Creatine supplementation influences substrate utilization at rest

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Huso, M. Erik, Jeffrey S Hampl, Carol S. Johnston, and Pamela D. Swan. Creatine supplementation influences substrate utilization at rest. J Appl Physiol 93: 2018–2022, 2002. First published August 16, 2002; 10.1152/japplphysiol.01170.2001.—The influence of creatine supplementation on substrate utilization during rest was investigated using a double-blind crossover design. Ten active men participated in 12 wk of weight training and were given creatine and placebo (20 g/day for 4 days, then 2 g/day for 17 days) in two trials separated by a 4-wk washout. Body composition, substrate utilization, and strength were assessed after weeks 2, 5, 9, and 12. Maximal isometric contraction (1 repetition maximum [RM]) leg press increased significantly (P < 0.05) after both treatments, but 1-RM bench press was increased (33 ± 8 kg, P < 0.05) only after creatine. Total body mass increased (1.6 ± 0.5 kg, P < 0.05) after creatine but not after placebo. Significant (P < 0.05) increases in fat-free mass were found after creatine and placebo supplementation (1.9 ± 0.8 and 2.2 ± 0.7 kg, respectively). Fat mass did not change significantly with creatine but decreased after the placebo trial (−2.4 ± 0.8 kg, P < 0.05). Carbohydrate oxidation was increased by creatine (8.9 ± 4.0%, P < 0.05), whereas there was a trend for increased respiratory exchange ratio after creatine supplementation (0.03 ± 0.01, P = 0.07). Changes in substrate oxidation may influence the inhibition of fat mass loss associated with creatine after weight training.

A reported effect of creatine supplementation is weight gain (7, 10, 11, 21). Various mechanisms have been proposed, including intramuscular water retention (8, 22) and increased muscle growth (7, 11). Only one known study has assessed the effect of creatine supplementation on substrate utilization. Stroud et al. (20) examined the effect of creatine supplementation (20 g/day for 5 days) on respiratory gas exchange during exercise and 15 min of recovery. Subjects ran on a treadmill at 50–90% maximal O2 consumption for 6 min at each of five intervals while gas samples were collected during the final 30 s at each workload. The results indicated that creatine had no effect on respiratory gas exchange during exercise or recovery. The authors explained that the measurements could have been too insensitive to quantify the small changes in metabolic measures during exercise and recovery that could potentially occur with creatine supplementation. There may be other factors that confound the measurement of substrate utilization after acute exercise, such as lactate concentration, that may mask any change in substrate. Thus a more steady-state measurement, such as during rest, is needed.

The effect of creatine supplementation on substrate utilization at rest has not been sufficiently investigated. Because fat is the primary fuel oxidized during inactivity, measuring the respiratory exchange ratio (RER) at rest could indicate whether fatty acid oxidation is suppressed as a result of elevated levels of creatine phosphate in the system. A shift in substrate utilization toward lower fat oxidation could lead to a concomitant change in body composition with increased body fat stores. On the basis of anecdotal evidence of weight gain, including a lack of fat loss, in persons taking creatine, a four-person pilot study was carried out to determine whether creatine had any effect on substrate utilization. The results were encouraging, which led the authors to pursue the present study. Thus we hypothesized that creatine supplementation would result in a shift in substrate utilization at rest toward greater carbohydrate oxidation and less fat oxidation, indicated by a rise in the RER.

**METHODS**

Subjects. In a double-blind, placebo-controlled crossover design, 10 healthy, nonsmoking, recreationally active male subjects (Table 1) were recruited from a campus population (Fig. 1). All subjects were free from chronic diseases and were not regularly taking prescription medications. Moreover, all subjects participated in moderate physical activity at least three times per week, were not vegetarians, were not taking any ergogenic aids, and had never supplemented with creatine. The study was approved by the Human Subjects Institutional Review Board at Arizona State University, and all subjects gave their voluntary and informed consent before participation.

Diet. Subjects were instructed to maintain their normal diet throughout the study, except to limit consumption of caffeinated beverages to two or fewer servings per day. Ran-
dom 24-h recalls were conducted via telephone at baseline and once during each test period to ensure that dietary intake remained normal. Food records were reviewed by a registered dietitian and analyzed using the Genesis R & D software (version 6.01, 1997, Esha Research, Salem, OR).

Exercise. Before initiation of creatine supplementation, subjects participated in a familiarization session and 2 wk of weight training. Subjects were then tested twice to determine baseline 1 repetition maximum (RM) for bench press and leg press. All 1-RM tests were performed on the same equipment (CYBEX International, Medway, MA) and overseen by the same trained technician. Subjects followed an exercise program adapted from a protocol previously shown to increase strength and body mass in subjects supplementing with creatine and/or placebo (21) (Table 2).

Respiratory measures. On the evenings before all RER testing (end of weeks 2, 5, 9, and 12), subjects consumed the same self-selected meal to standardize the immediate effect of diet on respiratory exchange. Subjects were instructed to avoid all food and drink (excluding water) for 12 h until the morning RER measurement. No subjects exercised within 24 h of their RER test.

Subjects were tested between 5 and 9 AM, and each individual subject was tested at the same time of day for each trial. On arrival at the laboratory, subjects were positioned in a reclining chair and habituated to the open-circuit spirometry metabolic analysis apparatus for 20 min. A respiratory mask was placed over the subject’s face and carefully checked to prevent air leakage. Before subject testing, the pneumotachometer (Hans Rudolph, Kansas City, MO) interfaced with the metabolic gas exchange apparatus for 20 min. A respiratory mask was placed over the subject’s face and carefully checked to prevent air leakage. Before subject testing, the pneumotachometer was calibrated using a 3-liter syringe to deliver standard gases accurate to 0.01%. The pneumotachometer was calibrated using a 3-liter syringe to deliver standard gases accurate to 0.01%.

All exercises were performed in 3 sets of 8–10 repetitions, with 60–120 s of rest between sets. DB, dumbbell.

Urinary analysis. Twenty-four-hour urine samples were collected before each RER measurement. Urine was analyzed for urea nitrogen and creatinine by colorimetric spectrophotometry to measure any changes in total body protein mass, to determine creatine uptake on the basis of the assumption that urinary creatinine clearance increases proportionally to muscle creatine uptake (8), and to allow for the protein RER determination. The samples were collected, stored, and analyzed by standard laboratory kits (Sigma Chemical, St. Louis, MO).

Body composition. Baseline body weight and body density were determined using whole body plethysmography (Bod Pod, Life-Measurement Instruments, Concord, CA). The Bod Pod uses whole body densitometry to determine body fat percentage using the Siri equation (2). The Bod Pod has been shown to be a reliable and valid tool for measuring body composition (2, 3, 12, 13). Subjects were directed to wear a Lycra swim cap and tight-fitting Lycra/spandex shorts or swimming briefs for each trial. Measurements were taken according to standard manufacturer procedures (2, 12). Additionally, lung volume was measured using a mouthpiece and tube. The initial lung volume was used for each subsequent test. All tests were performed by the same technician immediately after the RER test.

Creatine supplementation. In a double-blind manner, subjects were randomly assigned creatine monohydrate powder

Exercise protocol

<table>
<thead>
<tr>
<th>Monday</th>
<th>Wednesday</th>
<th>Friday</th>
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<tbody>
<tr>
<td>Smith machine squats</td>
<td>Leg press</td>
<td>Hack squats</td>
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<tr>
<td>Leg curls</td>
<td>Lunges</td>
<td>Leg extensions</td>
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<td>Bench press</td>
<td>Heal raise</td>
<td>Bench press</td>
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<tr>
<td>Row (machine)</td>
<td>Behind neck press</td>
<td>Shoulder press</td>
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<tr>
<td>DB shoulder press</td>
<td>DB row</td>
<td>Seated cable row</td>
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<tr>
<td>Wide grip pulldown</td>
<td>Triceps extension</td>
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<tr>
<td>Abdominal crunch</td>
<td>Alternating DB curls</td>
<td>Body weight pull-ups</td>
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<tr>
<td></td>
<td>Abdominal crunch</td>
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Creatine supplementation. In a double-blind manner, subjects were randomly assigned creatine monohydrate powder

Fig. 1. Crossover design. Subjects were divided into 2 groups: group 1 (solid line) was supplemented with creatine during weeks 3–5 and, after the 4-wk washout, ingested placebo during weeks 10–12; group 2 (dashed line) ingested placebo during weeks 3–5 and, after the 4-wk washout, was supplemented with creatine during weeks 10–12. All data were then combined to create a creatine group and a placebo group.
(a gift from X-Rated, Hi-Health, Scottsdale, AZ; 20 g creatine/day for 4 days, then 2 g creatine/day for 17 days) or a placebo similar in appearance and taste (20 g maltodextrine for 4 days, then 2 g for 17 days). Subjects were instructed to mix the powder in juice or water. Also, subjects were required to participate in resistance training at least three times per week and to keep a workout log. Subjects were required to submit their workout logs, and compliance was determined by the trained technician.

At the end of 3 wk, subjects were tested for changes in 1-RM bench and leg press, body composition, and RER. After a 4-wk washout period (6, 8), where supplementation was terminated but exercise continued, subjects were reassigned creatine or placebo and were tested again for a baseline measurement. After 3 wk of creatine or placebo, subjects returned to the laboratory for testing (Fig. 1).

Statistics. Values are means ± SE. Data analyses were performed on the Statistical Package for the Social Sciences for Windows (version 10.0, 2000, SPSS, Chicago, IL). A general linear model repeated-measures analysis was used to compare differences between means over the course of the study. Order effects were determined by using a “dummy” variable and assessing a trial-by-time interaction in the model. Post hoc comparisons were done by least significant differences because of the small number of pairwise comparisons. P < 0.05 was considered significant.

RESULTS

No negative side effects were reported in subjects taking creatine. For all measures, order effects were examined but were never significant. Energy intakes remained consistent throughout the duration of the study. With 3 wk of creatine supplementation, body mass increased significantly from 73.6 to 75.2 kg, a 2.2% increase (P < 0.05). There was no significant change in body mass during placebo use (Table 3).

Body composition. Fat-free mass (FFM) increased after the weight-lifting program regardless of treatment (from 63.1 to 65.0 kg with creatine (P < 0.05) and from 63.2 to 65.4 kg with placebo (P < 0.01). No significant differences in fat mass (FM) or percent body fat were observed in the creatine group. However, percent body fat (from 15.6 to 12.4%, P < 0.01) and FM (from 12.0 to 9.6 kg, P < 0.05) decreased significantly during placebo use.

Strength. Subjects in the creatine group experienced significant increases in strength with bench press

<table>
<thead>
<tr>
<th>Creatine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>73.6 ± 2.3</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>14.0 ± 1.5</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>63.1 ± 1.1</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>10.7 ± 1.4</td>
</tr>
<tr>
<td>1-RM bench press, kg</td>
<td>87 ± 4</td>
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<tr>
<td>1-RM leg press, kg</td>
<td>280 ± 19</td>
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Values are mean ± SE (n = 10). RM, repetition maximum. *P < 0.05 vs. before creatine. †P < 0.05 vs. before placebo. §P < 0.01 vs. before creatine. $P < 0.01 vs. before placebo.

<table>
<thead>
<tr>
<th>Creatine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>RER</td>
<td>0.78 ± 0.01</td>
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<tr>
<td>RMR, kcal</td>
<td>1,890 ± 73</td>
</tr>
<tr>
<td>Fat, %</td>
<td>63.2 ± 4.5</td>
</tr>
<tr>
<td>Carbohydrate, %</td>
<td>21.6 ± 3.9</td>
</tr>
<tr>
<td>Protein, %</td>
<td>15.2 ± 2.3</td>
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</tbody>
</table>

Values are means ± SE (n = 10). RER, respiratory exchange ratio, (protein-adjusted); RMR, resting metabolic rate. Fat, carbohydrate, and protein values represent percent participation of substrate in total energy utilization. *P = 0.07 vs. before creatine. †P < 0.05 vs. before creatine.

Table 4. Changes in substrate utilization at rest

Respiratory measures. There were no significant changes in RER for creatine or placebo (Table 4). The RER of the creatine group approached significance (P = 0.07) as RER increased from 0.78 ± 0.01 to 0.81 ± 0.02. Carbohydrate utilization, as a percentage of total energy utilization, increased significantly in the creatine group (from 21.6 to 30.5%, P < 0.05). Changes in RMR were not statistically significant.

Urinary analysis. After 3 wk of creatine supplementation, there was a significant increase in creatinine clearance (from 1.3 to 1.8 g/day, P < 0.05) but no significant change during placebo use (Table 5). There were no significant differences in urea nitrogen measures.

DISCUSSION

Previous research has indicated that subjects taking creatine supplements experienced a significant increase in weight gain (4, 11, 21). Researchers have looked to identify the source of weight gain to determine whether it is due to an increase in FFM or merely a significant increase in body mass. A significant increase in body mass was observed in the creatine group (from 63.2 to 65.4 kg, P < 0.01). Changes in RMR were not statistically significant.

Table 5. Results of urinary analysis

Previous research has indicated that subjects taking creatine supplements experienced a significant increase in weight gain (4, 11, 21). Researchers have looked to identify the source of weight gain to determine whether it is due to an increase in FFM or merely a significant increase in body mass. A significant increase in body mass was observed in the creatine group (from 63.2 to 65.4 kg, P < 0.01). Changes in RMR were not statistically significant.

Values are means ± SE in g/day. Normal values are 1.1–2.8 g/day for creatine and 9.3–16.2 g/day for urea nitrogen. *P < 0.05 vs. before creatine.
that creatine supplementation increases body mass with resistance training and indicates that creatine supplementation does not enhance percent body fat loss in recreationally active men (4, 11, 15, 21). The placebo group experienced the expected response to resistance training (16), i.e., they became leaner, whereas the creatine group experienced an inhibition of this expected fat loss.

Fracaux and Poortmans (7) proposed that increased myosin synthesis could be the mechanism behind the ergogenic effect of creatine on exercise. However, our data show that the increase in FFM was greater in subjects taking creatine or placebo. In addition, those supplementing with creatine experienced significantly greater gains in 1-RM bench press and leg press. Therefore, although it was not measured directly, we deduce that the ergogenic effect of creatine on exercise performance must be from a mechanism other than increased myosin synthesis.

Consistent with these body composition data, we also found a trend for change in RER ($P = 0.07$) that supports the difference in FM between the creatine and placebo groups. (Post hoc power analysis indicated that a sample of 12 would have been needed for statistical significance.) Although there was no significant change in RER among creatine subjects approached statistical significance, indicating that subjects utilized a greater percentage of carbohydrate than fat during creatine supplementation. The difference in carbohydrate oxidation before vs. after creatine was significant ($P = 0.05$; Fig. 2). This finding is notable, inasmuch as it is the first time that the effect of creatine on resting RER has been examined.

At the onset of exercise, with resistance training, and during transitions from lower to higher intensity exercise when energy demand is greater than energy production from aerobic sources, creatine phosphate is a readily available short-term fuel to produce ATP. The products of creatine phosphate hydrolysis include free creatine and PCr. PCr is a key activator of the phosphofructokinase enzyme, promoting glucose oxidation (1). The increased flux of glucose oxidation results in increased levels of malonyl-CoA (23).

Malonyl-CoA is a known regulator of fatty acid oxidation (9, 19, 23). As the first committed intermediate of fatty acid synthesis, malonyl-CoA is a powerful inhibitor of the carnitine palmitoyltransferase (CPT I) enzyme system responsible for shuttling fatty acids into the mitochondria for oxidation (17, 23). When glucose levels decline, malonyl-CoA also declines, allowing for increased fatty acid oxidation. Concentrations of malonyl-CoA drop during exercise and in the fasted state, relieving the inhibition of CPT I. This decrease in CPT I allows for an increased rate of fatty acid oxidation as fats become available (23). The depletion of ATP stores and subsequent increase in P$_i$ during activity result in an activation of the enzyme phosphofructokinase, causing an influx of carbohydrate to be oxidized. The infusion of glucose into exercising rats has been shown to terminate the decline in malonyl-CoA (5). Therefore, a promotion of glucose oxidation from elevated levels of P$_i$ could in theory suppress fatty acid oxidation. However, research has shown that P$_i$ levels return to normal in the rested state after creatine loading (18).

A more likely rationale would be the improved insulin sensitivity and antihyperglycemic activity that creatine analogs have been shown to possess (14). Although the mechanism is unknown, 3-guanidinopropionic acid administered to KKAy mice (a non-insulin-dependent diabetes mellitus model) resulted in augmented glucose uptake by the muscle tissue (14). As a guanidino analog to 3-guanidinopropionic acid, elevated levels of creatine could potentially exert a similar glycemic response, resulting in increased carbohydrate utilization by muscle tissue at rest.

In conclusion, subjects supplementing with creatine experienced greater gains in 1-RM bench press, 1-RM leg press, and weight gain than those using placebo. We found that the increase in FFM was nearly identical in subjects taking creatine or placebo. However, the results demonstrate that individuals taking creatine may reduce their ability to lose FM in response to exercise training. The results suggest that creatine loading may inhibit the normal fat loss that occurs in healthy active men implementing a strength-training program. Moreover, for the first time, it was shown that creatine supplementation led to a trend for increased RER at rest, a potential mechanism for the impaired fat loss. These conclusions affirm our hypothesis that creatine supplementation would result in a shift in substrate utilization at rest toward greater carbohydrate oxidation and less fat oxidation, indicated by a rise in the RER. Although there are ergogenic benefits from creatine supplementation, athletes participating in wrestling, swimming, gymnastics, and other weight-sensitive sports should first consider the potentially negative side effect of fat retention before choosing creatine supplementation.

![Graph](image.png)

**Fig. 2.** Percent participation of a substrate in total energy utilization. *P < 0.05, pre-creatine vs. post-creatine carbohydrate.
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REFERENCES