TITLE:

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

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The authors declare no conflict of interest.

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ABSTRACT

Objective. Rheumatoid cachexia (muscle wasting) in rheumatoid arthritis (RA) patients contributes to substantial reductions in strength and impaired physical function. The objective of this randomised control trial was to investigate the effectiveness of oral creatine (Cr) supplementation in increasing lean mass and improving strength and physical function in RA patients.

Method. In a double-blind design, 40 RA patients, were randomised to either 12 weeks supplementation of Cr or placebo. Body composition (dual energy x-ray absorptiometry, DXA, and bioelectrical impedance spectroscopy, BIS), strength and objectively-assessed physical function were measured at: baseline, day 6, week 12 and week 24. Data analysis was performed by ANCOVA.

Results. Creatine supplementation increased appendicular lean mass (ALM; a surrogate measure of muscle mass) by 0.52 (± 0.13) kg (P = 0.004 versus placebo), and total LM by 0.60 (± 0.37) kg (P = 0.158). The change in LM concurred with the gain in intracellular water (0.64 ± 0.22 L, P = 0.035) measured by BIS. Despite increasing ALM, Cr supplementation, relative to placebo, failed to improve isometric knee extensor (P = 0.408), handgrip strength (P = 0.833), or objectively-assessed physical function (*P's* = 0.335 – 0.764).

Conclusion. In patients with RA, creatine supplementation increased muscle mass, but not strength or objective physical function. No treatment-related adverse effects were reported suggesting that Cr supplementation may offer a safe and acceptable adjunct treatment for attenuating muscle loss; this treatment may be beneficial for patients suffering from severe rheumatoid cachexia.

ABSTRACT WORD COUNT: 240/250

SIGNIFICANCE AND INNOVATIONS:

- Oral creatine supplementation improves lean mass, but not strength and objectively-assessed physical function, in patients with rheumatoid arthritis (RA).

- Oral creatine supplementation offers a safe, low-cost and acceptable means of increasing muscle mass in RA patients.

INTRODUCTION

Substantial loss of lean mass (LM), termed 'rheumatoid cachexia' (1), is common in patients with rheumatoid arthritis (RA) (2). This loss is a major contributor to the decreased strength (3) and impaired physical function (2, 4-6) which characterise this disease. Unfortunately, current drug treatments for RA, including use of biologics and the 'treat-to-target (T2T)' strategy (7), do not reverse this LM loss, nor fully restore physical function (8-10). Whilst high-intensity exercise (specifically, progressive resistance training (PRT)) has been shown to be highly effective in restoring both LM and function in RA patients (5, 11), the lack of uptake and adherence to sufficiently intense training (12) means this form of therapy is not widely adopted. Anabolic nutritional supplementation offers a potential adjunct treatment intervention for increasing LM, and thereby improving physical function, that could be widely accepted. Indeed, our group (13) has previously demonstrated that 12 weeks of daily oral protein supplementation improved LM and some measures of strength and 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 supplementation (14, 15). Oral Cr supplementation is able to enhance ATP re-synthesis by increasing initial stores of phosphocreatine (PCr) in the muscle, and thereby aid recovery during and after physical activity (16). Creatine supplementation also increases LM (14). Following Cr uptake, extracellular water (ECW) is absorbed by muscle via osmosis in order to restore intramuscular protein levels (16-18), and the resulting increase in mechanical stress caused by the expansion in intracellular water (ICW) has been proposed to act as an anabolic signal for protein synthesis (18-20).

Creatine has been shown to be effective in increasing LM and improving performance in a range of athletic (e.g., (21, 22) and clinical populations (23), including muscular dystrophy patients and the elderly who, like RA patients, present with reduced muscle mass and impaired physical function (for a review see 24). However, to date only one study (25) has investigated the efficacy of Cr supplementation in RA patients.

In this short uncontrolled trial, twelve patients underwent 3 weeks of supplementation, and although strength increased, no changes in subjective function or muscle Cr levels were found, and body composition changes were not investigated. Thus, the findings of the trial are inconclusive, although they do provide some indication that Cr supplementation may be efficacious in RA patients.

The current study aimed to investigate the effects of 12 weeks of oral Cr supplementation on body composition, strength and objectively-assessed physical function in patients with RA. We hypothesised that Cr supplementation would (1) increase LM and (2) improve strength and objective physical function.

PATIENTS AND METHODS

A 24-week, double-blind, randomised, placebo-controlled trial was conducted between April 2013 and August 2014 at the School of Sport, Health and Exercise Science, Bangor University, UK. Patients with stable RA (i.e. no change in medication in the preceding 3 months) were recruited from outpatient clinics at the Peter Maddison Rheumatology Centre, Llandudno, North Wales, UK. For inclusion, participants had to: (a) fulfil the American College of Rheumatology/European League Against Rheumatism 2010 revised criteria for the diagnosis of RA (26); (b) be aged ≥18 years; (c) not be cognitively impaired; (d) be free of other cachectic conditions preventing safe participation; (e) have an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2 (i.e. no evidence of renal impairment); (f) not be taking anabolic supplements; (g) not be currently participating in regular, high-intensity exercise; and (h) not be pregnant. Research was carried out in compliance with the Helsinki Declaration, approved by the North Wales Research Ethics Committee–West and registered as ISRCTN37558313.

Supplementation and randomisation protocol

Participants were randomised to receive a drink containing either supplementary Cr (treatment) or placebo for 12 weeks. Randomisation was independently performed using a secure online system by the North Wales Organisation for Randomised Trials in Health (NWORTH), a registered clinical trials unit. Groups were matched for sex and age (stratification variables: 18-44, 45-59, 60+ years), and both experimenter (TJW) and participants were blinded to supplement assignment until trial completion.

In accordance with manufacturer recommendations, and previous strategies (e.g. 25, 27), the Cr group received 20g of Cr monohydrate (myprotein.co.uk, UK) (4x5g/day) for the initial 5-days (‘loading dose’) followed by 3g/day for the remainder of the 12 week period (‘maintenance dose’). The Cr was mixed with a mango-flavoured drink powder (Foster Clarks Ltd, EU) to improve taste. The placebo group received only the flavoured drink powder. Both groups received their supplements in individually portioned packets, which they were instructed to dilute with water to produce a fruit-flavoured drink. The appearance of the

treatment and placebo packets, and the flavouring and colouring of the drink mixtures, were indistinguishable. Adherence was monitored through return of the empty packets. Participants were asked to maintain routine physical activity and dietary habits and notify the investigators of any substantial lifestyle changes.

Assessments and outcome measures

Participants were assessed at baseline (pre-supplementation), day 6 (post-loading phase), week 12 (immediately after cessation of supplementation), and week 24 (follow-up, 12 weeks after cessation of supplementation). For each assessment, participants presented fasted, and having refrained from strenuous exercise, caffeine and alcohol in the preceding 24 hours. Demographic and clinical information was collected by interview and review of medical records.

Anthropometric measures. Body mass (BM) was measured to the nearest 0.1 kg using digital floor scales (SECA 635, UK), and height to the nearest 0.5 cm using a wall-mounted stadiometer (Body Care, UK), in accordance with standard procedures (28).

Body composition. Total and regional lean, fat, and bone masses were estimated using a whole body fan-beam dual energy X-ray absorptiometry (DXA) scanner (Hologic, QDR Discovery 45615, software V12.4). Appendicular LM (ALM; i.e. the summed LM of the arms and legs) was used as a surrogate measure of total body muscle mass (5, 11, 13). Total body water (TBW), ICW and ECW were estimated using bioelectrical impedance spectroscopy (BIS; Hydra 4200, Xitron Technologies, USA). The impedance measurements were taken in accordance with the manufacturer's wrist-to-ankle protocol.

Strength and objective physical function

Strength. Isometric maximal voluntary knee extensor strength (IKES) was measured using an isokinetic dynamometer (Humac Cybex Norm 2004, Computer Sports Medicine Inc, USA). Participants were seated

on the dynamometer chair, the hip and knee flexed to 90° and the dynamometer arm attached to the lower leg just above the malleolus, with the axis of rotation aligned with the lateral condyle of the femur. After a submaximal warm-up, participants were asked to exert maximum force (Newtons (N)) for ~3 seconds. Both the right and left leg were tested three times each, with a minutes rest between trials, and the average of the best score for each leg was used for statistical analysis. Maximal voluntary handgrip strength (HGS) was measured using a Grip-A dynamometer (Takei Kiki Kogyo, Japan). For this test, participants squeezed the dynamometer maximally whilst simultaneously adducting the arm. After a practice trial, each hand was tested three times, with a minutes rest between trials, with the overall best score (N), from either hand, recorded.

Physical function. Three objective physical function tests, specifically developed for assessing the capacity of older adults to perform activities of daily living (29) were performed: i) the 'sit-to-stand in 30 second' test (STS-30), which measures lower-body strength and balance, involves participants rising from a seated position on a fixed straight-back chair (seat height 43.2 cm / 17 inches) as many times as possible in 30 seconds while keeping their arms folded across their chest. The number of full repetitions completed was recorded; ii) the '8-foot up and go test' (8'UG) which assesses agility, speed and dynamic balance, requires participants to rise from the same seated position as for the STS-30 and walk forward around a cone 8 feet (2.44 m) away and return to a seated position as quickly as possible. For this test, the best time (out of two trials) was recorded; and iii) the '50-foot walk test' (50'W) records the time taken in seconds to walk 50' in a straight line as quickly as possible. For all tests, participants had one practice before performing the test maximally. All of these tests are routinely administered by our group (5, 7, 11-13, 30).

Aerobic capacity. The submaximal 'Siconolfi' step test (31) was used to estimate aerobic capacity (VO_2max). Whilst wearing a heart rate monitor (Polar Electro, UK) participants stepped up and down a 10 inch step for 3 x 3 minute stages or until the target heart rate (65% of predicted maximum heart rate (220–age)) was achieved. Step rate, which was maintained using a digital metronome (Metronome 3.0, ONYX),

was increased at every stage i.e. stage 1: 17 steps per minute (SPM), and if required, stage 2: 26 SPM and stage 3: 34 SPM. A predicted VO_2max was calculated using developed equations (31).

Clinical measures. Disease activity was assessed by the Disease Activity Score in 28 joints (DAS28), and systemic inflammation by C-reactive protein (CRP). Physical disability was subjectively assessed by the Multidimensional Health Assessment Questionnaire (MDHAQ) (32) To determine subject eligibility, and examine the effect on renal function, estimated glomerular filtration rate (eGFR) was monitored at baseline and then periodically over the course of the treatment period from patients' regular blood screenings.

Statistical analysis

An a-priori power calculation indicated that a minimum sample of 12 per group was required (based on a significant increase in muscle strength index (MSI) following Cr supplementation in RA patients: mean Δ = 7.4 MSI units (%), standard deviation (SD) Δ = 9.8, effect size (ES) = 0.8, $P = 0.05$, power = 0.80 (25)). To allow for dropouts we aimed to recruit 20 patients per group. The primary outcome measure was ALM (i.e. muscle mass). Differences between groups for outcome variables at each assessment point were tested by analysis of variance (ANCOVA), with baseline values controlled as a co-variant. Confidence intervals (CI) (95%) and ES (eta squared, η^2: small ≥ 0.01; medium ≥ 0.08; large ≥ 0.26; very large ≥ 0.50) were calculated, and Pearson product–moment correlation assessed relationships (r) of interest. Chi-squared tests were used for comparison of dichotomous variables. Unless otherwise stated, data is presented as mean (± standard error (SE)), with significance set at $P < 0.05$ and a trend as $P < 0.10$.

Where appropriate, the expectation-maximization algorithm (EM) was used to impute missing DXA (8% of data points missing; 12/140), IKES (6%; 9/140), HGS (5%; 7/140), STS-30 (5%; 7/140), 8'UG (5%; 7/140), 50'W (7%; 10/140)) values and restore sample size. Expectation-maximization is based on two iterating (50 iterations were used) steps – expectation and maximization – which generate means and variances for missing data based on known values for that variable. Little's MCAR test and Separate

Variance t-tests confirmed the suitability of using EM on our dataset. Statistical guidance was provided by NWORTH, and data was analysed using SPSS 20 software.

RESULTS

Baseline demographics

Forty patients were randomised and commenced treatment with either Cr (n = 18) or placebo (n = 22). The flow of patients through the study is shown in **Figure 1**. For patients who completed the trial (Cr: n = 15; placebo: n = 20), there were no statistically significant differences in demographic, disease, treatment, body composition, strength or objective physical function variables between the groups at baseline, although the placebo group were somewhat larger (BM, LM and FM) and consequently tended to be stronger (**Table 1**).

Treatment safety and compliance

Five patients withdrew from the trial. In the Cr group, one female (64 years) withdrew complaining of lethargy and aching muscles [this was not considered treatment related, and was attributed to fatigue following function testing due to poor physical fitness, obesity, being a smoker, and having moderate disease activity], and a female and a male were both withdrawn due to disease flare. In the placebo group, one male suffered from a reoccurrence of angina (prior history), and one female was withdrawn due to disease flare.

Over the 12 week treatment period, no changes in DAS28 were observed in either group (Cr = -0.1 ± 0.2; placebo = -0.1 ± 0.2; between-group difference: 0.0 (95% CI: -0.6-0.6), P = 0.990, η^2 = 0.00)). No treatment-related adverse side effects were reported in the Cr group, and all patients' eGFR remained ≥ 60 mL/min/1.73m^2. The supplementary drinks were well received, with no differences in compliance (P = 0.896; mean consumption of 99% of provided supplement consumed, range 87-100%; and mean 99%, range 80-100%, for Cr and placebo, respectively). All participants declared no substantial changes in diet, medication and lifestyle during the study.

231 **Treatment effectiveness**

232 *Body composition.* The effects of Cr supplementation on body composition are presented in **Table 2**.
233 Twelve weeks of Cr supplementation resulted in a significant increase in ALM of 0.52 (± 0.13) kg in the
234 Cr group, with no change in the placebo group (0.05 (± 0.13) kg; between-group $P = 0.004$, $\eta^2 = 0.23$
235 (medium)). Similarly, total LM increased by 0.60 (± 0.37) kg) following Cr supplementation, with no
236 change in the placebo group over the same period (-0.06 (± 0.29) kg), albeit the between-group change was
237 not significant ($P = 0.158$, $\eta^2 = 0.06$ (small)). The increase in LM accounted for most of the 1.10 (± 0.58)
238 kg BM gain observed in these patients from baseline to week 12 ($P = 0.195$, $\eta^2 = 0.06$ (small)). In the Cr
239 group there was an increase in ICW from baseline to week 12 (0.64 ± 0.22 L, $P = 0.035$, $\eta^2 = 0.13$ (medium))
240 and this change was weakly correlated with the ALM increase ($r = 0.481$, $P = 0.082$).
241
242 At week 24, the increases from baseline values for ALM ($P = 0.293$, $\eta^2 = 0.03$ (small)) and total LM ($P =$
243 0.977, $\eta^2 = 0.00$) were comparable for both groups. This indicates a regression back to baseline for ALM
244 and total LM in the Cr group following supplementation cessation and further supports a treatment effect.
245 From weeks 12 to 24, the decline in ALM in the Cr group corresponded with reductions in water
246 compartments (TBW ($r = 0.801$, $P = 0.001$) and, more pertinently, ICW ($r = 0.711$, $P = 0.004$). No changes
247 in total FM or body fat % were observed at any time point, and, similarly, no significant changes in any
248 aspect of body composition were detected at day 6, for either group.
249
250 *Strength and physical function.* The effects of Cr supplementation on strength and objective physical
251 function measures are displayed in **Table 3**. There was no change in IKES over the 12 week treatment
252 period with the increase over time between the groups comparable ($P = 0.408$, $\eta^2 = 0.02$ (small)). Following
253 12 weeks cessation of Cr supplementation, IKES was seemingly increased in the Cr group, as evidenced
254 by a 34.3 (± 13.7) N increase from baseline to week 24 ($P = 0.075$, $\eta^2 = 0.10$ (medium)) relative to the
255 placebo group. However, this trend was the result of one participant who improved by 143.0 N from
256 baseline to week 24. Removing this individual resulted in the loss of this trend (adjusted means, baseline

to week 24 change: Cr = 24.8 (± 13.6) N, placebo = 1.9 (± 11.3) N, between-group difference: 22.9 (95% CI: -14.0-59.7) P = .215, η^2 = 0.05 (small)). Similarly, there were no differences between the two groups in changes in HGS from baseline to week 12 (P = 0.833, η^2 = 0.00), or to week 24 (P = .969, η^2 = 0.00).

Consistent with the lack of effect on strength measures, there were no meaningful changes in any of the objective physical function measures, as both groups improved their STS-30, 8'UG and 50'W test performances comparably (between-group *P's* = 0.764, 0.555 and 0.335, respectively, for baseline to week 12 between-group changes). Creatine supplementation also had no effect on estimated VO_2max (L/min) (between-group P = 0.762, η^2 = 0.00), or self-reported physical disability (MDHAQ) (Cr = -0.1 ± 0.1, placebo = -0.1 ± 0.1; between-group difference, 0.0 (95% CI: -0.3-0.4), P = 0.836, η^2 = 0.06 (small)) over the 12 week supplementation period.

DISCUSSION

Our results indicate that Cr supplementation improves body composition, specifically muscle mass, but not strength or objective physical function in patients with RA. In the current study, ALM, by 0.52 kg, and total LM, by 0.60 kg, increased following 12 weeks Cr supplementation. Whilst there was a small and non-significant increase in FM as a consequence of Cr supplementation (0.41 ± 0.45 kg), the greater gain in ALM meant that proportional muscle mass (ALM/BM%) was not diminished (27.4% to 27.7%, respectively) from baseline to week 12. The addition of LM observed in the Cr group cannot be attributed to increased calorie intake. Twelve weeks of Cr supplementation resulted in an additional calorie intake of approximately 1348kcal (based on ~4kcal/g protein). Given that 1 kg FM ≈ 7700 kcal, this overnutrition would equate to a FM gain of ~0.18kg. The difference observed in FM gain between the Cr and placebo groups was 0.23g, therefore whilst the additional calories account for the majority of the difference in FM gain, they do not account for the difference in LM (a 0.60kg increase in the Cr group).

The magnitude of LM increase we observed is comparable to that seen previously in older men (33), older women (34, 35), and patients with muscle dystrophy (36) 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 (13)). These results, together with the response to PRT (5, 11), and the finding that muscle quality (i.e. maximal force exerted per unit muscle) is not impaired in RA patients (30), further emphasise that RA patients are not, as previously believed (37), resistant to muscle anabolic stimuli.

The changes in ALM following 12 weeks Cr supplementation were reflected in changes in body water, specifically a significant 1.08 L increase in TBW due to expansion of both ICW (0.64 L), and ECW (0.44 L) during this period. Similar changes in body water were observed in younger adults following Cr supplementation (17, 18, 20). The mechanisms by which Cr supplementation increases TBW and shifts fluid into the intracellular space are unclear (17). However, it is has been suggested that as skeletal muscle

296 cell Cr and PCr concentrations rise, ECW is drawn into the cell by osmosis to maintain intracellular protein
297 concentration (17, 18, 38). The uptake of Cr into the muscle following supplementation (16), and
298 subsequent increases in mechanical stress caused by the rise in ICW have been postulated to stimulate
299 protein synthesis (19), although it is unclear if Cr augments muscle protein by this mechanism (18). In our
300 trial, at week 24 (i.e. 12 weeks after Cr supplementation ceased), ICW returned towards its baseline level
301 and, over the same 'washout' period, 0.12 kg ALM and 0.38 kg total LM were lost. These reversions to, or
302 toward, baseline over the 12 week withdrawal period, provide further evidence that the changes seen at
303 week 12 are due to Cr supplementation. Interestingly, at week 24, despite the losses due to withdrawal of
304 Cr, ALM and total LM were still 0.40 kg and 0.21 kg, respectively, above baseline values, suggesting some
305 longer term retention of body composition changes following Cr supplementation.
306
307 The lack of a Cr-induced improvement in either strength or function that we observed in this study contrasts
308 with the 14% gain in composite strength reported by Willer et al (25) following short-term Cr
309 supplementation in RA patients. Similarly, improvements in both strength (IKES and HGS) and objective
310 physical function measures, such as the 5-repetition STS and 6m tandem walk test, following Cr
311 supplementation have been observed in older adults (24, 33-35, 39, 40), as well as other clinical groups
312 such as patients with fibromyalgia (41) and muscle dystophy (36). However, the effects of Cr
313 supplementation on measures of strength and function are equivocal. Creatine supplementation had no
314 effect on HGS, IKES, timed 30ft walk (30'W) and a timed four step climb test (SCT) in osteoarthritic
315 patients following surgery (44), whilst in patients with muscular dystrophy, supplementation with Cr failed
316 to improve HGS or IKES (42-44), or function: SCT, 30'W and time taken to stand from supine (36, 44,
317 45). Furthermore, despite eliciting an increase in LM, no improvement in ankle dorsiflexion strength was
318 reported by Sakkas et al (46) in 20 HIV–positive men following 2 weeks of Cr supplementation.
319 Additionally, several studies in older adults (24, 47-49) found no benefit of Cr supplementation on either
320 strength or function.
321

Since both groups in our trial had comparable improvements in the function tests, it suggests that, despite prior practice, performance was enhanced by a learning effect. In keeping with the literature, Cr supplementation in our investigation had no effect on aerobic capacity (21, 22, 41).

Responsiveness to Cr supplementation is reported to vary with only ~70-75% of individuals, irrespective of age, deemed to be 'responders' (16, 50). The main determinant of 'responsiveness' is thought to be initial muscle Cr concentrations, as when this is high (~150 mmol·kg^{-1}dw) supplementation does not appear to augment muscle Cr. (50). Consistent with this estimation, strength increases were noted in 67% of RA patients in the Willer et al study, and in our study, 80% of participants 'responded', when 'response' is defined by increased ALM ($\geq$ 0.24 kg).

In the current study, oral Cr supplementation was well tolerated, with high compliance and no adverse side effects. Additionally, supplementation had no effects on RA disease activity or renal function (eGFR), thus providing further evidence that supplementing with Cr is safe (18, 25, 33). 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 rheumatoid cachexia, 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 (2). The lack of efficacy demonstrated on physical function in this study further emphasises that sustained PRT (5, 11, 12) should be performed by RA patients wishing to substantially increase LM, and, subsequently, restore their strength and physical functioning.

CONCLUSION

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 rheumatoid cachexia to help restore muscle mass. However, for patients

wishing to improve their muscle mass *and* their strength and physical function, PRT should be performed as an adjunct therapy option.

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

	Creatine (n = 15)	Placebo (n = 20)	*P*
Age (years)	63.0 (± 10.0)	57.2 (± 10.4)	0.104
Sex (female) (%)	10 (67)	14 (70)	0.833
Disease duration (months)	112.4 (± 82.8)	141.4 (± 160.1)	0.493
Rheumatoid factor +, *n* (%)	8 (53)	13 (65)	0.376
Height (cm)	165.1 (± 7.9)	166.1 (± 9.1)	0.734
BM (kg)	67.31 (± 10.29)	76.73 (± 18.99)	0.092[#]
BMI (kg/m^2)	24.7 (± 3.6)	27.8 (± 6.6)	0.113
ALM (kg)	18.4 (± 4.2)	20.6 (± 5.7)	0.227
Total LM (kg)	45.9 (± 8.5)	50.1 (± 12.4)	0.274
Total FM (kg)	19.8 (± 7.2)	24.9 (± 10.5)	0.113
DAS28	2.8 (± 0.8)	2.6 (± 0.9)	0.608
Medications, n (%)			
NSAIDS	4 (27)	10 (50)	0.163
Methotrexate	9 (60)	12 (60)	1.000
Other DMARDS	6 (40)	7 (35)	0.889
Biologics	1 (7)	4 (20)	0.617
Current corticosteroids [a]	2 (13)	2 (10)	0.759
Strength and physical function measures			
IKES (N)	348.3 (± 156.3)	417.3 (± 126.9)	0.159
HGS (N)	236.6 (± 92.8)	237.9 (± 99.8)	0.969
STS-30 (reps)	11.7 (± 4.0)	13.2 (± 2.9)	0.206
8’UG (secs)	8.2 (± 3.3)	6.6 (± 1.7)	0.119

50'W (secs)	11.0 (± 4.0)	9.8 (± 2.2)	0.300
VO_2max (L/min)	1.8 (± 0.4)	1.7 (± 0.5)	0.918
MDHAQ	0.5 (± 0.5)	0.5 (± 0.4)	0.917

528 BM = body mass; BMI = body mass index; ALM = appendicular lean mass; FM = fat mass; DAS28 =
529 disease activity score in 28 joints; NSAIDS = non-steroidal anti-inflammatory drugs; DMARDS = disease
530 modifying anti-rheumatic drugs; IKES = isometric knee extensor strength; HGS = handgrip strength; STS-
531 30 = sit-to- stand in 30 second test; 8'UG = 8-foot up and go; 50'W = 50-foot walk; VO_2max = estimated
532 $V0_2$max from Siconolfi step test; MDHAQ = health assessment questionnaire. [a] = current corticosteroid
533 use, range 2.5–5.0 mg. Unless stated, data presented as mean (± SD). * = $P < 0.05$; [#] = $P < 0.10$.

534

535 **Table 2. Changes in body composition in rheumatoid arthritis patients following 12 weeks oral**
536 **creatine supplementation**

		Creatine (n = 15)	Placebo (n = 20)	Differences between-group for Δ		
		Mean (± SE)	Mean (± SE)	Mean (CI)	*P*	η^2
ALM (kg)	Δ B–12	0.52 (± 0.13)	0.01 (± 0.11)	0.52 (0.18-0.86)	0.004*	0.23
	Δ B–24	0.40 (± 0.18)	0.15 (± 0.15)	0.25 (-0.23-0.73)	0.293	0.03
Total LM (kg)	Δ B–12	0.60 (± 0.37)	-0.06 (± 0.29)	0.65 (-0.27-1.57)	0.158	0.06
	Δ B–24	0.21 (± 0.37)	0.19 (± 0.32)	0.01 (-0.99-1.01)	0.977	0.00
BM (kg)	Δ B–12	1.10 (± 0.58)	0.11 (± 0.46)	0.99 (-0.54-2.52)	0.195	0.06
	Δ B–24	0.61 (± 0.70)	0.92 (± 0.55)	-0.31 (-2.15-1.53)	0.736	0.00
Total FM (kg)	Δ B–12	0.41 (± 0.45)	0.18 (± 0.37)	0.23 (-0.94-1.40)	0.693	0.01
	Δ B–24	0.65 (± 0.52)	0.48 (± 0.45)	0.17 (-1.26-1.60)	0.810	0.00
Body fat (%)	Δ B–12	0.1 (± 0.4)	0.5 (± 0.3)	-0.3 (-1.4-0.8)	0.595	0.01
	Δ B–24	0.3 (± 0.5)	0.6 (± 0.4)	-0.3 (-1.6-1.0)	0.608	0.01
TBW (L)	Δ B–12	1.08 (± 0.27)	-0.01 (± 0.23)	1.07 (0.34-1.8)	0.005*	0.22
	Δ B–24	0.42 (± 0.31)	-0.11 (± 0.27)	0.53 (-0.32-1.37)	0.213	0.05
ICW (L)	Δ B–12	0.64 (± 0.22)	-0.01 (± 0.19)	0.65 (-0.05-1.24)	0.035*	0.13
	Δ B–24	0.12 (± 0.24)	-0.10 (± 0.20)	0.22 (-0.41-0.85)	0.481	0.02
ECW (L)	Δ B–12	0.44 (± 0.11)	0.0 (± 0.09)	0.44 (-0.15-0.73)	0.004*	0.23
	Δ B–24	0.36 (± 0.12)	0.03 (± 0.11)	0.36 (0.03-0.68)	0.035*	0.13

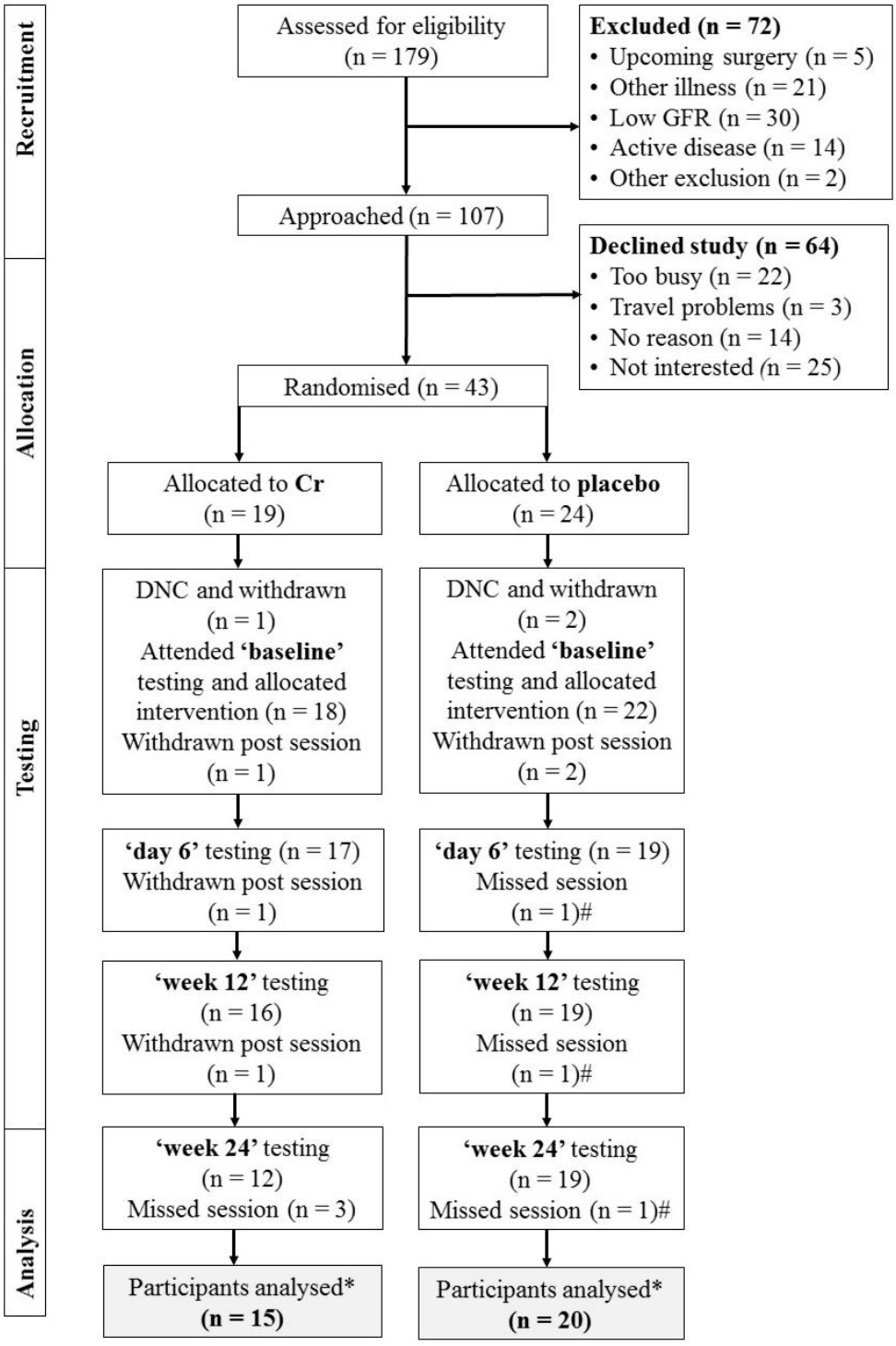
537 ALM = appendicular lean mass; BM = body mass (scales); FM = fat mass; TBW = total body water; ICW
538 = intracellular water; ECW = extracellular water. Changes (Δ) between time points (B = baseline, 12 =
539 week 12 (immediately post-supplementation); 24 = week 24 (12 weeks post-supplementation)) are
540 presented as the adjusted mean (± SE) from ANCOVA. The between-group difference for each Δ is
541 displayed with 95% confidence interval (CI) along and effect size, eta squared (η^2): small = 0.01; medium
542 = 0.08; large = 0.26; very large = 0.50. * = $P < 0.05$; # = $P < 0.10$.

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

		Creatine (n = 15)	Placebo (n = 20)	Differences between-group for Δ		
		Mean (± SE)	Mean (± SE)	Mean (CI)	*P*	η^2
IKES (N)	Δ B–12	25.8 (± 11.6)	12.8 (± 10.0)	13.0 (-18.6-44.6)	0.408	0.02
	Δ B–24	34.3 (± 13.7)	0.7 (± 11.8)	33.6 (-3.6-70.9)	0.075#	0.10
HGS (N)	Δ B–12	11.0 (± 6.8)	9.1 (± 5.9)	1.9 (-16.3-20.1)	0.833	0.00
	Δ B–24	9.5 (± 6.0)	9.2 (± 5.2)	0.3 (-15.9-16.6)	0.969	0.00
STS-30 (reps)	Δ B–12	2.0 (± 0.7)	1.8 (± 0.5)	0.2 (-1.6-1.9)	0.764	0.02
	Δ B–24	2.1 (± 0.7)	2.3 (± 0.6)	-0.2 (-1.9-1.4)	0.856	0.01
8'UG (secs)	Δ B–12	-0.44 (± 0.24)	-0.25 (± 0.21)	-0.19 (-0.85-0.46)	0.555	0.01
	Δ B–24	-0.29 (± 0.30)	-0.32 (± 0.26)	0.03 (-0.80-0.86)	0.943	0.00
50'W (secs)	Δ B–12	-0.31 (± 0.23)	-0.61 (± 0.20)	0.30 (-0.32-0.91)	0.335	0.03
	Δ B–24	-0.23 (± 0.25)	-0.40 (± 0.22)	0.17 (-0.50-0.85)	0.606	0.08
VO_2max (L/min)	Δ B–12	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (-0.1–0.1)	0.762	0.00
	Δ B–24	0.0 (± 0.1)	0.1 (± 0.0)	-0.1 (-0.2-0.1)	0.219	0.06

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 = 0.01; medium = 0.08; large = 0.26; very large = 0.50. * = $P < 0.05$; # = $P < 0.10$.

552 **Figure 1. Consort diagram showing recruitment and path of patients through the study**



553

554 Cr = Creatine supplementation group; DNC = randomised but did not commence treatment (i.e. did not
555 attend baseline and were subsequently withdrawn); * = due to missing data, final analysis for body
556 composition and physical function data included values using expectation-maximization imputed data; # =
557 missed sessions (placebo) at day 6, week 12 and week 24 were not the same participant.

558