Randomized Controlled Trial of Dietary Creatine as an Adjunct Therapy to Physical Training in Chronic Obstructive Pulmonary Disease

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Rationale: **Skeletal muscle strength and bulk are reduced in patients with chronic obstructive pulmonary disease (COPD) and influence quality of life, survival, and utilization of health care resources. Exercise training during pulmonary rehabilitation (PR) can reverse some of these effects. In athletes and healthy elderly individuals, dietary creatine supplementation (CrS) has been shown to augment high-intensity exercise training, thereby increasing muscle mass.**

Objectives: **This article examines the effect of CrS on functional exercise capacity and muscle performance in people with COPD.**

Methods: **One hundred subjects with COPD (mean [SD] age, 68.2 [8.2] yr; FEV_1, 44.0 [19.6] %predicted) were randomized to a double-blind, placebo-controlled, parallel group trial of CrS during 7 weeks of PR encompassing aerobic and resistance exercises. Subjects ingested creatine (22 g/d loading for 5 d; maintenance, 3.76 g/d throughout PR) or placebo. Baseline, postloading, and postrehabilitation measurements included pulmonary function, body composition, peripheral muscle strength, and functional performance (shuttle walking tests). A volunteer subgroup (n = 44) had pre- and postloading quadriceps muscle biopsies.**

Measurements and Main Results: **Eighty subjects completed the trial (38 creatine, 42 placebo). All outcome measures significantly improved after PR. There were no significant differences between groups post-PR (mean [SD] change in incremental shuttle walk distance, 84 [79] m in the creatine group vs. 83.8 [60] m in the placebo group; $P = 1.0$; knee extensor work, 19.2 [16] Nm [Newton meters] in the creatine group vs. 19.5 [17] Nm in the placebo group; $P = 0.9$). Muscle biopsies showed evidence of creatine uptake.**

Conclusions: **This adequately powered, randomized, placebo-controlled trial shows that CrS does not augment the substantial training effect of multidisciplinary PR for patients with COPD.**

Clinical trial registered with https://portal.nihr.ac.uk/Pages/NRRArchiveSearch.aspx (NO123138126).

Keywords: pulmonary rehabilitation; strength; dietary supplementation

Loss of muscle mass and strength accompanies aging and may be one of the determinants of disability and death in chronic obstructive pulmonary disease (COPD) (1, 2). Exercise limitation does not correlate with airway function and patients may complain of leg fatigue as much as breathlessness as their limiting symptom to exercise (3). One of the principal causes of peripheral muscle dysfunction in COPD is deconditioning (4–6). Exercise training is therefore a logical step to improve physical performance. The role of physical training in pulmonary rehabilitation (PR), particularly aerobic exercise, is well established and can improve exercise capacity, symptoms, and quality of life (7–11).

Dietary supplementation with creatine monohydrate, a naturally occurring substance, can increase muscle mass in healthy subjects by enhancing high-intensity exercise training. It is used by athletes to augment their performance and training (12). It is believed that creatine (Cr), in its phosphorylated form (phosphocreatine [PCr]), enhances performance by increasing the phosphagen pool available for rapid resynthesis of adenosine triphosphate (ATP) from adenosine diphosphate during periods of high ATP turnover. Such depletion may occur during short-duration, high-intensity anaerobic exercise. It may also stimulate PCr resynthesis (13). Uptake of Cr into muscle is enhanced by aerobic exercise and supplementation is likely to be most beneficial when combined with physical training (14). Dietary Cr supplementation (CrS) combined with 12 to 14 weeks of whole body resistance training programs in the elderly has been shown to have an ergogenic effect, enhancing isometric muscle strength, lower body endurance, and lean body mass, but not functional capacity (15, 16).

There is evidence from biopsy studies that muscle PCr content is lower in patients with COPD than in healthy age-matched subjects (17). We have previously demonstrated a correlation between resting preexercise PCr content in peripheral muscles with incremental shuttle walking distance in patients with COPD (18). The incremental shuttle walking test (ISWT), frequently used to assess performance after PR, is also related to muscle strength in patients with COPD (19). This could suggest a role for PCr in determining maximal walking performance and a potential therapeutic target to improve exercise performance.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

It is suggested that creatine supplementation increases fat-free mass, health status, and peripheral muscle strength, but not exercise capacity, in patients with chronic obstructive pulmonary disease.

What This Study Adds to the Field

Our study confirms the substantial benefits gained during pulmonary rehabilitation in people with chronic obstructive pulmonary disease and that strength training is a beneficial and acceptable addition to endurance training. Creatine supplementation does not augment these benefits.

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The impact of performance-enhancing therapy in COPD has received little attention. One study suggests that CrS increases fat-free mass (FFM), health status, peripheral muscle strength, and endurance, but not exercise capacity, in patients with COPD (20). However, as the accompanying editorial pointed out, this study was underpowered (21). We therefore conducted a large, randomized, double-blind, placebo-controlled trial of CrS to test our hypothesis that CrS, in association with exercise training, will enhance the functional benefits of PR. Some of the results of this study have previously been reported in the form of an abstract (22).

METHODS

Subjects

Subjects with COPD referred for PR were approached for inclusion (23). Those older than 85 years or unsuitable for the exercise program were excluded. Approval was obtained from Leicestershire Health Authority Research Ethics Committee. Subjects gave written, informed consent.

Study Design

This was a single-center, randomized, double-blind, placebo-controlled, parallel group trial of CrS during rehabilitation. Subjects were tested at baseline, after supplement loading (5 d without training), and after completion of 7 weeks of rehabilitation with supplementation (Figure 1).

Spirometry

Spirometry was measured seated to Association for Respiratory Technology and Physiology/British Thoracic Society standards (Vitalograph Model R; Vitalograph, Ltd., Bucks, UK) (24).

Body Composition

Body composition was measured noninvasively using bioelectrical impedance (Bodystat 1500; Bodystat Ltd, Douglas, Isle of Man, UK). FFM was estimated using disease-specific regression equations (25).

Whole Body Exercise Testing

Walking performance was measured using the ISWT, reproducible after one practice walk, and endurance shuttle walking test (ESWT) (26, 27).

Peripheral Muscle Performance

Dominant quadriceps, triceps, and biceps dynamic isokinetic performance and quadriceps isometric strength were measured using a Cybex II Norm dynamometer (Cybex International, Inc., Ronkonkoma, NY).

Lower limb isokinetic measurements used a continuous concentric–eccentric contraction protocol at 60°/second (28). Isometric maximum voluntary contractions were performed with the knee at an angle of 70° flexion (leg straight = 0°). Upper limb isokinetic measurements used a continuous concentric–concentric contraction protocol at 120°/second. Analysis used peak work or force. Additional details are available in the online supplement.

Peripheral Muscle Biopsy

Resting muscle biopsies were obtained in a volunteer subgroup (n = 44) from the nondominant quadriceps muscle before and after supplement loading and immediately frozen in liquid nitrogen (29). Samples were analyzed for Cr, total Cr (TCr), and PCr, normalized for nonmuscle constituents using ATP (14).

Quality-of-Life Assessment

The self-reported Chronic Respiratory Questionnaire (CRQ-SR) measured disease-specific health status (30). The clinically significant change for each domain is 0.5 (31).

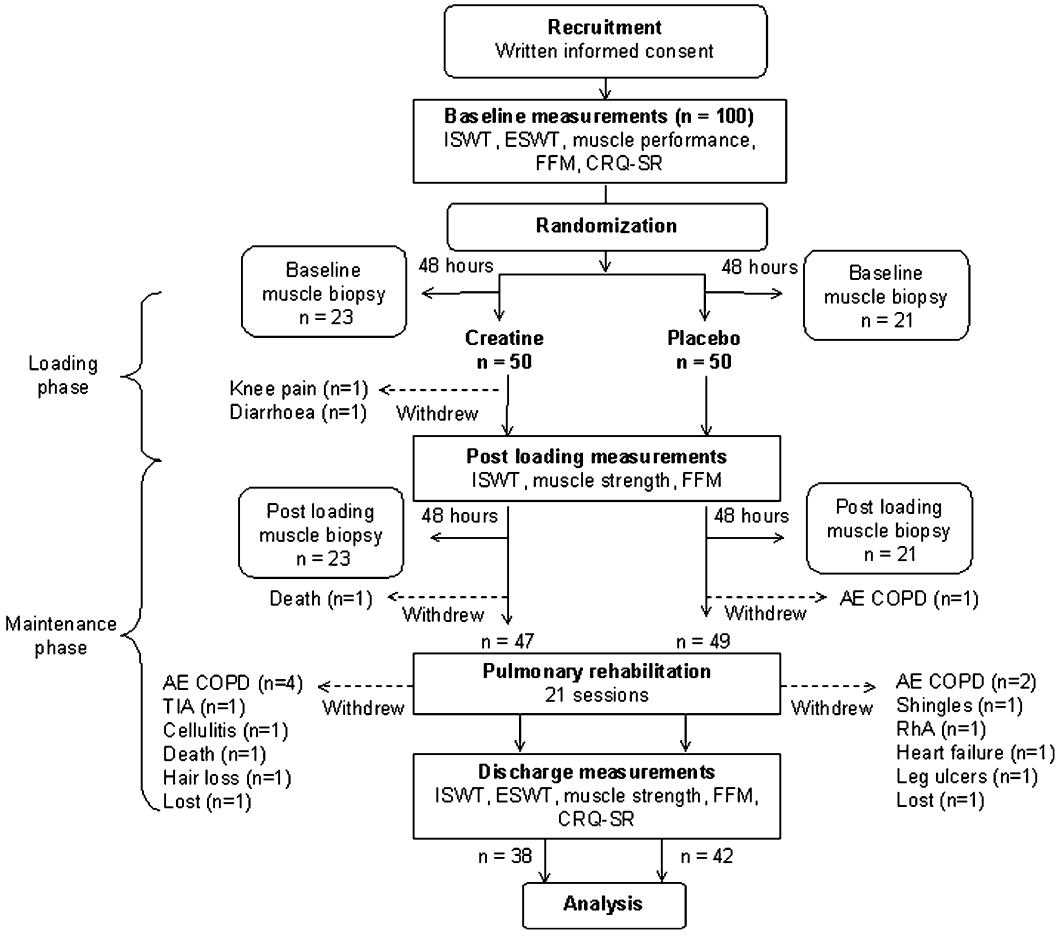

Figure 1. Outline of study design. AE = acute exacerbation; COPD = chronic obstructive pulmonary disease; CRQ = Chronic Respiratory Questionnaire; ESWT = endurance shuttle walking test; FFM = fat-free mass; ISWT = incremental shuttle walking test; RhA = rheumatoid arthritis; TIA = transient ischemic attack.

Supplementation

After baseline measurements, subjects were randomized (independently computer generated blocks of 20) to Cr (creatine monohydrate; Degussa, Trostberg, Germany) or placebo (lactose; Novalabs, Leicester, UK) supplementation. Supplements were packaged and dispensed by the hospital pharmacy. Powders had similar texture and appearance. Subjects loaded for 5 days (22 g Cr/24 g lactose daily, four divided doses), followed by maintenance during PR (3.76 g Cr/4 g lactose daily). Subjects, investigators, and rehabilitation staff were blinded.

Pulmonary Rehabilitation

Subjects participated in standard multidisciplinary outpatient rehabilitation comprising endurance training and individually prescribed resistance training, for 21 sessions over 7 weeks (32). Resistance training used gym equipment (Technogym, Gambettola, Italy) and free weights. Loads were initially set at 60 to 70% of one-repetition maximum and increased progressively.

Statistical Analysis

The ISWT was the primary outcome measure. Our PR achieves a mean improvement of 48 m. The sample size (100 subjects) was calculated to detect an additional 30-m improvement in the Cr group (80% power), assuming a 20% drop-out rate.

A comparative analysis (Statistical Package for Social Sciences version 11.0; SPSS, Chicago, IL) of those subjects who completed rehabilitation was undertaken (not an intention-to-treat analysis). Comparisons were made using paired (within-treatment effect) and unpaired (between-treatment effect) *t* tests, with a statistical significance of $P < 0.05$. The overall effect of supplement plus rehabilitation was also assessed using repeated-measures analysis of variance (ANOVA) and effects of covariates on outcomes using univariate analysis.

RESULTS

One hundred subjects were recruited and 80 completed the study (Figure 1). Dropouts (8 placebo, 12 Cr) were due to reasons that prevented completion of PR, not because of supplementation. Illnesses included exacerbation of COPD, heart failure, shingles, rheumatoid arthritis, leg ulcers, cellulitis, and stroke. Two subjects were lost to follow-up. Two blamed the supplement for side effects (loss of hair and stomach upset), and both subsequently withdrew from rehabilitation; and two subjects died (both of pneumonia, Cr group). Baseline characteristics were not statistically different between the dropouts and completers, except for the placebo dropouts, who had a lower baseline functional performance (mean [SD] ISWT, 137.5 [34.5] vs. 223.8 [135.3] m; $P < 0.01$).

Treatment groups were well matched at baseline in pulmonary function, functional performance, and muscle strength (Table 1). There were more men than women in the placebo group. Self-reported compliance for the supplement (96%) and empty tub return (81%) were excellent in both groups, with few adverse effects.

Loading Phase

Loading with CrS and placebo resulted in minor but statistically significant improvements in functional and muscle performance (Table 2); however, there were no statistically significant differences between Cr and placebo treatment groups (mean change [SD] ISWT, 36.8 [59] vs. 24.3 [53] m; $P = 0.3$; isometric strength, 8.9 [15] vs. 10 [10] Nm [Newton meters]; $P = 0.7$). Mean ISWT results at baseline, after loading, and after PR are shown (Figure 2).

The Cr group showed a significant increase from baseline in body weight, predominantly FFM, after loading (weight, 0.4 kg, $P < 0.01$, and FFM 1.1 kg, $P < 0.01$). The placebo group also significantly increased FFM from baseline after loading (0.7 kg, $P < 0.05$), but there were no significant differences between groups (Table 2).

Maintenance Phase

Functional performance and strength improved significantly from baseline after rehabilitation (mean change [SD] ISWT, 84 [79] m, $P < 0.001$, and 83.8 [60] m, $P < 0.001$; knee extensor peak work, 19.2 [16] Nm, $P < 0.001$, and 19.5 [17] Nm, $P < 0.001$; isometric strength, 19.6 [11] Nm, $P < 0.001$, and 23.1 [17] Nm, $P < 0.001$; Cr and placebo groups, respectively). CrS

TABLE 1. BASELINE CHARACTERISTICS OF SUBJECTS COMPLETING TRIAL

	Creatine (*n = 38*)	Placebo (*n = 42*)	*P* (two-tailed)
Age, yr	67.6 (7.4)	68.3 (8.2)	0.69
Sex, no. of males/females	19/19	31/11	
Smoking history, pack-years	53.5 (31.2)	46.8 (33.6)	0.36
MRC dyspnea score	3 (3, 4)	3 (3, 4)	
Pulmonary function			
FEV_1, L/min	1.1 (0.6)	1.1 (0.5)	0.65
FEV_1, % predicted	45.2 (21.8)	43.0 (19.0)	0.63
FVC, L	2.6 (0.8)	2.3 (0.8)	0.10
Body composition			
Weight, kg	74.9 (15.0)	72.8 (16.3)	0.54
BMI, kg/m^2	28.1 (5.4)	25.7 (5.2)	0.05
FFM, kg	47.4 (10.3)	49.5 (8.6)	0.33
FFMI, kg/m^2	17.6 (2.7)	17.4 (2.5)	0.81
Functional performance			
ISWT, m	208.7 (105.6)	223.8 (135.3)	0.58
ESWT, s	161.0 (106.4)	182.3 (106.2)	0.37
Sp_{O_2} rest	94.4 (2.3)	95.0 (2.4)	0.26
Sp_{O_2} exertion	88.2 (6.5)	89.8 (6.7)	0.29
Lower limb muscle performance			
Isokinetic concentric quadriceps, Nm	72.9 (28.0)	83.7 (32.2)	0.12
Isometric quadriceps, Nm	108.1 (41.7)	121.4 (42.8)	0.16
Upper limb muscle performance			
Isokinetic biceps, Nm	22.7 (10.8)	24.8 (10.6)	0.39
Isokinetic triceps, Nm	31.3 (12.5)	34.0 (10.5)	0.32

Definition of abbreviations: BMI = body mass index; ESWT = endurance shuttle walk test; FFM = fat-free mass; FFMI = fat-free mass index; ISWT = incremental shuttle walk test; MRC = Medical Research Council; Nm = Newton meters.

Data are presented as group mean (SD), except MRC dyspnea score, which is median (interquartile range). Independent Student's *t* test used for between-group comparisons; no significant difference between treatment groups, $P > 0.05$.

TABLE 2. WITHIN-GROUP AND BETWEEN-GROUP CHANGE FROM BASELINE AFTER LOADING

	Within-Group Changes		
	Creatine ($n = 38$)	Placebo ($n = 42$)	Between-Group Mean Difference
Body composition			
Weight, kg	0.4 (0.2 to 0.7)*	0.3 (−0.003 to 0.6)	0.1 (−0.3 to 0.5)
FFM, kg	1.1 (0.3 to 1.9)*	0.7 (0.1 to 1.3)†	0.4 (−0.6 to 1.3)
FM, kg	−0.7 (−1.3 to 0.02)	−0.4 (−1.0 to 0.2)	−0.3 (−1.1 to 0.6)
Functional performance			
ΔISWT, m	36.8 (17.6 to 56.1)*	24.3 (7.7 to 40.9)*	12.6 (−12.3 to 37.5)
Lower limb muscle performance			
Isokinetic concentric quadriceps, Nm	6.5 (3.1 to 9.8)*	9.9 (5.8 to 14.1)*	−3.5 (−8.8 to 1.9)
Isometric quadriceps, Nm	8.9 (4.1 to 13.7)	10.0 (6.7 to 13.2)*	−1.1 (−6.7 to 4.5)
Upper limb muscle performance			
Isokinetic biceps, Nm	1.6 (0.5 to 2.8)*	1.9 (0.6 to 3.2)*	−0.3 (−2.0 to 1.5)
Isokinetic triceps, Nm	1.3 (0.01 to 2.6)†	2.9 (1.3 to 4.6)*	−1.6 (−3.7 to 0.5)

Definition of abbreviations: FFM = fat-free mass; FM = fat mass; ISWT = incremental shuttle walk test; Nm = Newton meters.

Data are presented as treatment group mean change (95% confidence interval) for within-group changes. Comparisons were made using paired Student's *t* test for within-group difference. Independent Student's *t* test was used for between-group comparisons, no significant difference between treatment groups.

* Statistically significant difference (from baseline), $P < 0.01$.

† Statistically significant difference (from baseline), $P < 0.05$.

combined with rehabilitation resulted in no additional statistically significant improvements in whole body performance or muscle strength compared with rehabilitation alone (Table 3).

The Cr group showed a greater nonsignificant percentage of improvement in ISWT with loading and post-PR (32 vs. 14%, $P = 0.2$, and 72 vs. 45%, $P = 0.2$, respectively). Univariate analysis was therefore performed, adjusting for covariates such as baseline concentric quadriceps work. Repeated-measures ANOVA, including the loading and maintenance phase of the study, showed no overall effect on the outcome of rehabilitation with Cr against placebo ($P = 0.7$). Adjusting for covariates did not alter this outcome. This was also performed using 98 subjects who completed the postloading visit. The effects of supplement did not alter; there was no statistically significant difference between groups.

The Cr group showed a significant increase from baseline in body weight, predominantly FFM, after rehabilitation (weight, 0.7 kg, $P < 0.01$, and FFM 0.9 kg, $P < 0.05$), but there was no significant difference between groups (Table 3).

Health status, measured using the CRQ-SR, showed statistical and clinically significant improvements in all domains after PR (Table 4). There were no significant differences in the change in health status between groups after rehabilitation.

Muscle Biopsies

Paired pre- and postloading resting muscle biopsy samples (16 placebo, 15 Cr) showed a significant increase in TCr, Cr, and PCr content in the creatine group (34.3 mmol/kg of dry matter weight [mmol/kg/dm] or 34%, 24.2 mmol/kg/dm or 57%, 10.1 or 18% mmol/kg/dm, respectively; $P < 0.05$), confirming muscle uptake of Cr (Table 5 and Figure 3).

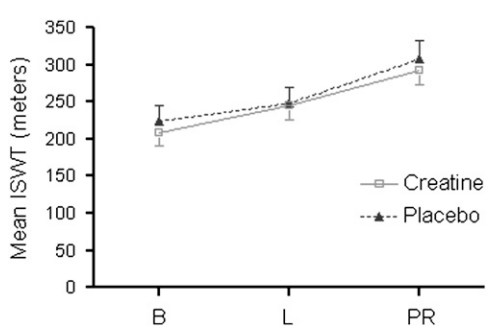

Figure 2. Mean incremental shuttle walking test (ISWT) (SEM) at baseline (B), after supplement loading (L) and after completion of pulmonary rehabilitation (PR).

DISCUSSION

This carefully designed, large, randomized, double-blind, placebo-controlled trial, powered to detect clinically important differences in functional performance, shows that CrS does not significantly augment the training effect of PR (21). Functional exercise capacity and muscle performance, as well as health status, were measured using well-established, reproducible measurements.

Supplements were well tolerated. Acute exacerbation of COPD and illness preventing the completion of rehabilitation were the main reasons for dropouts, not supplementation. The drop-out rate (20%) was as expected for our rehabilitation program. Two deaths (both secondary to pneumonia) occurred in subjects taking Cr, which was not considered to be related to these deaths.

All subjects benefited during the supplement-loading phase, with significant improvements in performance. Improvements were probably due to a learning and/or placebo effect because they occurred in both groups. To minimize learning effects, we incorporated a familiarization test into the warm-up before isokinetic testing. Pilot data within our department have shown this to be adequate in reducing learning effects. The ISWT is reproducible after a single practice walk, which all subjects had before baseline measurements (26, 27).

Our rehabilitation program is well established and effective in improving functional performance in patients with COPD. We enhanced our program with individually prescribed optimal strength training, to potentiate any effects of Cr during training (33). Our mean improvement in ISWT after PR was better than expected in both groups and is probably attributed to supervised strength training.

A previous randomized, double-blind, placebo-controlled study of CrS during PR in patients with COPD presented different conclusions compared with our study (20). Fuld and colleagues showed a significant increase in muscle performance in the Cr, compared with placebo, after a 2-week loading phase (15 g daily) and a further significant improvement after maintenance supple-

TABLE 3. WITHIN-GROUP AND BETWEEN-GROUP CHANGE FROM BASELINE AFTER PULMONARY REHABILITATION

	Within-Group Changes		Between-Group Mean Difference
	Creatine (*n* = *38*)	Placebo (*n* = *42*)	
Body composition			
Weight, kg	0.7 (0.2 to 1.3)*	0.2 (−0.4 to 0.8)	0.5 (−0.3 to 1.3)
FFM, kg	0.9 (0.1 to 1.7)†	0.8 (−0.05 to 1.6)	0.1 (−1.0 to 1.3)
FM, kg	−0.1 (−1.0 to 0.7)	−0.5 (−1.3 to 0.4)	0.3 (−0.8 to 1.5)
Functional performance			
ISWT, m	84.0 (58.0 to 109.9)*	83.8 (65.0 to 102.6)*	0.1 (−30.9 to 31.2)
ESWT, s	377.4 (248.6 to 506.3)*	487.4 (367.2 to 607.6)*	−110.0 (−283.3 to 63.3)
Lower limb muscle performance			
Isokinetic concentric quadriceps, Nm	19.2 (14.0 to 24.3)*	19.5 (14.2 to 24.7)*	−0.3 (−7.6 to 7.0)
Isometric quadriceps, Nm	19.6 (16.0 to 23.3)*	23.1 (17.8 to 28.4)*	−3.5 (−10.0 to 3.0)
Upper limb muscle performance			
Isokinetic biceps, Nm	2.8 (0.9 to 4.8)*	3.6 (1.9 to 5.4)*	−0.8 (−3.4 to 1.8)
Isokinetic triceps, Nm	1.8 (0.3 to 3.4)†	2.6 (1.0 to 4.2)*	−0.8 (−3.0 to 1.5)

Definition of abbreviations: FFM = fat-free mass; FM = fat mass; ESWT = endurance shuttle walk test; ISWT = incremental shuttle walk test; Nm = Newton meters.

Data are presented as treatment group mean change (95% confidence interval) for within-group changes. Comparisons were made using paired Student's *t* test for within-group difference. Independent Student's *t* test was used for between-group comparisons.

* Statistically significant differences (from baseline), $P < 0.01$.

† Statistically significant differences (from baseline), $P < 0.05$.

mentation (5 g daily) combined with 8 weeks of exercise training (20). Improvements were in lower limb strength and endurance and handgrip endurance, accompanied by an increase in body weight, predominantly FFM.

Both studies were powered to detect improvements in the ISWT and showed significant improvements after PR. Fuld and colleagues, however, had difficulties with recruitment and statistical power. These two studies differ in the length of loading phase (5 vs. 14 d) and Fuld and coworkers used Cr with glucose polymer, which may increase gastrointestinal uptake. However, we have evidence to show adequate muscle Cr uptake after loading.

Improvements in isokinetic lower limb performance after PR in the Cr group were of similar magnitude to ours (19.5 Nm, or 22.8%, vs. 19.2 Nm, or 30%) but we showed no additional improvement over placebo. Fuld and coworkers found no statistically significant improvements between groups in whole body functional performance, measured using ISWT, ESWT, and cycle ergometry, after initial loading, and Cr produced no additional effects on functional performance after training in this or in our study.

Patients with chronic heart failure have skeletal muscle abnormalities similar to those found in COPD and experience early exertional fatigue during exercise (34). Short-term CrS (10 d) in patients with chronic heart failure and low basal levels of Cr significantly increased quadriceps muscle strength (5%) and endurance (10–20%) in a double-blind, placebo-controlled study. However, only a small number of subjects (n = 17) were involved.

The effect of acute Cr loading without exercise training in the elderly has produced inconsistent results in a number of small studies (35, 36). CrS combined with resistance training (RT), however, has been shown by two meta-analyses to have positive effects on body composition and muscular strength in young healthy subjects (37, 38). They concluded that CrS can increase lean body mass, augment strength gains during RT, and improve performance during high-intensity intermittent exercise, together with increasing PCr muscle content (39). In the elderly, CrS combined with RT has produced conflicting results. CrS combined with 7 weeks of RT did not improve strength or resistance to fatigue compared with placebo, whereas 12 weeks of RT enhanced lower limb strength, endurance, and power, together with lean body mass (15, 40). Both studies recruited 30 elderly men but neither directly measured Cr content or functional outcomes. This was addressed in a study of CrS combined with 14 weeks of RT (16). CrS increased FFM and improved isometric knee extensor strength but not functional capacity despite evidence of increased muscle TCr.

TABLE 4. CHANGE IN HEALTH STATUS AFTER PULMONARY REHABILITATION

	Within-Group Changes		Between-Group Mean Difference
CRQ-SR	Creatine	Placebo	
Dyspnea	0.8 (0.5 to 1.1)*	0.9 (0.6 to 1.2)*	−0.1 (−0.5 to 0.3)
Fatigue	0.8 (0.5 to 1.2)*	0.8 (0.4 to 1.2)*	0.03 (−0.5 to 0.5)
Emotion	0.8 (0.4 to 1.2)*	0.8 (0.5 to 1.1)*	−0.04 (−0.5 to 0.4)
Mastery	0.8 (0.4 to 1.2)*	0.7 (0.4 to 1.0)*	0.09 (−0.4 to 0.6)

Definition of abbreviation: CRQ-SR = self-reported Chronic Respiratory Questionnaire.

CRQ-SR results are presented as mean scores per domain. Data are presented as treatment group mean change (95% confidence interval). Comparisons were made using paired Student's *t* test for within-group difference. Independent Student's *t* test was used for between-group comparisons; no significant difference between treatment groups, $P > 0.05$.

* Statistically significant differences (from baseline), $P < 0.01$.

TABLE 5. MEAN CHANGE IN MUSCLE BIOPSY TOTAL CREATINE, CREATINE, AND PHOSPHOCREATINE CONTENT (mmol/kg/dm) AFTER LOADING WITH SUPPLEMENT

	Within-Group Mean Change (*95% CI*)		Between-Group Mean Difference
Metabolite	Creatine (*n* = *15*)	Placebo (*n* = *16*)	
TCr	34.3 (14.2 to 54.4)*	7.6 (−0.9 to 16.2)	26.7 (6.2 to 47.0)†
Cr	24.2 (11.2 to 37.1)*	8.7 (1.6 to 15.7)*	15.5 (1.7 to 29.3)†
PCr	10.1 (0.9 to 19.3)*	−1.0 (−7.1 to 5.0)	11.1 (0.8 to 21.5)†

Definition of abbreviations: CI = confidence interval; Cr = creatine; PCr = phosphocreatine content in muscle biopsy sample (mmol/kg dry matter weight); TCr = total creatine.

* $P < 0.05$ within-group change from baseline after loading.

† $P < 0.05$ between-group mean difference after loading.

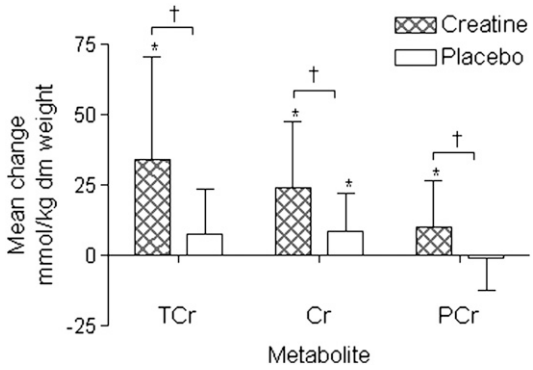

Figure 3. Change in mean (SD) muscle creatine content after loading with supplement. Cr = creatine; PCr = phosphocreatine; TCr = total creatine. $*P < 0.05$ within-group change from baseline; $^{\dagger}P < 0.05$ between-group difference.

Evidence suggests that Cr loading in athletes and healthy individuals can improve high-intensity, short-burst, intermittent exercise (41). There is less evidence that CrS enhances moderate to high-intensity prolonged exercise. This may explain why we did not identify any additional improvements with the ISWT or ESWT, because these measures may not be sensitive to this intervention. Home activity monitors may have been useful to pick up improvements in daily activities. It is unclear why our subjects did not show an improvement in muscle performance, particularly dynamic measures, and this may be related to the multifactorial nature of peripheral muscle dysfunction as seen in COPD or the age of our population. The most likely explanation is that any benefits of Cr have been submerged by the large training effect of the physical training alone.

The beneficial effects of CrS appear to be related to the extent of muscle Cr accumulation, with evidence that some subjects may be nonresponders (42). Acute CrS increases intramuscular TCr content by approximately 20% with 20 to 30% of the increase accounted for by PCr (43–45). The majority of uptake occurs in the first 2 days (44, 46). Muscle biopsy samples, used to assess TCr and PCr muscle content, have shown significant increases (15–40%) after short-term loading (20 g/d × 5 d) (41). We demonstrated a mean increase in TCr of 34% (Cr, 57%; PCr, 18%) after Cr loading. These increases were statistically significant against placebo.

Muscle biopsies after intense exercise show that CrS enhances resynthesis of PCr in the first 2 minutes of recovery (42). However, this was only seen in individuals who had increases in muscle TCr greater than 20 mmol/kg per day after loading. Our mean increase in TCr after Cr loading was 34.3 mmol/kg per day. Half the subjects achieved an increase of greater than 20 mmol/kg per day. We found no relationship between the degree of Cr uptake and subsequent physiologic improvement. It is possible that our numbers are too small to identify a subgroup of responders to Cr loading.

Gains in body mass, after acute Cr loading, are believed to be a result of intramuscular water retention due to the osmotic action of Cr in the muscle compartment and the influence of increased water content on protein synthesis (37, 44). Significant increases in body weight, averaging 1 kg after 6 days of Cr loading, have been demonstrated in young healthy subjects (46). Increases in FFM are not seen as often in the elderly (40, 47). We showed a mean change in FFM of 1.1 kg after Cr loading. Baseline body mass index (but not FFM) was slightly higher in our Cr group but this did not affect performance.

We have completed a large, adequately powered, randomized, double-blind, placebo-controlled trial and provided evidence of Cr uptake into peripheral muscle. This study strongly supports the extensive benefits of PR with excellent improvements in a range of outcome measures, including strength, functional measures, and health status. Our study suggests a placebo or learning effect during supplement loading before physical training, with small but significant improvements in strength and functional performance. We have evidence to suggest Cr uptake into muscles but are unable to explain why an increase in muscle Cr did not enhance training. Future work could look more closely at the effects of CrS on muscle protein synthesis and oxidative stress. In conclusion, CrS does not augment the substantial training effect of multidisciplinary PR for patients with COPD.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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References

1. American Thoracic Society; European Respiratory Society. Skeletal muscle dysfunction in chronic obstructive pulmonary disease: a statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999;159:S1–S40.
2. Swallow EB, Reyes D, Hopkinson NS, Man WD, Porcher R, Cetti EJ, Moore AJ, Moxham J, Polkey MI. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007;62:115–120.
3. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992;146:935–940.
4. Levy RD, Ernst P, Levine SM, Shennib H, Anzueto A, Bryan CL, Calhoon JH, Trinkle JK, Jenkinson SG, Gibbons WJ. Exercise performance after lung transplantation. *J Heart Lung Transplant* 1993;12: 27–33.
5. Gosselink R, Decramer M. Peripheral skeletal muscles and exercise performance in patients with chronic obstructive pulmonary disease. *Monaldi Arch Chest Dis* 1998;53:419–423.
6. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, Leblanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med* 1996;153:288–293.
7. Clark CJ, Cochrane L, Mackay E. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. *Eur Respir J* 1996;9:2590–2596.
8. Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996;348:1115–1119.
9. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001;56:779–784.
10. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG, Ionescu AA, *et al.* Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362–368.
11. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R, Herrerias C. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest* 2007;131:4S–42S.
12. Greenhaff PL. Creatine and its application as an ergogenic aid. *Int J Sport Nutr* 1995;5:S100–S110.
13. Casey A, Greenhaff PL. Does dietary creatine supplementation play a role in skeletal muscle metabolism and performance? *Am J Clin Nutr* 2000;72:607S–617S.
14. Harris RC, Soderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin Sci (Lond)* 1992;83:367–374.
15. Chrusch MJ, Chilibeck PD, Chad KE, Davison KS, Burke DG. Creatine supplementation combined with resistance training in older men. *Med Sci Sports Exerc* 2001;33:2111–2117.

16. Brose A, Parise G, Tarnopolsky MA. Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. *J Gerontol A Biol Sci Med Sci* 2003;58:11–19.
17. Fiaccadori E, Del Canale S, Vitali P, Coffrini E, Ronda N, Guariglia A. Skeletal muscle energetics, acid-base equilibrium and lactate metabolism in patients with severe hypercapnia and hypoxemia. *Chest* 1987; 92:883–887.
18. Steiner MC, Sewell L, Patel P, Singh SJ, Revill SM, Greenhaff PL, Morgan MD. A technique for sampling the quadriceps muscle during exercise in patients with COPD [abstract]. *Thorax* 2008;55(Suppl 3):A50.
19. Steiner MC, Singh SJ, Morgan MD. The contribution of peripheral muscle function to shuttle walking performance in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2005; 25:43–49.
20. Fuld JP, Kilduff LP, Neder JA, Pitsiladis Y, Lean ME, Ward SA, Cotton MM. Creatine supplementation during pulmonary rehabilitation in chronic obstructive pulmonary disease. *Thorax* 2005;60:531–537.
21. Griffiths TL, Proud D. Creatine supplementation as an exercise performance enhancer for patients with COPD? An idea to run with. *Thorax* 2005;60:525–526.
22. Deacon SJ, Vincent EE, Singh SJ, Greenhaff PL, Morgan MD. Creatine supplementation: an adjunct therapy in patients with COPD during pulmonary rehabilitation [abstract]. *Eur Respir J* 2008;28(Suppl 3):P3188.
23. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946.
24. British Thoracic Society; Association of Respiratory Technicians and Physiologists. Guidelines for the measurement of respiratory function: recommendations of the British Thoracic Society and the Association of Respiratory Technicians and Physiologists. *Respir Med* 1994;88:165–194.
25. Steiner MC, Barton RL, Singh SJ, Morgan MD. Bedside methods versus dual energy X-ray absorptiometry for body composition measurement in COPD. *Eur Respir J* 2002;19:626–631.
26. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;47:1019–1024.
27. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 1999;54: 213–222.
28. Li RC, Wu Y, Maffulli N, Chan KM, Chan JL. Eccentric and concentric isokinetic knee flexion and extension: a reliability study using the Cybex 6000 dynamometer. *Br J Sports Med* 1996;30:156–160.
29. Bergstrom J. Percutaneous needle biopsy of skeletal muscle in physiological and clinical research. *Scand J Clin Lab Invest* 1975;35:609–616.
30. Williams JE, Singh SJ, Sewell L, Guyatt GH, Morgan MD. Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). *Thorax* 2001;56:954–959.
31. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;47:81–87.
32. Sewell L, Singh SJ, Williams JE, Collier R, Morgan MD. How long should outpatient pulmonary rehabilitation be? A randomised controlled trial of 4 weeks versus 7 weeks. *Thorax* 2006;61:767–771.
33. American College of Sports Medicine. American College of Sports Medicine position stand: exercise and physical activity for older adults. *Med Sci Sports Exerc* 1998;30:992–1008.
34. Gordon A, Hultman E, Kaijser L, Kristjansson S, Rolf CJ, Nyquist O, Sylven C. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. *Cardiovasc Res* 1995;30:413–418.
35. Rawson ES, Clarkson PM. Acute creatine supplementation in older men. *Int J Sports Med* 2000;21:71–75.
36. Gotshalk LA, Volek JS, Staron RS, Denegar CR, Hagerman FC, Kraemer WJ. Creatine supplementation improves muscular performance in older men. *Med Sci Sports Exerc* 2002;34:537–543.
37. Branch JD. Effect of creatine supplementation on body composition and performance: a meta-analysis. *Int J Sport Nutr Exerc Metab* 2003;13: 198–226.
38. Nissen SL, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J Appl Physiol* 2003;94:651–659.
39. Vandenberghe K, Goris M, Van Hecke P, van Leemputte M, Vangerven L, Hespel P. Long-term creatine intake is beneficial to muscle performance during resistance training. *J Appl Physiol* 1997;83:2055–2063.
40. Bermon S, Venembre P, Sachet C, Valour S, Dolisi C. Effects of creatine monohydrate ingestion in sedentary and weight-trained older adults. *Acta Physiol Scand* 1998;164:147–155.
41. Kreider RB. Effects of creatine supplementation on performance and training adaptations. *Mol Cell Biochem* 2003;244:89–94.
42. Greenhaff PL, Bodin K, Soderlund K, Hultman E. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. *Am J Physiol* 1994;266:E725–E730.
43. Casey A, Constantin-Teodosiu D, Howell S, Hultman E, Greenhaff PL. Creatine ingestion favorably affects performance and muscle metabolism during maximal exercise in humans. *Am J Physiol* 1996;271: E31–E37.
44. Hultman E, Soderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in men. *J Appl Physiol* 1996;81:232–237.
45. Maughan R, Gleeson M, Greenhaff PL. Biochemistry of exercise and training. New York: Oxford University Press; 1997.
46. Gilliam JD, Hohzorn C, Martin D, Trimble MH. Effect of oral creatine supplementation on isokinetic torque production. *Med Sci Sports Exerc* 2000;32:993–996.
47. Eijnde BO, van Leemputte M, Goris M, Labarque V, Taes Y, Verbessem P, Vanhees L, Ramaekers M, Vanden Eynde B, Van Schuylenbergh R, *et al.* Effects of creatine supplementation and exercise training on fitness in men 55–75 yr old. *J Appl Physiol* 2003;95:818–828.