

Article

Comparison of Creatine Monohydrate Supplementation Immediately Before Versus Immediately After Resistance Training Sessions in Trained Young Healthy Adults

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Abstract

Background: Resistance training increases lean mass, muscle accretion and performance. These adaptations from resistance training can be further increased with 5 g of creatine monohydrate supplementation (CrM). In addition to dose, it has been proposed that the timing of CrM may be an important factor to consider to help improve these adaptations. However, whether the strategic ingestion of CrM during a resistance training program influences lean mass, muscle accretion and performance in trained young healthy adults compared to a placebo is unknown. Therefore, this study examined whether consuming CrM immediately before or after resistance training sessions for 16 weeks differentially affected body composition, limb muscle thickness or muscle performance in trained young healthy adults. Twenty-seven participants were randomized into one of three groups: Creatine Before ($n = 10$; 24 ± 6 years of age; 5 g CrM immediately before resistance training sessions and placebo immediately after training), Creatine After ($n = 9$; 26 ± 7 years of age, 5 g of CrM immediately after resistance training sessions and placebo immediately before training) or the Placebo ($n = 8$; 25 ± 6 years of age; placebo immediately before and after training). Body composition, limb muscle thickness and muscle performance was assessed before and following 16 weeks. Results showed that the strategic ingestion of CrM (before or after resistance training sessions compared to a placebo) had no effect on measures of body composition, limb muscle thickness or muscle performance ($p > 0.05$). In conclusion, 5 g of CrM (independent of the timing of ingestion) on resistance training days (or 280 g of CrM in total) was ineffective at augmenting muscle growth and performance in a small group of trained young healthy adults (18–39 years of age).



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Keywords: lean mass; muscle thickness; power; strength; endurance

1. Introduction

Resistance training increases measures of muscle growth and performance (i.e., strength, endurance, power) in young healthy adults [1]. These adaptations from resistance training can be further increased with CrM [2]. The seminal study by Harris et al. [3] showed that the bolus ingestion of 5 g of CrM in healthy adults increased plasma creatine levels, thereby increasing creatine availability for uptake into

skeletal muscle. Considering evidence that 3 g of CrM/day resulted in the saturation of intramuscular creatine stores after 4 weeks [4], it can be expected that a CrM dose of 5 g/day would lead to maximal levels after 3 weeks. Once intramuscular creatine stores are saturated, 5 g of CrM/day serves as a viable and effective quantity shown to improve lean mass, muscle accretion and performance when combined with resistance training [2]. These improvements are likely linked to CrM's influence on cellular hydration, calcium, glycogen and muscle protein kinetics, insulin-like growth-factor 1, myogenic transcription factors, satellite cells, inflammation and oxidative stress or by serving as a neurotransmitter [5].

In addition to dose, it has been proposed that the timing of CrM might influence body composition and muscle performance [6]. This notion likely arose from the previously discussed study by Harris et al. [3], who showed that muscle contractions augment intramuscular creatine levels, possibly due to an increase in blood flow kinetics [3] or through an increase in creatine transporter (SLC6A8) and/or Na⁺-K⁺ pump activity [7,8]. A few individual studies have shown similar muscle benefits from CrM immediately before and immediately after resistance training sessions in healthy populations [6]. However, a major limitation across these studies was that no placebo group was used as a comparator to CrM, which decreases the ability to determine the extent to which the timing of CrM was influential. In the only study to compare CrM to a placebo, Candow et al. [9] showed that CrM immediately before and immediately after resistance training sessions in healthy older adults significantly improved muscle strength more than the placebo. There were no differences between the CrM groups. What remains to be determined is whether the strategic ingestion of CrM influences the adaptations from resistance training in trained young healthy adults when compared to a placebo. Therefore, the purpose of this study was to compare the effects of CrM immediately before ($n = 10$ [5 females, 5 males], 24 ± 6 years of age, 4.75 ± 4.75 years of resistance training experience) versus immediately after resistance training sessions ($n = 9$ [5 females, 4 males], 26 ± 7 years of age, 6.91 ± 5.65 years of resistance training experience) versus a placebo and resistance training ($n = 8$ [5 females, 3 males], 25 ± 6 years of age, 4.75 ± 6.5 years of resistance training experience) on measures of body composition, limb muscle thickness and muscle performance. The CONSORT checklist can be found in Supplementary Material.

2. Materials and Methods

2.1. Participants

Participants (18–39 years of age who had been performing resistance training at least 2 days per week for at least 4 weeks) were enrolled into the study. Participants were excluded if they were pregnant or breastfeeding, had used creatine-containing products within one month prior to the start of the study or if they were allergic to the placebo. Participants were required to maintain their normal dietary and physical activity patterns during the study.

Burke et al. [10] previously showed that the combination of CrM and resistance training increased the limb muscle size more than a placebo and resistance training (controlled standardized mean difference = 0.23). Using a three-group, repeated measures (Between-Within) design, an F value of 3.19, a p -value of 0.05, 80% power, and an inter-measure correlation of 0.5, 17 participants per group were required (G*Power 3.1.9.7). However, after 9 months of extensive recruiting efforts, only 37 participants were randomized. Therefore, results from this study should be considered with caution as 80% power was not achieved. One participant in the Placebo group withdrew due to a personal issue not related to the study, and 9 participants (Creatine Before = 3, Creatine After = 3, Placebo = 3) discontinued (Figure 1). Ethics approval was obtained from the University of Saskatchewan (File # 4641)

and adopted by the University of Regina (clinical trial identifier: NCT06438887). Consent was obtained from each participant.

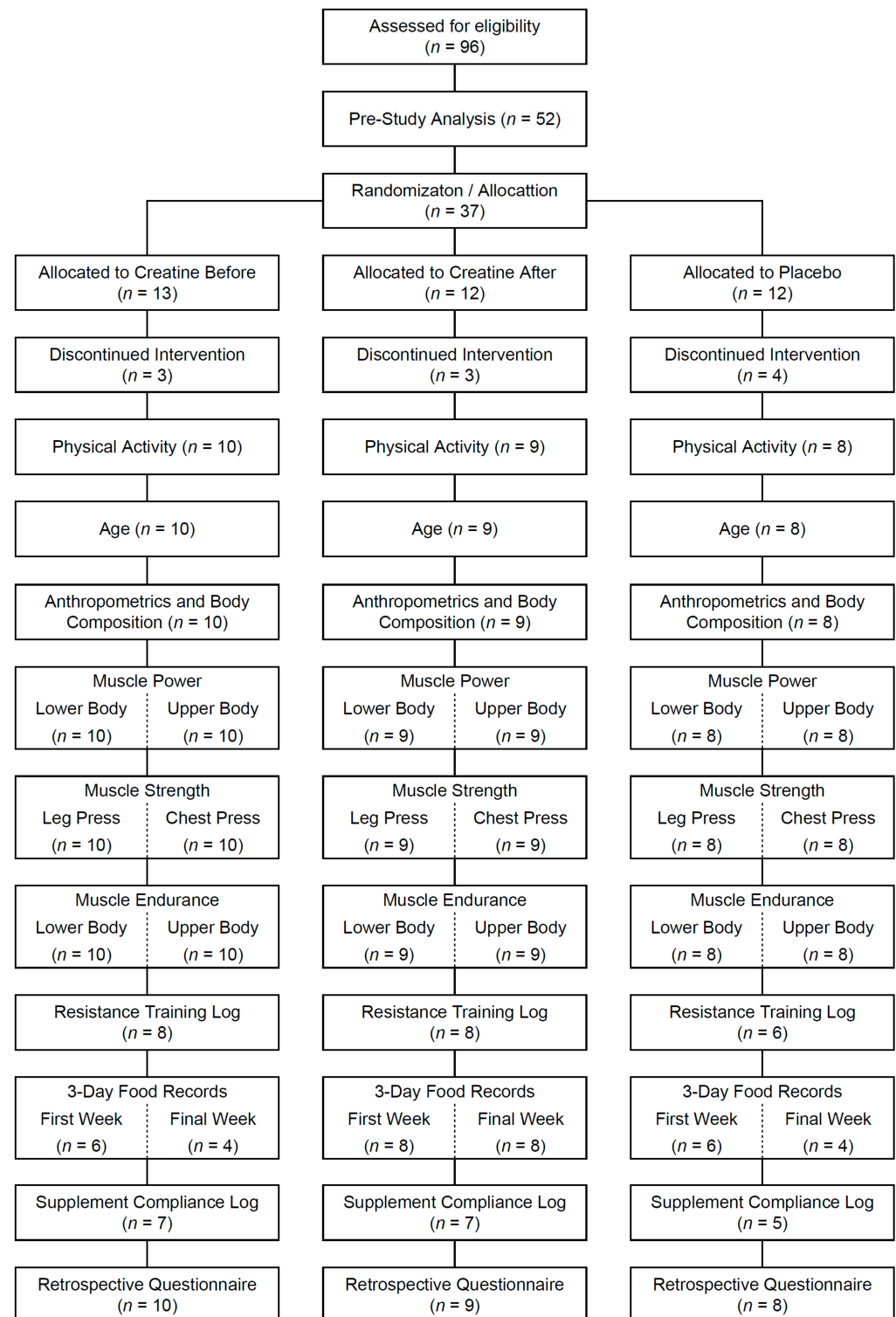


Figure 1. Summary of recruitment, allocation and analyses.

2.2. Experimental Design and Supplementation

After initially stratifying participants based on age, mass and biological sex, participants were randomized (double-blind) to one of three groups: Creatine Before (5 g CrM combined with 3 g placebo [corn starch maltodextrin] immediately before resistance training sessions and 8 g placebo immediately after resistance training sessions; total daily

amount: 5 g CrM and 11 g placebo), Creatine After (8 g of placebo immediately before resistance training sessions and 5 g of CrM + 3 g of placebo immediately after resistance training sessions; total daily amount: 5 g CrM and 11 g placebo) or Placebo (8 g of placebo immediately before and 8 g immediately after resistance training sessions; total daily amount: 0 g CrM and 16 g placebo) for 16 weeks. The total amount of CrM consumed over 16 weeks was 280 g. Supplements were in powdered form and very similar in color, taste, and appearance. Participants mixed and consumed their supplement in water. A supplementation log was used to assess compliance to the supplement regimen.

2.3. Resistance Training Program

Participants performed 3 sets of 6, 8, and 10 repetitions to volitional fatigue for each exercise. The load was reduced per set to achieve the specified number of repetitions. Each workout consisted of the following exercises in order: barbell back squat or leg press, bench or chest press, leg extension, lat pulldown or seated row, leg curl, shoulder press or lateral raise, calf raise, and bicep curl. Training occurred on alternating days for 16 weeks. Training logs were used to determine compliance, adherence and training volume (load $\times$ repetitions $\times$ sets; kg) performed over time.

2.4. Body Composition

Measures of body composition were assessed using bioelectrical impedance analysis (BIA; InBody 270 scan; Cerritos, CA, USA). Prior to each assessment, participants refrained from physical activity for 24 h, alcohol for 6 h, tobacco or nicotine for 3 h and food or drink for 3 h. The minimal detectable difference (MDD; $1.96 \times \sqrt{2} \times$ standard error of measurement [SEM] and test–retest reliability (intraclass correlation coefficient; ICC [95% confidence interval]) using a two-way mixed effects model were determined for 11 participants during the same testing session (5 min apart). Reliability measures were: body mass (MDD: 0.14 kg; ICC: 0.999 [0.999 to 1.000]; SEM: 0.05), total body water (MDD: 0.77 kg; ICC: 0.999 [0.997 to 0.999]; SEM: 0.28), lean mass (MDD: 1.08 kg; ICC: 0.999 [0.996 to 0.999]; SEM: 0.39), dry lean mass (MDD: 0.77 kg; ICC: 0.999 [0.997 to 0.999]; SEM: 0.28), skeletal muscle mass (MDD: 0.67 kg; ICC: 0.999 [0.997 to 0.999]; SEM: 0.24), skeletal muscle mass index (MDD: 0.06 kg/m²; ICC: 0.999 [0.999 to 1.000]; SEM: 0.02), fat mass (MDD: 1.14 kg; ICC: 0.998 [0.992 to 0.997]; SEM: 0.41), body fat % (MDD: 1.7404; ICC: 0.994 [0.975 to 0.999] SEM: 0.63), and basal metabolic rate (MDD: 21.9 kcal; ICC: 0.995 [0.981 to 0.999]; SEM: 7.9).

2.5. Limb Muscle Thickness and Muscle Performance

Muscle thickness of the biceps, triceps, quadriceps, hamstrings and calf was measured using ultrasound (LOGIQ e, GE Medical Systems, Wauwatosa, Wisconsin, USA). All assessments were performed by the same investigator. To minimize the effects of muscle edema on each measure, participants refrained from performing resistance training for 2 days prior to testing. Reliability measures, determined on 10 participants during the same testing session (20 min apart), were as follows: elbow flexor muscle thickness (MDD: 0.28 cm; ICC: 0.993 [0.970 to 0.999]; SEM: 0.10), elbow extensor muscle thickness (MDD: 0.36 cm; ICC: 0.989 [0.948 to 0.998]; SEM: 0.13), knee flexor muscle thickness (MDD: 0.30 cm; ICC: 0.994 [0.963 to 0.999]; SEM: 0.11), knee extensor muscle thickness (MDD: 0.25 cm; ICC: 0.995 [0.970 to 0.999]; SEM: 0.09), and ankle plantar flexor muscle thickness (MDD: 0.39 cm; ICC: 0.992 [0.953 to 0.999]; SEM: 0.14).

Muscle performance was measured in sequence: (a) vertical jump, (b) medicine ball throw, (c) leg press 1 repetition maximum (1-RM), (d) chest press 1-RM, (e) leg press endurance, and (f) chest press endurance.

2.6. Diet

Dietary intake was estimated using 3-day food diaries that were collected from participants during the first and final week of the study. MyFitnessPal (version 25.27.0) [11] was used to analyze the data. Participants' intake of creatine from food (independent of CrM) was estimated using these diaries [12,13].

2.7. Retrospective Supplement Identification Questionnaire

At the conclusion of this study, participants completed a retrospective supplementation identification questionnaire. They were asked to indicate whether they believed they received the CrM or the placebo or if they were unsure which supplement they had consumed during the study.

2.8. Statistical Analyses

To evaluate changes over time, separate group $\times$ time analyses of variance (ANOVAs) were conducted for each outcome measure. The same approach was applied to examine changes in dietary intake from week 1 and week 16. Baseline values, compliance with supplementation and training, total training volume performed over time and the relative (%) change for each variable were assessed using a one-factor ANOVA. An ANCOVA was performed to ensure post-test values were not affected by baseline values. Contrast analysis on % changes scores was also performed. Significance was set as $p < 0.05$. All results are expressed as means $\pm$ standard deviation. Eta squared (η^2) values are also presented (0.15: large differences, 0.06: medium differences, 0.01: small differences). Normality was assessed using the Shapiro–Wilk test on absolute change scores (Δ post-mean-pre-mean). Some groups demonstrated significant deviation (skeletal muscle mass: Creatine Before, $p = 0.033$; fat mass: Placebo, $p < 0.001$; body fat percentage: Placebo, $p = 0.008$; skeletal muscle mass index: Creatine Before, $p = 0.047$; knee flexor muscle thickness: Creatine Before, $p = 0.19$; leg press 1-RM: Creatine Before, $p = 0.009$; chest press reps: Placebo, $p = 0.002$; leg power: Creatine After, $p = 0.005$), but close examination of the Q-Q plots did not result in a substantial departure from the void analysis using ANOVA. Homogeneity of variance was assessed using Levine's test on absolute change scores (based on mean). The only violation was for medicine ball power ($p = 0.12$), but no extreme variances were evident. Statistical analyses were performed using IBM® SPSS® Statistics, v. 28 (Chicago, IL, USA).

3. Results

3.1. Participants

There were no differences between groups for any baseline measure (Table 1) or relative (%) change score (Table 2). The ANCOVA adjusted post-supplementation scores did not reveal any significant differences between groups.

Table 1. Participant characteristics at baseline.

Variable	Creatine Before ($n = 10$; 5 Male, 5 Female)	Creatine After ($n = 9$; 4 Male, 5 Female)	Placebo ($n = 8$; 3 Male, 5 Female)
Age (years)	24 (6)	26 (7)	25 (6)
Height (cm)	167.83 (8.06)	170.60 (10.33)	171.20 (6.41)
Body mass (kg)	80.11 (19.02)	84.87 (29.60)	78.62 (23.14)
Training experience (years)	4.75 (4.75)	6.91 (5.65)	4.75 (6.50)

Values are means (standard deviation).

Table 2. Relative changes (%) from baseline to week 16.

Variable	Creatine Before (<i>n</i> = 10; 5 Male, 5 Female)	Creatine After (<i>n</i> = 9; 4 Male, 5 Female)	Placebo (<i>n</i> = 8; 3 Male, 5 Female)
<i>Body Composition</i>			
Body mass (kg)	0.14 (5.30)	1.52 (3.54)	−2.00 (5.44)
Total body water (kg)	1.15 (3.92)	0.76 (4.75)	0.79 (3.38)
Lean mass (kg)	1.10 (3.88)	0.76 (4.79)	0.85 (3.34)
Dry lean mass (kg)	0.99 (3.81)	0.76 (4.92)	0.99 (3.31)
Skeletal muscle mass (kg)	1.49 (4.40)	1.08 (4.91)	0.82 (3.02)
Skeletal muscle mass index (kg/m ²)	1.77 (4.27)	1.49 (3.36)	−0.76 (2.03)
Fat mass (kg)	−3.92 (14.77)	3.76 (11.34)	−6.63 (14.23)
Fat mass (%)	−4.36 (10.45)	1.96 (9.71)	−4.90 (10.34)
Basal metabolic rate	0.75 (2.84)	0.50 (3.61)	0.61 (2.51)
<i>Limb Muscle Thickness</i>			
Biceps (cm)	0.41 (6.78)	−3.78 (5.68)	1.59 (4.87)
Triceps (cm)	2.99 (10.66)	6.92 (20.15)	−2.65 (9.67)
Hamstrings (cm)	0.63 (20.71)	3.16 (13.67)	8.37 (6.39)
Quadriceps (cm)	1.64 (8.94)	0.76 (10.92)	1.63 (8.98)
Calf (cm)	1.63 (12.94)	0.41 (7.14)	5.17 (8.23)
Sum of limbs (cm)	0.70 (5.49)	0.26 (5.77)	2.51 (2.50)
<i>Muscle Performance</i>			
Leg press (kg)	1.95 (38.55)	15.21 (20.17)	7.89 (15.39)
Chest press (kg)	5.54 (9.92)	19.24 (19.31)	5.53 (5.75)
Leg press (reps)	4.12 (43.84)	45.17 (41.41)	27.14 (36.60)
Chest press (reps)	11.90 (30.27)	31.26 (30.84)	11.27 (23.51)
Leg power (watts)	2.41 (5.62)	7.62 (9.95)	−1.17 (6.33)
Medicine ball (cm)	8.52 (7.31)	6.38 (15.41)	6.08 (4.43)
<i>Diet</i>			
Total energy (kcal)	−2.64 (23.37)	−4.72 (19.14)	−21.00 (11.19)
Carbohydrate (g/day)	−1.16 (13.74)	−3.52 (24.61)	−20.50 (12.01)
Fat (g/day)	1.28 (29.83)	−1.34 (32.17)	−29.50 (18.43)
Protein (g/day)	−9.08 (35.94)	−4.42 (45.27)	−7.25 (23.32)
Creatine (g/day)	15.00 (68.64)	24.12 (117.13)	−21.66 (46.24)

Values are means (standard deviation).

Resistance training compliance was similar between groups over time (Creatine Before: $62.75 \pm 30.63\%$; Creatine After: $87.12 \pm 20.29\%$; Placebo: $80.66 \pm 33.78\%$; $p = 0.232$). There was no statistical difference between groups over time for the amount of resistance training performed (Creatine Before: $412,941.58 \pm 381,935.70$ kg; Creatine After: $500,521.83 \pm 420,826.96$ kg; Placebo: $653,760.60 \pm 660,708.79$ kg; $p = 0.591$).

The supplementation compliance was similar between groups over time (Creatine Before: $61.10 \pm 25.27\%$; Creatine After: $85.33 \pm 21.74\%$; Placebo: $80.80 \pm 35.54\%$; $p = 0.243$).

In the Creatine Before group, six participants correctly guessed they were taking CrM before training sessions, three participants incorrectly guessed they were taking CrM before training sessions and one participant was unsure what supplement they were consuming. In the Creatine After group, two participants correctly guessed they were taking CrM after training sessions, two participants incorrectly guessed they were taking CrM after training sessions, one participant was not sure if they were taking CrM before or after training sessions and three participants were unsure whether they were taking CrM or a placebo. In the Placebo group, four participants correctly guessed they were taking a placebo, two participants incorrectly guessed they were taking a placebo and two participants were unsure what supplement they were consuming.

3.2. Body Composition, Metabolic Rate and Muscle Thickness

There were no changes ($p > 0.05$) over time for any measure of body composition, metabolic rate or muscle thickness (Tables 3 and 4).

Table 3. Body composition and metabolic rate measurements before and after 16 weeks of training and supplementation.

Variable	Creatine Before (<i>n</i> = 10; 5 Male, 5 Female)		Creatine After (<i>n</i> = 9; 4 Male, 5 Female)		Placebo (<i>n</i> = 8; 3 Male, 5 Female)	
	Baseline	Week 16	Baseline	Week 16	Baseline	Week 16
Body mass (kg)	80.11 (19.02)	80.27 (19.94) †	84.87 (29.60)	85.75 (28.46)	78.62 (23.14)	76.73 (22.22) †
Total body water (kg)	38.61 (9.47)	38.89 (9.01)	41.31 (9.77)	41.38 (8.74)	39.35 (8.13)	39.62 (7.98)
Lean mass (kg)	52.76 (12.97)	53.11 (12.31)	56.42 (13.34)	56.52 (11.92)	53.76 (11.11)	54.15 (10.84)
Dry lean mass (kg)	14.14 (3.47)	14.22 (3.29)	15.11 (3.57)	15.13 (3.17)	14.41 (2.98)	14.52 (2.85)
Skeletal muscle mass (kg)	29.53 (7.94)	29.81 (7.56)	31.61 (7.95)	31.75 (7.19)	30.11 (6.86)	30.31 (6.68)
Skeletal muscle index (kg/m ²)	7.74 (1.45)	7.85 (1.37) †	8.00 (1.32)	8.10 (1.22) †	7.56 (1.26)	7.50 (1.23) †
Fat mass (kg)	27.37 (12.06)	27.16 (13.81)	28.34 (20.25)	29.24 (21.41) †	24.85 (20.34)	22.58 (18.14) †
Fat mass (%)	15.13 (4.84)	14.75 (5.48)	14.20 (5.54)	14.40 (5.72)	13.05 (6.85)	12.31 (6.12)
Basal metabolic rate (kcal)	1509.40 (280.66)	1517.30 (266.27)	1588.55 (263.63)	1591.11 (257.91)	1531.50 (239.60)	1539.87 (234.36)

Values are means (standard deviation). † change exceeded MDD.

Table 4. Muscle thickness measurements (cm) before and after 16 weeks of training and supplementation.

Variable	Creatine Before (<i>n</i> = 10; 5 Male, 5 Female)		Creatine After (<i>n</i> = 9; 4 Male, 5 Female)		Placebo (<i>n</i> = 8; 3 Male, 5 Female)	
	Baseline	Week 16	Baseline	Week 16	Baseline	Week 16
Biceps	3.17 (0.40)	3.18 (0.92)	2.99 (0.51)	2.89 (0.60)	3.14 (0.90)	3.18 (0.92)
Triceps	2.40 (0.60)	2.51 (0.82)	2.26 (0.55)	2.43 (0.80)	2.72 (0.58)	2.63 (0.57)
Hamstrings	2.92 (0.74)	2.91 (0.72)	2.92 (0.49)	2.99 (0.47)	3.23 (0.48)	3.51 (0.57)
Quadriceps	3.54 (1.03)	3.59 (1.03)	3.52 (0.86)	3.51 (0.86)	3.27 (0.58)	3.32 (0.60)
Calf	2.80 (0.88)	2.78 (0.73)	3.08 (0.54)	3.06 (0.39)	2.76 (0.39)	2.90 (0.43)
Sum	14.85 (2.68)	14.98 (3.05)	14.78 (2.32)	14.79 (2.23)	15.30 (2.35)	14.34 (3.23)

Values are means (standard deviation).

3.3. Muscle Performance

There was a main time effect for leg press strength ($p = 0.002$; $\eta^2 = 0.337$), chest press strength ($p < 0.001$; $\eta^2 = 0.371$), leg press endurance ($p < 0.002$; $\eta^2 = 0.342$), chest press endurance ($p < 0.003$; $\eta^2 = 0.317$) and upper-body muscle power ($p = 0.015$; $\eta^2 = 0.233$), with no between-group differences (Table 5).

Table 5. Muscle performance measurements before and after 16 weeks of training and supplementation.

Variable	Creatine Before ($n = 10$; 5 Male, 5 Female)		Creatine After ($n = 9$; 4 Male, 5 Female)		Placebo ($n = 8$; 3 Male, 5 Female)	
	Baseline	Week 16	Baseline	Week 16	Baseline	Week 16
Leg press (1-RM; kg)	167.93 (72.60)	195.24 (104.07) *	152.71 (43.40)	169.91 (34.63) *	131.25 (38.47)	143.09 (51.90) *
Chest press (1-RM; kg)	67.58 (34.57)	71.89 (40.68) *	60.48 (23.34)	69.80 (20.15) *	62.54 (32.11)	65.42 (31.83) *
Leg press (reps)	44.11 (18.23)	49.66 (22.04) *	49.77 (26.63)	65.66 (27.12) *	40.62 (19.06)	51.62 (24.70) *
Chest press (reps)	28.90 (5.98)	31.50 (7.80) *	30.55 (4.97)	39.22 (6.55) *	31.37 (9.31)	34.62 (11.16) *
Medicine ball (inches)	105.75 (29.54)	113.80 (27.83) *	107.83 (28.71)	112.11 (20.20) *	99.85 (18.29)	105.92 (20.24) *
Leg power (watts)	3950.78 (1084.41)	4041.69 (1094.87)	3810.96 (1125.10)	4074.03 (1090.56)	3761.54 (1065.07)	3704.92 (1037.56)

Values are means (standard deviation). * Time main effect ($p < 0.05$).

The relative change for chest press strength approached significance ($p = 0.054$), which was likely driven by the larger increase in the Creatine After group compared to the Creatine Before and Placebo groups (Table 2; Figure 2).

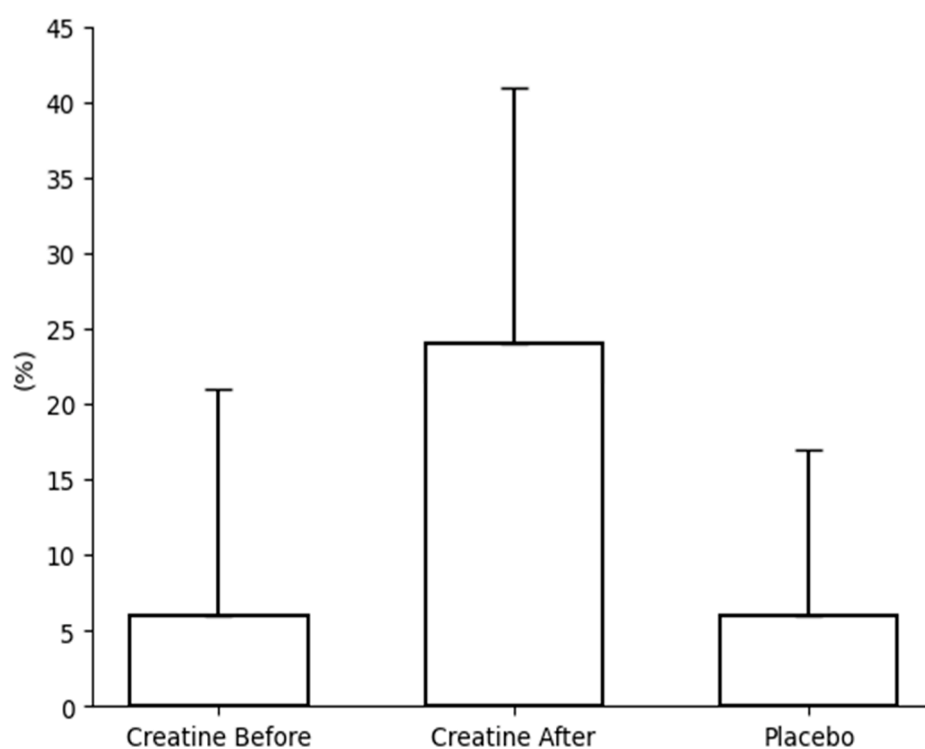


Figure 2. Change (%) in chest press 1-RM between groups over time.

3.4. Diet

There was a time main effect for total energy (kcal) ($p = 0.049$; $\eta^2 = 0.267$), with no other differences (Table 6).

Table 6. Dietary intake during the first and final week of supplementation and training.

Variable	Creatine Before ($n = 4$; 2 Male, 2 Female)		Creatine After ($n = 8$; 3 Male, 5 Female)		Placebo ($n = 4$; 2 Male, 2 Female)	
	Baseline	Week 16	Baseline	Week 16	Baseline	Week 16
Total energy (kcal/day)	2135.25 (742.13)	2063.00 (853.82) *	1857.25 (370.37)	1750.50 (431.33) *	2175.25 (937.15)	1670.00 (551.52) *
Carbohydrates (g/day)	225.25 (68.63)	226.00 (88.03)	185.50 (55.67)	170.62 (37.72)	212.50 (86.52)	168.50 (77.88)
Fat (g/day)	92.75 (42.50)	90.00 (44.32)	76.75 (21.63)	75.50 (34.810)	91.25 (51.25)	62.00 (29.26)
Protein (g/day)	100.50 (27.95)	87.00 (31.40)	106.25 (26.67)	96.87 (35.25)	126.25 (53.48)	109.75 (34.93)
Creatine (g/day)	1.14 (0.56)	1.08 (0.38)	1.66 (0.92)	1.56 (0.79)	1.60 (1.02)	1.00 (0.72)

Values are means (standard deviation). * Time main effect ($p < 0.05$).

4. Discussion

Overall, CrM immediately before and immediately after resistance training sessions produced comparable changes in body composition, limb muscle thickness and muscle performance after 16 weeks. These changes did not differ from the Placebo group.

Results of the present study are in contrast to those of Candow et al. [9], who showed that CrM immediately before (~8 g) or immediately after (~8 g) resistance training sessions for 32 weeks resulted in greater improvements in chest press and leg press strength compared to a placebo in untrained healthy adults (≥ 50 years of age). While speculative, the greater improvements in muscle performance in the Candow et al. [9] study compared to the results of the present study may be related to the CrM protocol used or the population assessed. The dose of CrM used in the Candow et al. [9] study was 0.1 g/kg/day or ~8 g/day (797 g of CrM in total), whereas 5 g/day or 280 g of CrM in total was implemented in the present study. It is possible that 5 g of CrM or 280 g of CrM in total was too low to produce significant benefits in trained young healthy adults over time. Furthermore, the length of supplementation in the Candow et al. [9] study was 32 weeks compared to 16 weeks in the present study. In addition, intramuscular creatine stores in the lower limbs may be reduced in older adults, which may increase their responsiveness to CrM [14]. Unfortunately, intramuscular creatine kinetics were not assessed in the present study, limiting our ability to determine baseline and post-CrM levels or changes following 5 g of CrM on resistance training days or identify the range and variability of intramuscular creatine concentrations in participants over time. There was a trend ($p = 0.054$) for a greater change (~19%; $\eta^2 = 0.216$) in chest press strength for those that consumed CrM immediately after resistance training sessions. This trend may be reflective of the higher (albeit non-significant) resistance training compliance (88%) in the Creatine After group compared to the other groups (Creatine Before: 81%; Placebo: 63%). Previous research has shown that prior muscle contractions augment intramuscular creatine levels in young adults [3]. An increase in PCr resynthesis (via CrM) during and following muscle contractions may increase muscle performance over time [2]. Furthermore, there is some evidence that CrM can influence glycogen/glucose kinetics [15,16] and calcium cycling from the sarcoplasmic reticulum, which may accelerate cross-bridge cycling over time [9]. Finally,

creatine acts as a neurotransmitter, which may influence the excitation coupling of skeletal muscle [5].

CrM immediately before and immediately after resistance training sessions resulted in similar changes in body composition and muscle performance over time. These results are in agreement with several other studies. In young adult populations, Dinan et al. [17] did not find significant differences between CrM (5 g) consumed within 1 h before or within 1 h after resistance training sessions (8 weeks) on measures of body composition and strength in physically active young adults (~20 years of age). Furthermore, Jurado-Castro et al. [18] showed that CrM (~19 g for the first 5 days and ~2 g/day for the remainder of the study) in the morning before resistance training sessions or in the evening after resistance training sessions for 12 weeks produced similar changes in body composition and muscle performance in elite young female handball players (18–35 years of age). Finally, Antonio and Ciccone [19] found similar improvements in body composition and strength when 5 g of CrM was consumed either immediately before or immediately after resistance training sessions for 4 weeks in young male bodybuilders (~23 years of age). Collectively, results across studies indicate that the specific timing of CrM during a resistance training program is inconsequential from a body composition and muscle performance perspective.

CrM had no effect on body composition, regional muscle thickness or muscle performance over time. These null findings may be related to biological and methodological factors. For example, from a biological perspective, pre-supplementation intramuscular creatine levels are a primary determinant of an individual's responsiveness to CrM [20]. Approximately one third of individuals are classified as “non-responders,” typically defined as demonstrating a <10% increase in intramuscular creatine content following CrM [21]. Potentially, some participants may not have responded to CrM. In addition, trained individuals may experience different effects of CrM due to factors such as a lower potential for muscle growth and performance; however, limited research on trained individuals has been conducted [10]. Furthermore, CrM is involved in various pathways and processes involved in the translation of muscle proteins [14] but has never been shown to directly increase the rates of myofibrillar protein synthesis [14]. From a methodological perspective, there is evidence to suggest that higher-dose CrM (>5 g/day) elicits favorable improvements in limb muscle size [10]. Thus, the daily CrM dose used in the present study may not have been high enough to produce significant muscle accretion over time. Finally, small reductions in total energy, protein and creatine intake may have blunted potential changes over time.

This study had several limitations, including a very small sample size which decreased the ability to detect small changes over time. Furthermore, some participants did not complete all assessments, which also reduced statistical power. Another limitation involved the biological sex imbalance between groups. One study showed that CrM had no influence on an indicator of muscle protein catabolism in young biological females, whereas CrM reduced this indicator in young biological males [22]. Furthermore, the habitual dietary intake of creatine was estimated using 3-day food diaries and not directly assessed. Although there was an effort to ensure the standardization and consistency of testing procedures, BIA has limitations regarding accuracy and precision when applied to trained populations; specifically BIA relies on populations' specific regression equations [23] and is highly sensitive to nutritional and the hydration status, body position, and previous physical activity [24]. Finally, ultrasound does not differentiate between contractile and non-contractile tissue (i.e., intramuscular adipose tissue, connective tissue). Therefore, muscle size measurements from ultrasound may have been underestimated. It

would be necessary to replicate this experiment using magnetic resonance spectroscopy to differentiate between contractile and non-contractile tissue.

5. Conclusions

In conclusion, 5 g of CrM immediately before or immediately after resistance training sessions or 280 g of CrM in total spread across 16 weeks of resistance training is insufficient to augment the physiological adaptations from resistance training in a very small cohort of resistance-trained individuals (>4 years of training experience). From a practical application perspective, resistance-trained individuals may need to consume creatine (≥ 5 g) on a daily basis and/or consider a creatine-loading phase to produce greater muscle benefits above resistance training alone.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/nutraceuticals6030042/s1>.

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Informed Consent Statement: Informed consent was obtained from all participants involved in this study.

Data Availability Statement: The original contributions presented in this study are included in the article; further inquiries can be directed to the corresponding author.

Conflicts of Interest: Darren G. Candow has received research grants and performed industry-sponsored research involving creatine supplementation and received a creatine donation for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. In addition, Darren G. Candow serves on the Scientific Advisory Board for Alzchem, Create and Iovate (companies that manufacture creatine) and as an expert witness/consultant in legal cases involving creatine supplementation. Scott. C. Forbes has received creatine donations for scientific studies and is a scientific advisor for Bear Balanced (Los Angeles, CA, USA) (a company that manufactures creatine products).

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