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ORIGINAL RESEARCH

Creatine Monohydrate Supplementation, but not Creatyl-L-Leucine, Increased Muscle Creatine Content in Healthy Young Adults: A Double-Blind Randomized Controlled Trial

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Creatine (Cr) supplementation is a well-established strategy to enhance gains in strength, lean body mass, and power from a period of resistance training. However, the effectiveness of creatyl-L-leucine (CLL), a purported Cr amide, is unknown. Therefore, the purpose of this study was to assess the effects of CLL on muscle Cr content. Twenty-nine healthy men ($n = 17$) and women ($n = 12$) consumed 5 g/day of either Cr monohydrate ($n = 8$; 28.5 ± 7.3 years, 172.1 ± 11.0 cm, 76.6 ± 10.7 kg), CLL ($n = 11$; 29.2 ± 9.3 years, 170.3 ± 10.5 cm, 71.9 ± 14.5 kg), or placebo ($n = 10$; 30.3 ± 6.9 years, 167.8 ± 9.9 cm, 69.9 ± 11.1 kg) for 14 days in a randomized, double-blind design. Participants completed three bouts of supervised resistance exercise per week. Muscle biopsies were collected before and after the intervention for quantification of muscle Cr. Cr monohydrate supplementation which significantly increased muscle Cr content with 14 days of supplementation. No changes in muscle Cr were observed for the placebo or CLL groups. Cr monohydrate supplementation is an effective strategy to augment muscle Cr content while CLL is not.

Keywords: nutritional supplements, dietary supplements, muscle hypertrophy, anabolism

Creatine (Cr) is one of the most researched dietary supplements and considered to have good-to-strong evidence for its efficacy to serve as an ergogenic aid by the International Olympic Committee (Maughan et al., 2018). Cr is a naturally occurring nonprotein amino acid derivative that can be synthesized endogenously from glycine, arginine, and methionine in the liver and kidneys. In addition, Cr can be obtained from dietary sources, such as meat and seafood, and the typical omnivorous diet is estimated to yield ~1–2 g of Cr per day (Ostojic, 2021). While relatively small quantities of the total body Cr pool are in other tissues, ~95% of total Cr is in skeletal muscle tissue.

During short-term, high-intensity muscle actions, the phosphorylated form of Cr, phosphocreatine (PCr) is degraded to Cr and a phosphate group to regenerate adenosine triphosphate via the energy and phosphate group released from PCr degradation. PCr is then replenished when Cr is bonded with another phosphate group via the reversible enzymatic action of Cr kinase. Thus, maintenance of intramuscular Cr and PCr concentration is important for sustaining muscular effort. While de novo synthesis and dietary sources of Cr are typically sufficient to replenish the ~1%–2% of the body's Cr pool that is degraded to creatinine per day (Hoberman et al., 1948; Picou et al., 1976), muscular Cr content can be augmented by ~30% via dietary supplementation with Cr. This increase in Cr allows for greater PCr resynthesis and enhanced performance in high-intensity, repetitive exercise bouts (Harris et al., 1992). Over time, this performance enhancement has been shown to lead to greater gains in muscular strength, lean body mass (LBM), and muscular endurance after a period of resistance training and other high-intensity exercise in both young and older adults (Branch, 2003; Devries & Phillips, 2014).

Indeed, most studies demonstrating the effectiveness of Cr supplementation have used Cr monohydrate (CrM). However, several purported analogs of Cr have been introduced into the consumer market since the late 1990s in an attempt to improve the efficacy of Cr supplementation on skeletal muscle content compared with CrM. Many of these molecules are purported to increase the bioavailability, solubility, or safety of Cr supplementation compared with CrM. Despite previous studies demonstrating that many of these putative forms of Cr fail to improve on the ergogenic effects of CrM and augment muscle Cr content (Jagim et al., 2012; Kreider et al., 2022; Spillane et al., 2009), novel supplements continue to be introduced to the market. For example, one such purported analog of Cr, creatyl-L-leucine (CLL), is currently on the market as part of a multi-ingredient blend and is sold under the name "Super Creatine®." Scientifically, it is not entirely clear what anabolic properties, if any, may manifest from consuming CLL. However, it is important to investigate the potential ergogenic effects of other analogs of Cr within the consumer market given the potential benefits of Cr to enhance

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muscle mass and strength for all adult ages. While the toxicological effects of CLL have been studied in rodents (Reddeman et al., 2018), to our knowledge, no studies to date have investigated the effects of CLL supplementation on muscle Cr content in humans. Therefore, the purpose of this study was to compare the effects of 2 weeks of dietary supplementation with CrM, CLL, or a placebo (PLA) on muscle Cr content in healthy males and females. We tested the hypothesis that both CrM and CLL would increase muscle Cr content compared with PLA with CrM supplementation yielding enhanced Cr content compared with CLL.

Materials and Methods

Subjects

Eighty-six males and females were assessed for eligibility to participate in this investigation. Only participants between 18 and 50 years of age with a body mass index between 18.5 and 29.99 kg/m^2 were considered for participation. Potential participants reporting supplemental Cr use within the 12 months preceding recruitment, adherence to a diet that varies from the typical U.S. eating style (e.g., vegetarian or carnivore), or regular consumption of greater than 100–200 mg of caffeine per day (~1–2 cups of coffee) were excluded from participation. Furthermore, potential participants with a history of allergy or hypersensitivity to local anesthetics; adverse metabolic, cardiovascular, hepatorenal, autoimmune, or neuromuscular conditions; chronic tobacco use within the 6 months preceding recruitment; bleeding or clotting disorders; use of any nutritional supplement purported to be ergogenic within the 12 months preceding recruitment; habitual dietary protein intake greater than 1.2 g·kg^{-1}·day^{-1}; and women who are or may be pregnant were excluded.

In total, 29 participants met inclusion criteria. Baseline characteristics for enrolled participants are presented in Table 1. Those who were eligible and wished to participate were explained the procedures and risks associated with participation prior to signing an informed consent document approved by the institutional review board at the University of Illinois at Urbana-Champaign (IRB no. 21181). All procedures involving human subjects were conducted in accordance with the Declaration of Helsinki, with the exception of preregistration.

Experimental Design

This study used a randomized, double-blind, PLA-controlled, parallel design to assess the effectiveness of CrM, CLL, or PLA supplementation for increasing muscle Cr content. An overview of the study design is presented in Figure 1. Upon enrollment, participants completed baseline strength testing. At least 72 hr after preliminary testing, participants underwent a preliminary trial where a baseline muscle sample was collected. Following the preliminary trial, participants supplemented their habitual dietary intake with either CrM, CLL, or PLA (discussed below) for 2 weeks and completed three supervised resistance exercise sessions per week. A second biopsy was collected following the conclusion of the supplementation period.

Preliminary Testing Session

Prior to assessment of muscular strength, eligibility was confirmed by measuring height and body mass to confirm body mass index was within range. Subsequently, participants warmed up by walking on a belt-driven treadmill for ~5 min. Participants' 10-repetition maximum (10RM) was then determined for the leg extension, chest press, leg press, shoulder press, leg curl, and seated row (in that order). To begin, participants completed a set of 8–10 repetitions at ~50% of their estimated 10RM. Following 1–2 min of rest, load was increased to ~90% of their estimated 10RM for a set of 10 repetitions. Load was then increased by 2%–5% following each successful attempt until participants could not complete 10 repetitions through a full range of motion. Participants achieved 10RM in 2.61 ± 1.04 attempts. At least 2 min of rest was given between sets and 5 min between exercises.

Preliminary and Final Trials

On the morning of the preliminary and final trials (at least 72 hr following strength testing), participants arrived to the laboratory via public transport or automobile following an overnight fast (>8 hr) and having refrained from activities outside of daily living, and alcohol consumption for at least 72 and 24 hr, respectively. Upon arrival, participants voided their bladder prior to having their height and body mass measured prior to determination of body composition via dual-energy X-ray absorptiometry (QDR 4500 A,

Table 1 Participant Characteristics at Baseline

Variable	PLA (5 M, 5 F)	CLL (7 M, 4 F)	CrM (5 M, 3 F)	Group effect
Age (years)	30.3 ± 6.9	29.2 ± 9.3	28.5 ± 7.3	0.896
Height (cm)	167.8 ± 9.9	170.3 ± 10.5	172.1 ± 11.0	0.679
Body mass (kg)	69.9 ± 11.1	71.9 ± 14.5	76.6 ± 10.7	0.514
BMI (kg/m^2)	24.7 ± 2.4	24.6 ± 2.9	25.8 ± 1.7	0.548
Σ Upper body 10RM (kg)[a]	114.2 ± 40.9	115.7 ± 44.9	123.1 ± 62.0	0.929
Σ Lower body 10RM (kg)[b]	239.4 ± 64.0	210.0 ± 61.0	220.3 ± 67.8	0.608
Energy intake (kcal/day)	1,882 ± 514	1,884 ± 754	1,949 ± 732	0.978
Protein intake (g/day)	94.8 ± 35.6	97.5 ± 39.1	94.2 ± 50.4	0.987
Protein intake (g·kg^{-1}·day^{-1})	1.3 ± 0.5	1.4 ± 0.6	1.2 ± 0.6	0.738
Fat intake (g/day)	73.5 ± 29.1	85.2 ± 49.4	91.8 ± 36.1	0.686
CHO intake (g/day)	202.1 ± 39.7	177.8 ± 77.3	193.5 ± 77.2	0.781

Note. Data are presented as mean ± *SD*. BMI = body mass index; CHO = carbohydrate; CLL = creatyl-L-leucine; CrM = creatine monohydrate; PLA = placebo; M = male; F = female; 10RM = 10-repetition maximum.
[a]Sum of chest press, shoulder press, and seated row 10RMs. [b]Sum of leg extension, leg press, and leg curl 10RMs.

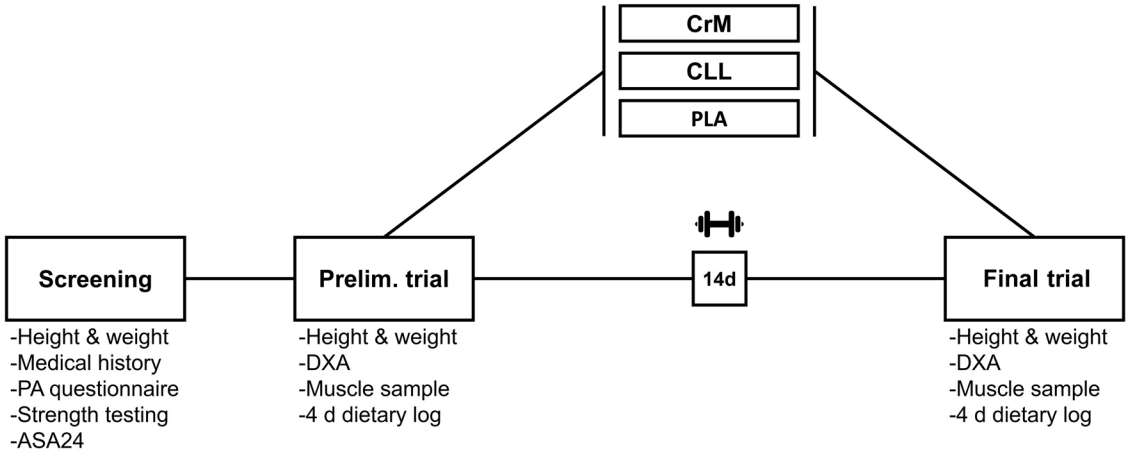

Figure 1 — Overview of the study protocol. PA = physical activity; ASA24 = Automated Self-Administered 24-hr Dietary Assessment Tool; CLL = creatyl-L-leucine; CrM = creatine monohydrate; PLA = placebo; DXA = dual-energy X-ray absorptiometry; Prelim. = preliminary.

Hologic) calibrated to manufacturer specifications. Subsequently, participants had their body water and blood pressure measured with a single channel, tetra polar bioimpedance spectroscopy device (SFB7, Impedimed Inc.) and an automated blood pressure cuff (HEM-907XL, Omron Healthcare Inc.), respectively, before being prepared for the biopsy procedure. Biopsies were collected from the middle region of the *vastus lateralis* of the participants' dominant leg using a Bergström needle modified for manual suction under local anesthesia (2% xylocaine with 1:200,000 epinephrine). Biopsies were freed from any visible blood, adipose, and connective tissue prior to being snap frozen in liquid nitrogen and stored at −80 °C for subsequent analysis.

Supplementation Protocol

The supplementation period lasted a total of 14 days and began on the day of participants' preliminary trial. During this time, participants consumed 5 g of either CrM (Creapure®, Bare Performance Nutrition), CLL, or PLA (maltodextrin, BulkSupplements) in a double-blind manner. CLL was provided by the sponsor (lot no. 201907016). Upon arrival of the supplements to the research facility, the powders were given to a researcher that was not involved in the study for transfer into identical containers labeled A, B, or C. The individual then recorded the contents of each container on a piece of paper, folded the paper, and subsequently sealed the blinding key with a signed and dated piece of tape. The blinding key was then stored in the office of the principal investigator (N.A. Burd) until all analysis was completed. Once blinded, 5 g portions of each condition were weighed to the nearest 0.1 g and transferred to plastic bottles for distribution to participants. Participants were instructed to consume the contents of one of these bottles at the same time daily by filling the bottle with ~12 oz of warm water, mixing until all the powder was dissolved, and promptly consuming the mixture (within 3 min of preparation). To promote compliance, participants returned empty supplement bottles on exercise days.

Resistance Exercise

On 3 days of each week during the supplementation period, participants reported to the laboratory for a supervised bout of resistance exercise. Exercise was included in the study in an attempt to standardize overall physical activity and to incentivize participants to refrain from outside exercise throughout the study as discrepancies between groups in exercise could result in differential accumulation of Cr in muscle (Harris et al., 1992). Upon arrival, participants completed a 5-min warm-up on a belt-driven treadmill followed by one warm-up set of 10 repetitions at 60% of 10RM. Participants then completed four sets of 10 repetitions with 80% of 10RM with 1–2 min of rest between sets. If participants were unable to complete 10 repetitions with the prescribed resistance, load was reduced by 2.5%–5% until 10 repetitions were completed. Exercises for each session alternated between two configurations. On one day, participants completed four sets each of leg extension, leg curl, and seated row with the next session being comprised of leg press, chest press, and shoulder press. The first exercise session was completed immediately following the preliminary trial. Exercise sessions were separated by at least 48 hr of rest, and the final exercise session was completed at least 48 hr prior to the second biopsy trial.

Experimental Control

Participants were asked to complete a 3-day diet record (two weekdays and one weekend day) prior to the start of the study using the Automated Self-Administered 24-hr Dietary Assessment Tool (version 2020, National Cancer Institute) to characterize habitual dietary habits and quantify energy and macronutrient consumption. Similarly, participants completed a 4-day diet record leading into the preliminary trial. This record was compiled, printed, and given to the participant to repeat leading into the final trial to ameliorate any differences between trials that may be due to the diet. Participants were instructed to complete another 4-day record leading into the final trial regardless of how closely they followed the initial record provided to them.

Moreover, participants' physical activity was monitored by a triaxial accelerometer (GT9X Link, ActiGraph LLC). Participants were provided with a sleep and wear log and asked to record any time period over 15 min when they took the unit off and when they got into/out of bed each day. These data were analyzed using the proprietary software of the accelerometer manufacturer (ActiLife, version 6.13.4). Nonwear time and sleep time were identified through participant logs and excluded from analyses. Sampling rate was set at 30 Hz, and data were scored using methods as described by Freedson et al. (1998).

Muscle Cr Analysis

One fraction of the muscle sample (~30 mg wet weight [WW]) was lyophilized and pulverized according to established methods (Harris et al., 1974). Powdered muscle samples (~5–10 mg dry weight) were weighed, transferred to a clean tube, and extracted with 0.5 M perchloric acid with 1 mM ethylenediaminetetraacetic acid (EDTA) at a ratio of 1 ml perchloric acid/EDTA: 12.5 mg dried muscle. Samples were then agitated on ice for 10 min prior to being centrifuged (10,000*g* for 3 min at 4 °C) to pellet any insoluble matter. Following transfer of supernatant to a clean tube, acid extracts were individually neutralized with 2.2 M potassium hydroxide until the pH reached between 6.5 and 8 and subsequently frozen at −80 °C for muscle Cr analysis. Samples were analyzed using a Triple Quadrupole LC/MS/MS system (TSQ Altis, Thermo Fisher Scientific). The software TraceFinder (version 4.1; Thermo Fisher Scientific) was used for data acquisition and analysis. The liquid chromatography (LC) separation was performed on a Thermo Accucore Vanquish C18+ column (2.1 × 100 mm, 1.5 µm) with Mobile phase A (2 mM ammonia acetate in water) and Mobile phase B (2 mM amonia acetate in acetonitrile). The flow rate was 0.3 mL/min. The linear gradient was as follows: 0–0.5 min, 0% B; 2–3 min, 100% B; and 3.5–5 min, 0% B. The autosampler and LC column chamber were set at 10 °C and 40 °C, respectively. The injection volume was 5 µl. Mass spectra were acquired under both positive and negative electrospray ionization. Multiple reaction monitoring was used for quantitation: Cr mass-to-charge ratio (*m/z)* 131.9 → *m/z* 87.0, PCr *m/z* 209.9 → *m/z* 78.9, and internal standard 4-choloro-phenylalanine *m/z* 199.9 → *m/z* 154.0.

Statistical Analyses

All data are expressed as mean ± *SD*. All inferential statistical analyses were performed using IBM SPSS Statistics for Windows (version 25.0). An a priori power analysis was conducted using data compiled from published research (Casey et al., 1996; Gordon et al., 1995; Greenhaff et al., 1994; Hultman et al., 1996; Jagim et al., 2012; McKenna et al., 1999) using a simulation-based power analysis system for factorial analysis of variance designs (Lakens & Caldwell, 2021). Based on an estimated effect size ($\eta_p^2 = .30$), and a desired power of 80%, our power analysis demonstrated that a sample size of 10 would be sufficient to detect a significant Group × Time interaction at $p < .05$ for a factorial design with a single between-subjects (three levels) and within-subjects (two levels) variable. Data were assessed for normality via inspection of skewness/kurtosis values and normal Q–Q plots. Differences in baseline participant characteristics, training load, and physical activity measures were assessed using a linear mixed-effects model with group (three levels) as a fixed factor. Similarly, pretrial nutritional intakes and body composition were also analyzed with linear mixed-effects models with group (three levels), time (two levels), and the interaction term as fixed factors. Given the numerical differences in baseline Cr content, muscle Cr was analyzed using a similar model (i.e., group, time, and Group × Time as fixed factors) but with baseline muscle Cr as a covariate. Statistical significance was set at $p < .050$. When a significant main effect or interaction was identified, Bonferroni post hoc adjustments were utilized for pairwise comparisons to identify these differences.

Results

Descriptive Characteristics and Body Composition

There were no differences observed between groups for any of the baseline characteristics analyzed (see Table 1). Neither systolic blood pressure nor fasting plasma glucose differed between groups or trials (grand mean = 126.5 ± 11.9 mmHg and 5.0 ± 0.7 mmol/L, respectively). However, there was a significant effect for group ($p = .039$) for diastolic blood pressure. Regardless of trial, PLA (70.6 ± 8.2 mmHg) was significantly lower than CrM (78.3 ± 5.6 mmHg) with no differences between CrM and CLL (73.7 ± 11.0 mmHg; $p = .412$) or PLA and CLL ($p = .804$). There was no change in body mass, body mass index, total body water, or LBM with supplementation ($p > .10$). However, regardless of condition, fat mass increased over the supplementation period ($p = .011$; see Table 2). Furthermore, dietary intake in the 4 days preceding each trial did not differ between groups nor time points (see Table 3).

Physical Activity and Exercise

Daily energy expenditure from physical activity, as measured via accelerometers, did not differ ($p = .280$) between CLL (315 ± 101 kcal/day), CrM (330 ± 171 kcal/day), or PLA (310 ± 170 kcal/day). Similarly, cumulative upper and lower body training volume load did not differ between groups (see Table 4). A single participant only completed five training sessions, whereas all other participants completed all six supervised exercise bouts.

Muscle Cr Content

There was a main effect of time ($p = .040$) and group ($p = .010$) for muscle Cr. Moreover, there was significant Group × Time interaction ($p = .010$). Cr content was unchanged after the supplementation

Table 2 Changes in Body Composition Before (Trial 1) and After (Trial 2) 14 Days of Supplementation

	PLA		CLL		CrM		*p*	
	Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2	Group	Time
Body mass (kg)	69.8 ± 10.2	70.0 ± 10.3	69.7 ± 13.2	69.2 ± 13.2	76.6 ± 10.5	77.4 ± 10.7	.325	.274
BMI (kg/m^2)	23.9 ± 1.7	24.0 ± 1.9	23.6 ± 2.9	23.5 ± 3.0	24.9 ± 1.8	25.2 ± 1.8	.379	.132
Fat mass (kg)	18.0 ± 3.0	18.4 ± 3.1	19.2 ± 7.4	19.5 ± 7.3	23.3 ± 6.8	23.7 ± 6.9	.172	.011
LBM (kg)	50.9 ± 11.1	50.9 ± 11.0	49.6 ± 11.3	48.7 ± 11.0	52.3 ± 9.6	52.8 ± 10.3	.802	.399
Body fat (%)	26.8 ± 6.6	27.2 ± 6.6	27.9 ± 8.6	28.7 ± 8.6	30.9 ± 7.8	31.2 ± 8.2	.544	.015
TBW (L)	37.7 ± 7.6	38.7 ± 7.8	38.2 ± 7.8	35.6 ± 7.1	40.3 ± 6.9	41.9 ± 7.3	.371	.996

Note. Data are presented as mean ± *SD*. CLL = creatyl-L-leucine; CrM = creatine monohydrate; PLA = placebo; BMI = body mass index; LBM = lean body mass; TBW = total body water.

Table 3 Dietary Intake Results From 4-Day Diet Records Leading Into the First and Second Muscle Biopsies

	PLA		CLL		CrM		*p*	
	Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2	Group	Time
Energy (kcal)	1,675 ± 413	1,693 ± 613	1,726 ± 494	1,745 ± 237	1,705 ± 413	1,548 ± 298	.837	.793
Protein (g/day)	78 ± 17	72 ± 41	82 ± 29	87 ± 18	80 ± 37	72 ± 21	.691	.761
Protein ($g \cdot kg^{-1} \cdot day^{-1}$)	1.2 ± 0.3	1.0 ± 0.5	1.1 ± 0.3	1.2 ± 0.3	1.0 ± 0.4	0.9 ± 0.2	.573	.495
Fat (g/day)	65 ± 29	63 ± 39	78 ± 24	79 ± 18	73 ± 19	72 ± 17	.447	.949
CHO (g/day)	196 ± 50	219 ± 46	176 ± 73	170 ± 57	188 ± 32	156 ± 34	.233	.781

Note. Data are presented as mean ± *SD*. CHO = carbohydrate; CLL = creatyl-L-leucine; CrM = creatine monohydrate; PLA = placebo.

Table 4 Average Total Volume Load and Repetitions Completed Throughout the Supplementation Period

Variable	PLA	CLL	CrM	Group effect
LB repetitions (*n*)	360 ± 0	355 ± 16	359 ± 22	0.892
LB volume load (kg)	21,021 ± 7,607	20,267 ± 5,633	20,600 ± 7,111	0.771
UB repetitions (*n*)	358 ± 4	359 ± 2	354 ± 15	0.429
UB volume load (kg)	11,121 ± 3,546	11,215 ± 4,354	12,352 ± 6,364	0.852

Note. Data are presented as mean ± *SD*. LB = lower body; UB = upper body; CLL = creatyl-L-leucine; CrM = creatine monohydrate; PLA = placebo.

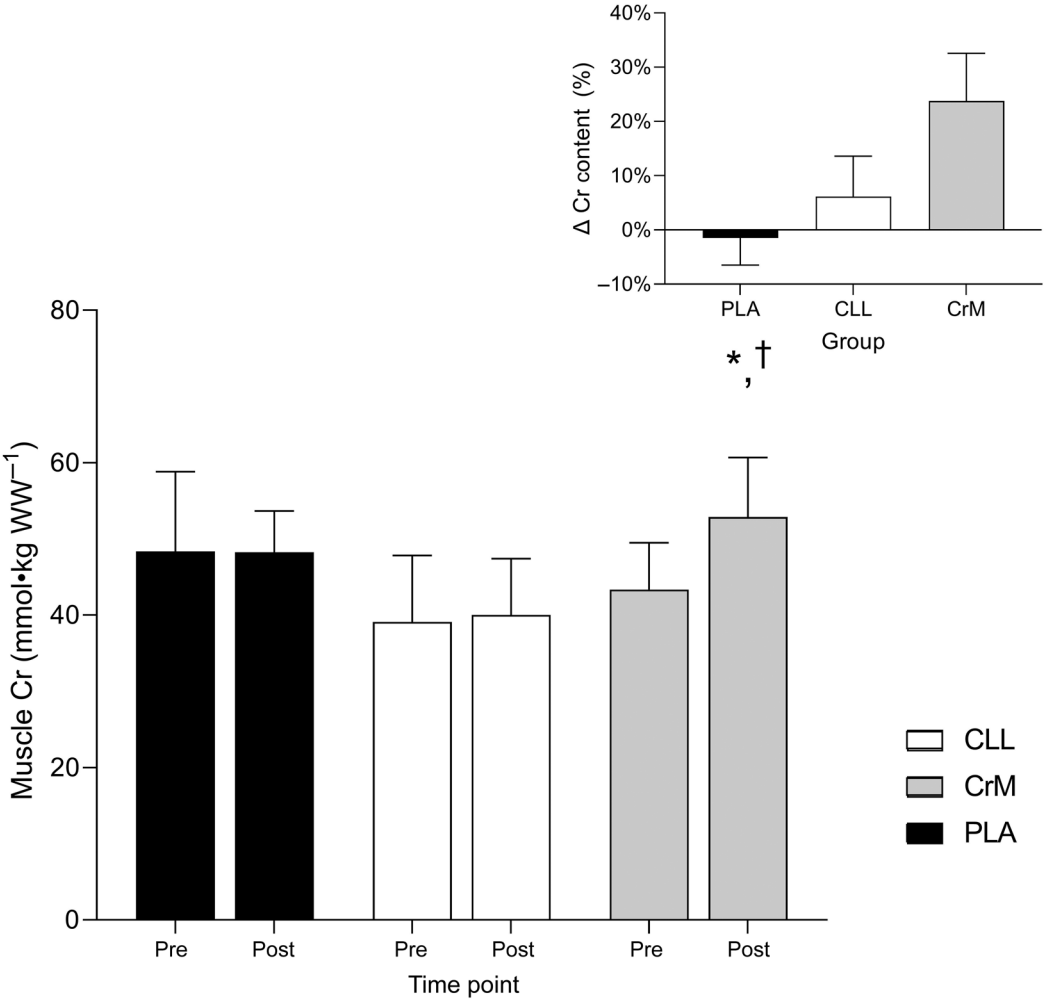

Figure 2 — Mean ± *SD* muscle creatine content before and after 14 days of supplementation. Cr = creatine; WW = wet weight; CLL = creatyl-L-leucine; CrM = creatine monohydrate; PLA = placebo. *Significantly greater than the presupplementation time point within group. †Significantly greater than PLA and CLL postsupplementation.

period for the CLL (39.1 ± 8.8 vs. 40.0 ± 7.4 mmol/kg WW; $p = .680$) and PLA (48.9 ± 7.9 vs. 47.4 ± 5.9 mmol/kg WW; $p = .504$) groups. However, there was a significant increase in the CrM group after supplementation (43.3 ± 6.2 vs. 52.9 ± 7.8 mmol/kg WW; $p = .010$). After the intervention, muscle Cr content was higher in CrM than both PLA ($p = .001$) and CLL ($p < .001$; see Figure 2).

Discussion

The identification of more effective Cr supplementation regimens has important implications for performance and clinical nutrition when the goal is to support muscle mass and strength. In this study, we examined the impact of CLL and CrM supplementation (5 g/day for 14 days) on muscle Cr content in healthy males and females against the backdrop of resistance training. The results presented herein demonstrated that 2 weeks of supplementation with CLL did not statistically significantly increase muscle Cr while CrM supplementation significantly increased muscle Cr content. Indeed, a past study evaluated a product (mixed ingredient supplement) containing CLL on strength and LBM outcomes (Schwarz et al., 2019). However, this particular study could not reach any firm conclusions on the potential independent ergogenic effects of CLL. Our study is the first to directly compare CLL versus Cr in isolation on muscle Cr and body composition in humans.

Previous studies on Cr supplementation have reported an increase of 10%–40% in muscle Cr content after a period of supplementation (Greenhaff et al., 1994; Hultman et al., 1996; Jagim et al., 2012). While there is significant heterogeneity in the response to Cr supplementation, this can be explained, in part, by differing supplementation strategies and durations of observation. Most studies use a loading phase (typically 20 g/day for 5–7 days) followed by a lower maintenance dose (~3–5 g/day). However, CLL, to our knowledge, is currently only available commercially in a multi-ingredient energy drink or preworkout supplement formulation. Hence, the typical use of CLL as a component of a beverage does not allow for a traditional loading phase. Thus, we elected to forgo the loading phase in our study. While this likely reduced the rate at which muscle Cr accumulated, foundational work in this area demonstrated that this strategy is a valid approach to saturate muscle Cr (Hultman et al., 1996). Along those lines, Hultman et al. (1996) report a ~12% increase in muscle Cr following 14 days supplementation with CrM (3 g/day). This is slightly lower than the ~24% increase we observed in our study for the CrM group, which is to be expected considering participants in the current investigation consumed a higher dose of CrM (5 g/day) compared with Hultman et al. (1996). Moreover, participants in our study completed supervised bouts of resistance exercise 3 days/week throughout the supplementation period. Exercise in combination with Cr supplementation has previously been shown to enhance muscle Cr above supplementation alone (Harris et al., 1992).

The mean increase in muscle Cr was ~24% for the CrM group with no increase for the CLL group. While no study has characterized the digestive fate of ingested CLL, the absorption of CrM is nearly 100% (Deldicque et al., 2008; Harris et al., 1992), and thus, the potential benefit of consuming a purported creatyl amide, such as CLL, for enhanced solubility and subsequent increase in muscle Cr content is not entirely clear. Future studies could test higher-dose CLL supplementation or a longer supplementation period to enhance muscle Cr. However, based on the results presented from the current study, it seems more straightforward to simply supplement with CrM, especially given we did not observe a statistically significant increase in muscle Cr content in the CLL condition.

We did not observe any changes to LBM as measured by dual-energy X-ray absorptiometry in any groups. While Cr supplementation is known to enhance the training-induced gain in LBM (Branch, 2003; Devries & Phillips, 2014), most demonstrating this effect employ a longer duration of supplementation (i.e., >8 weeks) in combination with a progressive resistance training program. One study reports a significant increase in fat-free mass following 3 days of loading and 7 days of maintenance supplementation at a dose of 20 and 5 g/day, respectively (Safdar et al., 2008). However, this gain in fat-free mass is most likely due to increased fluid retention following Cr supplementation (Bone et al., 2017; Powers et al., 2003) rather than a true increase in myofibrillar protein content. As such, the lack of a significant gain in LBM for our study is in line with what is expected in response to 2 weeks of Cr supplementation.

In conclusion, we demonstrated that CrM supplementation significantly increased muscle Cr content by ~24%, whereas there was no statistically significant change in muscle Cr content in the PLA and/or the CLL conditions. As such, this work does not support the use of CLL as an alternative dietary supplementation strategy to CrM to increase muscle Cr content in healthy males and females.

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