

# EDITORIAL

## CREATINE SUPPLEMENTATION: SAFE AS STEAK?

The supply of energy to exercising muscle requires the ongoing generation and regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP). At submaximal exercise, ATP is generated through the consumption of O<sub>2</sub> during aerobic glycolysis. During intense exercise, when demands for ATP may exceed rates of generation from aerobic metabolism, an alternate mechanism supplies ATP via the transfer of high-energy phosphate bonds from intracellular phosphocreatine to ADP. This reaction, known as the creatine phosphate shuttle, is summarized as follows:



In the resting state, when oxidative production of ATP exceeds energy needs, the high-energy bond of ATP is transferred to creatine (Cr) to produce phosphocreatine (P<sub>Cr</sub>) at the mitochondrial membrane.<sup>1,2</sup> During intense exercise, a rightward shift in the creatine phosphate shuttle occurs in the contracting muscle to regenerate ATP through the return of a high-energy phosphate bond to ADP from the phosphocreatine store.

Creatine can be synthesized endogenously from arginine, glycine, and methionine via coordinated pathways in the kidney and liver.<sup>1</sup> Creatine is transported at low concentration in blood to muscle where active uptake concentrates it within the cell to an average concentration of 125 mmol/kg dry muscle.<sup>3,4</sup> In resting muscle, phosphocreatine/creatine ratios average 2:1 to 2.5:1, while the phosphocreatine/ATP ratio is about 3:1 to 4:1.<sup>4,5</sup> Dietary creatine intake is generally 1 to 2 g daily, mostly from red meat in which the creatine content averages 4 g/kg.<sup>4</sup> In the complete absence of creatine intake, body creatine content is sustained at only about 70% to 80% of usual levels. Creatine is non-enzymatically dehydrated to the cyclic metabolite creatinine at a fairly constant rate that is proportional to total body muscle mass.<sup>1</sup> Negligible quantities of creatine are excreted in the urine, but the near constant ( $\approx 25$  mg/kg/day) urinary excretion of creatinine via glomerular filtra-

tion provides a convenient and familiar means of estimating renal function.

Both amateur and professional athletes have pushed to expand their physical prowess through a number of performance-enhancing techniques. Anabolic steroids, which increase muscle protein bulk, and blood doping with red cell transfusion, which has the potential to increase O<sub>2</sub> delivery to muscle, have both fallen into disfavor. Each has serious side effects, which has led to the banning of these practices in many sports. A popular trick currently used by athletes to enhance muscle performance is dietary creatine supplementation, a ploy aimed at making greater quantities of phosphocreatine available for ATP regeneration during intense bursts of muscle activity.

Common programs of creatine supplementation call for the ingestion of 5 g of creatine 4 times a day for a 5-day loading period, with a sustained intake of 2 to 5 g daily.<sup>4,5</sup> Under these conditions, muscle creatine and phosphocreatine content increase by 20% to 30%.<sup>3,4</sup> The uptake of muscle creatine apparently can be augmented with simultaneous carbohydrate ingestion, perhaps via insulin stimulation,<sup>6</sup> and muscle creatine levels remain elevated for up to 1 month after the loading scheme described.<sup>3,4</sup> Urinary creatine excretion increases to match intake, and urinary creatinine excretion increases in parallel to the increased muscle creatine content during long-term creatine supplementation.<sup>7</sup>

Several studies have shown that creatine loading improves muscle strength and performance, either during intense, maximal exercise or during repetitive exercise when compared with the pre-loaded state.<sup>2,3,5,6,8,9</sup> Thus, power lifters, sprint runners, rowers, and swimmers have all been shown to benefit from oral creatine supplementation.<sup>5,8,9</sup> In one study, college male athletes ingested either a placebo glucose/salt solution or the same solution with 15.75 g of creatine daily for 28 days. The creatine-loaded group achieved a significantly greater increase in bench-press lifting volume and a greater work performance in the first 5 of 12 repetitive 5-second bicycle ergometer sprints when compared with the placebo group.<sup>9</sup> Performance during sprints 6 to 12 did not differ, presumably due to the exhaustion of the phosphocreatine store in both groups after

the first repetitions.<sup>9</sup> Similar results were obtained with a daily ingestion of 20 g of creatine when performance was tested at 14 days and 28 days of supplementation.<sup>8</sup> Conversely, there appears to be no enhancement in muscle performance during submaximal, aerobic exercise, or during continuous endurance exercise.<sup>3</sup>

In the face of these positive influences of creatine on athletic performance, there is a counter consideration for the safety of a sustained high intake of this product. One hypothetical concern arises from the known effect of high-protein intake on kidney function and its relation to progressive dysfunction in previously diseased kidneys.<sup>10</sup> Ingestion of a high-protein meal or infusion of a solution of amino acids can increase renal blood flow and the glomerular filtration rate (GFR) in humans by up to 20%.<sup>11</sup> A sustained elevated intake of meat protein leads to an increase in total creatinine excretion—the consequence of increased creatine and creatinine ingestion—and a persisting increase in the GFR.<sup>11</sup> There is clear evidence from a number of animal models of renal injury that high protein intake increases proteinuria and hastens the progressive decline in GFR.<sup>10</sup> Whether creatine alone, as a product of amino acid metabolism, can produce similar effects is unknown.

One study has examined the renal effects of ingesting 20 g of creatine daily for 5 days.<sup>12</sup> Arterial creatine levels increased almost four-fold, while urinary creatine excretion increased from <150 mg/day to nearly 13 g/day ( $\approx 65\%$  of ingested load). In contrast, over this short period, the serum creatinine level increased negligibly, from 0.95 mg/dL to 1.0 mg/dL, and total urinary creatinine excretion was no different (2.17 g/day vs 2.32 g/day, before and after creatine loading, respectively). Most important, creatine loading led to a change in neither creatinine clearance nor urinary albumin excretion.<sup>12</sup> In another study, the ingestion of 20 g of creatine for 5 days resulted in an increase of approximately 30% in urinary creatinine excretion after 20 days of observation, with no reported effect on renal function.<sup>4</sup> While these short-term effects are reassuring, they may not reflect longer exposures in which new steady-state relations between creatine and creatinine develop.

In healthy athletes ingesting 15.75 g of creatine daily, there was a significant increase in the serum creatinine level, from 102  $\mu\text{mol/L}$

to 125  $\mu\text{mol/L}$  after 28 days of supplementation.<sup>9</sup> Interestingly, serum creatine kinase levels also increased from an average of 239 IU/L to 609 IU/L, an effect also seen in non-exercising adults receiving long-term creatine supplementation. Daily urinary creatinine excretion can be shown to vary widely, based on both protein and creatine intake. Studies have shown urinary creatinine excretion to decrease when creatine was eliminated from the diet, even at unchanged levels of protein ingestion.<sup>13</sup> Unfortunately, there are no parallel data to reflect glomerular filtration rates under similar circumstances.

A note of caution for patients with preexisting renal disease has been raised by a case report that describes a temporal relation between creatine supplementation, increases in the serum creatinine concentration, and reciprocal decreases in creatinine clearance.<sup>14</sup> A young man with chronic glomerulonephritis (focal segmental glomerulosclerosis) of 8 years' duration and stable renal function had an increase in the level of serum creatinine from 103  $\mu\text{mol/L}$  to 159  $\mu\text{mol/L}$  over 12 weeks and an ultimate increase to 180  $\mu\text{mol/L}$  after 16 weeks. The patient had begun creatine loading as described between the first two observations. After stopping creatine intake for 1 month, the serum creatinine level returned to 128  $\mu\text{mol/L}$ . In contrast to individuals with normal renal function, who had slight elevations of the serum creatinine level but no change in creatinine clearance with creatine supplementation, this patient had reciprocal decreases in measured GFR at each increase of the serum creatinine level.<sup>14</sup> No clear basis for this effect was forthcoming from this single observation.

In April 1998, the Food and Drug Administration (FDA) issued a warning to potential users of creatine for performance enhancement.<sup>15</sup> The FDA and the National Collegiate Athletic Association are investigating the deaths of three collegiate wrestlers who were taking creatine and two additional cases in which creatine users had grand mal seizures. The FDA has advised athletes to consult a physician or health care professional before embarking on any scheme of creatine loading or supplementation.<sup>15</sup> While no firm data indicate any injurious effects of creatine on renal function, nor a proved relationship with these events,<sup>14</sup> it seems prudent to collect more data on the long-term effects of creatine loading and supplementation before the practice can be sanctioned.

For the time being, the daily ingestion of 20 g of creatine, either as a dietary supplement or as 11 pounds of steak, must be considered when quantifying renal functions that rely on the near constancy of 24-hour urinary creatinine excretion.

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