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Opinion of the Scientific Committee on Food on safety aspects of creatine supplementation

(Adopted by the SCF on 7 September 2000)

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Introduction

A report on "the composition and specification of food intended to meet the expenditure of intense muscular effort, specially for sportsmen" was adopted by the SCF in June 2000. This report addressed efficacy but not safety issues. One aspect of the report concerned creatine and it was concluded that creatine supplementation can lead to improved exercise performance in events requiring explosive, high energy activity, especially of a repeated nature. The Committee has been asked to comment on the safety of recommended creatine supplementation regimes, since some of these involve consumption of relatively large doses. The Committee wishes to emphasise that this separate opinion on the safety of creatine should not be taken to imply that safety aspects of other components of sports foods may not also need to be addressed.

It is understood that the use of oral creatine supplements is common among professional and amateur sportsmen and women. Its use has spread to college athletes, recreational athletes and even children. Because creatine is considered a nutritional supplement, it is currently freely available from pharmacies, health food stores and supermarkets. In this context, a question was raised on the safety of the recommended ingestion protocols (see below). A Medline search (1998-March 2000 period) has been made, using the key words "creatine" and "safety", to review the current scientific information on creatine supplementation.

Creatine (N-(aminoiminomethyl)-N-methyl glycine) occurs naturally in foods such as meat, fish and other animal products. A typical diet includes 1-2 grams of creatine daily, but it may also be formed endogenously by liver, kidney and pancreas from the amino acids Gly, Arg and Met at the rate of 1-2 g/day (2, 10).

Muscle stores of creatine can be maximised by a regimen that initially loads the muscle and then maintains a maximal increased state when lower doses are ingested (8, 3). The dosing regimens suggested by the manufacturers are 20 g/day for 3 to 7 days and then 2-5 g/day as a maintenance dose. Loading doses in the range of 10-50 g/day for 5-7 days are currently used although it is accepted that the same effect can be achieved by a 3 g/day dose over a more prolonged period (28 days) without a loading phase (10, 11, 13).

It has been shown that oral creatine supplementation (at the doses described above) produces a significant increase (about 10-20 %) in skeletal muscle creatine, which is predominantly free creatine, although 20-40 % of the increase can be in the form of phosphocreatine (3). Simultaneous consumption of carbohydrate with creatine further increases the creatine and phosphocreatine levels in muscle and also can facilitate muscle glycogen storage.

In a healthy subject of 70 kg with a total creatine pool of 120 g (95% in skeletal muscle), the daily turnover is about 2 g. Taking into account the gastrointestinal absorption, this amount can be obtained by an intake of about 2-3 g/day (1, 13). Creatine is transported to muscle and nerve and crosses the cell membrane via a specific transporter system against a 200:1 gradient (8). Creatine is eliminated by its irreversible conversion to creatinine at a rate of about 1-2 g/day (1, 9). This is the amount of creatine that needs to be replaced each day, either by endogenous synthesis or from dietary sources. Thus, the loading dose of oral creatine taken by many sportspeople for short periods of time represents about 10 to 20 times the daily turnover.

Safety considerations

Creatine appears to be well tolerated in short term human trials. Dozens of clinical trials have been conducted (see references in 2, 10, 13), mostly in highly trained athletes, and no adverse effects have been noted, although many trials reported increased body mass. However, the primary objective of these studies was to assess the effects on exercise performance and not adverse effects. The assumption that short term use (fewer than 28 days) at recommended doses has not been shown to cause significant adverse effects is based on these studies, but they have involved small numbers of subjects and there are no sample size calculations to indicate the limitations on the power of the studies. Other reports have linked creatine supplementation to weight gain, cramping, dehydration, torn muscles, gastrointestinal distress and dizziness (2, 8, 12, 13). (See also annex I).

Because of the high nitrogen content of creatine, the potential for renal dysfunction in athletes treated with creatine has been raised. Two cases of decreased renal function have been described so far (5, 7). However one study (4) found no detrimental effects on the kidney in eight young men and one woman after short-term, medium-term, or long-term oral creatine supplementation (10 months to 5 years). In addition, although creatine is normally found not only in skeletal muscle but also in cardiac muscle, brain and testes, these three areas remain essentially unstudied (3, 12).

Another question that may be raised is whether inhibition of endogenous creatine synthesis, which is produced by creatine administration, is reversed when creatine supplementation is terminated. There is also some concern about taking creatine supplements if sportspeople become dehydrated or in conjunction with other supplements, since possible interactions are unknown (8). In addition, because marketed creatine products do not meet the same quality control standards of pharmaceuticals, there is a potential concern about impurities of unknown toxicity, particularly dicyandiamide and dihydrotriazines. The possibility has also been raised that doses higher than those recommended on the labelling may be consumed (2). These authors also pointed out that potential interactions of most supplements, including creatine, with drugs have not been studied (2).

Conclusions

It can be concluded that although many efficacy trials have studied the effects of creatine, large-scale, well-controlled studies are lacking. Available results observed in highly trained athletes cannot necessarily be extrapolated to the general public. Little information exists on the short-term or long-term safety of creatine and evidence of adequate quality control of the commercially marketed creatine is lacking and adequate specifications for food grade materials should be developed.

Although no important adverse effects have been reported in the efficacy trials, such evidence is insufficient to provide reassurance about the safety of creatine supplementation involving high loading doses: there are doubts about safety in relation to kidney function; studies on tissues in which creatine is known to concentrate are lacking; effects on endogenous creatine synthesis upon cessation of supplementation are also not well studied. For these reasons the Committee considers that high loading doses should be avoided. Consumption of lower doses of up to 3 g/day are similar to the daily turnover rate of about 2 g/day and are unlikely to pose any risk.

Future studies should evaluate short- and long-term effects of oral creatine on renal and hepatic systems as well as those organs where creatine plays a metabolic role. Such studies should include people who are not highly trained.

References

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ANNEX 1

A summary of creatine metabolism in various organ systems and concerns regarding the effects of oral creatine supplementation was reported by Juhn and Tarnopolsky (12) as follows:

<u>Organ system/Effect</u>	<u>Comments</u>
Cardiovascular	Effect of long term oral creatine on cardiac muscle creatine concentration and cardiac function is unknown. No effects seen in short term use (10 days).
Gastrointestinal	Diarrhoea and gastrointestinal pain anecdotally reported, but no direct relationship established.
Liver	Studies up to 8 weeks show minimal or no liver enzyme elevation. Concern exists regarding the reversibility of the suppression of endogenous creatine synthesis after long-term use.
Musculoskeletal	Because of water retention in the muscle cell, there is theoretical concern about muscle cramps and tears, but causal relation not established.
Neurologic	Creatine is naturally found in brain tissue. The effects of oral creatine on brain concentrations is unknown.
Oncologic	Creatine and phosphocreatine/creatine kinase system may influence cellular oncogenesis. Long-term studies would help determine if oral creatine supplementation is beneficial, detrimental, or has no effect on healthy subjects.
Paediatric/adolescent	Theoretical concerns exist regarding extra load placed on developing kidney/other organs and the effects of creatine on muscle/bone junctions in the skeletally immature.
Renal	Urinary excretion of creatine increases up to 90-fold, though glomerular filtration rate is unchanged, at least during the 5-day loading phase. Elevation of serum and urinary creatinine also occurs, but generally small in studies of less than 28 days. Concern lies with unknown effects of longer-term supplementation (*).
Reproductive organs	Creatine is normally synthesised in the testes by the Sertoli cells. Creatine and Phosphocreatine are involved in sperm metabolism, but no studies exist on the effects of oral creatine supplementation. As with liver, concern regarding reversibility of the suppression on endogenous creatine synthesis.
Weight gain	Proven to occur in many studies. Initially caused by water retention. With prolonged use, increased muscle synthesis may also occur; this is being investigated.
Dehydration	Intracellular fluid retention in the muscle cell may predispose to dehydration, but studies are lacking. Proper hydration during supplementation is encouraged.
Long term effects	Unknown in any organ. Studies involving 12 months or more are needed, preferably with larger sample sizes than previous studies.

(*): One limited long term study (4) showed no adverse effects