

Performance and muscle fiber adaptations to creatine supplementation and heavy resistance training

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Laboratory for Sports Medicine/Department of Kinesiology/Center for Sports Medicine, The Pennsylvania State University, University Park, PA 16802; The Human Performance Laboratory, Ball State University, Muncie, IN 47306; Department of Biological Sciences, College of Osteopathic Medicine, and School of Physical Therapy, Ohio University, Athens, OH 45701; and Department of Physiology, The University of Melbourne, Melbourne, AUSTRALIA

ABSTRACT

JEFF S. VOLEK, NOEL D. DUNCAN, SCOTT A. MAZZETTI, ROBERT S. STARON, MARGOT PUTUKIAN, ANA L. GÓMEZ, DAVID R. PEARSON, WILLIAM J. FINK, and WILLIAM J. KRAEMER. Performance and muscle fiber adaptations to creatine supplementation and heavy resistance training. *Med. Sci. Sports Exerc.*, Vol. 31, No. 8, pp. 1147–1156, 1999. **Purpose:** The purpose of this study was to examine the effect of creatine supplementation in conjunction with resistance training on physiological adaptations including muscle fiber hypertrophy and muscle creatine accumulation. **Methods:** Nineteen healthy resistance-trained men were matched and then randomly assigned in a double-blind fashion to either a creatine ($N = 10$) or placebo ($N = 9$) group. Periodized heavy resistance training was performed for 12 wk. Creatine or placebo capsules were consumed ($25 \text{ g}\cdot\text{d}^{-1}$) for 1 wk followed by a maintenance dose ($5 \text{ g}\cdot\text{d}^{-1}$) for the remainder of the training. **Results:** After 12 wk, significant ($P \leq 0.05$) increases in body mass and fat-free mass were greater in creatine (6.3% and 6.3%, respectively) than placebo (3.6% and 3.1%, respectively) subjects. After 12 wk, increases in bench press and squat were greater in creatine (24% and 32%, respectively) than placebo (16% and 24%, respectively) subjects. Compared with placebo subjects, creatine subjects demonstrated significantly greater increases in Type I (35% vs 11%), IIA (36% vs 15%), and IAB (35% vs 6%) muscle fiber cross-sectional areas. Muscle total creatine concentrations were unchanged in placebo subjects. Muscle creatine was significantly elevated after 1 wk in creatine subjects (22%), and values remained significantly greater than placebo subjects after 12 wk. Average volume lifted in the bench press during training was significantly greater in creatine subjects during weeks 5–8. No negative side effects to the supplementation were reported. **Conclusion:** Creatine supplementation enhanced fat-free mass, physical performance, and muscle morphology in response to heavy resistance training, presumably mediated via higher quality training sessions. **Key Words:** HYPERTROPHY, ERGOGENIC AID, HISTOCHEMISTRY, STRENGTH, EXERCISE

In the past 5 yr several studies have been published demonstrating that creatine ingestion greater than $20 \text{ g}\cdot\text{d}^{-1}$ for 5–7 d increases the concentrations of both creatine and phosphocreatine in skeletal muscle (15,18,20). Subsequent research has shown that similar creatine loading regimens lasting 5–7 d enhance body mass (2,4,14,15,33) and intermittent high-intensity activity (5,7,16,17,29), including resistance exercise (33). A recent study performed in our laboratory demonstrated a significant improvement in

the ability to perform multiple sets of dynamic resistance exercise after a 7-d creatine loading regimen (33).

There are few data concerning the influence of creatine supplementation on body composition, physical performance, skeletal muscle morphology, and muscle creatine concentrations during longer periods of training (10,24,32). Although creatine supplementation in conjunction with resistance training has been shown to augment gains in body mass, fat-free mass, and muscular strength in both men (10,24) and women (32), none of these studies determined the amount of total creatine accumulation in muscle and the magnitude of muscle fiber hypertrophy associated with creatine supplementation. Gyrate atrophy patients who consumed 1.5 g creatine per day for 1 yr demonstrated significant increases in Type II muscle fiber diameter (27).

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Patients with a fractured thigh submitted to rehabilitation and administration of creatine phosphate (500 mg daily i.m. for 20 d) demonstrated significantly greater recovery in echotomography-assessed muscle mass compared with patients not receiving creatine phosphate (26). These studies indicate a potential role of creatine in muscle fiber hypertrophy in instances where muscle atrophy is present.

Based on the positive findings of enhanced resistance exercise performance after 7 d of creatine supplementation, we hypothesized that physiological adaptations (i.e., increases in muscle strength, fat-free mass, and muscle fiber cross-sectional area) to 12 wk of periodized heavy resistance training and creatine supplementation would be optimized due to an enhanced capacity to perform individual weight training sessions. In this study, we obtained muscle biopsies before training and supplementation, after a 1-wk supplement loading period, and after 11 wk of resistance training during which a supplemental maintenance dose was consumed. Subsequent analyses of muscle biopsy samples allowed us to assess changes in muscle creatine and phosphocreatine in response to the supplementation regimen and the resistance training program. Furthermore, we quantified the extent of specific muscle fiber (i.e., Type I, IIA, IIB, and IIB) hypertrophy in response to resistance training using histochemical techniques, which has previously not been performed in creatine supplementation studies. The purpose of this study was to examine the effects of creatine supplementation in conjunction with 12 wk of heavy resistance exercise training on physical performance, body composition, skeletal muscle morphology, and creatine accumulation in men.

METHODS

Subjects. Nineteen healthy resistance-trained men volunteered to participate in a 12-wk training study designed to examine the combined effects of resistance exercise and creatine supplementation. Only subjects that had never supplemented with creatine monohydrate or taken anabolic steroids (determined via a questionnaire) were eligible for participation because the effects of prior use of creatine monohydrate or anabolic steroids on the extent of muscle creatine loading and subsequent physiological adaptations are unknown. After baseline testing, subjects were matched according to physical characteristics and maximal strength and then randomly assigned in a double-blind fashion to either a creatine ($N = 10$) or placebo ($N = 9$) group. One subject in the placebo group did not complete the training due to factors unrelated to the study. The physical characteristics of the creatine and placebo groups, respectively, were (mean \pm SD): age, 25.6 ± 4.8 and 25.4 ± 5.9 yr; height, 176.5 ± 7.5 and 175.6 ± 5.8 cm; body mass, 82.1 ± 11.8 and 82.9 ± 14.3 kg; body fat, 15.9 ± 5.6 and $16.6 \pm 6.0\%$; maximal squat, 107.8 ± 4.8 and 109.5 ± 10.9 kg; and maximal bench press, 93.0 ± 2.8 and 94.9 ± 4.9 kg. All

subjects were informed of the purpose and possible risks of the investigation before signing an informed consent document approved by the Institutional Review Board at the Pennsylvania State University and in adherence with the guidelines of the American College of Sports Medicine.

Experimental design. This study utilized a two-group, matched, doubled-blind, randomly assigned design. Paired subjects were of similar physical characteristics and all testing parameters had high test-retest reliabilities supporting the use of this design. Both groups of subjects performed the same 12-wk periodized heavy resistance exercise training program. Baseline testing was performed before any supplementation and training and included assessment of muscular performances, body composition, and muscle biopsy samples. After baseline testing, creatine subjects began consuming 25 g creatine monohydrate per day in capsule form divided into five equal dosages consumed every 2–3 h (Muscular Development Creatine, Hauppauge, NY) while the placebo group ingested an identical-looking and equivalent amount of placebo capsules (powdered cellulose) for 7 d. This dosage pattern of creatine administration has been shown to increase muscle creatine, on average, more than 20% in men of similar physical characteristics to the subjects used in this study (15,18,20). From day 7 until the end of the study, 5 g of supplement per day was consumed in a single dose. As little as 2 g creatine per day will maintain elevated muscle creatine stores in men not exercising strenuously (20). Because athletes were training intensely and slightly larger in body mass than subjects in prior studies, we reasoned that a 5-g dose would be necessary to maintain and possibly even increase creatine stores above that obtained after an acute 1-wk loading period. Subjects were instructed to consume the supplements with food, preferably carbohydrate, which has been shown to enhance creatine accumulation in muscle. Subjects were given enough capsules to last 2 wk; upon return of the empty container, they received another 2-wk supply. In addition to having subjects return the empty container, the time of day and number of capsules consumed during the loading phase were recorded on forms provided to the subjects. This document was subsequently signed by each subject to verify ingestion of the appropriate amount of supplement. Compliance to the supplement protocol was 100%. We also assessed creatine levels in the muscle to verify and support this approach.

Experimental procedures. Body mass was measured on a Toledo electronic scale (Reliance Electronic Co., Worthington, OH) to the nearest 100 g, and body density was determined via hydrodensitometry. A detailed description of the equipment and methodology used for underwater weighing tests performed in this investigation has been previously published (1). Underwater weight of the subject was determined by a scale utilizing four electronic force cubes (load cells). After a maximal exhalation, subjects were weighed underwater, and residual volume measurements were performed after each attempt while subjects were still in the tank using an open-circuit nitrogen washout

TABLE 1. Resistance training program.

General preparatory (weeks 1-2): 3 sets, 12 RM intensity, 60-120 s rest between sets			
Monday	Wednesday	Friday	
Abdominal crunch	Abdominal crunch	Abdominal crunch	
Barbell squats	Leg press	Deadlifts	
Hyperextension	Heel Raise	Leg extension	
Seated heel raise	DB incline press	Leg curl	
Bench press	DB reverse fly	Behind neck press	
Seated cable row	Pull ups (machine assisted)	Row (machine)	
Lateral raise (machine)	Triceps extension (machine)	Pec deck	
Narrow grip pulldown	EZ bar curls	Wide grip pulldown	
Hypertrophy phase (weeks 3-6): 3 sets, 8-10 RM intensity, 45-90 s rest between sets			
Monday	Tuesday	Thursday	Friday
Abdominal crunch	Abdominal crunch	Pull ups (machine)	Abdominal crunch
Barbell squats	DB incline press	Seated cable row	Bench press
Leg press	Lateral raise	Hyperextension	Behind neck press
Leg extension	Heel raise	Deadlifts	Chest press machine
Leg curl	EZ curls	Row (machine)	DB fly
DB row	Triceps extension	Narrow grip pulldown	DB shoulder press
Wide grip pulldown	DB curls	Single leg extension	DB lateral raise
DB reverse fly	Dips	Seated leg curl	Seated heel raise
Strength phase (weeks 7-10): 3-4 sets, 6-8 RM intensity, 60-120 s rest between sets			
Monday	Wednesday	Friday	
Smith machine squats	Leg press	Barbell squats	
Abdominal crunch	Abdominal crunch	Abdominal crunch	
Unilateral leg curl	Stiff legged deadlift	Leg extension	
Bench press	Heel raise	Seated leg curl	
Row (machine)	Behind neck press	Bench press	
DB shoulder press	DB row	Seated cable row	
Wide grip pulldown	Triceps extension (machine)	Shoulder press (machine)	
	Alternating DB curls	Body weight pull ups	
Peaking Phase (weeks 11-12): 2-3 sets, 3-6 RM intensity, 60-150 s rest between sets			
Monday	Wednesday	Friday	
Smith machine squats	Leg press	Barbell squats	
Abdominal crunch	Abdominal crunch	Abdominal crunch	
Leg curls	Stiff legged deadlift	Seated leg curl	
Bench press	DB incline press	Bench press	
Row (machine)	DB row	Seated cable row	
DB shoulder press	Upright row	Shoulder press (machine)	
Narrow grip pulldown	EZ bar curls	Body weight pull ups	
	Triceps extension (bar)		

technique. Percent body fat was calculated from body density (28).

Performance testing included assessment of one-repetition maximum (1-RM) bench press and squat strength, power production during a jump squat protocol, and muscular endurance during a bench press protocol. All exercise testing protocols were performed on a Plyometric Power System (PPS; Lismore, NSW, Australia) previously described (35). Resistance is provided by a barbell which can only move in the vertical direction. Linear bearings attached to either end of the bar allow it to slide up and down two steel shafts so that movements such as the squat may be performed in a dynamic, ballistic manner with minimal risk to the subject. The machine was connected to a rotary encoder that recorded the position and direction of the bar within an accuracy of 0.0002 m. This information was recorded by a computer that calculated the power output for each repetition of jump squats. Subjects were familiarized with the testing equipment and protocols before any testing. After a warm-up, subjects performed a 1-RM squat and bench press using standard methods in our laboratory (23). A successful lift in the squat entailed descending into a

parallel position defined by the trochanter head of the femur reaching the same horizontal plane as the superior border of the patella. A successful lift in the bench press entailed lowering the bar under control until it lightly touched the chest and then lifting the bar back to a straight-arm position with hips and feet remaining motionless throughout the lift. After a 10-min rest, subjects performed four sets of 10 continuous repetitions of jump squat with a resistance equal to 30% of their 1-RM squat. Thirty percent of the 1-RM was chosen as the resistance because mechanical power is maximized near this value (35). There was exactly a 2-min rest period between each set. Starting in an upright position, subjects were instructed to squat down and then jump repeatedly as high as possible without pausing between repetitions within a set. After a 10-min rest, subjects performed a single set of bench press to fatigue using a load equal to 80% of their 1-RM bench press. Fatigue was defined at the time point when the bar ceased to move or if the subject paused for more than 1 s when the arms were in the extended position. Two spotters immediately racked the bar when the investigator (same for all subjects) determined that fatigue had occurred. Repetitions were recorded to the near-

TABLE 2. Body composition data (kg).

Variable	Creatine	Placebo		P
Body mass				
Week 0	82.1 ± 4.1	82.9 ± 4.7	Group	0.936
Week 1	83.8 ± 4.1*	82.7 ± 4.7	Time	0.000
Week 12	87.3 ± 4.5*	85.9 ± 4.6*	Group × Time	0.076
Δ (12-0)	5.2 ± 1.1	3.0 ± 0.8	t-test	0.118
Fat-free mass				
Week 0	68.7 ± 2.1	68.6 ± 3.1	Group	0.689
Week 1	70.2 ± 2.5*†	67.8 ± 3.1	Time	0.000
Week 12	73.0 ± 2.7*†	70.7 ± 3.2*	Group × Time	0.007
Δ (12-0)	4.3 ± 0.8	2.1 ± 0.3	t-test	0.019
Fat mass				
Week 0	13.4 ± 2.2	14.3 ± 2.5	Group	0.733
Week 1	13.6 ± 1.9	14.9 ± 2.5	Time	0.087
Week 12	14.3 ± 2.0	15.2 ± 2.5	Group × Time	0.779
Δ (12-0)	0.9 ± 0.7	0.9 ± 0.7	t-test	0.965

Values are mean ± SE.

* $P \leq 0.05$ from corresponding week 0 value.

† $P \leq 0.05$ from corresponding placebo value.

est 1/4 of a full repetition. Each subject was asked to refrain from strenuous weight training for a period of 48 h before any of the testing.

Exercise training. Resistance training began the same day as administration of the supplement. Resistance training sessions consisted of periodized high-intensity workouts using a combination of free weights and exercise machines (see Table 1), individually supervised by a qualified personal trainer (same for all subjects). Workouts were partitioned into four consecutive phases including general preparatory, hypertrophy, strength, and peaking phases (12). The primary goals of the resistance training program were to increase maximal strength and muscle size. Therefore, a classical linear periodized protocol emphasizing hypertrophy and strength phases was used. Hypertrophy training utilized a split protocol where the primary aim was to increase muscle size by high-volume training and short rest periods between sets for each muscle group once per week thus optimizing the quantity of muscle activated and allowing for adequate recovery time between training sessions for each muscle group (34). The strength phase was designed to increase strength performance by utilizing heavy loads, higher frequency of training, longer rest periods, and exercise sequencing (exercises which train opposing muscle groups were alternated) thereby optimizing the activation and loading of the high recruitment threshold-type II muscle fibers. In addition, the squat and bench press exercises were performed twice per week during the strength and peaking phases, once using free weights and once on a Smith machine similar to that used in testing in order to optimize the specificity of training related to the testing exercises. Subjects were instructed not to engage in any strenuous or formal physical training outside of the exercises performed in this investigation so as not to compromise muscle size and strength gains (22).

Training intensity for the resistance training program was determined using repetition maximums (RM). Training resistances were progressively increased as subjects were able to perform the required number of repetitions using a given weight with proper exercise technique. As strength improvements were observed, the resistances were increased by the

personal trainer. Subject training logs were maintained throughout the 12 wk experimental period detailing the exercises, sets, and repetitions performed. The number of repetitions, sets, and kilograms used for the squat and bench press exercises were recorded and later analyzed to contrast the rate of progression between groups and to support the adaptational responses in other variables as previously described (9).

Before the training program, each subject was instructed by a registered dietitian and provided with specific verbal and written instructions and procedures for reporting detailed dietary intake. Subjects completed 3-d food records during weeks 1 and 12 of the study in order to assess total energy and macronutrient content using Nutritionist IV, Version 4 nutrient analysis software (N-Squared Computing, First Databank Division, The Hearst Corporation, San Bruno, CA). To assess potential side effects to the supplementation regimen, a questionnaire was provided to subjects after the 1-wk loading period and again after 12 wk of supplementation and training. Individual changes in recovery ability, appetite, thirst, skin, muscle soreness, muscle cramping, stomach distress, diarrhea, flatulence, headache,

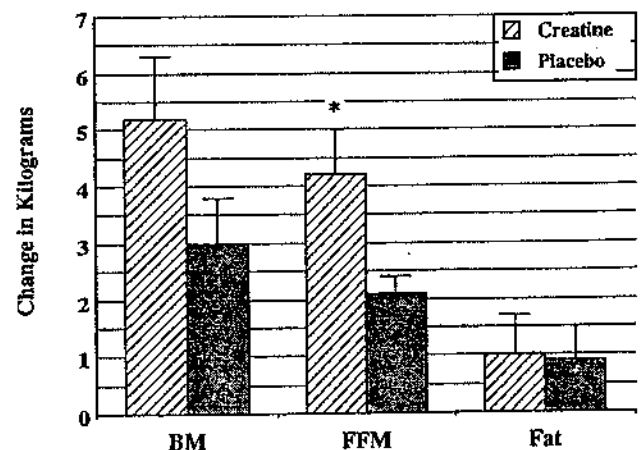


Figure 1—Delta changes in body mass (BM), fat-free mass (FFM), and fat mass after 12 wk of heavy resistance training in creatine and placebo subjects. * $P \leq 0.05$ from corresponding change in the placebo group. Values are mean ± SE.

TABLE 3. Maximal squat and bench press strength data (kg).

Exercise	Creatine	Placebo		P
Squat				
Week 0	107.8 ± 4.8	109.5 ± 10.9	Group	0.820
Week 1	112.2 ± 6.0	108.7 ± 10.4	Time	0.000
Week 12	142.1 ± 6.3*	135.3 ± 11.4*	Group × Time	0.186
Δ (12-0)	34.3 ± 4.0	25.8 ± 2.9	t-test	0.109
Bench press				
Week 0	93.0 ± 2.8	94.9 ± 4.9	Group	0.844
Week 1	98.0 ± 2.8*	97.6 ± 5.9	Time	0.000
Week 12	115.6 ± 4.9*	109.9 ± 6.5*	Group × Time	0.087
Δ (12-0)	22.6 ± 2.6	15.0 ± 2.8	t-test	0.059

Values are mean ± SE.

* $P \leq 0.05$ from corresponding week 0 value.

sex drive, sleepiness, nervousness, and aggression were documented.

Muscle biopsy and analysis. Before, after 1 wk, and after the 12-wk training program, muscle biopsies (50–400 mg) were obtained from the superficial portion of the vastus lateralis muscle using the percutaneous needle technique with suction to ensure adequate sample sizes (6,11). The initial and 12-wk muscle biopsies were obtained from the dominant leg, and the 1-wk biopsy was taken from the other leg. After the muscle samples were removed from the needle, the tissue sample was separated into two pieces for histochemical and creatine analysis. The biopsy after 1 wk was obtained to assess the extent of creatine accumulation, and no histochemical analysis was performed. For histochemistry, the sample was immediately oriented in traga-canth gum, snap-frozen in isopentane cooled by liquid nitrogen, and stored at -80°C until time of analysis. The remaining tissue sample was immediately placed in liquid nitrogen and stored at -80°C until time of creatine, phosphocreatine, and ATP analysis. In three creatine subjects and two placebo subjects, inadequate muscle tissue was extracted for determination of total creatine. Thus, muscle creatine data are based on six subjects per group. To minimize potential variations in fiber type distribution throughout the vastus lateralis, an attempt was made during the pre- and post-training biopsy to extract tissue from approximately the same location using the prebiopsy scar and depth markings on the needle (22,30).

Biopsy samples were serially sectioned (12 μm thick) on a cryostat microtome (International Equipment Company, Needham, MA) at -20°C . Pre- and post-training cross-sections from the same individual were placed on one glass cover slip and assayed simultaneously for myofibrillar ATPase activity using preincubation solutions of pH 4.3, 4.6, and 10.4 (8). Determination of muscle fiber cross-sectional areas were accomplished using the methods of Staron et al. (31). Fiber analyses were analyzed with a National Institutes of Health (NIH) program (NIH Image 1.55b 20) and a Macintosh Quadra 800 computer interfaced to an Olympus BH-2 microscope. Classification of fibers into Types I, IIA, IIAB, and IIB were distinguished based on staining intensities. Area and fiber type measurements were based on the average of approximately 150–400 total fibers. The remaining tissue sample was freeze-dried, weighed, extracted with perchloric acid, and analyzed in duplicate for

ATP, phosphocreatine, and creatine using fluorometric techniques (19). Total creatine was calculated as the sum of free creatine and phosphocreatine relative to ATP which corrects for potential variance resulting from differences in blood and/or connective tissue between biopsy samples (18). Intra-assay variances for ATP, phosphocreatine, and creatine were 0.3, 1.2, and 5.3%, respectively.

Statistical analyses. Statistical evaluation of the data was accomplished by using a two-way analysis of variance (ANOVA) with repeated measures design. When a significant F -value was achieved, a Fisher's LSD test was used to locate the pairwise differences between means. Baseline values and delta changes between groups were analyzed via independent t -tests. There were no significant differences between groups in any variables at week 0 except for muscle fiber cross-sectional areas. Thus, area measurements were analyzed via ANCOVA using baseline area values as the covariate. Simple regression was used to determine significant relationships among the delta changes for selected variables. Performance variables demonstrated intraclass test-retest reliabilities of $R \geq 0.95$. Statistical power ranged from 0.78 to 0.80 at a P value equal to 0.05. The level of significance was set at $P \leq 0.05$.

RESULTS

Body composition. The results for body composition and presented in Table 2 and Figure 1. Percent body fat and fat mass were not significantly different at any time point over the 12-wk training period in either group. In creatine subjects, body mass increased 1.7 kg after 1 wk and 5.2 kg after 12 wk. In placebo subjects, body mass decreased 0.2 kg after 1 wk and increased 3.0 kg after 12 wk. In creatine subjects, fat free mass (FFM) increased 1.5 kg after 1 wk and 4.3 after 12 wk. In placebo subjects, FFM decreased 0.8 kg after 1 wk and increased 2.1 kg after 12 wk. The delta change in FFM from week 0 to week 1 and from week 0 to week 12 were significantly greater in creatine subjects. For all subjects combined, dietary energy intake was similar

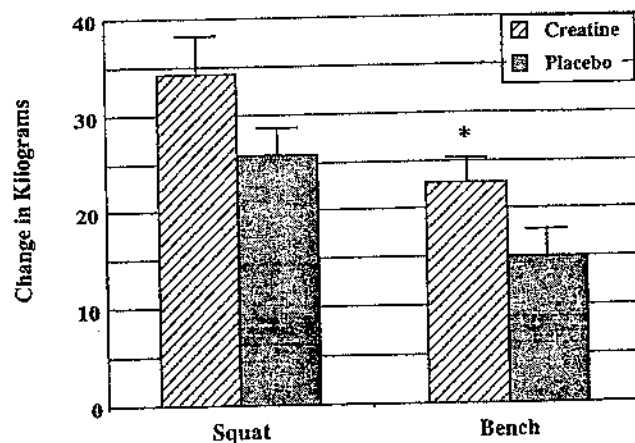


Figure 2—Delta changes in one-repetition maximum squat and bench press after 12 wk of heavy resistance training in creatine and placebo subjects. * $P \leq 0.05$ from corresponding change in the placebo group. Values are mean ± SE.

TABLE 4. Total repetitions of bench press performed using 80% of the one-repetition maximum.

	Creatine	Placebo		P
Week 0	7.2 ± 0.5	8.4 ± 0.8	Group	0.062
Week 1	6.5 ± 0.3	8.0 ± 0.9	Time	0.412
Week 12	6.6 ± 0.4	8.1 ± 0.6	Group × Time	0.955

Values are mean ± SE.

before and after training (3156 and 3249, respectively) as well as the distribution of energy from carbohydrate (55 and 51%, respectively), protein (18 and 19%, respectively), fat (26 and 27%, respectively), and alcohol (2 and 3%, respectively). There were no differences in the frequency of reported side effects between creatine and placebo subjects.

Exercise performance. Maximal 1-RM squat and bench press are shown in Table 3 and Figure 2. In creatine subjects, 1-RM squat values increased slightly after 1 wk (4%) and significantly after 12 wk (32%). In placebo subjects, 1-RM squat values decreased slightly after 1 wk (1%) and increased significantly after 12 wk (24%). In creatine subjects, 1-RM bench press values increased significantly after 1 wk (5%) and increased further after 12 wk (24%). In placebo subjects, 1-RM bench press values increased slightly after 1 wk (3%) and increased significantly after 12 wk (16%). There were no significant changes in the number of repetitions performed using 80% of the 1-RM bench press at any time point (Table 4).

Jump squat performance data are presented in Table 5. After 1 wk, peak power increased significantly on sets 3 and 4 in creatine subjects and on set 2 in placebo subjects. After 12 wk of training, peak power was significantly increased on all four sets for both groups. Although the mean delta changes in peak power after 12 wk of training were larger in creatine subjects, only the last set was significantly greater compared with the change in placebo subjects (Fig. 3).

Muscle characteristics. Muscle fiber cross-sectional areas and proportions are shown in Table 6. After 12 wk, creatine subjects demonstrated significant increases in muscle cross-sectional areas in type I, IIA, IIAB, and IIB fibers (35%, 36%, 35%, and 29%, respectively). Muscle fiber

increases in Type I, IIA, IIAB, and IIB fibers were smaller in placebo subjects (11%, 15%, 6%, and 8%, respectively) with only Type IIA fibers reaching significance. The delta changes in Type I, IIA, and IIAB muscle fibers were significantly greater after 12 wk in creatine subjects (Fig. 4). There was a significant increase in the proportion of histochemically assessed Type IIA fibers in creatine subjects (9%) compared with placebo subjects (7%) and a significant decrease in Type IIB fibers in both the creatine and placebo groups (9% and 6%, respectively) after training. Muscle creatine concentrations are shown in Table 7. No change in muscle ATP concentrations was observed in either group nor were there any significant changes in phosphocreatine or free creatine in placebo subjects. After 1 wk of loading in creatine subjects, accumulation of free creatine and phosphocreatine led to a significant increase in the muscle total creatine concentration (22%). In creatine subjects, total creatine concentrations at week 12 remained significantly greater than placebo subjects and tended ($P = 0.07$) to remain greater than baseline values.

Training volume. To determine whether there were any significant differences between groups in the quality of training, volume (defined as the product of the number of repetitions performed and the kilograms lifted) was calculated for every set of bench press and squat exercise and averaged over 2-wk intervals (Fig. 5). During the general preparatory phase (i.e., weeks 1–2), placebo subjects performed a significantly greater volume for the bench press. However, during the end of the hypertrophy and beginning of the strength phases (i.e., weeks 5–8), the volume lifted was significantly greater in creatine subjects. There were no significant differences between groups in the volume lifted for the squat.

For all subjects combined, significant positive correlations were detected between the delta change in FFM after 12 wk and the delta changes in Type IIA area ($r = 0.63$) and percentage ($r = 0.47$), Type IIAB area ($r = 0.56$), 1-RM squat ($r = 0.67$), 1-RM bench press ($r = 0.51$), and jump squat peak power during sets 3 ($r = 0.57$) and 4 ($r = 0.69$). There was a negative correlation between the delta change

TABLE 5. Jump squat peak power output (Watts) during four sets of 10 repetitions using 30% of the one-repetition maximum squat.

		Creatine	Placebo		P
Week 0	Set 1	1254 ± 65	1231 ± 111	Group	0.856
Week 1	Set 1	1291 ± 72	1297 ± 133	Time	0.000
Week 12	Set 1	1514 ± 76*	1453 ± 134*	Group × Time	0.352
Week 0	Set 2	1246 ± 70	1216 ± 130	Group	0.823
Week 1	Set 2	1308 ± 74	1310 ± 143*	Time	0.000
Week 12	Set 2	1515 ± 67*	1442 ± 135*	Group × Time	0.423
Week 0	Set 3	1206 ± 70	1245 ± 126	Group	0.857
Week 1	Set 3	1317 ± 86*	1279 ± 135	Group × Time	0.000
Week 12	Set 3	1488 ± 75*	1414 ± 134*	Time	0.170
Week 0	Set 4	1189 ± 72	1236 ± 108	Group	0.818
Week 1	Set 4	1283 ± 69*	1251 ± 140	Time	0.000
Week 12	Set 4	1506 ± 74*†	1395 ± 124*	Group × Time	0.022

Values are mean ± SE.

* $P \leq 0.05$ from corresponding week 0 value.

† $P \leq 0.05$ from corresponding placebo value.

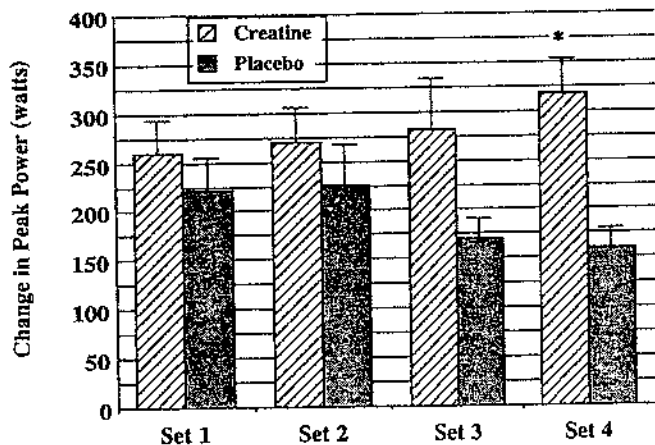


Figure 3—Delta changes in jump squat peak power output during four sets of 10 repetitions using 30% of the one-repetition maximum after 12 wk of heavy resistance training in creatine and placebo subjects. * $P \leq 0.05$ from corresponding change in the placebo group. Values are mean \pm SE.

in FFM and the percentage of Type IIB fibers ($r = -0.70$) after 12 wk. The delta change in body mass after 12 wk was not significantly correlated to the changes in any of these variables. There was also a significant correlation between the delta change in FFM and the delta change in 1-RM squat after 1 wk ($r = 0.66$).

DISCUSSION

A number of studies have demonstrated that short-term creatine supplementation enhances a variety of high-intensity activities (5,7,16,17,29), including resistance exercise (10,24,32). Fewer studies have evaluated the efficacy of creatine supplementation during longer periods of training. In moderately trained men, a 7-d creatine loading regimen ($25 \text{ g} \cdot \text{d}^{-1}$) followed by an 11-wk maintenance phase ($5 \text{ g} \cdot \text{d}^{-1}$) enhanced development of muscular strength, FFM, skeletal muscle hypertrophy, and muscle total creatine con-

centrations in response to heavy resistance exercise training. These findings corroborate our original hypothesis that creatine supplementation would enhance the physiological adaptations to resistance training and extend the previously documented benefits of a 5-g maintenance dose in untrained women (32) to include moderately resistance-trained men as well.

The acute increase in body mass observed in creatine subjects (1.7 kg) is in agreement with our previous study (33) and others (2,4,14,15). We also observed a significant increase in hydrostatically assessed FFM (1.5 kg) in creatine subjects after 1 wk that has been hypothesized to be due to retention of body water (3,20); however, this notion has not been addressed adequately. An increase in body mass due to water has been shown to influence hydrostatic weighing results. Girandola et al. (13) hydrostatically weighed subjects before and after ingestion of 1.8 L of water. Body mass increased 1.8 kg, but underwater weight and residual volume were unchanged. Thus, body density decreased and percent fat increased slightly. Similarly, subjects in this study gained 1.7 kg after 1 wk of creatine supplementation, but in contrast to the previous study underwater weight was increased as well (3.588 to 3.712 kg). Thus, the acute increase in body mass after 1 wk of creatine supplementation may be due to more than just accumulation of water. One difference between these studies is that subjects were hydrostatically weighed immediately after ingestion of water in the study by Girandola et al. (13) whereas subjects were weighed after 1 wk in this investigation. The increase in underwater weight obtained with creatine supplementation may be explained by enhanced protein synthesis and/or differences in the extracellular and intracellular processing of water that occur over a 1-wk period compared with acute ingestion.

After 12 wk of training, body mass increased further in creatine subjects but not significantly different than placebo subjects. However, the increase in FFM in creatine subjects (4.3 kg) was over twice that observed in placebo subjects (2.1 kg). Vandenberghe et al. (32) also demonstrated a significant

TABLE 6. Muscle fiber cross-sectional areas and percentages.

Fiber Type	Creatine	Placebo	P	Creatine	Placebo
	Area (μm^2)			Percentage	
Type I					
Week 0	3291 \pm 255†	4054 \pm 199	Group	38 \pm 2	40 \pm 3
Week 12	4439 \pm 195*	4508 \pm 114	Time	39 \pm 2	40 \pm 3
Δ (12-0)	1148 \pm 278	454 \pm 184	Group \times Time		
			t-test		
Type IIA					
Week 0	4114 \pm 254†	5149 \pm 356	Group	36 \pm 4	34 \pm 3
Week 12	5577 \pm 303*	5903 \pm 361*	Time	45 \pm 3*	41 \pm 3
Δ (12-0)	1463 \pm 265	755 \pm 209	Group \times Time		
			t-test		
Type I/AB					
Week 0	3924 \pm 206†	4989 \pm 510	Group	8 \pm 1	11 \pm 2
Week 12	5296 \pm 414*	5318 \pm 366	Time	8 \pm 2	10 \pm 2
Δ (12-0)	1372 \pm 338	319 \pm 302	Group \times Time		
			t-test		
Type IIB					
Week 0	3747 \pm 315	4220 \pm 354	Group	17 \pm 3	15 \pm 2
Week 12	4849 \pm 289*	4552 \pm 453	Time	8 \pm 2*	9 \pm 2*
Δ (12-0)	1102 \pm 342	332 \pm 508	Group \times Time		
			t-test		

Values are mean \pm SE.

* $P \leq 0.05$ from corresponding week 0 value.

† $P \leq 0.05$ from corresponding placebo value.

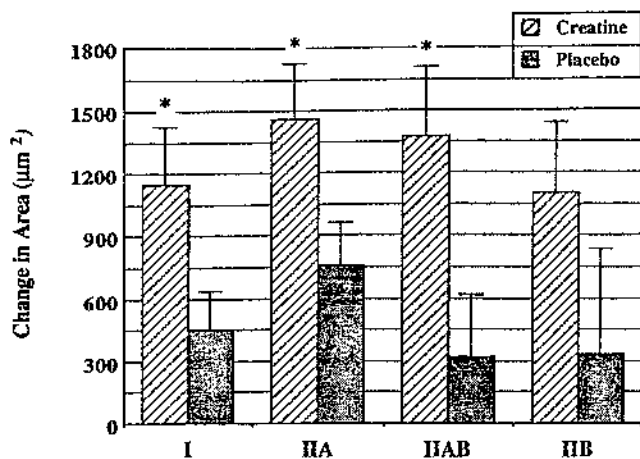


Figure 4—Delta changes in cross-sectional areas of specific muscle fiber types after 12 wk of heavy resistance training in creatine and placebo subjects. * $P \leq 0.05$ from corresponding change in the placebo group. Values are mean \pm SE.

increase in hydrostatically determined FFM (2.6 kg) after 10 wk of resistance training in previously untrained women supplemented with a 5-g·d⁻¹ maintenance dose of creatine. Higher doses of creatine (15–20 g·d⁻¹) during 4 wk of resistance training has also been shown to enhance DEXA determined fat/bone-free mass (2.4 kg) in collegiate football players (24) and hydrostatically determined FFM (1.5 kg) in resistance-trained men (10). The relatively greater increase in FFM in this study compared with others (10,24,32) is most likely due to the longer duration and/or greater intensity of training. These data indicate that the augmentation of FFM induced by creatine supplementation extend beyond 4 and 10 wk of training to 12 wk and perhaps longer.

The significantly greater increases in FFM with creatine supplementation are predominantly a result of greater skeletal muscle fiber hypertrophy. The percentage increases in cross-sectional area for all fiber types in creatine subjects ranged from 29 to 35%, more than twice the increase observed in placebo subjects, which ranged from 6 to 15%. In

a similar group of aerobically fit but not resistance-trained men, Kraemer et al. (22) reported significant increases in Type I and IIA muscle fiber areas of 12% and 24%, respectively, after 12 wk of periodized heavy resistance training. Creatine subjects in this study possessed smaller muscle fiber areas before the training and supplementation program compared with placebo subjects. Whether initial muscle fiber size has any influence on the potential to increase in fiber cross-sectional area in response to training is unknown. Typically, the larger Type II muscle fibers respond more favorably to resistance training compared with the smaller Type I muscle fibers in men (22). Whether this holds true within a specific muscle fiber population is unknown.

Greater muscle fiber hypertrophy implies enhanced myofibrillar protein synthesis and/or reduced degradation. There is some indication that creatine may play a direct role in myosin synthesis *in vitro* (21); however, it is unclear whether creatine supplementation impacts protein metabolism *in vivo* other than indirectly via potential enhancement of training intensity. In patients with gyrate atrophy, a disease characterized by deficient synthesis of creatine and a progressive atrophy of Type II muscle fibers, 1 yr of creatine supplementation (1.5 g·d⁻¹) resulted in a significant increase in Type II (34%) but not Type I muscle fiber diameter (27). Creatine supplementation may have simply corrected a creatine deficiency and reversed the muscle atrophy, influenced protein metabolism directly, and/or enhanced the training intensity in these subjects subsequently leading to greater muscle fiber hypertrophy. Without a control or placebo group these data should be interpreted cautiously. The significant decrease in the percentage of Type IIB muscle fibers is a common adaptation to resistance training (22,29) as transformations (i.e., IIB \rightarrow IAB \rightarrow IIA) have been detected after as few as five workouts (29).

Bench press and squat 1-RM strength were higher in creatine subjects after 12 wk. A greater training stimulus induced by elevated creatine stores may have contributed to the greater maximal strength gains observed in creatine subjects. In turn, the greater adaptations in FFM and muscle fiber hypertrophy may also contribute to the enhancement of muscular strength. Delta changes in FFM explained 45% and 26% of the shared variation in 1-RM squat and bench press strength, respectively, indirectly indicating an association between increases in FFM and functional improvements in force production capabilities. However, the significant increase in 1-RM bench press (5.0 kg) after just 7 d of creatine supplementation challenges this notion. Earnest et al. (10) also reported a significant increase in 1-RM bench press (6%) in athletes who consumed 20 g of creatine per day for 28 d. Expression of 1-RM strength is generally not thought to be limited by phosphagen metabolism, and 1 wk is viewed as too short a time period for adaptations resulting in increased force production to take place, especially in trained individuals. Thus, the acute increase in bench press strength was unexpected. The increase in 1-RM squat (4.4 kg) in creatine subjects was not statistically significant ($P = 0.15$). Nevertheless, the potential role of creatine supple-

TABLE 7. Muscle creatine concentrations.

	Creatine	Placebo		P
Total creatine				
Week 0	122.9 \pm 8.6	114.3 \pm 6.5	Group	0.038
Week 1	149.9 \pm 8.5*	119.1 \pm 4.5	Time	0.013
Week 12	135.9 \pm 6.8	114.3 \pm 7.6	Group \times Time	0.097
Δ (1-0)	27.0 \pm 8.8	4.8 \pm 6.4	t-test	0.069
Δ (12-0)	13.0 \pm 6.9	0.0 \pm 8.1	t-test	0.250
Phosphocreatine				
Week 0	65.6 \pm 8.1	56.6 \pm 3.9	Group	0.031
Week 1	79.0 \pm 7.1	61.4 \pm 3.7	Time	0.207
Week 12	69.1 \pm 3.7	58.3 \pm 4.5	Group \times Time	0.675
Δ (1-0)	13.4 \pm 6.1	4.8 \pm 6.4	t-test	0.352
Δ (12-0)	3.5 \pm 9.6	1.8 \pm 5.6	t-test	0.882
Free creatine				
Week 0	57.3 \pm 2.0	57.7 \pm 2.8	Group	0.143
Week 1	70.8 \pm 2.7	57.8 \pm 7.9	Time	0.256
Week 12	66.9 \pm 6.0	56.0 \pm 4.3	Group \times Time	0.215
Δ (1-0)	13.5 \pm 4.0	0.1 \pm 7.6	t-test	0.150
Δ (12-0)	9.6 \pm 5.8	-1.8 \pm 4.4	t-test	0.150

Values are mean \pm SE for 6 subjects in each group. All values are mmol·kg⁻¹ dry weight. Creatine subjects consumed 25 g creatine per day until week 1 and 5 g·d⁻¹ until week 12.

* $P \leq 0.05$ from corresponding week 0 value.

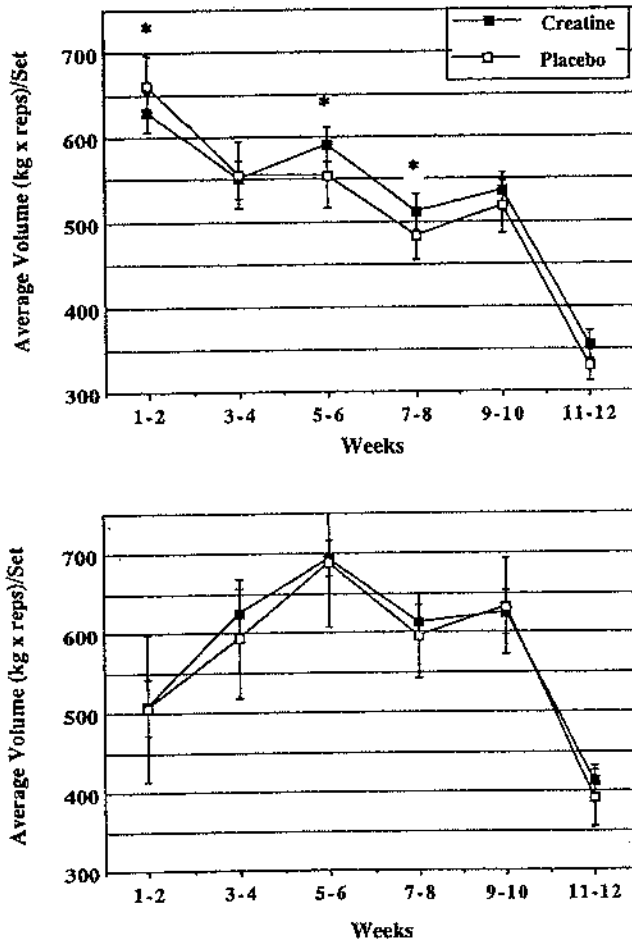


Figure 5—Average volume (kilograms lifted \times repetitions) per set for the bench press (upper graph) and squat (lower graph) exercises during 2-wk intervals. * Indicates a significant ($P \leq 0.05$) difference between groups. Values are mean \pm SE.

mentation and phosphagen metabolism in mediating acute increases in maximal strength warrants attention.

Significant improvements in jump squat peak power were evident on sets 3 and 4 in creatine subjects after 1 wk and on all four sets after 12 wk in both groups. The increase in power after 12 wk was significantly greater on set 4 in creatine subjects. Previously, we showed a significant improvement during all sets of a similar jump squat protocol after 1 wk of creatine supplementation (33). Different from our prior study, 1-RM squat strength was retested after 1 and 12 wk in the present investigation. Because 1-RM strength increased 4.4 kg after 1 wk in creatine subjects, the relative resistance used was greater and may have negatively impacted power production thus accounting for the lack of significant improvements during sets 1 and 2. Total repetitions of a single set of bench press using 80% of the 1-RM was not different after 1 or 12 wk in either group. The nonsignificant improvement in peak power during the initial sets of jump squat at 30% of the 1-RM and the lack of change in the number of bench press repetitions performed at 80% of the 1-RM suggests that creatine supplementation is not beneficial during single set resistance exercise if the

relative intensity is kept constant. Performance benefits may still be evident, however, if repeated bouts are performed, as shown in our jump squat data, supporting the role of increased phosphocreatine resynthesis as the primary mechanism explaining the ergogenic potential of creatine (15).

The significant increase in muscle total creatine concentrations after 1 wk of creatine supplementation is in agreement with previous studies (15,18,20). Creatine values at week 12 were slightly lower but still significantly greater than placebo subjects. The small decline in muscle creatine was unexpected as previous work had shown that 2 g creatine per day was adequate to maintain creatine stores for 30 d after an initial 6-d loading regimen in men of similar age and body mass as subjects in this investigation (20). However, subjects in that study refrained from strenuous physical activity during the supplementation period, suggesting that heavy resistance training may increase the maintenance dose required to retain elevated muscle creatine stores. Alternatively, a 5-g versus a 2-g maintenance dose may raise the extracellular creatine concentration to a greater extent and subsequently inhibit creatine transport into muscle, which has been shown *in vitro* (25). The optimal maintenance dose of creatine for athletes training intensely still remains unknown.

A major strength of this investigation was the individual one-on-one personalized training that allowed for standardized progression of the resistances utilized in training and motivation of subjects. All subjects were highly encouraged to increase the amount of weight lifted within the specified repetition range for a given phase of training. This is an important point in lieu of our hypothesis stating that enhanced physiological adaptations to resistance training would occur with creatine supplementation (based on the premise that subjects would be capable of progressing at a faster rate and training at a higher intensity level). Indeed, creatine subjects utilized significantly greater resistances during weeks 5–8 in the bench press, which may reflect an accelerated rate of phosphocreatine resynthesis and recovery between sets. Creatine supplementation has been shown to enhance the rate of phosphocreatine resynthesis after 2 min of recovery from 20 electrically evoked isometric muscle actions (15). Rest periods ranged between 1 and 2 min for the bench press during weeks 5–8 in this investigation. Lifting volumes for other exercises (e.g., leg press) were not quantified but may have also contributed to the overall greater adaptations with creatine supplementation.

In summary, a 12-wk periodized heavy resistance training program resulted in significant increases in body mass, FFM, maximal strength, peak power, and skeletal muscle hypertrophy in men who started the investigation as moderately resistance-trained. Subjects who were loaded with 25 g creatine per day for 7 d followed by a maintenance dose of 5 g \cdot d⁻¹ experienced no side effects and greater gains in upper and lower body 1-RM strength, FFM, and muscle total creatine concentrations. The greater increase in FFM in creatine subjects was supported by significantly greater hypertrophy in Type I, IIA, and IIAB muscle fibers. Based on

our prior work demonstrating an enhanced ability to perform repeated sets of dynamic resistance exercise after 1 wk of creatine supplementation (33), we propose that these enhanced responses are a result of intensified training leading to accelerated physiological adaptations to a periodized resistance training program.

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