

Introduction

Creatine phosphate (CP) (figure 1), the phosphorylated form of the amino acid creatine, is a high-energy compound that is able to donate a phosphate to adenosine diphosphate (ADP) to make adenosine triphosphate (ATP) in muscle. In the initial stages of exercise, ATP that is broken down to ADP can be rephosphorylated. Thus, creatine phosphate may be thought of as a reservoir of fuel for working muscles. This reserve is normally quite small but it is the only fuel available to form ATP during short bouts of exercise (1).

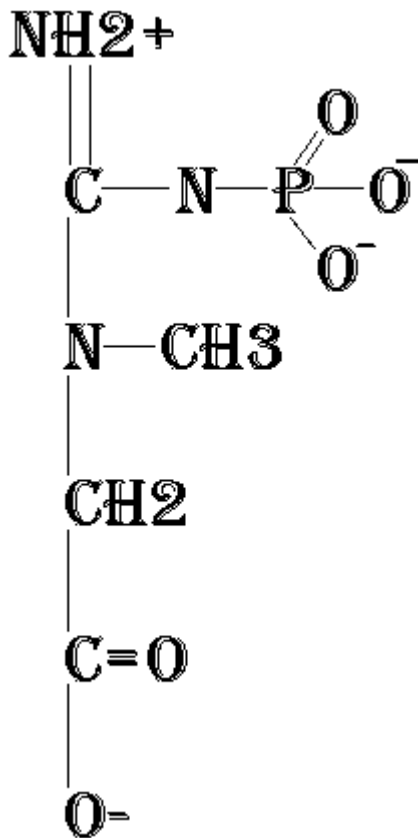


Figure 1. Creatine Phosphate

Creatine is synthesized by the liver, pancreas and kidneys. It is synthesized from glycine, the guanido group of arginine and the methyl group from S-adenosylmethionine. It is transported across the membranes of muscle and nerve cells by a specific transporter system against a 200:1 gradient. The enzyme creatine kinase catalyzes the phosphorylation of creatine to CP. Approximately 95% of the reserve of creatine-CP is in muscle (mainly skeletal muscle). The ratio of CP to creatine is about 2:1 (2).

Creatine and CP are degraded to form creatinine that is excreted in the urine. Thus, about 2 g of creatine must be synthesized or taken in from the diet to replace this loss. Dietary sources of creatine come mainly from meat, but also milk and fish (2).

In the past few years, however, many athletes have used creatine supplementation in an attempt to increase their reservoir of fuel. Many studies have shown that supplementation does in fact increase intramuscular stores. Feldman (2) 1998 found that ingestion of 5g of creatine monohydrate, four or six times a day for 2 or more days gave significant increase in total creatine content in the quadriceps muscle. In some, the increase was as great as 50% (Figure 2)! Harris (3) 1992 found similar results with approximately 20% of the creatine stored being phosphocreatine (3). The 1997 Guide to Nutrition and Fitness Resources reports that 20 to 25 g/day of creatine supplementation increases muscle content 20 to 30% (4).

Although there does seem to be some benefit from creatine supplementation for short-term exercise and perhaps for some medical treatments, there may be potential side effects as well. Creatine, unlike other ergogenic products that are considered controlled substances, is a dietary supplement and is thus not regulated by the FDA. Therefore, detrimental effects (especially long-term) have not been sufficiently studied.

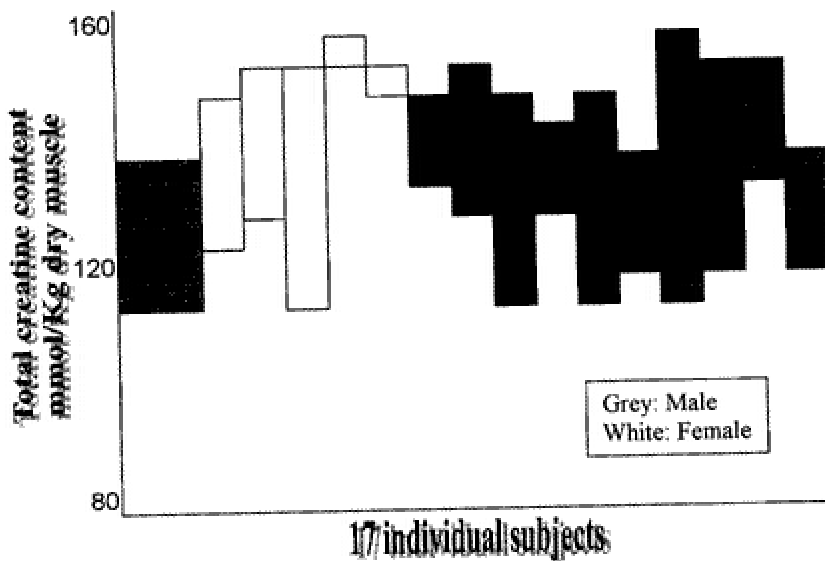


Figure 2: The change in creatine levels in the quadriceps femoris muscle of 17 subjects. Lower bar = before supplementation. Upper bar = after supplementation. Adapted from Feldman (2).

The Benefits for Short-Term Exercise

Many studies of creatine supplementation have demonstrated some ergogenic benefit for short-term activities requiring strength and power (5-8). Studies have tested effects on cycling, running, jumping, swimming, weight lifting, rowing, kayaking, etc.

Bosco (5) 1997 studied the effect of supplementation on duration of maximal power output for trained runners and jumpers. Supplementation was compared to placebo in a double blind design. The participants ingested twenty grams of creatine daily for five days. The effect on performance was tested during 45 s of maximal continuous jumping

as well as time till exhaustion during 20-km/hr treadmill running. The creatine group showed a significant enhancement compared to the placebo group. An enhancement of 7% was seen during the first 15 s of jumping and 12 % during the second 15 s. No improvement was seen in the last 15 s. Evidently, the larger "reservoir" of creatine was depleted within the first 30 s. The time till exhaustion on the treadmill increased by 13%. This study showed that supplementation may help to extend the duration of maximal power output (5).

In 1997 Grindstaff and colleagues (6) found that creatine supplementation could also enhance the performance of swimmers. 18 male and female amateur competitive swimmers ingested 21 g/day of creatine or placebo for 9 days. The athletes swam three 100-m freestyle sprints in a 50-m pool with 60s rest in-between. The creatine group swam significantly faster than the placebo group in heat 1 and heat 2, but not heat 3. The depletion of the extra stores again explains the lack of benefit in the latter stages of exercise (6).

Interestingly, in 1996 Burke and colleagues (7) conducted a similar study on swimming performance that did not show benefits from creatine supplementation. Grindstaff and colleagues speculate that this study may not have been able to find a benefit for many reasons. It is possible that this study had a different outcome because of a shorter supplementation period (5 days), shorter pool (25-m), longer recovery periods (2-3 minutes), and the use of elite swimmers (7). Nevertheless, the 1997 study showed that creatine supplementation may provide ergogenic benefit to sprint swimmers.

The two 1997 studies illustrate the possible benefit of creatine supplementation to amateur athletes. McNaughton and Dalton in 1998 studied supplementation in elite athletes. Sixteen elite male kayakers were given either a placebo or 20 g of creatine a day for 5 days. Three maximal kayak ergometer tests of 90, 150 and 300 s duration were given. Pretest differences were insignificant. After the 5 days, the creatine group did significantly better in all three tests. Unfortunately, partial times were not given for the longer duration 300 s test. Based on the previous studies one might expect a decrease in benefit in the latter stages of the test. This study supports the notion that creatine loading may have some ergogenic benefit to elite athletes as well as amateurs. (8)

The many studies on the effects of creatine supplementation on short-term exercise provide extensive evidence for its positive ergogenic benefit. There needs to be further research however into the exact molecular mechanisms, the sports that creatine does and does not benefit, which sports it may actually hinder, male and female differences, and the optimal amount and delivery regimen for ingestion.

Medical Benefits of Supplementation

Recently, creatine supplementation has also been studied for possible medical benefit. One such benefit being studied is for heart failure. The thought is that higher intracellular creatine levels may increase the energy reserve of the heart like it does for skeletal muscle. Korge and colleagues (9) 1998 tested the effect of creatine phosphate on the

contractile activity in acutely failing rat hearts. They produced the acute failure by constriction of the aorta and resulting increased afterload. After failure was reached, the constriction was removed and saline, saline and CP, saline and creatine, or saline and creatine plus phosphate were infused. Normal cardiac function was recovered only in the saline-CP infused rats. The failing hearts all had a decline in CP, ATP and calcium uptake and an increase in lactate. These concentrations were normal in the recovered rats. This study shows that creatine supplementation may be effective in patients with acutely failing hearts (9).

Horn and colleagues (10) 1998 however did not find any benefit. They studied the effects of chronic feeding in rats on cardiac energy metabolism and on creatine content in the heart, skeletal muscle, brain, liver and kidney. They found that myocardial energy reserve could not be increased by creatine supplementation. Creatine content only increased in the liver and in the kidney. However, the fact that creatine levels in the skeletal muscle remained unchanged raises some speculation. Perhaps not enough creatine was administered to see an effect (10).

Cisowski and colleagues (11) 1998 studied the effect of creatine supplementation on human patients undergoing coronary artery bypass surgery. A main element in myocardial injury during heart surgeries is an inadequate energy supply in myocardial cells. Thus, increasing myocardial cell CP level may reduce injury. Forty patients undergoing coronary artery received either CP-enriched cardioplegic solution (group 1) or standard cardioplegic solution (group 2). Group 1 received 6 g/day for 3 days before surgery, 10-mmol/l drip infusion during surgery, and 4 g/day 2 days post-operatively. This study showed that group 1 had significantly lower average number of shocks needed to restore cardiac function, a significant effect on ventricular arrhythmias, significantly lower need of inotropic drugs and significantly lower degree of sarcolemmal damage. Thus, exogenous creatine phosphate may have some protective effect against heart damage during heart surgery (11).

A further role for creatine phosphate in medicine may be as an ATP buffer. Lara and colleagues (12) 1998 studied this theory. Rats underwent a cecal ligation and puncture to introduce a systemic infection. They were fed either a creatine analogue to replace endogenous stores of creatine phosphate or a gel (placebo) for 14 days. Both groups of rats had altered bioenergetics but the rats receiving the analogue had a greater decrease in energy state. Thus, creatine supplementation may have use in patients with systemic infection (12).

Lastly, Pulido and colleagues (13) 1998 studied the therapeutic role creatine may have in patients with Duchenne's muscular dystrophy (DMD). Affected patients and mice have increased cytosolic calcium concentrations. Treatment of DMD muscle myotube for 6-12 days with creatine increased levels of phosphocreatine. This treatment lowered calcium by stimulating the sarcoplasmic reticulum calcium ATPase. Also, there was significantly increased myotube formation and survival (13).

These studies on the use of creatine supplementation for medical treatment have given some promising results. However, this research is relatively new and many more studies need to be conducted in order to find anything conclusive.

The Risks of Supplementation

The fact that creatine is considered a dietary supplement instead of a controlled substance has led to insufficient testing of this ergogenic aid. Furthermore, almost all the studies have only concentrated on short-term risk. This is rather alarming considering the popularity of creatine. Thus far, there does not seem to be any detrimental effects of short-term creatine supplementation besides reports of cramping, muscle tears and pulls, dehydration, and nausea (4). Scientific studies on these effects however have not been conducted. It is known that supplementation can lead to weight gain. It is controversial whether this is due to water retention or increased muscle mass or both (4). Increased weight gain can actually impede performance in activities like running and swimming although increased muscle mass may make up for this.

One natural area of concern is the effect on the kidney. Poortmans and colleagues (14) 1997 studied the effect of short-term use on the kidneys. Five subjects ingested either placebo or 20 g/day of creatine monohydrate for 5 days. Blood and urine was analyzed for creatine, creatinine, protein and albumin. The glomerular filtration and excretion rates remained normal. Thus, this study does not show that there are any adverse effects on the kidney from creatine supplementation. Note, that this was a small sample size and therefore the study had low power (14). Pritchard and Kaira, however, gave conflicting evidence in a letter to Lancet in 1998. They described a patient with nephrotic syndrome who developed glomerulosclerosis after taking creatine. This reversed itself after supplementation was discontinued (15). However, neither of these studies was well designed and therefore it is hard to state anything conclusive. Obviously, more research on the affects on the kidney needs to be conducted.

One potential long-term risk that has been studied is down-regulation of the expression of the creatine transporter protein. This transporter is responsible for uptake of creatine into cells. Guerrero-Ontiveros (16) 1998 found that chronic creatine supplementation in rats may down regulate the expression of the creatine transporter protein. Thus, theoretically a chronic user of creatine who stops supplementation could become creatine deficient because of this effect (16).

Conclusion

The fact that creatine is considered a dietary supplement instead of a controlled substance has led to insufficient testing of the risks and benefits of supplementation. Recent studies on creatine have supported that supplementation increases intramuscular stores of creatine phosphate (CP) and can in turn act as an ergogenic aid in short term exercise. Furthermore, there is some data that shows supplementation may prove to be useful as a medical treatment for patients with systemic infections, acute cardiac arrest, and diseases like muscular dystrophy, and as a prophylactic against ischemic injury during heart

surgery. This research is relatively new however and more research needs to be conducted to find conclusive results. A more immediate need for research is to identify the health risks of supplementation. It is alarming to know that so many have used creatine in hopes of enhancing strength and power (including myself!) without knowing all the risks. Two potential risks may be kidney damage and down regulation of the creatine transporter protein.

Some issues that future well designed studies need to consider are which sports do and do not benefit, possible drug interactions, age and gender differences, medical usage, deleterious physiological effects (especially from long term use), and exact molecular mechanisms. If one does decide to take exogenous creatine he/she should know that this ergogenic aid has not been sufficiently studied to detect potential for abuse.

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