

Effects of Whey Isolate, Creatine, and Resistance Training on Muscle Hypertrophy

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Wednesday, February 26, 2020 2:11 PM

Introduction

This study investigates the effect seen from creatine, whey protein, or carbohydrates on muscle strength and muscle size.

Conclusions

Resistance training increases muscle size and strength, but mostly in type 2a and type 2b muscle cells.

Creatine has the most robust effect for muscle size.

There is a strong association between muscle size and muscle strength.

Amendments

Study Design

33 bodybuilders (recreational) were included in this study. They had to have been lifting for 6 months, at least 3 times a week, and their program was assessed by the researchers - to ensure this was the case, all participants underwent a 12 week resistance program before the start of the study. They had to stop all supplementation for 12 weeks leading up to the study. Once all these bases were set, they were assigned a strict training routine for 10-11 weeks (every day was supervised by trainers). At baseline (start of the study), they had their 1 repetition maximum tested for squat, bench press, and lat pull down. They had muscle biopsies taken to assess muscle cell size pre and post study period. Body composition was assessed by DEXA scan.

Participants were split between 4 groups: Participants of all 4 groups (Carbohydrate only, Whey Protein only, Carbohydrate + Creatine, Whey + Creatine) consumed 1.5 grams per kilogram bodyweight of their supplement (unknown to them) every day for 11 weeks. Each participant was instructed to maintain their normal diet with each supplement consisting of approximately 400 kcalories (+/- 50 kcalories).

Effects of Whey Isolate, Creatine, and Resistance Training on Muscle Hypertrophy

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ABSTRACT

CRIBB, P. J., A. D. WILLIAMS, C. G. STATHIS, M. F. CAREY, and A. HAYES. Effects of Whey Isolate, Creatine, and Resistance Training on Muscle Hypertrophy. *Med. Sci. Sports Exerc.*, Vol. 39, No. 2, pp. 298–307, 2007. **Purpose:** Studies that have attributed gains in lean body mass to dietary supplementation during resistance exercise (RE) training have not reported these changes alongside adaptations at the cellular and subcellular levels. Therefore, the purpose of this study was to examine the effects of two popular supplements—whey protein (WP) and creatine monohydrate (CrM) (both separately and in combination)—on body composition, muscle strength, fiber-specific hypertrophy (i.e., type I, IIa, IIx), and contractile protein accrual during RE training. **Methods:** In a double-blind randomized protocol, resistance-trained males were matched for strength and placed into one of four groups: creatine/carbohydrate (CrCHO), creatine/whey protein (CrWP), WP only, or carbohydrate only (CHO) (1.5 g·kg⁻¹ body weight per day). All assessments were completed the week before and after an 11-wk structured, supervised RE program. Assessments included strength (1RM, three exercises), body composition (DEXA), and vastus lateralis muscle biopsies for determination of muscle fiber type (I, IIa, IIx), cross-sectional area (CSA), contractile protein, and creatine (Cr) content. **Results:** Supplementation with CrCHO, WP, and CrWP resulted in significantly greater ($P < 0.05$) 1RM strength improvements (three of three assessments) and muscle hypertrophy compared with CHO. Up to 76% of the strength improvements in the squat could be attributed to hypertrophy of muscle involved in this exercise. However, the hypertrophy responses within these groups varied at the three levels assessed (i.e., changes in lean mass, fiber-specific hypertrophy, and contractile protein content). **Conclusions:** Although WP and/or CrM seem to promote greater strength gains and muscle morphology during RE training, the hypertrophy responses within the groups varied. These differences in skeletal muscle morphology may have important implications for various populations and, therefore, warrant further investigation. **Key Words:** PROTEIN SUPPLEMENTATION, HISTOCHEMISTRY, SKELETAL MUSCLE STRENGTH, FIBER AREA, CONTRACTILE PROTEIN

BASIC SCIENCES

Whey protein (WP) and creatine monohydrate (CrM) are two dietary supplements commonly used to promote muscle strength and hypertrophy during resistance exercise (RE) (5,24). WP supplements generally contain a higher concentration of essential amino acids (EAA) than other protein sources (5) and have rapid absorption kinetics (9). Supplementation results in a high blood amino acid peak and stimulation of protein synthesis similar to a dose of EAA (21). WP-containing meals provide a higher postprandial leucine balance and net protein gain in young and older men compared with isonitrogenous casein meals (9). Although some studies have shown greater strength and/or lean body mass (LBM) gains with WP compared with matched groups given carbohydrate (CHO) (6) or casein (8) during RE training, no studies have assessed skeletal muscle adaptations in

response to RE training and WP supplementation. The chronic use of CrM to increase muscle strength and LBM is also a common strategy among various adult populations that exercise (24). The beneficial effects of oral CrM supplementation are thought to be dependent on the extent of Cr accumulation within muscle (14). However, this response can be highly variable between subjects (17). For this reason, dietary strategies such as combining CrM with carbohydrate (CHO) (16) or protein (27) have been used to enhance Cr uptake.

Studies that have attributed gains in LBM to dietary supplementation during RE training have not reported these changes alongside adaptations at the cellular level (i.e., fiber-specific type I, IIa, or IIx hypertrophy) (4,6,8,16,25). Those that have reported fiber-specific hypertrophy (1,10,28) have not confirmed this response with changes at the subcellular level (i.e., contractile protein content). For example, the combination of CrM with CHO has been shown to provide greater improvements in strength and body composition (i.e., increase LBM with no increase in fat mass) compared with CHO alone (16). CrM combined with WP also has been shown to augment muscle strength and LBM when compared with CHO or WP-only supplementation (6). However, no studies have examined the effects of CrM and WP supplementation on strength and body composition changes alongside muscle characteristics such as fiber-specific (i.e., type-I, IIa, or IIx) hypertrophy and contractile

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Submitted for publication August 2006.
Accepted for publication September 2006.

0195-9131/07/3902-0298\$0
MEDICINE & SCIENCE IN SPORTS & EXERCISE
Copyright © 2007 by the American College of Sports Medicine
DOI: 10.1249/01.mss.0000247002.32589.ef

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protein content. Therefore, the aim of this study was to examine the effects of combining CrM with CHO and with WP during RE training, in comparison with WP and CHO alone, on strength, body composition, and fiber-specific (i.e., type I, IIa, or IIx) hypertrophy as well as muscle Cr and contractile protein content. The first hypothesis was that supplementation with CrM and WP or CrM and CHO would provide greater benefits than WP or CHO alone. Because of the benefits reported previously with WP (6,8), a secondary hypothesis was that the combination of CrM and WP would provide greater benefits than the combination of CrM and CHO.

METHODS

Participants. Thirty-three recreational male bodybuilders met the requirements to participate in this study, which involved pre-post assessments and supplementation during 11 wk of RE training. To qualify as participants, the men were required to (a) have no current or past history of anabolic steroid use, (b) have been training consistently (i.e., 3–5 d·wk⁻¹) for the previous 6 months, (c) have submitted a detailed description of their current training program, (d) have not ingested any ergogenic supplement for 12 wk before the start of supplementation, and (e) agree not to ingest any other nutritional supplements or nonprescription drugs that might affect muscle growth or the ability to train intensely during the study. All participants were informed of the potential risks of the investigation before signing an informed consent document approved by the human research ethics committee of Victoria University and the Department of Human Services, Victoria, Australia. All procedures conformed to National Health and Medical Research Council guidelines for the involvement of human subjects for research and conformed to the policy statement regarding the use of human subjects and written informed consent published by *Medicine & Science in Sports & Exercise*.

After baseline assessments, the men were matched for maximal strength (1RM) in three weight lifting exercises (see strength assessments) and were then randomly assigned to one of four supplement groups in a double-blind fashion: whey protein (WP), CrM and whey protein (CrWP), CrM and carbohydrate (CrCHO), or carbohydrate only (CHO).

Supplementation. Participants were instructed to consume 1.5 g of the supplement per kilogram of body weight per day (1.5 g·kg⁻¹·d⁻¹) while maintaining their habitual daily diet. The chosen supplement dose was based on previously reported intake by this population (18). The supplements were tested to comply with label claims before leaving the place of manufacture (AST Sports Science, Golden, CO). Additionally, the WP supplement was independently assessed by Naturalac Nutrition LTD (Level 2/18 Normanby Rd Mt Eden, New Zealand) on two separate occasions, and matched labeled ingredients on both occasions. The supplements were provided in identical containers with sealed, tamper-proof lids, and

they were similar in energy content on a grams-per-kilogram basis. For example, an 80-kg participant in the WP group consumed 120 g·d⁻¹ of a supplement that contained approximately 103 g of protein, <6 g of carbohydrate, <1.2 g of fat, and 1864 kJ (447 kcal), whereas an 80-kg participant in the CHO group consumed the same dose of a supplement that contained 106 g of carbohydrate, 0 protein or fat, and 1770 kJ (424 kcal). The Cr-containing supplements (CrCHO and CrWP) contained a 1-wk loading phase with CrM (0.3 g·kg⁻¹·d⁻¹) that was followed by a maintenance phase (0.1 g·kg⁻¹·d⁻¹) for the duration of the study (weeks 2–11)—a protocol that has been shown previously to augment muscle strength and hypertrophy during RE training (28). For example, an 80-kg participant in the CrCHO group consumed 120 g·d⁻¹ of a loading phase supplement that contained 85 g of carbohydrate, 24 g of CrM, and 1420 kJ (340 kcal), and then a maintenance phase supplement (weeks 2–11) that provided 98.9 g of carbohydrate, 8.4 g of CrM, and 1651 kJ (396 kcal). A participant of the same weight in the CrWP group consumed a loading phase supplement (week 1) that contained 83 g of protein, <4.8 g of carbohydrate, <1 g of fat, 24 g of CrM, and 1500 kJ (359 kcal), followed by a maintenance phase supplement (weeks 2–11) that contained 96 g of protein, <5.5 g of carbohydrate, <1 g of fat, 8.4 g of CrM, and 1729 kJ (415 kcal).

The participants were asked to consume their supplement dose in three equal servings throughout the day (described with measuring scoops provided). For example, the participants were asked to consume one serving midmorning, one serving as soon as they finished each workout in the afternoon (or similar time on nontraining days), and one serving in the evening before sleep. The participants were weighed on a Seca 703 stainless steel digital medical scale (Seca, Perth, WA) every week to track body mass. Where a substantial change in body mass (approximately 2 kg) from baseline was observed, the participant was shown how to adjust the supplement dose to correspond with the increase in body weight. Participants were given an approximately 1-wk supply of the supplement at the start of each week and were asked to return the container before they received the next week's supply, as an act of compliance to the dosing procedure. In addition to having to return the container, the participants were asked to document the time of day they took the supplement in nutrition diaries that were provided. The participants' diets were monitored and assessed as previously described (7). In brief, each participant was asked to submit three written dietary recordings: one before and two during the study (each recording consisted of 3 d) for the calculation of macronutrient and energy intake. Energy intake is expressed in kilocalories per kilogram of body weight per day; protein and carbohydrate are expressed in grams per kilogram of body weight per day. The participants were asked to report any adverse events from the supplements in the nutrition diaries provided. No adverse events were reported by the participants.

Resistance training protocol. Questionnaires demonstrated that the participants had been training consistently

Participants of all 4 groups (Carbohydrate only, Whey Protein only, Carbohydrate + Creatine, Whey + Creatine) consumed 1.5 grams per kilogram bodyweight of their supplement (unknown to them) every day for 11 weeks. Each participant was instructed to maintain their normal diet with each supplement consisting of approximately 400 kcalories (+/- 50 kcalories).

(i.e., 3–5 d·wk⁻¹) for at least 6 months before expressing interest in this investigation. However, to ensure that the participants were trained and to minimize the impact of a new program on strength and hypertrophy adaptations, the men underwent a structured training program (similar to the one used in this study) for 8–12 wk before commencing this trial. The 11-wk RE program used in the study (*Max-OT*, AST Sport Science, Golden, CO) has been described elsewhere (7,8) and began the week immediately after baseline assessments. In brief, the program was designed specifically to increase strength and muscle size. It consisted of high-intensity (overload) workouts using mostly compound exercises with free weights. Training intensity for the program was determined using repetition maximums (RM). Qualified personnel supervised each participant on a one-to-one basis during every workout. Aside from the personal training each participant received during the 10-wk program, they also kept training diaries to record exercises, sets, repetitions performed, and the weight used throughout the program, and these were viewed by the trainer on a weekly basis. The following assessments occurred in the weeks before and after the RE program.

Strength testing. Strength assessments consisted of the maximal weight that could be lifted once (1RM) in three weight training exercises: barbell bench press, squat, and cable pulldown. A recognized 1RM testing protocol and exercise execution guidelines were followed, as has been previously documented (2). Briefly, each participant's maximal lift was determined within no more than five single-repetition attempts after three progressively heavier warm-up sets. Participants were required to successfully lift each weight before attempting a heavier weight. Each exercise was completed before the next attempt, and in the same order. Reproducibility for these tests was determined on two separate occasions; intraclass correlations (ICC) and standard error of measurement (SEM) for 1RM tests were bench press: $r = 0.998$, SEM = 1.0 kg; squat: $r = 0.995$, SEM = 2.5 kg; and pulldown: $r = 0.982$, SEM = 2.5 kg.

Body composition. Lean body mass (total fat-free mass), fat mass, and body fat percentage were determined using a Hologic QDR-4500 dual-energy x-ray absorptiometry (DEXA) with the Hologic version V 7, REV F software (Waltham, MA). Whole-body scans were performed on the same apparatus, by the same licensed operator. Quality-control calibration and scanning procedures were performed as previously described (8). Participants were scanned at the same time of day (i.e., in the morning) in a fasted state. For longitudinal studies in which relatively small changes in body composition are to be detected, whole-body scanning with this instrument has been shown to be accurate and reliable (CV 0.8–2.8%) (23).

Muscle analyses. Muscle biopsies for determination of muscle fiber type, cross-sectional area (CSA), contractile protein content, and Cr concentrations were taken in the week before and after the RE program. Biopsies (100–450 mg) were taken using the percutaneous needle technique with suction to ensure adequate sample size (12) at a similar depth in the vastus lateralis muscle by the same medical

practitioner. A small part of the sample was immediately frozen for assessment of contractile protein content and Cr. The remaining tissue was mounted using OCT medium and snap frozen in isopentane, which was precooled in liquid nitrogen and stored at -80°C for histochemical analysis to classify muscle fiber types I, IIa, and IIx on the basis of the stability of their ATPase activity, as previously described (7). Fiber-type percentages and CSA were determined from sections containing a mean of 210 (range 130–400) fibers. Samples were measured on two separate occasions for day-to-day reproducibility; ICC and SEM for fiber-type distribution were type I: $r = 0.822$, SEM = 1.8%; type IIa: $r = 0.941$, SEM = 1.3%; and type IIx: $r = 0.945$, SEM = 1.2%. For mean area of fiber type I, $r = 0.972$, SEM = 87 μm^2 ; for type IIa, $r = 0.984$, SEM = 100 μm^2 ; and for type IIx, $r = 0.967$, SEM = 141 μm^2 . Approximately 5 mg of muscle was used to determine contractile protein content, as detailed by Beitzel et al. (3) and reported previously (7). Two milligrams of muscle was used to analyze Cr concentrations using fluorimetric techniques, as in Hultman et al. (14); data are expressed as millimoles per kilogram of dry weight. Samples were run twice on two separate occasions; ICC and SEM for contractile protein content were $r = 0.984$, SEM = 2.1 $\text{mg}\cdot\text{g}^{-1}$; Cr: $r = 0.881$, SEM = 22.

Statistics. Statistical evaluation of the data was accomplished by two-way repeated-measures analysis of variance (ANOVA) with group (supplement) and time (training) as the factors using SPSS statistical analysis software (SPSS v 11.0; Chicago, IL). Where significant main effects were identified by ANOVA, Tukey *post hoc* analysis was performed to locate differences. A *priori* power testing was based on previous data on changes in strength, body composition, and contractile protein data obtained by our laboratory (7,8) and others (30). The testing indicated that group sizes of four to seven participants were required to show significance at an alpha level of 0.05 and a power of 0.8. Test-retest reliability was quantified using the intraclass correlation coefficient (ICC) two-way ANOVA (mixed effects model) and the SEM (29). Simple regression was used to determine significant relationships among the deltas for selected variables. A *P* value of less than 0.05 was designated to indicate statistical significance. A *P* value of less than 0.09 was considered a trend.

RESULTS

Starting characteristics. Four participants did not attend the required amount of supervised training sessions (75%) or provide all dietary records. Therefore, their data were not included. Additionally, three participants chose not to return for final biopsies. This reduced the group sizes to seven in the CHO group, five in the WP group, eight in the CrCHO group, and six in the CrWP group. Starting characteristics for these participants are shown in Table 1. There were no differences between the groups in any variables at the start of the study ($P > 0.05$).

Dietary analyses. Table 2 shows the average of 3-d written dietary recalls for energy ($\text{kcal}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) and

TABLE 1. Baseline characteristics.

	CHO	WP	CrCHO	CrWP
Age (yr)	24 ± 7	24 ± 5	25 ± 6	25 ± 4
Training age (yr)	6 ± 3	5 ± 2	6 ± 3	4 ± 2
Height (cm)	177 ± 5	181 ± 8	177 ± 6	180 ± 7
Body mass (kg)	76 ± 12	70 ± 11	84 ± 14	84 ± 12
Lean mass (kg)	52 ± 7	59 ± 7	67 ± 8	69 ± 6
Fat mass (kg)	13 ± 7	11 ± 4	17 ± 7	16 ± 6
CSA type I (μm ²)	3662 ± 273	3423 ± 88	3656 ± 593	3699 ± 274
CSA type IIa (μm ²)	4674 ± 803	4529 ± 223	4673 ± 661	4458 ± 919
CSA type IIx (μm ²)	4293 ± 656	4220 ± 223	4354 ± 972	4057 ± 604
1RM bench (kg)	99 ± 16	96 ± 13	104 ± 22	106 ± 26
1RM squat (kg)	125 ± 25	116 ± 26	118 ± 18	123 ± 37
1RM pull-down (kg)	90 ± 12	86 ± 11	89 ± 16	89 ± 13

Values are means ± SD. CHO, carbohydrate-only group; WP, whey protein-only group; CrCHO, creatine/carbohydrate group; CrWP, creatine/whey protein group.

carbohydrate and protein (g·kg⁻¹·d⁻¹) of the groups before and in the first and last weeks of the training program. Data do not include supplementation. No differences were identified between the groups or across time with regard to energy or macronutrient intake ($P > 0.05$).

Body composition. All groups demonstrated a gain in body mass (time, $P = 0.001$) (Table 3), but no group or group × time interaction was detected for body mass. No interactions for fat mass or body fat percentage were detected between the groups or across time. However, a group × time interaction ($P = 0.043$) was observed for LBM (Table 3). Whereas each of the groups demonstrated an increase (time, $P = 0.001$) in LBM after the program (CrCHO, +3.7 kg; CrWP, +3.4; WP, +2.3 kg; CHO, -0.7), only the CrCHO group's increase in LBM was significantly greater than that of the CHO group (*post hoc* $P < 0.05$).

Strength. 1RM strength data (kg) barbell bench press, cable pulldown, and barbell squat are presented in Figure 1a, b, and c respectively. All groups demonstrated an improvement in strength in each exercise after the program (time: $P = 0.0001$), and a group × time interaction ($P = 0.0001$) was observed for each exercise. The CrCHO, CrWP, and WP groups demonstrated a greater increase in strength in each exercise compared with the CHO group (*post hoc* $P < 0.05$). However, no differences were detected between the CrCHO, CrWP, and WP groups.

Muscle characteristics. No changes in fiber-type proportions between the groups or across time were

detected (Table 4). All groups demonstrated an increase in CSA ($P < 0.05$) of the type IIa and IIx fibers after the program. Additionally, a group × time interaction in CSA was detected for the type I ($P = 0.001$; Fig. 2a), IIa ($P = 0.001$; Fig. 2b), and IIx ($P = 0.001$; Fig. 2c) fibers. The CrCHO and CrWP groups demonstrated a greater increase in CSA in each fiber type compared with the CHO group (*post hoc* $P < 0.05$). The CrCHO and CrWP groups also demonstrated a greater increase in CSA in the type I fibers when compared with the WP group (*post hoc* $P < 0.05$). A trend for a greater hypertrophy of the type IIa and IIx fibers ($P = 0.077$ and $P = 0.078$, respectively) was also observed in the WP group compared with the CHO group.

A group × time interaction ($P = 0.001$) for contractile (myofibrillar) protein content was also detected. The CrCHO, CrWP, and WP groups each showed a greater increase in contractile protein compared with the CHO group after the program (*post hoc* $P < 0.05$) (Fig. 2d). Additionally, the CrCHO and CrWP groups demonstrated a trend ($P = 0.07$ and 0.08 , respectively) for a greater increase in myofibrillar protein content compared with the WP group.

A group difference ($P = 0.03$) was detected for the Cr-treated groups in muscle Cr (Table 5). Both the CrCHO and CrWP groups showed a higher ($P < 0.05$) concentration (mmol·kg⁻¹ dry weight) of Cr compared with the WP and CHO group after the training program, but there was no difference between the CrCHO and CrWP groups.

Correlations. For all participants combined, positive correlations ($P < 0.01$) were detected between changes in muscle fiber CSA (in all fiber types) and strength gained in the 1RM squat exercise (Fig. 3). A positive correlation ($P < 0.05$) was also detected between the change in contractile protein (mg·g⁻¹) and (1RM) strength improvements in the squat (Fig. 4). Additionally, positive correlations ($P < 0.01$) were detected between the increase in contractile protein and increase in muscle fiber CSA, in all fiber types (Fig. 5).

DISCUSSION

The most important finding of this investigation was that although there were no differences between the groups at

TABLE 2. Dietary analyses.

	CHO	WP	CrCHO	CrWP
Energy intake (kcal·kg ⁻¹ ·d ⁻¹)				
Before	36.8 ± 7.2	41.6 ± 4.8	42.0 ± 6.1	40.8 ± 3.6
Week 1	36.5 ± 5.3	40.5 ± 3.5	37.3 ± 3.8	39.9 ± 2.9
Week 11	36.4 ± 5.8	39.1 ± 3.3	38.4 ± 4.1	39.9 ± 3
Carbohydrate (g·kg ⁻¹ ·d ⁻¹)				
Before	2.9 ± 0.6	4.0 ± 0.6	4.4 ± 1.2	3.8 ± 1.4
Week 1	2.8 ± 0.6	3.7 ± 0.4	3.7 ± 1.0	3.9 ± 1.4
Week 11	2.7 ± 0.4	4.0 ± 1.2	3.7 ± 0.6	4.7 ± 1.9
Protein (g·kg ⁻¹ ·d ⁻¹)				
Before	1.6 ± 0.3	1.6 ± 0.2	1.5 ± 0.3	2.1 ± 1.0
Week 1	1.7 ± 0.2	1.7 ± 0.2	1.5 ± 0.3	1.9 ± 0.8
Week 11	1.6 ± 0.1	1.6 ± 0.1	1.5 ± 0.3	1.7 ± 0.7
Fat (g·kg ⁻¹ ·d ⁻¹)				
Before	2.1 ± 0.6	2.2 ± 0.4	2.0 ± 0.6	2.1 ± 1.0
Week 1	2.1 ± 0.5	2.1 ± 0.4	1.9 ± 0.6	1.9 ± 0.8
Week 11	2.1 ± 0.6	2.0 ± 0.3	2.0 ± 0.7	1.7 ± 0.7

Values are means ± SD. CHO, carbohydrate-only group; WP, whey protein-only group; CrCHO, creatine/carbohydrate group; CrWP, creatine/whey protein group.

TABLE 3. Body mass and composition.

	CHO	WP	CrCHO	CrWP
Body mass (kg)				
Pre	75.6 ± 4.7	69.7 ± 5.0	84.2 ± 4.9	83.9 ± 4.8
Post*	77.0 ± 4.8	72.3 ± 4.3	88.2 ± 5.0	87.9 ± 5.0
Lean mass (kg)				
Pre	62.3 ± 2.8	59.0 ± 3.2	67.0 ± 2.6	67.9 ± 2.6
Post*	63.0 ± 2.7	61.3 ± 3.0	71.3 ± 3.0*	71.3 ± 2.8
Fat mass (kg)				
Pre	13.2 ± 2.8	10.6 ± 1.9	16.6 ± 2.6	15.9 ± 2.5
Post	14.0 ± 2.9	11.0 ± 1.6	17.0 ± 2.1	16.6 ± 2.6
% Fat				
Pre	16.9 ± 2.4	14.9 ± 1.7	18.1 ± 1.9	18.5 ± 1.9
Post	17.6 ± 2.5	15.0 ± 1.3	18.8 ± 1.3	18.5 ± 1.9

Values are means ± SE. CHO, carbohydrate-only group; WP, whey protein-only group; CrCHO, creatine/carbohydrate group; CrWP, creatine/whey protein group. * Training effect for all groups ($P < 0.001$); † greater increase than CHO group ($P = 0.043$, effect size = 0.282; power = 0.642).

Table 1: The researchers are showing the baseline (pre-study) measurements between the four groups - you hope there are no statistical differences so that whatever differences show up later will be a result of the intervention. **CHO:** Carbohydrate, **CrCHO:** Creatine + Carbohydrate, **WP:** Whey Protein, **CrWP:** Creatine + Whey Protein. **Body mass** is body weight; **Lean mass** is muscle, bone, and any other non-fat mass; **CSA** is cross sectional area and speaks to the size of the muscle (the type is based on the type of muscle cell - type 1 is slow twitch, oxidative, for example); **1RM** is one repetition maximum and is the maximal amount a person can lift with good form.

Results:

- There are no differences between the groups at baseline by any of the measures listed.

Take Away: What changes we see at the end of the study are more likely to be due to the intervention.

Table 2: This table indicates the amount of energy (kcalories) consumed, protein, fat, and carbohydrate between the 4 groups at baseline (pre-study), then again one week into the study (having consumed their supplements), and then again at the end of the study (week 11). **CHO:** Carbohydrate, **CrCHO:** Creatine + Carbohydrate, **WP:** Whey Protein, **CrWP:** Creatine + Whey Protein

Results:

- No differences between groups on any of these measurements.

Take Away: Nutritionally, all four groups were similar, reducing the probability of it as a confounding variable.

Table 3: This table indicates the body mass, lean mass (muscle, skeleton, etc.), and fat mass pre-study (baseline) and after the 11 weeks of training with supplementation for each of the 4 groups. **CHO:** Carbohydrate, **CrCHO:** Creatine + Carbohydrate, **WP:** Whey Protein, **CrWP:** Creatine + Whey Protein

Primary Results:

- For all groups, body mass and lean mass (but, not fat mass) increased with the interventions.

Take Away: The training, regardless of condition/group, increased lean mass (likely muscle mass).

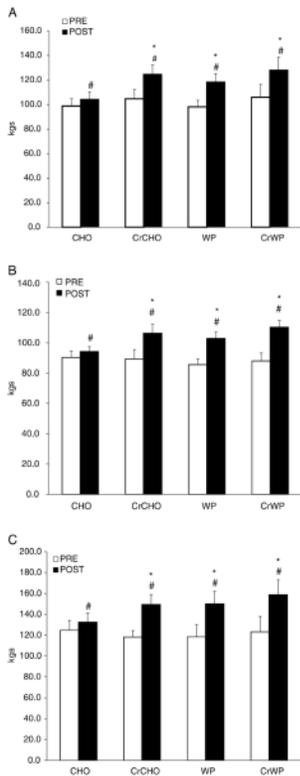


FIGURE 1—a. Bench press (1RM) strength. ^a Training effect; * greater increase than CHO group ($P = 0.0001$, effect size = 0.585, power = 0.994) (mean \pm SE). ^b Paddock (1RM) strength. ^a Training effect; * greater increase than CHO group ($P = 0.0001$, effect size = 0.585, power = 0.995) (mean \pm SE). c. Squat (1RM) strength. ^a Training effect; * greater increase than CHO group ($P = 0.0001$, effect size = 0.592, power = 0.996) (mean \pm SE).

the start of this study, and each group consumed a protein-rich diet, supplementation with CrCHO, WP, and CrWP resulted in greater hypertrophy responses (in at least one

of three assessments) and 1RM strength gains (in three of three assessments) compared with CHO. Additionally, the changes in 1RM squat strength correlated strongly ($r \geq 0.7$; $P < 0.01$) with the changes in muscle morphology across all groups. However, compared with CHO, the hypertrophy response from supplementation with CrCHO, WP, and CrWP varied at the three levels of muscle physiology that were assessed (i.e., LBM, fiber-specific hypertrophy, and contractile protein content). These findings are novel in that we are aware of no other RE training studies that have reported changes in body composition from dietary intervention alongside adaptations at the cellular level (i.e., fiber-specific hypertrophy) (4,6,8,16,25) and the subcellular level (i.e., contractile protein content) (1,10,28).

Our findings only partly support the first hypothesis proposed. That is, treatment with CrCHO or CrWP provided greater improvements in strength and muscle hypertrophy when compared with CHO but not WP. Additionally, the results do not support the second hypothesis proposed. That is, no greater benefit was observed from combining CrM and WP when compared with the combination of CrM and CHO. It is possible that small numbers of subjects in some of the groups that completed this trial may have reduced the capacity to adequately detect some differences between the groups, particularly in major variables of interest such as changes in LBM. For example, although the WP, CrCHO, and CrWP groups each demonstrated relatively large changes in LBM (3.7, 5.5, and 5%, respectively), compared with the CHO (1.1%) group, the only change in LBM deemed significantly greater than for the CHO group was the CrCHO group. We commenced this study with 34 participants that provided similar group sizes to our previous work (7,8) and others (28,30) that have involved supplementation and RE training. These investigations reported significant differences between groups in LBM, strength, and/or muscle hypertrophy with subject group sizes of six to nine in each group. For example, in a previous study completed by this laboratory (8) that used RE-trained participants and a similar protocol, supplementation with WP ($N = 6$) ($1.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for 10 wk) produced significantly greater gains in LBM and strength compared with a group given an equivalent dose of casein ($N = 7$). In another investigation that also involved RE-trained participants undertaking a 10-wk RE program, we were able to detect significantly different gains in LBM between two groups ($N = 8$ and 9) that consumed the exact same supplement at different times of the day (7). Volek

TABLE 4. Muscle fiber type (%).

	CHO	WP	CrCHO	CrWP
% Type I				
Pre	43 \pm 5.9	49.9 \pm 2.6	43.9 \pm 2.5	41.4 \pm 3.5
Post	41 \pm 4.5	44.6 \pm 4.3	46.7 \pm 3.5	43.2 \pm 3.2
% Type IIa				
Pre	38.3 \pm 5.3	30.0 \pm 3.1	38.3 \pm 3.3	36.9 \pm 2.8
Post	39.0 \pm 4.0	35.3 \pm 4.0	36.7 \pm 4.0	33.7 \pm 2.5
% Type IIx				
Pre	18.7 \pm 2.8	18.0 \pm 1.7	17.8 \pm 1.0	21.6 \pm 2.4
Post	20.2 \pm 2.5	17.7 \pm 2.7	16.5 \pm 1.4	23.1 \pm 1.4

Values are mean \pm SE. CHO, carbohydrate-only group; WP, whey protein-only group; CrCHO, creatine/carbohydrate group; CrWP, creatine/whey protein group.

Figure 1: This data shows the difference between the baseline strength measurements and after 11 weeks of the same training program for all four groups on bench press (A), lat pull down (B), and squat (C). # = significant difference between PRE (baseline) and POST (after training). * indicates a difference between the carbohydrate only group (CHO) and the other group (in this case, all of them have significant differences by comparison).

Primary Results:

- All groups increased strength in all three lifts.
- All groups involving whey and/or creatine increased strength more than carbohydrate only group.

Take Away:

The training was effective at increasing strength, and the supplements (especially creatine and whey - together or not) lead to even greater increases in strength.

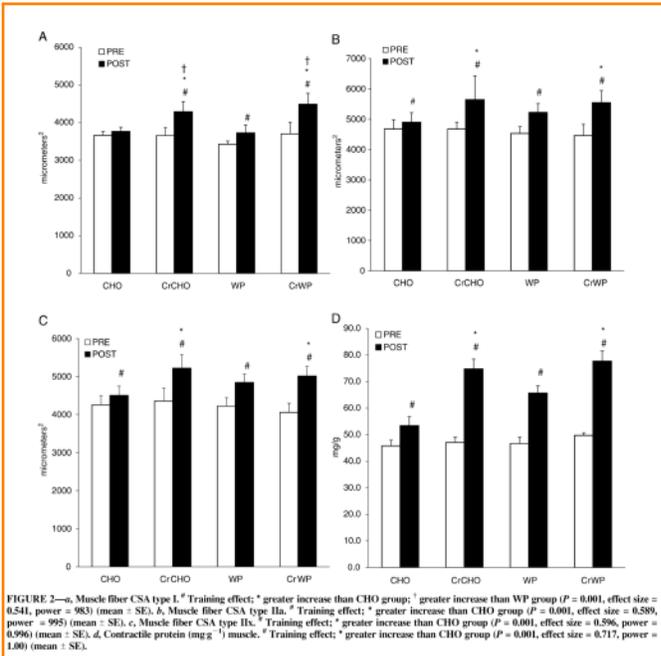


FIGURE 2—a. Muscle fiber CSA type I. * Training effect; † greater increase than CHO group; # greater increase than WP group ($P = 0.001$, effect size = 0.541, power = 983) (mean ± SE). b. Muscle fiber CSA type IIa. * Training effect; † greater increase than CHO group ($P = 0.001$, effect size = 0.589, power = 995) (mean ± SE). c. Muscle fiber CSA type IIx. * Training effect; † greater increase than CHO group ($P = 0.001$, effect size = 0.596, power = 0.996) (mean ± SE). d. Contractile protein (mg g⁻¹) muscle. * Training effect; † greater increase than CHO group ($P = 0.001$, effect size = 0.717, power = 1.00) (mean ± SE).

et al. (28) also used RE-trained participants and an RE program and CrM-supplementation protocol similar to those of the present study, and reported comparable results. That is, after the 12-wk training period, CrM supplementation ($N = 9$) resulted in a significantly greater gain in LBM, 1RM squat strength, and muscle fiber hypertrophy in all fiber types assessed compared with a matched placebo-treated group ($N = 10$) (28). Willoughby and Rosene (30) reported that supplementation with CrM ($N = 8$) during 12 wk of RE resulted in a greater increase in LBM (assessed by skinfold caliper), thigh volume, (relative) muscle strength, and myofibrillar protein content than a placebo-treated group ($N = 8$) and a control group ($N = 6$). On the basis of prior investigations (7,8,28,30), it was reasonable to assume that commencing the present study with 34 participants would be adequate. However, a lower than anticipated number of finishing subjects in some of the groups probably reduced

the capacity to detect differences between the groups in LBM. We acknowledge that the small sample size of the groups is an important limitation of this study. Nevertheless, unlike other investigations that have reported changes in body composition from dietary intervention, the changes in LBM in this study are supported by a number of significant differences between the groups in skeletal muscle morphology that were detected at the cellular and subcellular levels.

TABLE 3. Muscle creatine

	CHO	WP	CrCHO	CrWP
Total creatine (mmol kg ⁻¹ dry weight)				
Pre	94.2 ± 10.1	107.1 ± 8.7	103.6 ± 8.3	109 ± 16.6
Post	95.3 ± 10.5	100.5 ± 9.5	113 ± 24.1*	125.3 ± 19.6*

Values are means ± SE. CHO, carbohydrate-only group; WP, whey protein-only group; CrCHO, creatine/carbohydrate group; CrWP, creatine/whey protein group. * Greater than WP and CHO groups ($P = 0.03$, effect size = 0.340, power = 0.683).

Figure 2: These graphs show the difference in muscle fiber/cell size PRE (baseline/before supplementation) and POST (11 weeks or training + supplementation) of all 4 groups. Figure 2A shows type 1 muscle cells (which are typically considered lower force producing, but more fatigue resistant, also known as red fibers). 2B shows type 2a muscle cells (which are considered greater force producing than type 1, but less fatigue resistant); 2C shows type 2x muscle cells (which are the most force producing, but least fatigue resistant - also considered "white" fibers); 2D shows the amount of overall contractile protein (proteins that are involved in muscle contractions, generating force) CHO: Carbohydrate, CrCHO: Creatine + Carbohydrate, WP: Whey Protein, CrWP: Creatine + Whey Protein. # = Training effect. * - Different vs CHO group, † = Difference vs Whey Protein.

Primary Results:

- There is an increase in type 1 muscle cell size with creatine (either group) that exceeds the carbohydrate group, as well as the whey protein group.
- In type 1 cells, there is a training effect with all groups except the carbohydrate group.
- In type 2a and 2x cells, there is a training effect in all groups.
- In type 2a and 2x cells, there is an increase in size with creatine supplementation vs the carbohydrate group.
- In muscle cells (total, including all three types), there is a training effect for all groups increasing contractile protein content.
- In muscle cells (total, including all three types), there is an increase with creatine supplementation (both groups).

Take Away:

Resistance training increases all muscle cell sizes except type 1, unless supplementation occurs (creatine or whey). Creatine leads to the greatest muscle size increase effect, even higher than whey protein with type 1 muscle cells. Overall, creatine leads to the most potent increase in muscle cell size.

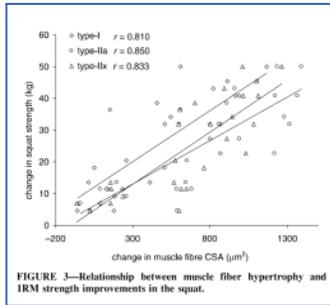


FIGURE 3—Relationship between muscle fiber hypertrophy and IRM strength improvements in the squat.

Few have used matched placebo-treated groups and have quantified the extent of specific muscle fiber type (i.e., type I, IIa, and IIx) hypertrophy in response to RE training and supplementation. Volek et al. (28) reported that treatment with CrM resulted in significantly greater muscle fiber hypertrophy in all fiber types assessed compared with a matched placebo-treated group. Andersen et al. (1) reported significantly greater hypertrophy of both type I and II fibers as well as squat jump height in a group that received a pre- and postworkout protein supplement (25 g each serving) compared with an equivalent dose of CHO during 14 wk of RE. In the present study, significant differences between the groups in muscle fiber hypertrophy across all fiber types were detected. For example, both the CrCHO and CrWP groups demonstrated a greater increase in CSA in the type I, IIa, and IIx fibers (Fig. 2a, b and c) compared with the CHO group, as well as a greater increase in CSA in the type I compared with the WP group (Fig. 2a). However, no differences were detected between the WP, CrWP, and CrCHO type II fiber CSA. Unlike previous studies (1,10,28) that have reported muscle fiber CSA changes in response to training and supplementation, this study was able to confirm these hypertrophy responses with changes in contractile protein content.

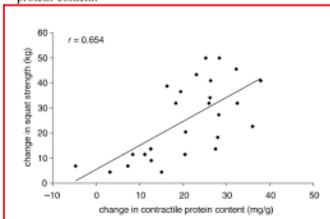


FIGURE 4—Relationship between change in contractile protein content and IRM strength gains in the squat.

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The CrCHO, CrWP, and WP groups in this study each demonstrated a significantly greater increase in contractile protein content (milligrams per gram of muscle) compared with the CHO group after the training program (Fig. 2d). This reflects the changes in CSA that were detected, particularly in the CrCHO and CrWP groups and, to a lesser extent, the WP group; a trend ($P < 0.09$) for greater hypertrophy of the type IIa and IIx fibers was observed for the WP group when compared with the CHO group. Although no significant differences were detected between the WP, CrCHO, and CrWP groups in LBM gains or type II fiber hypertrophy, a trend ($P < 0.09$) for a greater increase in myofibrillar protein content was also detected in the CrCHO and CrWP groups compared with the WP group. RE-induced muscle fiber hypertrophy is thought to be primarily responsible for improvements in force production and strength that are observed in RE-trained participants (26). An increase in contractile protein is thought to be an important stimulus that results in an increase in muscle fiber CSA (22). When all participants were combined, a strong relationship between changes in muscle fiber CSA (across all fiber types) and strength improvements in the squat exercise were evident (Fig. 3). A similar relationship between changes in contractile protein content and strength improvements in the squat was also detected (Fig. 4). Additionally, a strong relationship between changes in contractile protein content and muscle fiber hypertrophy (for all types) was observed (Fig. 5). The r values obtained suggest that a substantial portion (50–76%) of the strength improvements observed across all groups could be attributed to the changes in skeletal muscle morphology. These correlations reflect a direct relationship between muscle adaptation (hypertrophy) and an improvement in functional strength. The barbell squat exercise was the focus of these correlation assessments simply because, unlike the bench press and pulldown exercise, the vastus lateralis is recruited heavily during this exercise. Therefore, although differences between the groups in terms of changes in body composition were less evident, some statistically significant differences (and strong trends) were detected between the groups

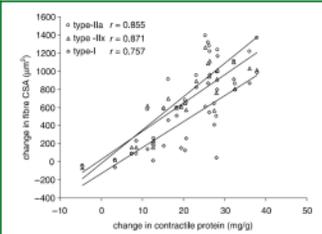


FIGURE 5—Relationship between contractile protein content and muscle fiber hypertrophy.

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regarding muscle fiber hypertrophy and contractile protein accrual. Additionally, it was these alterations in skeletal muscle morphology that were largely responsible for the improvements in strength in an exercise involving a related muscle group. However, although these results suggest a cause-and-effect relationship between muscle hypertrophy and strength, no mechanistic assessments were attempted.

Willoughby and Rosene (30) completed one of very few studies that have linked an enhanced hypertrophy response from RE and supplementation (i.e., increase in strength, LBM, and thigh volume) to alterations at the molecular level that may explain these benefits. In this study, supplementation with CrM (6 g d^{-1}) during 12 wk of RE resulted in greater increases in LBM, muscle strength, and myofibrillar protein content with matched placebo-treated and control groups. These alterations corresponded with the upregulation of the genes and myogenic regulatory factors associated with (myosin heavy chain) contractile protein synthesis. A review of 22 studies involving supplementation during RE training clearly shows that CrM enhances weightlifting performance and the development of strength (24), and this is probably attributable to increased Cr availability during intense muscle contraction (14). More recently, Olsen et al. (20) reported that CrM supplementation during 16 wk of RE amplified the training-induced increase in satellite cell number and myonuclei concentration in human skeletal muscle fibers, thereby allowing an enhanced muscle fiber growth in response to strength training. Therefore, supplementation with CrM may result in superior strength and hypertrophy responses by inducing greater satellite cell numbers and myonuclei concentration alongside transcriptional changes in muscle gene expression, which may contribute to, or be a product of, CrM's ability to enhance the bioenergetics of the phosphagen system. Although these findings help to form a tempting mechanistic explanation for the greater hypertrophy responses observed in the Cr-treated groups in the present study, they do not explain the greater increases in strength and contractile protein accrual detected in the WP-supplemented group.

Although previous studies have shown that WP supplementation ($1.2\text{--}1.5 \text{ g kg}^{-1} \text{ d}^{-1}$) results in greater LBM and strength compared with matched CHO (6) and casein-treated groups (8), this study is the first to report changes in

recently, supplementation with WP during RE has been shown to provide a similar effect in at least one of the signaling proteins that regulate protein synthesis through translational initiation (13). WP meals are shown to provide a high stimulation of protein synthesis and greater net postprandial protein gain compared with other high-quality protein sources (9). Therefore, the frequent consumption of WP throughout the RE program in this study may have resulted in a greater anabolic response (i.e., a higher rate of protein synthesis and net protein accretion) that resulted in greater synthesis of contractile protein. Although the findings with WP supplementation in this study are consistent with this theory, the mechanisms that underlie the benefits obtained from WP during RE have yet to be fully elucidated. The ability of the WP group to achieve similar strength gains without the large increase in LBM, as seen in the CrCHO and CrWP groups in this study, may have important sport-specific implications for individuals who compete in weight-restricted events. Thus, further studies on the chronic effects of WP during RE are warranted, particularly at the molecular level.

On the basis of the mechanistic explanations that have been proposed, one may expect an additive effect from combining CrM and WP on muscle strength and hypertrophy. However, in this study, no greater effect was observed from this supplement combination compared with the combination of CrM and CHO. One explanation for this may be the influence of the CHO (contained in CrCHO but not in the CrWP supplement). For example, all groups consumed a high protein intake aside from supplementation, and the results of at least one longitudinal study suggest that once dietary protein requirements have been met, it is the energy content of the diet that has the largest effect on hypertrophy during RE (25). In other words, when CrM is consumed in the presence of a high-protein diet, the addition of CHO may be more beneficial than extra protein. However, the results also suggest that the consumption of CrM with WP provides similar benefits to those of CrM with CHO. This may have important implications for populations that desire improvements from exercise but for whom the consumption of large amounts of glucose is undesirable, such as those with (or at risk of) type II diabetes. Because this is the only study that has compared the effects of two different CrM-containing

Figure 3: These data are correlational - they show the relationship between two variables. In this case, the researchers are showing a relationship between squat strength (on the Y-axis) and muscle cell size (X-axis). Each point on the graph is a participant's output value (Type 1 are diamonds, Type 2a are circles, Type 2x are triangles).

Primary Results:
- As muscle cell size increases, squat strength increases.

Take Away: There is a strong direct association between muscle fiber cell size and squat strength (more size, more strength) - regardless of muscle cell type (all three have strong associations).

Figure 4: These data are correlational - they show the relationship between two variables. In this case, the researchers are showing a relationship between squat strength (on the Y-axis) and muscle contractile protein amount (X-axis). Each point on the graph is a participant's output value.

Primary Results:
- There is a moderately strong association between contractile protein amount and squat strength.

Take Away: Having more myofibrillar (muscle) contractile proteins is moderately strongly associated with a stronger squat.

Figure 5: These data are correlational - they show the relationship between two variables. In this case, the researchers are showing a relationship between cross sectional area - size of the cell (on the Y-axis) and muscle contractile protein content (X-axis). Each point on the graph is a participant's output value (Type 1 are diamonds, Type 2a are circles, Type 2x are triangles).

Primary Results:
- There is a strong positive relationship/association between type 2a and type 2x contractile protein content and changes in cross sectional area.
- There is a moderately strong positive relationship/association between type 1 contractile protein content and changes in cross sectional area.

Take Away: There is a strong association between increasing muscle contractile protein content and muscle cell size.

explain the greater increases in strength and contractile protein accrual detected in the WP-supplemented group.

Although previous studies have shown that WP supplementation ($1.2\text{--}1.5\text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) results in greater LBM and strength compared with matched CHO (6) and casein-treated groups (8), this study is the first to report changes in skeletal muscle morphology in response to RE training and WP supplementation. In this study, the WP group demonstrated greater improvements in IRM strength (in all three tests) compared with the CHO-treated group (Fig. 1). On the basis of the correlations observed, these strength improvements can be attributed mostly to skeletal muscle morphology. The protein used in this study (whey isolate) is considered a rich source of EAA, particularly the branch chain amino acids (BCAA) (5). Supplementation with the BCAA during and after RE is shown to result in greater phosphorylation (activation) of p70^{S6k} in skeletal muscle, a rate-limiting kinase in the signaling network controlling protein synthesis through translational initiation (15). More

to those of CrM with CHO. This may have important implications for populations that desire improvements from exercise but for whom the consumption of large amounts of glucose is undesirable, such as those with (or at risk of) type II diabetes. Because this is the only study that has compared the effects of two different CrM-containing supplements on skeletal muscle morphology during RE, our results warrant further study.

Aside from the statistical evaluation of diet and the assessment of muscle hypertrophy at three levels, another strength of this investigation was the personalized training of the participants (one-to-one or one-to-two instruction of all participants during every workout). This level of supervision has been shown to ensure better control of workout intensity and greater strength improvements during training (19). A personal training approach to RE supervision in RE training studies that involve supplementation is particularly important as it ensures a better chance of enhanced physiological adaptations from supplementation

(28). This is based on the premise that those treated with supplements such as CrM and WP would be capable of training at a higher intensity level and progressing at a faster rate. It is important to remember that the instructors were blinded to the supplement groups, yet the WP, CrCHO, and CrWP groups demonstrated significantly greater hypertrophy (in at least one of three assessments) and gains in IRM strength (in three of three assessments), which, thus, generally supports our theory. Training and dietary strategies that augment the adaptations desired from RE should continue to receive greater attention from within the scientific community, because this research has important implications for an aging population and also for others who have reduced capacity for exercise, such as the frail elderly, cardiac rehabilitation patients, or those living with cachectic conditions such as HIV or various forms of cancer.

In conclusion, this study examined the effects of supplementation with CrCHO, CrWP, WP, or CHO ($1.5\text{ g}\cdot\text{kg}^{-1}$ body weight per day) using four groups of matched RE-trained males during 11 wk of supervised RE training. Pre-

post assessments demonstrated that supplementation with CrCHO, WP, and CrWP resulted in significantly greater increases in IRM strength (in three assessments) compared with supplementation with CHO. Up to 76% of the strength improvements in the squat could be attributed to hypertrophy of muscle involved in this exercise. However, the hypertrophy response from CrCHO, WP, and CrWP varied at the three levels assessed (i.e., changes in lean mass, fiber-specific hypertrophy, and contractile protein content). Therefore, although supplementation with WP and/or CrM seems to promote greater strength gains and muscle hypertrophy during RE training, the small number of participants within the groups that completed this investigation makes it difficult to draw firm conclusions regarding the effects of the different supplement combinations used in this study, and thus further investigation is warranted.

The lead investigator is a consultant to AST Sports Science. The results of the present study do not constitute endorsement of the product by the authors or ACSM.

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