Does Creatine Supplementation Increase the Risk of Rhabdomyolysis?

The case report by Robinson[1] in this issue of *The Journal* represents the most serious published report to date of an adverse effect in a person taking oral creatine supplements. In light of its severity, it is prudent to speculate on the likelihood that this man's creatine consumption contributed to his rhabdomyolysis.

Rhabdomyolysis results from a breakdown of the muscle cell wall, which leads to cell necrosis. It is thought to be the result of a plasma membrane defect or a disturbance in the sodium-potassium pump that allows an influx of calcium into the cell, which triggers a cascade of events leading to cell necrosis.[2] Robinson speculates that intracellular water retention led to increased skeletal muscle compartment pressures, which placed the patient at risk for cellular wall breakdown.

Such a hypothesis is simplistic yet worthy of consideration. It is accepted that oral creatine supplementation results in a rapid weight gain, easily noted within 24 hours.[3,4] Clearly, 24 hours is not enough to induce skeletal muscle hypertrophy; the gain is the result of intracellular and extracellular fluid retention. Although no studies have evaluated creatine supplementation and its effect on muscle compartment pressures, anecdotal evidence of athletes feeling "tight" or "cramped" abounds. Muscle cramping remains one of the most common side effects reported by those taking creatine.[5,6]

Risk factors for rhabdomyolysis include dehydration, alcoholism, illicit drug use, trauma, strenuous exercise, hypophosphatemia, and a hyperosmolal state.[2,7,8] Robinson's patient had exercised the day before Robinson saw him, though his fluid and electrolyte status were not known. It has been hypothesized that creatine supplementation increases the risk of dehydration from intravascular volume depletion. Even creatine manufacturers recommend a healthy fluid intake while on creatine supplements.

Rhabdomyolysis has been reported in athletes who were not taking creatine supplements. There are factors, however, that suggest creatine was at least a contributing factor. First, as do many athletes who believe more is better, this patient was taking a very high dose for an extended time. Such high doses and long periods are not only contrary to recommendations, but they are also unstudied. Second, he was previously healthy and had been body building for 5 years; only during the last year was he taking creatine supplements. Third, he was not taking any other supplement that could be a contributing factor.

Advocates of creatine supplementation often state there is no direct evidence of a causal relation between oral creatine supplementation and any adverse side effect. Such a statement is often misinterpreted as proof that creatine is safe. Establishing a statistically significant relation, however, between a catastrophic event such as rhabdomyolysis and any type of supplement is unrealistic, particularly when using human subjects.

As clinicians, we need to evaluate such cases by incorporating a balance between healthy skepticism and open-mindedness. Given the metabolic and physiologic changes that occur with oral creatine supplementation, combined with the excessive dosing, Robinson's case adds support to the hypothesis that the use of oral creatine supplements can lead to serious adverse effects. More importantly, it brings to mind the question that has been plaguing many for years about the role of ergogenic aids for sport: Is it really worth it?

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Submitted 5 November 1999.
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