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Creatine for treating muscle disorders (Review)

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[Intervention Review]

Creatine for treating muscle disorders

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ABSTRACT

Background

Progressive muscle weakness is a main symptom of most hereditary and acquired muscle diseases. Creatine improves muscle performance in healthy individuals. This is an update of our 2007 Cochrane review that evaluated creatine treatment in muscle disorders. Previous updates were in 2009 and 2011.

Objectives

To evaluate the efficacy of creatine compared to placebo for the treatment of muscle weakness in muscle diseases.

Search methods

On 11 September 2012, we searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL (2012, Issue 9 in *The Cochrane Library*), MEDLINE (January 1966 to September 2012) and EMBASE (January 1980 to September 2012) for randomised controlled trials (RCTs) of creatine used to treat muscle diseases.

Selection criteria

RCTs or quasi-RCTs of creatine treatment compared to placebo in hereditary muscle diseases or idiopathic inflammatory myopathies.

Data collection and analysis

Two authors independently applied the selection criteria, assessed trial quality and extracted data. We obtained missing data from investigators.

Main results

A total of 14 trials, including 364 randomised participants, met the selection criteria. The risk of bias was low in most studies. Only one trial had a high risk of selection, performance and detection bias. No new studies were identified at this update.

Meta-analysis of six trials in muscular dystrophies including 192 participants revealed a significant increase in muscle strength in the creatine group compared to placebo, with a mean difference of 8.47%; (95% confidence intervals (CI) 3.55 to 13.38). Pooled data of four trials including 115 participants showed that a significantly higher number of participants felt better during creatine treatment compared to placebo with a risk ratio of 4.51 (95% CI 2.33 to 8.74). One trial in 37 participants with idiopathic inflammatory myopathies also showed a significant improvement in functional performance. No trial reported any clinically relevant adverse event.

In metabolic myopathies, meta-analyses of three cross-over trials including 33 participants revealed no significant difference in muscle strength. One trial reported a significant deterioration of activities of daily living (mean difference 0.54 on a 1 to 10 scale; 95% CI 0.14 to 0.93) and an increase in muscle pain during high-dose creatine treatment in McArdle disease.

Authors' conclusions

High quality evidence from RCTs shows that short- and medium-term creatine treatment increases muscle strength in muscular dystrophies. There is also evidence that creatine improves functional performance in muscular dystrophy and idiopathic inflammatory myopathy. Creatine is well tolerated in these people. High quality but limited evidence from RCTs does not show significant improvement in muscle strength in metabolic myopathies. High-dose creatine treatment impaired activities of daily living and increased muscle pain in McArdle disease.

PLAIN LANGUAGE SUMMARY

Creatine for treating muscle disorders

Hereditary muscle diseases usually lead to a progressive muscle weakness. Treatment is mainly symptomatic because curative therapies are lacking. Creatine, a popular nutritional supplement among athletes, improves muscle performance in healthy individuals. This is an update of our review evaluating creatine treatment in muscle disorders that was first published in 2007. At this update we identified no new studies but we had previously found 14 randomised controlled trials with 364 participants which met our defined selection criteria. The methodological quality of these studies was high, with only one exception. Analysis of pooled results showed a significant increase in muscle strength in muscular dystrophies and an improvement in activities of daily living in muscular dystrophies and inflammatory myopathies during creatine treatment compared to placebo. Significant adverse events occurred only in people with glycogen storage disease type V presenting as an increase in muscle pain episodes and impairment in activities of daily living.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Creatine for treating muscular dystrophies

Creatine for treating muscular dystrophies

Patient or population: patients with muscular dystrophies

Settings: outpatient treatment

Intervention: creatine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	creatine				
Maximum voluntary contraction in dystrophinopathies %	The mean maximum voluntary contraction in dystrophinopathies in the control groups was 30.8 N (mean value of combined testing) ¹	The mean maximum voluntary contraction in dystrophinopathies in the intervention groups was 9.2 higher (3.52 to 14.88 higher)		121 (3 studies)	⊕⊕⊕⊕ high	
Maximum voluntary contraction in myotonic dystrophy type 1 %	The mean maximum voluntary contraction in myotonic dystrophy type 1 in the control groups was 104.4 Nm (knee extension) ²	The mean maximum voluntary contraction in myotonic dystrophy type 1 in the intervention groups was 4.39 higher (8.61 lower to 17.39 higher)		76 (2 studies)	⊕⊕⊕⊖ moderate ³	
Maximum voluntary contraction in myotonic dystrophy type 2 %	The mean maximum voluntary contraction in myotonic dystrophy type 2 in the control groups was 52.4 kPa (grip strength) ⁴	The mean maximum voluntary contraction in myotonic dystrophy type 2 in the intervention groups was 8.8 higher (6.12 lower to 23.72 higher)		10 (1 study)	⊕⊕⊕⊕ high	
Adverse events	See comment	See comment		261 (8 studies)	⊕⊕⊕⊕ high	Differences in side effect profiles of

creatine and placebo treatment were not detected. No trial reported any clinically relevant adverse event.

Global assessment of improvement felt better	98 per 1000	442 per 1000 (228 to 857)	RR 4.51 (2.33 to 8.74)	183 (4 studies)	⊕⊕⊕⊕ high ⁵

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Mean value of combined quantitative muscle testing (QMT) of elbow flexors and extensors, knee flexors and extensors, and grip at the end of placebo treatment ([Escobar 2005](#)).

² Measurement at the end of placebo treatment ([Tarnopolsky 2004b](#)).

³ Quality of evidence was decreased due to inconsistency: one trial reported an increase in MVC (MD 8.4%, 95% CI -7.7 to 24.5; [Walter 2002](#)) and one trial showed a decrease in MVC (MD -3.1%, 95% CI -25 to 19.0; [Tarnopolsky 2004b](#)).

⁴ Measurement at the end of placebo treatment ([Schneider-Gold 2003](#)).

⁵ One single blinded study was included ([Banerjee 2010](#)) but result would also be significant and similar if this study would not be considered (RR 4.71, 95% CI 2.22 to 10.00).

Summary of findings 2. Creatine for treating metabolic myopathies

Creatine for treating metabolic myopathies

Patient or population: patients with metabolic myopathies

Settings: outpatient treatment

Intervention: creatine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
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	Assumed risk	Corresponding risk		
	placebo	creatine		
Maximum voluntary contraction in mitochondrial diseases %	The mean maximum voluntary contraction in mitochondrial diseases in the control groups was 693.43 N (foot plantar flexion) ¹	The mean maximum voluntary contraction in mitochondrial diseases in the intervention groups was 3.65 lower (11.17 lower to 3.86 higher)	38 (2 studies)	⊕⊕⊕⊕ high
Maximum voluntary contraction in glycogen storage disease type V %	The mean maximum voluntary contraction in glycogen storage disease type v in the control groups was 942.71 N (foot plantar flexion)	The mean maximum voluntary contraction in glycogen storage disease type V in the intervention groups was 1.69 lower (6.48 lower to 3.09 higher)	28 (1 study)	⊕⊕⊕⊕ high
Impairment of activities of daily living (ADL) in glycogen storage disease type V Visual numeric scale. Scale from: 1 to 10.	The mean impairment of activities of daily living (ADL) in glycogen storage disease type v in the control groups was 2.8 ^{2,3}	The mean impairment of activities of daily living (ADL) in glycogen storage disease type V in the intervention groups was 0.54 higher (0.14 to 0.93 higher) ³	19 (1 study)	⊕⊕⊕⊕ high
Adverse events in mitochondrial diseases	See comment	See comment	38 (3 studies)	Two patients reported muscle cramps during cre-

				atine treatment.
Adverse events in glycogen storage disease type V	See comment	See comment	28 (2 studies)	Significant increase in muscle pain episodes in one trial.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Data obtained from the study by Kornblum et al. ([Kornblum 2005](#)).

² Additional data from the study by Vorgerd et al. ([Vorgerd 2002](#)).

³ Higher values indicate more impairment.

Summary of findings 3. Creatine for treating idiopathic inflammatory myopathies

Creatine for treating idiopathic inflammatory myopathies

Patient or population: patients with idiopathic inflammatory myopathies

Settings: outpatient treatment

Intervention: creatine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	creatine				
Aggregate functional performance time (AFPT), intention-to-treat analysis %	The mean aggregate functional performance time (AFPT), intention-to-treat analysis in the control groups was 28 s	The mean aggregate functional performance time (AFPT), intention-to-treat analysis in the intervention groups was 8.4 lower		37 (1 study)	⊕⊕⊕⊕ high	

	(15.4 to 1.49 lower)				
AFPT, valid compliant completer analysis %	The mean AFPT, valid compliant completer analysis in the control groups was 28 s	The mean AFPT, valid compliant completer analysis in the intervention groups was 11.6 lower (19.59 to 3.6 lower)	29 (1 study)	⊕⊕⊕⊕ high	
Adverse events	See comment	See comment	37 (1 study)	See comment	No clinically relevant adverse events were associated with creatine treatment.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

BACKGROUND

Myopathies affect primarily skeletal muscle and can cause a wide variety of complaints including progressive muscle weakness and wasting, myalgias, early fatigue and painful muscle cramps. The main hereditary myopathies are classified into muscular dystrophies (for example, X-linked dystrophinopathies (Duchenne and Becker muscular dystrophy), facioscapulohumeral muscular dystrophy (FSHD), limb girdle muscular dystrophies (LGMD), congenital muscular dystrophies (CMD)), myotonic dystrophies (type 1 myotonic dystrophy or DM1 (Curschmann-Steinert disease) and type 2 myotonic dystrophy (DM2) or proximal myotonic myopathy (PROMM)), ion channel disorders (for example, periodic paralysis, congenital myotonias), metabolic myopathies (lipid and glycogen storage diseases, mitochondrial myopathies), congenital myopathies, distal myopathies and myofibrillar myopathies (MFM). Important progress has been made in the discovery of the molecular causes and pathogenesis of these hereditary myopathies. However, curative therapies such as gene or protein replacement, splice-modulation therapy, stem cell therapy or specific drug treatment are still not available or at the experimental stage with the exception of glycogenosis type II (Pompe disease) in which an enzyme replacement therapy have been available since 2006. Treatment is mainly symptom-oriented and includes regular physical therapy, aerobic exercise training, orthopaedic corrections, artificial ventilation in respiratory insufficiency and pharmacologic interventions, for example corticosteroids in Duchenne muscular dystrophy (DMD). Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of acquired muscular disorders characterised by inflammation of the skeletal muscle not caused by a pathogen. The most common IIM of autoimmune origin are dermatomyositis (DM), polymyositis (PM) and sporadic inclusion body myositis (s-IBM). DM and PM are usually responsive to immunosuppressive therapy but side effects are frequent.

Creatine is a naturally occurring compound that is found in meat and fish in high concentration. It is produced endogenously in the liver and the kidneys (Guthmiller 1994). Creatine is transported freely in the blood and is mainly taken up into muscle, testes and brain (Guimbal 1993; Wyss 2000). Creatine has a role in high energy phosphoryl group transfer during skeletal muscle contraction via the creatine kinase reaction. It also plays a role in transferring energy from the mitochondria to the cytosol in tissues with a high energy requirement such as brain and skeletal muscle (Wyss 1992). Finally, creatine may play a role in the regulation of muscle protein metabolism (Parise 2001). Creatine has been proposed as a potential pharmacological treatment for several neuromuscular diseases.

In healthy humans, creatine monohydrate supplementation has been shown to result in an increase in muscle total creatine and phosphocreatine (PCr) concentration in skeletal muscle (Harris 1992; Hultman 1996) and brain (Dechent 1999). An increase in muscle creatine concentration in skeletal muscle is seen with a dose of about 0.3 g/kg/d for six days or 0.04 g/kg/d for 30 days (Hultman 1996). The magnitude of the increase in skeletal muscle appears greatest in persons with low endogenous stores (Harris 1992). Both prospective and retrospective studies in humans have not found evidence for long- or short-term significant side effects from creatine monohydrate supplementation taken in recommended doses (Mihic 2000; Poortmans 1999; Poortmans 2000; Poortmans 2005). The possibility of idiosyncratic reactions

from creatine monohydrate must be considered but they are rare (Terjung 2000).

People with neuromuscular disorders can have lower skeletal muscle total creatine and PCr concentrations than control subjects (Matthews 1990; Matthews 1991; Park 1994; Park 1995; Tarnopolsky 1999a; Tarnopolsky 2001; Banerjee 2010). This may be a function of lower creatine transporter content or an impairment of energy charge (a measure of the relative amounts of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) in the cell) in these groups (Tarnopolsky 1999a; Tarnopolsky 2001). Therefore, the potential for creatine monohydrate supplementation to enhance performance may be greater in people who have reduced endogenous stores, such as those with neuromuscular disease. The dosing and magnitude of the response from creatine monohydrate supplementation in people with secondary defects in the creatine transporter has not been fully elucidated.

Creatine monohydrate supplementation has been shown to enhance force output in healthy volunteers by approximately 10% (Casey 1996; Tarnopolsky 2000; Terjung 2000). Another reported consequence of creatine monohydrate supplementation is an increase in fat-free mass of about one kilogram (Harris 1992; Hultman 1996; Mihic 2000; Safdar 2008). This seems to be an effect of fluid retention in myocytes due to osmotic potential of high intracellular creatine abundance and an increased expression of genes and proteins related to muscle hypertrophy (Deldicque 2008; Safdar 2008). In animal models of neurodegenerative disease, creatine monohydrate supplementation has been shown to increase brain energy charge, reduce oxidative stress and attenuate neuronal degeneration (Andreassen 2001; Dedeoglu 2003; Ferrante 2000; Hersch 2006; Klivenyi 1999; Klivenyi 2004; Malcon 2000; Matthews 1998; Zhu 2004). Improved calcium handling resulting in lower intra-cellular calcium concentrations and enhanced cell survival have been shown in cultured dystrophin-deficient mdx cells, a mouse model of dystrophinopathy (Pulido 1998). Improvement in muscle function in mdx mice has also been noted following creatine supplementation (Passaquin 2002).

In theory, creatine monohydrate supplementation may benefit people with muscle disorders by non-specifically enhancing muscle force output (temporal energy buffering) or the accretion of fat-free mass, assuming this is muscle, or more directly by enhancing energy shuttling, reducing intra-cellular calcium accumulation and apoptosis (Sullivan 2000), preventing oxidative stress (primary and secondary effect), activating glycolysis and glycogenolysis, and attenuating cell death (Gualano 2010; Klivenyi 1999; Klivenyi 2004; Passaquin 2002; Pulido 1998). Together, these considerations support the initiation of trials in people with myopathies that result in a reduction in energy charge.

The first prospective randomised study reporting the use of creatine monohydrate in a neurometabolic condition was published in 1997 (Tarnopolsky 1997). This study reported an increase in high intensity power output of hand grip and dorsi-flexion, with no increase in endurance performance (Tarnopolsky 1997). Based upon these results, the apparent safety and efficacy in enhancing power output in athletes (Casey 1996; Poortmans 1999; Tarnopolsky 2000; Terjung 2000), and the theoretical benefits to people with muscle disorders (Klivenyi 1999; Park 1995; Passaquin 2002; Pulido 1998; Tarnopolsky 1999a; Tarnopolsky 2001; Wyss 1998), several human trials were initiated. There was significant

interest in the results of an open (N = 81 participants) and single blinded (N = 21) study that found an increase in high intensity power output with creatine monohydrate supplementation in a heterogeneous group of people with neuromuscular disorders (Tarnopolsky 1999b). Because this study was not randomised and the subgroups were not defined a priori this pilot study provided a catalyst for future studies.

This is an update of our systematic Cochrane review (Kley 2007) evaluating benefits of creatine treatment in muscle disorders. It was previously updated in 2008 and 2011 (Kley 2011).

OBJECTIVES

To evaluate the efficacy of oral creatine supplementation in muscle diseases.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for all randomised controlled trials (RCTs) or quasi-randomised controlled trials of creatine treatment in hereditary muscle diseases and idiopathic inflammatory myopathies.

Types of participants

We included participants of all ages with a proven diagnosis of hereditary muscle disorder (including muscular dystrophies and metabolic myopathies) or idiopathic inflammatory myopathy. Criteria for diagnosis depended on the type of muscle disease. They included clinical features, electromyographic characteristics, muscle biopsy findings and genetic results. People with motor neuron disease or (spino-)cerebellar degeneration (for example, Friedreich's ataxia) were excluded.

Types of interventions

We considered any treatment with oral creatine supplementation of at least 0.04 g/kg body weight/day. If the loading dose was at least 0.3 g/kg/d for two days, a maintenance dose of at least 0.03 g/kg/d was accepted. Cross-over trials with washout periods shorter than 28 days required statistical examination of carryover effects to be included. These inclusion criteria took into account the knowledge about the clinical pharmacology of creatine (Harris 1992; Hultman 1996; Persky 2003; Rawson 2004).

Types of outcome measures

The duration of supplementation lasted between three weeks and six months. Due to studies in healthy persons, we assumed that the maximum intramuscular concentration of creatine was reached in all trials. We did not categorise the trials into short-term and long-term supplementation because of lack of evidence on differences in efficacy and accepted all time points of measurements.

Primary outcomes

1. Changes in muscle strength measured by quantitative muscle testing.

Secondary outcomes

1. Changes in activities of daily living (ADL) assessed by questionnaires or functional tests.

2. Changes in muscle strength measured by manual muscle testing.
3. Changes in muscle energy parameters assessed by ³¹P phosphorous resonance spectroscopy.
4. Percentage changes in muscle mass or a surrogate for muscle mass.
5. Adverse events during supplementation.

Search methods for identification of studies

Electronic searches

On 11 September 2012, we searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL (2012, Issue 9 in *The Cochrane Library*), MEDLINE (January 2010 to September 2012) and EMBASE (January 1980 to September 2012) for RCTs on the use of creatine for treating muscle diseases. We reviewed the bibliographies of the RCTs identified and contacted the authors and known experts in the field to identify additional published or unpublished data.

The detailed search strategies are in the appendices: CENTRAL [Appendix 1](#), MEDLINE [Appendix 2](#) and EMBASE [Appendix 3](#).

We also performed searches of trials registries (ClinicalTrials.gov, <http://clinicaltrials.gov>) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP, <http://apps.who.int/trialsearch/>) for ongoing trials (search date 20 February 2013, search term "creatine").

Data collection and analysis

Selection of studies

Two review authors screened the titles and abstracts of the articles identified by the database searches. We obtained the full text of all potentially relevant studies for independent assessment by two authors. The review authors resolved any differences regarding which studies to include by consensus reached after discussion.

Data extraction and management

Two review authors independently extracted the data from the original reports using a data extraction form. If possible, we obtained missing data from the trial authors.

Assessment of risk of bias in included studies

For each trial fulfilling the inclusion requirements, two review authors independently assessed risk of bias (Higgins 2011). The review authors contacted authors of studies when the need for additional information arose. They resolved differences in assessment by consensus.

Data synthesis

We performed fixed-effect meta-analyses using the generic inverse variance (GIV) and inverse variance weighting facilities in Review Manager (RevMan, current version 5.2 (RevMan 2012)), the Cochrane statistical package. Results were expressed as mean differences (MD) and 95% confidence intervals (CI). We analysed primary and secondary outcomes under consideration whenever the data allowed. Due to its long ordinal scale, we analysed Medical Research Council (MRC) sum scores as continuous data. We used P values described as < 0.05 as 0.05 in calculation of standard errors.

This is a conservative approach because derived standard errors are generally larger than those used by the authors in the analysis.

We did not scale the treatment effects and standard errors to a specified follow-up period because we have supposed a nearly constant treatment effect shortly after the beginning of creatine supplementation instead of a constant rate of change over time. This assumption relies on many studies in healthy people. For example, the maximum increase in muscle force seems to correlate with the achievement of the upper limit of intramuscular creatine concentration, which can be reached after a few days of creatine ingestion depending on its dosage (Persky 2003). However, most of these studies are short-term trials. Studies on the effects of prolonged creatine supplementation are rare and the results inconsistent.

For the primary outcome measure 'muscle strength measured by quantitative muscle testing', we calculated changes after treatment phases as percentage of baseline values to make measurements of different muscle groups comparable. In the case of cross-over trials, differences between creatine and placebo phases were converted into percentage of baseline values of the placebo phase. In the absence of baseline data we used the available values of the placebo phase. One trial reported only differences between treatment periods (Walter 2002). In this case, we decided to use the baseline data of Tarnopolsky 2004b for participants affected by the same muscle disease, since the mean age of the participants and the muscle groups examined were similar. In the case of measurements of more than one muscle group, we accepted sum scores (Escobar 2005) or chose a muscle group measured in other trials of the same muscle disorder. In case of bilateral measurements, we chose the right side (Schneider-Gold 2003).

For the secondary outcome measure 'Changes in activities of daily living (ADL) assessed by questionnaires or functional tests', participants' global assessment of improvement was converted into dichotomous data (improvement yes/no). We calculated mean differences (MD) and confidence intervals (CIs) of aggregate functional performance time (AFPT, trial of Chung 2007) using t-tests.

For the secondary outcome measure 'muscle strength measured by manual muscle testing', we calculated percentage changes of MRC sum scores. We replaced missing change-from-baseline standard deviations in the trial from Tarnopolsky 2004b by standard deviations from Walter 2002 (see above for explanation). On the same grounds, we used correlation coefficients derived from data of the trial from Escobar 2005 for imputing change-from-baseline standard deviations for the trial from Tarnopolsky 2004a.

Where meta-analysis was possible for a disease intervention, we constructed a 'Summary of findings' table for each appropriate group of diseases. The pre-defined outcomes were our primary outcome, change in muscle strength measured by quantitative muscle testing, the changes in activities of daily living (ADL) assessed by questionnaires or functional tests, the patient global assessment, and adverse events.

Subgroup analysis and investigation of heterogeneity

Due to detected heterogeneity across the trials, we separated data of dystrophic and metabolic myopathies. We classified inflammatory myopathies in a third group. This decision took into

account pathophysiological and genetic differences between these groups of myopathies. We also performed a subgroup analysis regarding the type of treated myopathy.

RESULTS

Description of studies

See Tables: [Characteristics of included studies](#)

In the searches for this update there were 900 references from MEDLINE, 794 from EMBASE, 177 from CENTRAL and 86 from the Cochrane Neuromuscular Disease Group Register. We identified no new trials for inclusion from these most recent searches. Our searches of trials registries revealed records for 204 trials in ClinicalTrials.gov and for 71 trials in ICTRP. We detected one ongoing creatine trial in juvenile dermatomyositis (see [Characteristics of ongoing studies](#)) that may be included in a future update of this review.

Our previous and recent searches revealed a total of 28 papers that were selected for closer scrutiny. We identified 15 RCTs that met the inclusion criteria for this review. One trial (Sejersen 2000) was only published in abstract form and we could not obtain full details; we therefore excluded it (see [Characteristics of excluded studies](#)). The remaining 14 trials fulfilling the selection criteria included a total number of 364 randomised participants. One three-arm trial compared creatine and glutamine treatment with placebo (Escobar 2005). The other 13 trials compared creatine treatment with placebo. A total of 277 participants received creatine and 275 participants received placebo due to the fact that 10 of the 14 trials used a cross-over design. The duration of supplementation periods lasted between three weeks (Tarnopolsky 1997) and six months (Escobar 2005; Chung 2007). The doses of creatine varied from 3 to 20 g daily.

Four trials examined the effect of creatine in people with dystrophinopathies (Banerjee 2010; Escobar 2005; Louis 2003; Tarnopolsky 2004a). One RCT compared creatine with placebo in various types of muscular dystrophies (Walter 2000). Three trials studied the efficacy of creatine in myotonic dystrophies, two in people with type 1 myotonic dystrophy (Tarnopolsky 2004b; Walter 2002) and one in persons with type 2 myotonic dystrophy (Schneider-Gold 2003). Three trials compared creatine with placebo in people with mitochondrial cytopathy (Klopstock 2000; Kornblum 2005; Tarnopolsky 1997) and two trials evaluated the effect of creatine in glycogen storage disease type V (McArdle disease) (Vorgerd 2000; Vorgerd 2002). One trial tested the hypothesis that creatine with exercise is more effective than exercise with placebo in people with polymyositis or dermatomyositis (Chung 2007).

We excluded 14 studies that did not fulfill the inclusion criteria (see [Characteristics of excluded studies](#)). Twelve of these studies were case reports or non-controlled trials. One controlled study was not randomised and one trial used a combination therapy (creatine, coenzyme Q10 and lipoic acid).

Risk of bias in included studies

See [Characteristics of included studies](#) (risk of bias tables) and [Figure 1](#).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Banerjee 2010	?	+	+	+	?	+
Chung 2007	+	+	+	+	?	+
Escolar 2005	+	+	+	+	+	+
Klopstock 2000	+	+	+	+	+	?
Kornblum 2005	+	+	+	+	+	+
Louis 2003	+	+	+	+	+	+
Schneider-Gold 2003	+	+	+	+	+	+
Tarnopolsky 1997	+	+	+	+	+	+
Tarnopolsky 2004a	+	+	+	+	+	+
Tarnopolsky 2004b	+	+	+	+	+	+
Vorgerd 2000	+	+	+	+	+	+
Vorgerd 2002	+	+	+	+	+	+
Walter 2000	+	+	+	+	+	+
Walter 2002	+	+	+	+	+	+

We based our 'Risk of bias' assessments on information described in the text and additional information obtained from study authors. We assessed sequence generation and allocation concealment as adequate in 13 of 14 trials. One study was only single-blinded (Banerjee 2010). In the other trials, participants and observers were blinded. Incomplete outcome data were adequately addressed. In one cross-over trial (Walter 2000), the washout period lasted only three weeks and carry-over effects were detected. Therefore, authors included only data from the group of participants who received placebo in the first and creatine in the second period in the final statistical evaluation. In the other nine cross-over trials, the washout period was sufficient except for two participants in one trial (Klopstock 2000) who had a washout period of 24 and 26 days. We assessed the diagnostic criteria as adequate in all trials. In

the majority of cases, diagnosis of hereditary muscle disease was confirmed by genetic analysis. Significant differences in baseline values between study groups were not detected.

Effects of interventions

See: [Summary of findings for the main comparison](#) Creatine for treating muscular dystrophies; [Summary of findings 2](#) Creatine for treating metabolic myopathies; [Summary of findings 3](#) Creatine for treating idiopathic inflammatory myopathies

Primary outcome measure:

Changes in muscle strength measured by quantitative muscle testing

Muscular dystrophies

This outcome was available for six of eight studies (Escobar 2005; Louis 2003; Schneider-Gold 2003; Tarnopolsky 2004a; Tarnopolsky 2004b; Walter 2002). Overall, 138 participants received creatine and 139 placebo. The follow-up periods ranged from eight weeks to six months (see [Characteristics of included studies](#)). Five trials measured the isometric maximum voluntary contraction (MVC) of various muscle groups (see [Characteristics of included studies](#)).

One trial (Schneider-Gold 2003) used a hand-held dynamometer to calculate a compound strength score of proximal arm and leg muscles as well as a grip balloon dynamometer to evaluate the maximum grip strength.

Analysis of pooled data demonstrated a statistically significant improvement in maximum voluntary contraction after creatine treatment as compared to placebo, with a mean difference (MD) of 8.47% (95% CI 3.55 to 13.38) (see [Analysis 1.1](#); [Figure 2](#)). In studies on dystrophinopathies, the standard errors were smaller in the cross-over trials (Louis 2003; Tarnopolsky 2004a) than in the parallel group trial (Escobar 2005). A change of standard errors dependent on the follow-up period was not found.

Figure 2. Forest plot of comparison: 1 Creatine versus placebo, outcome: 1.1 Maximum voluntary contraction (MVC) in muscular dystrophies.

Metabolic myopathies

Four of five studies performed an isometric MVC measurement (Klopstock 2000; Kornblum 2005; Tarnopolsky 1997; Vorgerd 2002). The length of follow-up ranged from three (Tarnopolsky 1997) to six weeks (Kornblum 2005). The trial by Klopstock et al. (Klopstock 2000) in 16 participants with mitochondrial diseases found no

significant treatment effect on maximum voluntary muscle torques of biceps and quadriceps muscle. The meta-analysis of the other three cross-over trials including 33 participants also showed no significant change in MVC after creatine treatment compared to placebo (Kornblum 2005; Tarnopolsky 1997; Vorgerd 2002) (see [Analysis 1.2](#); [Figure 3](#)).

Figure 3. Forest plot of comparison: 1 Creatine versus placebo, outcome: 1.2 MVC in metabolic myopathies.

Inflammatory myopathies

A quantitative muscle testing was not performed in the study by Chung et al. (Chung 2007).

Secondary outcome measures:

Changes in activities of daily living assessed by questionnaires or functional tests

Muscular dystrophies

Seven trials evaluated this outcome in a variety of ways (Banerjee 2010; Escolar 2005; Schneider-Gold 2003; Tarnopolsky 2004a; Tarnopolsky 2004b; Walter 2000; Walter 2002).

Two trials in participants with Duchenne muscular dystrophy (Escolar 2005; Tarnopolsky 2004a) and one trial in myotonic dystrophy type I (Tarnopolsky 2004b) performed functional tests. In Escolar 2005, there was a significant lesser deterioration of time to climb 4 stairs and of time to run 10 metres after six months of creatine treatment (14 participants) compared to placebo (14 participants) (mean difference of changes between groups: time to climb 4 stairs -3.4 s (95% CI -6.18 to -0.56), time to walk 10 metres -1.0 s (95% CI -1.60 to -0.34)). Moreover, post hoc analysis in boys younger than seven years (26 participants) revealed significant improved scores on time to stand from supine position in the creatine group when compared with placebo group. Differences in the trials by Tarnopolsky et al. (Tarnopolsky 2004a; Tarnopolsky 2004b) were not significant.

In four trials, participants (Schneider-Gold 2003; Walter 2000; Walter 2002) or parents of participants (Banerjee 2010) were asked for global assessment of improvement during treatment periods. One trial in Duchenne muscular dystrophy reported that this statement considered changes in activity levels, falls and time needed for motor tasks (Banerjee 2010). Overall 91 participants received creatine and 92 placebo. Analysis of pooled data revealed that an improvement was reported significantly more frequently after creatine treatment compared to placebo, with a risk ratio (RR) of 4.51 (95% CI 2.33 to 8.74) (see Analysis 1.3; Figure 4). The result was also significant and similar when the single-blinded study with a higher risk of bias (Banerjee 2010) was not included (RR 4.71; 95% CI 2.22 to 10.00, 156 participants). Three trials (Schneider-Gold 2003; Walter 2000; Walter 2002) used the Neuromuscular Symptom Score (NSS) (Soueidan 1993) to assess the subjective impairment of participants in 14 activities of daily living (ADL) but analysis of pooled data did not show a significant change in NSS after creatine supplementation compared to placebo (see Analysis 1.4; Figure 5). Two trials used visual analogue scales (VAS) for assessment of daily activities (Schneider-Gold 2003; Tarnopolsky 2004b). In 20 people with type 2 myotonic dystrophy (Schneider-Gold 2003), VAS revealed greater absolute but not percentage improvement in the creatine group compared to placebo (difference of 20.0 points (scale from 0 to 100), P < 0.05). The trial by Tarnopolsky et al. (Tarnopolsky 2004b) in 34 participants with type 1 myotonic dystrophy reported no significant differences between creatine treatment and placebo.

Figure 4. Forest plot of comparison: 1 Creatine versus placebo, outcome: 1.3 Global assessment of improvement in muscular dystrophies.

Figure 5. Forest plot of comparison: 1 Creatine versus placebo, outcome: 1.4 Neuromuscular Symptoms Score (NSS) in muscular dystrophies.

Metabolic myopathies

Three studies in mitochondriopathies (Klopstock 2000; Kornblum 2005; Tarnopolsky 1997) and one trial in glycogenosis type V (Vorgerd 2002) reported changes in ADL.

In mitochondriopathies, two trials used a VAS for patients own assessment of six ADL (Tarnopolsky 1997) and general activity (Klopstock 2000). Tarnopolsky et al. also performed a two-minute walk test (Tarnopolsky 1997). In Klopstock 2000, measurements included the Hammersmith motor ability score (Scott 1982), NSS and function time tests. One trial utilised the modified Boston score (testing of activities as climbing a stair, squat and sitting up, elevation of arms) (Kornblum 2005). There was no significant change after creatine treatment compared to placebo in any of these tests.

In the cross-over trial in glycogenosis type V (Vorgerd 2002), participants daily assessed impairment of ADL on a visual numeric scale (scale of 1 to 10, higher values indicated more impairment). Statistical analysis of data from 17 participants revealed a significant deterioration of ADL during creatine treatment compared to placebo (MD of 0.54 on visual numeric scale, 95% CI 0.14 to 0.93). Participants' global assessment of study periods showed a significant difference in assignment favouring placebo period (eleven individuals felt better in placebo period, three in creatine phase and three persons did not perceived a clear-cut difference).

Inflammatory myopathies

Aggregate functional performance time (AFPT) was the primary outcome in Chung 2007. AFPT aggregates four functional assessments measured in seconds: 1. 50-foot walk, 2. get up and go test involving a 50-foot walk, 3. stair ascent test (19 steps), 4. stair descent test (19 steps). Intention-to-treat (ITT) analysis (37 participants) and valid compliant completer (VCC) analysis (29 participants) revealed a significant improvement of AFPT at six months of creatine supplementation compared to placebo, with a MD of -8.4% (95% CI -15.40 to -1.49; ITT analysis) and -11.6% (95% CI -19.59 to -3.60; VCC analysis). Differences at three months were not significant.

In the same trial, a functional index in myositis (Josefson 1996) was used to evaluate endurance of activities. The differences in changes between creatine and placebo group were not significant (Chung 2007).

Changes in muscle strength measured by manual muscle testing

Muscular dystrophies

Six trials reported Medical Research Council (MRC) sum scores (Escolar 2005; Schneider-Gold 2003; Tarnopolsky 2004a; Tarnopolsky 2004b; Walter 2000; Walter 2002). Overall 138 participants received creatine and 137 placebo. Analysis of pooled data showed a significant increase in MRC sum score after creatine treatment compared to placebo. The MD was 1.10% (95% CI 0.37 to 1.82) (see Analysis 1.5; Figure 6). One trial in Duchenne muscular dystrophy also performed manual muscle testing of 34 muscle

groups using a 1 to 10 scale (Banerjee 2010). The adjusted mean MMT score in the creatine group including 13 participants (6.2, 95%

CI 5.9 to 6.5) was significantly higher compared to the placebo group including 14 participants (5.8, 95% CI 5.5 to 6.1).

Figure 6. Forest plot of comparison: 1 Creatine versus placebo, outcome: 1.5 Percentage change in MRC sum score in muscular dystrophies.

Metabolic myopathies

Only one study (Klopstock 2000), with 16 participants, reported MRC sum scores. The improvement following creatine treatment was not significant.

Inflammatory myopathies

Only selected muscle groups were assessed by manual muscle testing (Chung 2007). MRC sum scores were not reported. Shoulder abduction and hip flexion improved significantly after three and six months of creatine treatment in 19 participants compared to placebo (18 participants). Significant improvement of elbow flexion and knee extension compared to placebo was only detected after three months of creatine supplementation.

Muscle energy parameters assessed by 31 phosphorous resonance spectroscopy

Muscular dystrophies

Three trials measured the ratio of PCr to beta-ATP. Louis 2003 examined six participants with dystrophinopathies. After creatine supplementation, the investigators observed an increase of PCr/beta-ATP ratio of about 8% whereas the ratio remained almost unchanged in the placebo group. The difference was described as

not significant in the text but a P value of 0.04 was presented in a table (level of statistical significance was set at $P < 0.05$). In a second trial in Duchenne muscular dystrophy (Banerjee 2010), differences between creatine and placebo group were not significant. In a cross-over trial in 34 participants with type 1 myotonic dystrophy, the PCr/beta-ATP ratios were not significantly different in the creatine and placebo periods (Tarnopolsky 2004b).

In the study by Banerjee et al. (Banerjee 2010), analysis of covariance (ANCOVA) taking into account the age and stature showed that the adjusted mean ratio of PCr to Pi in the creatine group (4.7, 95% CI 3.9 to 5.6, 13 participants) was significantly higher compared to the placebo group (3.3, 95% CI 2.5 to 4.2, 14 participants).

Metabolic myopathies

This outcome was published in two studies in participants with glycogen storage disease type V including seven (Vorgerd 2000) and 14 (Vorgerd 2002) participants as well as in one trial in 13 participants with mitochondriopathies (Kornblum 2005). The treatment periods lasted five (Vorgerd 2000; Vorgerd 2002) and six weeks (Kornblum 2005). Analysis of pooled data showed no significant increase in PCr/beta-ATP ratio after creatine treatment as compared to placebo (see Analysis 1.6).

All three studies used the same standardised calf muscle ergometric test to assess the effects of treatment on skeletal muscle bioenergetics. In the first study by Vorgerd et al. (Vorgerd 2000), the PCr depletion increased during aerobic and ischaemic exercise. Moreover they reported an increase in accumulation of inorganic phosphate during ischaemic exercise. However, the force-time integral during ischaemic exercise was significantly higher with creatine. In the other two trials (Kornblum 2005; Vorgerd 2002), there were neither significant changes in PCr consumption nor in increases in Pi and ADP values during aerobic and ischaemic exercise. Meta-analysis demonstrated a reduction of ATP consumption during aerobic exercise in the creatine phase as compared to placebo with a MD of -1.75 %PCr_i (95% CI -2.98 to -0.51) (see Analysis 1.7). This indicates a higher resynthesis of ATP by phosphoryl group transfer from PCr to ADP via creatine kinase reaction. This might be interpreted as a favourable increase in exercise tolerance. Changes in ATP consumption during ischaemic exercise did not reach statistical significance (see Analysis 1.8). Moreover meta-analysis revealed no significant improvement in time constants (tau) for oxidative PCr recovery from aerobic (see Analysis 1.9) and ischaemic (see Analysis 1.10) exercise.

Inflammatory myopathies

The PCr/beta-nucleoside triphosphate (NTP) ratio was evaluated in a subset of 24 participants (Chung 2007). Fourteen participants received creatine and ten placebo. A significant increase in mean PCr/beta-NTP was only detected in the creatine group (5.4% at three months, 3.4% at six months).

Percentage changes in muscle mass or a surrogate for muscle mass

Muscular dystrophies

This outcome was available for three cross-over studies including 98 participants. Walter 2002 assessed the lean body mass (LBM) from reactance and resistance measurements with bioelectrical impedance analysis. In two trials by Tarnopolsky et al. (Tarnopolsky 2004a; Tarnopolsky 2004b), participants underwent a whole-body dual-energy X-ray absorptiometry (DEXA) scan for determination of fat-free mass (FFM). Meta-analysis demonstrated a significant increase in LBM during creatine treatment compared to placebo. The MD was 0.63 kg (95% CI 0.02 to 1.25) (see Analysis 1.11).

Metabolic myopathies

This outcome was not published for any of the trials.

Inflammatory myopathies

This was not an outcome measure in Chung 2007.

Adverse events during supplementation

Muscular dystrophies

In one trial in 34 participants with type 1 myotonic dystrophy, the serum creatinine concentration increased with creatine supplementation (Tarnopolsky 2004b). However, an effect of creatine on serum creatinine clearance was not found in three studies, which included 79 participants (Louis 2003; Tarnopolsky 2004a; Tarnopolsky 2004b). Side effect profiles were similar to placebo treatment without significant differences (Escobar 2005; Tarnopolsky 2004b). No trial reported any clinically relevant adverse events.

Metabolic myopathies

In the first trial (nine participants) on glycogen storage disease type V, one participant reported slight headache and dizziness during the first four days of the creatine phase (Vorgerd 2000). In the second trial, which involved 17 participants, a significant increase in muscle pain episodes occurred (Vorgerd 2002). Studies on mitochondrial myopathy participants reported muscle cramps in two participants (Klopstock 2000) and in another trial, flatulence during creatine intake in three of 15 participants (during placebo treatment in one of 13 participants) (Kornblum 2005). In one cross-over trial (7 participants), participants did not complain of any side effects (Tarnopolsky 1997).

Inflammatory myopathies

No clinically relevant adverse events were associated with creatine treatment (Chung 2007).

DISCUSSION

The data analysis reveals that there is high quality evidence that short- to intermediate-term supplementation with creatine monohydrate in people with muscular dystrophy resulted in a modest, but significant, increase in maximal isometric force of approximately 8.5% using quantitative muscle testing, with a less robust improvement noted using MRC manual muscle testing scores (1.1%) (Summary of findings for the main comparison). These findings were associated with a significant increase in fat free mass of 0.63 kg. Meta-analysis of changes in activities of daily living was complicated by the fact that a variety of tests were used to evaluate this outcome. Pooled data of participants' global assessment of improvement showed that 44% felt better during creatine treatment compared to less than 10% in the placebo groups. Improvement in functional tests and participants' own assessment of activities of daily living also indicate that creatine increases functional performance in muscular dystrophies. Changes in Neuromuscular Symptom Score were not significant but it may be that this score is not very sensitive to detect effects of creatine supplementation.

Most of the clinically relevant effects were seen in dystrophinopathy and type 2 myotonic dystrophy, but not consistently in type 1 myotonic dystrophy. This latter finding suggests that there may be clinical heterogeneity in the response and findings in one type of dystrophy, for example dystrophinopathy, cannot be applied directly to another, for example facioscapulohumeral dystrophy (FSHD). Although no specific trial of creatine in FSHD has been performed, 12 of the 32 muscular dystrophy patients studied by (Walter 2000) had FSHD and another Cochrane review has extracted the FSHD data (Rose 2004). These data seemed to show no benefit for creatine in FSHD but the numbers were small and the data were not analysed in the same way as for this review.

The different lengths of follow-up period among the trials included in this meta-analysis should be kept in mind. Even though a significant heterogeneity was not detected, changes in treatment effects depending on the duration of supplementation could not be excluded. It may be possible that there is a decline in response with longer intake. It would be useful to study the effects of long-term creatine supplementation and it may be interesting to compare continuous long-term ingestion with a cyclic intake.

There is also evidence that creatine improves functional performance in dermatomyositis and polymyositis. In metabolic myopathies (including mitochondrial myopathies) there was high quality evidence, but from only three diverse studies, that creatine has no effect on increasing strength by any measurement ([Summary of findings 2](#)), although ATP consumption during exercise was slightly attenuated. There is also evidence that creatine improved functional performance in idiopathic inflammatory myopathy ([Summary of findings 3](#)). The discrepancy between the fairly consistent effects noted in muscular dystrophy and possible effects in idiopathic inflammatory myopathy compared with metabolic myopathies is not entirely clear. However, it is possible that having fewer participants led to a type II statistical error (failing to detect an effect when in truth there is one).

Overall, the finding of an increased fat free mass and maximal strength are consistent with the balance of data in young healthy individuals ([Casey 1996](#); [Harris 1992](#); [Hultman 1996](#); [Mihic 2000](#); [Tarnopolsky 2000](#)) and older adults ([Brose 2003](#); [Burke 2003](#); [Chilibeck 2004](#); [Chrusch 2001](#)). Quantitative muscle testing seems to be more sensitive to detect moderate changes in strength than manual muscle testing. This conclusion is in accordance with findings in Duchenne muscular dystrophy: In a 6-month trial by Fenichel et al. ([Fenichel 2001](#)), QMT revealed a significant deterioration in strength of about -11% in the placebo group whereas MMT showed a non-significant change of about -2%. Similar changes have been reported in the trial by Escolar et al. ([Escolar 2005](#)). The increase in muscle creatine and phosphocreatine documented using magnetic resonance spectroscopy appears to be somewhat less in people with muscular dystrophy and metabolic myopathies as compared to healthy individuals ([Brose 2003](#); [Casey 1996](#); [Harris 1992](#); [Hultman 1996](#)). However, the participant numbers were quite small and studies using direct measurements from muscle biopsies have not been completed.

Long-term studies (greater than one year) are not currently available to assess the safety of creatine monohydrate supplementation in people with muscle disorders. However, in studies up to six months in duration there did not appear to be any significant side effects except for a significant increase in muscle pain and impairment in ADL in people with glycogenosis type V ([Vorgerd 2002](#)). The reason for this exacerbation of pain remains to be elucidated. Most studies in healthy participants did not report any significant increase in symptoms over placebo ([Greenwood 2003](#); [Kreider 2003](#); [Mihic 2000](#); [Poortmans 1999](#); [Poortmans 2000](#); [Shao 2006](#); [Terjung 2000](#)). An increase in serum creatinine of approximately 10% to 15 % is likely indicative of increased rate of delivery of creatinine to the nephron with no evidence of alterations in creatinine clearance rate ([Brose 2003](#); [Poortmans 1999](#); [Poortmans 2005](#)). These safety results are very similar to those reporting few side effects in trials in people with neurological disorders (amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease and Huntington's disease) ([Chetlin 2004](#); [Groeneveld 2005](#); [Hersch 2006](#); [Shefner 2004](#); [Verbessem 2003](#)).

Given that a reduction in total muscle mass and strength are characteristic hallmarks of muscular dystrophy, even a

slight improvement in these variables seen with creatine supplementation could potentially be of functional significance. For example, corticosteroids are a mainstay of therapy in dystrophinopathy in spite of the known side effects, due to the fact that modest increases in strength appear to translate into longer-term improvements in functional status and outcome ([Manzur 2004](#)). Preliminary evidence suggests that creatine monohydrate supplementation increased strength and fat-free mass in boys with dystrophinopathy who were already taking corticosteroids ([Tarnopolsky 2004a](#)). Whether or not a protective effect of creatine monohydrate with respect to bone mass ([Chilibeck 2005](#); [Roy 2002](#); [Tarnopolsky 2004a](#)), or type II muscle fibre atrophy ([Roy 2002](#)), will be realised in clinical trials in participants with muscular dystrophy taking corticosteroids remains possible, but unproven. To date, the functional implications of the short-term increases in strength and fat free mass following creatine supplementation have not been subjected to longer-term trials. There is a need for longer-term studies of the efficacy and side effects of creatine in muscle diseases.

AUTHORS' CONCLUSIONS

Implications for practice

There is high quality evidence from RCTs that short- and intermediate-term creatine treatment can significantly improve muscle strength in people with muscular dystrophies. There is also evidence that creatine improved functional performance in muscular dystrophy and idiopathic inflammatory myopathy. Creatine was well tolerated in these people. Limited but high quality evidence from RCTs did not show significant improvement in muscle strength in metabolic myopathies. High-dose creatine treatment impaired ADL and increased muscle pain in glycogenosis type V.

Implications for research

There is a need for long-term studies of creatine in muscle diseases. Particular attention should be given to the specific type of myopathy. Diseases such as FSHD or myofibrillar myopathies have not yet been specifically targeted for evaluation. There is also a need for more studies in the metabolic myopathies due to the fact that dose dependent paradoxical effects were seen in McArdle disease and no studies have been conducted in other metabolic disorders such as fatty acid oxidation defects.

There is a need for standardisation of outcome measures, particularly with regard to activities of daily living. Regarding strength measurement, quantitative muscle testing should be chosen in preference to manual muscle testing.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Banerjee 2010

Methods	Randomised, single-blind, placebo-controlled trial
Participants	33 steroid-naive DMD boys (age range, 3 to 12 years)
Interventions	Creatine 5 g per day versus placebo (500 mg vitamin C) for 8 weeks
Outcomes	Manual muscle testing Vignos' functional scale Parents' overall response to intervention (change in the activity levels, falls, time taken for daily motor tasks) P-31 MRS (right calf muscle) Adverse events

Creatine for treating muscle disorders (Review)

Banerjee 2010 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	High risk	One experimenter who was involved in recruitment, randomisation and treatment of participants was aware of the treatment group allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were blinded but one experimenter was not blinded (see above). Creatine and placebo (vitamin C) may be different in taste
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were not balanced in numbers across intervention groups (5 dropouts in creatine group, 1 dropout in placebo group) but reasons were unlikely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	The study appears to be free of other sources of bias

Chung 2007

Methods	Randomised, double-blind, placebo-controlled trial
Participants	37 participants with polymyositis (22 participants) or dermatomyositis (15 participants), mean age 59 years (creatine group) and 50 years (placebo group)
Interventions	Creatine (loading dosage of 20 g/day for 8 days followed by a maintenance dosage of 3 g/day) versus placebo, 6 months duration
Outcomes	Aggregate functional performance time (AFPT) Functional index in myositis Manual muscle testing using the Medical Research Council (MRC) extended scale Serum creatine kinase (CK) levels Health status using the Nottingham Health Profile (NHP) Short Form McGill Pain Questionnaire Hospital Anxiety and Depression Scales Chalder fatigue score

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was organised by hospital pharmacies using random number lists

Chung 2007 (Continued)

Allocation concealment (selection bias)	Low risk	Creatine and placebo were prepared by the hospital pharmacies and were provided in identical containers. Sequences were concealed until the study had ended and the statistical analysis had been completed
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, supervising clinicians, and assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome. Intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	The study appears to be free of other sources of bias

Escolar 2005

Methods	Randomised, double-blind, placebo-controlled, three-arm multicentre trial
Participants	50 steroid-naïve DMD boys aged 4 to 10 years recruited at 10 Cooperative International Neuromuscular Research Group (CINRG) Centres
Interventions	Creatine 5 g daily (15 participants) or glutamine 0.6 mg/kg daily (19 participants) or placebo (16 participants) 6 months duration
Outcomes	Quantitative muscle testing (QMT) of bilateral elbow flexors and extensors, knee flexors and extensors, and grip Combined QMT arm and leg scores Manual muscle testing score of 34 muscle groups Functional test Pulmonary function testing
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An adaptive, biased-coin (urn) randomisation technique was applied
Allocation concealment (selection bias)	Low risk	Central allocation by the Biostatistics Centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Creatine and placebo were given as powders of identical colour, texture and taste in predetermined proportions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups

Escobar 2005 (Continued)

Selective reporting (re-reporting bias)	Low risk	All of the study's pre-specified outcomes described on http://clinicaltrials.gov that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Klopstock 2000

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	16 participants with mitochondrial cytopathies (mean age 46.4 ± SD 17.2 years)
Interventions	Creatine 20 g per day versus placebo (microcrystalline cellulose) 4-week treatment phases Washout period of at least 29 days in all participants except two (24 and 26 days)
Outcomes	Maximum isometric strength of biceps and quadriceps muscle Isokinetic biceps and quadriceps contractions with 15% of MVC until muscular exhaustion Manual muscle testing using MRC scale, Hammersmith motor ability score (HMAS), neuromuscular symptom score (NSS) Function time test, function ranking test, ataxia score Aerobic cycle ergometry with pre- and post-lactate measurements Neuro-orthoptic examination Subjective muscle weakness and general activity using a visual analogue scale
Notes	Two participants had muscle cramps during the creatine period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer random number generator was used
Allocation concealment (selection bias)	Low risk	Hospital pharmacy did the randomisation and distributed the study agents. Opaque, sealed envelopes and sealed drug containers of identical appearance were sequentially numbered and opened sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Creatine and placebo were undistinguishable
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (re-reporting bias)	Low risk	All of the study's pre-specified outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear risk	Washout period may be too short in two participants

Kornblum 2005

Methods	Randomised, double-blind, placebo-controlled cross-over trial
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Creatine for treating muscle disorders (Review)

Kornblum 2005 (Continued)

Participants	15 participants with mitochondrial cytopathies (mean age 49 ± 9 years)
Interventions	Creatine 0.15 g/kg daily versus placebo Each treatment phase lasted 6 weeks 4-week washout period
Outcomes	Isometric maximum voluntary contraction of the calf muscles Tensiometric hand grip test P-31 MRS during calf muscle ergometric test (aerobic and ischaemic exercise at 30% of MVC) Skeletal muscle function assessed by modified Boston score Subjective endurance performance and general physical condition using individual rating scales Creatine and creatinine plasma levels

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer random number generator was used
Allocation concealment (selection bias)	Low risk	Central allocation by hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Capsules used for administration of creatine and placebo were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes that are of interest in the review have been reported
Other bias	Low risk	The study appears to be free of other sources of bias

Louis 2003

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	15 participants with muscular dystrophy (mean age 10.8 ± 2.8 years): <ul style="list-style-type: none"> 12 participants with DMD, 3 participants with BMD
Interventions	Creatine 3 g daily versus placebo (maltodextrin) 3-month treatment phases Washout period of 2 months
Outcomes	Maximal voluntary contraction of isometric elbow flexion Fatigue resistance at 75% MVC, total joint stiffness at 50% MVC Intramuscular PCr/beta-ATP ratio at rest measured by P-31 MRS Bone mineral density determined by dual energy X-ray absorptiometry Body mass

Louis 2003 (Continued)

Plasma creatine level, serum CK activity
Hepatic and renal function assessed by blood and urine studies

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin tossing was used for sequence generation
Allocation concealment (selection bias)	Low risk	Sealed drug containers of identical appearance were sequentially numbered and opened sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All outcomes specified in the study protocol have been reported
Other bias	Low risk	The study appears to be free of other sources of bias

Schneider-Gold 2003

Methods	Randomised, double-blind, placebo-controlled trial
Participants	20 participants with PROMM (mean age 57.7 ± 8.7 years)
Interventions	Creatine 10 g per day (10 participants) versus placebo (10 participants), 3 months duration
Outcomes	Maximum grip strength Compound strength score of proximal arm and leg muscles calculated from hand-held dynamometry MRC, NSS Subjective assessment of activity in daily life using a visual analogue scale
Notes	In the creatine group, myalgia improved in two participants and chest pain resolved in another patient

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer random number generator was used
Allocation concealment (selection bias)	Low risk	Central allocation by hospital pharmacy. Creatine and placebo were filled in coded boxes of identical appearance. Code numbers were broken only at the final data evaluation

Schneider-Gold 2003 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Creatine and placebo were administered in an identical powder form
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Tarnopolsky 1997

Methods	Randomised, double-blind, placebo-controlled cross-over trial	
Participants	7 participants with mitochondrial cytopathies (mean age 42 ± 14 years)	
Interventions	Creatine (10 g daily for 2 weeks followed by 4 g per day for 1 week) versus placebo 5-week washout period	
Outcomes	<p>Evoked and voluntary isometric contraction strength of the dorsiflexors</p> <p>Nonischemic, isometric, dorsiflexion torque (NIDFT, 2 min)</p> <p>Ischaemic isometric handgrip strength (1 min)</p> <p>Basal and postischemic exercise lactate</p> <p>Aerobic cycle ergometry with pre- and post-lactate measurements</p> <p>Activities of daily living assessed by a visual analogue scale</p> <p>Lean body mass measured by DEXA scanning</p>	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pieces of labelled paper were put into envelopes and shuffled
Allocation concealment (selection bias)	Low risk	An independent person who was not a co-author allocated sequentially numbered, opaque, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Creatine and placebo were administered in an identical and indistinguishable powder form
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Tarnopolsky 2004a

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	31 participants with DMD (mean age 10 ± 3 years)
Interventions	Creatine 0.1 g/kg daily versus placebo 4-month treatment phases 6-week washout period
Outcomes	Maximal isometric handgrip strength Manual muscle testing Pulmonary function testing Fat-free mass, body fat, bone mineral content and density measured by DEXA scanning Functional tests and Activity Scale for Kids questionnaire Serum CK activity, gamma glutamyl transferase activity, serum and urine creatinine concentration DNA oxidative damage assessed by urinary 8-hydroxy-2-deoxy-guanosine Bone breakdown measured by N-telopeptide excretion in urine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pieces of labelled paper were put into envelopes and shuffled in blocks
Allocation concealment (selection bias)	Low risk	An independent person who was not a co-author allocated sequentially numbered, opaque, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Creatine and placebo were indistinguishable (flavoured tablets)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Tarnopolsky 2004b

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	42 participants with DM1 (mean age 41 ± 10 years)
Interventions	Creatine 5 g per day versus placebo 4-month treatment phases 6-week washout period
Outcomes	Maximum isometric strength (handgrip, foot dorsiflexion, knee extension) Manual muscle testing

Creatine for treating muscle disorders (Review)

Tarnopolsky 2004b (Continued)

Pulmonary function assessed by spirometry
 PCr/beta-ATP ratio measured by P-31 MRS
 Functional tasks
 Assessment of activities of daily living using a visual analogue scale
 Body mass
 Fat-free mass, body fat, bone mineral content and density measured by DEXA scanning
 Side effects using a questionnaire
 Serum activities of CK, aspartate aminotransferase, gamma glutamyl transferase
 Serum bilirubin concentration, serum and urine creatinine concentration

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pieces of labelled paper were put into envelopes and shuffled in blocks
Allocation concealment (selection bias)	Low risk	An independent person who was not a co-author allocated sequentially numbered, opaque, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Creatine and placebo were indistinguishable (flavoured tablets)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups. Reasons for missing data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Vorgerd 2000

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	9 participants with glycogen storage disease type V (mean age 39.1 ± 17.9 years)
Interventions	Creatine 0.15 g/kg daily for 1 week followed by 0.06 g/kg daily for 4 weeks versus placebo 4-week washout period
Outcomes	Ergometer exercise test Fatigue Severity Scale, muscle cramp scale P-31 MRS and S-EMG during calf muscle ergometric test (aerobic and ischaemic exercise with 30% of MVC) Serum creatine level and CK activity

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Creatine for treating muscle disorders (Review)

Vorgerd 2000 (Continued)

Random sequence generation (selection bias)	Low risk	A computer random number generator was used
Allocation concealment (selection bias)	Low risk	Hospital pharmacy did the randomisation and distributed the study agents. Drug containers of identical appearance were sequentially numbered and opened sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Capsules used for administration of creatine and placebo were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Vorgerd 2002

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	19 participants with glycogen storage disease type V (mean age 33.8 ± 11.8)
Interventions	Creatine 0.15 g/kg daily versus placebo Each treatment phase lasted 5 weeks 4-week washout period
Outcomes	Isometric maximum voluntary contraction of the calf muscles P-31 MRS and S-EMG during calf muscle ergometric test (aerobic and ischaemic exercise with 30% of MVC) Exercise intolerance and adverse effects using a diary Serum creatine level and CK activity Body mass index
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer random number generator was used
Allocation concealment (selection bias)	Low risk	Hospital pharmacy did the randomisation and distributed the study agents. Drug containers of identical appearance were sequentially numbered and opened sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Capsules used for administration of creatine and placebo were identical in appearance
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing outcome data unlikely to be related to true outcome

Creatine for treating muscle disorders (Review)

Vorgerd 2002 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

Walter 2000

Methods	Randomised, double-blind, placebo-controlled cross-over trial	
Participants	36 participants with muscular dystrophies (mean age 26 ± 16 years): <ul style="list-style-type: none"> 12 participants with FSHD (37 ± 19 years) 10 participants with BMD (23 ± 10 years) 8 participants with DMD (10 ± 3 years) 6 participants with sarcoglycan-deficient LGMD (30 ± 12 years) 	
Interventions	Creatine (adults 10 g/day, children 5 g/day) versus placebo, 8-weeks treatment phases, washout period of 3 weeks	
Outcomes	MRC score NSS vital capacity, subjective assessment of improvement	
Notes	Only the placebo-creatine sequence was included in the final evaluation because of carryover effects in the creatine-placebo sequence	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer random number generator was used
Allocation concealment (selection bias)	Low risk	Hospital pharmacy did the randomisation and distributed the study agents. Opaque, sealed envelopes and sealed drug containers of identical appearance were sequentially numbered and opened sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel. Creatine and placebo were administered in identical powder form
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes have been reported in the pre-specified way
Other bias	Low risk	Small carryover effects have been detected but this point was considered in the final evaluation (only data of placebo - creatine sequence was included). The study appears to be free of other sources of bias

Creatine for treating muscle disorders (Review)

Walter 2002

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	34 participants with DM1 (mean age 44 ± 13 years)
Interventions	Creatine (10.6 g daily for 10 days followed by 5.3 g daily for 46 days) versus placebo, 6-week washout period
Outcomes	Maximum isometric strength of biceps and quadriceps muscle MRC, NSS Body weight and lean body mass Spirometry Patients' global assessment of improvement
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer random number generator was used
Allocation concealment (selection bias)	Low risk	Hospital pharmacy did the randomisation and distributed the study agents. Opaque, sealed envelopes and sealed drug containers of identical appearance were sequentially numbered and opened sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias

BMD: Becker muscular dystrophy

CK: creatine kinase

DMD: Duchenne muscular dystrophy

DM1: myotonic dystrophy type 1

DM2 or PROMM: myotonic dystrophy type II or proximal myotonic dystrophy

FSHD: facioscapulohumeral muscular dystrophy

LGMD: limb girdle muscular dystrophy

NSS: neuromuscular symptoms score

QMT: quantitative muscle testing

SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Barisic 2002	Case report (1 participant with MELAS)
Beurey 1967	Case report (1 participant with polymyositis)
Borchert 1999	Non-controlled trial (4 people with mitochondrial encephalomyopathies)
Duperrat 1972	Case report (1 participant with dermatomyositis)
Felber 2000	Case report (1 participant with DMD)
Freddi 1979	Non-controlled trial (9 participants with myotonic dystrophy type 1)
Hagenfeldt 1994	Case report (1 participant with MELAS)
Komura 2003	Non-controlled trial (2 people with mitochondrial encephalomyopathy)
Matsumura 2004	Open, non-controlled trial (22 muscular dystrophy participants)
Rodriguez 2007	Combination therapy (creatine monohydrate, coenzyme Q10, lipoic acid; 16 participants with mitochondrial cytopathies)
Sejersen 2000	Trial on 38 participants with DMD, published in abstract form. Necessary details could not be obtained
Stout 2001	Case study (1 participant with myasthenia gravis)
Tarnopolsky 1999	Study 1 (81 participants with neuromuscular disease): open, non-controlled trial; study 2 (n = 21): single-blinded, non-randomised trial
Tarnopolsky 2004	Case report (1 participant with mitochondriopathy)

DMD: Duchenne muscular dystrophy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

Characteristics of ongoing studies *[ordered by study ID]*

NCT01217320

Trial name or title	Creatine supplementation in pediatric rheumatology
Methods	Randomised, double-blind, placebo-controlled trial
Participants	Estimated enrollment of 40 participants (age 6 to 18 years) with juvenile systemic lupus erythematosus or juvenile dermatomyositis
Interventions	Creatine 5 g per day versus placebo (dextrose 5 g/day) for 12 weeks
Outcomes	Quality of life, muscle function, kidney function parameters
Starting date	January 2011
Contact information	Bruno Gualano, PhD, University of Sao Paulo, Brazil, gualano@usp.br
Notes	

DATA AND ANALYSES

Comparison 1. Creatine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum voluntary contraction (MVC) in muscular dystrophies	6	277	changes in MVC [%] (Fixed, 95% CI)	8.47 [3.55, 13.38]
1.1 dystrophinopathies	3	121	changes in MVC [%] (Fixed, 95% CI)	9.20 [3.52, 14.88]
1.2 myotonic dystrophy type 1	2	136	changes in MVC [%] (Fixed, 95% CI)	4.39 [-8.61, 17.39]
1.3 myotonic dystrophy type 2	1	20	changes in MVC [%] (Fixed, 95% CI)	8.8 [-6.12, 23.72]
2 MVC in metabolic myopathies	3	66	changes in MVC [%] (Fixed, 95% CI)	-2.26 [-6.29, 1.78]
2.1 mitochondrial diseases	2	38	changes in MVC [%] (Fixed, 95% CI)	-3.65 [-11.17, 3.86]
2.2 glycogen storage disease	1	28	changes in MVC [%] (Fixed, 95% CI)	-1.69 [-6.48, 3.09]
3 Global assessment of improvement in muscular dystrophies	4	183	Risk Ratio (M-H, Fixed, 95% CI)	4.51 [2.33, 8.74]
4 Neuromuscular Symptoms Score (NSS) in muscular dystrophies	3	120	Mean Difference (IV, Fixed, 95% CI)	0.83 [-0.43, 2.08]
5 Percentage change in MRC sum score in muscular dystrophies	6	275	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.37, 1.82]
5.1 dystrophinopathies	2	91	Mean Difference (IV, Fixed, 95% CI)	0.93 [-0.39, 2.26]
5.2 myotonic dystrophy type 1	2	132	Mean Difference (IV, Fixed, 95% CI)	0.68 [-0.38, 1.73]
5.3 myotonic dystrophy type 2	1	20	Mean Difference (IV, Fixed, 95% CI)	1.40 [-0.32, 3.12]
5.4 mixed muscular dystrophies	1	32	Mean Difference (IV, Fixed, 95% CI)	5.0 [1.75, 8.25]
6 PCr/beta-ATP ratio in metabolic myopathies	3	68	changes [%] (Fixed, 95% CI)	2.00 [-1.76, 5.76]
7 ATP consumption during aerobic exercise in metabolic myopathies	2	54	ATP consumpt. [%PCr] (Fixed, 95% CI)	-1.75 [-2.98, -0.51]
8 ATP consumption during ischaemic exercise in metabolic myopathies	2	54	ATP consumpt. [%PCr] (Fixed, 95% CI)	-0.77 [-2.13, 0.59]
9 tau after aerobic exercise in metabolic myopathies	2	50	changes in tau [s] (Fixed, 95% CI)	11.30 [-7.97, 30.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 tau after ischaemic exercise in metabolic myopathies	2	54	changes in tau [s] (Fixed, 95% CI)	-2.18 [-21.79, 17.43]
11 Lean body mass (LBM) in muscular dystrophies	3	196	changes in LBM [kg] (Fixed, 95% CI)	0.63 [0.02, 1.25]

Analysis 1.1. Comparison 1 Creatine versus placebo, Outcome 1 Maximum voluntary contraction (MVC) in muscular dystrophies.

Analysis 1.2. Comparison 1 Creatine versus placebo, Outcome 2 MVC in metabolic myopathies.

Analysis 1.3. Comparison 1 Creatine versus placebo, Outcome 3 Global assessment of improvement in muscular dystrophies.

Analysis 1.4. Comparison 1 Creatine versus placebo, Outcome 4 Neuromuscular Symptoms Score (NSS) in muscular dystrophies.

Analysis 1.5. Comparison 1 Creatine versus placebo, Outcome 5 Percentage change in MRC sum score in muscular dystrophies.

Analysis 1.6. Comparison 1 Creatine versus placebo, Outcome 6 PCr/beta-ATP ratio in metabolic myopathies.

**Analysis 1.7. Comparison 1 Creatine versus placebo, Outcome 7
ATP consumption during aerobic exercise in metabolic myopathies.**

**Analysis 1.8. Comparison 1 Creatine versus placebo, Outcome 8 ATP
consumption during ischaemic exercise in metabolic myopathies.**

Analysis 1.9. Comparison 1 Creatine versus placebo, Outcome 9 tau after aerobic exercise in metabolic myopathies.

Analysis 1.10. Comparison 1 Creatine versus placebo, Outcome 10 tau after ischaemic exercise in metabolic myopathies.

Analysis 1.11. Comparison 1 Creatine versus placebo, Outcome 11 Lean body mass (LBM) in muscular dystrophies.

APPENDICES

Appendix 1. CENTRAL search strategy

```
#1creatine
#2MeSH descriptor Neuromuscular Diseases explode all trees
#3MeSH descriptor Muscular Diseases explode all trees
#4MeSH descriptor Myositis explode all trees
#5("neuromuscular disease*" or "neuromuscular disorder*" or "muscular disease*" or "muscular disorder*" or "muscle disease*")
#6"myotoni* dystroph*" or "myotoni* disorder*" or "muscular dystroph*" or myopath* or "myotonia congenita" or "paramyotonia congenita"
#7"periodic paralys*" or "central core disease*" or "mitochondrial cytopath*"
#8"glycogen storage disease" or "glycogen storage disorder" or "fatty oxidation disorder" or polymyositis or dermatomyositis or "inclusion body myositis"
#9(#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10(#1 AND #9)
```

Appendix 2. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to August Week 5 2012>

Search Strategy:

```
1 randomized controlled trial.pt. (336136)
2 controlled clinical trial.pt. (85111)
3 randomized.ab. (239114)
```

4 placebo.ab. (134375)
 5 drug therapy.fs. (1566004)
 6 randomly.ab. (171899)
 7 trial.ab. (247764)
 8 groups.ab. (1125860)
 9 or/1-8 (2913768)
 10 exp animals/ not humans.sh. (3778623)
 11 9 not 10 (2475023)
 12 Creatine/ (7617)
 13 creatine.tw. (28948)
 14 12 or 13 (32644)
 15 exp Neuromuscular Disease/ (233769)
 16 exp Muscular Disease/ or exp Myositis/ (124360)
 17 (neuromuscular disease\$ or neuromuscular disorder\$ or muscular disease\$ or muscular disorder\$ or muscle disease\$.tw. (9569)
 18 (myotoni\$ dystroph\$ or myotoni\$ disorder\$ or muscular dystroph\$ or myopath\$ or myotonia congenita or paramyotonia congenita).tw. (35774)
 19 (periodic paraly\$ or central core disease\$ or mitochondrial cytopath\$.mp. (2384)
 20 (glycogen storage disease\$ or glycogen storage disorder\$ or fatty oxidation disorder\$ or inflammatory myopath\$ or polymyositis or dermatomyositis or inclusion body myositis or endocrine myopath\$.mp. (16300)
 21 or/15-20 (303716)
 22 11 and 14 and 21 (900)

Appendix 3. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2012 Week 36>

Search Strategy:

1 crossover-procedure.sh. (34922)
 2 double-blind procedure.sh. (110736)
 3 single-blind procedure.sh. (16360)
 4 randomized controlled trial.sh. (328650)
 5 (random\$ or crossover\$ or cross over\$ or placebo\$ or (doubl\$ adj blind\$) or allocat\$.tw,ot. (895595)
 6 trial.ti. (134856)
 7 clinical trial/ (871161)
 8 or/1-7 (1494644)
 9 (animal/ or nonhuman/ or animal experiment/) and human/ (1205207)
 10 animal/ or nonanimal/ or animal experiment/ (3308636)
 11 10 not 9 (2740220)
 12 8 not 11 (1406577)
 13 limit 12 to embase (1090148)
 14 CREATINE/ (9796)
 15 14 or creatine.tw. (37379)
 16 exp muscle disease/ (306916)
 17 (neuromuscular disease\$ or neuromuscular disorder\$ or muscular disease\$ or muscular disorder\$ or muscle disease\$.tw. (11977)
 18 (myotoni\$ dystroph\$ or myotoni\$ disorder\$ or muscular dystroph\$ or myopath\$ or myotonia congenita or paramyotonia congenita).mp. (57327)
 19 (periodic paraly\$ or central core disease\$ or mitochondrial cytopath\$.mp. (3372)
 20 (glycogen storage disease\$ or glycogen storage disorder\$ or fatty oxidation disorder\$ or polymyositis or dermatomyositis or inclusion body myositis).mp. (21455)
 21 or/16-20 (322472)
 22 13 and 15 and 21 (797)
 23 remove duplicates from 22 (794)

WHAT'S NEW

Date	Event	Description
20 February 2013	New search has been performed	Searches of trial registries added. Minor revisions to text including description of one ongoing trial.

Date	Event	Description
28 September 2012	New citation required but conclusions have not changed	A review of the updated search results revealed no new relevant trials.

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 1, 2007

Date	Event	Description
22 December 2010	New citation required and conclusions have changed	Searches updated to October 2010. One new trial identified and added. Meta-analysis of global assessment of improvement added. SoF tables added. Changes in ADL moved to the secondary outcome measures. Discussion and conclusions updated.
17 August 2010	New search has been performed	Searches updated to July 2009. One new study identified and included. Added 'Changes in activities of daily living' as second primary outcome measure. Meta-analyses extended. Risk of bias tables added. Discussion and conclusions updated.
3 November 2008	Amended	Converted to RevMan 5
15 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All authors searched for relevant trials. RAK and MV assessed methodological quality, extracted the data and performed meta-analysis. All three authors wrote the text of the review and agreed the final version.

DECLARATIONS OF INTEREST

RAK was involved in one and MV in two double blinded trials with creatine supplementation in McArdle disease. Furthermore, MV was co-author in a trial that examined the effect of creatine in participants with single mitochondrial DNA deletions.

MAT has coordinated a single blinded trial that studied efficacy of creatine in participants with neuromuscular disorders and three double blinded trials that compared creatine with placebo in participants with mitochondrial cytopathies, Duchenne muscular dystrophy and myotonic dystrophy type 1. He was on the scientific advisory board of a sports nutrition company, EAS (2001-2005). Neither trial was industry funded. MAT is the Chief Scientific Officer for Life Science Nutritionals. This company makes gummie omega 3 supplements, vitamin D and multivitamins for children. It does not manufacture any product containing creatine and does not have plans to do so in the foreseeable future.

SOURCES OF SUPPORT

Internal sources

- Neuromuscular Center Ruhrgebiet/Kliniken Bergmannsheil, Ruhr-University Bochum, Germany.
- Hamilton Health Sciences Corporation, Dept. of Rehabilitation, Canada.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added 'Changes in activities of daily living' as second primary outcome measure because of its clinical relevance and deleted 'Electrophysiological parameters of surface-EMG' as secondary outcome measure because of its low relevance. We decided to accept all time points of measurements for meta-analysis because there is no evidence that the effect of short- and medium-term creatine treatment changes in a function of time. We included searches of ClinicalTrials.gov and ICTRP in our search strategy for identification of studies and adapted the assessment of methodological quality and risks of bias to the new Cochrane methodology. The review also includes 'Summary of findings' tables.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements [adverse effects]; Creatine [adverse effects] [*therapeutic use]; Muscle Contraction [drug effects]; Muscle Strength [*drug effects] [physiology]; Muscular Diseases [*drug therapy] [genetics]; Muscular Dystrophies [drug therapy]; Myositis [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans