

Resistance Training With Creatine Monohydrate Improves Upper-Body Strength in Patients With Parkinson Disease: A Randomized Trial

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Background. Persons with Parkinson disease (PD) exhibit decreased muscular fitness including decreased muscle mass, muscle strength, bioenergetic capabilities and increased fatigability. **Objective.** This purpose of this investigation was to evaluate the therapeutic effects of resistance training with and without creatine supplementation in patients with mild to moderate PD. **Methods.** Twenty patients with idiopathic PD were randomized to receive creatine monohydrate supplementation plus resistance training (CRE) or placebo (lactose monohydrate) plus resistance training (PLA), using a double-blind procedure. Creatine and placebo supplementation consisted of 20 g/d for the first 5 days and 5 g/d thereafter. Both groups participated in progressive resistance training (24 sessions, 2 times per week, 1 set of 8-12 repetitions, 9 exercises). Participants performed 1-repetition maximum (1-RM) for chest press, leg extension, and biceps curl. Muscular endurance was evaluated for chest press and leg extension as the number of repetitions to failure using 60% of baseline 1-RM. Functional performance was evaluated as the time to perform 3 consecutive chair rises. **Results.** Statistical analyses (ANOVA) revealed significant Group \times Time interactions for chest press strength and biceps curl strength, and post hoc testing revealed that the improvement was significantly greater for CRE. Chair rise performance significantly improved only for CRE (12%, $P = .03$). Both PLA and CRE significantly improved 1-RM for leg extension (PLA: 16%; CRE: 18%). Muscular endurance improved significantly for both groups. **Conclusions.** These findings demonstrate that creatine supplementation can enhance the benefits of resistance training in patients with PD.

Key Words: *Parkinsonism—Exercise—Strength—Supplementation.*

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Parkinson disease (PD) is a neurodegenerative disorder characterized by progressive bradykinesia, rigidity, tremor, and gait abnormalities. The progression of PD symptoms is coupled with central and peripheral defects in cellular bioenergetics, progressive loss of muscle mass, decreased muscular strength and endurance, and gradual increases in musculoskeletal symptoms including muscle and joint pain.^{1,2} Indeed, several studies have documented impaired lower extremity strength and reduced peak torque production in hip extension, knee extension, knee flexion, and ankle dorsiflexion in patients with PD.³⁻⁵ These reductions in lower extremity strength have also been shown to deleteriously affect performance of activities of daily living, such as rising from a chair.⁵⁻⁷

Glendinning and Enoka⁸ reported abnormalities in muscle activation in PD that include irregular and intermittent motor unit discharge patterns and increased coactivation of antagonist muscles, which limit muscular performance. In addition, bioenergetic defects in muscle may also play a role in some of the symptoms of PD^{9,10} and may exacerbate the development of sarcopenia, the age-related condition characterized by muscle atrophy and weakness often accompanied by fatigue symptoms.¹¹ Increased muscular fatigability with the symptoms of fatigue leads to reduced functional capacity and physical function in this population.¹²⁻¹⁴ Furthermore, PD patients exhibit significant lean body mass depletion.¹⁵ Thus, the reduction in muscular fitness observed in PD patients is likely multifactorial stemming in part from a gradual reduction in mobility and physical activity dictated by the symptoms as well as central and peripheral neural and bioenergetic-mediated changes that limit muscle activation, leading to atrophy and decreased strength.

Resistance training is an effective intervention against aging- and disease-related loss of muscle mass, strength, and function,¹⁶ leading to improved functional status, maintenance of independence, and the prevention of disability.¹⁷ Thus, resistance training may have important therapeutic value in the treatment of PD.^{18,19} Another intervention that might enhance physical fitness, augment the benefits of resistance training, and provide potential

bioenergetic and neuroprotective benefits in PD is creatine monohydrate supplementation. Creatine supplementation has been shown to increase brain and muscle creatine and phosphocreatine concentrations and improve muscular performance in adults.^{20,21} The mechanisms of performance enhancement may include increased intramuscular phosphocreatine, enhanced energy shuttling, and/or stimulation of protein synthesis.²¹ When combined with resistance training, supplementation enhances the training-related improvements in muscle mass, strength, endurance, and average power in older adults^{22,23} and in patients with neuromuscular disease.²⁴ Thus, supplementation enhances the therapeutic value of resistance training in these populations. Because muscle weakness, fatigue, and atrophy are common to PD, there may be important therapeutic uses for creatine monohydrate combined with resistance training. This potential is strengthened by the observation of bioenergetic defects in platelets, skeletal muscle, and the brain of PD patients.^{10,25} In addition, creatine supplementation has exhibited neuroprotective capabilities in animal models of PD.²⁶

Given that patients with PD exhibit decreased muscle mass, muscle strength, and bioenergetic capabilities and increased fatigability, it is important that potential treatments be tested in a prospective, randomized fashion. To our knowledge, no study has specifically examined the effects of resistance training with and without creatine supplementation in patients with PD. Accordingly, the specific aim of this investigation was to examine whether comprehensive progressive resistance training and oral creatine supplementation would improve muscular fitness (fat-free mass, strength, endurance) in patients with PD compared to training alone.

METHODS

Twenty patients (17 men and 3 women; mean age 62.5 \pm 8.1 years) with idiopathic PD participated in this study. These patients were recruited from fliers posted in the movement disorders clinics at the university's School of Medicine and neurology offices in the surrounding metropolitan area and from presentations given at local American Parkinson's Disease Association support groups. All PD patients were ambulatory, clinically stable, nonfluctuating, and classified as Hoehn and Yahr (H&Y) stage 3 or lower (H&Y 3, 25%; H&Y 2.5, 15%; H&Y 2.0, 30%; H&Y 1.5, 30% of participant pool).

The participants had not participated in any consistent exercise program or experimental study for at least 6 months prior to enrollment. Exclusion criteria included the presence of active medical or psychiatric conditions or any orthopedic or rheumatic conditions that would preclude their ability to participate in the exercises. Also

excluded were subjects with a previous history of renal disorders and those who were experiencing more than mild cognitive impairment (Mini-Mental Status Examination score of $<26/30$).²⁷ Each participant read and signed a consent form approved by the Kennesaw State and the Emory University Institutional Review Boards.

Data Collection Protocol

Data collection began with a 2-week acclimation phase in which patients were orientated to the exercise machines and performed 3 minimal resistance (4.5-10 kg) exercise sessions (48 hours apart). Thereafter, patients underwent 5 baseline testing sessions: neurological and Parkinsonian evaluation (session 1), measurement of maximal dynamic muscular strength (sessions 2 and 4); muscle endurance evaluation (session 3), and body composition and chair stands assessment (session 5). Each testing session was separated by a minimum of 48 hours of rest (no physical activity). All patients were tested in the clinically "on" state (fully medicated) in the morning within 1.5 hours of taking their last dose of antiparkinsonian medication. Prior to data collection during sessions 2 to 4 and the chair stand evaluation, participants performed a 5-minute warm-up on aerobic exercise machines (ie, treadmills, exercise cycles, elliptical trainers). These standardized procedures were followed again for the posttest (following 12 weeks of training) evaluations.

Neurologic Evaluation

Participants were evaluated in the morning during their period of maximal therapeutic benefit on motor function using the H&Y staging and the Unified Parkinson Disease Rating Scale (UPDRS) by a board-certified neurologist (JL).

Dynamic Muscular Strength Testing

The 1-repetition maximum (1-RM) was used as a measure of dynamic concentric muscle strength of the legs, chest, and biceps using the leg extension, chest press, and biceps curl machines (Nautilus Corp, Vancouver, Wash). The leg extension and chest press exercises were evaluated to provide a global sense of total body strength because they stress the large-muscle groups of the lower and upper body. The biceps curl was evaluated as a representative measure of an isolated single-joint, small-muscle-mass movement.

All 1-RM testing was conducted on the same resistance-training machines with identical subject/equipment positioning for both baseline (pretraining) and posttesting (following 12 weeks of training). For each exercise, subjects warmed up with a light resistance (1 or 2 plates for women and 3 to 4 plates for men) and performed 10 repetitions. Thereafter, resistance was increased in incremental loads until failure occurred despite verbal encouragement to exert maximal effort. Failure was defined as a lift short of a full range of motion. The 1-RM was determined within 5 attempts. Dynamic muscular strength testing was repeated 1 week later, and the highest value obtained during the 2 testing sessions was recorded and used for statistical analyses.

The 3 minimal-resistance-level workouts and the repeated 1-RM testing were conducted because prior reports in young adults²⁸ indicate that differences in force may exist between the first and second testing session as a result of familiarization with the experimental situation as well as learning how to perform maximal voluntary contractions. In addition, we wanted to ensure proper positioning of the subject within the machines to enhance comfort and familiarity with the exercises and to account for any possible day-to-day variability in strength measures in this population.

Prior to statistical analyses, 1-RM strength was then normalized to fat-free mass. This normalization was done because of the unequal number of men and women in the study and the unequal number of women in the 2 experimental groups. This normalization will reduce any possible gender bias.

Muscular Endurance Testing

Muscular endurance was measured for the chest press and leg extension. The subjects were asked to lift a weight representing 60% of 1-RM until they could not successfully perform an additional lift throughout the full range of motion. The maximum number of repetitions was recorded.

Body Composition Analysis

Body mass was measured to the nearest 0.1 kg using a Health-O-Meter, model 402K1S scale. Measurements of skin-fold diameter to the nearest 0.5 mm using a Lange caliper (Cambridge Scientific Industries, Cambridge, Mass) were taken at the following sites on the right side of the body: chest, axilla, triceps, subscapular, abdomen, suprailiac, and anterior thigh. All anthropometric measurements were taken in accordance with the methods of Pollock and Wilmore.²⁹ To eliminate interobserver variability, the same highly trained investigator performed

these procedures. Body density was then determined using the equation of Jackson and Pollock³⁰ for men and Jackson et al³¹ for women. Relative body fat was calculated using the Siri equation.

Functional Test

Individuals performed 3 consecutive chair stands as a functional measure of lower extremity performance.³² This functional test was measured by the same evaluator and was timed to the nearest 0.1 second using an electronic stopwatch. All participants performed the test from a standard-height chair and were instructed to rise and sit as fast as possible without the use of their arms (arms were folded across the chest). Participants practiced the test on a separate occasion. During the testing session, they performed the test twice, and the fastest time was recorded and used for statistical analysis.

Nutritional Supplementation

Following the completion of baseline testing protocol, the 20 participants were randomly assigned in a double-blind manner to receive either creatine (creatine monohydrate; JR Carlson Labs, Arlington Heights, Ill) or placebo (lactose monohydrate; Rx Compounding, Atlanta, Ga). Both treatment groups began the supplementation procedures outlined below on the day immediately after the last baseline testing visit. Creatine was administered under Investigational New Drug 66355 issued to JLJ. Typical creatine supplementation protocols consist of 20 g/d for 5 to 7 days followed by a maintenance dose of 3 to 5 g/d.^{33,34} Based on these guidelines, the creatine-supplemented group was required to consume 20 g of creatine for the first 5 days (loading phase) and 5 g of creatine thereafter, until completion of the posttraining evaluations. The placebo-supplemented group consumed lactose monohydrate using an identical dosing scheme. The creatine and lactose monohydrate were compounded into 500-mg capsules of identical appearance, and participants were encouraged to consume supplements in approximately 4 equal intervals throughout the day. In addition, participants were instructed not to take the supplements within 1 hour of taking their antiparkinsonian medicines. Participants were given the capsules in pill containers in 3 installments: (1) loading phase, (2) first 6 weeks of training, and (3) second 6 weeks of training and testing. They were reminded weekly about proper compliance with the experimental protocol. After installments 1 and 2, compliance was established by asking the patients if they had forgotten to take any of the doses and verifying that the returned bottles were empty before dispensing

the next batch of the experimental drug. Based on this, compliance was estimated at greater than 90%.

Strength Training

Following 5 days of supplement/placebo loading, participants began a whole-body resistance-training program that was performed twice weekly. Each training session began with a 5-minute warm-up on aerobic exercise machines (ie, treadmills, exercise cycles, elliptical trainers). Participants then performed 1 set of 8 to 12 repetitions to volitional fatigue (as recommended by the American College of Sports Medicine Guidelines for patients with PD³⁵) of the following 9 exercises: leg extension, leg flexion, chest press, lat pull down, overhead press, triceps extension, biceps curl, and back extension using dynamic variable-resistance exercise training machines (Nautilus Corp, Vancouver, Wash) and seated calf raises. In addition, participants performed 1 set of the leg extension and leg flexion exercises with light loads as fast as possible. This type of training was added because (1) the age-related loss of muscle power in older adults is greater than that of muscle strength, (2) patients with PD have a reduced rate of maximal force development,⁶ and (3) previous investigators have concluded that training that incorporates rapid rate of force development movements is safe in older adults and results in significant gains in muscle power and physical performance.³⁶⁻³⁸

Initial training resistance for the chest press, leg extension, and biceps curl was set at 70% of 1-RM strength. Initial resistance for the other exercises was increased 10% from each subject's training weight taken from the last workout during the acclimation period. Training load for the fast as possible exercises was set at 50% of 1-RM. Subjects were instructed to perform each repetition with a 2-second concentric phase followed by a 4-second eccentric phase. During the execution of the fast-as-possible repetitions, however, the patients were instructed to lift the weight "as fast as possible with good form." Participants were allowed to rest up to approximately 2 minutes between exercises. The training resistance was increased by 5% to 10% for the next workout when subjects were able to perform 12 repetitions or more of the particular exercise. For the explosive exercises, training weight was increased by 5% to 10% when 20 or more repetitions were completed. Training resistance, number of repetitions performed, and the rating of perceived exertion (Borg 6-20 Scale) were recorded after each exercise to document progression of training intensity and perceived effort. The exercise sessions were conducted and monitored by a certified health fitness instructor/personal trainer and

the investigators. Subjects were encouraged to exert maximal effort on all exercises.

As mentioned, this study used a double-blind, placebo-controlled design. Thus, all of the evaluators and trainers were blinded to the treatment group assignments. This is important, as much of the data collected may be susceptible to potential investigator bias.

Data Analyses

Descriptive statistics for age, weight, and parkinsonian disability were calculated for both groups. Measures of central tendency and variability were calculated for all dependent variables of interest. Baseline values were compared between groups using an independent *t* test in which no differences were found. Therefore, pretest and posttest variables for the groups were compared using a 2 (Group) \times 2 (Time) ANOVA with repeated measures on the last factor. Statistical significance was accepted at $P \leq .05$. A Tukey post hoc test was used to determine pairwise differences.

RESULTS

Descriptive and demographic characteristics ($M \pm SEM$) of the 20 patients participating in the study are shown in Table 1 and did not differ between the treatment groups at baseline.

Creatine and placebo supplementation were well tolerated with no side effects reported. The resistance-training protocol was also well tolerated. One participant needed to decrease the training intensity for 2 sessions because of musculoskeletal soreness, and 1 participant experienced shoulder pain when resistance was increased on the chest press exercise. This participant was advised by a physician to reduce the intensity of that one exercise. As a result, this participant's data were not included for any chest press evaluations. As observed in Table 1, the participants did not experience any significant changes in their parkinsonian disability as measured by both the H&Y and UPDRS rating scales ($P > .05$).

Dynamic Muscular Strength Testing

Changes in relative muscular strength with training and supplementation are shown in Figure 1. A significant Group \times Time interaction was observed for the chest press and biceps curl ($P \leq .05$). Tukey post hoc analyses revealed that the creatine-supplemented group significantly improved strength over time for both exercises. Both groups experienced a significant increase in relative strength for the leg extension exercise ($P \leq .05$).

Table 1. Descriptive Characteristics of the Participants

	PLA (n = 10)			CRE (n = 10)		
	Pretraining	Posttraining	<i>P</i>	Pretraining	Posttraining	<i>P</i>
Hoehn & Yahr	2.2 ± 0.2	2.6 ± 0.2	.02	2.1 ± 0.2	2.1 ± 0.2	1.00
UPDRS total	41.8 ± 7.1	42.8 ± 7.1	.69	34.2 ± 5.0	33.5 ± 5.0	.90
UPDRS mental	2.7 ± 0.5	2.1 ± 0.5	.11	1.3 ± 0.6	1.1 ± 0.6	.74
UPDRS ADL	13.4 ± 2.1	12.4 ± 2.2	.34	10.9 ± 2.3	9.7 ± 2.5	.31
UPDRS motor	25.7 ± 4.4	28.3 ± 4.5	.43	22.1 ± 4.9	20.8 ± 5.0	.73
Mass, kg	95.7 ± 5.9	97.3 ± 5.2	.06	81.9 ± 5.9	83.9 ± 6.4	.06
Body fat, %	27.7 ± 2.0	26.4 ± 1.6	.24	21.8 ± 2.0	21.1 ± 2.0	.17
Fat mass, kg	27.2 ± 2.8	26.2 ± 2.6	.76	18.2 ± 2.5	18.3 ± 2.8	.76
Fat-free mass, kg	68.1 ± 3.8	71.1 ± 6.6	.01	63.7 ± 3.6	65.6 ± 3.7	.02
Age, y	62.8 ± 2.6			62.2 ± 2.6		
Gender						
Male	9			8		
Female	1			2		
Disease duration, mo	59.0 ± 14.8			47.8 ± 8.3		

PLA = placebo-supplemented group; CRE = creatine-supplemented group; UPDRS = Unified Parkinson's Disease Rating Scale; ADL = activity of daily living. Values are M ± SEM. The groups did not differ significantly from each other at baseline. Reported *P* value is from results of pairwise comparisons.

Overall, the placebo group increased chest press strength by 9%, leg extension strength by 16%, and biceps curl strength by 8%. The creatine-supplemented group improved chest strength by 21%, leg strength by 18%, and biceps strength by 23%.

Muscle Endurance

Muscle endurance increased significantly ($P \leq .05$) for chest press and leg extension in both treatment groups. The placebo-supplemented group increased endurance for chest press and leg extension by 33% and 59%, respectively. The creatine-supplemented group increased endurance by 38% and 95% for chest press and leg extension, respectively. However, there were no significant differences observed between the groups.

Functional Measure

The time to perform 3 consecutive chair stands improved significantly (Figure 2) following training in the creatine supplemented group (11% improvement). Conversely, the placebo-supplemented group did not experience a significant improvement in chair stand performance (6% improvement).

Body Composition

Both exercise groups experienced a significant increase in fat-free mass following the 12 weeks of training ($P = .002$) with no additional benefit due to creatine

supplementation. No changes were observed in percentage body fat.

DISCUSSION

This study demonstrated that 12 weeks of resistance training increased fat-free mass, muscle strength, local muscular endurance, and chair rise performance in patients with mild to moderate PD. In addition, this is the first study to demonstrate an ergogenic effect of creatine supplementation in patients with PD. Creatine monohydrate enhanced the exercise-induced gains in 1-RM strength for the chest press and biceps curl and improved chair rise performance. Together, these results help substantiate that 1) resistance training is an effective countermeasure to the sarcopenia and strength loss associated with PD and 2) creatine supplementation combined with resistance training increases upper-body strength and performance of a functional task as compared to resistance training alone. The ability of patients with PD to reverse the losses in strength and the impairment in activities of daily living performance (chair rise time) that are associated with the disease through resistance exercise augmented with creatine supplementation may lead to an improved quality of life in these individuals.

Patients with PD were able to increase their 1-RM strength from 9% to 23% following the 12 weeks of training with the additional benefits of creatine supplementation ranging from 13% (leg extension) to 188% (biceps curl). Conflicting results are apparent in the literature regarding the ability of creatine supplementation to enhance the exercise-induced benefits of resistance

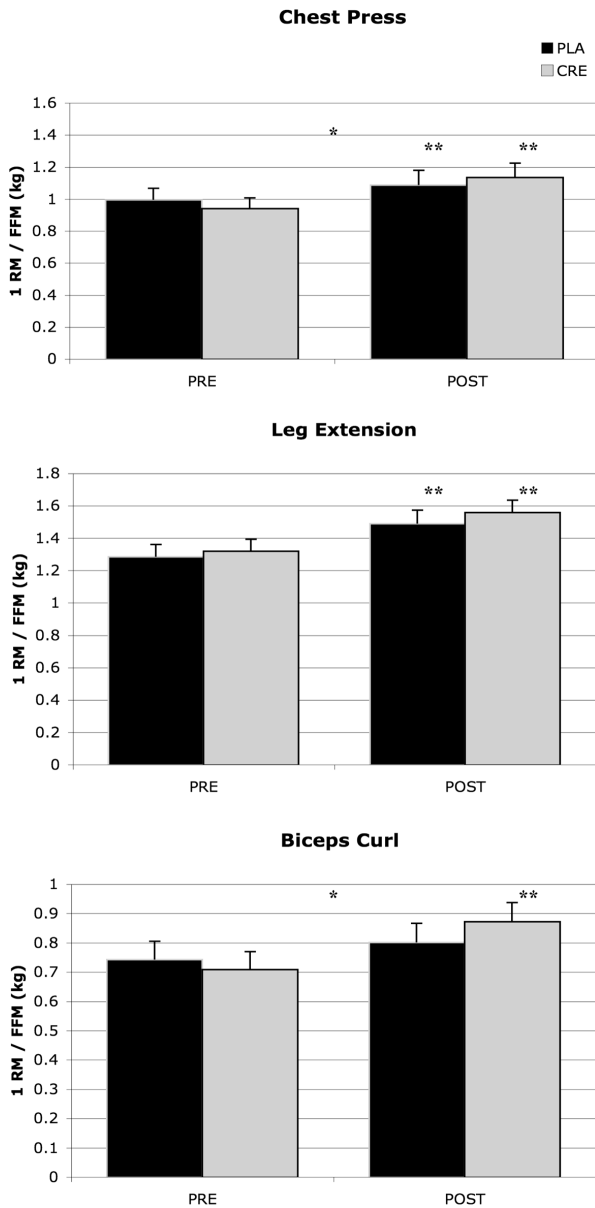


Figure 1. Normalized 1-RM strength (kg/FFM) during pretesting and posttesting for the placebo- and creatine-supplemented groups for chest press, leg extension, and biceps curl. Reported values are $M \pm SEM$. * $P < .05$ indicates significant Group \times Time interaction. **Post hoc comparison revealed the value significantly different from the pretest value. PLA = placebo (lactose monohydrate) plus resistance training; CRE = creatine monohydrate supplementation plus resistance training; 1 RM = 1-repetition maximum; FFM = fat-free mass.

training among older adults. Two studies have reported that supplementation did not enhance gains in strength.^{39,40} However, it may be argued that supplementation did not enhance performance in these studies due to low statistical power, short training durations, differences in training and testing procedures (bilateral

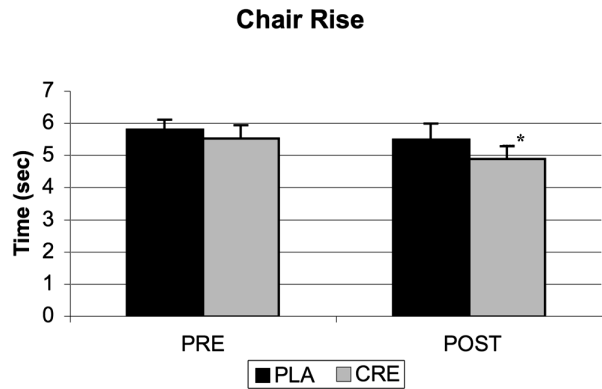


Figure 2. Chair rise performance (seconds) for placebo- and creatine-supplemented groups. Reported values are $M \pm SEM$. * $P < 0.05$ from pretest value. PLA = placebo (lactose monohydrate) plus resistance training; CRE = creatine monohydrate supplementation plus resistance training.

variable resistance training versus unilateral isometric testing), interactions between the adaptations to the strength and aerobic training, and low to moderate training intensity. In the present investigation, the creatine-supplemented group improved relative strength on the chest press and biceps curl, and the interaction effect suggests that the rate of improvement was significantly greater. Our findings are consistent with 2 other studies that reported improved muscle strength characteristics after either 12 or 14 weeks of creatine intake in conjunction with a moderate-heavy resistance-training program in older adults.^{22,23}

Proposed mechanisms of action for the ergogenic effect of creatine supplementation include 1) aiding in the rephosphorylation of adenosine diphosphate back to adenosine triphosphate, 2) enhancement of the capacity of high-energy phosphate diffusion between mitochondria and myosin heads, 3) pH buffering, 4) muscle hypertrophy through an osmotic loading effect, 5) a reduction in relaxation time by facilitating calcium uptake in the sarcoplasmic reticulum, and 6) improved ability to tolerate the training stimulus leading to greater volume and intensity of training.³³ Further research is needed to assess whether the enhanced improvements in functional performance observed in this investigation are a result of improved bioenergetics at the muscle level or increased muscular work.

Despite improvements in strength in both exercise groups, chair rise performance improved only for the creatine-supplemented group. Other studies evaluating the effects of resistance exercise on chair stand ability have produced equivocal results.^{41,42} Generally, in disabled individuals, improvements in functional performance have been associated with observed improvements in muscle strength.^{43,44} Thus, the average 10% greater

improvement in strength (21% vs 11%) in the creatine-supplemented group likely contributed to the significant improvement in functional performance. Brose and colleagues²³ reported that creatine supplementation did not enhance the exercise-induced improvement in chair stand performance following 14 weeks of training. This may be explained by the relatively small difference in strength improvement between the 2 interventions (only ~4% greater in the supplemented group). It is also possible that the bioenergetic effects of increased creatine availability during the performance of the task led to greater improvements. In addition, it is possible that subtle changes in functional performance might not be detected because of the inherent variability in using these type of tests, and that either a greater sample size or a longer treatment period would have been required. Future studies should consider a more comprehensive functional evaluation including gait- and balance-related evaluations.

The benefit of movement therapy and exercise on improved motor disability in PD has been observed in some studies^{45,46} but not others.^{47,48} For more detailed information on the effects of exercise therapy on PD, please see recent reviews by de Goede et al,⁴⁹ Robichaud and Corcos,⁵⁰ and Suchowersky et al.⁵¹ To our knowledge, no previous study has reported the influence of progressive-intensity resistance training on clinical scores of parkinsonian impairment. We did not observe any improvements in disability as measured by the UPDRS or H&Y. This may be because of the relative low volume of resistance training, because the UPDRS and H&Y may not contain measures of the types of impairments where we expect to see change, and because this type of intervention may not be effective in improving certain aspects of parkinsonian disability. Because of the relatively small number of subjects, however, we cannot rule out the possibility that the study was underpowered to find difference in the UPDRS scores.

Our study has certain limitations. This investigation lacked any direct measurement of creatine content. Thus, it is possible that the current supplementation scheme (though standard practice in the literature) was not optimal for maximizing creatine content in muscle in this specific population; thus, the potential benefits of the supplementation may have been muted. In addition, we did not directly measure systemic levels of creatine and thus strict supplementation compliance. However, patients were reminded weekly of the dosing regimen. To our knowledge, no literature exists addressing the effects of antiparkinsonian drugs on the response to resistance training or creatine supplementation. Thus, it is assumed that these drugs will not significantly alter the results. No patients reported any noticeable effects of the supplementation and efficacy of their medications. A more rigorous investigation of the possible

interaction between medication and this supplement is needed to shed light on this area. The lack of statistical differences in the adaptations between the 2 groups for many of the variables may be a result of the low-volume training regimen prescribed and its relatively short duration, as this type of program may not significantly stress bioenergetic pathways. The current training program was chosen based on current guidelines for resistance training in patients with PD and its established efficacy in the 2 previous studies in the literature.^{18,19,35} The efficacy of higher volumes of resistance training with and without supplementation in this population certainly warrants future investigation. Last, it is possible that a larger sample size or a longer treatment period would have been required because of the inherent variability in performance in this population.

In summary, 12 weeks of resistance training combined with creatine supplementation resulted in greater increases in relative upper-body strength and chair stand ability than did resistance training alone. Both groups significantly improved muscular fitness following training. These findings highlight the applicability of resistance-training programs performed in accordance with the guidelines from the American College of Sports Medicine for this population. Patients can safely perform 1 set of resistance exercises conditioning the major muscle groups 2 times per week. Additional volumes of training (ie, more sets or greater frequency) could be progressed as tolerated based on the individual's goals and disease severity. Creatine monohydrate may be a promising supplement for improving fitness and, based on recent futility trials, a potentially disease-modifying compound for PD. In the National Institute of Neurological Disorders and Stroke Neuroprotection Exploratory Trials in Parkinson's Disease (NET-PD),⁵² the effect on UPDRS scores seen with creatine was comparable to the effect reported with 1200 mg/d of coenzyme Q10. Based on data from the present trial and NET-PD, it appears that early and mild-to-moderately affected patients can tolerate 5 to 10 g of creatine per day. However, patients should be monitored for known side effects and for supplement-drug interactions.

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REFERENCES

1. Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. *Brain*. 2001;124(pt 11): 2131-2146.
2. Sato Y, Kaji M, Tsuru T, Oizumi K. Risk factors for hip fracture among elderly patients with Parkinson's disease. *J Neurol Sci*. 2001;182:89-93.
3. Kakinuma S, Nogaki H, Pramanik B, Morimatsu M. Muscle weakness in Parkinson's disease: isokinetic study of the lower limbs. *Eur Neurol*. 1998;39:218-222.
4. Corcos DM, Chen CM, Quinn NP, McAuley J, Rothwell JC. Strength in Parkinson's disease: relationship to rate of force generation and clinical status. *Ann Neurol*. 1996;39:79-88.
5. Inkster LM, Eng JJ, MacIntyre DL, Stoessl AJ. Leg muscle strength is reduced in Parkinson's disease and relates to the ability to rise from a chair. *Mov Disord*. 2003;18:157-162.
6. Paasuke M, Ereline J, Gepeyeva H, Joost K, Mottus K, Taba P. Leg-extension strength and chair-rise performance in elderly women with Parkinson's disease. *J Aging Phys Act*. 2004;12:511-524.
7. Paasuke M, Mottus K, Ereline J, Gepeyeva H, Taba P. Lower limb performance in older female patients with Parkinson's disease. *Aging Clin Exp Res*. 2002;14:185-191.
8. Glendinning DS, Enoka RM. Motor unit behavior in Parkinson's disease. *Phys Ther*. 1994;74:61-70.
9. Cardellach F, Marti MJ, Fernandez-Sola J, et al. Mitochondrial respiratory chain activity in skeletal muscle from patients with Parkinson's disease. *Neurology*. 1993;43:2258-2262.
10. Schapira AH. Mitochondrial involvement in Parkinson's disease, Huntington's disease, hereditary spastic paraplegia and Friedreich's ataxia. *Biochim Biophys Acta*. 1999;1410:159-170.
11. Bua EA, McKiernan SH, Wanagat J, McKenzie D, Aiken JM. Mitochondrial abnormalities are more frequent in muscles undergoing sarcopenia. *J Appl Physiol*. 2002;92:2617-2624.
12. Garber CE, Friedman JH. Effects of fatigue on physical activity and function in patients with Parkinson's disease. *Neurology*. 2003;60:1119-1124.
13. Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. *Mov Disord*. 2001;16:190-196.
14. Ziv I, Avraham M, Michaelov Y, et al. Enhanced fatigue during motor performance in patients with Parkinson's disease. *Neurology*. 1998;51:1583-1586.
15. Petroni ML, Albani G, Bicchiera V, et al. Body composition in advanced-stage Parkinson's disease. *Acta Diabetol*. 2003;40(suppl 1):S187-S190.
16. Macaluso A, De Vito G. Muscle strength, power and adaptations to resistance training in older people. *Eur J Appl Physiol*. 2004;91:450-472.
17. Warburton DE, Gledhill N, Quinney A. Musculoskeletal fitness and health. *Can J Appl Physiol*. 2001;26:217-237.
18. Hirsch MA, Toole T, Maitland CG, Rider RA. The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. *Arch Phys Med Rehabil*. 2003;84:1109-1117.
19. Scandalis TA, Bosak A, Berliner JC, Helman LL, Wells MR. Resistance training and gait function in patients with Parkinson's disease. *Am J Phys Med Rehabil*. 2001;80:38-43.
20. Dechent P, Pouwels PJ, Wilken B, Hanefeld F, Frahm J. Increase of total creatine in human brain after oral supplementation of creatine-mono-hydrate. *Am J Physiol*. 1999;277(3 pt 2):R698-R704.
21. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. *Physiol Rev*. 2000;80:1107-1213.
22. 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.
23. 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.
24. Tarnopolsky M, Martin J. Creatine monohydrate increases strength in patients with neuromuscular disease. *Neurology*. 1999;52:854-857.
25. Shoffner JM, Watts RL, Juncos JL, Torroni A, Wallace DC. Mitochondrial oxidative phosphorylation defects in Parkinson's disease. *Ann Neurol*. 1991;30:332-339.
26. Matthews RT, Ferrante RJ, Klivenyi P, et al. Creatine and cyclocreatine attenuate MPTP neurotoxicity. *Exp Neurol*. 1999;157:142-149.
27. Hobson P, Meara J. The detection of dementia and cognitive impairment in a community population of elderly people with Parkinson's disease by use of the CAMCOG neuropsychological test. *Age Ageing*. 1999;28:39-43.
28. Maganaris CN, Maughan RJ. Creatine supplementation enhances maximum voluntary isometric force and endurance capacity in resistance trained men. *Acta Physiol Scand*. 1998;163:279-287.
29. Pollock ML, Willmore J. *Exercise in Health and Disease: Evaluation and Prescription for Prevention and Rehabilitation*. 2nd ed. Philadelphia, Pa: W. B. Saunders; 1990.
30. Jackson AS, Pollock ML. Generalized equations for predicting body density in men. *Br J Nutr*. 1978;40:497-504.
31. Jackson AS, Pollock ML, Ward A. Generalized equations for predicting body density of women. *Med Sci Sports Exerc*. 1980;12:175-181.
32. Gill TM, Williams CS, Tinetti M. Assessing risk for the onset of functional dependence among older adults: the role of physical performance. *J Am Geriatr Soc*. 1995;43:603-609.
33. Bemben MG, Lamont HS. Creatine supplementation and exercise performance: recent findings. *Sports Med*. 2005;35:107-125.
34. Terjung RL, Clarkson P, Eichner ER, et al. American College of Sports Medicine roundtable: the physiological and health effects of oral creatine supplementation. *Med Sci Sports Exerc*. 2000;32:706-717.
35. Protas E, Stanley R. Parkinson's disease. In: Durstein JL, Moore GE, eds. *ACSM's Exercise Management for Persons With Chronic Diseases and Disabilities*. Champaign, Ill: Human Kinetics; 2003:295-302.
36. Hakkinen K, Kallinen M, Izquierdo M, et al. Changes in agonist-antagonist EMG, muscle CSA, and force during strength training in middle-aged and older people. *J Appl Physiol*. 1998;84:1341-1349.
37. Hakkinen K, Kraemer WJ, Newton RU, Alen M. Changes in electromyographic activity, muscle fibre and force production characteristics during heavy resistance/power strength training in middle-aged and older men and women. *Acta Physiol Scand*. 2001;171:51-62.
38. Henwood TR, Taaffe DR. Improved physical performance in older adults undertaking a short-term programme of high-velocity resistance training. *Gerontology*. 2005;51:108-115.
39. 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.
40. Eijnde BO, Van Leemputte M, Goris M, et al. Effects of creatine supplementation and exercise training on fitness in men 55-75 yr old. *J Appl Physiol*. 2003;95:818-828.
41. Skelton DA, Young A, Greig CA, Malbut KE. Effects of resistance training on strength, power, and selected functional abilities of women aged 75 and older. *J Am Geriatr Soc*. 1995;43:1081-1087.
42. Schlicht J, Camaione DN, Owen SV. Effect of intense strength training on standing balance, walking speed, and sit-to-stand performance in older adults. *J Gerontol A Biol Sci Med Sci*. 2001;56:M281-M286.

43. Chandler JM, Duncan PW, Kochersberger G, Studenski S. Is lower extremity strength gain associated with improvement in physical performance and disability in frail, community-dwelling elders? *Arch Phys Med Rehabil.* 1998;79:24-30.
44. Weiss A, Suzuki T, Bean J, Fielding RA. High intensity strength training improves strength and functional performance after stroke. *Am J Phys Med Rehabil.* 2000;79:369-376.
45. Formisano R, Pratesi L, Modarelli FT, Bonifati V, Meco G. Rehabilitation and Parkinson's disease. *Scand J Rehabil Med.* 1992;24:157-160.
46. Reuter I, Engelhardt M, Stecker K, Baas H. Therapeutic value of exercise training in Parkinson's disease. *Med Sci Sports Exerc.* 1999;31:1544-1549.
47. Ellis T, de Goede CJ, Feldman RG, Wolters EC, Kwakkel G, Wagenaar RC. Efficacy of a physical therapy program in patients with Parkinson's disease: a randomized controlled trial. *Arch Phys Med Rehabil.* 2005;86:626-632.
48. Gibberd FB, Page NG, Spencer KM, Kinnear E, Hawksworth JB. Controlled trial of physiotherapy and occupational therapy for Parkinson's disease. *Br Med J (Clin Res Ed).* 1981;282:1196.
49. de Goede CJ, Keus SH, Kwakkel G, et al. The effects of physical therapy in Parkinson's disease: a research synthesis. *Arch Phys Med Rehabil.* 2001;82:509-515.
50. Robichaud JA, Corcos DM. Motor deficits, exercise, and Parkinson's disease. *Quest.* 2005;57:79-101.
51. Suchowersky O, Gronseth G, Perlmutter J, et al. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;66:976-982.
52. NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. *Neurology.* 2006;66:664-671.