Acute creatine loading increases fat-free mass, but does not affect blood pressure, plasma creatinine, or CK activity in men and women

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ABSTRACT
MIHIC, S., J. R. MACDONALD, S. MCKENZIE, and M. A. TARNOPOLSKY. Acute creatine loading increases fat-free mass but does not affect blood pressure, plasma creatinine, or CK activity in men and women. Med. Sci. Sports Exerc., Vol. 32, No. 2, pp. 291–296, 2000. Creatine monohydrate (CrM) administration may enhance high intensity exercise performance and increase body mass, yet few studies have examined for potential adverse effects, and no studies have directly considered potential gender differences. Purpose: The purpose of this study was to examine the effect of acute creatine supplementation upon total and lean mass and to determine potential side effects in both men and women. Methods: The effect of acute CrM (20 g d⁻¹ × 5 d) administration upon systolic, diastolic, and mean BP, plasma creatinine, plasma CK activity, and body composition was examined in 15 men and 15 women in a randomized, double-blind experiment. Additionally, ischemic isometric handgrip strength was measured before and after CrM or placebo (PL). Results: CrM did not affect blood pressure, plasma creatinine, estimated creatinine clearance, plasma CK activity, or handgrip strength (P > 0.05). In contrast, CrM significantly increased fat-free mass (FFM) and total body mass (P < 0.05) as compared with PL, with no changes in body fat. The observed mass changes were greater for men versus women. Conclusions: These findings suggest that acute CrM administration does not affect blood pressure, renal function, or plasma CK activity, but increases FFM. The effect of CrM upon FFM may be greater in men as compared with that in women. Key Words: NUTRITIONAL SUPPLEMENT, ERGOGENIC AID, SIDE EFFECTS, RENAL FUNCTION, CREATININE

The use of creatine monohydrate (CrM) as a potential ergogenic agent has been examined extensively (1–3,7–9,12,13,20,23,25). Studies have demonstrated an increase in intra-muscular total creatine (TCr) and phosphocreatine (PCr) (13,14,16), while others have found enhanced athletic performance (2,3,8,12,20). In addition to functioning as a temporal energy buffer (14,35), acute CrM administration may also increase total body mass (TBM) (1,2,8,13,22). These factors may contribute to the potential utility of CrM as an ergogenic agent in sporting events requiring a high energy output and/or a high body mass. These properties also predict that CrM could be used as an adjunctive treatment in patients with muscle wasting (i.e., neuromuscular disease, AIDS, postsurgery).

If CrM is to be useful as an ergogenic or therapeutic strategy, it is important to determine whether there are gender specific differences in the response to its administration. There is evidence that intra-muscular TCr concentration relative to fat-free tissue is higher in women than men (10). If TCr is higher in women, there may be an attenuated ability to derive therapeutic benefit from CrM administration (14). The mechanism(s) behind the increase in body mass in response to CrM are unclear; however, it is probable that in the early phase this is caused by an increase in intra-cellular water retention (14,16,35). A confounding variable in many studies is the super-imposition of exercise during the acute CrM loading phase which makes it difficult to factor out a potential interaction between CrM and exercise. For this reason, we chose to study the effects of acute CrM administration per se upon body mass accretion without the co-intervention of exercise training.

In spite of the extensive use of CrM supplementation for performance enhancement, there have been few studies examining or reporting potential side effects. Several anecdotal reports of elevated blood pressure and plasma creatine kinase (CK) activity have appeared on the internet and in lay publications. Some anecdotes have suggested that three recent hyperthermia/dehydration related deaths in college athletes were linked to the simultaneous use of CrM; however, a review by the U.S. Center for Disease Control concluded that CrM ingestion was not a contributing factor (17). A recent case report suggested that CrM administration was responsible for reversible renal deterioration in a young male with pre-existing focal segmental glomerulosclerosis.
In contrast to these anecdotal reports, there have been few side effects reported in both acute/short-term (5–28 d)
(1–3,7,8,12,14,16,20,23,25) and long-term protocols (>1 yr) (34). Given the extensive use of CrM among athletes and the potential for important therapeutic uses in patients, it is important that studies examine the potential side effects in randomized double-blind trials.

An ergogenic effect of CrM administration has been demonstrated in short duration high-intensity exercise (2,3,8,12). These effects have been related to increased PCr availability and/or the rate of PCr re-synthesis during prolonged repeated muscle contractions (13). In the current study an ischemic exercise protocol was used to eliminate the possibility of PCr re-synthesis during the intermittent recovery phase. This technique allowed the separation of the aforementioned mechanistic possibilities.

This study was designed to address two principal questions with respect to acute CrM administration: 1) Are there effects upon blood pressure, renal function (as assessed by plasma creatinine and estimated creatinine clearance), and plasma CK activity?; and 2) Do men and women have similar increases in TBM and what is the compositional content (BMC), fat, and lean mass were calculated using the version 5.56 software. FFM was taken as BMC + lean. All subjects were scanned with their hands supinated at their sides and feet between 25–30 cm apart. The same investigator completed all testing and recorded the subject position on the first trial to ensure similar positioning for the subsequent trial. Each subject had the standard bar placed to the right of the body, and a spine phantom was used each morning to enhance day-to-day reliability. The same machine and software used in the current study had been tested previously in our laboratory (4). In a reproducibility experiment it was found that the coefficients of variation (CV) were 1.6, 1.4, and 1.8%, for whole-body BMC, lean mass, and fat mass, respectively, in 21 young women (20.9 ± 1.6 yr) tested between 1 and 2 wk apart (4). From this data it was calculated that a sample size of 11 was sufficient to detect a change in whole body lean mass of 2.0% (4). Given that most acute creatine loading studies demonstrated increases in mass of about 2–2.5% (1,2,8,13,23), it was concluded that the power was adequate to avoid a type II statistical error in the current study.

Following these measurements, participants reported to the laboratory following an overnight fast and a 12-h abstinence from caffeine for the first testing session. They were seated comfortably, with the right arm positioned on a desk in front of them. The blood pressure cuff (Finapres, Ohmeda 2300, Englewood, CO) was placed around the medial phalanx of the right middle finger. The size of the cuff was adjusted to each subject, as well as the height of the chair and the desk, and recorded such that size/position was maintained between trials. They were then left in a temperature-controlled chamber (22 ± 1°C; 60–70% R.H.) for ~20 min. When stable values for systolic and diastolic BP
were observed (minimum of 15 min), data was recorded during the next 2 min. The Finapres cuff has been validated by a number of researchers (20,26) and has been found to have correlation coefficients as high as 0.95 (20,26) with indwelling pressure monitoring. To confirm these findings, we also performed Finapres comparisons with simultaneous intra-arterial measurements. In our experience, resting Finapres measurements slightly but consistently underestimated intra-arterial recordings (<10%) but tracked the pressure wave-form remarkably well. This underestimation was more pronounced in the diastolic readings. This held true during any activity of mild to moderate intensity in which the upper body was static (i.e., static and dynamic leg press and Valsalva maneuver) (MacDonald, J. R., M. A. Tarnopolsky, and J. D. MacDougall, unpublished observations, 1998).

After the BP measurements were taken, the cuff was released, and a 22-g plastic catheter was inserted into an antecubital vein of the dominant arm. A 10-mL baseline blood sample was drawn into a prechilled heparinized tube, which was immediately centrifuged, aliquoted, and stored at −50°C for subsequent analysis. Then a forearm ischemic exercise test (FIT) was performed for determination of the maximal voluntary strength (MVC) during six 9-s isometric contractions, separated by 1-s recovery periods (total of 60 s). Ischemia to the working forearm muscles was achieved using a blood pressure cuff around the upper arm inflated to ~180 mm Hg before onset of exercise. The cuff was immediately deflated after the exercise bout. Blood samples were then taken at +1 min and +5 min following exercise. Details of the testing method have been described (32).

After initial testing, participants were assigned to either a CrM (7 men, 8 women) or PL (8 men, 7 women) group in a randomized, double-blinded fashion. The administration consisted of 4 × 5 g/day × 5 d of either CrM (99% pure, ISA, Hamilton, ON, Canada) or a glucose polymer, which were similar in taste, smell, and consistency. The supplements were taken after meals and dissolved in cold or warm juice, milk, or warm tea. On day 6 supplement consumption was similar in taste, smell, and consistency. The supplement was composed of 33.1 g of CrM (99% pure) and 22.5 g of PL (Sigma Diagnostics, Kit DG147-K, St. Louis, MO), and creatinine concentration (CV = 6.0%) (Sigma Diagnostics, Kit 555-A), and hematocrit (Hct). Creatinine clearance was estimated from the following formula (5): creatinine clearance (mL/min⁻¹·1.73 m²) = [(140 – age) × weight (kg)/72 × plasma creatinine (mg/dL)⁻¹. For women the value was multiplied by 0.85 (5). Plasma lactate concentration was determined at rest and following FIT using a lactate analyzer (YSI Model 23 L, Yellow Springs, OH). We verified that the biochemical purity of the supplied CrM (ISA, Hamilton, Ontario, Canada) was ~99% by comparison with a certified standard (Sigma Chemicals, St. Louis, MO) by an enzymatic assay (14).

Statistical analysis. Analyses consisted of three-way (treatment × gender × time) repeated measure analysis of variance (ANOVA) with a Tukey post-hoc test employed to locate pair-wise differences between the variables. Pearson product-moment correlation coefficient (r) was used to correlate changes in FFM with those of TBM. Confidence level of P < 0.05 was considered to be statistically significant. Results are presented as means ± SD.

RESULTS

Blood pressure, plasma creatinine, estimated creatinine clearance, plasma CK activity, and Hct. No effects of treatment were found for systolic, diastolic, or mean blood pressure (Fig. 1). There was no difference in

![Figure 1—Systolic, diastolic, and mean blood pressure before and after ingestion of CrM and PL. All values are means ± SD.](image)

| Table 2: Plasma creatinine, estimated creatinine clearance, and plasma creatine kinase activity before and after ingestion of PL and CrM. |
|-----------------|-----------------|-----------------|
|                | CrM             | PL              |
| Plasma creatinine (µmol/L) | 92.0 ± 21.9  | 92.3 ± 22.5  |
| Creatinine clearance* (mL/min⁻¹·1.73 m²) | 103.9 ± 17.3 | 99.5 ± 14.0  |
| Plasma CK activity (U/L⁻¹) | 58.1 ± 44.4  | 41.7 ± 33.1  |

* Values are means ± SD collapsed across gender.

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plasma creatinine for CrM versus PL ($P > 0.05$)(Table 2). Accordingly, estimated creatinine clearance did not change (Table 2), suggesting that renal function was not altered following treatment. Plasma creatinine was higher for men than women (103.4 ± 16.0 μmolL$^{-1}$ vs 78.1 ± 9.2 μmolL$^{-1}$) ($P < 0.05$). Plasma CK activity was unaffected by either CrM or PL intervention (Table 2). A significantly lower CK activity was found for women as compared with that for men (34.7 ± 28.8 U·L$^{-1}$ vs 95.3 ± 66.1 U·L$^{-1}$) ($P < 0.05$). Finally, Hct did not change following treatment, yet it was higher for men than women ($P < 0.05$) (data not shown).

**Body composition.** Men had higher TBM and FFM and lower body fat percent than women ($P < 0.05$)(Table 3). Total body mass (TBM) increased for CrM as compared with PL ($P < 0.05$)(Table 3). The average increase for CrM was 1.04 ± 0.87 kg ($P < 0.05$), which did not change for PL (Fig. 2). Additionally, these treatment-induced changes were greater for men as compared with those for women ($P < 0.05$)(Fig. 2). Significant differences in CrM versus PL administration were also found for FFM ($P < 0.05$)(Fig. 2). The increase in FFM ± 0.62 kg accounted for most of the gain in TBM ($r = 0.84$; $P < 0.05$). With respect to gender, increments in FFM showed a very strong trend ($P = 0.052$) for men (1.3 ± 0.4 kg) to increase more than women (0.4 ± 0.4 kg)(Fig. 2) and this trend was identical even when expressed as kilogram increase/kilogram total body mass. There was no effect of treatment on percent body fat (Table 3).

**Forearm ischemic test (data not shown).** The average maximal force over the six isometric contractions during FIT was not affected by treatment. Men were stronger as compared with women ($P < 0.05$). Plasma lactate concentration increased ~ seven-fold following ischemic exercise ($P < 0.05$); however, neither resting nor postexercise (+1, +5 min) plasma lactate concentration was different for CrM as compared with PL.

**DISCUSSION**

This trial examined body composition and potential side effects from acute CrM administration in both men and women. There was no evidence for significant alterations in blood pressure, plasma creatinine, estimated creatinine clearance, or plasma CK activity. Acute CrM administration did result in FFM increases that were greater for men as compared with those for women. Taken together, this data provided evidence that acute CrM administration to young healthy men and women was well tolerated and did not alter indices of renal function or blood pressure. Importantly, there appear to be gender specific responses in FFM and TBM that may attenuate the potential athletic and therapeutic efficacy of CrM administration in women.

The current study found no evidence for impaired renal function in response to acute CrM administration in young healthy men and women. This finding is consistent with several other reports in the literature where acute CrM ingestion did not increase plasma creatinine concentration (14,27). One study did find a 23% increase in plasma creatinine, following 28 d of CrM supplementation in male football players (20); however, these values were still within the “normal” range for this group of athletes. A single case reported that CrM induced a reversible impairment of creatinine clearance and glomerular filtration rate (GFR) in a patient with glomerulosclerosis (28). Without any long-term data at this point, it would be prudent for those with renal dysfunction to be monitored closely if CrM supplementation is contemplated.

A second potential side effect is an increase in muscle enzyme activity in plasma that was reported by Kreider et al. (20). This group found that the activity of several muscle enzymes (CK, ALT, LDH) was higher after 28 d of CrM supplementation in male football players as compared with

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**Table 3. Body composition data before and after PL and CrM administration.**

<table>
<thead>
<tr>
<th></th>
<th>PL</th>
<th>CrM</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>TBM (kg)</td>
<td>69.3 ± 14.6</td>
<td>69.2 ± 14.2</td>
</tr>
<tr>
<td>Men*</td>
<td>81.5 ± 9.1</td>
<td>81.2 ± 8.5</td>
</tr>
<tr>
<td>Women</td>
<td>57.1 ± 6.1</td>
<td>57.2 ± 5.9</td>
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<tr>
<td>FFM (kg)</td>
<td>54.3 ± 13.9</td>
<td>54.3 ± 13.2</td>
</tr>
<tr>
<td>Men*</td>
<td>68.2 ± 7.7</td>
<td>68.0 ± 6.8</td>
</tr>
<tr>
<td>Women</td>
<td>42.5 ± 4.1</td>
<td>42.6 ± 4.3</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>18.3 ± 4.6</td>
<td>18.2 ± 4.7</td>
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</tbody>
</table>

Values are means ± SD. TBM, total body mass; FFM, fat-free mass.

* Significant ($P < 0.05$) CrM treatment effect as compared to PL.

** Gender effect for body mass changes.

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A second potential side effect is an increase in muscle enzyme activity in plasma that was reported by Kreider et al. (20). This group found that the activity of several muscle enzymes (CK, ALT, LDH) was higher after 28 d of CrM supplementation in male football players as compared with
that of those given a placebo. The mechanism by which CrM supplementation could instigate damage to the sarclemma is not clear, but speculation is that it may involve myocyte swelling (15) and/or an up-regulation of CK activity. However, after controlling for several factors that affect plasma CK activity (i.e., exercise, health status), the current study found no CrM treatment-induced increases in plasma CK activity. Additionally, the lower CK activity in women has been demonstrated and is positively correlated with total muscle mass (24).

A final side effect that has been anecdotally linked to CrM administration is that of elevated blood pressure. Because the gain in TBM is associated with net water retention (14,16,35), it was considered possible that fluid retention may elevate blood pressure by increasing cardiac preload if the fluid retention is in the intravascular space. However, neither systolic, diastolic, nor mean blood pressure were affected following the acute (5 d) administration of CrM (20 g d⁻¹). Further evidence for the cardiovascular safety of CrM came from a recent study showing improved exercise capacity and no reported cardiovascular effects in congestive heart failure patients (11). Furthermore, in vitro data suggests that there may be cardio-protective effects from CrM administration (33).

Acute CrM administration (4–14 d) has been shown consistently to increase total body mass by about 1 kg (1,2,8,13,23). Despite the fact that increased TBM has been seen commonly after 5–7 (1,2,13) and 28 d (8) of CrM administration, few studies have determined the composition of this weight gain (8). Earnest et al. (8) demonstrated a strong trend toward increased fat-free mass (P < 0.054) after 28 d of CrM administration in resistance-trained male athletes. The current results confirm that the increased TBM seen following CrM treatment is predominantly FFM with no change in fat mass. In combination with the observation that ~90% of TCr is found in skeletal muscle (36), these findings suggest that intra-myofibrillar water retention may account for most of the increases in FFM. Creatine is taken up by the muscle via an insulin stimulated (31) and sodium-dependent transporter (30). This process generates active sodium and amino acid gradients across the plasma membrane, which draws water into the cell (15). Although the acute effects of CrM administration are predominantly related to water retention, in the long-term an increase in cellular hydration (cellular swelling) may be an anabolic signal that improves net nitrogen retention (15). In addition to a putative acute effect of creatine upon cellular water retention, Ingwall et al. (18,19) have demonstrated that creatine per se may stimulate myofibrillar protein synthesis in isolated skeletal and cardiac tissue cultures. Given the potential therapeutic benefits that may be achieved from such an agent, it will be important to examine the potential role or CrM in the control of muscle protein synthesis in vivo and its mechanism(s) of action.

To date no study that has directly compared the response to CrM in both men and women in spite of reports that muscle TCr may be different between the genders (10). The current study found an increase in TBM for men and not women and found a strong trend toward a lesser increase in FFM for women (P = 0.052) in response to CrM supplementation. Average increases for TBM and FFM in male subjects were ~1.6 kg and ~1.3 kg, respectively, whereas for women they were only ~0.45 kg (TBM) and ~0.44 kg (FFM). It was not anticipated a priori that such large sex differences would exist in response to CrM loading, given that the subjects were matched for age and training status. It is possible that the lower TBM and FFM may have contributed to the absolute increases; however, when the increases are expressed in a relative fashion, the men increased TBM by 2.0% and FFM by 2.0%, whereas the women increased by 0.8 and 1.0%, respectively. It is also possible that the women had higher muscle TCr concentrations before loading (10,14), which could attenuate loading potential of the female participants (14).

Finally, there was no effect of CrM treatment upon grip strength during forearm ischemic test (FIT). This suggested that the ergogenic effects of CrM administration may result from PCr re-synthesis during aerobic recovery (2,3,8,13). However, using an identical ischemic testing method, Tarapolsky et al. (32) did find significant improvements in grip strength in mitochondrial cytopathy patients (CrM vs PL trial; P < 0.01). It is possible that different designs (cross-over trial), and/or a greater potential for patients with mitochondrial cytopathies to increase basal intra-muscular TCr concentration (32) could have accounted for the differing results. The lack of a significant effect of CrM upon resting and postexercise plasma lactate concentration is consistent with several studies (3,12,23).

In summary, there were no adverse effects following 5 d of CrM administration in young men and women. Both total and FFM were increased following treatment, with a greater effect in men. In addition to athletic endeavors, an increase in FFM could be a potential benefit from CrM treatment in patients with muscle atrophy as a primary (i.e., ALS, muscular dystrophy, neuropathy) or secondary (i.e., AIDS, postoperative orthopedic surgery) manifestation of their impairment. Already, a potential therapeutic benefit from CrM administration has been demonstrated for patients with cardiomyopathy (11), mitochondrial cytopathy (32), gyrate atrophy of the choroid (34), and for those following knee surgery (29). Animal models suggest that CrM administration may be of benefit in Huntington’s chorea (22), cardiac ischemia (33), and under a period of increased oxidative stress (6,22). Acute administration appears to be safe in healthy young men and women with normal renal function. Future research should examine the potential side effects from long-term administration.

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