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Can creatine supplementation improve body composition and objective physical function in rheumatoid arthritis patients? A randomized controlled trial

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Abstract

Objective: Muscle wasting ('rheumatoid cachexia') is evident in most rheumatoid arthritis (RA) patients, including those with well-controlled disease, and contributes substantially to the reductions in strength and physical function that are characteristic of this disease. The aim of this randomized controlled trial was to investigate the efficacy of oral creatine (Cr) supplementation on improving muscle mass, strength and function in stable RA patients.

Method: Forty RA patients were randomized to 12 weeks supplementation of Cr or placebo, in a double-blind fashion. Body composition (by whole-body dual-energy X-ray absorptiometry, DXA, and bioelectrical impedance spectroscopy, BIS), strength and objectively-assessed physical function measures were taken at baseline, week 12, and week 24 (i.e. after 12 weeks of treatment withdrawal). Data was analyzed by ANCOVA.

Results: Cr supplementation increased appendicular lean mass (ALM; a surrogate DXA measure of muscle mass) by (mean±SE) 0.52±0.13kg (*P*=0.004 vs placebo), and total LM by 0.60±0.37kg (*P*=0.158 vs placebo). The increment in LM by DXA corresponded with the elevation in intracellular water (ICW) estimated by BIS (0.64±0.22 L, *P*=0.035 vs placebo). However, the observed increases in ALM, total LM and ICW were not accompanied by improvements in isometric knee extensor strength (*P*=0.408), hand-grip strength (*P*=0.833), or objectively assessed function (30s sit-to-stand, 50' walk, 8' up-&-go, estimated VO2max; *P*'s=0.335-0.764)

Conclusion: Twelve weeks of Cr supplementation improved muscle mass, but not strength or objectively-measured physical function in RA patients. As no adverse treatment-related effects occurred, Cr supplementation appears to be a safe and acceptable adjunct treatment for attenuating muscle loss in RA patients. This treatment may be especially suitable for patients with severe rheumatoid cachexia.

KEYWORDS: rheumatoid cachexia, body composition, function, rheumatoid arthritis

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Supplement: Patients with RA usually experience substantial loss of lean mass (LM) (known as 'rheumatoid cachexia' (RC) (**1**). This loss of LM is a major contributor to the decreased strength and impaired physical function (**2,3**) that characterizes RA.

Unfortunately, current pharmacologic treatments for RA do not ameliorate this LM loss, nor fully restore physical function (**3**). Whilst exercise (specifically, progressive resistance training (PRT)) has been shown to be highly effective in restoring both LM and function in RA patients (**2**), the lack of adherence to sufficiently intense training means this form of therapy is unlikely to be widely adopted (**4**). Anabolic nutritional supplementation offers a potential adjunct treatment intervention for improving LM and function that should be widely acceptable. Indeed, our group (**5**) has previously demonstrated that daily oral protein supplementation for 12 weeks improved LM and some measures of objectively-assessed physical function in RA patients.

Creatine (Cr), a combination of essential amino acids, is a popular dietary supplement generally shown to have greater benefits on both LM and physical function than generic protein. To date, only one study (**6**) has investigated the efficacy of oral Cr supplementation in RA patients. In this uncontrolled trial, twelve patients underwent three weeks of supplementation, and although strength increased, body composition changes were not investigated.

To further investigate the efficacy of Cr supplementation in improving LM, strength and function in RA patients, we recruited 40 patients with stable RA disease (i.e. no change in medications in the preceding 3 months) from outpatient clinics. Participants were randomised to receive either supplementary Cr or

placebo drinks for 12 weeks, with the groups matched for age and sex. Both the principle researcher (TW) and participants were blinded to supplement assignment.

In accordance with manufacture recommendations, and previous strategies (e.g. **6,7**), the Cr group received 20 g of Cr monohydrate (4 x 5 g/day) for a 5-day 'loading phase' followed by 3 g/day for the remainder of the 12 week supplementation period ('maintenance dose'). The Cr was mixed with a mango-flavoured drink powder to improve taste. The placebo group received only the mango-flavoured drink powder. The appearance of the different treatment packets were indistinguishable, as were the flavouring and colouring of the drinks.

The flow of patients through the study is shown in **Figure 1**. Subjects' baseline demographics are presented in **Table 1**, and the effects of Cr supplementation on body composition in **Table 2**. Twelve weeks of Cr supplementation resulted in a significant increase in ALM of 0.52 (±0.13) kg in the Cr group, with no change in the placebo group (0.05 (±0.13) kg; between-group P = .004, effect size (η^2) = .23 (medium)). Similarly, total LM increased by 0.60 (±0.37) kg) following Cr supplementation, with no change in the placebo group over the same period (-0.06 (±0.29) kg), albeit the between-group change was not significant (P = .158, η^2 = .06 (small)). In the Cr group there was an increase in intra-cellular water (ICW) from baseline to week 12 (0.64 ±0.22 L, P = .035, η^2 = .13 (medium)).

After 12 weeks of cessation of Cr supplementation (week 24), there was a regression towards baseline for ALM and total LM, which further supports a Cr treatment effect. No changes in FM or body fat % were observed at any time point for either group.

In contrast to the effects on muscle mass, Cr supplementation had no effect on objectively-assessed physical function (**Table 3)**.

The magnitude of LM increase we observed is comparable to that seen previously in older men and women following Cr supplementation. The body composition changes are also similar to those we previously observed following 12 weeks of protein supplementation in RA patients (i.e. increases of 0.40 kg in ALM and 0.73 kg in total LM, whilst FM remained unchanged (**5**)). These results, together with the response to PRT (**2**), and the finding that muscle quality (i.e. maximal force exerted per unit muscle) is not impaired in RA patients (**8**), further emphasise that RA patients are not, as once believed (**9**), resistant to muscle anabolic stimuli.

Interestingly, at week 24, despite the losses due to withdrawal of Cr, ALM and total LM were still 0.40 kg and 0.21 kg, respectively, above baseline values, suggesting some longer term retention of muscle mass following Cr supplementation.

The lack of a Cr-induced improvement in either strength or function that we observed in this study contrasts with the 14% gain in composite strength reported by Willer et al. (**6**) following short-term Cr supplementation in RA patients. However, the reported effects of Cr supplementation on measures of

strength and function in older individuals are equivocal. Additionally, responsiveness to Cr supplementation is reported to vary, with only ~70–75% of individuals, irrespective of age, deemed to be 'responders' (**7**). Consistent with this estimation, 80% of our participants 'responded', when 'response' is defined by increased ALM (≥0.24 kg).

Although the lack of effects on strength and physical function are disappointing, the increase in LM we demonstrated suggests that Cr supplementation may be beneficial in patients with severe RC, since a marked loss of LM both impairs the body's ability to fight infection due to limited expendable protein reserve for immune cell production, and increases the risk of mortality. The lack of efficacy demonstrated on physical function in this study further emphasises that sustained PRT (**2**) should be performed by RA patients wishing to substantially increase LM, and, subsequently, restore their strength and physical functioning.

The importance of this study: In patients with RA, 12 weeks of oral Cr supplementation had beneficial effects on muscle mass, but not on strength or objectively-assessed physical function. Given compliance to Cr was high, and no adverse treatment-related effects were observed, Cr may offer an acceptable, safe, low-cost, and reasonably effective means for RA patients with severe RC to help restore muscle mass.

References

1. Summers G, Deighton C, Rennie M, Booth A. Rheumatoid cachexia: a clinical perspective. Rheumatology 2008; 47: 1124-31.

2. 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 Care Res 2009; 61: 1726-34.

3. Lemmey AB, Clayton R, Wilkinson T, Sheikh F, Ahmad Y, Whale J, Jones HSJ, Ahmad YA, Chitale S, Jones JG, Maddison PJ, O'Brien TD. Tight control of disease activity fails to improve body composition or physical function in rheumatoid arthritis patients. Rheumatology 2016; (in press) Advance Access June 10, 2016.

4. 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 2012; 64: 71-75.

5. Marcora S, Lemmey A, Maddison P. Dietary treatment of rheumatoid cachexia with β-hydroxy-β-methylbutyrate, glutamine and arginine: A randomised controlled trial. Clin Nutr 2005; 24: 442-54.

6. Willer B, Stucki G, Hoppeler H, Brühlmann P, Krähenbühl S. Effects of creatine supplementation on muscle weakness in patients with rheumatoid arthritis. Rheumatology 2000; 39: 293-98.

7. Greenhaff P, Bodin K, Soderlund K, Hultman E. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. Am J Physiol Endocrinol Metab 1994; 266: E725-E30.

8. Matschke V, Murphy P, Lemmey AB, Maddison PJ, Thom JM. Muscle quality, architecture, and activation in cachectic patients with rheumatoid arthritis. J Rheumatol 2010; 37: 282-84.

9. Rall LC, Meydani SN, Kehayias JJ, Dawson-Hughes B, Roubenoff R. The effect of progressive resistance training in rheumatoid arthritis. Increased strength without changes in energy balance or body composition. Arthritis Rheum 1996; 39: 415-26.

Table 1. Baseline demographics of rheumatoid arthritis patients who underwent 12 weeks of oral creatine or placebo supplementation

	Creatine (*n* = 15)	Placebo (*n* = 20)	*P*
Age (years)	63.0 (±10.0)	57.2 (±10.4)	.104
Sex (female) (%)	10 (67)	14 (70)	.833
Disease duration (months)	112.4 (±82.8)	141.4 (±160.1)	.493
Rheumatoid factor +, *n* (%)	8 (53)	13 (65)	.376
Height (cm)	165.1 (±7.9)	166.1 (±9.1)	.734
BM (kg)	67.31 (±10.29)	76.73 (±18.99)	.092[#]
BMI (kg/m^2)	24.7 (±3.6)	27.8 (±6.6)	.113
ALM (kg)	18.4 (±4.2)	20.6 (±5.7)	.227
Total LM (kg)	45.9 (±8.5)	50.1 (±12.4)	.274
Total FM (kg)	19.8 (±7.2)	24.9 (±10.5)	.113
DAS28	2.8 (±0.8)	2.6 (±0.9)	.608
Strength and physical function measures			
IKES (N)	348 (±156)	417 (±127)	.159
HGS (N)	236.6 (±92.8)	237.9 (±99.8)	.969
STS-30 (reps)	11.7 (±4.0)	13.2 (±2.9)	.206
8'UG (secs)	8.2 (±3.3)	6.6 (±1.7)	.119
50'W (secs)	11.0 (±4.0)	9.8 (±2.2)	.300
VO_2max (L/min)	1.8 (±0.4)	1.7 (±0.5)	.918
MDHAQ	0.5 (±0.5)	0.5 (±0.4)	.917

BM = body mass; BMI = body mass index; ALM = appendicular lean mass; FM = fat mass; DAS28 = disease activity score in 28 joints; NSAIDS = non-steroidal anti-inflammatory drugs; DMARDs = disease modifying anti-rheumatic drugs; IKES = isometric knee extensor strength; HGS = handgrip strength; STS-30 = sit-to- stand in 30 second test; 8'UG = 8-foot up and go; 50'W = 50-foot walk; VO_2max = estimated $V0_2$max from Siconolfi step test; MDHAQ = Multi-dimensional Health Assessment Questionnaire. [a] = current corticosteroid use, range 2.5–5.0 mg. Unless stated, data presented as mean (±SD). * *P* < .05; [#] *P* = .05–.10.

Table 2. Changes in body composition in rheumatoid arthritis patients following 12 weeks oral creatine supplementation and 12 weeks withdrawal from supplementation.

		Creatine (*n* = 15)	Placebo (*n* = 20)	Differences between-group for Δ		
		Mean	Mean	Mean (CI)	*P*	η^2
ALM (kg)	Δ B–12	+0.52 (±0.13)	+0.01 (±0.11)	**0.52 (0.18–0.86)**	**.004***	**.23**
	Δ B–24	+0.40 (±0.18)	+0.15 (±0.15)	0.25 (-0.23–0.73)	.293	.03
Total LM (kg)	Δ B–12	+0.60 (±0.37)	-0.06 (±0.29)	0.65 (-0.27–1.57)	.158	.06
	Δ B–24	+0.21 (±0.37)	+0.19 (±0.32)	0.01 (-0.99–1.01)	.977	.00
BM (kg)	Δ B–12	+1.10 (±0.58)	+0.11 (±0.46)	0.99 (-0.54–2.52)	.195	.06
	Δ B–24	+0.61 (±0.70)	+0.92 (±0.55)	-0.31 (-2.15–1.53)	.736	.00
Total FM (kg)	Δ B–12	+0.41 (±0.45)	+0.18 (±0.37)	0.23 (-0.94–1.40)	.693	.01
	Δ B–24	+0.65 (±0.52)	+0.48 (±0.45)	0.17 (-1.26–1.60)	.810	.00
Body fat (%)	Δ B–12	+0.1 (±0.4)	+0.5 (±0.3)	-0.3 (-1.4–0.8)	.595	.01
	Δ B–24	+0.3 (±0.5)	+0.6 (±0.4)	-0.3 (-1.6–1.0)	.608	.01
Water compartments						
TBW (L)	Δ B–12	+1.08 (±0.27)	-0.01 (±0.23)	**1.07 (0.34–1.8)**	**.005***	**.22**
	Δ B–24	+0.42 (±0.31)	-0.11 (±0.27)	0.53 (-0.32–1.37)	.213	.05

ICW (L)	Δ B–12	+0.64 (±0.22)	-0.01 (±0.19)	**0.65 (-0.05–1.24)**	**.035***	**.13**
	Δ B–24	+0.12 (±0.24)	-0.10 (±0.20)	0.22 (-0.41–0.85)	.481	.02
ECW (L)	Δ B–12	+0.44 (±0.11)	0.0 (±0.09)	**0.44 (-0.15–0.73)**	**.004***	**.23**
	Δ B–24	+0.36 (±0.12)	+0.03 (±0.11)	**0.36 (0.03–0.68)**	**.035***	**.13**

ALM = appendicular lean mass; BM = body mass (scales); FM = fat mass; TBW = total body water; ICW = intracellular water; ECW = extracellular water. Changes (Δ) between time points (B = baseline, 12 = week 12 (immediately post-supplementation); 24 = week 24 (12 weeks post-supplementation)) are presented as the adjusted mean (±SE) from ANCOVA. The between-group difference for each Δ is displayed with 95% confidence interval (CI) along and effect size, eta squared (η^2): small = .01; medium = .08; large = .26; very large = .50. * $P < .05$.

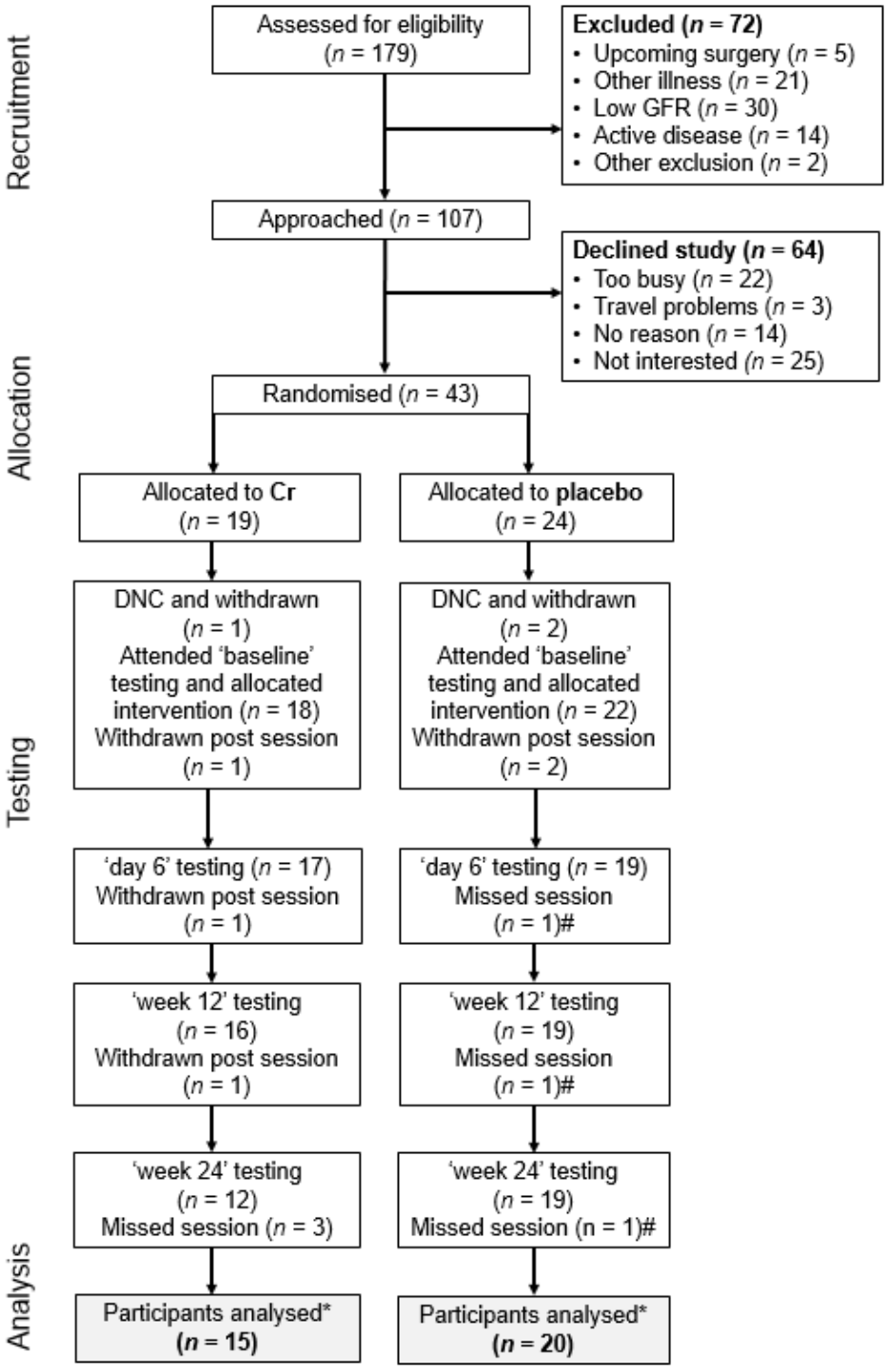
Table 3. Changes in strength and objective physical function measures in rheumatoid arthritis patients following 12 weeks oral creatine supplementation and 12 weeks withdrawal from supplementation.

		Creatine (*n* = 15)	Placebo (*n* = 20)	Differences between-group for Δ		
		Mean	Mean	Mean (CI)	*P*	η^2
Strength measures						
IKES (N)	Δ B–12	+26 (±12)	+13 (±10)	13 (-19–45)	.408	.02
	Δ B–24	+34.3 (±13.7)	+0.7 (±11.8)	33.6 (-3.6–70.9)	.075[#]	.10
HGS (N)	Δ B–12	+11.0 (±6.8)	+9.1 (±5.9)	1.9 (-16.3–20.1)	.833	.00
	Δ B–24	+9.5 (±6.0)	+9.2 (±5.2)	0.3 (-15.9–16.6)	.969	.00
Objective physical function measures						
STS-30 (reps)	Δ B–12	+2.0 (±0.7)	+1.8 (±0.5)	0.2 (-1.6–1.9)	.764	.02
	Δ B–24	+2.1 (±0.7)	+2.3 (±0.6)	-0.2 (-1.9–1.4)	.856	.01
8’UG (secs)	Δ B–12	-0.44 (±0.24)	-0.25 (±0.21)	-0.19 (-0.85–0.46)	.555	.01
	Δ B–24	-0.29 (±0.30)	-0.32 (±0.26)	0.03 (-0.80–0.86)	.943	.00
50’W (secs)	Δ B–12	-0.31 (±0.23)	-0.61 (±0.20)	0.30 (-0.32–0.91)	.335	.03
	Δ B–24	-0.23 (±0.25)	-0.40 (±0.22)	0.17 (-0.50–0.85)	.606	.08

VO_2max (L/min)	Δ B–12	0.0 (±0.0)	0.0 (±0.0)	0.0 (-0.1–0.1)	.762	.00
	Δ B–24	0.0 (±0.1)	+0.1 (±0.0)	-0.1 (-0.2–0.1)	.219	.06

IKES = isometric knee extensor strength; HGS = handgrip strength; STS-30 = sit-to- stand in 30 second test; 8'UG = 8-foot up and go; 50'W = 50-foot walk; VO_2max = estimated $V0_2$max from Siconolfi step test. Changes (Δ) between time points (B = baseline, 12 = week 12 (immediately post-supplementation); 24 = week 24 (12 weeks post-supplementation)) are presented as the adjusted mean (±SE) from ANCOVA. The between-group difference for each Δ is displayed with 95% confidence interval (CI) and effect size, eta squared (η^2): small = .01; medium = .08; large = .26; very large = .50. * $P < .05$; # $P = .05$–.10.

Figure 1. CONSORT diagram showing recruitment and path of patients through the study



GFR = (estimated) glomerular filtration rate; Cr = Creatine supplementation group; DNC = randomised but did not commence treatment (i.e. did not attend baseline and were subsequently withdrawn); * = due to missing data, final analysis for body composition data included values using Expectation-Maximization imputed data; # = missed sessions (placebo) at day 6, week 12 and week 24 were not the same participant.