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ORIGINAL ARTICLE

Creatine Supplements in Patients With Idiopathic Inflammatory Myopathies Who Are Clinically Weak After Conventional Pharmacologic Treatment: Six-Month, Double-Blind, Randomized, Placebo-Controlled Trial

YUEN-LI CHUNG,[1] HELENE ALEXANDERSON,[2] NICOLÓ PIPITONE,[3] CATHERINE MORRISON,[3] MARYAM DASTMALCHI,[4] CHRISTINA STÅHL-HALLENGREN,[5] SELWYN RICHARDS,[3] E. LOUISE THOMAS,[6] GAVIN HAMILTON,[6] JIMMY D. BELL,[6] INGRID E. LUNDBERG,[5] AND DAVID L. SCOTT[3]

Objective. **To test the hypothesis that oral creatine supplements with exercise are more effective than exercise alone in improving muscle function in patients with established dermatomyositis or polymyositis receiving chronic medical therapies who are clinically weak yet stable.**

Methods. **In a 6-month, 2-center, double-blind, randomized controlled trial, patients were randomized to receive oral creatine supplements (8 days, 20 gm/day then 3 gm/day) or placebo. All patients followed a home exercise program. The primary outcome was aggregate functional performance time (AFPT), reflecting the ability to undertake high-intensity exercise. Secondary outcomes included a functional index measuring endurance and muscle bioenergetics on ^{31}P magnetic resonance spectroscopy (^{31}P MRS). Patients were receiving stable immunosuppressive treatment and/or corticosteroids.**

Results. **A total of 37 patients with polymyositis or dermatomyositis were randomized (19 to creatine, 18 to placebo); 29 completed 6 months. Intent-to-treat analyses demonstrated that AFPT improved significantly at 6 months with creatine (median decrease 13%, range –32–8%) compared with placebo (median decrease 3%, range –13–16%; $P = 0.029$ by Mann-Whitney U test). A completer analysis also showed significant benefits from creatine ($P = 0.014$). The functional index improved significantly with both creatine and placebo ($P < 0.05$ by paired Wilcoxon's rank sum test), with a significant benefit between groups in the completer analysis only. Phosphocreatine/β-nucleoside triphosphate ratios using MRS increased significantly in the creatine group ($P < 0.05$) but not in the control group. No clinically relevant adverse events were associated with creatine.**

Conclusion. **Oral creatine supplements combined with home exercises improve functional performance without significant adverse effects in patients with polymyositis or dermatomyositis. They appear safe, effective, and inexpensive.**

KEY WORDS. Dermatomyositis; Polymyositis; Creatine supplementation; Exercise; Muscle function; ^{31}P magnetic resonance spectroscopy.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs), including dermatomyositis and polymyositis, often result in continuing muscle weakness and disability despite optimal conventional treatment with corticosteroids and other immunosuppressives (1). The explanation is unclear, but an acquired metabolic disturbance is suggested from studies of

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[1]Yuen-Li Chung, PhD (current address: Cancer Research UK Biomedical Magnetic Resonance Research Group, St George's University of London, UK): King's College London School of Medicine, and the MRC Clinical Science Centre, Hammersmith Hospital, Imperial College School of Medicine, London, UK; [2]Helene Alexanderson, PhD: Karolinska University Hospital, Stockholm, Sweden: [3]Nicoló Pipitone, MD, Catherine Morrison, BSc, Selwyn Richards, MRCP, David L. Scott, MD: King's College London School of Medicine, London, UK; [4]Maryam Dastmalchi, MD: Malmo University Hospital, Malmo, Sweden; [5]Christina Ståhl-Hallengren, MD, Ingrid E. Lundberg, MD, PhD: Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden; [6]E. Louise Thomas, PhD, Gavin Hamilton, PhD, Jimmy D. Bell, PhD: MRC Clinical Science Centre, Hammersmith Hospital, Imperial College School of Medicine, London, UK.

Address correspondence to Yuen-Li Chung, PhD, Cancer Research UK Biomedical Magnetic Resonance Research Group, Department of Basic Medical Sciences, St George's University of London, Cranmer Terrace, London SW17 0RE, UK. E-mail: ychung@sgul.ac.uk.

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muscle bioenergetics in which low levels of phosphocreatine (PCr) and nucleotide triphosphates were recorded by ^{31}P magnetic resonance spectroscopy (^{31}P MRS) (2). In stable treated patients with IIM exercise is safe and improves function and aerobic fitness (3) and muscle strength (4–6). Oral creatine supplements are generally considered to improve athletic and sporting performance (7). Because high levels of urinary creatine are characteristic of IIM (8,9) most likely reflecting dysfunctional muscle metabolism, patients with IIM may be particularly likely to benefit from oral creatine supplements. A crucial question is whether patients with established treated IIM who have persisting weakness show additional benefits when an exercise regimen is combined with oral creatine supplements. We therefore evaluated the efficacy of oral creatine supplements in patients with IIM while they were following an exercise regimen.

The research protocol was performed in 2 stages. First, a pilot study was undertaken to provide sufficient evidence that creatine supplements were beneficial to justify a randomized trial. Second, a randomized placebo-controlled trial was undertaken to test the hypothesis that oral creatine supplements with exercise improve function in patients with IIM who are clinically weak after receiving conventional pharmacologic treatment. We assessed changes in muscle PCr levels in vivo using ^{31}P MRS in both studies to ensure there was a physiologic basis to improvements in function with creatine supplementation.

PATIENTS AND METHODS

Trial design. A 6-month, randomized, placebo-controlled trial compared oral creatine supplements plus exercise with exercise alone in patients with IIM. Patients were assessed at screening, trial entry, 3 months, and 6 months by a physician and a physical therapist or trained nurse at each site. Local research ethics committees approved the study.

Patients. The study was undertaken in rheumatology clinics in the UK (King's College Hospital, London) and Sweden (Karolinska University Hospital, Stockholm, and Malmo University Hospital, Malmo). Many patients were recruited as consecutive cases in our clinics who met the trial entry criteria after screening. Some patients were referred specifically to be considered for the trial. ^{31}P MRS was performed at Imperial College London. All patients gave informed consent to enter the trial.

Inclusion criteria were as follows: 1) men and women ages >18 years; 2) diagnosis of polymyositis or dermatomyositis using the clinical, biochemical, histopathologic, and electrophysiology criteria of Bohan and Peter (10) with disease durations >6 months and neither clinical nor histologic evidence of inclusion body myositis (11); 3) quadriceps muscle strength at least 20% below predicted values based on the judgment of the assessing clinician in the context of current knowledge of normal quadriceps function and changes with age (12–15); 4) sufficient mobility to participate in the study; 5) previous therapy with systemic steroids for at least 6 months with current oral prednisolone stable for 2 months; 6) stable patients whose disease activity was low by the physician's assessment; and 7) stable doses of immunosuppressive drugs for 3 months (if used). Exclusion criteria included 1) a formal active exercise program within the last 6 months, 2) unable to exercise sufficiently to participate, 3) concomitant serious medical disorders such as renal and liver disease, 4) pregnancy or of childbearing age unless adequate contraceptive precautions were taken, and 5) metal implants (which could affect MRS measurements).

Interventions. *Creatine.* Oral creatine or placebo was administered as a loading dosage of 20 gm/day for 8 days followed by a maintenance dosage of 3 gm/day. Creatine was obtained (as highly purified creatine monohydrate) from Flamma, Ltd (Bergamo, Italy). Placebo was made by the same company based on lactose and other inert constituents.

Exercise. Patients were asked to undertake a home exercise program, based on a previously published regimen (6). Patients followed this program for 5 days per week. The exercise program comprised resistive exercises for upper and lower limbs as well as the neck and trunk. The program also included range of motion exercises, stretching, and a 15-minute daily walk. We gave patients a leaflet demonstrating the exercise program, asked them to read it, and encouraged them to ask any questions relative to the program. Compliance with medication and the exercise program was monitored by interviewing patients at each visit.

Outcomes. The primary outcome measure was aggregate functional performance time (AFPT) (12,16), which aggregates 4 objective functional assessments measured in seconds: 50-foot timed walk; the get up and go test, which also involves a 50-foot walk; and a stair ascent test and stair descent test, which were both 19 steps. Reductions in the performance time reflect improvements in function. This composite measure was selected on the basis of prior experience in clinical trials because it is simple, reproducible, and relevant to daily living in measuring several activities routinely undertaken by patients, and it reflects the ability to undertake high-intensity physical activity rather than endurance.

The key secondary outcome measure was a functional index in myositis (maximum score 64) (17), which was selected because it reflects the endurance of activities. Other secondary measures included manual muscle testing using the Medical Research Council extended (0–5) scale (18), serum creatine kinase (CK) levels, health status (using the Nottingham Health Profile [NHP], which has previously been used in myositis [19]), the Short Form McGill Pain Questionnaire (20), the Hospital Anxiety and Depression Scales (21), the Chalder fatigue score (22), and adverse events (clinical questioning, full blood count, renal and liver function tests). Standardization involved training between centers on assessing muscle function.

Muscle bioenergetics. Muscle bioenergetics was evaluated by ^{31}P MRS using a 1.5T Eclipse Marconi Medical MR

System (Philips, Eindhover, The Netherlands). Patients were positioned supine with the left leg outstretched. A flexible phosphorus surface coil was placed around the patient's left calf. ^{31}P MR spectra were acquired at repetition time 20,000 msec with 16 averages. Spectra were then analyzed using a commercial spectra analysis program (NMR1; Tripos, St. Louis, MO), which performs line fittings and integration. Levels of PCr α-nucleoside triphosphate (α-NTP), β-NTP, γ-NTP, phosphodiester, and inorganic phosphate (Pi) were evaluated. Intracellular pH in muscles was determined by the chemical shift of the Pi resonance relative to the PCr signal. Each patient was examined before and after 3 and 6 months of the trial.

Sample size. The pilot study (see below) demonstrated that creatine supplementation increased quadriceps strength by 9% and that the SD of the change was 10%. To show that this increase would be significant within groups at the 5% level with 90% power using a paired sample analysis would require 15 cases per group. Insufficient data were available on longer treatment to make a formal sample size calculation, and as a consequence an estimation was used with a proposed sample size of 56 patients, which incorporated a planned 20% drop out rate. Recruitment was stopped when 60 patients had been screened and 23 excluded because the rate of exclusion was higher than anticipated, the rate of inclusion was consequently lower, and the recruitment could not be further extended for practical purposes. As a consequence, a post hoc power analysis was performed using the data obtained in the trial. This demonstrated that the mean ± SD change in AFPT of 13.7% ± 13.0% with creatine compared with the 2.9% ± 13.6% change in AFPT with placebo at a significance level of 5% had 75% power.

Randomization. Sequence generation was organized by the hospital pharmacies using random number lists, and patients were allocated to 1 of the 2 groups. The 2 centers were randomized separately. No stratification was used.

Creatine and matching placebo were prepared by the hospital pharmacies and were provided in identical containers. The sequences were concealed until the study had ended, and knowledge of which patients were in active and placebo groups was not released until the statistical analysis had been completed.

Patients were enrolled by study clinicians and nurses. Patients, supervising clinicians, and assessors were blinded.

Statistical methods. Data were entered into a spreadsheet and analyzed with SPSS software (SPSS, Chicago, IL) using an intent-to-treat approach with last observation carried forward. For the principal outcomes, median values with interquartile ranges were used with patients compared between groups by the Mann-Whitney U test and within groups by the Wilcoxon signed rank test. The ^{31}P MRS findings were analyzed using paired *t*-tests.

Pilot study. This study, which had been approved by a local research ethics committee, involved 5 patients with IIM who all gave informed consent. Their functional performance and muscle bioenergetics assessed by ^{31}P MRS were determined initially, after 2 weeks supplementation with creatine 20 gm/day, and 2 months after supplementation had ended.

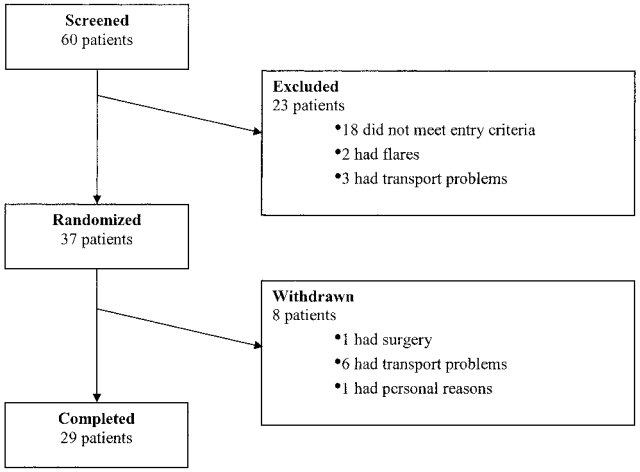

Figure 1. Flow chart of patients who were screened, randomized, and completed the study.

Following 2 weeks of creatine supplementation, mean AFPT decreased by 9.4% of initial values; after 2 months it decreased by another 0.3%. During 2 weeks of creatine supplementation, mean PCr/β-NTP ratios increased by 8% (4.21 to 4.56). Two months later they had decreased to 4.06. These initial results provided sufficient rationale to proceed to a full randomized controlled trial.

RESULTS

Patients studied. Patients were entered and followup was completed between 1999 and 2003. Recruitment was stopped when 60 patients had been screened because trial entry could not be extended beyond 4 years. A total of 16 women and 3 men received creatine, and 15 women and 3 men received placebo. The mean ages of the creatine and placebo groups were 59 years and 50 years, respectively. The flow of patients through the study is shown in Figure 1. Details of patients' disease and medications at the time of study are summarized for the randomized cases in Table 1; there were no significant differences between groups or between centers. There was no evidence of poor compliance with either creatine supplements or the exercise program.

Aggregate functional performance time. *Initial scores.* A number of factors influenced initial AFPT and were evaluated using linear regression modeling to ensure that the measure had the appropriate characteristics for a primary outcome measure. The AFPT was not normally distributed and therefore AFPT scores were logarithmically transformed prior to this analysis. Backwards stepwise linear regression analysis predicted 94% of the variation in the logarithmically transformed AFPT scores based on measures in the NHP physical, sleep, mental health, and

Table 1. Details of patients studied*

	Creatine (n = 19)	Placebo (n = 18)
Centers, no. of patients		
London	15	13
Stockholm/Malmo	4	5
Diagnosis, no.		
Polymyositis	10	12
Dermatomyositis	9	6
Disease duration, median (range) years	9.2 (1–52)	8.6 (1–23)
Immunosuppressive therapy, no.†	12	7
Azathioprine	6	2
Methotrexate	6	5
Steroid therapy, no.	11	10
Mean dosage, mg/day	10.5	7.5
Weight, median (range) kg	73 (48–102)	79 (52–125)
Height, median (range) cm	164 (152–184)	168 (152–197)
McGill overall pain	36 ± 27	25 ± 24
NHP pain	38 ± 33	30 ± 29
NHP sleep	33 ± 32	32 ± 30
NHP emotion	34 ± 30	25 ± 26
NHP physical function	34 ± 23	30 ± 25
NHP social	21 ± 25	9 ± 14
NHP energy	66 ± 43	67 ± 39
ESR, mm/hour	19 ± 15	39 ± 21
Creatine, mmoles/liter	75 ± 15	59 ± 16
CK, % upper limit	139 ± 127	97 ± 218
Red cell count, $\times 10^9$/liter	4.2 ± 0.5	4.1 ± 1.1
White cell count, $\times 10^9$/liter	7.0 ± 1.8	7.3 ± 2.3
Platelet count, $\times 10^9$/liter	269 ± 43	279 ± 62

* Values are the mean ± SD unless otherwise indicated. NHP = Nottingham Health Profile; ESR = erythrocyte sedimentation rate; CK = creatine kinase.
† Median dosages were azathioprine 100 mg daily and methotrexate 15 mg weekly.

energy domains; diagnosis (polymyositis or dermatomyositis); initial functional index of myositis scores; prednisolone dose; and center. Disease duration, NHP social, NHP pain, and immunosuppressive therapy were not related.

Disease duration, NHP social and pain domains, and immunosuppressive therapy did not contribute additional variation in the AFPT. The initial median AFPT scores were similar in both groups: 30 seconds (range 24–414 seconds) in the placebo group and 31 seconds (range 22–51 seconds) in the creatine group.

Comparisons between groups at 6 months. Due to the relatively large differences in initial AFPT scores between individual patients, all comparisons were made in terms of percentages of the initial value. The groups were compared using an intent-to-treat analysis at the study end point, which was 6 months (Figure 2A). The percentage change from initial performance time showed a median decrease of 11.4% in AFPT (range –32–8%) with creatine supplementation. This was compared with a 3.7% decrease (range –20–15%) with placebo at 6 months. This difference between groups was highly significant ($P = 0.029$ by Mann-Whitney U test). A 6-month completer analysis showed a similar significant difference ($P = 0.014$); median AFPT changed –13.2% (range –32–8%) with creatine supplementation and –3.0% (range –13–16%) with placebo.

Changes within creatine group. An intent-to-treat analysis showed a median decrease in AFPT scores (which represents an improvement) of 4 seconds over 6 months (ranging from a decrease of 13 seconds to an increase of 2 seconds). Wilcoxon's signed rank test using paired samples demonstrated that this difference was highly significant ($P < 0.001$). A 6-month completer analysis showed a similar significant difference.

Changes with placebo. An intent-to-treat analysis showed a median decrease in AFPT scores (which represents an improvement) of 2 seconds over 6 months (ranging from a decrease of 15 seconds to an increase of 6 seconds). Wilcoxon's signed rank test using paired samples demonstrated that this difference was not significant. The findings were similar using a 6-month completer analysis.

Changes at 3 months. An intent-to-treat analysis at 3 months demonstrated that the AFPT had decreased by a median of 10.9% with creatine (range –41–9%) compared with a decrease of 5.1% (range –42–14%) with placebo. These differences between groups were not significant. However, there were significant improvements within both groups at 3 months. With creatine, the median AFPT

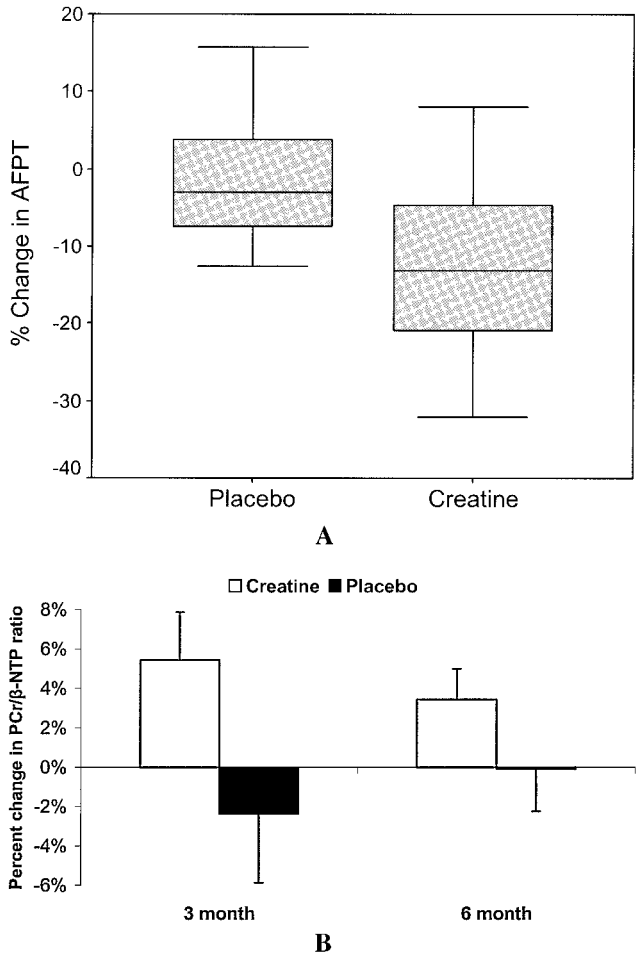

Figure 2. A, Percent changes in aggregate functional performance time (AFPT) over 6 months. Because AFPT is the time to perform 4 standard tasks, decreases represent improvements. Intent-to-treat median values, interquartile ranges, and ranges are shown. Intergroup analyses demonstrated a significant difference (P = 0.029 by Mann-Whitney U test). **B,** Changes in muscle phosphocreatine (PCr)/β-nucleoside triphosphate (β-NTP) ratios with creatine and placebo therapy. Percent changes are shown with SEM. Intragroup analysis demonstrated a significant increase with creatine (P = 0.05 at 6 months by paired t-test) and no change with placebo.

was initially 31 seconds (range 22–51) and it decreased to 28 seconds (range 19–41; P = 0.002 by paired Wilcoxon's rank sum test). In the placebo group, the median AFPT was initially 30 seconds (range 24–414) and it decreased to 28 seconds (range 21–395; P = 0.035 by paired Wilcoxon's rank sum test).

Changes in other outcome measures. *Functional index of myositis.* Changes in the functional index evaluated with an intent-to-treat analysis are summarized in Table 2. In the creatine group, the initial median score was 50.3 (range 32–64). At 6 months this increased to a median of 57.0 (range 32–64), which was a significant increase (P = 0.034 by Wilcoxon's signed rank test). In the placebo group, the initial median score was 46.3 (range 24–58). At 6 months this increased significantly to a median of 51.8 (range 32–64) using intent-to-treat analysis (P = 0.015).

Comparison of creatine and placebo cases showed no initial difference between groups. At 6 months an intent-to-treat analysis also showed no significant difference between groups. However, a completer analysis showed a significantly higher median functional index in the creatine therapy group than controls (P = 0.030 by Mann-Whitney U test). There were no differences between groups when evaluating mean percent changes of initial functional indices in either intent-to-treat or completer analyses.

Strength in individual muscle groups. Shoulder abduction and hip flexion measured by manual muscle testing showed significant differences ($P \leq 0.05$) at 3 and 6 months in patients treated with creatine compared with controls analyzed on an intent-to-treat basis (Table 3). There were small differences at 3 months with elbow flexion and knee extension, but these differences were not sustained. There were no differences in ankle dorsiflexion.

Other measures. NHP, Short Form McGill Pain Questionnaire, Hospital Anxiety and Depression Scales, and Chalder fatigue scores did not change with treatment and showed no differences between groups.

Changes in muscle bioenergetics. Muscle bioenergetics changes were evaluated in a subset of 24 patients from the UK. In 14 patients who received creatine, mean ± SE muscle PCr/β-NTP ratios increased from 4.83 ± 0.13 to 5.07 ± 0.15 at 3 months and 4.98 ± 0.12 at 6 months. The mean percent increase was 5.4% at 3 months (P = 0.06 by paired t-test) and 3.4% at 6 months (P = 0.05 by paired t-test), as shown in Figure 2B. In 10 controls, muscle PCr/β-NTP ratios remained unchanged; the mean ± SE value was 4.03 ± 0.29 at baseline, 3.96 ± 0.32 at 3 months,

Table 2. Functional index at baseline, 3 months, and 6 months*

	Creatine/exercise (n = 19)		Placebo/exercise (n = 18)		
	Median (IQR)	Significance within groups, P	Median (IQR)	Significance within groups, P	Significance between groups
Baseline	50.3 (43.5–54.8)	—	46.3 (36.0–53.4)	—	NS
3 months	51.8 (49.0–60.3)	0.019	51.5 (36.3–57.8)	0.009	NS
6 months (VCC)	57.0 (48.0–59.5)	0.034	49.0 (39.6–54.4)	0.075	0.03
6 months (ITT)	57.0 (48.0–60.0)	0.012	51.8 (38.4–57.3)	0.015	NS

* Six-month results are shown as valid compliant completer analysis (VCC) and intent-to-treat analysis (ITT). IQR = interquartile range; NS = not significant.

Table 3. Manual Muscle Tests at baseline, 3 months, and 6 months*

	Creatine			Control			Between-group significance, *P*	
	Baseline	3 month	6 month	Baseline	3 month	6 month	3 month	6 month
Shoulder abduction, left	3.83 (3.33–4.50)	4.00 (3.33–5.00)	4.00 (2.66–4.50)	3.66 (3.00–4.50)	3.66 (2.66–4.00)	3.66 (2.66–4.50)	< 0.01	< 0.05
Shoulder abduction, right	4.00 (3.00–4.50)	4.25 (3.66–5.00)	4.00 (2.66–5.00)	3.66 (2.66–4.50)	3.66 (2.66–4.00)	3.66 (2.66–4.50)	< 0.01	< 0.05
Elbow flexion, left	4.00 (3.33–4.50)	4.50 (3.66–5.00)	4.50 (4.00–5.00)	4.00 (3.33–5.50)	4.00 (3.33–5.00)	4.00 (3.00–5.00)	< 0.05	NS
Elbow flexion, right	4.00 (3.33–4.50)	4.25 (3.66–5.00)	4.50 (4.00–5.00)	4.00 (3.33–4.50)	3.66 (3.33–5.00)	4.00 (3.00–5.00)	< 0.05	NS
Hip flexion, left	3.66 (2.66–4.00)	3.83 (3.33–4.50)	3.66 (2.66–5.00)	3.33 (2.33–3.66)	3.33 (2.33–4.00)	3.33 (2.33–3.66)	< 0.01	< 0.01
Hip flexion, right	3.66 (2.66–4.50)	4.00 (3.33–4.50)	3.66 (2.66–5.00)	3.50 (2.33–4.00)	3.33 (2.33–4.00)	3.33 (2.33–4.00)	< 0.01	< 0.01
Knee extension, left	3.66 (2.66–5.00)	4.50 (3.33–5.00)	4.00 (3.33–5.00)	3.66 (1.50–4.50)	3.66 (1.50–4.50)	3.70 (1.50–4.50)	< 0.05	NS
Knee extension, right	4.00 (2.66–5.00)	4.50 (3.33–5.00)	4.50 (2.70–5.00)	3.66 (2.00–4.50)	4.00 (1.50–4.50)	4.00 (1.50–4.50)	< 0.05	NS
Dorsi flexion, left ankle	4.55 (3.33–5.00)	5.00 (4.00–5.00)	4.50 (4.00–5.00)	4.00 (2.66–5.00)	4.50 (1.50–5.00)	4.50 (3.00–5.00)	NS	NS
Dorsi flexion, right ankle	4.50 (3.33–5.00)	4.75 (4.00–5.00)	4.50 (3.70–5.00)	4.00 (2.66–5.00)	4.50 (1.50–5.00)	4.50 (2.70–5.00)	NS	NS

* Values are the median (interquartile range) unless otherwise indicated. Six-month results are intent-to-treat analysis. NS = not significant.

Table 4. Changes in blood tests during therapy*

Assessment	3 months	6 months
ESR, mm/hour		
Placebo group	−1 (−20, 4)	2 (−10, 8)
Creatine group	−3 (−12, 8)	−4 (−8, 9)
Creatine kinase, % initial value		
Placebo group	−8 (−64, 400)	4 (−33, 188)
Creatine group	41 (−30, 188)	4 (−33, 188)
Creatinine, % initial value		
Placebo group	3 (−18, 20)	−3 (−15, 33)
Creatine group	0 (−34, 36)	−2 (−34, 38)

* Values are the median (range). ESR = erythrocyte sedimentation rate.

and 4.05 ± 0.31 at 6 months. There were no changes in the ratios of Pi to β-NTP in either group.

Laboratory data. The erythrocyte sedimentation rate, serum CK levels, and serum creatinine levels showed no significant changes within groups or between groups at 3 and 6 months (Table 4).

Adverse events. There were 22 adverse events in 13 patients (6–7 in each group), including 8 infections, 6 falls, and 2 gastrointestinal events (gastric ulcer and bowel symptoms requiring colonoscopy). None of the reactions was considered as being related to creatine treatment or other medication administered to treat IIM during the trial.

DISCUSSION

By randomizing 37 patients we completed one of the largest reported randomized, placebo-controlled trials in IIM (23). The major finding was that oral creatine supplements, combined with home exercise, improved muscle performance assessed both by functional tests reflecting ability to undertake high-intensity muscular exercise and endurance work compared with exercise alone. This functional improvement was associated with increased muscle PCr levels measured by ^{31}P MRS and was achieved without significant adverse effects. These findings suggest that combining creatine supplements with exercise will provide a safe, effective, and inexpensive adjunct to conventional medical treatment for patients with chronic stable IIM. Observational studies demonstrate that many patients with treated IIM may be suitable for creatine supplements as they continue to have muscle weakness and consequent functional impairment (1,24).

Although this is one of the largest controlled trials ever performed in polymyositis and dermatomyositis, the size of the study was still insufficient to know if specific subgroups of patients with IIM would preferentially benefit from the intervention. We specifically excluded patients with inclusion body myositis, an entity with a different clinical phenotype, and a separate study would be needed to examine any benefit from creatine supplements in these patients. We refrained from secondary analyses examining the impact of initial disease classification on outcome

because the study was not powered for such a purpose, although we found that initial AFPT was influenced by NHP physical, energy, sleep, and mental domains.

Our results confirmed that simple exercise alone benefited patients, particularly improving muscle endurance shown by increases in the functional index (6,24,25). Such benefits from exercise have been previously reported (3–6,26,27). Creatine appears to increase the benefits of exercise on endurance and improve the ability to undertake high-intensity exercise, an effect maintained over 5 months.

In vivo ^{31}P MRS studies have shown that patients with IIM have difficulty undertaking repeated bouts of short-term high-intensity exercise (28). Our results indicate that this can be specifically improved by oral creatine supplements, because changes in AFPT reflect improvements in the ability to undertake this type of exercise. The timescale of these changes suggests that they reflect the impact of training on the muscles in the presence of creatine, and that patients reach a plateau in their response to exercise and creatine. Furthermore, the improved clinical results corresponded to increased ratios of PCr/β-NTP by ^{31}P MRS, in keeping with other studies of ^{31}P MRS in patients with myositis or healthy individuals (29–32). We found less relative benefit on the functional index, which improved with exercise without creatine supplements, although results were still higher in the completers taking creatine. One explanation is that AFPT and the functional index measure different types of performance; the functional index most likely measures more sustained performance, which is influenced by the training effects of the home exercise program that was included in our protocol.

Creatine supplements have been tested in a variety of disorders in which there is muscle dysfunction. Randomized controlled trials of varying size and sophistication have demonstrated positive effects in muscular dystrophies (33) and McArdle's disease (34). However, creatine supplements have not improved neurologic disorders such as Huntington's disease (35), amyotrophic lateral sclerosis (36), Friedreich's ataxia (37), myotonic dystrophy (38), and tetraplegia (39), nor does creatine improve muscle function after knee surgery (40). It is likely that creatine supplements have modest impacts on muscle bioenergetics that are useful in clinical settings with a primary muscle dysfunction. In highly trained athletes these supplements have variable effects, which may reflect the use of different functional measures and the fact that not all performances can be enhanced by creatine. During training creatine supplementation promotes gains in strength and performance of high-intensity exercise tasks (7). These effects mirror our findings in patients with myositis. Although we found no evidence of poor compliance with either creatine supplements or home exercises, compliance could have limited the response to dietary supplements.

We found no clinically significant adverse event in the study, although there were a number of minor infections in keeping with the increased rate of infections in patients with IIM (41,42). The safety of oral creatine supplements has been emphasized by Groeneveld and colleagues (43). Although there have been concerns about the potential toxicity of creatine supplements, in particular renal toxicity (44), there is little evidence that this is a clinical problem, provided creatine is highly purified and comes from an approved manufacturer, and there is no preexisting renal disease or serious underlying medical disorders.

One limitation of our study is the lack of a validated outcome measure for disease activity and organ damage to describe the patient population, but the study was also designed before the outcome measurements for disease activity, organ damage, and health-related quality of life proposed by the International Myositis and Clinical Studies Group (45) were available. Nonetheless, we found no evidence that creatine supplements had any impact on the underlying disease process. For example, measures such as CK levels, health status, and fatigue were all unchanged. AFPT has not been fully validated for patients with IIM, and another limitation is that AFPT measures performance in the lower extremities only and knee joint problems could affect AFPT results. The improved AFPT results were confirmed by improved performance of hip flexion of the Manual Muscle Test. Furthermore, improved strength in other muscle groups that were part of the exercise program, the proximal arm muscles, was recorded by the Manual Muscle Test in the creatine group versus the placebo group. Patients with pronounced knee joint problems would never have been included in our study because sufficient mobility to participate in the exercise program was required. AFPT is a relevant assessment of muscle function in both young and elderly adults (13) and has been used in a number of disorders in which muscle weakness can be improved by exercise or other treatments, including osteoarthritis (15), rheumatoid arthritis (12), and impaired vitamin D status in the elderly (46). The functional index was included as a clinical outcome measure because this was the only available disease-specific reliable outcome measure of muscle function for patients with myositis at the time of study, and because it has good inter- and intrarater reliability (6,24). In our previous studies (6), we observed a ceiling effect with the original functional index that was used in this study. The score 64 is easy to achieve and we found that some patients achieved this score despite the fact that they perceived muscle impairment in daily living. A score of 46–50 represents a moderate to severe impairment in ambulatory patients.

In conclusion, just as creatine supplements provide small benefits in sports activities, they also appear to confer modest benefits in patients with stable IIM. We consider creatine supplements to be a useful adjuvant therapy in adult patients with polymyositis or dermatomyositis, although they should not replace specific immunotherapies targeting the underlying disease process. Our results support the hypothesis that oral creatine supplements combined with exercise are more effective in improving function than exercise alone in clinically weak patients with IIM who have received adequate conventional medical treatment. We believe that exercise regimens are a key component of the rehabilitation of patients with IIM, and that oral creatine supplements will enhance the benefit of exercise without incurring substantial risks.

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AUTHOR CONTRIBUTIONS

Dr. Chung had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Chung, Morrison, Richards, Bell, Lundberg, Scott.
Acquisition of data. Chung, Alexanderson, Pipitone, Morrison, Dastmalchi, Ståhl-Hallengren, Richards, Thomas, Bell, Scott.
Analysis and interpretation of data. Chung, Alexanderson, Pipitone, Thomas, Hamilton, Bell, Lundberg, Scott.
Manuscript preparation. Chung, Alexanderson, Pipitone, Dastmalchi, Ståhl-Hallengren, Thomas, Bell, Lundberg, Scott.
Statistical analysis. Chung, Alexanderson, Scott.

REFERENCES

1. Sultan SM, Ioannou Y, Moss K, Isenberg DA. Outcome in patients with idiopathic inflammatory myositis: morbidity and mortality. Rheumatology (Oxford) 2002;41:22–6.
2. Park JH, Vital TL, Ryder NM, Hernanz-Schulman M, Partain CL, Price RR, et al. Magnetic resonance imaging and P-31 magnetic resonance spectroscopy provide unique quantitative data useful in the longitudinal management of patients with dermatomyositis. Arthritis Rheum 1994;37:736–46.
3. Wiesinger GF, Quittan M, Nuhr M, Volc-Platzer B, Ebenbichler G, Zehetgruber M, et al. Aerobic capacity in adult dermatomyositis/polymyositis patients and healthy controls. Arch Phys Med Rehabil 2000;81:1–5.
4. Hicks JE, Miller F, Plotz P, Chen TH, Gerber L. Isometric exercise increases strength and does not produce sustained creatinine phosphokinase increases in a patient with polymyositis. J Rheumatol 1993;20:1399–401.
5. Escalante A, Miller L, Beardmore TD. Resistive exercise in the rehabilitation of polymyositis/dermatomyositis. J Rheumatol 1993;20:1340–4.
6. Alexanderson H, Stenstrom CH, Lundberg I. Safety of a home exercise programme in patients with polymyositis and dermatomyositis: a pilot study. Rheumatology (Oxford) 1999; 38:608–11.
7. Kreider RB. Effects of creatine supplementation on performance and training adaptations [review]. Mol Cell Biochem 2003;244:89–94.
8. Chung YL, Wassif WS, Bell JD, Hurley M, Scott DL. Urinary levels of creatine and other metabolites in the assessment of polymyositis and dermatomyositis. Rheumatology (Oxford) 2003;42:298–303.
9. Chung YL, Rider LG, Bell JD, Summers RM, Zemel LS, Rennebohm RM, et al, for the Juvenile Dermatomyositis Disease Activity Collaborative Study Group. Muscle metabolites, detected in urine by proton spectroscopy, correlate with disease damage in juvenile idiopathic inflammatory myopathies. Arthritis Rheum 2005;53:565–70.
10. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts) [review]. N Engl J Med 1975;292:344–7.
11. Griggs RC, Askanas V, DiMauro S, Engel A, Karpati G, Mendell JR, et al. Inclusion body myositis and myopathies. Ann Neurol 1995;38:705–13.
12. Hurley MV, Scott DL, Rees J, Newham DJ. Sensorimotor changes and functional performance in patients with knee osteoarthritis. Ann Rheum Dis 1997;56:641–8.
13. Hurley MV, Rees J, Newham DJ. Quadriceps function, proprioceptive acuity and functional performance in healthy young, middle-aged and elderly subjects. Age Ageing 1998;27:55–62.
14. Young A, Stokes M, Crowe M. The size and strength of the quadriceps muscles of old and young men. Clin Physiol 1985; 5:145–54.
15. Young A, Stokes M, Crowe M. Size and strength of the quadriceps muscles of old and young women. Eur J Clin Invest 1984;14:282–7.
16. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology (Oxford) 2002;41:157–66.
17. Josefson A, Romanus E, Carlsson J. A functional index in myositis. J Rheumatol 1996;23:1380–4.
18. Kendall FP, McCreary EK, Provance PG. Muscle: testing and function. 4th ed. Baltimore: Williams & Wilkins; 1993.
19. Chung YL, Mitchell HL, Houssien DA, Al-Mahrouki H, Carr AJ, Scott DL. A comparative study of outcome in myositis and other musculoskeletal disorders assessed using the Nottingham health profile. Clin Exp Rheumatol 2001;19:447–50.
20. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–99.
21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
22. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res 1993;37:147–53.
23. Choy EH, Isenberg DA. Treatment of dermatomyositis and polymyositis [review]. Rheumatology (Oxford) 2002;41:7–13.
24. Ponyi A, Borgulya G, Constantin T, Vancsa A, Gergely L, Danko K. Functional outcome and quality of life in adult patients with idiopathic inflammatory myositis. Rheumatology (Oxford) 2005;44:83–8.
25. Alexanderson H, Broman L, Tollback A, Josefson A, Lundberg IE, Stenstrom CH. Functional index-2: validity and reliability of a disease-specific measure of impairment in patients with polymyositis and dermatomyositis. Arthritis Rheum 2006;55: 114–22.
26. Alexanderson H, Lundberg IE. The role of exercise in the rehabilitation of idiopathic inflammatory myopathies [review]. Curr Opin Rheumatol 2005;17:164–71.
27. Alexanderson H, Stenstrom CH, Jenner G, Lundberg I. The safety of a resistive home exercise program in patients with recent onset active polymyositis or dermatomyositis. Scand J Rheumatol 2000;29:295–301.
28. Pfleiderer B, Lange J, Loske KD, Sunderkotter C. Metabolic disturbances during short exercises in dermatomyositis revealed by real-time functional 31P magnetic resonance spectroscopy. Rheumatology (Oxford) 2004;43:696–703.
29. Scott DL, Kingsley GH. Use of imaging to assess patients with muscle disease. Curr Opin Rheumatol 2004;16:678–83.
30. Park JH, Niermann KJ, Ryder NM, Nelson AE, Das A, Lawton AR, et al. Muscle abnormalities in juvenile dermatomyositis patients: P-31 magnetic resonance spectroscopy studies. Arthritis Rheum 2000;43:2359–67.
31. Rico-Sanz J, Zehnder M, Buchli R, Kuhne G, Boutellier U. Noninvasive measurement of muscle high-energy phosphates and glycogen concentrations in elite soccer players by 31P- and 13C-MRS. Med Sci Sports Exerc 1999;31:1580–6.
32. Schunk K, Pitton M, Duber C, Kersjes W, Schadmand-Fischer S, Thelen M. Dynamic phosphorus-31 magnetic resonance spectroscopy of the quadriceps muscle: effects of age and sex on spectroscopic results. Invest Radiol 1999;34:116–25.
33. Tarnopolsky MA, Mahoney DJ, Vajsar J, Rodriguez C, Doherty TJ, Roy BD, et al. Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. Neurology 2004;62:1771–7.
34. Vorgerd M, Grehl T, Jager M, Muller K, Freitag G, Patzold T, et al. Creatine therapy in myophosphorylase deficiency (McArdle disease): a placebo-controlled crossover trial. Arch Neurol 2000;57:956–63.
35. Verbessem P, Lemiere J, Eijnde BO, Swinnen S, Vanhees L, van Leemputte M, et al. Creatine supplementation in Huntington's disease: a placebo-controlled pilot trial. Neurology 2003;61:925–30.
36. Groeneveld GJ, Veldink JH, van der Tweel I, Kalmijn S, Beijer C, de Visser M, et al. A randomized sequential trial of creatine in amyotrophic lateral sclerosis. Ann Neurol 2003;53:437–45.
37. Schols L, Zange J, Abele M, Schillings M, Skipka G, Kuntz-

Hehner S, et al. L-carnitine and creatine in Friedreich's ataxia: a randomized, placebo-controlled crossover trial. J Neural Transm 2005;112:789–96.
38. Walter MC, Reilich P, Lochmuller H, Kohnen R, Schlotter B, Hautmann H, et al. Creatine monohydrate in myotonic dystrophy: a double-blind, placebo-controlled clinical study. J Neurol 2002;249:1717–22.
39. Kendall RW, Jacquemin G, Frost R, Burns SP. Creatine supplementation for weak muscles in persons with chronic tetraplegia: a randomized double-blind placebo-controlled crossover trial. J Spinal Cord Med 2005;28:208–13.
40. Tyler TF, Nicholas SJ, Hershman EB, Glace BW, Mullaney MJ, McHugh MP. The effect of creatine supplementation on strength recovery after anterior cruciate ligament (ACL) reconstruction: a randomized, placebo-controlled, double-blind trial. Am J Sports Med 2004;32:383–8.
41. Pachman LM, Lipton R, Ramsey-Goldman R, Shamiyeh E, Abbott K, Mendez EP, et al. History of infection before the onset of juvenile dermatomyositis: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Research Registry. Arthritis Rheum 2005;53:166–72.
42. Marie I, Hachulla E, Cherin P, Hellot MF, Herson S, Levesque H, et al. Opportunistic infections in polymyositis and dermatomyositis. Arthritis Rheum 2005;53:155–65.
43. Groeneveld GJ, Beijer C, Veldink JH, Kalmijn S, Wokke JH, van den Berg LH. Few adverse effects of long-term creatine supplementation in a placebo-controlled trial. Int J Sports Med 2005;26:307–13.
44. Poortmans JR, Francaux M. Renal dysfunction accompanying oral creatine supplements [letter]. Lancet 1998;352:234.
45. Isenberg DA, Allen E, Farewell V, Ehrenstein MR, Hanna MG, Lundberg IE, et al, and the International Myositis and Clinical Studies Group (IMACS). International consensus outcome measures for patients with idiopathic inflammatory myopathies: development and initial validation of myositis activity and damage indices in patients with adult onset disease. Rheumatology (Oxford) 2004;43:49–54.
46. Dhesi JK, Jackson SH, Bearne LM, Moniz C, Hurley MV, Swift CG, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing 2004;33:589–95.