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Creatine Supplementation and Exercise Performance

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Creatine phosphate allows high rates of adenosine triphosphate resynthesis to occur in muscle and therefore plays a vital role in the performance of high-intensity exercise. Recent studies have shown that feeding large amounts of creatine (typically 20 g per day for 5 days) increases muscle total creatine (and phosphocreatine) content. The extent of the increase that is normally observed is inversely related to the presupplementation level. Vegetarians, who have a very low dietary creatine intake, generally show the largest increases. Creatine supplementation has been shown to increase performance in situations where the availability of creatine phosphate is important; thus, performance is improved in very high-intensity exercise and especially where repeated sprints are performed with short recovery periods. Creatine supplementation is widely practiced by athletes in many sports and does not contravene current doping regulations. There are no reports of harmful side effects at the recommended dosage.

Key Words: creatine phosphate, fatigue, ATP resynthesis

Athletes are forever searching for nutritional supplements that will give them a significant advantage over their competitors. This accounts in part for the reports of widespread use of illegal drugs in sport, yet the secret is to find something that is effective in improving performance but is not against the rules. It is also important that any chemical substance to be used in this way should not have harmful side effects.

There have been many claims for the performance-enhancing properties of a wide range of dietary supplements. Because of their supposed ability to enhance exercise performance, these diverse substances are collectively referred to as ergogenic aids. Sales figures for supplements such as bee pollen, royal jelly, and pangamic acid, together with a wide range of vitamins and minerals, demonstrate that many athletes remain convinced of their effectiveness. In spite of the limited and conflicting evidence, however, the balance of available information suggests that there is no benefit from these substances for healthy individuals consuming a normal diet (23). When a beneficial effect is obtained, this is often due to the presence of illegal substances; for example, ephedrine and related

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compounds are common ingredients of many herbal remedies, and the use of these products renders the athlete liable to disqualification.

Within the last few years, however, a new ergogenic aid has been used by many successful athletes, particularly in track and field but also in other sports. The substance in question is creatine. Its use as a supplement by athletes is not in fact new, and it is to be found in a normal diet. What distinguishes it from other ergogenic aids is that it seems to be effective in improving performance. More significantly perhaps, its use is not prohibited by the governing bodies of sport, and there appear to be no harmful side effects even when very large doses are taken, at least in the quantities needed to produce an ergogenic effect.

Metabolic Role of Creatine

The biochemistry of creatine metabolism is covered in standard textbooks of biochemistry and will not be discussed in detail here. The highest tissue concentrations of creatine are found in skeletal muscle, and approximately two-thirds of the total is in the form of creatine phosphate (9). Creatine phosphate (CP) itself is present in resting muscle in a concentration approximately three to four times that of adenosine triphosphate (ATP), the immediate energy source for muscle contraction. The amount of ATP in muscle cells is small, and only a fraction of this can be viewed as an energy store. When the cellular ATP concentration falls too far, fatigue ensues. Although it has been suggested that the ATP content of some individual fibers may be almost zero after very high intensity exercise in the horse, this has not been seen in humans (14), and the whole muscle ATP content rarely falls by more than about 25 to 30% at the point of fatigue in high intensity exercise (15).

Because muscle fatigue is associated with decreased intracellular ATP concentrations, regeneration of ATP at a rate close to that of ATP hydrolysis is essential if fatigue is to be delayed. Transfer of the phosphate group from CP to adenosine diphosphate (ADP) is catalyzed by the enzyme creatine kinase, resulting in the restoration of ATP and the release of free creatine (C). The situation during muscle contraction can be represented as follows:

$$\mathrm{ATP} \rightarrow \mathrm{ADP} + \mathrm{Pi}$$

$$\mathrm{CP} + \mathrm{ADP} \rightarrow \mathrm{ATP} + \mathrm{C}.$$

The rate of ATP hydrolysis is set by the power output of the muscle: In electrically induced isometric contractions of the quadriceps muscle of 1.26 sec duration, an ATP turnover rate of approximately 11 mmol/kg dry muscle/s has been reported (13). The resting ATP content of muscle is about 24 mmol/kg, but this cannot fall by more than about 30%, so the need for rephosphorylation of the ADP formed during contraction is obvious. The creatine kinase reaction is extremely rapid, and since the muscle CP concentration can fall to almost zero (15), it can make a significant contribution to the energy supply needed for brief bursts of very high intensity exercise. The CP store is finite, however, and increasing the CP content of muscle ought to allow a greater amount of work to be done using this energy source.

During the recovery process after exercise, the creatine kinase reaction is reversed, using energy made available by oxidative metabolism that occurs within the mitochondria:

$$C + ATP \rightarrow CP + ADP$$

$$ADP + Pi + \text{metabolism} \rightarrow ATP.$$

In high intensity exercise, glycolysis will result in the formation of pyruvate at a rate higher than that at which it can be removed by oxidative metabolism, leading to an accumulation of lactate within the muscle. The hydrogen ions associated with anaerobic glycolysis cause muscle pH to fall, and this fall in pH has been implicated in the fatigue process (20). A number of buffers within the cell resist changes in pH, and the breakdown of CP is such a mechanism. The creatine kinase reaction can be rewritten to take account of the changes involved:

$$CP^{2-} + ADP^{3-} + H^{+} \rightarrow ATP^{4-} + C.$$

An increased availability of CP for breakdown has the potential to increase the intramuscular buffering capacity, delaying the point at which pH reaches a critically low level.

CP plays another role within the muscle cell. It transfers ATP equivalents from within the mitochondria, where ATP is generated by oxidative phosphorylation, to the cytoplasm, where it is required for cellular metabolism (3, 16). There is no evidence that this process is limited by the availability of creatine, but this may perhaps be worthy of investigation.

Creatine Supplementation and Muscle CP Concentration

Creatine is an amino acid (methylguanidine-acetic acid) that occurs naturally in the diet, being present in meat and fish. The normal daily intake is less than 1 gram (12), but the estimated daily requirement for the average individual is about 2 grams (22). The body has a limited capacity to synthesize creatine in the liver, kidney, pancreas and other tissues, but the primary site of synthesis in humans is the kidney. This supplies the amount required in excess of the dietary intake, and is also the only way vegetarians can meet their requirement. Synthesis occurs from amino acid precursors (arginine and glycine), but the synthetic pathway is suppressed when dietary creatine intake is high.

Studies of resting human skeletal muscle have shown the CP concentration to be about 75 mmol/kg dry weight and the free creatine concentration to be about 50 mmol/kg (9). The literature reports quite a large range of values, however, and it seems clear that there is considerable interindividual variability. A number of factors may account for this, including differences in the composition of the diet. The muscle fiber composition may also be of some importance: Rehunen and Harkonen (19) showed a higher CP content in slow-twitch fibers than in fast-twitch fibers in women, although in men the difference was not statistically significant. There is some evidence that the muscle creatine content is higher in women than in men.

The first study to systematically investigate the effects of supplementation of large amounts of creatine was that of Harris et al. (10). In a comprehensive study they showed that ingestion of small amounts of creatine (1 g or less) had a negligible effect on the circulating creatine concentration, whereas higher doses (5 g) resulted in an approximately fifteen-fold increase. Repeated feeding of 5 g doses every 2 hrs maintained the plasma concentration at about 1 mmol/L over an 8-hr period. Repeated feeding of creatine (5 g four times a day) over a period of 4 to 5 days resulted in a marked increase in total creatine content of the quadriceps femoris muscle. An increase in muscle creatine content was apparent within 2 days of starting this regimen, and the increase was greatest in those with a low initial level: in some cases an increase of 50% was observed. Approximately 20% of the increase in total muscle creatine content was accounted for by creatine phosphate.

It seems clear there is an upper limit to the creatine and CP levels that can be achieved in muscle, and this is not unexpected. There was some evidence, from a model wherein one leg was exercised during a period of creatine supplementation while the other leg was rested, that exercise enhanced the effect of creatine supplementation on the muscle creatine content. There was no effect of creatine supplementation on the ATP content of the muscle, and no adverse side effects were noted, even when 30 g/day were taken for 7 days. In contrast to these reported effects of creatine supplementation on muscle creatine and CP content of human skeletal muscle, there seems to be little effect in the rat (18).

Creatine Supplementation and Exercise Performance

Because of the newness of the concept, only a few scientific studies have reported the effects of dietary creatine supplementation on muscle function and exercise performance. Presently the results of many of these investigations are available only in preliminary form. Most of the studies have been well controlled, but crossover designs are impractical because of the long washout period from the muscle. When high doses are ingested over a period of 4 to 6 days, the muscle creatine content will remain elevated for several weeks (Greenhaff, personal communication). If athletes are used as subjects, the increased training loads that seem possible after creatine supplementation make it difficult to interpret results of crossover studies in which placebo was administered as the second treatment.

For these reasons, most of the reported studies have used matched groups of subjects. From these results there appears to be no beneficial effect on the peak power output that can be achieved in a range of tests, but the balance of the available evidence suggests that performance is improved in high intensity exercise tasks, especially when repeated exercise bouts are carried out.

Greenhaff et al. (7) measured the ability of two groups of subjects to complete five bouts of 30 maximal voluntary contractions on an isokinetic dynamometer: half the group then received a placebo and the others received 24 g of creatine per day for 5 days. Peak torque did not differ after the placebo treatment compared with the initial measurements, but the creatine-supplemented group demonstrated significantly improved peak torque production.

Harris et al. (11) used a creatine dose of 30 g per day for 6 days and again compared parallel treatment and placebo groups. The subjects in their study were trained runners and two different exercise tests were conducted on separate days. One test consisted of four 300-m runs with a 4-min rest between runs, and the other test consisted of four 1,000-m runs with a 3-min rest between runs. The results showed a significant benefit of creatine supplementation: At the 300-m distance the improvement was only statistically significant for the last run of the set; at the 1,000-m distance the total time for all four runs improved by a mean of 13.0 sec, with the improvement on the last run being 5.5 sec.

Other recent studies (1, 21) have confirmed the beneficial effect of creatine supplementation in high doses (20 g/day for 6 days) on high intensity exercise performance, although these same researchers have also reported one study that gave inconclusive results (8).

Another placebo-controlled matched-pairs study was recently reported by Earnest et al. (4), using a dose of 20 g/day for 4 days. The exercise test consisted of three 30-sec Wingate tests on a cycle ergometer with 5-min rest periods between tests. Peak anaerobic power was measured as the highest power output in a 5-sec period and anaerobic capacity as the total work done in the 30-sec period. Peak power was not affected by treatment. Anaerobic capacity was higher in all three tests after creatine supplementation, but there was no difference with placebo treatment.

No beneficial effect of creatine supplementation was reported by Odland et al. (17). They used a crossover design involving control, placebo, and creatine supplementation trials; creatine was administered for 3 days (20 g/day). The exercise test consisted of a single 3-sec Wingate test. Muscle free creatine content and the muscle total creatine/ATP ratio were enhanced by the treatment, but neither total creatine nor CP content were significantly altered. There were no differences between the three experimental conditions in any of the exercise test parameters. The clear difference between the study by Odland et al. and the others reported above, apart from the fact that it failed to demonstrate enhancement of exercise performance after creatine supplementation, is that the experimental model consisted of a single exercise test rather than multiple exercise bouts. It is worth noting, however, that Earnest et al. (4) did show an increased total work output in the first of the three 30-sec tests used in their study. It is also the case, however, that the total creatine dose was smaller (60 g) in their study than in any of the others mentioned, wherein the dose used was generally 80 to 180 g.

There is little information on the effects of creatine supplementation on the performance of more prolonged exercise. In an incremental treadmill running test, Green et al. (5) found no effect of creatine supplementation on the cardiorespiratory or metabolic response to submaximal exercise, but they did not measure exercise performance. However, Balsom et al. (2) found no beneficial effect of creatine supplementation on performance in an endurance test.

Creatine Supplementation and Metabolic Response to Exercise

The mechanism by which creatine supplementation might improve performance is not entirely clear, although it does seem clear that this effect is related to the increased muscle CP content. Recent results indicate that the rate of CP resynthesis after intense exercise is enhanced after high-dose creatine supplementation (6). This allows faster recovery after sprints and allows more work to be done during each subsequent high intensity effort. These effects will allow more work to be done in training and should therefore result in a greater training response. This may be particularly important in view of the fact that the muscle creatine content remains high for weeks or even months after only a few days of high-dose dietary creatine supplementation.

Greenhaff et al. (7) found that postexercise plasma ammonia concentration was lower after creatine supplementation, although there was no difference in blood lactate concentration, but interpretation of the results is complicated by the fact that total work output was higher in this condition. Likewise, Earnest et al. (4) found no difference in blood lactate between the creatine-supplemented and placebo trials in spite of differences in power output; they also found a suggestion of a lower blood ammonia concentration after creatine supplementation. Green et al. (5) reported no effect of creatine supplementation (20 g/day for 5 days) on oxygen consumption or on blood lactate concentration during an incremental treadmill running test at intensities of 50 to 80% of maximum oxygen uptake. However, they did find this treatment regimen effective in improving the performance of these same subjects in a test consisting of repeated bouts of isometric exercise.

In contrast to the lactate results obtained in these three studies, Soderlund et al. (21) reported a lower muscle lactate, in spite of a higher total work output, after creatine supplementation; in their study the exercise test consisted of a series of 6-sec high intensity sprints on a cycle ergometer.

There are many anecdotal reports of elite athletes benefiting from creatine supplementation in preparation for competition, but as with all other ergogenic aids, there can be no certainty as to the truth of these reports. Many athletes also claim to have experimented with creatine supplementation but to no avail. In this latter case, at least in the UK, most have been taking a creatine dose of about 4 g per day for prolonged periods, according to the recommendations of the suppliers. The scientific studies that have shown beneficial effects have involved the use of much higher doses (20 to 30 g per day) for short periods of time, and there is currently no evidence that performance will benefit from the dosage regimen recommended by the suppliers.

The use of any nutritional supplement that is effective in improving performance inevitably raises ethical issues. Ergogenic aids are banned by the governing bodies of sport for one of two reasons: on the grounds that they pose a threat to the health of the individual, or because they confer what is seen to be an unfair advantage. Although there is no evidence of any risks to health associated with the long-term use of high doses of creatine, the studies mentioned above that have used high doses, on the order of 20 to 30 g per day, have been of relatively short duration (5 to 14 days). The normal daily diet of nonvegetarians contains less than 1 g of creatine (12), but in populations with a high meat consumption, this will be substantially higher. However, there is no reason to believe that diseases, primarily cancer of the colon, which are more common in populations with high meat consumption, are in any way associated with dietary creatine intake.

Studies are currently under way to investigate some of the effects of long-term creatine supplementation, and this information will become available in due course. This leads to the ethical question of whether the use of creatine should be disallowed on the grounds of its ergogenic effect, as is the case with other normal dietary components such as caffeine. There seems to be no logic to the argument for accepting the use of creatine in any dose but restricting the amount of caffeine that may be used. However, there may be an intuitive opposition to the use of substances that have an effect on the central nervous system, as caffeine does in high doses, which does not apply to substances whose effects are purely peripheral. As more information emerges, this issue will be resolved and the governing bodies of sport will make a decision.

In conclusion, it seems clear that ingestion of high doses (20 to 30 g) of creatine over a period of 4 to 5 days causes a marked elevation of the free creatine and CP content of skeletal muscle. This results in an improved capacity to maintain power output during high intensity exercise, especially when repeated exercise bouts with only short recovery periods are involved. The effects on muscle CP content and on performance are likely to be greatest in individuals who normally have a low muscle CP content, perhaps as a result of a low dietary intake. Creatine is a normal dietary component and its use is not contrary to the rules of any governing bodies of sport. There have been no reported adverse effects resulting from the ingestion of creatine.

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Note

Since this paper was submitted, another review of the effects of creatine supplementation on performance has been published by P.D. Balsom, K. Soderlund, and B. Ekblom: Creatine in humans with special reference to creatine supplementation. *Sports Med.* 18:268-280, 1994.