**Name of journal: *World Journal of Rheumatology***

**ESPS Manuscript NO: 12240**

**Columns: REVIEW**

**Oral creatine supplementation: A potential adjunct therapy for rheumatoid arthritis patients**

Wilkinson TJ *et al.* Oral creatine supplementation

Thomas James Wilkinson, Thomas Daniel O’Brien, Andrew Bruce Lemmey

**Thomas James Wilkinson, Thomas Daniel O’Brien, Andrew Bruce Lemmey,** School of Sport, Health and Exercise Sciences, Bangor University, LL57 2PZ Wales, United Kingdom

**Thomas Daniel O’Brien,** Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, L3 3AF England, United Kingdom

**Author contributions:** Wilkinson TJ gathered literature information and drafted manuscript; O’Brien TD and Lemmey AB advised on search methodology and critically revised the manuscript.

**Correspondence to: Andrew Bruce Lemmey, Professor,** School of Sport, Health and Exercise Sciences, Bangor University, George Building, Normal Site, Holyhead Road, LL57 2PZ Wales, United Kingdom. a.b.lemmey@bangor.ac.uk

**Telephone:** +44-1248-383932

**Received:** June 28, 2014 **Revised:** September 19, 2014

**Accepted:** October 1, 2014

**Published online:**

**Abstract**

Creatine is one of the most popular forms of protein supplements and is known to improve performance in healthy athletic populations *via* enhanced muscle mass and adenosine triphosphate energy regeneration. Clinical use of creatine may similarly benefit patients with rheumatoid arthritis (RA), an inflammatory condition characterised by generalised muscle loss termed “rheumatoid cachexia”. The adverse consequences of rheumatoid cachexia include reduced strength, physical function and, as a consequence, quality of life. Whilst regular high-intensity exercise training has been shown to increase muscle mass and restore function in RA patients, this form of therapy has very low uptake amongst RA patients. Thus, acceptable alternatives are required. The aim of this review is to consider the potential efficacy of creatine as an anabolic and ergonomic therapy for RA patients. To date, only one study has supplemented RA patients with creatine, and the findings from this investigation were inconclusive. However, trials in populations with similar losses of muscle mass and function as RA, including older adults and those with other muscle wasting conditions, indicate that creatine is an efficacious way of improving muscle mass, strength and physical function, and may offer an easy, safe and cheap means of treating rheumatoid cachexia and its consequences..

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Creatine supplementation; Nutritional supplement; Rheumatoid arthritis; Rheumatoid cachexia; Physical function

**Core tip:** Creatine supplementation primarily improves physical function by enhancing the re-synthesis of adenosine triphosphate *via* increased stores of phosphocreatine in the muscle. Through this pathway it provides greater levels of energy during physical activity and improves recovery. Creatine also augments muscle protein synthesis, thereby increasing muscle mass. These dual effects increase strength, reduce fatigue, and thereby improve function. In patients with conditions such as rheumatoid arthritis that are characterised by muscle loss and subsequent reductions in strength and physical function, creatine offers a potential therapeutic intervention for augmenting muscle mass and function that is safe, easy and inexpensive to administer.

Wilkinson TJ, O’Brien TD, Lemmey AB. Oral creatine supplementation: A potential adjunct therapy for rheumatoid arthritis patients. *World J Rheumatol* 2014; In press

**INTRODUCTION**

Patients with rheumatoid arthritis (RA) often experience a substantial loss of muscle mass (cachexia), which results in significant adverse consequences such as decreased strength, impaired physical function, and a reduction in quality of life. Unfortunately, current drug treatments for RA do not attenuate this muscle loss, nor fully restore physical function[1,2], and whilst exercise has been shown to be effective in restoring both muscle mass and function in RA patients (*e.g.*[3],) the lack of uptake and adherence to sufficiently intense training means this form of therapy is unlikely to be widely adopted. Nutritional supplements offer a potential alternate therapeutic intervention that would be more easily adopted. One such nutritional supplement is oral administration of creatine (Cr). Creatine is a popular form of protein supplementation that has been widely demonstrated to improve physical function *via* enhanced energy regeneration and increased muscle mass[4]. Consequently, Cr supplementation potentially offers a low-cost and generally acceptable means for RA patients to restore muscle mass and functional capacity.

This article reviews the evidence regarding the potential of Cr as an adjunct treatment to improve muscle mass and function in RA patients. In the course of doing this, rheumatoid cachexia, its effect on patients, and the rationale for nutritional supplementation (such as Cr) to improve body composition and physical function will be discussed. Then the mechanisms and effectiveness of Cr in athletic populations will be described before we present a review of the existing evidence regarding the efficacy of Cr in RA-relevant clinical trials.

**RHEUMATOID ARTHRITIS, CACHEXIA AND MUSCLE LOSS**

Rheumatoid arthritis is an autoimmune disease predominantly affecting middle-aged and older females and is characterised by persistent synovitis, systemic inflammation, and the presence of specific autoantibodies[5]. This inflammation is associated with damage to the articular cartilage and bone[5], and a range of co-morbidities including cardiovascular disease[6], obesity[7], diabetes[8], osteoporosis[9], fatigue[10] and depression[11].

Additionally, RA is characterised by aberrant changes in body composition. The involuntary loss of muscle, often coupled with elevated adiposity, has been termed “rheumatoid cachexia”[12], and occurs in approximately 67% of patients[3,12–16] including those with controlled disease[12]. Much like sarcopenia (muscle loss due to ageing[17]), rheumatoid cachexia leads to a loss of strength[18] and reduced physical functioning[19,20] impairing performance of activities of daily living such as standing independently from a chair, walking, climbing stairs, and lifting and carrying[21]. Additionally, muscle wasting impairs immune function[22], and is a significant predictor of cardio-vascular disease and overall mortality[23-28].

The aetiology of rheumatoid cachexia is multifactorial and may involve increased production of excess inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukins -1 and -6 (IL-1, IL-6) which are also implicated in the pathophysiology of RA itself[13,24–26]. On a cellular level, several key signalling pathways, such as nuclear factor-kappa B (NF-ĸB; catabolic) and insulin-growth factor-I (IGF-I; anabolic), regulate protein synthesis and degradation in the muscle[27]. Changes to these pathways “tip” the metabolic activity from anabolic to catabolic, thereby inducing muscle wasting[22].

**TREATMENTS OF MUSCLE WASTING**

Interventions that are effective in increasing muscle mass have been shown to improve physical function, reduce disability, and enhance quality of life in RA patients[29]. However, efficacious and safe anabolic interventions which are widely acceptable to rheumatoid patients have yet to be identified.

***Medication and drug treatments***

Rheumatoid cachexia and relatively poor physical function remain prevalent even in RA patients with well-controlled disease activity (*i.e*., approximately 20%-30% below the level seen in age- and sex-matched sedentary healthy controls[1,3]). Therefore, it is apparent that controlling disease activity alone is insufficient to restore body composition and function. Roubenoff *et al*[13] hypothesised that TNF-α was central in causing rheumatoid cachexia, so it might be expected that anti-TNF-α biologics would be the pharmaceutical anti-rheumatic treatment most likely to reverse rheumatoid cachexia. However, even these agents have proved ineffective in this regard[2,30,31]. In fact, in the trials conducted to date, anti-TNF-α therapy have not only failed to increase lean mass in recent-onset[2,30] and established[31] RA patients, but appear to increase fat mass[2] and more disturbingly, trunk fat mass[31] relative to standard disease modifying anti-rheumatic drugs.

Similarly, yet to be published data from an on-going study by our group suggests that even in the current “Treat to Target” era, when disease activity is more tightly and successfully controlled, and clinical “remission” is regularly achieved, RA patients still experience significant loss of muscle (~10%), increased adiposity (approximately 12%), and relatively poor physical function (~20-30% decreased), compared to age- and sex-matched healthy sedentary controls.

***Progressive resistance training***

High-intensity progressive resistance training (PRT) has been shown to substantially increase muscle mass, and as a consequence dramatically improve strength and restore normal levels of physical function in RA patients (*e.g.*[3,16,32]). However, patient uptake of exercise is poor[33], and even patients who experience significant benefits of structured exercise cease training when supervision is withdrawn[34]. Thus, sustained exercise training is unlikely to be widely adopted as a therapy for reversing cachexia and restoring function.

***Nutritional supplementation***

Anabolic nutritional supplementation offers a potential treatment option that is easily administered, inexpensive, and makes limited demands of the patient. It has been reported that up to 75% of RA patients believe that food and nutrition may play an important role in their symptom severity, with up to 50% of RA patients reportedly trying some form of dietary manipulation in an attempt to attenuate symptomology[35]. Scientific evidence continues to suggest that diet should be part of routine care in those with wasting disorders (for review see Stamp[35]).

Our group previously investigated the effects of 12 wk of a mixture of ß-hydroxy-ß-methylbutyrate, glutamine and arginine (HMB/GLN/ARG) protein supplementation in 40 RA patients[15]. The results showed that both HMB/GLN/ARG and a control mixture of other, non-essential, amino acids (alanine, glutamic acid, glycine, and serine) were effective in increasing muscle mass and improving physical function in RA patients. Thus it appears that protein per se is capable of significantly improving lean mass, total body protein and objective measures of physical function which reflect the ability to perform activities of daily living in RA patients.

Creatine, a combination of essential amino acids, has generally been shown to be more effective than other protein-based supplements in increasing lean mass. For example, Cribb *et al*[36] showed that Cr (1.5 g/kg per day for 11 wk) was able to significantly improve lean mass by +5.5%, compared to whey protein (+3.7%; *P* < 0.05) in 33 trained males. Further to this, in a meta-analysis[37] of 48 studies, both lean mass and strength gain were unaffected by whey protein and other supplementation such as androstenedione when compared to a placebo treatment, and only supplementation with either Cr or HMB resulted in a significant gains (Table 1). The superior gains in lean mass and strength from Cr relative to HMB, combined with the additional benefits of Cr to energy production and recovery identifies Cr as a potentially highly effective adjunct treatment for improving rheumatoid cachexia and physical function.

**WHAT IS CREATINE?**

Creatine, or methylguanidine-acetic acid, is a naturally occurring compound made from 3 amino acids; arginine, glycine, and methionine[4], and is synthesized within the body, primarily in the liver, kidney and pancreas[38].

Most (approximately 95%) of the total Cr pool is contained in skeletal muscle, with around 60% [75 mmol· kg dry weight (dw)-1] in the phosphorylated form, phosphocreatine (PCr)[39,40], and the remaining 40% (50 mmol· kg dw-1) existing as free Cr[41]. Muscle does not synthesize Cr itself but is dependent on Cr uptake through specific membrane sodium dependent transporters[42].

**WHAT DOES CREATINE DO?**

***Changes in ATP energy synthesis***

Creatine performs many roles in the body, the most important of which is in generating energy for the muscles. Muscle relaxation and contraction, and therefore the movement of the body, is fuelled by energy liberated from the dephosphorylation of adenosine triphosphate (ATP).

**ATP ↔ adenosine diphosphate (ADP) + phosphate (P) + energy** (catalysed by the enzyme ATPase)

The ATP stores in the body are limited (concentration in skeletal muscle approximately 24 mmol· kg/dw[40]), and without a means of resynthesizing ATP at an equally rapid rate, maximal exercise exhausts these stores within 1–2 s[43]. To overcome this storage limitation, the body is able to maintain a continuous ATP supply through different metabolic resynthesis pathways: either anaerobically in the cytosol, or aerobically in the mitochondrion.

As stated previously, Cr is primarily stored in the body in a phosphorylated form as PCr, with the muscle content of PCr 3-4 times higher than that of ATP[41]. In a process called dephosphorylation, some energy for ATP resynthesis comes directly from the hydrolysis (splitting) of phosphate from PCr[41].

**PCr ↔ Cr + P + Energy** [catalysed by the enzyme creatine kinase (CK)]

In this process, the liberated phosphate group can then combine with ADP in a reaction catalysed by CK to restore ATP levels[44] and maintain high cellular ATP/ADP ratios[45]:

**ADP + P ↔ ATP + Cr** (catalysed by CK)

As a consequence, it would be anticipated that increasing initial Cr stores and thereby delaying PCr depletion would enhance resynthesis of ATP and augment performance[46,47]. Ingestion of Cr supplements (20 g a day for 5 d) has been shown to increase the total Cr and PCr concentration of human skeletal (Table 2), and indeed, reduced blood lactate concentrations have been observed after high-intensity[48] and endurance exercise[49]; although these findings are not universal[50].

***Changes in muscle mass and protein synthesis***

Creatine is an osmotically active substance. Thus, as skeletal muscle cell Cr and PCr concentrations rise, the cell will rapidly draw in extracellular water *via* osmosis in order to maintain equilibrium[51]. The uptake of Cr and water into the muscle accounts for the increases in body mass (approximately 1-2 kg) usually observed after a few days of supplementation (*e.g.*[52]). Total body water has been reported to increase up to 3 litres (+9%)[45];of which intra-cellular water has been shown to increase by between 0.77-3.0 litre (an increase of +3%-9 % from baseline values) (*e.g.*[53–56]) in the absence of changes in extra-cellular water[54].

The intramuscular uptake of Cr and the associated increase in intracellular water increases osmotic pressure, which in turn stimulates protein synthesis. Cellular hydration state is an important factor in controlling cellular protein turnover, *i.e.*, an increase in cellular hydration inhibits proteolysis and stimulates protein synthesis[57], whereas cell shrinkage has opposite effects[51,58–61]. However, it is unclear whether acute Cr supplementation augments muscle protein by this mechanism[62,63].

Creatine has also been shown to stimulate muscle hypertrophy by inducing expression of muscle myogenic factors such as MRF4, MyoD and myogenin[64].

Deldicque *et al*[65,66] showed that the muscle gene expression of IGF-I was raised following Cr supplementation. This finding was corroborated by Burke *et al*[67] who found increased muscle content of IGF-I as a result of Cr supplementation combined with 8 wk of PRT. These findings are highly relevant to Cr’s anabolic potency as IGF-1 produced locally in the muscle (mIGF-1) is thought to regulate adult skeletal muscle maintenance and hypertrophy[68]. Conversely, Cr supplementation in conjunction with PRT has been shown to lower serum levels of myostatin[69], a hormone that is highly expressed in RA synovial tissues and inhibits muscle growth by reducing myoblast (muscle) proliferation[71,72] and thus is associated with muscle atrophy[72] and joint destruction[73]. The anabolic response to Cr supplementation is particularly evident in type II muscle fibres[60,74], which is particularly interesting because RA patients present with preferential atrophy of Type II fibres[75].

***Reduction in inflammatory cytokines***

Patients with RA exhibit high synovial levels and serum concentration of the cytokines TNF-α and IL-1ß[22]. These cytokines, in addition to causing synovial inflammation[76], also modulate the expression of enzymes controlling muscle protein degradation[27]. Bassit *et al*[77] investigated the effects of Cr supplementation (20 g/d for 5 d prior to competition) on plasma levels of the pro-inflammatory cytokines: TNF-α, IL-1ß, and prostaglandin E2 (PGE2) in triathletes after a half-ironman competition. These cytokines are typically raised following prolonged strenuous exercise[78], but Cr supplementation attenuated the increases in TNF-α by 42% and 64%, IL-1ß by 72% and 71%, and PGE2 by 85.5% and 91 %, 24 and 48 h post, respectively.

***Creatine and bone degradation***

RA patients are at 2-fold increased risk of having osteoporosis and approximately 28% of patients develop this condition[9,14]. In wheelchair-independent patients experiencing Duchenne dystrophy, Cr supplementation was able to enhance bone mineral density (+3%) and reduce urinary cross-linked N telopeptides of type I collagen (NTx) excretion, a marker for bone resorption[62]. In addition, Candow *et al*[79] also reported a reduction in NTx (-27%) *vs* placebo (+13%; *P* < 0.005), and similar findings were reported by Chilliback *et al*[80] who showed that in elderly men, Cr was able to improve arm bone mineral density by +3.2% (*P* < 0.001) *vs* placebo (-1%) However, more research is needed in this area to understand the mechanisms behind this action.

***Athletic performance***

Creatine has repeatedly demonstrated efficacy in improving high-intensity short-term exercise performance and subsequent recovery. For example, in cycling, Cr supplementation has been shown to significantly enhance peak power output[48,81,82] and maximal work[39] during repetitive sprints. Similarly, runners who supplemented with Cr decreased their 100-m sprint time and total time for 6 m × 60 m sprint intervals[83], and highly trained football players improved their repeated sprint performance (6 m × 15 m sprints with 30 s recovery) and attenuated fatigue-induced decline in jumping ability following Cr supplementation[84]. Creatine supplementation has also been found to be effective in improving performance of a variety of sustained high-intensity activities (e.g., kayaking for 5 min[85]; 1000 m rowing[86]; and running 300 and 1000 m intervals (3-4 min rest)[87]). These functional benefits are attributed to increased ATP resynthesis, heightened availability of PCr in Type II fibres, and increased total Cr stores[41]. These effects may be particularly beneficial to older adults or clinical populations who experience difficulty performing short-term, high intensity activities such as hurrying for a bus, crossing roads, climbing stairs, or digging in the garden.

Creatine has also been shown to improve strength related measures. In an analysis of 22 studies, athletes supplementing with Cr had an average +8% greater increase in muscle strength than placebo (for a review see Rawson *et al*[88]). Furthermore, Cr supplementation when combined with PRT has been shown to be more effective at increasing strength and weightlifting performance than PRT alone[89,90]. Improvements in strength translate into increased work capacity, and thus improved ability to perform activities of daily living such as walking, carrying shopping, doing housework etc[16,19,21]..

Although approximately 70%[91] of short-term studies on Cr supplementation report some ergogenic benefit, the responses are often variable amongst individuals[88], and supplementation generally does not result in improvements in endurance performance (*e.g.*, repeated 6km treadmill and terrain run performance)[48,58,92,93].

**CRITICAL REVIEW OF RELEVANT CLINICAL LITERATURE**

***Aim***

The aim of this review is to examine existing evidence assessing the efficacy of Cr supplementation in improving muscle mass and physical function, with particular reference to its potential use in treating rheumatoid cachexia and its consequences. To achieve this we searched for, and extracted relevant data from published research papers in RA and other conditions for which findings are likely transferable to the RA population, *e.g.*, ageing population and other musculoskeletal and wasting diseases.

***Search methods***

Peer-reviewed research articles were included in this review provided they: (1) investigated the effects of Cr supplementation in RA patients or other populations deemed relevant to RA (i.e. elderly populations (> 60 years) or musculoskeletal disorders featuring loss of muscle and physical function); (2) included body composition (muscle and/or fat mass) and/or physical function as outcome measures; and (3) conducted an intervention of any design in RA patients; or undertook a blinded placebo-controlled trial for non-RA populations, to ensure only evidence of higher certainty of evidence was included. As the purpose of this review is to investigate alternative treatments to high-intensity exercise for restoring muscle mass and physical function, data on the additive effects of Cr supplementation and PRT were excluded. Publications were also excluded if they were a literature review, thesis, abstract, or a letter or comment, and the search was limited to English language citations.

PubMed and Google Scholar were searched from April to May 2014 using the search term “creatine supplementation” combined with “cachexia”; “clinical”; “patient”; “older adults”; “elderly”; “sarcopenia” and “rheumatoid arthritis”. In addition, the reference sections of the selected papers were hand-searched for relevant ancestral references. The title and abstract of each search result was first screened for relevance according to the inclusion criteria above, before full articles were obtained. Full-text articles were then screened before final inclusion in this review.

***Search results***

The initial search returned 758 articles, excluding duplicates, of which 27 met the inclusion criteria and were selected for this review. One trail investigating Cr supplementation of RA patients was found[94]. This study was not controlled in any way so is considered to provide evidence of low certainty. The body composition and physical function data extracted from trials in older adults are presented in Table 3, and data extracted from trials in other relevant clinical populations appear in Table 4.

***Rheumatoid arthritis***

Willer *et al*[94] was the only study identified that completed a trial of Cr in an RA population. Twelve RA patients were un-blinded to the Cr supplementation and no placebo group or control arm existed. Participants were given oral Cr supplementation for 21 d using recommended doses (day 1-5: 20 g/d; day 6-21: 2 g/d) and the effects on muscle strength, subjectively assessed function during activities of daily living (Health Assessment Questionnaire), and disease activity were examined. It was found that Cr supplementation increased muscle strength in 8 out of the 12 patients by an average of +14% (*P* = 0.02), as determined by the muscle strength index (the mean of 8 strength measurements during flexion and extension of the knee and elbow/max sample strength\*100[95]). This increase in muscle strength was not associated with changes in skeletal muscle Cr or PCr levels. Routine clinical measures of disease activity and subjectively evaluated physical function showed no changes.

The authors attributed the “limited effectiveness of Cr” to “alterations in the kinetics of Cr in patients with RA (*e.g.*, reduced transport into the muscle, increased metabolism and/or excretion)”. However, this interpretation places emphasis on the subjectively assessed function, which was unchanged, rather than the objectively measured strength, which did improve significantly. It is known that the Health Assessment Questionnaire is weakly associated with objective measures of physical condition such as strength (*r* = -0.35) and joint mobility (*r* = 0.27)[96], and is often insensitive to changes in objective function (*e.g.*,[3,96]). Additionally, only 12 patients were used in the study, and with Cr supplementation reported to be ineffective in approximately 30% of individuals[46], it would be anticipated that only 8 of the RA patients in this investigation would see any benefit. Consistent with this prediction, strength increases were noted in 8 patients. Moreover, the study supplementation period only lasted 3 wk, much less than the 8-12 wk recommended by manufacturers and used by other studies. Thus, whilst the findings of Willer *et al*[94]’s trial are inconclusive, they do provide some indications that Cr may be effective in the RA population. Clearly more research is needed in this area.

***Ageing and sarcopenia***

Nine studies[55,97–104] were identified that investigated the effects of Cr supplementation in older adults and met the inclusion criteria. Four of these studies, reported that Cr increased body mass by 0.49-1.86 kg[55,98,100,102] and that this gain was predominantly lean mass (LM), with increases in muscle mass of up to +2.22 kg[55]. In contrast, no significant changes in body mass or LM were found in the remaining five studies[99–101,103,104], although a trend of increased LM (+0.3%) following Cr supplementation relative to placebo (*P* = 0.062) was found by one of these[104]. As expected, no significant changes in % body fat subsequent to Cr supplementation in older subjects were reported[55,99,100].

Three of the six studies that measured muscle strength changes reported improvements following Cr supplementation[55,98,101]. Gotshalk *et al*[55] reported strength increases of both maximal leg press (+7%-8%), knee extensor (+9%) and knee flexor muscles (+15%) in older males, whilst in females increases in leg press (+3.4% or 5.2 kg) and bench press (+4.4% or 1.7 kg) were found[98]. In a cross-over design, Stout *et al*[101] found that Cr significantly increased maximal isometric grip strength by +6.7%[101]. Conversely, Jakobi *et al*[102] found that 5 d of Cr supplementation was unable to increase elbow flexor maximal voluntary strength or any other muscle contractile properties (twitch and tetanic recordings from electrical stimulation of the muscles). Similar findings were reported by Rawson *et al*[100], who found no significant effect on isometric elbow flexor strength after 5 d supplementation, and Bermon *et al*[103] who found no increase in chest or strength compared to a placebo (*P* > 0.05).

All studies assessing short-term physical function reported significant improvements in lower-extremity functional tests such as the sit-to-stand in 30 s (SST-30) by up to 12%[55,97,98,105], and a tandem gait test by 6%[55] to 9%[98] following Cr supplementation. Lower body power (as assessed by a 10-s Wingate test) was shown to improve by +11%[55] and Rawson *et al*[99] reported that leg fatigue (as expressed as a % change in the total peak torque generate and assessed by 5 × 30 s knee extensions at 180° on an isokinetic dynamometer) was reduced by 9% (compared to a 5% increase in the placebo group, *P* < 0.05). Similar findings by Stout *et al*[101] showed lower body muscle endurance (cycling capacity at fatigue threshold) was improved by 15.6% compared to the placebo group. However, assessments of endurance capacity (*i.e.*, 1-mile walk test; and gross mechanical efficiency, ventilatory threshold, and peak oxygen intake determined during cycle ergometry) were not significantly improved following Cr supplementation[97].

***Trials in other clinical populations***

One study[106] trialled Cr supplementation in osteoarthritis (OA). OA is the most common form of arthritis, and as with RA, is characterised by joint damage, muscle weakness, poor physical function[107], and predominantly affects females[108]. In this investigation, Roy *et al*[106] reported limited effects of Cr supplementation in OA patients recovering from total knee arthroplasty, despite a significant increase in serum Cr concentration, with no improvements in muscle strength (handgrip, dorsiflexion and quadriceps strength, 30-foot timed walk and 4-step climb) observed after 40 d (10 d pre surgery and 30 d post-surgery) of Cr supplementation relative to placebo.

One trial[109] reported the use of Cr supplementation in fibromyalgia, another chronic syndrome of unknown etiology, characterized by some similarities in symptomology to RA, including pain, muscle dysfunction, disability and fatigue[110]. Some of the fibromyalgia symptoms such as muscle dysfunction and fatigue could, in theory, be due to low muscle levels of ATP and PCr[109]. A randomised controlled trial of Cr supplementation in fibromyalgia patients[109] found that muscle PCr content increased and muscle strength improved relative to the placebo group (leg-press by 9.8%, *P* = 0.02; chest-press by 1.2%, *P* = 0.02; and isometric hand-grip strength by 6.4%, *P* = 0.07) in the Cr group.

Myopathy is a muscle wasting disorder which primarily affects skeletal muscle. Much like rheumatoid cachexia seen in RA patients, this can cause a variety of complaints including progressive weakness and wasting of skeletal muscle, and fatigue (for a review see Kley[111]). Eight trials of Cr supplementation in populations with myopathies were found, with these investigations finding mixed results on the efficacy of oral Cr. In a cross-over design trial in 30 Duchenne muscular dystrophy (DMD) adolescents[112], the Cr supplementation phase increased lean mass by +0.7 kg and grip strength by approximately 20% compared to the placebo phase. In a similar design, Cr supplementation improved maximal strength and fatigue resistance in 15 other patients with DMD[62]. Further to these trials, improvements in muscle PCr/P ratio and preservation of calf muscle strength were also reported by Banerjee *et al*[113] in 18 DMD patients.

In contrast, in cross-over design trials of patients with Mytonic muscular dystrophy 1 (DM1), Cr failed to induce any changes in muscle strength, lean mass or disease symptoms128[114,115], or improve function or strength in DMD patients[116] or patients with myotonic dystrophy type 2 (DM2)[117].

Two studies[118,119] were found that reported trials of Cr supplementation in cancer patients. Up to 80% of cancer patients have associated muscle wasting which is termed “cancer cachexia”[120]. Like other forms of cachexia, this is characterised by a preferential loss of skeletal muscle mass (with or without a loss of fat mass) which cannot be reversed through conventional methods of nutrition[121]. In patients with cancer, Cr supplementation improved handgrip strength by 5.5% (*P* = 0.019)[118] and reduced body fat accumulation (-3.5%; *P* < 0.05) relative to a placebo group[119].

***Review Conclusions***

Around 70% of RA patients are middle-aged or elderly females[122], and the existing evidence indicates that Cr can be successful in countering the effects of sarcopenia in older populations independent of exercise training[123], specifically in older females[124,125]. Of the thirteen included trials that have supplemented the elderly with Cr, only three[100,102,103] found no beneficial effect on lean mass, strength, or physical function. However, the magnitude of effect appears to be reduced relative to that observed in young healthy individuals[126], and the limited number of studies indicates that further work is needed to fully evaluate the role of Cr supplementation[127].

Creatine has been shown to be effective in a range of clinical conditions including muscle wasting disorders[62,112,113], and cancer cachexia[128]. Despite the inconclusive findings of the solitary RA study[94], of the thirteen clinical trials identified, seven showed positive effects of Cr on muscle mass and/or strength and function measures.

**FACTORS AFFECTING CREATINE EFFECTIVENESS IN CERTAIN INDIVIDUALS OR POPULATIONS**

Apart from inadequate supplement duration or dose, various other factors influence Cr effectiveness. It has been reported that 20%-30% of individuals do not respond to Cr supplementation; when “non-responsiveness” is defined as an increase in resting total muscle Cr of < 10 mmol· kg/dwfollowing 5 d loading at 20 g per day[46,88]. Syrotuik *et al*[129] found that based on pre-existing biological and physiological factors, “responders” (defined in that study as ≥ 20 mmol· kg/dwincrease in intramuscular Cr) possessed a biological profile of (1) low initial levels of total Cr or PCr (approximately < 110 mmol· kg/dw); (2) higher percentage of type II fibres (> 63.1%); and (3) a higher preload muscle fibre cross-sectional area (CSA) (approximately > 1500 μm2). For individuals whose initial muscle Cr concentrations approach 150 mmol· kg/dw, Cr supplementation does not appear to augment muscle Cr uptake, increase PCr resynthesis, or improve performance[4,129,130]. Not surprisingly, optimal responses to Cr supplementation are generally observed in groups with reduced serum and muscle levels of Cr such as vegetarians and low meat eaters, which include many older individuals[58,125,130,131].

Although the majority of the studies reviewed found benefits of Cr supplementation in the elderly, it has been suggested that uptake of Cr into muscle is reduced in older adults (> 60 years) relative to younger subjects[99,132], and that subsequently older adults may require a longer Cr treatment period[56].

**SAFETY OF CREATINE**

Concerns about possible side effects of Cr supplementation have been raised in lay publications, mailing lists and online forums. However, none of the studies included in this review reported any adverse incidents during the trials ranging from 5 d to 36 wk. This is consistent with other studies of long term (10 mo to 5 years) (*e.g*.,[53,133,134]) or high dose Cr supplementation (10 g/d) (*e.g.*,[135,136]) that have reported no adverse side effects. According to Walliman[137], current evidence does “not hint towards any negative health effects of Cr”. Therefore, the anecdotal reports remain unsubstantiated and may be unrelated to Cr supplementation[44].

Concerns about the long-term safety of Cr have specifically been related to kidney function. Theoretically, the high nitrogen content (approximately 32%) of Cr could place additional strain on the kidney if taken in large excess for a long period of time[133]. Glomerular filtration rate (GFR) is widely accepted as the best overall measure of kidney function, with serum and urine creatinine levels the most commonly used markers for estimating GFR[136]. However, since Cr is converted to creatinine[47], it is normal for individuals who take Cr supplements to have elevated creatinine levels[138], thus falsely suggesting renal function impairment. Use of alternative GFR markers such as Cystatin C has shown that Cr supplementation does not promote renal dysfunction[136].

There is currently limited research on the effects of Cr supplementation in patients with exiting low GFR. A prospective report[139] suggests that short-term (35 d) Cr supplementation (5 d of 20 g/d followed by 5 g/d) does not affect kidney function in individuals with a single kidney and mildly decreased GFR. However, more research is needed in this area. Similarly, no evidence has emerged that Cr supplementation results in impaired liver function or liver damage[41,44,140,141].

**PRESCRIPTION OF CREATINE TO PATIENTS**

***Type***

Creatine supplements are usually taken as a tablet or powder (mixed with water), and exist in a variety of forms including Cr ethyl ester, Cr hydrochloride and the most commonly available Cr monohydrate (Cr complexed with a molecule of water). No differences in effectiveness have been found between these different Cr forms[142].

***“Loading” dosage***

Cr should be “loaded” into the muscle (using a high dose) for the first few days followed by a lower maintenance dose[41]. The most common “loading” dosage recommendation for Cr supplementation is 20 g/d (in four 5 g doses) for 5 d, as stores appear to be maximised within 5 to 6 d at this dose[130]. Alternate loading phases exist including daily doses based on body mass such as 0.25 g/kg[41] or 0.15 g/kg[143]. However, a constant dose of 3 g/d, without an intensive loading phase, achieved an increase in total Cr levels equal to a standard 5 d loading protocol and subsequent maintenance phase after 28 d[144].

***“Maintenance”and frequency***

Total muscle Cr can be maintained for at least 4-6 wk after the initial loading phase by the ingestion of small daily Cr doses of 2-5 g[41,144]. This period of low dosage is called the “maintenance phase”. Here, Cr is usually taken in 8 to 12 wk cycles, with a 4 to 5 wk “washout” period in between to allow serum Cr to return to baseline levels.

**CONCLUSION**

RA is characterised by a loss of muscle which causes reduced strength and physical functioning. Current anti-rheumatic pharmaceutical treatments are unable to reverse the effects of cachexia, and although high intensity exercise is highly effective in rectifying body composition and restoring physical function, uptake of, and adherence to, exercise training by RA patients is poor. Thus, other treatment options need investigation. Oral Cr supplementation offers a potentially efficacious, cheap and widely acceptable therapy for achieving these outcomes in RA patients. Creatine works primarily by enhancing the re-synthesis of ATP *via* increased stores of PCr in the muscle, and thus improving recovery during and after physical activity. Creatine also augments muscle protein synthesis thereby increasing muscle mass.

This review found only one study in which RA patients were supplemented with Cr[94] and its findings, whilst promising, were inconclusive. However, trials in populations with similar presentation to RA (*i.e.*, reduced muscle mass and impaired physical function), including older females, indicate that Cr is an efficacious way to improve muscle mass, strength and physical function. Therefore, additional studies in RA populations are advocated, as confirmation of the efficacy of Cr supplementation would provide an easy, safe and effective means of reversing the effects of rheumatoid cachexia in the majority of the RA population.

**REFERENCES**

1 **Lunt M**, Watson KD, Dixon WG, Symmons DP, Hyrich KL. No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2010; **62**: 3145-3153 [PMID: 20662063 DOI: 10.1002/art.27660]

2 **Engvall IL**, Tengstrand B, Brismar K, Hafström I. Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of changes in disease activity and levels of leptin and adiponectin: a randomised study over 21 months. *Arthritis Res Ther* 2010; **12**: R197 [PMID: 20964833 DOI: 10.1186/ar3169]

3 **Lemmey AB**, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. *Arthritis Rheum* 2009; **61**: 1726-1734 [PMID: 19950325 DOI: 10.1002/art.24891]

4 **Casey A**, Greenhaff PL. Does dietary creatine supplementation play a role in skeletal muscle metabolism and performance? *Am J Clin Nutr* 2000; **72**: 607S-617S [PMID: 10919967]

5 **Scott DL**, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010; **376**: 1094-1108 [PMID: 20870100 DOI: 10.1016/S0140-6736(10)60826-4]

6 **Gremese E**, Ferraccioli G. The metabolic syndrome: the crossroads between rheumatoid arthritis and cardiovascular risk. *Autoimmun Rev* 2011; **10**: 582-589 [PMID: 21539940 DOI: 10.1016/j.autrev.2011.04.018]

7 **García-Poma A**, Segami MI, Mora CS, Ugarte MF, Terrazas HN, Rhor EA, García E, Ramos MP, Alva M, Castañeda I, Chung CP. Obesity is independently associated with impaired quality of life in patients with rheumatoid arthritis. *Clin Rheumatol* 2007; **26**: 1831-1835 [PMID: 17340047]

8 **Lee TJ**, Park BH, Son HK, Song R, Shin KC, Lee EB, Song YW. Cost of illness and quality of life of patients with rheumatoid arthritis in South Korea. *Value Health* 2012; **15**: S43-S49 [PMID: 22265066 DOI: 10.1016/j.jval.2011.11.020]

9 **Haugeberg G**, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum* 2000; **43**: 522-530 [PMID: 10728744]

10 **Helal AMH**, Shahine EM, Hassan MM, Hashad DI, Moneim RA. Fatigue in rheumatoid arthritis and its relation to interleukin-6 serum level. *Egypt Rheum* 2012; **34**: 153-157

11 **Sheehy C**, Murphy E, Barry M. Depression in rheumatoid arthritis--underscoring the problem. *Rheumatology (Oxford)* 2006; **45**: 1325-1327 [PMID: 16908510]

12 **Roubenoff R**, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. *J Rheumatol* 1992; **19**: 1505-1510 [PMID: 1464859]

13 **Roubenoff R**, Roubenoff RA, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, Dinarello CA, Rosenberg IH. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. *J Clin Invest* 1994; **93**: 2379-2386 [PMID: 8200971]

14 **Engvall IL**, Svensson B, Tengstrand B, Brismar K, Hafström I. Impact of low-dose prednisolone on bone synthesis and resorption in early rheumatoid arthritis: experiences from a two-year randomized study. *Arthritis Res Ther* 2008; **10**: R128 [PMID: 18986531 DOI: 10.1186/ar2542]

15 **Marcora S**, Lemmey A, Maddison P. Dietary treatment of rheumatoid cachexia with beta-hydroxy-beta-methylbutyrate, glutamine and arginine: a randomised controlled trial. *Clin Nutr* 2005; **24**: 442-454 [PMID: 15896432]

16 **Marcora SM**, Lemmey AB, Maddison PJ. Can progressive resistance training reverse cachexia in patients with rheumatoid arthritis? Results of a pilot study. *J Rheumatol* 2005; **32**: 1031-1039 [PMID: 15940763]

17 **Morley JE**, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, Cederholm T, Coats AJ, Cummings SR, Evans WJ, Fearon K, Ferrucci L, Fielding RA, Guralnik JM, Harris TB, Inui A, Kalantar-Zadeh K, Kirwan BA, Mantovani G, Muscaritoli M, Newman AB, Rossi-Fanelli F, Rosano GM, Roubenoff R, Schambelan M, Sokol GH, Storer TW, Vellas B, von Haehling S, Yeh SS, Anker SD. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc* 2011; **12**: 403-409 [PMID: 21640657 DOI: 10.1016/j.jamda.2011.04.014]

18 **van Bokhorst-de van der Schueren MA**, Konijn NP, Bultink IE, Lems WF, Earthman CP, van Tuyl LH. Relevance of the new pre-cachexia and cachexia definitions for patients with rheumatoid arthritis. *Clin Nutr* 2012; **31**: 1008-1010 [PMID: 22695407 DOI: 10.1016/j.clnu.2012.05.012]

19 **Giles JT**, Ling SM, Ferrucci L, Bartlett SJ, Andersen RE, Towns M, Muller D, Fontaine KR, Bathon JM. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. *Arthritis Rheum* 2008; **59**: 807-815 [PMID: 18512711 DOI: 10.1002/art.23719]

20 **Summers GD**, Deighton CM, Rennie MJ, Booth AH. Rheumatoid cachexia: a clinical perspective. *Rheumatology (Oxford)* 2008; **47**: 1124-1131 [PMID: 18448480 DOI: 10.1093/rheumatology/ken146]

21 **Baumgartner RN**, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 2004; **12**: 1995-2004 [PMID: 15687401]

22 **Walsmith J**, Roubenoff R. Cachexia in rheumatoid arthritis. *Int J Cardiol* 2002; **85**: 89-99 [PMID: 12163213]

23 **Malmstrom TK**, Miller DK, Herning MM, Morley JE. Low appendicular skeletal muscle mass (ASM) with limited mobility and poor health outcomes in middle-aged African Americans. *J Cachexia Sarcopenia Muscle* 2013; **4**: 179-186 [PMID: 23532635 DOI: 10.1007/s13539-013-0106-x]

24 **Rall LC**, Rosen CJ, Dolnikowski G, Hartman WJ, Lundgren N, Abad LW, Dinarello CA, Roubenoff R. Protein metabolism in rheumatoid arthritis and aging. Effects of muscle strength training and tumor necrosis factor alpha. *Arthritis Rheum* 1996; **39**: 1115-1124 [PMID: 8670319]

25 **Roubenoff R**, Walsmith J, Lundgren N, Snydman L, Dolnikowski GJ, Roberts S. Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: implications for dietary intake recommendations. *Am J Clin Nutr* 2002; **76**: 774-779 [PMID: 12324290]

26 **Rall LC**, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. *Rheumatology (Oxford)* 2004; **43**: 1219-1223 [PMID: 15292530]

27 **Fanzani A**, Conraads VM, Penna F, Martinet W. Molecular and cellular mechanisms of skeletal muscle atrophy: an update. *J Cachexia Sarcopenia Muscle* 2012; **3**: 163-179 [PMID: 22673968 DOI: 10.1007/s13539-012-0074-6]

28 **Giles JT**, Allison M, Blumenthal RS, Post W, Gelber AC, Petri M, Tracy R, Szklo M, Bathon JM. Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. *Arthritis Rheum* 2010; **62**: 3173-3182 [PMID: 20589684 DOI: 10.1002/art.27629]

29 **Lemmey AB.** Efficacy of progressive resistance training for patients with rheumatoid arthritis and recommendation regarding its prescription. *Int J Clin Rheum* 2011; **6**: 189-205

30 **Marcora SM**, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. *Am J Clin Nutr* 2006; **84**: 1463-1472 [PMID: 17158431]

31 **Metsios GS**, Stavropoulos-Kalinoglou A, Douglas KM, Koutedakis Y, Nevill AM, Panoulas VF, Kita M, Kitas GD. Blockade of tumour necrosis factor-alpha in rheumatoid arthritis: effects on components of rheumatoid cachexia. *Rheumatology (Oxford)* 2007; **46**: 1824-1827 [PMID: 18032540]

32 **Sharif S**, Thomas JM, Donley DA, Gilleland DL, Bonner DE, McCrory JL, Hornsby WG, Zhao H, Lively MW, Hornsby JA, Alway SE. Resistance exercise reduces skeletal muscle cachexia and improves muscle function in rheumatoid arthritis. *Case Rep Med* 2011; **2011**: 205691 [PMID: 22203849 DOI: 10.1155/2011/205691]

33 **Sokka T**, Kautiainen H, Pincus T, Verstappen SM, Aggarwal A, Alten R, Andersone D, Badsha H, Baecklund E, Belmonte M, Craig-Müller J, da Mota LM, Dimic A, Fathi NA, Ferraccioli G, Fukuda W, Géher P, Gogus F, Hajjaj-Hassouni N, Hamoud H, Haugeberg G, Henrohn D, Horslev-Petersen K, Ionescu R, Karateew D, Kuuse R, Laurindo IM, Lazovskis J, Luukkainen R, Mofti A, Murphy E, Nakajima A, Oyoo O, Pandya SC, Pohl C, Predeteanu D, Rexhepi M, Rexhepi S, Sharma B, Shono E, Sibilia J, Sierakowski S, Skopouli FN, Stropuviene S, Toloza S, Valter I, Woolf A, Yamanaka H. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. *Arthritis Res Ther* 2010; **12**: R42 [PMID: 20226018 DOI: 10.1186/ar2951]

34 **Lemmey AB**, Williams SL, Marcora SM, Jones J, Maddison PJ. Are the benefits of a high-intensity progressive resistance training program sustained in rheumatoid arthritis patients? A 3-year followup study. *Arthritis Care Res (Hoboken)* 2012; **64**: 71-75 [PMID: 21671413 DOI: 10.1002/acr.20523]

35 **Stamp LK**, James MJ, Cleland LG. Diet and rheumatoid arthritis: a review of the literature. *Semin Arthritis Rheum* 2005; **35**: 77-94 [PMID: 16194694]

36 **Cribb PJ**, Williams AD, Stathis CG, Carey MF, Hayes A. Effects of whey isolate, creatine, and resistance training on muscle hypertrophy. *Med Sci Sports Exerc* 2007; **39**: 298-307 [PMID: 17277594]

37 **Nissen SL**, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J Appl Physiol (1985)* 2003; **94**: 651-659 [PMID: 12433852]

38 **American College of Sports Medicine**. The physiological and health effects of oral creatine supplementation. *Med Sci Sports Exerc* 2010; **32:** 706-717

39 **Casey A**, Constantin-Teodosiu D, Howell S, Hultman E, Greenhaff PL. Creatine ingestion favorably affects performance and muscle metabolism during maximal exercise in humans. *Am J Physiol* 1996; **271**: E31-E37 [PMID: 8760078]

40 **Harris RC**, Hultman E, Nordesjö LO. Glycogen, glycolytic intermediates and high-energy phosphates determined in biopsy samples of musculus quadriceps femoris of man at rest. Methods and variance of values. *Scand J Clin Lab Invest* 1974; **33**: 109-120 [PMID: 4852173]

41 **Bogdanis GC,** Papaspyrou A, Maridaki M. Muscle Metabolism and Fatigue During Sprint Exercise: Effects Of Creatine Supplementation. *Serb J Sport Sci* 2007; **1**: 37-57

42 **Longo N**, Ardon O, Vanzo R, Schwartz E, Pasquali M. Disorders of creatine transport and metabolism. *Am J Med Genet C Semin Med Genet* 2011; **157C**: 72-78 [PMID: 21308988 DOI: 10.1002/ajmg.c.30292]

43 **Burton DA**, Stokes K, Hall GM. Physiological effects of exercise. *Contin Educ Anaesth Crit Care Pain* 2004; **4:** 185-188

44 **Kreider RB**, Ferreira M, Wilson M, Grindstaff P, Plisk S, Reinardy J, Cantler E, Almada AL. Effects of creatine supplementation on body composition, strength, and sprint performance. *Med Sci Sports Exerc* 1998; **30**: 73-82 [PMID: 9475647]

45 **Bemben MG**, Bemben DA, Loftiss DD, Knehans AW. Creatine supplementation during resistance training in college football athletes. *Med Sci Sports Exerc* 2001; **33**: 1667-1673 [PMID: 11581550]

46 **Greenhaff PL**. Creatine and its application as an ergogenic aid. *Int J Sport Nutr* 1995; **5 Suppl**: S100-S110 [PMID: 7550252]

47 **Wyss M**, Kaddurah-Daouk R. Creatine and creatinine metabolism. *Physiol Rev* 2000; **80**: 1107-1213 [PMID: 10893433]

48 **Balsom PD**, Söderlund K, Sjödin B, Ekblom B. Skeletal muscle metabolism during short duration high-intensity exercise: influence of creatine supplementation. *Acta Physiol Scand* 1995; **154**: 303-310 [PMID: 7572228]

49 **Tang FC**, Chan CC, Kuo PL. Contribution of creatine to protein homeostasis in athletes after endurance and sprint running. *Eur J Nutr* 2014; **53**: 61-71 [PMID: 23392621 DOI: 10.1007/s00394-013-0498-6]

50 **Engelhardt M**, Neumann G, Berbalk A, Reuter I. Creatine supplementation in endurance sports. *Med Sci Sports Exerc* 1998; **30**: 1123-1129 [PMID: 9662683]

51 **Lang F**, Busch GL, Ritter M, Völkl H, Waldegger S, Gulbins E, Häussinger D. Functional significance of cell volume regulatory mechanisms. *Physiol Rev* 1998; **78**: 247-306 [PMID: 9457175]

52 **Powers ME**, Arnold BL, Weltman AL, Perrin DH, Mistry D, Kahler DM, Kraemer W, Volek J. Creatine Supplementation Increases Total Body Water Without Altering Fluid Distribution. *J Athl Train* 2003; **38**: 44-50 [PMID: 12937471]

53 **Poortmans JR**, Francaux M. Long-term oral creatine supplementation does not impair renal function in healthy athletes. *Med Sci Sports Exerc* 1999; **31**: 1108-1110 [PMID: 10449011]

54 **Ziegenfuss TN**, Lowery LM, Lemon PW. Acute fluid volume changes in men during three days of creatine supplementation. *J Ex Physiol* 1998; **1**: 1-9

55 **Gotshalk LA**, Volek JS, Staron RS, Denegar CR, Hagerman FC, Kraemer WJ. Creatine supplementation improves muscular performance in older men. *Med Sci Sports Exerc* 2002; **34**: 537-543 [PMID: 11880821]

56 **Chrusch MJ**, Chilibeck PD, Chad KE, Davison KS, Burke DG. Creatine supplementation combined with resistance training in older men. *Med Sci Sports Exerc* 2001; **33**: 2111-2117 [PMID: 11740307]

57 **Ingwall JS**, Weiner CD, Morales MF, Davis E, Stockdale FE. Specificity of creatine in the control of muscle protein synthesis. *J Cell Biol* 1974; **62**: 145-151 [PMID: 4407046]

58 **Balsom PD**, Harridge SD, Söderlund K, Sjödin B, Ekblom B. Creatine supplementation per se does not enhance endurance exercise performance. *Acta Physiol Scand* 1993; **149**: 521-523 [PMID: 8128901]

59 **Bessman SP,** Savabi F. The role of the phosphocreatine energy shuttle in exercise and muscle hypertrophy. Creatine and Creatine phosphate: Scientific and Clinical Perspectives. 1st ed. Academic Press: 1988; 185-198

60 **Sipilä I**, Rapola J, Simell O, Vannas A. Supplementary creatine as a treatment for gyrate atrophy of the choroid and retina. *N Engl J Med* 1981; **304**: 867-870 [PMID: 7207523]

61 **Häussinger D**, Roth E, Lang F, Gerok W. Cellular hydration state: an important determinant of protein catabolism in health and disease. *Lancet* 1993; **341**: 1330-1332 [PMID: 8098459]

62 **Louis M**, Lebacq J, Poortmans JR, Belpaire-Dethiou MC, Devogelaer JP, Van Hecke P, Goubel F, Francaux M. Beneficial effects of creatine supplementation in dystrophic patients. *Muscle Nerve* 2003; **27**: 604-610 [PMID: 12707981]

63 **Parise G**, Mihic S, MacLennan D, Yarasheski KE, Tarnopolsky MA. Effects of acute creatine monohydrate supplementation on leucine kinetics and mixed-muscle protein synthesis. *J Appl Physiol (1985)* 2001; **91**: 1041-1047 [PMID: 11509496]

64 **Hespel P**, Op't Eijnde B, Van Leemputte M, Ursø B, Greenhaff PL, Labarque V, Dymarkowski S, Van Hecke P, Richter EA. Oral creatine supplementation facilitates the rehabilitation of disuse atrophy and alters the expression of muscle myogenic factors in humans. *J Physiol* 2001; **536**: 625-633 [PMID: 11600695]

65 **Deldicque L**, Louis M, Theisen D, Nielens H, Dehoux M, Thissen JP, Rennie MJ, Francaux M. Increased IGF mRNA in human skeletal muscle after creatine supplementation. *Med Sci Sports Exerc* 2005; **37**: 731-736 [PMID: 15870625]

66 **Deldicque L**, Atherton P, Patel R, Theisen D, Nielens H, Rennie MJ, Francaux M. Effects of resistance exercise with and without creatine supplementation on gene expression and cell signaling in human skeletal muscle. *J Appl Physiol (1985)* 2008; **104**: 371-378 [PMID: 18048590]

67 **Burke DG**, Candow DG, Chilibeck PD, MacNeil LG, Roy BD, Tarnopolsky MA, Ziegenfuss T. Effect of creatine supplementation and resistance-exercise training on muscle insulin-like growth factor in young adults. *Int J Sport Nutr Exerc Metab* 2008; **18**: 389-398 [PMID: 18708688]

68 **Adams GR**. Invited Review: Autocrine/paracrine IGF-I and skeletal muscle adaptation. *J Appl Physiol (1985)* 2002; **93**: 1159-1167 [PMID: 12183514]

69 **Saremi A**, Gharakhanloo R, Sharghi S, Gharaati MR, Larijani B, Omidfar K. Effects of oral creatine and resistance training on serum myostatin and GASP-1. *Mol Cell Endocrinol* 2010; **317**: 25-30 [PMID: 20026378 DOI: 10.1016/j.mce.2009.12.019]

70 **Elkina Y**, von Haehling S, Anker SD, Springer J. The role of myostatin in muscle wasting: an overview. *J Cachexia Sarcopenia Muscle* 2011; **2**: 143-151 [PMID: 21966641]

71 **Schiaffino S**, Dyar KA, Ciciliot S, Blaauw B, Sandri M. Mechanisms regulating skeletal muscle growth and atrophy. *FEBS J* 2013; **280**: 4294-4314 [PMID: 23517348 DOI: 10.1111/febs.12253]

72 **Zimmers TA**, Davies MV, Koniaris LG, Haynes P, Esquela AF, Tomkinson KN, McPherron AC, Wolfman NM, Lee SJ. Induction of cachexia in mice by systemically administered myostatin. *Science* 2002; **296**: 1486-1488 [PMID: 12029139]

73 **Dankbar B**, Wunrau C, Wehmeyer C, Pap T. Myostatin–a new player in inflammatory bone loss. *Ann Rheum Diseases* 2011; **70**: A75-A76

74 **Söderlund K**, Greenhaff PL, Hultman E. Energy metabolism in type I and type II human muscle fibres during short term electrical stimulation at different frequencies. *Acta Physiol Scand* 1992; **144**: 15-22 [PMID: 1595349]

75 **Wortmann RL**. Inflammatory diseases of muscle. Textbook of Rheumatology. 4th ed. Philadelphia: WB Saunders Company; 1993: 1159–1188

76 **Choy E**. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology (Oxford)* 2012; **51** Suppl 5: v3-11 [PMID: 22718924 DOI: 10.1093/rheumatology/kes113]

77 **Bassit RA**, Curi R, Costa Rosa LF. Creatine supplementation reduces plasma levels of pro-inflammatory cytokines and PGE2 after a half-ironman competition. *Amino Acids* 2008; **35**: 425-431 [PMID: 17917696]

78 **Morley JE**, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. *J Lab Clin Med* 2001; **137**: 231-243 [PMID: 11283518]

79 **Candow DG**, Little JP, Chilibeck PD, Abeysekara S, Zello GA, Kazachkov M, Cornish SM, Yu PH. Low-dose creatine combined with protein during resistance training in older men. *Med Sci Sports Exerc* 2008; **40**: 1645-1652 [PMID: 18685526 DOI: 10.1249/MSS.0b013e318176b310]

80 **Chilibeck PD**, Chrusch MJ, Chad KE, Shawn Davison K, Burke DG. Creatine monohydrate and resistance training increase bone mineral content and density in older men. *J Nutr Health Aging* 2005; **9**: 352-353 [PMID: 16222402]

81 **Tarnopolsky MA**. Potential benefits of creatine monohydrate supplementation in the elderly. *Curr Opin Clin Nutr Metab Care* 2000; **3**: 497-502 [PMID: 11085837]

82 **Wiroth JB**, Bermon S, Andreï S, Dalloz E, Hébuterne X, Dolisi C. Effects of oral creatine supplementation on maximal pedalling performance in older adults. *Eur J Appl Physiol* 2001; **84**: 533-539 [PMID: 11482548]

83 **Skare OC**, Skadberg AR. Creatine supplementation improves sprint performance in male sprinters. *Scand J Med Sci Sports* 2001; **11**: 96-102 [PMID: 11252467]

84 **Mujika I**, Padilla S, Ibañez J, Izquierdo M, Gorostiaga E. Creatine supplementation and sprint performance in soccer players. *Med Sci Sports Exerc* 2000; **32**: 518-525 [PMID: 10694141]

85 **McNaughton LR**, Dalton B, Tarr J. The effects of creatine supplementation on high-intensity exercise performance in elite performers. *Eur J Appl Physiol Occup Physiol* 1998; **78**: 236-240 [PMID: 9721002]

86 **Rossiter HB**, Cannell ER, Jakeman PM. The effect of oral creatine supplementation on the 1000-m performance of competitive rowers. *J Sports Sci* 1996; **14**: 175-179 [PMID: 8737325]

87 **Harris RC,** Viru M, Greenhaff PL, Hultman E. The effect of oral creatine supplementation on running performance during maximal short-term exercise in man. *J Physiol* 1993; **467**: 74-74

88 **Rawson ES**, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. *J Strength Cond Res* 2003; **17**: 822-831 [PMID: 14636102]

89 **Volek JS**, Kraemer WJ, Bush JA, Boetes M, Incledon T, Clark KL, Lynch JM. Creatine supplementation enhances muscular performance during high-intensity resistance exercise. *J Am Diet Assoc* 1997; **97**: 765-770 [PMID: 9216554]

90 **Larson-Meyer DE**, Hunter GR, Trowbridge CA, Turk JC, Ernest JM, Torman SL, Harbin PA. The effect of creatine supplementation on muscle strength and body composition during off-season training in female soccer players. *J Strength Con Res h* 2000; **14**: 434-442

91 **Kreider RB**. Effects of creatine supplementation on performance and training adaptations. *Mol Cell Biochem* 2003; **244**: 89-94 [PMID: 12701815]

92 **Stroud MA**, Holliman D, Bell D, Green AL, Macdonald IA, Greenhaff PL. Effect of oral creatine supplementation on respiratory gas exchange and blood lactate accumulation during steady-state incremental treadmill exercise and recovery in man. *Clin Sci (Lond)* 1994; **87**: 707-710 [PMID: 7874863]

93 **Chilibeck PD**, Magnus C, Anderson M. Effect of in-season creatine supplementation on body composition and performance in rugby union football players. *Appl Physiol Nutr Metab* 2007; **32**: 1052-1057 [PMID: 18059577]

94 **Willer B**, Stucki G, Hoppeler H, Brühlmann P, Krähenbühl S. Effects of creatine supplementation on muscle weakness in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2000; **39**: 293-298 [PMID: 10788538]

95 **Stucki G**, Schönbächler J, Brühlmann P, Mariacher S, Stoll T, Michel BA. Does a muscle strength index provide complementary information to traditional disease activity variables in patients with rheumatoid arthritis? *J Rheumatol* 1994; **21**: 2200-2205 [PMID: 7699619]

96 **van den Ende CH**, Breedveld FC, Dijkmans BA, Hazes JM. The limited value of the Health Assessment Questionnaire as an outcome measure in short term exercise trials. *J Rheumatol* 1997; **24**: 1972-1977 [PMID: 9330941]

97 **Cañete S**, San Juan AF, Pérez M, Gómez-Gallego F, López-Mojares LM, Earnest CP, Fleck SJ, Lucia A. Does creatine supplementation improve functional capacity in elderly women? *J Strength Cond Res* 2006; **20**: 22-28 [PMID: 16503684]

98 **Gotshalk LA**, Kraemer WJ, Mendonca MA, Vingren JL, Kenny AM, Spiering BA, Hatfield DL, Fragala MS, Volek JS. Creatine supplementation improves muscular performance in older women. *Eur J Appl Physiol* 2008; **102**: 223-231 [PMID: 17943308]

99 **Rawson ES**, Wehnert ML, Clarkson PM. Effects of 30 days of creatine ingestion in older men. *Eur J Appl Physiol Occup Physiol* 1999; **80**: 139-144 [PMID: 10408325]

100 **Rawson ES**, Clarkson PM. Acute creatine supplementation in older men. *Int J Sports Med* 2000; **21**: 71-75 [PMID: 10683103]

101 **Stout JR**, Sue Graves B, Cramer JT, Goldstein ER, Costa PB, Smith AE, Walter AA. Effects of creatine supplementation on the onset of neuromuscular fatigue threshold and muscle strength in elderly men and women (64 - 86 years). *J Nutr Health Aging* 2007; **11**: 459-464 [PMID: 17985060]

102 **Jakobi JM**, Rice CL, Curtin SV, Marsh GD. Neuromuscular properties and fatigue in older men following acute creatine supplementation. *Eur J Appl Physiol* 2001; **84**: 321-328 [PMID: 11374116]

103 **Bermon S**, Venembre P, Sachet C, Valour S, Dolisi C. Effects of creatine monohydrate ingestion in sedentary and weight-trained older adults. *Acta Physiol Scand* 1998; **164**: 147-155 [PMID: 9805101]

104 **Gualano B**, Macedo AR, Alves CR, Roschel H, Benatti FB, Takayama L, de Sá Pinto AL, Lima FR, Pereira RM. Creatine supplementation and resistance training in vulnerable older women: A randomized double-blind placebo-controlled clinical trial. *Exp Gerontol* 2014; **53**: 7-15

105 **Neves M**, Gualano B, Roschel H, Lima FR, Lúcia de Sá-Pinto A, Seguro AC, Shimizu MH, Sapienza MT, Fuller R, Lancha AH, Bonfá E. Effect of creatine supplementation on measured glomerular filtration rate in postmenopausal women. *Appl Physiol Nutr Metab* 2011; **36**: 419-422 [PMID: 21574777]

106 **Roy BD**, de Beer J, Harvey D, Tarnopolsky MA. Creatine monohydrate supplementation does not improve functional recovery after total knee arthroplasty. *Arch Phys Med Rehabil* 2005; **86**: 1293-1298 [PMID: 16003653]

107 **Slemenda C**, Brandt KD, Heilman DK, Mazzuca S, Braunstein EM, Katz BP, Wolinsky FD. Quadriceps weakness and osteoarthritis of the knee. *Ann Intern Med* 1997; **127**: 97-104 [PMID: 9230035]

108 **Lawrence RC**, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; **58**: 26-35 [PMID: 18163497 DOI: 10.1002/art.23176]

109 **Alves CR**, Santiago BM, Lima FR, Otaduy MC, Calich AL, Tritto AC, de Sá Pinto AL, Roschel H, Leite CC, Benatti FB, Bonfá E, Gualano B. Creatine supplementation in fibromyalgia: a randomized, double-blind, placebo-controlled trial. *Arthritis Care Res (Hoboken)* 2013; **65**: 1449-1459 [PMID: 23554283 DOI: 10.1002/acr.22020]

110 **Leader A**, Amital D, Rubinow A, Amital H. An open-label study adding creatine monohydrate to ongoing medical regimens in patients with the fibromyalgia syndrome. *Ann N Y Acad Sci* 2009; **1173**: 829-836 [PMID: 19758235 DOI: 10.1111/j.1749-6632.2009.04811.x]

111 **Kley RA**, Tarnopolsky MA, Vorgerd M. Creatine for treating muscle disorders. *Cochrane Database Syst Rev* 2011; **16**: CD004760 [PMID: 21328269 DOI: 10.1002/14651858.CD004760.pub3]

112 **Tarnopolsky MA**, Mahoney DJ, Vajsar J, Rodriguez C, Doherty TJ, Roy BD, Biggar D. Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. *Neurology* 2004; **62**: 1771-1777 [PMID: 15159476]

113 **Banerjee B**, Sharma U, Balasubramanian K, Kalaivani M, Kalra V, Jagannathan NR. Effect of creatine monohydrate in improving cellular energetics and muscle strength in ambulatory Duchenne muscular dystrophy patients: a randomized, placebo-controlled 31P MRS study. *Magn Reson Imaging* 2010; **28**: 698-707 [PMID: 20395096 DOI: 10.1016/j.mri.2010.03.008]

114 **Walter MC**, Reilich P, Lochmüller H, Kohnen R, Schlotter B, Hautmann H, Dunkl E, Pongratz D, Müller-Felber W. Creatine monohydrate in myotonic dystrophy: a double-blind, placebo-controlled clinical study. *J Neurol* 2002; **249**: 1717-1722 [PMID: 12529796]

115 **Tarnopolsky M**, Mahoney D, Thompson T, Naylor H, Doherty TJ. Creatine monohydrate supplementation does not increase muscle strength, lean body mass, or muscle phosphocreatine in patients with myotonic dystrophy type 1. *Muscle Nerve* 2004; **29**: 51-58 [PMID: 14694498]

116 **Escolar DM**, Buyse G, Henricson E, Leshner R, Florence J, Mayhew J, Tesi-Rocha C, Gorni K, Pasquali L, Patel KM, McCarter R, Huang J, Mayhew T, Bertorini T, Carlo J, Connolly AM, Clemens PR, Goemans N, Iannaccone ST, Igarashi M, Nevo Y, Pestronk A, Subramony SH, Vedanarayanan VV, Wessel H. CINRG randomized controlled trial of creatine and glutamine in Duchenne muscular dystrophy. *Ann Neurol* 2005; **58**: 151-155 [PMID: 15984021]

117 **Schneider-Gold C**, Beck M, Wessig C, George A, Kele H, Reiners K, Toyka KV. Creatine monohydrate in DM2/PROMM: a double-blind placebo-controlled clinical study. Proximal myotonic myopathy. *Neurology* 2003; **60**: 500-502 [PMID: 12578937]

118 **Norman K**, Stübler D, Baier P, Schütz T, Ocran K, Holm E, Lochs H, Pirlich M. Effects of creatine supplementation on nutritional status, muscle function and quality of life in patients with colorectal cancer--a double blind randomised controlled trial. *Clin Nutr* 2006; **25**: 596-605 [PMID: 16701923]

119 **Bourgeois JM**, Nagel K, Pearce E, Wright M, Barr RD, Tarnopolsky MA. Creatine monohydrate attenuates body fat accumulation in children with acute lymphoblastic leukemia during maintenance chemotherapy. *Pediatr Blood Cancer* 2008; **51**: 183-187 [PMID: 18421708 DOI: 10.1002/pbc.21571]

120 **Tan BH**, Fearon KC. Cachexia: prevalence and impact in medicine. *Curr Opin Clin Nutr Metab Care* 2008; **11**: 400-407 [PMID: 18541999 DOI: 10.1097/MCO.0b013e328300ecc1]

121 **Fearon K**, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; **12**: 489-495 [PMID: 21296615 DOI: 10.1016/S1470-2045(10)70218-7]

122 **Symmons D**, Turner G, Webb R, Asten P, Barrett E, Lunt M, Scott D, Silman A. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology (Oxford)* 2002; **41**: 793-800 [PMID: 12096230]

123 **Rawson ES**, Venezia AC. Use of creatine in the elderly and evidence for effects on cognitive function in young and old. *Amino Acids* 2011; **40**: 1349-1362 [PMID: 21394604 DOI: 10.1007/s00726-011-0855-9]

124 **Aguiar AF**, Januário RS, Junior RP, Gerage AM, Pina FL, do Nascimento MA, Padovani CR, Cyrino ES. Long-term creatine supplementation improves muscular performance during resistance training in older women. *Eur J Appl Physiol* 2013; **113**: 987-996 [PMID: 23053133 DOI: 10.1007/s00421-012-2514-623053133]

125 **Brose A**, Parise G, Tarnopolsky MA. Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. *J Gerontol A Biol Sci Med Sci* 2003; **58**: 11-19 [PMID: 12560406]

126 **Moon A**, Heywood L, Rutherford S, Cobbold C. Creatine supplementation: can it improve quality of life in the elderly without associated resistance training? *Curr Aging Sci* 2013; **6**: 251-257 [PMID: 24304199]

127 **Devries MC**, Phillips SM. Creatine supplementation during resistance training in older adults-a meta-analysis. *Med Sci Sports Exerc* 2014; **46**: 1194-1203 [PMID: 24576864]

128 **Chung YL**, Alexanderson H, Pipitone N, Morrison C, Dastmalchi M, Ståhl-Hallengren C, Richards S, Thomas EL, Hamilton G, Bell JD, Lundberg IE, Scott DL. Creatine supplements in patients with idiopathic inflammatory myopathies who are clinically weak after conventional pharmacologic treatment: Six-month, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2007; **57**: 694-702 [PMID: 17471547]

129 **Syrotuik DG**, Bell GJ, Burnham R, Sim IL, Calvert RA, Maclean IM. Absolute and relative strength performance following creatine monohydrate supplementation combined with periodized resistance training. *J Strength Con Res* 2000; **14:** 182-190

130 **Harris RC**, Söderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin Sci (Lond)* 1992; **83**: 367-374 [PMID: 1327657]

131 **Delanghe J**, De Slypere JP, De Buyzere M, Robbrecht J, Wieme R, Vermeulen A. Normal reference values for creatine, creatinine, and carnitine are lower in vegetarians. *Clin Chem* 1989; **35**: 1802-1803 [PMID: 2758659]

132 **Stec ES**, Rawson MJ. Benefits of creatine supplementation for older adults. *Braz J Biomotric* 2010; **4:** 215-226

133 **Poortmans JR**, Auquier H, Renaut V, Durussel A, Saugy M, Brisson GR. Effect of short-term creatine supplementation on renal responses in men. *Eur J Appl Physiol Occup Physiol* 1997; **76**: 566-567 [PMID: 9404870]

134 **Poortmans JR**, Francaux M. Renal dysfunction accompanying oral creatine supplements. *Lancet* 1998; **352**: 234 [PMID: 9683236]

135 **Earnest CP**, Almada AL, Mitchell TL. High-performance capillary electrophoresis-pure creatine monohydrate reduces blood lipids in men and women. *Clin Sci (Lond)* 1996; **91**: 113-118 [PMID: 8774269]

136 **Lemon PW**. Dietary creatine supplementation and exercise performance: why inconsistent results? *Can J Appl Physiol* 2002; **27**: 663-681 [PMID: 12501003]

137 **Walliman T**. Comment on “Creatine is an approved, effective and safe dietary supplement that is NOT causing toxic hepatitis!” *Food Chem Toxicol* 2013; **51**: 453–454

138 **Shao A**, Hathcock JN. Risk assessment for creatine monohydrate. *Regul Toxicol Pharmacol* 2006; **45**: 242-251 [PMID: 16814437]

139 **Gualano B**, Ugrinowitsch C, Novaes RB, Artioli GG, Shimizu MH, Seguro AC, Harris RC, Lancha AH. Effects of creatine supplementation on renal function: a randomized, double-blind, placebo-controlled clinical trial. *Eur J Appl Physiol* 2008; **103**: 33-40 [PMID: 18188581 DOI: 10.1007/s00421-007-0669-3]

140 **Mayhew DL**, Mayhew JL, Ware JS. Effects of long-term creatine supplementation on liver and kidney functions in American college football players. *Int J Sport Nutr Exerc Metab* 2002; **12**: 453-460 [PMID: 12500988]

141 **Schröder H**, Terrados N, Tramullas A. Risk assessment of the potential side effects of long-term creatine supplementation in team sport athletes. *Eur J Nutr* 2005; **44**: 255-261 [PMID: 15309421]

142 **Spillane M**, Schoch R, Cooke M, Harvey T, Greenwood M, Kreider R, Willoughby DS. The effects of creatine ethyl ester supplementation combined with heavy resistance training on body composition, muscle performance, and serum and muscle creatine levels. *J Int Soc Sports Nutr* 2009; **6**: 6 [PMID: 19228401 DOI: 10.1186/1550-2783-6-6]

143 **Vorgerd M**, Grehl T, Jager M, Muller K, Freitag G, Patzold T, Bruns N, Fabian K, Tegenthoff M, Mortier W, Luttmann A, Zange J, Malin JP. Creatine therapy in myophosphorylase deficiency (McArdle disease): a placebo-controlled crossover trial. *Arch Neurol* 2000; **57**: 956-963 [PMID: 10891977]

144 **Hultman E**, Söderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in men. *J Appl Physiol (1985)* 1996; **81**: 232-237 [PMID: 8828669]

**P-Reviewer:** Kemal NAS, Turiel M **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Summary of the results from the meta-analysis by Nissen *et al***[37]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Supplement (*n* = studies)** | **Average dosage****(maintenance dose)** | **Duration****(wk)** | **Net lean mass change** | **Net strength change** |
| Cr (*n* = 18) | 19.4 g/d for 5.3 d (6.7 g/d) | 7.5 | +0.36%/wka | +1.09%/wka |
| HMB (*n* = 9) | 3 g/d | 8 | +0.28%/wka | +1.40%/wka |
| Chromium (*n* = 12) | 485 ug/d | 11.2 | +0.08%/wk | +0.25%/wk |
| Androstenedione (*n* = 3) | 200 mg/d | 10.7 | +0.05%/wk | -0.06%/wk |
| Protein (*n* = 4) | 1.15 g/kg per day | 6.3 | +0.12%/wk | -0.18%/wk |
| DHEA (*n* = 2) | 125 mg/d | 10 | +0.12%/wk | +0.06%/wk |

The net change is expressed as % change per week. Only Cr and HMB resulted in significant changes; a*P* < 0.005. Cr: Creatine; HMB: ß-hydroxy-ß-methylbutyrate; DHEA: Dehydroepiandrosterone.

**Table 2 Changes in creatine and phosphocreatine levels following Cr supplementation**

|  |  |  |
| --- | --- | --- |
|  | **Mean baseline Cr levels1** | **Increase after 20 g/day for 5 days** |
| Creatine | Approximately 125 mmol· kg/dw[130](90 to 160 mmol· kg/dw)[4]  | + 25 mmol· kg/dw (approximately 20%)[144]  |
| Phosphocreatine | Approximately 50 mmol· kg/dw[41] | + 8 mmol· kg/dw (approximately 15%) [132] |

1Typical values for an average 70 kg male.

**Table 3 Summary of studies investigating the effects of creatine supplementation on sarcopenia and function in older adults over 60 years**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment arm (mean age** ± **SD)** | **Supplementation period** | **Study design** | **Body composition changes** | **Physical function changes** | **Ref.** |
| 10 males(66.7 ± 1.9 yr) | 20 g/d for 10 d followed by 4 g/d for 20 d | *vs* PL group (dextrose) (*n* = 10) | 2Body density, 2LM, 2% BF | 1Leg fatigue performance | [99] |
| 9 males(65.0 ± 2.1 yr) | 20 g/d for 5 d | *vs* PL group (sucrose) (*n* = 8) | 1BM, 2LM | 2Strength | [100] |
| 10 females(67.0 ± 6.0 yr) | 0.3 g per kg/day for 7 d | *vs* PL group (*n* = 6) | No details | 1Objective function tests, 2Endurance capacity | [97] |
| 10 males(65.4 ± 1.5 yr) | 0.3 g per kg/day for 7 d | *vs* PL group (powdered cellulose) (*n* = 8) | 1BM, 1LM | 1Strength, 1Power, 1Objective function tests | [55] |
| 15 females (63.3 ± 1.2 yr) | 0.3 g per kg/day for 7 d | *vs* PL group (powdered cellulose) (*n* = 12) | 1BM, 1LM, 2%BF | 1Strength, 1Objective function tests | [98] |
| 7 males and 8 females(74.5 ± 6.4 yr) | 20 g/d for 7 d followed by 10 g/d for 7 d | Cross-over design | 2BM | 1Strength, 1Endurance (cycling capacity at fatigue threshold), 2Objective function tests | [101] |
| 7 males(72.5 ± 2.5 yr | 20 g/d for 5 d | *vs* PL group (maltodrextin) (*n* = 5) | 1BM, 2LM | 2MVC or contractile force | [102] |
| 4 males and 4 females(71.0 ± 1.9 yr) | 20 g/d for 5 d followed by 3 g/d for 8 wk | *vs* PL (glucose) (*n* = 8) | 2Lower limb volume, 2BM, 2%BF | 2Strength2Endurance | [103] |
| 15 females (66.1 ± 4.8 yr) | 20 g/d for 5 d followed by 5 g/d for 23 wk | *vs* PL (dextrose) (*n* = 15) | 1LM, 2FM | 1Strength1Objective function tests | [104] |

1Significant increase/improvement; 2No significant change (a*P* < 0.05 for interaction between placebo and Cr group). Cr: Creatine; PL: Placebo; BM: Body mass; %BF: Percent body fat; FM: Fat mass; LM: Lean mass; MVC: Maximal voluntary contraction; No details: No details are specified or this measure was not made.

**Table 4 Summary of clinical trials investigating the effects of creatine supplementation on body composition and physical function**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Condition** | **Treatment arm** | **Supplementation period** | **Control arm** | **Body composition changes** | **Physical function changes** | **Other effects** | **Ref.** |
| Osteoarthritis | *n* = 18  | 10 g/d pre surgery; 5 g/d for 30 d post-surgery | *vs* PL (*n* = 19)(dextrose) | 2%BF, 2FM, 3LM (CSA), 3BW | 3Strength | 3PCr | [106] |
| Fibromyalgia | *n* = 16 | 20 g/d for 5 d followed by 5 g/d for 16 wk | *vs* PL (*n* = 16)(dextrose) | Not measured | 1Strength | 3QoL scores, 3Pain, 3Cognition, 1PCr | [109] |
| Cancer (cachexia) | *n* = 16 (colorectal cancer) | 20 g/d for 5 d followed by 5 g/d for 8 wk | *vs* PL (*n* = 15)(cellulose) | 3LM | 1Strength | 3QoL scores | [118] |
| *n* = 9 (adolescents with leukaemia (acute lymphoblastic) | 2 sets of 8 wk (with a 6 wk wash out in-between) | *vs* control “natural history group” (*n* = 50) | 3LM, 2%BF | No details | 3Bone mineral content | [119] |
| Duchenne muscular dystrophy (DMD) | *n* = 18 (adolescents) | 5 g/d for 8 wk | *vs* PL (*n* = 15)(vitamin C) | No details | 1Strength | 1PCr | [113] |
| *n* = 15 (adolescents) | 5 g/d for 24 wk | *vs* PL (*n* = 16)(cocoa powder) | No details | 3Strength, 3Objective function tests |  | [116] |
| *n* = 30 adolescents | 0.10 g per kg/day for 16 wk | Cross-over design (PL group dextrose) | 1LM | 1Strength | 2Bone breakdown markers | [112] |
| *n* = 15 adolescents (12 with DMD and 3 with Becker dystrophy) | 3 g/d for 13 wk | Cross-over design (PL group maltodextrin) | No details | 1Strength (MVC), 1Fatigue resistance |  | [62] |
| Mytonic muscular dystrophy 1 (DM1) | *n* = 34 | 5 g/d for 36 wk | Cross-over design (PL group dextrose) | 3LM | 3Strength, 3Objective function tests |  | [115] |
| *n* = 34 | 10.6 g/d for 10 d followed by 5.3 g/d for 45 d | Cross-over design (PL group cellulose) | 3LM | 3Strength | 3ADL, 3QoL scores | [114] |
| Mytonic muscular dystrophy 2 (DM2) | *n* = 10 | 10 g/d for 13 wk | *vs* PL (*n* = 10) | No details | 3Strength | 3QoL scores | [117] |

1Significant increase/improvement; 2Significant decrease/reduction; 3No significant change (a*P* < 0.05 for interaction between placebo and Cr group). Cr: Creatine; PL: Placebo; CSA: Cross sectional area; ADL: Activities of daily living; PCr: Phosphocreatine; QoL: Quality of life; MVC: Maximal voluntary contraction; BM: Body mass; FM: Fat mass; LM: Lean mass; PRT = Progressive resistance training; No details: No details are specified or this measure was not made.