

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

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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.

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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.

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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- α (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- κ B; 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.*^[31] 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 (approximately 10%), increased adiposity (approximately 12%), and relatively poor physical function (approximately 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

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

Supplement (<i>n</i> = studies)	Average dosage (maintenance dose)	Duration (wk)	Net lean mass change	Net strength change
Cr (<i>n</i> = 18)	19.4 g/d for 5.3 d (6.7 g/d)	7.5	+0.36%/wk ^b	+1.09%/wk ^b
HMB (<i>n</i> = 9)	3 g/d	8	+0.28%/wk ^b	+1.40%/wk ^b
Chromium (<i>n</i> = 12)	485 µg/d	11.2	+0.08%/wk	+0.25%/wk
Androstenedione (<i>n</i> = 3)	200 mg/d	10.7	+0.05%/wk	-0.06%/wk
Protein (<i>n</i> = 4)	1.15 g/kg per day	6.3	+0.12%/wk	-0.18%/wk
DHEA (<i>n</i> = 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; ^b*P* < 0.005. Cr: Creatine; HMB: β-hydroxy-β-methylbutyrate; DHEA: Dehydroepiandrosterone.

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 β-hydroxy-β-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

Table 2 Changes in creatine and phosphocreatine levels following Cr supplementation

	Mean baseline Cr levels ¹	Increase after 20 g/d for 5 d
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. Cr: Creatine.

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-I produced locally in the muscle (mIGF-I) 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^[70–72] 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-1 β ^[22]. These cytokines, in addition to causing synovial inflam-

mation^[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-1 β , 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-1 β 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 Chilibeck *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 \times 60 m sprint intervals^[83], and highly trained football players improved their repeated sprint performance (6 m \times 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 effec-

tive 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 6 km 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 dupli-

cates, of which 21 met the inclusion criteria and were selected for this review. One trial 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 $\times 100$ ^[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

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

¹Significant increase/improvement; ²No significant change ($^aP < 0.05$ 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.

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 \times 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

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

¹Significant increase/improvement; ²Significant decrease/reduction; ³No significant change ([†]*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.

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 *et al.*^[111]). Seven 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 symptoms^[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 nine 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^[128] including muscle wasting disorders^[62,112,113], and cancer cachexia^[118]. Despite the inconclusive findings of the solitary RA study^[94], of the twelve clinical trials identified, six 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/dw following 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/dw increase 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 μm^2). 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 Walilman^[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.

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