Arthritis Care & Research
Vol. 65, No. 9, September 2013, pp 1449–1459
DOI 10.1002/acr.22020

ORIGINAL ARTICLE

Creatine Supplementation in Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. **To investigate the efficacy and safety of creatine supplementation in fibromyalgia patients.**

Methods. **A 16-week, randomized, double-blind, placebo-controlled, parallel-group trial was conducted. Fibromyalgia patients were randomly assigned to receive either creatine monohydrate or placebo in a double-blind manner. The patients were evaluated at baseline and after 16 weeks. Muscle function, aerobic conditioning, cognitive function, quality of sleep, quality of life, kidney function, and adverse events were assessed. Muscle phosphorylcreatine content was measured through ^{31}P magnetic resonance spectroscopy.**

Results. **After the intervention, the creatine group presented higher muscle phosphorylcreatine content when compared with the placebo group (+80.3% versus −2.7%; $P = 0.04$). Furthermore, the creatine group presented greater muscle strength than the placebo group in the leg press and chest press exercises (+9.8% and +1.2% for creatine versus −0.5% and −7.2% for placebo, respectively; $P = 0.02$ and $P = 0.002$, respectively). Isometric strength was greater in the creatine group than in the placebo group (+6.4% versus −3.2%; $P = 0.007$). However, no general changes were observed in aerobic conditioning, pain, cognitive function, quality of sleep, and quality of life. Food intake remained unaltered and no side effects were reported.**

Conclusion. **Creatine supplementation increased intramuscular phosphorylcreatine content and improved lower- and upper-body muscle function, with minor changes in other fibromyalgia features. These findings introduce creatine supplementation as a useful dietary intervention to improve muscle function in fibromyalgia patients.**

INTRODUCTION

Creatine plays a crucial role in rapid energy provision during muscle contraction involving the transfer of an N-phosphoryl group from phosphorylcreatine to ADP to regenerate ATP, through a reversible reaction catalyzed by creatine kinase. Moreover, creatine can act as a "spatial energy buffer" by transferring energy from mitochondria to cytosol, which is possible due to the presence of different creatine kinase isoforms linking the sites of ATP generation (i.e., mitochondria) to those of ATP consumption (i.e., skeletal muscle and brain) (1).

Creatine supplementation recently has been recognized as a potential adjunct treatment in a broad spectrum of diseases, including those characterized by muscle wasting and dysfunction (2), low bone mass (3), joint syndromes (4), and central nervous (5) and metabolic disorders (6,7).

Fibromyalgia is a chronic syndrome of unknown etiology characterized by generalized pain, muscle dysfunction, disability, fatigue, psychological distress, cognitive dysfunction, and sleep and mood disturbances (8,9). The conventional treatment of fibromyalgia involves drug therapy (e.g., antidepressants, opioids, sedatives, and antiepileptic medications) along with nonpharmacologic measures (e.g., physical exercise, massage, and behavioral therapy) (10,11). Nonetheless, the current treatment has limited efficacy and some adverse effects (12).

There is evidence suggesting that abnormal muscle bioenergetics may underlie the physiopathology of fibromy-

ClinicalTrials.gov identifier: NCT00749983.
Supported by CNPq and FAPESP (FBB: 2011/08302-0).
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Submitted for publication October 10, 2012; accepted in revised form March 20, 2013.

Significance & Innovations

- This is the first randomized controlled trial to investigate the efficacy and safety of creatine supplementation in fibromyalgia patients.
- Sixteen weeks of creatine supplementation significantly increased muscle phosphorylcreatine content and lower- and upper-body muscle function, but had only minor effects in fibromyalgia general symptoms.
- These findings reveal the potential of creatine supplementation as a useful dietary intervention to improve muscle function in fibromyalgia patients.

algia (13,14). In this respect, Park et al (14) used ^{31}P magnetic resonance spectroscopy (^{31}P-MRS) to show that patients with fibromyalgia present reduced intramuscular ATP and phosphorylcreatine content when compared to healthy peers. Furthermore, the authors reported that patients had lower oxidative potential and total oxidative capacity than controls, as estimated by the concentration of phosphagen metabolites. In theory, low ATP and phosphorylcreatine concentration could explain muscle dysfunction (13,14), which is often associated with other common clinical features seen in fibromyalgia, including poor quality of life, pain, and fatigue (15). The putative role of creatine supplementation in restoring the phosphagen reservoir could attenuate muscle dysfunction and possibly confer clinical benefits to fibromyalgia patients. In addition to the aforementioned hypothesis, it has been speculated that creatine supplementation could improve fibromyalgia symptoms by increasing brain creatine content (16), which seems to be reduced in psychiatric illnesses such as posttraumatic stress disorder (17). Even though some authors have suggested the latter as a potential mechanism to explain the benefits of creatine supplementation in fibromyalgia (8), the evidence supporting the efficacy of creatine supplementation in augmenting brain creatine content remains controversial.

Leader et al (8) performed an uncontrolled study to assess the efficacy of supplementing creatine as an "add on" to existing therapies in patients with fibromyalgia. The authors observed significant improvements in parameters related to the severity of the disease, quality of life, sleep, disability, and pain. However, the lack of a control group, the short-term nature of the intervention, the large withdrawal rate of 47%, the lack of mechanistic investigations, and the individual disparity in response to creatine supplementation among the patients precluded drawing broad conclusions.

Therefore, this 16-week, randomized, double-blind, placebo-controlled clinical trial aimed to investigate the effects of creatine supplementation in fibromyalgia patients. Based on the well-established role of creatine on skeletal muscle bioenergetics (1), muscle function was considered the primary outcome in this study, whereas the overall symptoms were considered as secondary outcomes.

Table 1. Patients' characteristics and drug regimens*

	Placebo (n = 13)	Creatine (n = 15)
Age, years	49.0 ± 10.1	48.7 ± 8.4
Weight, kg	65.0 ± 14.1	70.8 ± 16.5
Height, meters	1.56 ± 0.06	1.58 ± 0.08
BMI, kg/m^2	26.7 ± 5.1	28.1 ± 4.8
Disease duration, years	4 ± 2	4 ± 5
Medications, no. (%)		
Acetaminophen	3 (23.1)	5 (33.3)
Amitriptyline	3 (23.1)	4 (26.7)
Amlodipine	1 (7.7)	0 (0.0)
Atenolol	1 (7.7)	2 (13.3)
Celecoxib	1 (7.7)	2 (13.3)
Cyclobenzaprine	7 (53.8)	5 (33.3)
Clonazepam	1 (7.7)	0 (0.0)
Diacerein	0 (0.0)	1 (6.7)
Fluoxetine	4 (30.8)	3 (20)
Gabapentin	0 (0.0)	2 (13.3)
Glibenclamide	0 (0.0)	1 (6.7)
Omeprazole	2 (15.4)	5 (33.3)
Propranolol	0 (0.0)	1 (6.7)
Ranitidine	0 (0.0)	1 (6.7)
Sertraline	1 (7.7)	3 (20)

* Values are the mean ± SD unless otherwise indicated. BMI = body mass index.

SUBJECTS AND METHODS

Subjects. The sample consisted of women diagnosed with primary fibromyalgia according to the revised American College of Rheumatology preliminary criteria (18). Exclusion criteria consisted of 1) cardiovascular involvement (e.g., arrhythmias, arterial hypertension, heart failure, conduction disturbances, myocarditis, and pericarditis), 2) tobacco usage, and 3) all other chronic diseases (e.g., rheumatic diseases, cardiovascular diseases, metabolic diseases, and chronic kidney diseases). Drug therapy remained stable throughout the trial. Patients' main characteristics and their medication regimens are shown in Table 1. This study was approved by the local ethical committee and all subjects signed the written informed consent. All of the procedures were in accordance with the Helsinki Declaration revised in 2008.

Experimental protocol. A 16-week, centrally randomized, double-blind, placebo-controlled, parallel-group trial was conducted between March 2011 and July 2012 at the School of Medicine, University of Sao Paulo (Sao Paulo, Brazil), and reported according to the guidelines of the Consolidated Standards of Reporting Trials statement.

The patients were randomly assigned to receive either creatine monohydrate or placebo in a double-blind fashion. We assigned patients to the treatment sequence by using a computer-generated randomization code (Minitab, version 15) in blocks of 4 in a 1:1 ratio. The patients were assessed at baseline (PRE) and after 16 weeks (POST). Muscle function, as assessed by strength tests, was considered the primary outcome. Aerobic conditioning, cognitive function, disease-specific clinical parameters, quality of

sleep, kidney function, and quality of life were considered as secondary outcomes. Adverse events were recorded throughout the trial. Possible differences in dietary intake were assessed by three 24-hour dietary recalls. In a subset of randomly selected patients (n = 8 per group), muscle phosphorylcreatine content was measured through ^{31}P-MRS.

Creatine supplementation protocol. The creatine group received 20 gm of creatine monohydrate for 5 days divided into 4 equal doses, followed by 5 gm/day as a single dosage throughout the trial. The placebo group was given the same dose of dextrose. The individuals were advised to consume their supplements preferably along with meals (e.g., breakfast, lunch, afternoon snack, and dinner). The supplement packages were coded so that neither the investigators nor the participants were aware of the contents until completion of the analyses. The supplements were provided by a staff member of our research team who did not have any participation in the data acquisition, analyses, and interpretation. Adherence to the intervention was monitored by the same staff member who called the subjects on a weekly basis inquiring about the compliance to the supplementation protocol. In order to verify the purity of the creatine used, a sample was analyzed by high-performance liquid chromatography and purity was established as 99.9%.

Muscle function tests. Prior to the actual muscle function tests, the patients underwent 3 familiarization sessions, separated for at least 72 hours. Prior to the 1-repetition maximum (1-RM) tests, 2 warm-up sets interspaced by 2-minute intervals were performed. Thereafter, the patients had up to 5 attempts to achieve the 1-RM load (e.g., maximum weight that could be lifted once with the proper technique), with a 3-minute interval between attempts. Tests of 1-RM were conducted for the chest press and leg press exercises. Additionally, upper extremity isometric strength was determined by a handgrip test. All of these tests have been commonly used to assess muscle function in a variety of populations (including rheumatic diseases) (19) and were performed following standard recommendations (20).

Maximum Vo_2 (Vo_{2max}) test. All of the subjects underwent a treadmill cardiopulmonary test before and after the intervention. Attainment of Vo_{2max} was accepted when 2 of the following 3 criteria were met: 1) a plateau in Vo_2, 2) a respiratory exchange ratio >1.1, and/or 3) volitional exhaustion. The ventilatory anaerobic threshold was determined to occur at the break point between the increase of carbon dioxide output and Vo_2. The respiratory compensation point was determined to occur where the ventilatory equivalent for carbon dioxide was the lowest before a systematic increase.

Assessments of pain, quality of sleep, and quality of life. In order to assess the impact of the disease, we applied the Fibromyalgia Impact Questionnaire (FIQ) (21). This questionnaire comprises 10 scaled questions regarding functional disability, pain intensity, sleep disorders, anxiety, depression, and well-being over the past week. The score is directly proportional to the disease's impact, with higher total scores indicating greater dysfunction. Pain was assessed by the visual analog scale and by the McGill Pain Questionnaire (MPQ) (22), which consists of 4 groups of pain domains (i.e., sensory, affective, evaluative, and miscellaneous). In both, higher scores correspond to higher pain.

To assess the quality of sleep, the Post-Sleep Inventory (PSI) was applied. This questionnaire comprises 30 items divided into 3 categories, including presleep (bedtime), during sleep, and postsleep (23), with higher scores indicating better quality of sleep. Moreover, to measure the quality of life, the Short Form 36 (SF-36) health survey was used (24). This instrument is divided into 8 domains, including physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health. Raw data were transformed into scores ranging from 0–100, with higher scores indicating better quality of life. The Brazilian validated versions of the mentioned instruments were used in this study.

Assessments of cognitive function. Cognitive performance was measured by a battery of tests comprised of the following: Mini-Mental State Examination (25), Stroop Test (26), Trail-Making Test (27), Digit Span Test (28), and Delayed Recall Test (29).

The Mini-Mental State Examination has been used as a brief neuropsychological screening consisting of questions on temporal and special orientation, immediate memory, attention/concentration, and delayed recall. Higher scores indicate better performance in the test. The Stroop Test (Victoria version) has been considered as a measure of the selective attention and the susceptibility to interference from conflicting stimuli. It includes 3 conditions that consist of naming the color of dots (i.e., "color"), neutral words (i.e., "non-color word"), and color words printed in incongruent colors (i.e., "color word"). Performance is assessed based on the time to complete each condition. The Trail-Making Test has been used to assess inhibition function. It includes 2 conditions (i.e., "part A" and "part B"), where the part A condition reflects motor and visual control and the part B condition reflects the additional executive control needed to switch between the number and letter sequences. Performance is assessed based on the time to complete each condition. In order to assess the short-term memory, we applied the Digit Span Test, which requires the participant to orally repeat a sequence of digits forward and backward. Performance is assessed based on the number of digits that the participant is able to correctly recall. We also used the Delayed Recall Test from the Brief Cognitive Battery, which consists of 10 line drawings that are presented 3 times to the participant, and 5 minutes later, the subject is asked to recall as many drawings as possible. The aforementioned instruments were previously validated in Brazilian cohorts.

Kidney function. Blood samples were obtained from an antecubital vein, following a 12-hour overnight fast. Sub-

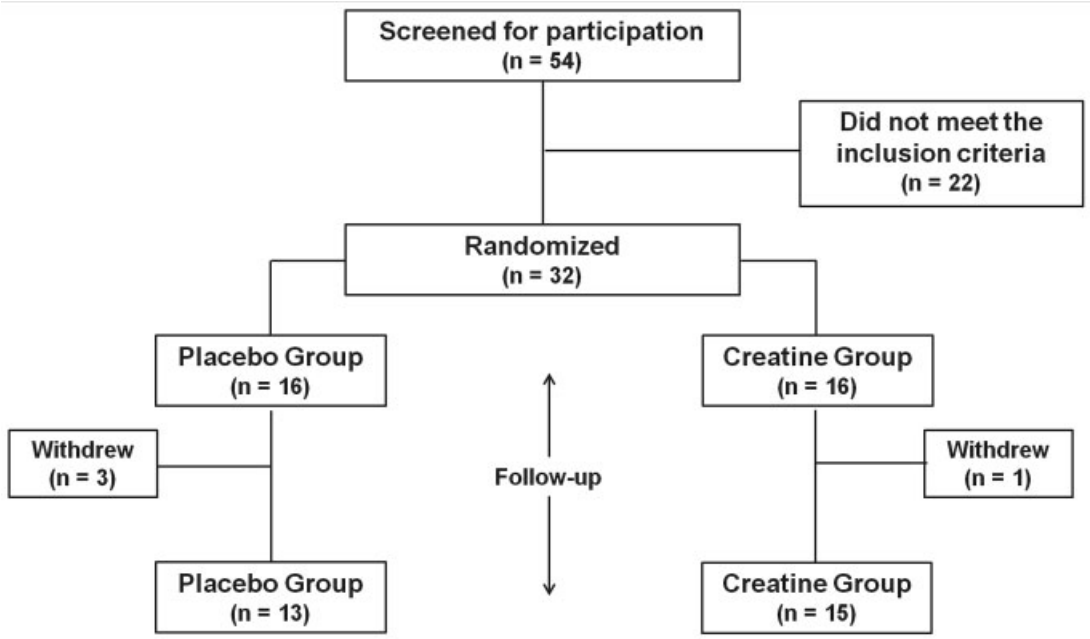

Figure 1. Patients' disposition.

jects followed their normal diet consumption during the 24-hour urine collection. Urine samples were stored at approximately 4°C. Creatinine was determined using Jaffe's kinetic method. Urinary sodium and potassium were assessed by using a flame photometer. Urea was assessed by an ultraviolet kinetic method. Albuminuria was determined by means of nephelometry and proteinuria was measured through the benzethonium chloride method. All samples were analyzed in duplicate and the mean value was used for data analysis.

Muscle phosphorylcreatine content. Muscle phosphorylcreatine content was assessed in vivo by ^{31}P-MRS using a whole-body 3.0T magnetic resonance imaging scanner (Achieva Intera, Philips) and a ^{31}P surface coil with a diameter of 14 cm. In brief, the surface coil was placed centered under the calf muscle of the left leg. The scanner body coil was used to obtain conventional anatomic T1-weighted magnetic resonance images in the 3 orthogonal planes. ^{31}P-MRS was acquired using the image selected in the in vivo spectroscopy sequence with an echo time and repetition time of 0.62 msec and 4,500 msec, respectively. Spectrum bandwidth was 3,000 Hz with 2,048 data points and 64 repetitions. Spectrum raw data were analyzed with Java magnetic resonance user interface software, and processing steps included apodization to 5 Hz, Fourier transform, and phase correction. For spectrum quantification, the AMARES (advanced method for accurate, robust, and efficient spectral fitting) algorithm was used, taking into account the prior knowledge of inorganic phosphate, phosphodiester, and phosphorylcreatine singlets; α-ATP and γ-ATP doublets; and β-ATP triplets. The phosphorylcreatine signal was quantified relative to the β-ATP signal, assuming a constant β-ATP concentration of 4.7 mmoles/kg (14). No corrections were performed for saturation effects related to different relaxation times of phosphorylcreatine and ATP.

Food intake assessment. Food intake was assessed by three 24-hour dietary recalls undertaken on separate days (2 weekdays and 1 weekend day) using a visual aid photo album of real foods. The 24-hour dietary recall consists of listing the foods and the beverages consumed during 24 hours prior to the recall. Energy and macronutrient intakes were analyzed by the Brazilian software Virtual Nutri.

Sample size and statistical analysis. Sample size was determined with the aid of G-Power software, version 3.1.2. The analysis was conducted by inputting the alpha error (0.05), the power (1 − beta error = 0.95), and the effect size (0.59) calculated from a previous study evaluating the effects of creatine supplementation on muscle function in an elderly population (30). Calculation was based on an analysis of variance with repeated measures (within–between interaction) and the total sample size was 24 patients. In order to account for midtrial withdrawals, we enlarged our sample to 30 participants.

All values were converted into delta scores (i.e., POST − PRE values) and thereafter tested by unpaired Student's *t*-test. Additionally, Cohen's d was used to determine the effect size for the dependent variables (31). Baseline data were compared using Fisher's exact test. The significance level was previously set at P values less than 0.05, with a trend toward significance being accepted at P values less than 0.1. Data are shown as the mean ± SD, difference between delta changes, and 95% confidence interval (95% CI), except when otherwise stated.

RESULTS

Patients. Figure 1 shows the patients' disposition. Fifty-four patients were screened for participation and 32 met

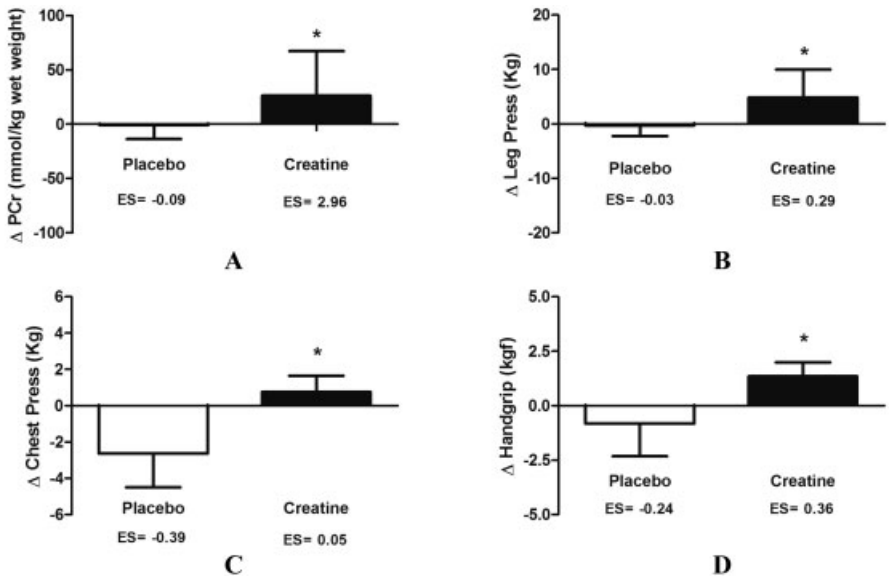

Figure 2. Changes in muscle phosphorylcreatine (PCr) and muscle function after creatine or placebo supplementation. **A,** Muscle PCr data, **B,** Leg press data, **C,** Chest press data, and **D,** Handgrip data. * = significant difference between the groups ($P = 0.04$, $P = 0.02$, $P = 0.002$, and $P = 0.007$ for **A, B, C,** and **D,** respectively); ES = effect size.

the inclusion criteria. These patients were randomly assigned to either the creatine (n = 16) or placebo (n = 16) group. Four patients withdrew due to personal reasons (3 from the placebo group and 1 from the creatine group) during the pretest period. Therefore, 28 patients who completed the trial were analyzed (n = 15 creatine, n = 13 placebo).

Food intake, assessment of blinding, and adherence to the supplementation protocol. Mean ± SD total energy (creatine: PRE = 1,745.6 ± 241.8 kcal and POST = 1,554.3 ± 379.6 kcal, placebo: PRE = 1,391.0 ± 383.6 kcal and POST = 1,229.5 ± 409.0 kcal; $P = 0.88$), carbohydrate (creatine: PRE = 225.4 ± 59.0 gm and POST = 196.0 ± 39.9 gm, placebo: PRE = 175.3 ± 31.6 gm and POST = 161.3 ± 61.1 gm; $P = 0.50$), lipid (creatine: PRE = 63.5 ± 13.1 gm and POST = 58.6 ± 24.5 gm, placebo: PRE = 54.4 ± 27.2 gm and POST = 43.4 ± 15.4 gm; $P = 0.68$), and protein (creatine: PRE = 68.2 ± 20.0 gm and POST = 60.7 ± 24.8 gm, placebo: PRE = 55.0 ± 23.6 gm and POST = 48.4 ± 22.1 gm; $P = 0.96$) intake did not significantly differ between the groups.

Seven (53.8%) of the patients correctly identified the supplement in the placebo group, whereas 9 patients (60.0%) were able to identify the correct supplement in the creatine group ($P = 0.70$ by Fisher's exact test). The self-reported adherence to the supplementation protocol was 100%.

Muscle phosphorylcreatine content. After the intervention, the creatine group presented higher muscle phosphorylcreatine content when compared with the placebo group (+80.3% versus −2.7%, mean ± SD difference between delta changes −27.2 ± 15.3 [95% CI −59.9, 5.6]; $P = 0.04$) (Figure 2A).

Muscle function and aerobic capacity. Following the intervention, the creatine group presented greater strength than the placebo group in the leg press (+9.8% versus −0.5%, mean ± SD difference between delta changes −5.1 ± 2.2 [95% CI −9.6, −0.6]; $P = 0.02$) and chest press exercises (+1.2% versus −7.2%, mean ± SD difference between delta changes −3.4 ± 1.0 [95% CI −5.5, −1.3]; $P = 0.002$) (Figures 2B and C). Likewise, isometric strength was greater in the creatine group than in the placebo group (+6.4% versus −3.2%, mean ± SD difference between delta changes −2.1 ± 0.7 [95% CI −3.6, −0.6]; $P = 0.007$) (Figure 2D). In contrast, the parameters related to aerobic capacity were not altered by creatine supplementation ($P > 0.05$ for all variables in Table 2).

Pain, quality of sleep, and quality of life. The results regarding pain, quality of sleep, and quality of life are shown in Table 3. FIQ and MPQ domains were not altered as a result of the intervention. The presleep domain from the PSI questionnaire was positively changed by creatine supplementation (+9.1%; $P = 0.006$ versus placebo). The remaining PSI domains remained unchanged ($P > 0.05$ for all). The mental health domain of the SF-36 was improved following creatine supplementation (+29.3%; $P = 0.03$ versus placebo). The other SF-36 domains were not modified in both groups ($P > 0.05$ for all domains).

Cognitive performance. The results regarding cognitive performance are shown in Table 4. Except for incidental memory from the Delayed Recall Test, which tended to improve after creatine supplementation (+11.8 %; $P = 0.07$), no other parameter was changed after the intervention ($P > 0.05$ for all).

Table 2. Aerobic capacity at baseline and after 16 weeks of creatine or placebo supplementation*

	Placebo (n = 13)				Creatine (n = 15)				Placebo vs. creatine		
Variable	PRE	POST	Δ	ES	PRE	POST	Δ	ES	Difference in Δ	95% CI	*P*
Vo_{2max}, liters × $mins^{-1}$	1.3 ± 0.3	1.5 ± 0.6	0.2 ± 0.4	0.7	1.5 ± 0.3	1.7 ± 0.5	0.2 ± 0.3	0.7	0.0 ± 0.1	−0.3, 0.3	0.50
Vo_{2max}, ml × $mins^{-1}$ × kg^{-1}	21.7 ± 4.3	24.8 ± 6.8	3.1 ± 5.8	0.7	22.7 ± 3.0	24.6 ± 5.0	1.9 ± 4.3	0.6	1.2 ± 1.9	−2.7, 5.1	0.27
Time to achieve Vo_{2max}, mins	10.5 ± 2.2	11.6 ± 1.8	1.1 ± 1.3	0.5	10.9 ± 3.2	11.5 ± 3.1	0.5 ± 1.4	0.2	0.6 ± 0.5	−0.4, 1.6	0.13
VAT, liters × $mins^{-1}$	0.9 ± 0.3	1.0 ± 0.4	0.1 ± 0.2	0.3	0.9 ± 0.2	1.1 ± 0.3	0.2 ± 0.3	1.0	−0.1 ± 0.1	−0.3, 0.1	0.16
Time to achieve VAT, mins	4.7 ± 1.8	5.7 ± 2.8	1.0 ± 1.5	0.5	5.2 ± 1.3	5.8 ± 1.3	0.6 ± 0.7	0.5	0.4 ± 0.4	−0.5, 1.3	0.18
RCP, liters × $mins^{-1}$	1.2 ± 0.3	1.3 ± 0.4	0.1 ± 0.3	0.3	1.3 ± 0.2	1.4 ± 0.3	0.1 ± 0.3	0.5	0.0 ± 0.1	−0.2, 0.2	0.50
Time to achieve RCP, mins	7.6 ± 1.9	8.0 ± 1.8	0.3 ± 1.8	0.2	8.8 ± 2.7	8.7 ± 2.3	−0.1 ± 1.4	0.0	0.4 ± 0.6	−0.8, 1.6	0.25

* Values are the mean ± SD unless otherwise indicated. There were no significant differences between the groups. PRE = baseline; POST = posttest; Δ = absolute delta change; ES = effect size; 95% CI = 95% confidence interval; Vo_{2max} = maximum Vo_2; VAT = ventilatory anaerobic threshold; RCP = respiratory compensation point.

Kidney function assessment and self-reported side effects. All serum and urinary parameters related to kidney function remained within the normal range and were comparable between the groups after the intervention ($P > 0.05$ for all parameters) (Table 5). There were no self-reported side effects throughout the study.

DISCUSSION

To our knowledge, this is the first randomized controlled trial to investigate the efficacy and safety of creatine supplementation in patients with fibromyalgia. The current findings revealed that 16 weeks of creatine supplementation significantly increased muscle phosphorylcreatine content and lower- and upper-body muscle function, but had only a minor effect on fibromyalgia general symptoms.

^{31}P-MRS studies have pointed out abnormalities in intramuscular phosphagen metabolism (e.g., reduced ATP and phosphorylcreatine contents) in patients with fibromyalgia (29). Importantly, the current study demonstrated for the first time that creatine supplementation can significantly augment intramuscular phosphorylcreatine content in fibromyalgia patients. Moreover, the extent of the increase in phosphorylcreatine content seen in our patients was noticeably superior to that usually seen in healthy subjects (~80% versus ~8–13%) (30–32). This finding further supports previous evidence suggesting that intramuscular creatine and phosphorylcreatine accumulation in response to creatine supplementation is inversely associated with initial intramuscular creatine and phosphorylcreatine content (32). Creatine supplementation was able to restore the muscle phosphorylcreatine reservoir in fibromyalgia, which likely explains the improvements in muscle strength observed in this study.

It is currently unclear why patients with fibromyalgia present with lower intramuscular phosphagen compounds and oxidative capacity than healthy subjects. However, it has been suggested that abnormally thickened capillaries with impaired diffusion and decreased blood flow in the muscles of patients with fibromyalgia could lead to reduced tissue oxygenation, which could in turn cause reductions in ATP synthesis and phosphorylcreatine content (13,14). Interestingly, this hypothesis is in line with Bennett's assertion that the diminished strength and aerobic conditioning in fibromyalgia partially would be a consequence of pain that could reflexively inhibit muscle contraction (13). Bennett (13) further suggests that pain could be a consequence of muscle damage caused by focal areas of ischemia with resultant decreases in ATP synthesis. This injury would in turn promote an influx of calcium ions and an efflux of potassium ions. Therefore, ATP levels would be further diminished and the cycle of damage, pain, and intramuscular energy dysfunction would become self-perpetuating (13,32). The current findings allow the suggestion that creatine supplementation could block this vicious circle by inducing an increase in intramuscular phosphorylcreatine, possibly reestablishing ATP homeostasis.

We also hypothesized that the potential creatine supplementation–induced augmentation in intramuscular phosphorylcreatine content and the consequent ATP homeostasis reestablishment would promote improvements not only in muscle function, but also in other fibromyalgia clinical symptoms such as pain and aerobic deconditioning, possibly leading to better quality of life. In fact, a nonrandomized study provided preliminary findings showing that 8 weeks of creatine supplementation as an "add on" to existing therapies improved the inventory scores concerning quality of sleep, pain levels, and patient impression of disease burden in fibromyalgia patients (8). Conversely, none of these parameters consistently improved after creatine supplementation in the current study, with the exception of the presleep and mental health subscales of the PSI and SF-36, respectively. Differences in study design may partially explain these conflicting results. In this respect, it is worthy to note that Leader et al (8) adopted a nonrandomized design, whereas we adopted a randomized, double-blind, placebo-controlled design. Therefore, it is impossible to rule out the influence of a placebo effect on the extensive positive results re-

Table 3. Pain, sleep, and quality of life parameters at baseline and after 16 weeks of creatine or placebo supplementation*

Variable (score range)	Placebo (n = 13)				Creatine (n = 15)				Placebo vs. creatine		
	PRE	POST	Δ	ES	PRE	POST	Δ	ES	Difference in Δ	95% CI	*P*
FIQ											
Physical impairment (0–10)	3.2 ± 1.7	2.3 ± 1.3	−0.9 ± 1.9	−0.5	3.9 ± 2.6	2.5 ± 2.5	−1.4 ± 2.6	−0.5	0.5 ± 0.9	−1.3, 2.3	0.29
Feel good (0–10)	4.0 ± 2.3	4.4 ± 3.1	0.4 ± 2.4	0.2	3.7 ± 3.1	5.7 ± 2.9	2.0 ± 4.5	0.7	−1.6 ± 1.4	−4.4, 1.2	0.13
Absence from work (0–10)	3.2 ± 3.0	0.8 ± 1.1	−2.4 ± 3.5	−0.8	1.2 ± 2.4	1.3 ± 2.5	0.1 ± 5.0	0.0	−2.5 ± 1.7	−5.9, 0.9	0.14
Ability to work (0–10)	7.8 ± 1.7	5.3 ± 3.3	−2.5 ± 3.0	−1.5	7.0 ± 3.0	5.4 ± 3.5	−1.6 ± 4.3	−0.5	−0.9 ± 1.4	−3.8, 2.0	0.27
Pain (0–10)	8.3 ± 1.5	7.2 ± 2.7	−1.0 ± 2.0	−0.7	8.3 ± 2.4	6.0 ± 3.1	−2.4 ± 4.0	−1.0	1.4 ± 1.2	−1.1, 3.9	0.15
Fatigue (0–10)	8.0 ± 1.8	6.9 ± 3.4	−1.1 ± 2.2	−0.6	8.9 ± 1.5	6.9 ± 2.9	−2.0 ± 3.3	−1.3	0.9 ± 1.1	−1.3, 3.1	0.20
Rested (0–10)	7.1 ± 2.8	5.0 ± 3.7	−2.0 ± 3.6	0.7	9.2 ± 0.8	6.9 ± 3.2	−2.3 ± 3.2	−3.0	0.3 ± 1.3	−2.3, 2.9	0.41
Stiffness (0–10)	7.4 ± 2.6	5.5 ± 3.5	−1.9 ± 3.9	−0.7	6.8 ± 3.9	4.8 ± 3.9	−2.0 ± 4.6	−0.5	0.1 ± 1.6	−3.2, 3.4	0.48
Anxiety (0–10)	6.8 ± 3.2	4.9 ± 3.9	−1.9 ± 3.7	−0.6	8.0 ± 3.4	7.2 ± 2.8	−0.8 ± 4.7	−0.2	1.1 ± 1.6	−4.4, 2.2	0.25
Depression (0–10)	6.4 ± 2.9	5.8 ± 3.9	−0.7 ± 4.7	−0.2	8.3 ± 2.8	5.9 ± 3.6	−2.3 ± 3.5	−0.8	1.6 ± 1.5	−1.6, 4.8	0.16
Total score (0–100)	62.2 ± 0.8	48.1 ± 16.3	−14.1 ± 16.2	−1.3	65.3 ± 10.4	52.6 ± 18.5	−12.7 ± 19.0	−1.2	−1.4 ± 7.0	−15.2, 12.4	0.42
Pain (MPQ)											
Sensory (0–42)	22.0 ± 3.8	19.7 ± 7.7	−2.3 ± 7.4	−0.6	22.2 ± 7.0	18.7 ± 4.8	−3.5 ± 8.3	−0.5	1.2 ± 3.0	−4.9, 7.3	0.35
Affective (0–14)	7.6 ± 2.9	6.2 ± 4.1	−1.4 ± 4.6	−0.5	7.0 ± 3.0	4.7 ± 2.6	−2.2 ± 4.1	−0.8	−0.8 ± 1.6	−2.6, 4.2	0.30
Evaluative (0–5)	3.3 ± 1.3	2.6 ± 1.7	−0.8 ± 1.0	−0.6	3.3 ± 1.5	2.5 ± 1.5	−0.8 ± 1.8	−0.5	0.0 ± 0.6	−1.2, 1.2	0.47
Miscellaneous (0–17)	9.3 ± 3.0	7.4 ± 3.3	−1.9 ± 3.2	−0.6	8.8 ± 3.3	5.1 ± 3.4	−3.7 ± 5.1	−1.1	1.8 ± 1.6	−1.6, 5.2	0.15
Total score (0–78)	42.2 ± 8.3	36.0 ± 17.5	−6.4 ± 13.6	−1.1	41.3 ± 12.8	31.0 ± 10.9	−10.3 ± 16.6	−0.9	3.9 ± 5.8	−8.0, 15.8	0.26
Visual analog scale (0–10)	5.7 ± 2.5	3.9 ± 2.3	−1.8 ± 1.8	−0.7	5.2 ± 2.8	2.8 ± 3.0	−2.4 ± 4.6	−0.9	0.6 ± 1.4	−2.2, 3.4	0.33
Sleep (PSI)											
Presleep (8–104)	63.7 ± 17.6	48.2 ± 15.7	−15.5 ± 17.6	−0.9	39.8 ± 14.3	43.4 ± 15.3	3.6 ± 19.0	0.2	−19.1 ± 7.0	−33.4, −4.8	0.006†
During the night (13–169)	82.6 ± 15.5	83.8 ± 18.1	1.2 ± 16.5	0.1	78.5 ± 19.8	83.7 ± 22.0	5.2 ± 15.9	0.3	−4.0 ± 6.1	−16.6, 8.6	0.26
Postsleep (9–117)	54.0 ± 18.6	59.2 ± 18.4	5.2 ± 15.0	0.4	52.3 ± 19.7	54.9 ± 14.1	2.6 ± 20.9	0.1	2.6 ± 7.0	−11.7, 16.9	0.36
Total score (13–390)	200.3 ± 37.8	191.1 ± 43.1	−9.2 ± 31.5	−0.2	170.6 ± 43.0	182.1 ± 45.0	11.5 ± 42.7	0.3	−20.7 ± 14.4	−50.3, 8.9	0.09
SF-36 domains											
Physical functioning (0–100)	29.6 ± 24.1	33.8 ± 18.7	4.2 ± 24.2	0.2	35.0 ± 23.5	47.7 ± 23.9	12.7 ± 20.8	0.5	−8.5 ± 8.5	−26.0, 9.0	0.17
Physical role functioning (0–100)	8.8 ± 10.3	10.0 ± 9.0	1.3 ± 11.5	0.1	6.5 ± 6.9	10.8 ± 8.9	4.2 ± 10.2	0.6	−2.9 ± 4.1	−11.3, 5.5	0.25
Bodily pain (0–100)	41.4 ± 8.6	38.9 ± 7.8	−2.5 ± 14.1	−0.3	35.2 ± 2.2	38.5 ± 6.6	3.2 ± 12.1	0.3	−5.7 ± 5.0	−15.9, 4.5	0.14
General health (0–100)	40.4 ± 27.9	44.2 ± 27.9	3.8 ± 24.2	0.1	47.7 ± 19.2	52.3 ± 24.6	4.6 ± 12.8	0.2	−0.8 ± 7.2	−15.5, 13.9	0.45
Vitality (0–100)	39.2 ± 26.3	39.2 ± 24.6	0.0 ± 27.6	0.0	33.1 ± 21.0	41.9 ± 27.0	8.8 ± 23.2	0.4	−8.8 ± 6.0	−28.5, 10.9	0.20
Social role functioning (0–100)	50.0 ± 27.7	51.0 ± 26.4	1.0 ± 22.3	0.0	55.8 ± 24.8	63.5 ± 28.6	7.7 ± 30.4	0.3	−6.7 ± 10.2	−27.7, 14.3	0.27
Emotional role functioning (0–100)	9.6 ± 10.4	10.2 ± 9.5	0.6 ± 11.5	0.1	9.4 ± 8.9	14.8 ± 9.7	5.4 ± 11.4	0.6	−4.8 ± 4.3	−13.7, 4.1	0.16
Mental health (0–100)	48.0 ± 22.1	43.0 ± 21.9	−5.0 ± 20.8	−0.2	40.9 ± 18.6	52.9 ± 20.1	12.0 ± 22.3	0.6	−17.0 ± 8.2	−33.8, −0.2	0.03†

* Values are the mean ± SD unless otherwise indicated. PRE = baseline; POST = posttest; Δ = absolute delta change; ES = effect size; 95% CI = 95% confidence interval; FIQ = Fibromyalgia Impact Questionnaire; MPQ = McGill Pain Questionnaire; PSI = Post-Sleep Inventory; SF-36 = Short Form 36 health survey.
† Significant difference between the groups.

Table 4. Cognitive performance at baseline and after 16 weeks of creatine or placebo supplementation*

Variable (score range)	Placebo (n = 13)				Creatine (n = 15)				Placebo vs. creatine		
	PRE	POST	Δ	ES	PRE	POST	Δ	ES	Difference in Δ	95% CI	*P*
MMSE (0–30)	23.7 ± 3.4	24.8 ± 3.3	1.1 ± 2.1	0.3	25.7 ± 2.6	26.6 ± 2.1	0.9 ± 2.7	0.3	0.2 ± 0.9	−1.7, 2.1	0.41
Delayed Recall Test											
Naming (0–10)	9.8 ± 0.4	9.9 ± 0.3	0.1 ± 0.3	0.2	9.9 ± 0.3	9.9 ± 0.2	0.0 ± 0.4	0.0	0.1 ± 0.1	−0.2, 0.4	0.23
Incidental memory (0–10)	6.8 ± 1.3	6.7 ± 1.2	−0.1 ± 1.7	−0.1	6.6 ± 1.3	7.4 ± 1.5	0.8 ± 1.4	0.6	−0.9 ± 0.6	−2.2, 0.4	0.07
Immediate memory (0–10)	9.0 ± 1.0	9.0 ± 0.9	0.0 ± 1.3	0.0	9.0 ± 0.9	9.0 ± 1.2	0.0 ± 1.0	0.0	0.0 ± 0.5	−0.9, 0.9	0.50
Learning (0–10)	9.6 ± 0.5	9.5 ± 1.0	−0.1 ± 1.0	−0.2	9.0 ± 1.0	9.0 ± 1.2	0.0 ± 1.0	0.0	−0.1 ± 0.4	0.9, 0.7	0.40
Delayed recall (0–10)	9.1 ± 0.8	8.9 ± 0.7	−0.2 ± 1.0	−0.3	8.8 ± 1.2	8.7 ± 1.4	−0.1 ± 1.0	−0.1	−0.1 ± 0.4	−0.9, 0.7	0.39
Digit Span Test											
Forward order (0–7)	4.7 ± 1.2	4.5 ± 1.1	−0.2 ± 0.6	−0.1	4.9 ± 0.7	4.8 ± 0.9	−0.1 ± 0.7	−0.1	−0.1 ± 0.2	−0.6, 0.4	0.34
Backward order (0–7)	3.0 ± 1.5	2.7 ± 1.3	−0.3 ± 1.5	−0.2	2.9 ± 0.9	3.0 ± 0.9	0.1 ± 1.1	0.1	−0.4 ± 0.5	−1.5, 0.7	0.21
Stroop Test											
Color condition	19.8 ± 6.8	17.5 ± 5.9	−2.3 ± 4.5	−0.3	17.0 ± 3.2	15.6 ± 3.2	−1.5 ± 2.3	−0.5	−0.8 ± 1.3	−3.5, 1.9	0.27
Non-color word condition	23.5 ± 5.4	23.5 ± 8.6	0.0 ± 7.5	0.0	21.7 ± 6.5	20.6 ± 5.9	−1.1 ± 2.9	−0.2	1.1 ± 2.3	−3.2, 5.4	0.31
Color word condition	38.7 ± 10.7	39.9 ± 13.2	1.2 ± 10.0	0.1	31.8 ± 11.9	30.4 ± 10.1	−1.3 ± 7.3	−0.1	2.5 ± 3.5	−4.2, 9.2	0.22
Trail-Making Test											
Part A	55.2 ± 22.9	50.8 ± 23.7	−4.4 ± 30.2	−0.2	61.1 ± 21.8	52.7 ± 21.6	−8.3 ± 11.5	−0.4	3.9 ± 9.2	−15.2, 23.0	0.32
Part B	128.0 ± 46.8	109.7 ± 17.1	−18.3 ± 35.5	−0.4	120.8 ± 36.9	119.3 ± 58.8	−1.5 ± 72.6	0.0	−16.8 ± 21.9	−62.0, 28.4	0.23

* Values are the mean ± SD unless otherwise indicated. PRE = baseline; POST = posttest; Δ = absolute delta change; ES = effect size; 95% CI = 95% confidence interval; MMSE = Mini-Mental State Examination.

Table 5. Kidney function parameters at baseline and after 16 weeks of creatine or placebo supplementation*

Variable	Placebo (n = 13)				Creatine (n = 15)				Placebo vs. creatine		
	PRE	POST	Δ	ES	PRE	POST	Δ	ES	Difference in Δ	95% CI	*P*
Microalbuminuria, mg/24 hrs	6.3 ± 3.1	5.2 ± 2.1	−1.0 ± 3.9	−0.3	6.2 ± 4.3	6.5 ± 4.7	0.2 ± 1.7	0.1	−1.2 ± 2.1	−6.0, 3.6	0.56
Proteinuria, gm/24 hrs	0.11 ± 0.03	0.13 ± 0.05	0.02 ± 0.05	0.6	0.12 ± 0.05	0.12 ± 0.07	0.00 ± 0.08	0.0	0.02 ± 0.04	−0.1, 0.1	0.63
Urinary potassium, mEq/24 hrs	49.0 ± 17.7	54.0 ± 15.3	5.0 ± 28.9	0.3	54.2 ± 11.9	41.2 ± 6.6	−13.0 ± 15.6	−1.1	18.0 ± 16.0	−18.9, 54.9	0.29
Serum potassium, mEq/liter	4.3 ± 0.4	4.5 ± 0.2	0.2 ± 0.5	0.4	4.4 ± 0.4	4.3 ± 0.3	−0.1 ± 0.2	−0.2	0.3 ± 0.2	−0.6, 0.7	0.10
Urinary sodium, mEq/24 hrs	150.5 ± 30.8	185.5 ± 38.5	35.0 ± 44.4	1.1	161.0 ± 84.7	170.7 ± 50.0	9.7 ± 112.5	0.1	25.3 ± 49.9	−89.8, 140.4	0.63
Serum sodium, mEq/liter	143.2 ± 1.4	143.6 ± 2.8	0.4 ± 3.0	−0.3	144.3 ± 5.1	142.8 ± 2.3	−1.5 ± 6.0	−0.3	1.9 ± 2.1	−2.6, 6.4	0.38
Urinary urea, mEq/24 hrs	16.6 ± 3.8	19.6 ± 2.6	3.0 ± 5.2	0.8	22.8 ± 5.4	20.5 ± 3.7	−2.4 ± 2.6	−0.4	5.4 ± 2.5	−0.3, 11.1	0.09
Serum urea, mg/dl	28.3 ± 6.3	31.4 ± 7.2	3.1 ± 7.1	0.5	27.2 ± 5.7	28.9 ± 7.1	1.7 ± 7.6	0.3	1.4 ± 3.2	−5.3, 8.1	0.62
Urinary creatinine, gm/24 hrs	1.07 ± 0.25	1.22 ± 0.15	0.15 ± 0.39	0.6	1.25 ± 0.34	1.17 ± 0.25	−0.08 ± 0.30	−0.2	0.23 ± 0.22	−0.3, 0.7	0.34
Serum creatinine, mg/dl	0.77 ± 0.14	0.80 ± 0.13	0.04 ± 0.08	0.3	0.70 ± 0.12	0.72 ± 0.13	0.02 ± 0.11	0.1	0.02 ± 0.04	−0.1, 0.1	0.60

* Values are the mean ± SD unless otherwise indicated. There were no significant differences between the groups. PRE = baseline; POST = posttest; Δ = absolute delta change; ES = effect size; 95% CI = 95% confidence interval.

ported by Leader et al (8). Based on our findings, we may assume that creatine supplementation, as compared to placebo, promotes a minimal (if any) effect upon aerobic conditioning, quality of sleep, impact of disease, and quality of life in patients with fibromyalgia, despite the clinically relevant improvements in muscle function. Alternatively, one may argue that our sample did not have sufficient power to detect significant changes for all dependent variables, so that a Type II statistical error cannot be ruled out in the current study.

It has been suggested that creatine supplementation can penetrate the blood–brain barrier, thereby improving brain energy metabolism and, therefore, cognitive function (33–35). In support of this hypothesis, some studies (37,38), but not all (36), have demonstrated that creatine supplementation may improve cognitive performance in young and elderly people. Furthermore, it was reported that creatine supplementation may also alleviate mental fatigue induced by a stressor stimulus (i.e., mathematical calculus) (39) and sleep deprivation (40). It has been demonstrated that the brain creatine concentration is reduced in posttraumatic stress disorder (17), which displays overlapping characteristics with fibromyalgia (41). These data collectively led us to speculate that creatine supplementation could improve cognitive performance in patients with fibromyalgia. However, there was no effect of creatine on any cognitive parameters assessed by our battery of tests. Therefore, it is possible to speculate that creatine supplementation in fibromyalgia patients either increases brain creatine content at a certain level that does not have any repercussion upon cognitive performance, or does not increase brain creatine content at all. In fact, it has been demonstrated that the creatine supplementation–induced brain creatine augmentation is approximately half that of the skeletal muscle (42). Further studies using MRS techniques to assess brain creatine and/or phosphorylcreatine in response to creatine supplementation in fibromyalgia patients and even in healthy subjects are indeed necessary.

Finally, it is important to emphasize that creatine supplementation did not affect any kidney function parameters. Moreover, no adverse events were reported throughout the trial. Therefore, it is possible to affirm that creatine supplementation appeared to be safe for patients with fibromyalgia, reinforcing an extensive body of literature indicating that this is the case for many other populations (43–47).

This study is not without limitations. First, most of our patients were taking medications throughout the trial. Therefore, we actually assessed the effects of creatine supplementation combined with conservative drug therapies, and the results cannot be extrapolated to patients not taking medications. In spite of this limitation, both groups presented similar medication regimens at baseline and throughout the trial, so that it cannot be considered a confounding factor in the study. Second, we calculated the sample size based on muscle function. However, it is possible that this study had no sufficient power to detect changes in some parameters that present high variability and/or are usually less sensitive to creatine supplementation (e.g., cognitive measurements) (42). Certainly, studies with larger samples are imperative to elucidate the effects

of creatine supplementation in fibromyalgia. Third, we were unable to measure brain creatine or phosphorylcreatine content, which might have helped to explain our findings. Indeed, further MRS studies examining both muscle and brain creatine or phosphorylcreatine content after creatine supplementation in fibromyalgia patients may be relevant. Fourth, the improvements in the mental health domain of the SF-36 should be interpreted with caution, since the creatine group had a greater (although non–statistically significant) number of patients treated with antidepressants, particularly amitriptyline and sertraline, which may have partially accounted for the positive results after creatine ingestion. Finally, it is important to note that a number of studies have demonstrated additive effects of creatine supplementation along with exercise training in a variety of diseases (48). Given the well-known benefits of the latter intervention on fibromyalgia, future studies should investigate the combined effects of creatine supplementation and exercise training in this syndrome.

To conclude, creatine supplementation increased intramuscular phosphorylcreatine content by ~80% and improved lower- and upper-body muscle function, with minor effects in fibromyalgia general symptoms. Importantly, no side effects were noticed. Altogether, these findings reveal the potential of creatine supplementation as a useful dietary intervention to improve muscle function in patients with fibromyalgia.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gualano 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.

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