

Does dietary creatine supplementation play a role in skeletal muscle metabolism and performance?¹⁻⁴

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ABSTRACT Fatigue sustained during short-term, high-intensity exercise in humans is associated with the inability of skeletal muscle to maintain a high rate of anaerobic ATP production from phosphocreatine hydrolysis. Ingestion of creatine monohydrate at a rate of 20 g/d for 5–6 d was shown to increase the total creatine concentration of human skeletal muscle by ≈ 25 mmol/kg dry mass, some 30% of this in phosphorylated form as phosphocreatine. A positive relation was then shown between muscle creatine uptake and improvements in performance during repeated bouts of maximal exercise. However, there is no evidence that increasing intake >20 – 30 g/d for 5–6 d has any potentiating effect on creatine uptake or performance. In individuals in whom the initial total creatine concentration already approached 150 mmol/kg dry mass, neither creatine uptake nor an effect on phosphocreatine resynthesis or performance was found after supplementation. Loss of ATP during heavy anaerobic exercise was found to decline after creatine ingestion, despite an increase in work production. These results suggest that improvements in performance are due to parallel improvements in ATP resynthesis during exercise as a consequence of increased phosphocreatine availability. Creatine uptake is augmented by combining creatine supplementation with exercise and with carbohydrate ingestion. *Am J Clin Nutr* 2000;72(suppl):607S–17S.

KEY WORDS Creatine uptake, phosphocreatine, ATP resynthesis, exercise performance, human skeletal muscle

INTRODUCTION

The popular media have paid great attention to the use of creatine supplementation by athletes, a strategy used widely to enhance performance. The weight of scientific evidence, together with anecdotal reports from athletes, points to an important role for creatine supplementation; in this article we describe the scientific foundation of such supplementation.

In broad terms, exercise can be characterized as “short-term, high-intensity” and “prolonged, submaximal.” For many years, athletes undertaking prolonged exercise have been aware of the benefits of carbohydrate loading, but until recently there has been little in the way of dietary supplementation that has been shown scientifically to aid high-intensity exercise performance.

THE ROLE OF CREATINE IN HUMAN MUSCLE METABOLISM

Creatine, or methylguanidine-acetic acid, is a naturally occurring compound synthesized from arginine, glycine, and methionine (1). It is found in meat and fish and is endogenously synthesized by humans in the liver and pancreas, both of which are capable of de novo creatine synthesis (2). In an average 70-kg adult, the total creatine pool in the body amounts to ≈ 120 g; this pool is subject to continuous degradation to creatinine, which is excreted in the urine at a rate of ≈ 2 g/d. Replenishment of creatine at a similar rate is achieved by a combination of dietary intake and endogenous synthesis (2). Most of the total creatine pool is contained in skeletal muscle (3), $\approx 65\%$ in a phosphorylated form as phosphocreatine (4).

Phosphocreatine assumes a pivotal role in the energetics of muscle contraction during high-intensity (maximal) exercise. Muscle contraction and relaxation are fueled exclusively by free energy liberated from the dephosphorylation of ATP, and thus muscle function depends critically on ATP availability. The ATP concentration of skeletal muscle amounts to ≈ 24 mmol/kg dry mass (5), but ATP use during maximal, short-term, voluntary exercise (6, 7) is such that the store of skeletal muscle ATP would be exhausted within 1–2 s of the onset of contraction without a means of resynthesizing ATP at an equally rapid rate. During such exercise, resynthesis of ATP is achieved predominantly by the anaerobic degradation of phosphocreatine and glycogen (8) resulting in a cumulative rate of ATP production approaching $15 \text{ mmol} \cdot \text{kg dry mass}^{-1} \cdot \text{s}^{-1}$ during the first 6 s of maximal exercise (6). In this manner the concentration of skeletal muscle ATP can be maintained to some degree during both a single bout (9, 10) and repeated bouts (6, 11) of short-term maximal exercise.

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High ATP turnover rates are not sustained indefinitely, however, and total anaerobic ATP production from phosphocreatine and glycogen begins to fall within a few seconds (12), continuing to decline over the course of 30 s of exercise by up to 80% (8). An ability to arrest this fall in ATP turnover rate is necessitated by its apparent association with a decline in performance (13), which the subject is unable to arrest voluntarily (14).

Together, these findings raise the question of just how important is the availability of phosphocreatine and glycogen to ATP resynthesis, and thus to performance, during high-intensity exercise. It is well documented that in mixed muscle the glycogen concentration is still relatively high at the end of this type of exercise (11), and supplementation with oral carbohydrate does not serve to improve maximal exercise performance (15). In fact, sufficient glycogen seems to be available to support repeated bouts of high-intensity exercise, and the ability to use the glycogen present appears to decrease as exercise progresses. A decreased contribution by glycogenolysis to anaerobic ATP production has been observed during successive bouts of maximal, dynamic exercise (11, 16) and may be mediated by a glucose-6-phosphate (17) or hydrogen ion (18) inhibition of phosphorylase, together with the more energetically efficient use of glycogen by oxidative combustion of glucose (19).

Phosphocreatine availability

In relation to sport, the issue of phosphocreatine availability can be considered for a single bout of exercise, for the recovery phase, and for repeated bouts of exercise. The rate of phosphocreatine utilization is extremely rapid during the initial seconds of high-intensity exercise, when the primary function of phosphocreatine is thought to be serving as a buffer to the delay in energy provision from glycogenolysis (12). Even so, a substantial portion of the resting phosphocreatine concentration has consistently been found at the termination of a single bout of maximal, dynamic exercise (7, 20). These findings, however, are likely to provide an underestimation of phosphocreatine use because some resynthesis will have occurred in the interval between the cessation of exercise and biopsy sampling. Thus, Bogdanis et al (7), who modeled phosphocreatine resynthesis to predict postexercise values after zero recovery, found that the phosphocreatine concentration was almost totally depleted after this type of exercise. Furthermore, the postexercise phosphocreatine concentration measured in biopsy samples obtained after intense, electrically evoked contraction from a limb with occluded circulation was only 7% of the precontraction value (21, 22).

In 1986 Katz et al (23) showed that fatigue during short-term, exhaustive exercise was related more closely to a low phosphocreatine concentration than to a high lactate concentration, which suggests that substrate availability, rather than product inhibition, might be an important determinant of fatigue during this type of exercise. More recently, it was shown that depletion of phosphocreatine coincides with a fairly precipitous decline in the production of isometric force during a single bout of intermittent electrical stimulation with occluded circulation (8). Accordingly, the decline in ATP production during exercise has been attributed by numerous authors to a reduced capacity to resynthesize ATP, due in turn to a decrease in phosphocreatine availability (24).

The restoration of peak isometric force (25), peak power, and average power output (7) during a second bout of exercise has been shown to depend on the extent of phosphocreatine resyn-

thesis during the intervening recovery period. In these 2 studies, performance recovered despite a prevailing low muscle pH. A study from our laboratory confirmed these findings (4). In that study, 9 subjects performed 2 bouts of 30-s, maximal, isokinetic cycling exercise, separated by a 4-min recovery period. Phosphocreatine resynthesis during the recovery period was positively correlated with the restoration of total work production during bout 2 ($r = 0.80$, $P < 0.05$). As in previous studies, no correlation was found between the decline in work production during each bout of exercise and the muscle lactate concentration.

Studies involving repeated bouts of maximal exercise have also illustrated the importance of phosphocreatine availability. Gai-tanos et al (6), who conducted a study involving 10 bouts of maximal exercise (6 s each), showed that although the phosphocreatine concentration fell by almost 85% over the course of exercise, dephosphorylation of phosphocreatine was responsible for 80% of anaerobic ATP production by the end of exercise, even though anaerobic ATP production had itself declined by two-thirds.

Skeletal muscle fiber metabolism

Human skeletal muscle is composed of several fiber types that differ substantially in functional and metabolic characteristics. These range from type I, slow-twitch fibers, to type IIx, fast-twitch fibers. Type I fibers are suited to aerobic energy production and are characterized by a high mitochondrial density, high oxidative enzyme activity profile, high cytochrome *c* concentration, a rich capillary supply, high myoglobin concentration, and low myosin ATPase activity. Type IIx fibers are suited to anaerobic energy production and are characterized by a low mitochondrial density, high glycolytic enzyme activity profile, high creatine phosphokinase activity, a poor capillary supply, low myoglobin concentration, and high myosin ATPase activity (26–29).

The metabolic responses of human type I and II muscle fibers were investigated during single bouts of maximal, electrically evoked isometric contraction (24), voluntary isokinetic contraction (30), and treadmill running (31), all of which showed that phosphocreatine utilization during exercise was greater (10–33%) in type II than in type I fibers. Indeed, the study by Soderlund et al (24), to our knowledge the only one to investigate phosphocreatine utilization in type I and II fibers during contraction in human skeletal muscle, showed that the decline in the rate of phosphocreatine utilization during the second half of 20 s of contraction was up to 4 times greater in type II than in type I fibers. The authors concluded that although it was not possible to relate the observed decline in the rate of type II fiber phosphocreatine utilization directly to the loss of muscle force, the decline in force production during contraction may have been a consequence of the rapid loss of phosphocreatine stores in this fiber type.

A factor that might compound a prohibitively high rate of phosphocreatine utilization is that the phosphocreatine concentration of type II fibers is not restored in the first few minutes after exercise to the same extent as it is in type I fibers. In the previously referenced study from our laboratory that involved 2 bouts of 30 s of maximal exercise separated by a 4-min recovery (4), it was found that because of the greater utilization of phosphocreatine during exercise, restoration of phosphocreatine during the recovery phase was >25% lower in type II than in type I fibers. As a consequence, phosphocreatine availability at the beginning of the second bout was greatly reduced in type II fibers. Rates of phosphocreatine utilization during each of the 2 bouts of exercise are given in **Table 1**.

TABLE 1

ATP and phosphocreatine (PCr) utilization in human type I and type II skeletal muscle fibers during 2 bouts of 30-s maximal isokinetic cycling exercise¹

	Bout 1		Bout 2	
	Type I	Type II	Type I	Type II
	<i>mmol/kg dry mass</i>			
Δ ATP	2.74 \pm 0.82	12.67 \pm 2.56 ²	3.29 \pm 1.26	4.42 \pm 1.13 ³
Δ PCr	49.23 \pm 4.07	66.26 \pm 5.12 ⁴	42.66 \pm 4.63	44.70 \pm 4.21 ³

¹ $\bar{x} \pm \text{SEM}$; $n = 9$. Each bout of exercise was conducted at 80 rev/min and separated by 4 min of passive recovery.

^{2,4}Significantly different from type I: ² $P < 0.01$, ⁴ $P < 0.05$.

³Significantly different from bout 1, $P < 0.01$.

Clearly, the reduced availability of phosphocreatine in type II fibers translated into a marked fall in phosphocreatine utilization in this fiber type during the second bout of exercise. This fall in phosphocreatine utilization of $\approx 33\%$ may explain the reduction in work capacity of $\approx 40\%$ observed during the second bout of exercise. In contrast, phosphocreatine utilization in type I fibers, in which restoration of phosphocreatine was almost complete, did not fall during the second bout of exercise.

These points are of interest because type II fibers have been heavily implicated in the development of force during maximal exercise, and these data may help explain the reduction in power output habitually seen during repeated bouts of high-intensity exercise. Together, these findings suggest that availability of phosphocreatine is crucial to ATP resynthesis and high-intensity exercise performance.

CREATINE SUPPLEMENTATION

Functional and metabolic effects

Harris et al (32) were the first to show that mixed muscle phosphocreatine availability could be increased as part of an overall increase in the total creatine (free creatine + phosphocreatine) concentration after ingestion of creatine monohydrate by humans. These authors showed that 5 g creatine taken 4–6 times/d for several consecutive days increased the total creatine concentration of human skeletal muscle by an average of 25 mmol/kg dry mass, some 30% of which occurred in phosphorylated form as phosphocreatine. Thus, the authors suggested that creatine supplementation might improve exercise performance in humans.

The first published investigation into the effect of oral creatine supplementation on exercise performance in humans was conducted by our laboratory in the early 1990s (33). Ingestion of creatine at a rate of 20 g/d for 5 d was found to improve performance during repeated bouts of maximal, isokinetic knee-extensor exercise, decreasing fatigue by up to 6%. No change in performance was found in a placebo group. Several studies have since confirmed these results with experimental models involving cycling, running, and swimming (34–37). An additional finding in the original study was a reduction in plasma ammonia accumulation (33), which was also confirmed in a series of subsequent investigations in which improved exercise performance after creatine ingestion was accompanied by a reduction in both ammonia and hypoxanthine accumulation during exercise (34, 36). As a consequence of these findings, the ergogenic effect of

creatine ingestion was attributed to improvements in the ability of muscle to sustain ATP resynthesis during exercise, because both ammonia and hypoxanthine are accepted markers of muscle adenine nucleotide loss during maximal exercise (38).

In a subsequent, more invasive study, subjects performed 2 bouts of maximal, isokinetic cycling exercise before and after creatine ingestion at identical rates of 20 g/d for 5 d (39). Each exercise bout lasted 30 s, and the recovery period between bouts was 4 min; muscle biopsies were obtained from the vastus lateralis before and after each bout. Ingestion of creatine resulted in an increase in muscle total creatine concentration of 23 mmol/kg dry mass, of which approximately one-third was phosphocreatine and the remainder free creatine (Figure 1). These data illustrate the large variation between individuals that is found in creatine uptake after creatine supplementation, in this case from 6–38 mmol/kg dry mass.

Previously published results (32) indicate that the total creatine concentration in muscle before supplementation is an important determinant of creatine uptake but not the sole determinant (Figure 1). Subjects 2 and 3, for example, had the same initial total creatine concentration, but subject 2 had 6 times the increase in muscle total creatine concentration experienced by subject 3. Because animal studies have shown both dietary and hormonal effects on creatine biosynthesis and muscle creatine uptake and retention (2), future work aimed at maximizing muscle creatine uptake during oral supplementation might focus on the factors regulating uptake in humans.

In the study illustrated in Figure 1 (and Figures 2 and 3) (39), total work production increased during both bouts of exercise after creatine supplementation. Most subjects also showed an increase in maximum work production (Figure 2). The mean increase in performance, including both maximum and total work production during exercise bouts 1 and 2, amounted to $\approx 4\%$ in each case.

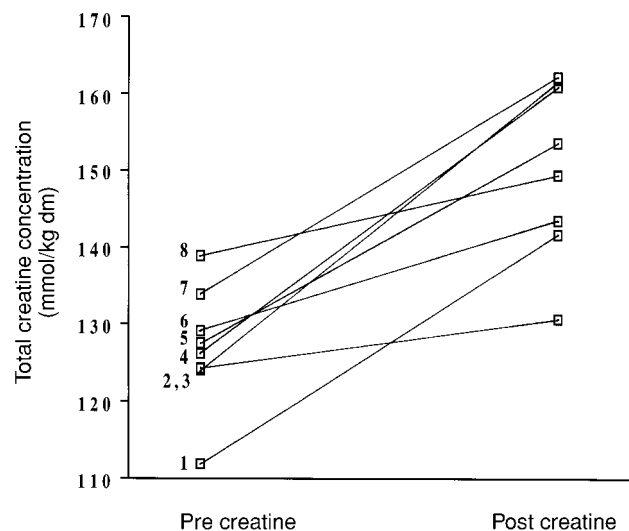


FIGURE 1. Mixed muscle total creatine concentration in individual subjects before and after supplementation with 4×5 g creatine/d for 5 d. Subjects were numbered 1 through 8 according to their initial muscle total creatine concentration. dm, dry mass. Reproduced with permission from Casey et al (39).

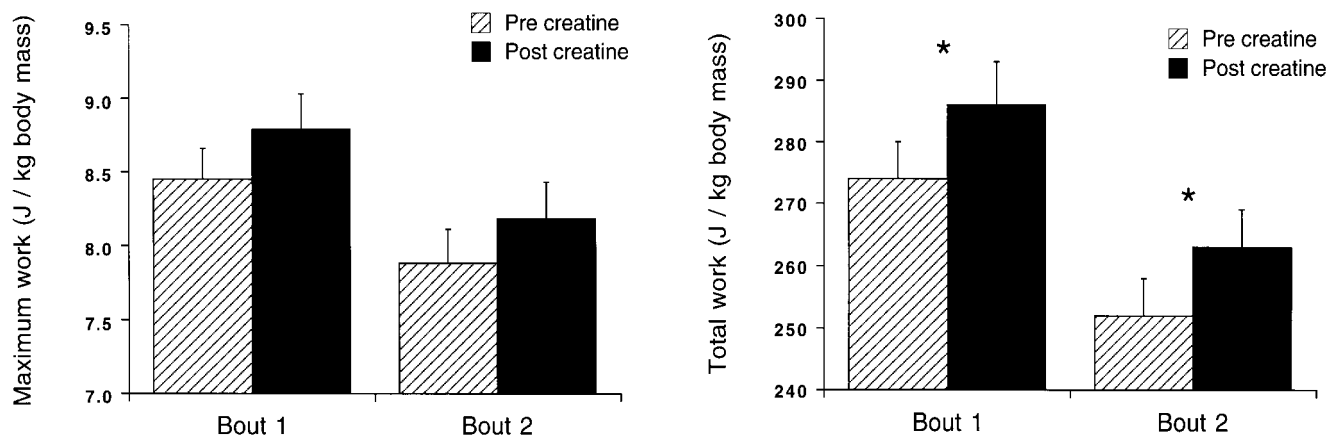


FIGURE 2. Mean (\pm SEM) maximum and total work production during 2 bouts of 30-s maximal, isokinetic cycling exercise. Values are given before and after supplementation with 4×5 g creatine/d for 5 d. *Significant difference before and after creatine supplementation, $P < 0.05$. Reproduced with permission from Casey et al (39).

Changes in both maximum work production ($r = 0.71$, $P < 0.05$) and total work production ($r = 0.71$, $P < 0.05$) were related to muscle creatine uptake (Figure 3). In addition, the increase in phosphocreatine concentration before exercise bouts 1 and 2 in type II fibers, which approached 40 mmol/kg dry mass in one person, was positively correlated with both an increase in phosphocreatine utilization during exercise in this fiber type ($r = 0.78$, $P < 0.01$) and the increase in total work production ($r = 0.66$, $P < 0.05$). No corresponding correlations in type I fibers were found between the change in phosphocreatine concentration before exercise bouts 1 and 2, after creatine ingestion, and the changes in phosphocreatine utilization during exercise ($r = 0.22$) or total work production ($r = 0.32$).

An additional finding of interest was a 30% reduction in cumulative ATP loss during exercise after creatine supplementation.

This finding extends work discussed earlier in this article in which a reduction in ammonia and hypoxanthine accumulation was found. Considered alongside the increase in total work production, this combination of evidence strongly suggests that ADP rephosphorylation to ATP during exercise was improved as a consequence of creatine ingestion.

These data clearly show that the greater the creatine uptake, the greater the improvement in performance. Perhaps not surprisingly, the relation between the increase in phosphocreatine and the subsequent improvement in performance (registered principally as a reduction in fatigue) appears to be confined largely to type II fibers (39). These are the fast-contracting, fast-fatiguing muscle fibers deployed during high-intensity exercise and responsible for both the high power output generated during

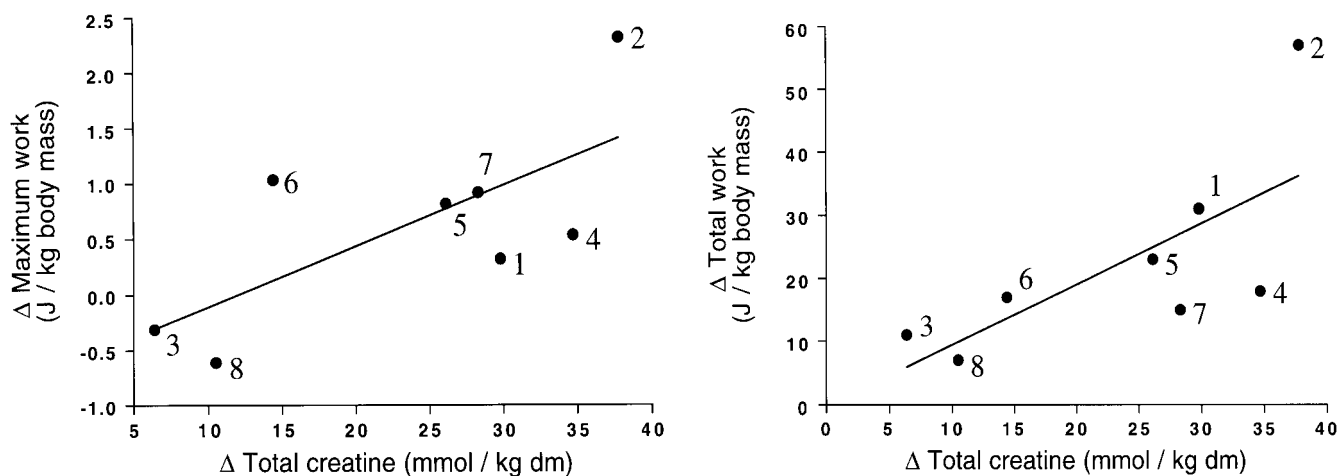


FIGURE 3. The relation between individual changes in mixed muscle total creatine concentration and changes in maximum ($r = 0.71$, $P < 0.05$) and total ($r = 0.71$, $P < 0.05$) work production after supplementation with 4×5 g creatine/d for 5 d. Work production was measured during 2 bouts of 30-s maximal, isokinetic cycling exercise. Numbers 1 through 8 refer to the same subjects depicted in Figure 1. dm, dry mass. Reproduced with permission from Casey et al (39).

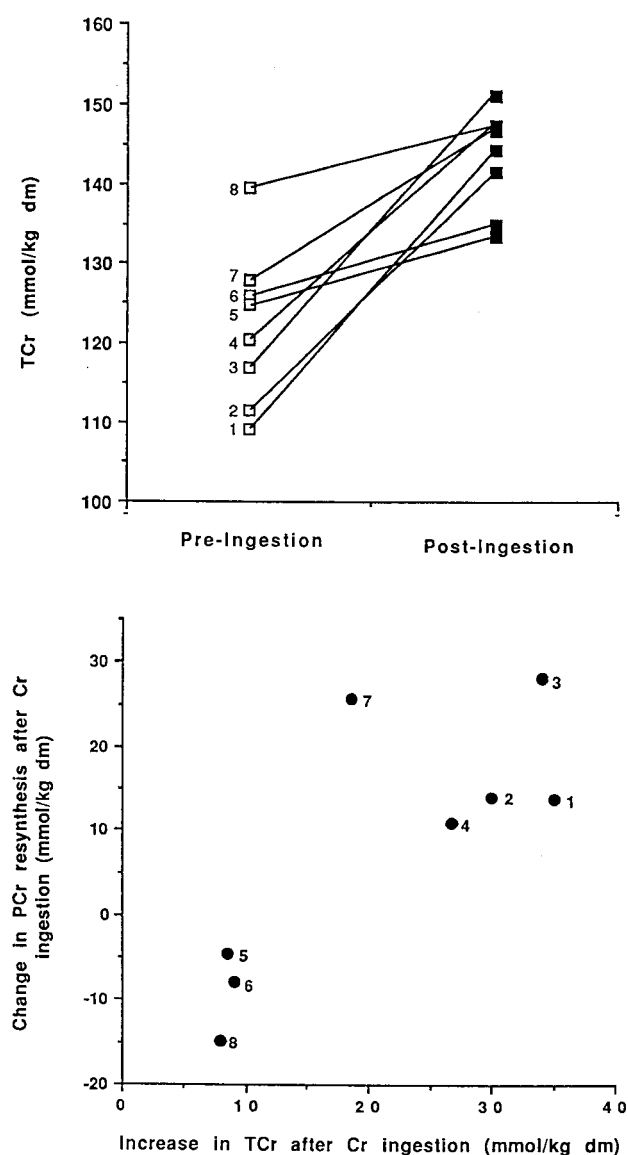


FIGURE 4. Mixed muscle total creatine concentration (TCr) in individual subjects before and after supplementation with 4×5 g creatine/d for 5 d and individual changes in TCr and in phosphocreatine (PCr) resynthesis after creatine (Cr) supplementation. Phosphocreatine resynthesis was measured during the recovery period after intense, electrically evoked isometric contraction. Subjects were numbered 1 through 8 according to their initial muscle total creatine concentration. Reproduced with permission from Greenhaff et al (41).

such exercise and the high rate of fatigue (40). Furthermore, these results suggest that improvements in performance are due to parallel improvements in ATP resynthesis during exercise as a consequence of increased phosphocreatine availability in type II fibers. To summarize, by reducing the extent of fatigue in type II fibers, creatine supplementation preserves the ability of the muscle to perform exercise requiring speed and power.

An increase in phosphocreatine availability will increase the amount of substrate available to fuel ATP resynthesis (39) and may be manifested as an increase in the resting phosphocreatine

concentration, as shown previously (39), or as an increase in phosphocreatine resynthesis during exercise. Indeed, a further demonstrable effect of creatine supplementation is the potentiation of phosphocreatine resynthesis during the recovery phase after high-intensity exercise (41). This effect is illustrated in **Figure 4**, which shows the increase in total creatine concentration after creatine supplementation at a rate of 20 g/d for 5 d and the relation between the change in total creatine concentration and the change in phosphocreatine resynthesis after intense electrically evoked isometric contraction. As was the case in the study described earlier (39), creatine uptake after creatine supplementation varied greatly.

Several points are of interest here: First, creatine supplementation appears to hasten phosphocreatine resynthesis during recovery; second, the greater the increase in total creatine concentration, the greater the potentiating effect on phosphocreatine resynthesis; and third, a measurable effect was only observed in those subjects who exhibited close to or more than a 20-mmol/kg dry mass increase in total creatine concentration. Similarly, as discussed previously, Casey et al (39) observed that the greater the uptake of creatine by the muscle, the greater the beneficial effect on muscle metabolism and performance. In addition, the magnitude of creatine uptake required to produce these beneficial effects was of the same order as that shown to facilitate phosphocreatine resynthesis (41).

Both the increase in resting phosphocreatine concentration and the increase in phosphocreatine resynthesis will occur because of an increase in mitochondrial ATP production. Oxidative ATP production is thought to be regulated by the availability of mitochondrial ADP, and it was hypothesized that mitochondrial ADP formation and ATP resynthesis are linked to the phosphorylation of free creatine at the mitochondrial membrane (42, 43). It is possible that the rate of phosphocreatine resynthesis from mitochondrial ATP, particularly during the recovery period after exercise, accelerates after creatine ingestion because of the potentiating effect of an increased free creatine concentration in muscle on the rate of flux through the creatine kinase reaction at the mitochondrial membrane. This hypothesis is supported by studies showing that the increase in muscle total creatine concentration after creatine ingestion is principally in the form of free creatine (32, 41). In vitro studies have shown that creatine can be used to increase the rate of respiration in skeletal muscle mitochondria (44) and skinned cardiac muscle fibers (45), and the role of creatine as an acceptor of mitochondrial ATP was discussed in a series of papers (43, 44, 46).

Changes in the free creatine concentration of different human muscle fiber types have not been investigated to date. However, given that the total creatine concentration of rat skeletal fast-twitch muscle is 45% greater than that of rat slow-twitch muscle (47) and that the increase in phosphocreatine concentration after creatine supplementation is greater in type II fibers (39), it seems likely that free creatine concentration is greater in this type. Thus, creatine supplementation may improve exercise performance by increasing mitochondrial ATP production in type II fibers.

An increase in body mass is commonly associated with creatine ingestion, and there has been great speculation as to the cause of this effect. Water retention is one explanation; in one study, subjects undertook 11 24-h urine collections: 2 before ingesting 20 g creatine/d for 5 d, 2 during the ingestion period, and 7 >20 d after inges-

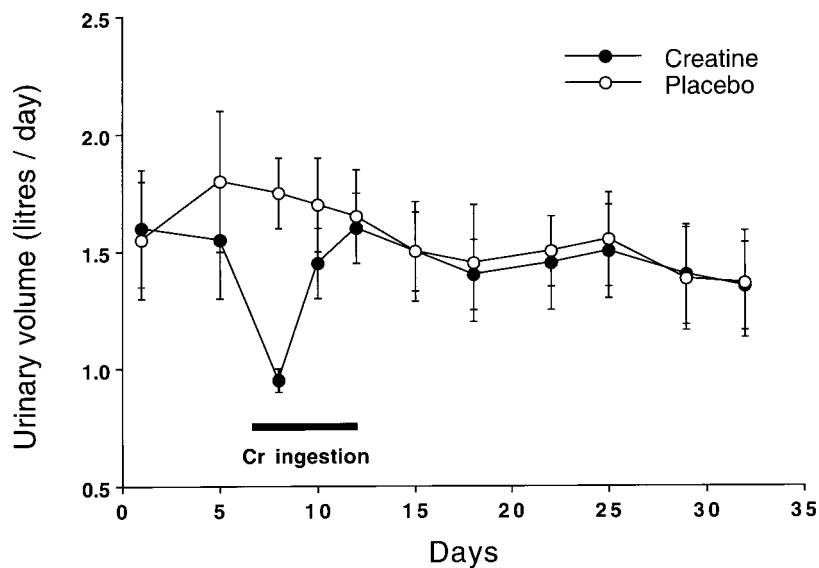


FIGURE 5. Mean (\pm SEM) urinary volume before and after either placebo or creatine (Cr) ingestion. Creatine was administered as 4×5 g/d for 5 d. Reproduced with permission from Hultman et al (48).

tion (48). Urinary volume (**Figure 5**) varied a great deal between subjects, but creatine ingestion was accompanied by a marked reduction in urinary volume during the initial days of supplementation. Of interest, this reduction in urinary volume was of the same magnitude as the increase in body mass observed during this type of supplementation protocol and suggests that water retention indeed explains the increase in body mass. In addition, the increase is approximately the same as that observed after carbohydrate loading; any deleterious effects associated with an increase in body mass, for example in weight-bearing events, are offset by the increase in exercise capacity. There have been anecdotal reports of muscle cramping during periods of creatine loading, but to date there has been no systematic investigation of this phenomenon, and no studies have reported cramping as a side effect of creatine supplementation.

Daily urinary creatinine excretion before, during, and after placebo and creatine ingestion at a rate of 20 g/d for 5 d is shown in **Figure 6** (48). Again, a large amount of variation was seen between subjects, but creatinine excretion was ≈ 2.8 mmol/d higher after creatine ingestion than after placebo ingestion. In this study, the increase in creatinine excretion closely matched the loss of creatine from the muscle. This finding confirms the widely held belief that the rate of creatinine formation is directly proportional to the muscle creatine concentration and also indicates that because the muscle creatine concentration returned to the presupplementation amount, endogenous production of creatine is not inhibited indefinitely after creatine supplementation.

Several studies reported no effect of creatine supplementation on exercise performance. For example, Cooke et al (49) found no

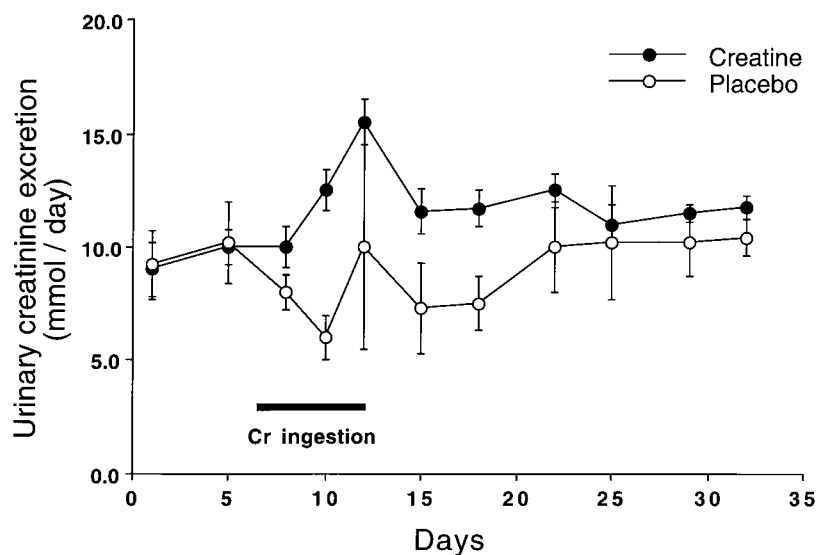


FIGURE 6. Mean (\pm SEM) urinary creatinine excretion before and after either placebo or creatine (Cr) ingestion. Creatine was administered as 4×5 g/d for 5 d. Reproduced with permission from Hultman et al (48).

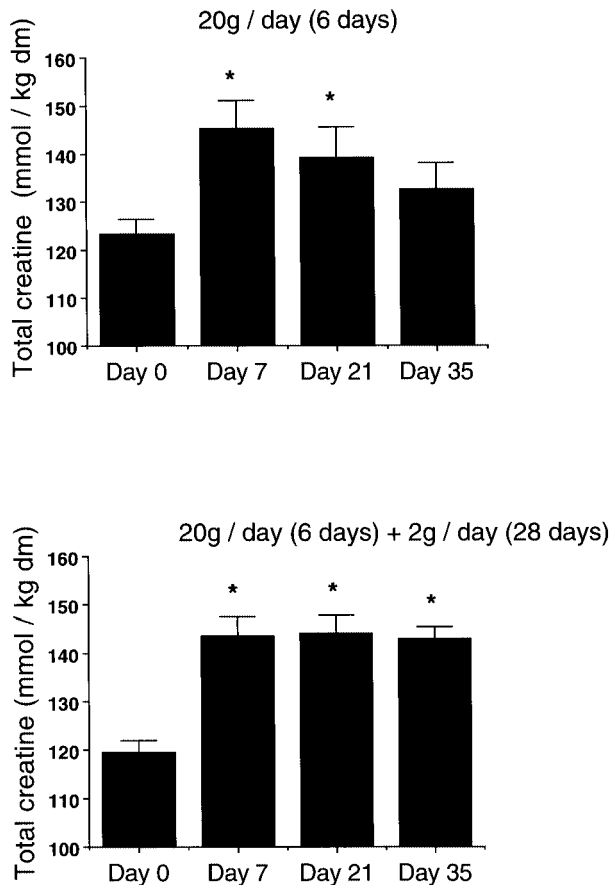


FIGURE 7. Mean (\pm SEM) mixed muscle total creatine concentration before (day 0) and after (days 7, 21, and 35) supplementation with either 4×5 g creatine/d for 6 d or 4×5 g creatine/d for 6 d, followed by 2 g/d for the next 28 d. dm, dry mass. *Significantly different from day 0, $P < 0.05$. Reproduced with permission from Hultman et al (48).

effect on power output during 2 bouts of 15-s maximal exercise separated by a recovery period of 20 min, but this finding may reflect the experimental design. An ergogenic effect of creatine has been attributed to both a reduction in force loss (33, 39) and an increase in the rate of postexercise phosphocreatine resynthesis during the second minute of recovery (41), but a reduction in force loss is seen only after several bouts of exercise of <30 s duration (34). Furthermore, because phosphocreatine resynthesis has a half time of 30–60 s after maximal exercise without creatine ingestion (7), the recovery interval in the study by Cooke et al would appear to be too long for measurable effects of creatine supplementation to be seen. In addition, Cooke et al did not measure changes in intramuscular creatine concentration, which raises the possibility that total creatine may not have increased by the amount needed to elicit changes in performance. This was the case in a recent study (50) that showed no effect of creatine supplementation on performance during a single 20-s bout of maximal exercise. Total creatine concentration was found to increase by a mere 9%, rather than the customary mean value of 18–25% found in studies showing positive effects of creatine supplementation (39, 41). Mean increases in total creatine concentration of 15% were found in a similar cohort of untrained volunteers (51); this value still remains in the low range of previously reported mean values obtained after

similar supplementation protocols (32, 39, 41).

Mujika et al (52) found no effect of creatine supplementation on performances during single bouts of maximal exercise lasting 15, 30, and 60 s in elite swimmers, but interpreting these results is difficult because there were no measurements of intramuscular creatine uptake. Similarly, Odland et al (53) found no effect of creatine supplementation (compared with placebo) on performance during a single bout of 30-s maximal exercise. This result may be related to a shorter than customary supplementation period (3 d), and in fact no changes in phosphocreatine concentration were found despite a small increase in total creatine concentration.

In another study, no changes in muscle creatine concentration or performance were found after a small dose of creatine (2 g/d) ingested over some weeks (54). This is perhaps not surprising, because the dose did not exceed the reported rate of creatine degradation to creatine (2). This study used a predominantly aerobic exercise task of 10–15 min duration, confirming the absence of an effect of creatine supplementation on performance and metabolism when a significant proportion of the energy cost of contraction is derived from aerobic metabolism (51, 55, 56).

Supplementation strategies

Total creatine concentrations in human skeletal muscle before and after creatine supplementation are shown in **Figure 7** (48). The data show that ≈ 1 mo after supplementation with 20 g/d for 6 d, the total creatine concentration is not significantly different from the presupplementation value. It is also evident from this study that consumption of a small maintenance dose of 2 g/d after the initial loading phase will maintain a high total creatine concentration in the muscle for a period of ≥ 28 d. The efficacy of the maintenance dose in sustaining muscle creatine concentration beyond this period is unknown.

The preceding discussion shows several times that the greatest increases in phosphocreatine availability and the largest improvements in performance appear to be found in persons with the largest increases in muscle creatine concentration. This suggests that an ergogenic effect of creatine ingestion on metabolism and performance during exercise and recovery may critically depend on the extent of muscle creatine uptake during ingestion. It also points to the importance of maximizing tissue creatine uptake when attempting to increase exercise performance via creatine ingestion. However, these findings do not constitute a license for the indiscriminate use of creatine. First, most muscle creatine uptake takes place during the initial days of creatine supplementation. In a study in which subjects consumed 30 g/d for 4 d, $\approx 30\%$ of the total intake was retained during the initial 2 d of supplementation, compared with 15% from days 2–4 (32). There is no evidence that increasing intake above 20–30 g/d for 5–6 d has any potentiating effect on muscle creatine uptake (32, 48). In fact, a consistent finding from several studies is that there appears to be a definable upper limit to the intramuscular total creatine concentration of ≈ 160 mmol/kg dry mass (32, 39); once this limit is reached, further supplementation will simply result in excretion of creatine in the urine.

Another point to consider is that several factors identified as governing the extent of creatine uptake are largely independent of the amount consumed. One is the muscle total creatine concentration before supplementation; in general, the lower the initial total creatine concentration, the greater the extent of muscle

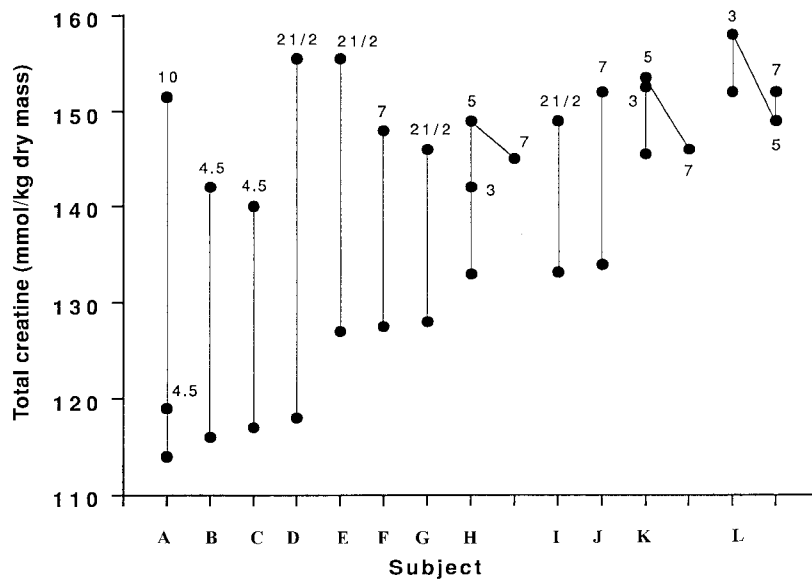


FIGURE 8. Mixed muscle total creatine concentration in individual subjects before and after creatine supplementation. Numbers refer to the supplementation period (days). Adapted from Harris et al (32).

creatine uptake (32, 39, 41). This precept is clearly illustrated in **Figure 8** from work by Harris et al (32), and it is worth noting that even the lowest presupplementation values here fall well within the normal range. In individuals in whom the initial total creatine concentration is already relatively high, neither an appreciable uptake of creatine nor an effect on phosphocreatine resynthesis or performance has been found after creatine supplementation (39, 41). Thus, creatine supplementation can be considered to optimize the store of available high-energy phosphates in those individuals whose total creatine concentration lies at the lower end of the normal range, in the same manner as carbohydrate loading optimizes the muscle glycogen stores.

Several means of promoting creatine uptake that 1) allow more individuals to approach the apparent upper limit to the muscle total creatine concentration and 2) do not involve increasing the creatine load have now been identified. One approach, described by Harris et al (32), is to combine creatine supplementation with exercise (**Figure 9**). In this study, 5 subjects receiving creatine supplementation performed 1 h of continuous, submaximal cycling exercise on each day of supplementation. Subjects conducted the exercise using one leg; the contralateral leg served as a control. As with creatine supplementation alone, a large interindividual variation occurred in response to the combination of creatine and exercise. However, the mean total creatine concentration of the muscle increased by 37% (the equivalent of 44 mmol/kg dry mass) when creatine was combined with exercise, as opposed to 26% (30 mmol/kg dry mass) with creatine supplementation alone.

A second approach is to combine creatine ingestion with carbohydrate, a regimen that has a large potentiating effect on creatine uptake (49). This approach also reduces the amount of variation habitually seen in the extent of creatine uptake after creatine supplementation alone or in combination with exercise. In one study (57), 3 groups consumed 20 g creatine/d for 3 d (**Figure 10**). One of these groups consumed four 5-g doses of creatine dissolved in 250 mL of a warm, sugar-free, diluted

orange drink. A second group followed each 5-g creatine load with 500 mL of a commercially available 18.5% simple carbohydrate solution (Lucozade; SmithKline Beecham, London, United Kingdom). A third group consumed creatine and simple carbohydrate in the same manner, with the addition of 1 h of cycling at 70% of maximal oxygen uptake on the morning of each day of supplementation immediately before creatine ingestion. A fourth group acted as a control and consumed only the sugar-free orange drink. Energy and macronutrient

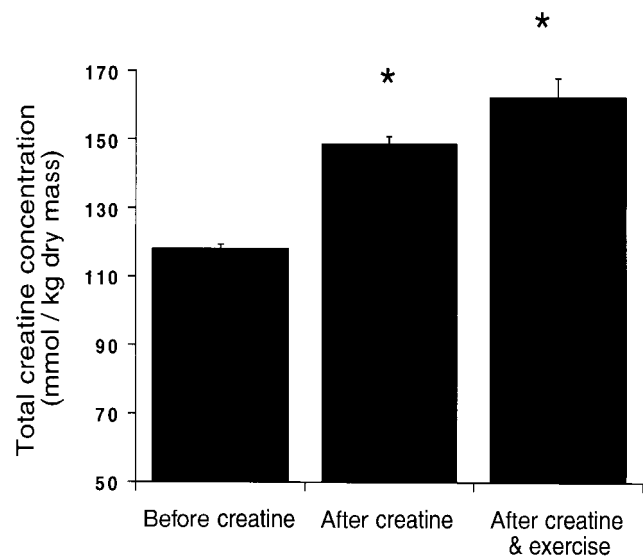


FIGURE 9. Mean (\pm SEM) mixed muscle total creatine concentration before and after supplementation with $4\text{--}6 \times 5$ g creatine/d for 4–7 d (ie, 20–30), in conjunction with and without 1 h of continuous, submaximal cycling exercise on each day of supplementation. *Significantly different from before supplementation, $P < 0.05$. Adapted from Harris et al (32).

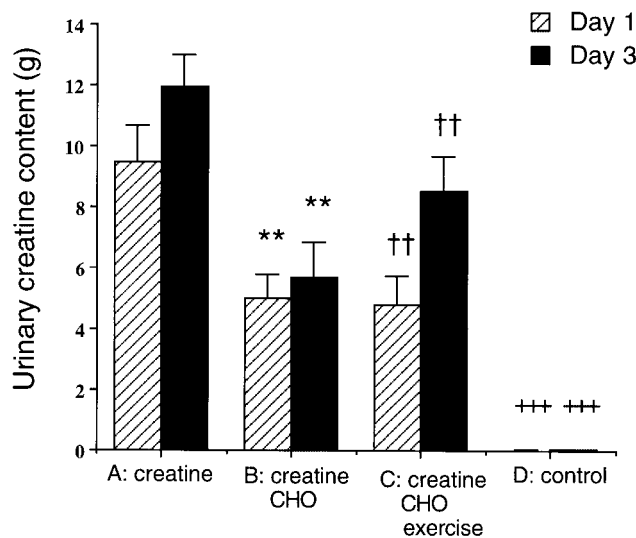


FIGURE 10. Mean (\pm SEM) urinary creatine content on days 1 and 3 of supplementation with 4×5 g creatine/d (groups A–C) or placebo ingestion (group D). Group B followed each 5-g creatine load with 500 mL of an 18.5% glucose solution. Group C followed the same procedure with the addition of 1 h of submaximal exercise on each day of supplementation. **,††,+++Significantly different from group A: ** $P < 0.01$, †† $P < 0.01$, +++ $P < 0.001$. There were no significant differences between groups B and C. Reproduced with permission from Green et al (57).

intakes were controlled throughout the study in all groups. Serum insulin was significantly elevated after carbohydrate ingestion when compared with creatine or placebo ingestion. Whole-body creatine retention was significantly increased when ingested in combination with the carbohydrate solution, probably because of a stimulatory effect of insulin. As shown in Figure 10, exercise did not add to creatine retention. Thus, combining creatine supplementation with carbohydrate ingestion appears to obviate the need for exercise during the supplementation period.

There is no evidence that creatine supplementation in the quantities described in this article produces any discomfort or harmful side effects. When full hematologic and clinical chemistry screening was carried out before and after creatine supplementation of 20 g/d for 5 d (33), no alteration in markers of liver or kidney function were reported, a finding subsequently confirmed in several other studies (58, 59). However, the long-term effects of creatine supplementation, for several months, for example, are not known.

CONCLUSION

In conclusion, creatine supplementation affords a legal and scientifically proven means of improving performance during exercise of high to maximal intensity. Potentially, its use could benefit a wide range of sports involving either single bouts of high-intensity exercise (eg, sprint running, swimming, and cycling) or multiple bouts (eg, soccer, rugby, and hockey). In addition, creatine supplementation has the potential to benefit any athlete engaged in training that involves repetitive bouts of high-intensity exercise. The increased training load that could be tolerated by athletes might be greatly beneficial to their eventual competitive performance. There is no evidence to suggest crea-

tine supplementation can benefit prolonged, submaximal exercise (eg, middle or long distance running).

RESEARCH NEEDS

Further research is needed to accomplish the following:

- 1) elucidate the factors governing tissue creatine transport in humans,
- 2) identify the optimal amount or form of carbohydrate needed to promote skeletal muscle uptake,
- 3) demonstrate the effect of combining creatine and carbohydrate ingestion on creatine uptake and subsequent exercise performance,
- 4) investigate the role of training status and insulin sensitivity on creatine uptake and performance, and
- 5) investigate the effects of long-term creatine supplementation on skeletal muscle structure, metabolism, and function. 🌱

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