Proton buffering	Mitochondrial myopathies	Stoichiometry of the reaction
Antioxidant potential	Muscular dystrophy, mitochondrial disease, glycogen storage disease	Lawler et al. (2002), Yang et al. (2009)
Reduced apoptosis	Muscular dystrophy, mitochondrial disease	Zhu et al. (2004), Tarnopolsky (2008), Tarnopolsky et al. (2004)
Lower intracellular calcium	Muscular dystrophy	Pulido et al. (1998), Hespel et al. (2002)

($P = 0.16$) showed trends that led the authors to conclude that further studies were required (Klopstock et al. 2000). Finally, a study in 15 patients with mtDNA deletions (CPEO and KSS) evaluated the clinical effects and MRS findings in response to 6 weeks of creatine supplementation (0.15 g/kg/day) administered in a randomized, double-blind, cross-over fashion (Kornblum et al. 2005). Muscle PCr/ATP did not change at rest nor were recovery kinetics altered (the latter indicative of mitochondrial capacity), and there was no effect upon any other MRS outcome; however, maximal voluntary strength of the plantar flexors after endurance exercise trended higher ($P = 0.14$) in response to creatine (Kornblum et al. 2005). Again, the conclusion of the paper was that further research was required (Kornblum et al. 2005).

Overall, the effects of creatine supplementation in patients with mitochondrial myopathy are unclear. It appears that the type of disease is important for the outcomes that were generally more positive in those with MELAS and related disorders as compared to the less severe and later onset disorders with mtDNA deletions (CPEO). In addition, most studies do not show an effect on peak strength, but when repeated high-intensity contractions are completed, a positive effect was noted (Tarnopolsky et al. 1997). The latter findings are consistent with studies in healthy young volunteers (Tarnopolsky and MacLennan 2000). The study by Kornblum also suggests that uptake of creatine into muscle may also be a factor that limits clinical efficacy (Kornblum et al. 2005). We have used a combination of creatine, alpha-lipoic acid, and coenzyme Q10 in adults with mitochondrial cytopathy in a randomized, double-blind, cross-over study and showed lower lactate and markers of oxidative stress (Rodriguez et al. 2007). Of interest, we have also shown that alpha-lipoic acid enhances creatine uptake into muscle (Burke et al. 2003), and this may well be an important consideration in the treatment plan for such patients. We have suggested that the optimal treatment for many neurometabolic disorders will involve the use of multiple compounds that target the several final common pathways of cell degeneration (Tarnopolsky and Beal 2001). In addition to combination nutraceutical intervention, it is well known that both endurance (Murphy et al. 2008; Taivassalo et al. 2006), and resistance (Murphy et al. 2008), exercise is beneficial to patients with mitochondrial disease, and creatine could be an important adjunctive intervention in those performing exercise therapy.

Glycogen storage disease

McArdle's disease is an autosomal recessive glycogen storage disease due to mutations in the myophosphorylase gene. These patients have significant muscle fatigue and cramps with high-intensity exercise often resulting in a painful muscle contracture and myalgias that may lead to rhabdomyolysis. Anaerobic glycogenolysis is the most important contributor to high-intensity exercise energy needs; however, phosphocreatine provides a high-intensity temporal anaerobic energy buffer, and increased stores may be of clinical relevance in such patients.

Vorgerd et al. (2000) supplemented nine McArdle's patients with creatine monohydrate for a 5-week period with 150 mg/kg/day for 5 days and then 60 mg/kg/day for 4.5 weeks with a 4-week wash-out and the alternative allocation using a randomized, double-blind cross-over design. Muscle force–time integrals ($P = 0.03$) and phosphocreatine depletion ($P = 0.04$) were greater during ischemic exercise, and phosphocreatine depletion was greater during aerobic exercise ($P = 0.006$) on active treatment. No side effects were noted and 5/9 reported fewer muscle symptoms during the creatine allocation (Vorgerd et al. 2000). This same group supplemented 19

McArdle's patients with 150 mg creatine/kg/day for 5 weeks using a nearly identical protocol to that described above and found that muscle pain during exercise was worse on active treatment ($P = 0.02$) with more limitations in daily activity ($P = 0.005$) and a higher body mass index ($P = 0.008$) (Vorgerd et al. 2002). We have shown that patients with McArdle's disease up-regulate phosphofructokinase (PFK) protein and enzyme activity as a compensatory mechanism for the impaired glycogenolytic flux (Robertshaw et al. 2008). Additionally, high levels of intracellular creatine have been shown to inhibit PFK activity (Storey and Hochachka 1974). Patients with McArdle's disease do not show intracellular acidosis in response to high-intensity exercise due to the absence of carboxyl group formation. As a result, proton uptake with phosphocreatine hydrolysis will give rise to a small increase in pHi. This could explain the apparent worsening of some symptoms and lack of effect on others in the higher dose Vorgerd study (Vorgerd et al. 2002). It should be noted that the increase in body mass index in the latter study was perceived as a negative effect (Vorgerd et al. 2002); however, it was likely fat-free mass, and this may well be a benefit and not a negative effect.

In theory, creatine should provide temporal energy buffering in other anaerobic glycolytic and glycogenolytic defects; however, the rarity of these disorders (i.e., PFK deficiency, phosphorylase *b* kinase deficiency, etc.) would preclude the possibility of clinical trials in the future. Nevertheless, the Vorgerd data with the lower dose protocol (Vorgerd et al. 2000) and the established safety data in many trials (also see article by Poortmans) would suggest that a supervised trial of low-dose creatine monohydrate could be considered in such patients.

Fatty acid oxidation defects

The final major category of metabolic myopathy is the fatty acid oxidation defects (FAODs). These disorders present with myalgia and pigmenturia (myoglobin) with prolonged fasting, super-imposed illness, and/or prolonged exercise. The potential role for creatine supplementation in such disorders is not as clear as for the mitochondrial myopathies or the glycogen storage disorders; however, patients with β-oxidation defects often have muscle atrophy and weakness and may also have cardiomyopathy. A patient with long chain β-OH acyl CoA-dehydraogenase (LCHAD) deficiency with muscle atrophy and weakness lost the ability to ambulate at 11 years of age and was started within 1 month of this event on creatine supplementation (0.13 g/kg/day) and showed "striking" improvement in motor function and can still walk, cycle and climb stairs at 16 years of age with ongoing treatment (Korenke et al. 2003).

Inflammatory myopathies

Inflammatory myopathies represent a heterogeneous group of disorders characterized by muscle inflammation. These disorders present with either proximal weakness (dermatomyositis, polymyositis, overlap myositis) or a characteristic pattern of deep finger flexion weakness and severe quadriceps muscle atrophy and weakness (inclusion body myositis). The creatine kinase activity in serum is usually elevated due to the muscle membrane disruption, and this gives a characteristic EMG pattern and inflammation in the muscle biopsy (B cells in dermatomyositis; T cells in the other types). We have shown that total creatine and phosphocreatine are low in patients with inflammatory myopathies (Tarnopolsky and Parise 1999), and studies have shown lower phosphocreatine content with MR spectroscopy in patients with dermatomyositis (Park et al. 1994).

A recent randomized double-blind study evaluated the efficacy of creatine monohydrate therapy in 37 patients with polymyositis or dermatomyositis who are stable on corticosteroids and immuno-suppressive agents over a 6-month period (Chung et al. 2007). The subjects were allocated to creatine ($N = 19$, 20 g/day $\times$ 8 days $>$ 3 g/day for the balance of 6 months) or placebo ($N = 18$) treatment while also completing home exercises (Chung et al. 2007). There were eight patients who withdrew for non-treatment-related issues, and 29 were available for efficacy outcome analysis. Those randomized to creatine therapy showed an improvement in performance time, aggregate functional performance time ($P = 0.029$), functional index ($P < 0.05$ only for completers of study and not intention to treat analysis), and ^{31}P-MRS determined phosphocreatine/β-NTP (Chung et al. 2007). Importantly, there were also no reported clinical side effects, and plasma CK activity and creatinine did not change (Chung et al. 2007). We studied a total of 14 with inflammatory myopathy in our larger open cohort ($N = 81$) and found improvements in strength of $\sim$11% in the entire cohort (Tarnopolsky and Martin 1999), with similar short-term effects in those with inflammatory myopathy (data not published separately).

Inclusion body myositis does not respond to any immune modulating treatment, but one study shows significant benefits from resistance exercise training (Arnardottir et al. 2003). The consistent beneficial effects of creatine and resistance exercise training upon muscle mass and strength (Brose et al. 2003; Chrusch et al. 2001) suggest that this may well be a very effective therapeutic intervention for inclusion body myositis and deserves formal assessment. The mainstay of therapy for all but inclusion body myositis is corticosteroids often with disease modifying agents. Exercise is also safe and effective in other types of myositis (Alexanderson 2005;

Alexanderson et al. 2007), and the interactive role of creatine under such conditions warrants further investigation.

Conclusions

The theoretical basis for creatine supplementation in myopathies is strong and multi-faceted. The research to data strongly indicates that several months of creatine monohydrate supplementation at ~0.075–0.1 g/kg/day improves strength (~9%) and fat-free mass (~0.63 kg) in patients with muscular dystrophy. It is likely that the magnitude of the beneficial response will differ between different sub-groups, and data to date suggests that patients with myotonic dystrophy do not show a consistent or robust effect, and this could be due to uptake issues possibly related to creatine transport issues and require high doses. Creatine monohydrate supplementation has strongest theoretical potential in glycogen storage diseases; however, the evidence shows modest benefits only at lower doses and possibly negative effects (cramping) at higher doses. The reason for the limited effects seen in the GSDs could be due to inhibition of PFK and/or the lack of protons not allowing the phosphocreatine reaction to proceed in the forward direction. The data in patients with FAODs are preliminary to render any conclusions. Patients with MELAS syndrome show more evidence of benefit from creatine supplementation as compared with CPEO. The latter observation is likely due to the fact that the clinical presentation for patients with CPEO is predominantly one of the eye movement restrictions with less severe impact upon muscle strength and endurance as compared to MELAS syndrome. The evidence for side effects or negative impact upon serological metrics from creatine supplementation is almost non-existent and pale in comparison to the very substantial and well-known side effects from our current chemotherapeutic interventions for myopathies (i.e., corticosteroids).

In the future, it will be important to determine the potential long-term benefits from creatine monohydrate supplementation in myopathies. Some important long-term outcomes that could well be influenced positively by creatine supplementation include delaying the time to wheelchair use in DMD, prevention/attenuation of corticosteroid side effects, reduction in the frequency of seizures or stroke-like episodes in MELAS patients, maintenance of functional independence in progressive myopathies, and improvement in bone mass and prevention of osteopenia/osteoporosis. Probably, the most effective therapeutic intervention in most of the myopathies would be a combination of exercise and creatine monohydrate (Brose et al. 2003; Chrusch et al. 2001; Murphy et al. 2008; Taivassalo et al. 2006).

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