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ORIGINAL ARTICLE

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The effects of creatine supplementation on muscular performance and body composition responses to short-term resistance training overreaching

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Abstract To determine the effects of creatine supplementation during short-term resistance training overreaching on performance, body composition, and resting hormone concentrations, 17 men were randomly assigned to supplement with 0.3 g/kg per day of creatine monohydrate (CrM: $n=9$) or placebo (P: $n=8$) while performing resistance exercise (5 days/week for 4 weeks) followed by a 2-week taper phase. Maximal squat and bench press and explosive power in the bench press were reduced during the initial weeks of training in P but not CrM. Explosive power in the bench press, body mass, and lean body mass (LBM) in the legs were augmented to a greater extent in CrM ($P \leq 0.05$) by the end of the 6-week period. A tendency for greater 1-RM squat improvement ($P=0.09$) was also observed in CrM. Total testosterone (TT) and the free androgen index (TT/SHBG) decreased in CrM and P, reaching a nadir at week 3, whereas sex hormone binding globulin (SHBG) responded in an opposite direction. Cortisol significantly increased after week 1 in CrM (+29%), and returned to baseline at week 2. Insulin was significantly depressed at week 1 (−24%) and drifted back toward baseline during weeks 2–4. Growth hormone and IGF-I levels were not affected. Therefore, some measures of muscular performance and body composition are enhanced to a greater extent following the rebound phase of short-term resistance training overreaching with creatine supplementation and these changes are not related to changes in circulating hormone concentrations obtained in the resting, postabsorptive state. In addition, creatine supplementation appears to be effective for maintaining muscular performance during the initial phase of high-volume resistance training overreaching that otherwise results in small performance decrements.

Keywords Cortisol · Muscle strength · Overtraining · Power · Testosterone · Weight training

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Introduction

We have previously demonstrated that creatine supplementation enhances performance of maximal strength, explosive power, and muscular endurance after 7 days (Volek et al. 1997b, 1999). In a follow-up study, we reported that creatine supplementation in conjunction with a resistance training program augmented gains in muscular strength, lean body mass, and muscular hypertrophy (Volek et al. 1999). Several others studies lasting 3 weeks (Burke et al. 2000) to 13 weeks (Larson-Meyer et al. 2000) have reported similar ergogenic effects of creatine on adaptations to resistance training. The mechanism(s) by which creatine exerts this ergogenic effect on chronic adaptations to training is/are controversial and may be due to greater gains in lean body mass (Volek et al. 1999), an effect on protein metabolism (Parise et al. 2001), an increase in myosin heavy chain mRNA and protein expression (Willoughby and Rosene 2001), an alteration in the expression of myogenic transcription factors (Hespel et al. 2001), an increase in satellite cell mitotic activity (Dangott et al. 1999), an increase protein synthesis secondary to an increase in cell swelling (Bemben et al. 2001; Haussinger et al. 1993),

or simply an increase in the intensity of individual workouts resulting from a better match between ATP supply and demand during exercise (Casey et al. 1996).

Resistance training results in increases in muscle fiber hypertrophy and muscle size, a result of an increase in net protein balance. The magnitude of muscle hypertrophy is heavily influenced by nutrition and the anabolic and catabolic hormonal milieu (Kraemer et al. 1995). Such hormonal signals create greater stimuli for increased receptor interactions and gene level transcription and translation of proteins (Turner et al. 1988). In turn, protein synthesis is increased, which sets the stage for greater protein accretion and muscle fiber hypertrophy with chronic resistance training. Only a few studies have examined whether the ergogenic effect of creatine on adaptations to training is mediated by a change in circulating hormones. Our laboratory reported that acute creatine supplementation for 7 days did not alter responses of testosterone, cortisol, and hormones involved in regulation of water balance (renin, aldosterone, angiotensin, arginine vasopressin) to a single bout of heavy resistance exercise (Volek et al. 1997b, 2001). Creatine supplementation (20 g/day for 5 days) failed to alter testosterone, cortisol, and growth hormone (GH) responses to a single bout of heavy resistance exercise (Op 'T Eijnde and Hespel 2001). Although acute creatine supplementation does not appear to alter the responses of testosterone, cortisol, and GH to a single bout of resistance exercise, hormone levels could be altered over a prolonged resistance training program, especially an overreaching-type program, which often results in perturbations of the endocrine system (Fry et al. 1993).

We have previously shown that amino acid supplementation is effective for maintaining muscular strength and power during high-volume resistance training overreaching (Ratamess et al. 2003). In that investigation, we developed a model of overreaching that resulted in performance decrements initially, followed by a substantial "rebound effect" leading to improvements in muscular strength and power. However, the effect of creatine supplementation on resistance training overreaching is not well understood. Therefore, the primary purpose of the present study was to investigate whether creatine supplementation affected the hormonal responses to short-term resistance training overreaching and the relationship to changes in muscular performance and body composition.

Methods

Experimental design

A double-blind, randomized study was employed using two experimental groups (creatine or placebo supplementation) who underwent 4 weeks of resistance training (5 days/week) and supplementation. The training program consisted of 2 weeks of moderate-intensity/high-volume and 2 weeks of high-intensity/moderate-volume resistance training. Acute overreaching was produced by training the whole body on consecutive days, thereby minimizing recovery in between workouts (Ratamess et al. 2003). At the end of each training week, resting blood samples were obtained and muscular performance was assessed. This experimental design enabled us to investigate the time course of potential ergogenic effects of creatine supplementation (e.g., recovery enhancement) during resistance training overreaching in resistance-trained men.

Subjects

Seventeen resistance-trained men were randomly assigned to a creatine monohydrate (CrM) or a placebo (P) group. The subjects had the following characteristics [mean(SE)]: CrM group ($n = 9$): age = 20.7 (1.9) years; height = 179.3 (4.7) cm; body mass = 88.5 (17.0) kg; and training experience = 5.4 (2.1) years; P group ($n = 8$): age = 21.3 (3.0) years; height = 179.4 (6.4) cm; body mass = 88.9 (11.1) kg; and training experience = 5.1 (3.0) years. There were no significant differences between groups in physical characteristics. Each of the subjects was informed of the benefits and risks of the investigation and subsequently signed an approved consent form in accordance with the guidelines of the University Institutional Review Board for use of human subjects. No subject had any medical or orthopedic problem that would compromise his participation and performance in the study. None of the subjects were taking any medications, nutrition supplements (including creatine for at least 8 weeks), or anabolic drugs that would confound the results of this study.

Resistance training

Prior to initiation of the 4-week overreaching program, each participant underwent 4 weeks of base resistance training. This ensured that each subject began the study in a trained state. Base training consisted of five exercises per workout (squat, bench press, lat pull down, leg press, and seated shoulder press) for three sets of 8–10 repetitions with 1–3 min of rest in between sets performed for 2 days/week. Multiple-set, periodized resistance training was performed on 4 consecutive days using a total-body program (Table 1). Due to time limitation constraints with the subjects, the overreaching program utilized training each muscle group on consecutive days, thereby limiting recovery. The first 2 weeks consisted of a higher volume, moderate intensity of resistance exercise whereas the last 2 weeks consisted of high intensity with a moderate volume of resistance exercise. All sets were performed with repetition maximum (RM) loads such that all sets were either performed to or near muscular exhaustion. When each subject was able to complete the desired number of repetitions with the current load, weight was added to subsequent sets or during the next workout. All workouts were supervised by a certified strength and conditioning specialist who also monitored the training loads (Mazzetti et al. 2000). Following the 4-week experimental period, each participant underwent a 2-week reduced-volume/frequency resistance training phase. The program used during this phase was identical to the base resistance training program used prior to initiation of the 4-week overreaching protocol. Only week squat, bench press, peak power attained during the ballistic bench press, and jump squat were assessed following this training 2-week phase.

Supplementation and nutritional protocol

Subjects assigned to the CrM group ingested creatine monohydrate in capsule form (Creatine Fuel, Twin Laboratories, Hauppauge, N.Y., USA) at a dose 0.3 g/kg per day (divided into three equal doses) for the 1st week and 0.05 g/kg per day (one dose) for the remaining 3 weeks of training. This supplementation protocol increased muscle creatine levels in our prior work (Volek et al. 1999). Subjects in the P group consumed the same number of capsules identical in appearance (powdered cellulose). All supplement doses were administered by a registered dietician who calculated each serving size and distributed the supplements in clearly marked

Table 1 Resistance–training program

Monday, Wednesday	Tuesday, Thursday	Friday
Week 1		
Back squat 3×10–12[a]	Leg press 3×10–12[a]	1-RM squat
Bench press 3×10–12[a]	Incline bench press 3×10–12[a]	1-RM bench press
Lat pulldown 3×10–12[c]	Bent-over row 3×10–12[c]	
Lunge 3×10–12[c]	Stiff-leg deadlift 3×10–12[c]	
Seated shoulder press 3×10–12[c]	Upright row 3×10–12[c]	
Dumbbell curl 3×10–12[c]	Barbell curl 3×10–12[c]	
Lying triceps extension 3×10–12[c]	Dips 3×10–12[c]	
Leg raise 3×20[a]	Sit-ups 3×20[a]	
Week 2		
Back squat 3×8–10[a]	Leg press 3×8–10[a]	Squat
Bench press 3×8–10[a]	Incline bench press 3×8–10[a]	Bench press
Lat pulldown 3×8–10[c]	Bent-over row 3×8–10[c]	Jump squats
Lunge 3×8–10[c]	Stiff-leg deadlift 3×8–10[c]	Ballistic bench press
Seated shoulder press 3×8–10[c]	Upright row 3×8–10[c]	
Dumbbell curl 3×8–10[c]	Barbell curl 3×8–10[c]	
Lying triceps extension 3×8–10[c]	Dips 3×8–10[c]	
Leg raise 3×20[a]	Sit-ups 3×20[a]	
Week 3		
Back squat 5×5[a]	Leg press 5×5[a]	Squat
Bench press 5×5[a]	Incline bench press 5×5[a]	Bench press
Deadlift 5×5[c]	High pull 5×5[c]	
Lat pulldown 5×5[c]	Bent-over row 5×5[c]	
Seated shoulder press 5×5[c]	Close-grip bench press 5×5[c]	
Week 4		
Back squat 5×3[a]	Leg press 5×3[a]	Squat
Bench press 5×3[a]	Incline bench press 5×3[a]	Bench press
Deadlift 5×3[c]	High pull 5×3[c]	Jump squats
Lat pulldown 5×3[c]	Bent-over row 5×3[c]	Ballistic bench press
Seated shoulder press 5×3[c]	Close-grip bench press 5×3[c]	

[a]3 min of rest between sets
[b]2 min of rest between sets
[c]1 min of rest between sets

plastic bags. All subjects recorded the times of supplementation in accordance with the investigator's instructions. In order to control for possible confounding effects of alterations in dietary intake over the training period and to isolate the independent effects of the supplementation treatments, an attempt was made to standardize dietary nutrient intake at an isocaloric level for each subject. Prior to beginning the study, subjects were weighed before and after a seven-day period during which time they recorded all fooday/beverages consumed according to instructions provided by the same registered dietitian. If body weight fluctuated >1 kg during the 7-day period, then subjects were provided with nutritional counseling to either increase or decrease food intake in order to maintain body weight. The seven-day food records were subsequently photocopied and returned to subjects. Subjects reproduced this 7-day diet during each week of the training and supplementation period.

Performance testing

Muscle testing (strength, power, local muscular endurance) was performed prior to initiation of the 4-week overreaching period, and after the completion of each training week. In addition, 1-RM testing was performed after a 2-week reduced volume and frequency period. 1-RM strength was determined for the free-weight squat and bench-press exercises according to methods previously described by Kraemer and Fry (1995). A warm-up set of five to ten repetitions was performed using 40–60% of the perceived maximum 1-RM. After a 1-min rest period, a set of two to three repetitions was performed at 60–80% of the perceived maximum 1-RM. Subsequently, three to four maximal trials (one-repetition sets) were performed to determine the 1-RM. Rest periods in between trials were 2–3 min. A complete range of motion and proper technique were required for each successful 1-RM trial. For the squat exercise, each subject was instructed to descend until the upper thighs were parallel to the ground. A research assistant was located lateral to the subject and gave a verbal "up" signal to initiate the concentric action of the exercise. For the bench press, each subject lowered the bar until it came in contact with the chest musculature. "Bouncing" the weight off of the chest and excessive arching of the back were not permitted. Strength testing was performed at the same time each session and approximately 24 h following the last training session. All subjects refrained from activity not related to the present investigation for at least 24 h prior to testing.

Power testing was performed prior to initiation of the training program and after each 2-week phase. Upper and lower body power was measured using the ballistic bench press and jump squat exercises, respectively, with the Ballistic Measurement System (BMS; Norsearch Limited, Lismore, Australia). The BMS enables ballistic movement and has been described in detail elsewhere (Volek et al. 1997b). For the jump squat, each subject descended to a position in which the thigh musculature was parallel to the ground. In a ballistic manner, each subject ascended as rapidly as possible and proceeded to jump as high as possible while minimizing any contributions from the arms. The weight was released upon jumping and bar displacement was calculated via a rotary encoder attached to the BMS and interfaced with a computer. For the ballistic bench press, each subject lowered the weight from the fully extended elbow position until it came in contact with the chest musculature. The concentric action of the exercise was performed as rapidly as possible and the weight was released upon completion. The BMS incorporates a unidirectional electromagnetic braking system, which immediately prevented descending bar movement once engaged; thus, the bar was safely released. The jump squat and ballistic bench press were performed with a load corresponding to 30% of the squat and bench press 1-RM, respectively, attained during the pre-training testing period. Testing order was randomized such that half of the subjects began with the squat jump and half began with the ballistic bench press. Each subject was given three to five maximal trials with 2 min of rest in between trials and the largest power output attained was recorded for analysis.

Following peak power testing, each subject performed a 20-repetition jump squat protocol used to measure high-intensity local muscle endurance. Loading for this assessment consisted of 30% of each subject's pre-training 1-RM squat. Subjects were instructed to jump as high as possible for each repetition while maintaining proper exercise technique and range of motion. Mean power was assessed at five repetition intervals and the percentage decline was calculated: [(mean power reps. 1–5)−(mean power reps 16–20)/mean power rep 1–5]×100.

Body composition

Body mass was measured on a digital platform scale to the nearest 100 g. Total body water (TBW) was estimated via bioelectrical impedance analysis using a modified scale platform

mounted with pressure electrodes in contact with the feet (TBF-105 Body Fat Analyzer; Tanita Corporation of America, Skokie, Ill., USA). Repeat TBW measurements obtained on 12 men on four occasions separated by 1 week between tests demonstrated a coefficient of variation of 1.8%. Percentage body fat and bone mineral density were obtained using dual-energy X-ray absorptiometry (DEXA) with a total body scanner (Prodigy; Lunar Corporation, Madison, Wis., USA) that uses a constant potential X-ray source of 76 kVp and a cerium filter that produces dual-energy peaks of 38 and 62 keV. All analyses were performed by the same technician using computer algorithms (software version 2.17.008). Quality assurance was assessed by analyzing a phantom spine provided by the company and daily calibrations were performed prior to all scans using a calibration block provided by the manufacturer. Intra-class correlation coefficients ($R \geq 0.98$) were obtained for bone mineral content, lean body mass, and fat mass from repeated scans on a group of ten men and women in our laboratory who were tested on 2 consecutive days.

Side effects

Resting pulse was measured by palpation of the radial artery and blood pressure was measured with a sphygmomanometer by the same investigator. In order to assess potential side effects and subjective changes in body function to the supplementation regimen a questionnaire used in prior creatine studies by our laboratory (Volek et al. 2000, 2001) was provided to subjects at the end of the study. The questionnaire asked subjects which group they thought were in and assessed changes in appetite, thirst, skin, muscle cramping, stomach distress, diarrhea, flatulence, headache, sex drive, sleepiness, nervousness, and aggression.

Biochemical analyses

Blood samples were obtained before and after each training week via venipuncture, after 5 min in a supine position, in the early morning hours (between 0500 and 0930 hours), and after a 10-h overnight fast and abstinence from exercise for at least 12 h. Blood sampling occurred during a standardized time of day for each subject in order to minimize the effects of diurnal hormonal variations. Whole blood samples were processed and centrifuged at 1,500 *g*. Serum and/or plasma was harvested and stored at −80°C until analyzed. Whole blood was used to determine hemoglobin in duplicate using the cyanmethemoglobin method at 540 nm (Sigma Diagnostics, St. Louis, Mo., USA) and hematocrit was analyzed in triplicate via standard microcapillary techniques and microcentrifugation. Serum glucose concentrations were measured in duplicate using standard colorimetric procedures at 450 nm (Sigma Diagnostics). Serum creatine kinase (CK) and plasma ammonia concentrations were determined in duplicate using standard colorimetric procedures at 340 nm (Sigma Diagnostics). Serum uric acid concentrations were determined in duplicate using standard colorimetric procedures at 520 nm (Sigma Diagnostics). Serum total testosterone, human GH, sex-hormone binding globulin (SHBG), insulin-like growth factor-1 (IGF-1), insulin, and cortisol concentrations were determined in duplicate using standard radioimmunoassay (RIA) techniques. Serum total testosterone, cortisol, insulin, and SHBG were measured with ^{125}I solid-phase RIA (Diagnostic Products, Los Angeles, Calif., USA). Serum IGF-1 was measured with ^{125}I solid-phase RIA using an extraction procedure (Diagnostic Products). Serum 22 kDa GH was measured using a ^{125}I liquid-phase RIA with double-antibody technique (Nichols Institute Diagnostics, San Juan Capistrano, Calif., USA). All samples for each hormone were determined in duplicate in the same assay to avoid interassay variance and were thawed only once for each assay procedure. Intra-assay variance was less than 5% for all hormones.

Statistical analyses

Statistical evaluation of the data was accomplished by using a two-way analysis of variance (ANOVA) with one between- (CrM and P) and one within- (time) factor after normal data distribution was determined. When a significant F value was achieved, a Fisher's LSD test was used to locate the pairwise differences between means. An independent t-test was used to analyze the delta change in performance improvements between 0 and 6 weeks of the study. Relationships among baseline hormones and the changes in hormone concentrations to changes in performance and body composition measures were examined using Pearson's product-moment correlation coefficients. Using the nQuery Advisor software (Statistical Solutions, Saugus, Mass., USA) the statistical power for the n size used ranged from 0.80 to 0.92. Significance was set at $P \leq 0.05$.

Results

Performance

There were significant main time effects for 1-RM squat and bench press and a significant interaction effect for the squat when considering the change from week 0 to week 1 (Fig. 1). Maximal squat was unchanged at week 1 in CrM and progressively increased each week thereafter. However, 1-RM squat was significantly reduced after week 1 in P but returned to baseline values by week 2. 1-RM bench press significantly decreased in P but remained unchanged in CrM at week 1, was not different from baseline at week 2, and progressively increased each week thereafter. Analysis of the delta change in 1-RM squat performance from weeks 0–6 revealed only a trend for greater improvement in CrM than P ($P = 0.09$) but not with the 1-RM bench press. There were significant main time effects for explosive peak power in the jump squat and a significant time and interaction effect for the ballistic bench press (Fig. 2). Jump-squat peak power was unchanged at weeks 2 and 4 and significantly increased after the reduced frequency/volume phase. There was a trend for the CrM group to experience a greater increase at week 6 (group×time, $P = 0.154$). Ballistic bench press peak power significantly decreased at week 2 in P but did not change in CrM (group×time, $P = 0.053$) and was significantly higher at weeks 4 and 6 in CrM than P. The decline in mean power during the 20 repetition jump squat protocol ranged between –12% and –14% for both groups. Power output was unchanged at weeks 2 and 4 but increased significantly after the reduced volume/frequency phase at week 6 (Table 2).

Body composition

There were significant main time effects for changes in total body mass, lean body mass, fat mass and percentage body fat (Table 3). The increases in body mass and lean body mass tended to be greater in the CrM group. A similar pattern of response was observed for the legs with the CrM group demonstrating

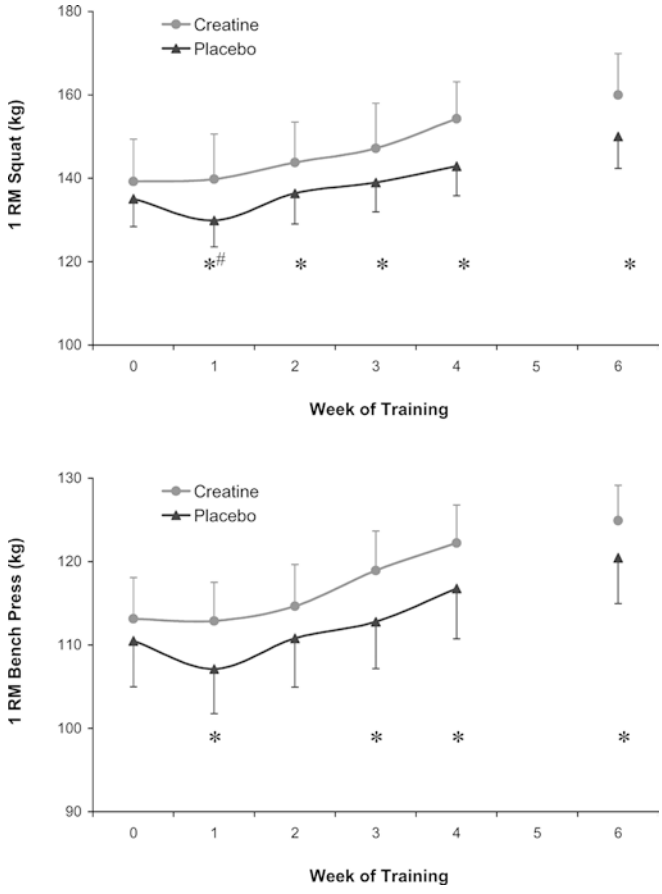

Fig. 1 Maximal squat (*upper graph*) and bench press (*lower graph*) strength during 4 weeks of resistance training overreaching and after a 2-week reduced volume/frequency phase. Data analyzed with a 2×6 (weeks 0–6) and 2×2 (week 0–1) ANOVA. $*P \leq 0.05$ from baseline for collapsed means; $^{\#}$significant ($P \leq 0.05$) group×–time (week 0–1) interaction effect. Values are mean (SE)

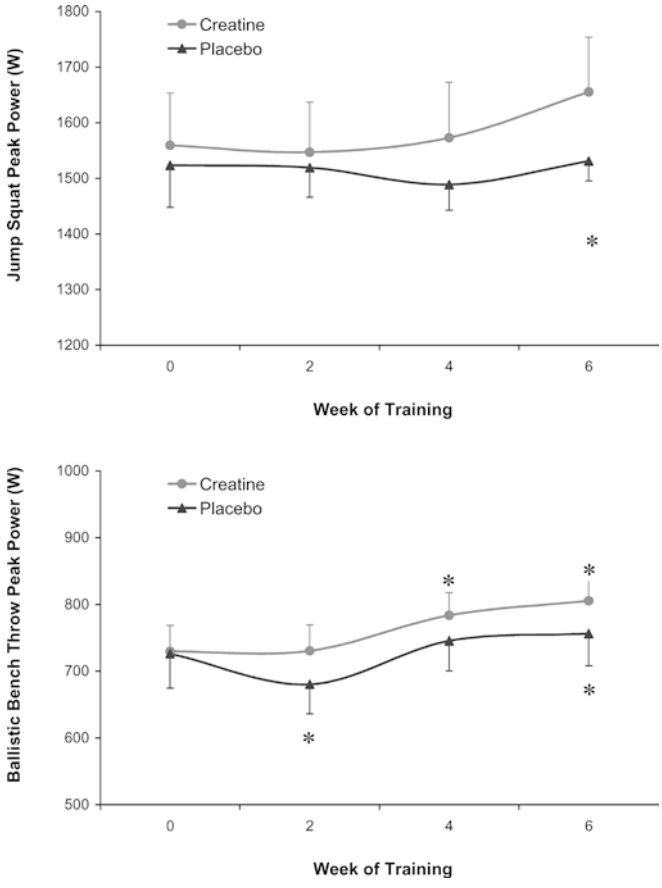

Fig. 2 Peak power during the jump squat (*upper graph*) and ballistic bench press (*lower graph*) during 4 weeks of resistance training overreaching and after a 2-week reduced volume/frequency phase. There were significant main time effects and a group×time interaction effect for the ballistic bench press. $*P \leq 0.05$ from baseline for collapsed means (*upper graph*) and from corresponding creatine or placebo baseline (*lower graph*). Values are mean (SE)

a significantly greater increase in lean body mass in this region. Compared to baseline, total body water (kg) was significantly increased at weeks 1, 2, 3, and 4 in the creatine group. There were no significant changes in TBW expressed as a percent of body mass nor were there any changes in bone mineral content or bone mineral density for either group (data not shown).

Hormonal responses

Hormonal responses are presented in Table 4. There were significant main time effects for total testosterone, free androgen index (FAI: total testosterone/SHBG), cortisol, and insulin, and a trend for SHBG ($P < 0.06$). Total testosterone decreased in CrM and P, reaching a nadir at week 3 (−11% and –19%,

Table 2 Mean power output (W) during the 20-repetition jump-squat protocol. Values are mean (SD). % Decline = [(mean power repetitions 1–5)−(mean power repetitions 16–20)/mean power repetitions 1–5]×100

		Repetitions				% Decline	Main time effect	Group× time
		1–5	6–10	11–15	16–20			
Week 0	CrM	1,522 (293)	1,457 (282)	1,387 (282)	1,319 (240)	−13.4%	0.068	0.674
	P	1,470 (193)	1,410 (189)	1,361 (172)	1,278 (154)	−13.1%		
Week 2	CrM	1,502 (292)	1,455 (288)	1,404 (285)	1,310 (247)	−12.8%	0.024	0.619
	P	1,461 (136)	1,408 (131)	1,347 (115)	1,272 (133)	−12.9%		
Week 4	CrM	1,498 (320)	1,462 (296)	1,391 (260)	1,287 (248)	−14.1%	0.016	0.503
	P	1,441 (128)	1,399 (115)	1,321 (86)	1,242 (979	−13.8%		
Week 6	CrM	1,586 (298)	1,551 (298)	1,491 (290)	1,396 (289)	−12.0%	0.057	0.792
	P	1,485 (89)	1,445 (88)	1,386 (83)	1,304 (102)	−12.2%		

Table 3 Total and regional body composition responses determined using dual-energy X-ray absorptiometry (DXA). Values are mean (SD). *BM* Body mass,*LBM* soft tissue lean body mass, *FM* fat mass, *BMC* bone mineral content

Total	Creatine group			Placebo group			*P*	
	Week 0	Week 4	Δ	Week 0	Week 4	Δ	Main time effect	Group× time
BM_{scale} (kg)	86.7 (16.9)	89.2 (16.7)	+2.5	88.9 (11.1)	89.8 (10.5)	+0.9	0.000	0.002
BM_{DXA} (kg)	87.3 (16.5)	89.9 (16.6)	+2.6	89.3 (11.1)	90.5 (10.2)	+1.2	0.000	0.115
% Fat	17.4 (9.2)	16.1 (9.5)	−1.3	20.2 (8.8)	19.3 (8.6)	−0.9	0.001	0.467
LBM (kg)	67.2 (5.6)	70.6 (5.8)	+3.4	66.9 (5.4)	68.9 (6.0)	+2.0	0.000	0.153
FM (kg)	16.5 (12.1)	15.8 (12.5)	−0.7	18.8 (10.4)	18.1 (9.9)	−0.7	0.022	0.994
BMC (g)	3,577 (401)	3,555 (395)	−22	3,652 (302)	3,566 (247)	−86	0.105	0.321
Arms								
% Fat	15.1 (10.3)	16.0 (11.4)	+0.9	17.5 (9.0)	16.6 (8.6)	−0.9	0.994	0.557
LBM (kg)	8.7 (0.6)	8.3 (2.9)	−0.4	8.3 (0.7)	8.8 (1.1)	+0.5	0.858	0.374
FM (kg)	1.8 (1.4)	1.7 (1.6)	−0.1	2.0 (1.2)	1.9 (1.0)	−0.1	0.080	0.611
BMC (g)	528 (70)	519 (67)	−9	588 (123)	534 (61)	−54	0.108	0.245
Legs								
%Fat	18.0 (8.0)	16.4 (8.0)	−1.6	20.2 (7.2)	18.7 (7.7)	−1.5	0.002	0.417
LBM (kg)	22.0 (2.5)	23.6 (2.7)	+1.6	21.7 (2.0)	22.3 (1.9)	+0.6	0.000	0.022
FM (kg)	5.5 (3.4)	5.3 (3.6)	−0.2	6.0 (2.7)	5.8 (2.6)	−0.2	0.046	0.927
BMC (g)	1,425 (134)	1,426 (139)	+1	1,291 (461)	1,391 (106)	+100	0.422	0.430
Trunk								
% Fat	18.3 (10.6)	17.3 (10.8)	−1.0	21.9 (10.3)	20.9 (10.1)	−1.0	0.112	0.940
LBM (kg)	32.5 (2.9)	33.7 (2.7)	+1.2	32.8 (3.5)	33.8 (3.0)	+1.0	0.007	0.699
FM (kg)	8.6 (7.1)	8.3 (7.1)	−0.3	10.2 (6.3)	9.9 (6.2)	−0.3	0.116	0.973
BMC (g)	1,132 (190)	1,012 (385)	−120	1,151 (131)	1,151 (100)	0	0.342	0.336

Table 4 Blood hormonal responses in subjects who supplemented with creatine monohydrate (*CrM*) or placebo (*P*). Values are mean (SD).*FAI* Free androgen index, *GH* growth hormone, *IGF-I* insulin-like growth factor-I, *SHBG* sex hormone binding globulin, *TT* total testosterone

		Week 0	Week 1	Week 2	Week 3	Week 4	Main time effect	Group×time
TT (nmol/l)	CrM	34.8 (9.8)	34.2 (7.6)	34.0 (6.9)	31.0 (10.9)*	33.3 (8.0)	0.019	0.715
	P	29.9 (6.2)	27.0 (5.6)	26.2 (2.8)	24.3 (3.1)	28.7 (6.8)		
SHBG (nmol/l)	CrM	21.4 (10.2)	22.6 (12.2)	22.7 (10.8)	22.2 (6.2)*	23.7 (9.7)*	0.053	0.150
	P	22.9 (8.9)	24.9 (10.1)	25.2 (10.4)	27.6 (12.0)	24.9 (10.9)		
FAI (TT/SHBG)	CrM	1.77 (0.53)	1.66 (0.37)*	1.64 (0.46)*	1.41 (0.39)*	1.49 (0.36)*	0.000	0.437
	P	1.51 (0.69)	1.25 (0.52)	1.19 (0.45)	1.02 (0.38)	1.29 (0.47)		
Free T (pmol/l)	CrM	126 (37)	124 (29)	129 (33)	120 (33)	125 (24)	0.554	0.500
	P	105 (25)	94 (28)	89 (18)	93 (32)	97 (27)		
Cortisol (nmol/l)	CrM	614 (164)	792 (314)**, ***	582 (186)	607 (154)	465 (219)**	0.009	0.008
	P	590 (157)	465 (138)	483 (159)	454 (145)	467 (62)		
Insulin (IU/ml)	CrM	11.0 (9.5)	8.2 (6.5)*	8.5 (5.8)*	8.7 (6.1)*	9.2 (5.9)	0.042	0.972
	P	10.7 (8.2)	8.2 (5.7)	9.4 (7.9)	8.6 (6.9)	9.5 (9.0)		
GH (ng/ml)	CrM	0.23 (0.08)	0.21 (0.06)	0.24 (0.11)	0.30 (0.27)	0.23 (0.08)	0.249	0.586
	P	0.22 (0.07)	0.31 (0.14)	0.29 (0.11)	0.32 (0.14)	0.32 (0.14)		
IGF-I (nmol/l)	CrM	39.9 (5.9)		38.9 (3.6)		38.1 (2.4)	0.414	0.167
	P	43.8 (9.9)		47.0 (13.0)		45.0 (10.8)		

*Significantly different ($P \leq 0.05$) from week 0 value for collapsed group means
**Significantly different ($P \leq 0.05$) from week 0 value for CrM group
***Significantly different ($P \leq 0.05$) from corresponding value for P group

respectively) and returning to baseline at week 4. Serum SHBG responded in an opposite direction to that of total testosterone. The FAI was significantly decreased at week 1 and reached the lowest point at week 3. Free testosterone responded in a similar fashion but the changes were not significant. The CrM group exhibited a significant increase in cortisol after week 1 (+29%), which returned to baseline by week 2; whereas cortisol was unchanged in the P group. Insulin levels were significantly depressed at week 1 and drifted back toward baseline during weeks 2–4. GH and IGF-I levels were not significantly altered over the training study. There were no significant relationships between baseline hormone levels or the changes in hormones with changes in performance or body composition.

Blood metabolite responses

Metabolic responses are presented in Table 5. There was a significant time and interaction effect for uric acid. Uric acid increased in the P group at week 1 (+18%) and gradually returned to baseline by week 3, whereas values declined in the CrM group at week 1 (−11%) and remained below baseline through week 4. Ammonia values were reduced at week 1 and tended to remain below baseline through week 4. CK was significantly elevated at week 1 and returned toward baseline over the remainder of the study. Glucose was significantly lower at week 1 and remained below baseline through week 4. There were no significant changes in total cholesterol and triglycerides. Hemoglobin and hematocrit values were reduced at week 1 and remained below baseline through week 4. Plasma creatinine was significantly increased in the CrM group (+5–8%) and unchanged in the P group.

Side effects

There were no significant changes in resting heart rate or blood pressure responses. Reported side effects were minimal and occurred at a similar frequency for both groups. The most common complaint was increased thirst (two placebo and three creatine subjects) and sleepiness (three creatine subjects). In the CrM group, seven subjects reported not knowing their supplement group and two thought they were in the P group. In the P group, two subjects reported not knowing their supplement group, five thought they were in the CrM group, and one thought he was in the P group.

Discussion

A major aim of this study was to assess whether the resting circulating hormonal milieu was altered by creatine supplementation and whether this was related to changes in performance and body composition during resistance training overreaching. The findings from this study indicate that alterations in resting hormones do not explain the performance and body composition responses to creatine supplementation and short-term resistance training overreaching in a group of men with similar training backgrounds. Although the overreaching protocol resulted in significant changes in the circulating endocrine milieu, creatine supplementation does not appear to be mediating its effect though hormonal mechanisms. These results were obtained in a homogenous group of resistance-trained men. We intentionally chose men with a resistance training background in order to reduce the large variations that can occur in strength gains at the onset of a structured program in untrained individuals (e.g., neural adaptations which could potentially mask any supplementation benefits). To further equate the training status of all subjects, we trained each subject for 4 weeks using a structured base program before matching and randomizing subjects into supplementation groups. This type of standardization is also necessary in order to minimize the effect of differences in hormone concentrations that may exist between subjects as a result of training.

Previous work indicates that 5–7 days of creatine supplementation does not alter hormonal responses to a single bout of heavy resistance exercise (Op 'T Eijnde and Hespel 2001; Volek et al. 1997a, 2001). However,

Table 5 Blood metabolite responses in subjects supplemented with creatine monohydrate (*CrM*) or placebo (*P*). Values are mean (SD). *CK* Creatine kinase, *TC* total cholesterol, *TG* triglycerides, *Hb* hemoglobin, *Hct* hematocrit

		Week 0	Week 1	Week 2	Week 3	Week 4	Main time effect	Group×time
Uric acid (mg/dl)	CrM	6.1 (1.3)	5.4 (1.5)**	5.3 (1.6)**	5.1 (1.4)**	5.0 (1.4)**	0.000	0.002
	P	6.1 (1.6)	7.2 (2.4)**	6.6 (1.7)	6.1 (1.7)	5.6 (1.8)		
Ammonia (μmol/l)	CrM	42.8 (19.1)	24.1 (21.3)*	23.8 (18.0)*	34.5 (17.4)	27.0 (19.0)	0.000	0.424
	P	38.2 (18.4)	20.5 (13.3)	17.1 (5.0)	35.5 (18.7)	37.2 (13.2)		
CK (IU/l)	CrM	91 (69)	836 (920)*	242 (124)	228 (146)	142 (74)	0.000	0.617
	P	72 (38)	1297 (1630)	177 (79)	162 (106)	88 (47)		
Glucose (mg/dl)	CrM	95.4 (10.5)	87.1 (7.2)*	92.8 (7.2)*	88.5 (6.3)*	90.4 (7.0)*	0.000	0.472
	P	97.9 (8.9)	90.0 (10.0)	92.8 (9.3)	89.0 (8.6)	88.2 (4.5)		
TC (mg/dl)	CrM	190 (38)	181 (38)	187 (45)	189 (41)	193 (30)	0.406	0.430
	P	189 (46)	181 (38)	191 (36)	180 (35)	180 (51)		
TG (mg/dl)	CrM	81 (31)	69 (32)	82 (40)	89 (42)	92 (44)	0.292	0.127
	P	126 (91)	99 (74)	126 (94)	102 (59)	90 (63)		
Hb (g/dl)	CrM	15.2 (1.0)	15.1 (1.2)*	14.9 (1.0)*	14.7 (0.9)*	14.9 (0.8)*	0.005	0.192
	P	15.7 (1.1)	14.6 (1.0)	15.0 (0.6)	14.8 (1.0)	14.8 (0.6)		
Hct (%)	CrM	44.9 (2.4)	42.2 (1.9)*	42.3 (1.9)*	43.1 (1.9)*	43.2 (1.5)*	0.000	0.957
	P	44.4 (2.0)	41.3 (2.4)	42.0 (1.6)	42.4 (2.0)	42.8 (1.3)		
Creatinine (mg/dl)	CrM	1.65 (0.09)	1.74 (0.09)**	1.76 (0.13)**, ***	1.77 (0.09)**, ***	1.79 (0.13)**, ***	0.005	0.000
	P	1.60 (0.07)	1.60 (0.07)	1.54 (0.04)	1.57 (0.03)	1.61 (0.06)		

*Significantly different ($P \leq 0.05$) from week 0 value for collapsed group means

**Significantly different ($P \leq 0.05$) from week 0 value for corresponding CrM or P group

***Significantly different ($P \leq 0.05$) from corresponding value for P group

exercise-induced (acute) and resting (chronic) hormone concentrations may be controlled by different regulatory mechanisms and reflect the system's ability to cope with an applied exercise stress versus a regulatory mechanism to which the involved tissues are constantly exposed (Fry et al. 1991). Since changes in resting hormones would be more likely to contribute to the changes in performance and body composition resulting from a training program, this study focused on the effects of creatine supplementation on resting hormones. The overreaching protocol resulted in significant decreases in total testosterone, FAI, and insulin whereas SHBG and cortisol were significantly increased.

The reduction in total testosterone was expected since it has been shown that resting total testosterone decreases during high volume or high intensity resistance training overreaching (Fry et al. 1993; Raastad et al. 2001). Although not significant, SHBG concentrations tended to increase more in the P group, which may have been due to the need to increase the carrying capacity of testosterone stimulated by a reduced availability of free testosterone. It has been previously shown that free testosterone also decreases when the volume anday/or intensity are significantly increased (Häkkinen et al. 1987; Häkkinen and Pakarinen 1991).

The significant increase in cortisol concentrations at week 1 in the CrM but not the P group was unexpected since we failed to observe changes in resting or exercise-induced levels of cortisol after 7 days of creatine supplementation in our prior work (Volek et al. 1997b, 2001). However, Op 'Teijnde and Hespel (2001) recently reported that cortisol levels were significantly higher 90 and 120 min after an acute bout of heavy resistance exercise following 5 days of creatine supplementation. Resting concentrations of cortisol have been shown to be highly variable over the course of various resistance training programs (Fry and Kraemer 1997). Generally, significant increases in volume or intensity result in higher resting concentrations of cortisol (Häkkinen et al. 1987; Häkkinen and Pakarinen 1991). The increased cortisol response at week 1 could have been due to a direct effect of creatine or more likely due to the greater force-producing capabilities (and exertion during training) exhibited by the CrM group.

Resting concentrations of serum 22-kD GH were not significantly altered by the resistance training program, which is consistent with our prior work in younger and older populations (Kraemer et al. 1999). A recent study demonstrated that creatine supplementation augmented the GH response to a bout of heavy resistance exercise (Schedel et al. 2000); however, creatine had no effect on GH responses to resistance exercise in another study (Op 'T Eijnde and Hespel 2001). GH has been shown to stimulate the release of IGF-I from the liver with peak values of IGF-I occurring approximately 16–28 h following GH stimulation (Copeland et al. 1980). Circulating IGF-I levels also tend to be more sensitive to changes in nutritional intake than exercise stress, and can be elevated by protein and carbohydrate supplementation in young men engaged in daily bouts of heavy resistance exercise (Kraemer et al. 1999). The results of the present study indicate that short-term resistance training overreaching, with or without creatine supplementation, does not alter resting concentrations of GH or IGF-1.

Resting serum glucose and serum insulin concentrations were reduced throughout the experimental period in both groups at several time points. These findings are unique as to our knowledge reductions in resting serum glucose have not typically been observed during resistance training. However, basal concentrations of insulin are not regulated by normal basal serum glucose concentrations (e.g., 80–100 mg/dl) and have been shown to be lower during strength training (Miller et al. 1984) and in bodybuilders with large muscle mass (Szczypaczewska et al. 1989). Although insulin secretion is pulsatile and a basal value may not be indicative of a positive training adaptation, our data support previous investigations and may show greater insulin sensitivity during resistance training overreaching.

In several of our performance measures, creatine supplementation generally resulted in improved performance responses to the overreaching protocol [i.e., maintenance of muscular performance during the high-volume phase, a statistically greater improvement in the ballistic bench press peak power output, and a tendency ($P = 0.09$) for a greater improvement in week squat]. Several other studies have reported that creatine supplementation augments gains in muscular after resistance training programs lasting 3 weeks (Burke et al. 2000), 4 weeks (Arciero et al. 2001; Earnest et al. 1995; Kelly and Jenkins 1998; Kreider et al. 1998), 5 weeks (Stone et al. 1999), 6 weeks (Burke et al. 2001), 8 weeks (Noonan et al. 1998), 9 weeks (Bemben et al. 2001), 10 weeks (Vandenberghe et al. 1997), 12 weeks (Volek et al. 1999), and 13 weeks (Larson-Meyer et al. 2000). Unique to this study, the same muscle groups were trained 5 days in a row, thus reducing the amount of recovery time between workouts to less than 24 h. The mechanism for the performance improvements in the creatine group could be due to a number of factors, but a hormonal-mediated effect is not likely.

Creatine supplementation during resistance training has been shown to accentuate muscle fiber hypertrophy (Hespel et al. 2001; Volek et al. 1999), muscle cross-sectional area (Hespel et al. 2001), myosin heavy chain mRNA and protein expression (Willoughby et al. 2001), and whole body leucine oxidation and plasma leucine rate of appearance (Parise et al. 2001). In the present study, the CrM group gained more lean body mass and this was statistically significant in the legs. The magnitude of change in total body lean body mass (+3.4 kg) was slightly greater than previously reported gains ranging from 1.6 to 2.5 kg after 4 weeks of resistance training and creatine in previous studies (Arciero et al. 2001; Earnest et al. 1995; Kelly and Jenkins 1998; Kreider et al. 1998). This may be attributed to the overreaching program used in the present study. The

short-term program used in the present study was periodized (i.e., variation in the volume and intensity) and supervised by a certified strength and conditioning specialist, thus ensuring optimal effort during training (Mazzetti et al. 2000). In addition, the subjects had ~5 years of resistance training experience. It has been shown that hypertrophy may be the major mechanism for strength improvement in trained individuals whereas neural mechanisms predominate in novice lifters (Häkkinen 1989). Thus, training status may have been an influential factor affecting the magnitude of lean body mass gain in the present study and in other studies using previously untrained individuals.

Serum concentrations of uric acid were significantly elevated in the P group, whereas values were reduced in the CrM group. Elevated concentrations of uric acid may reflect an intracellular energy deficit (via greater stimulation of the purine nucleotide cycle) and may be a possible indicator of training stress (Rowbottom et al. 1997). This suggestion was based on endurance training where uric acid was inversely correlated to endurance performance (Rowbottom et al. 1997). We recently reported that a moderate-intensity/high-volume squat protocol resulted in significant increases in resting uric acid concentrations for 4 days into recovery and that carnitine supplementation attenuated this response, presumably via increasing blood flow (Volek et al. 2002). Interestingly, creatine supplementation has been shown to increase limb blood flow measured by venous occlusive plethysmography (Arciero et al. 2001). The importance of creatine-induced effects on blood flow and biomarkers for exercise stress in mediating adaptations to resistance training warrants further investigation.

There were no changes in total cholesterol and triglycerides, which is consistent with our prior work (Volek et al. 2000). In contrast, creatine supplementation reduced triglycerides in subjects with moderate hypercholesteremia who maintained their habitual training (Earnest et al. 1996) and improved HDL-cholesterol and VLDL-cholesterol in healthy young athletic men who performed a combination of resistance and sprint/agility training (Kreider et al. 1998). As expected, there was a significant increase in serum creatinine (within normal ranges), which is consistent with prior work in healthy men (Volek et al. 2000, 2001). As muscle creatine breakdown has been shown to occur at a constant rate, this small increase in creatinine is likely a result of the larger muscle creatine stores after creatine supplementation. There were small but significant decreases in hemoglobin and hematocrit, which may have been due to increases in plasma volume. Alternatively, plasma proteins and erythrocytes may be broken down to support protein anabolism during stressful training. Hemolysis and subsequent reductions in blood hemoglobin has been shown to occur in endurance athletes but also during strength training as evidenced by reductions in blood hemoglobin and haptoglobin (Schobersberger et al. 1990).

In summary, the lack of correlation among the changes in resting circulating hormones and performance/body composition suggests that resting hormonal concentrations do not explain the performance and body composition responses to creatine supplementation during short-term resistance training overreaching in resistance-trained men. Our data do not, however, address acute post-exercise endocrine responses to a workout (i.e., those anabolic responses suggested to be the primary mediators of tissue growth and repair following resistance exercise), 24-h hormonal fluctuations, nor do they address hormone kinetics including potential affects at the level of synthesis/secretion, target tissue receptor interaction, or degradation of hormones. The increases in lean body mass with creatine supplementation are consistent with other resistance training studies.

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