Introduction:
Competition and the drive for excellence motivated the application of biochemical physiology knowledge to athletic training regimens. One of the first such applications is that of creatine monohydrate (CrM) for world-class athletes, the use of which dates to the 1970's, when state-sponsored Olympic Games athletes from the Soviet Union used creatine as an ergogenic aid.[1] The prominent Ukrainian biochemist Olexander Pallandin, who trained under Ivan Pavlov, showed in the 1930's that levels of creatine and phosphocreatine change with contraction strength and exertion and are increased by training. He also showed levels are higher in fast-twitch, white fibers than slow-twitch, red fibers. Based upon this pioneering work, the research and subsequent use of creatine as an ergogenic dietary supplement for elite athletes was sponsored by the Central Institute of Physical Culture in Moscow.

The history of the use of CrM supplementation illustrates the culture of competitive athletics, wherein the pursuit of improved performance often overrides caution about possible health risks. Even amidst isolated case reports of severe toxicity and the absence of comprehensive long term studies of safety, creatine supplementation remains extremely common: Metzl et al. showed that 28% of collegiate athletes and many high school athletes, particularly 11^{th} and 12^{th} grade males, take creatinine.[2]

Biochemical Physiology:
The use of creatine monohydrate (CrM) as an athletic supplement is based on the physiological presence of creatine (Cr) and phosphoryl creatine (PCr) in skeletal muscle, where PCr acts as a minor store of high energy compounds, which may rapidly but only transiently be recruited to replenish the depleted energy stores in vigorously contracting muscles. The CrM supplement theory postulates that, by increasing the concentration of Cr in skeletal muscle, CrM will allow muscle to achieve a higher anaerobic threshold and to undergo higher intensity training.

Creatine is a non-essential amino acid that is formed in the liver, pancreas and kidney and also consumed in the diet from the ingestion of animal products. Cr has the ability to bind a high energy phosphate, forming PCr. During high intensity exercise, muscle drains its adenosine triphosphate (ATP) stores. PCr donates its high energy phosphate to adenosine diphosphate (ADP), leading to the re-synthesis of adenosine triphosphate (ATP). Thus, PCr acts as a short-term energy buffer during periods of rapid ATP turnover. The system is high power (large amounts of ATP may be produced) but low capacity (storage amounts are normally drained in less than 20 seconds), thus fitting a role in anaerobic activity.[9]

Skeletal muscle is the body's primary repository for Cr, and thus is the target for CrM supplementation. Muscle Cr stores break down at a relatively constant rate of approximately 2 grams/day into creatinine. Cr is normally filtered at a consistent rate by the kidney, thus making Cr a useful measure of kidney function.

Purported Benefits:

CrM is generally considered an effective enhancer for high intensity, short duration activity but not for longer duration, endurance / aerobic activity. Over 500 research studies have examined the effect of CrM on athletic performance. Most studies on the potential value of CrM as an ergogenic augmenter report statistically significant gains in creatine takers.[16] A number of recent randomized controlled trials of selected populations of athletes confirms this finding. Mero et al. show that interval swimming performance is improved with CrM.[18] Ostojic demonstrated that soccer-specific skill performance is enhanced with CrM.[19] Biwer et al. showed that submaximal running interspersed within high intensity intervals is not improved with CrM.[23]

Given the normal physiological role of PCr in skeletal muscle, CrM is used therapeutically for a wide variety of diseases. Recent studies have confirmed the efficacy of CrM for selected diseases. Tarnopolsky et al. report that the use of CrM enhances muscle strength and fat free mass in children with Duchenne muscular dystrophy.[17] Lebacq et al. corroborated this by showing improved strength and bone mineral density and decreased fatigue in patients with Duchenne and Becker dystrophy.[22] Korenke et al. report that CrM led to long term improvement for a girl with ataxia and weakness due to a long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency.[21] However, Bohnhorst et al. report that the use of CrM in infants with apnea of prematurity is not clinically helpful.[20]

Side Effects:
The question of whether creatine poses short or long term health risks remains unresolved. In the absence of large scale, long term randomized study, the safety of the routine use of creatine among young athletes cannot be definitively confirmed. Two key risks categories exist today: 1) the potential for direct toxic injury and 2) the lack of quality control.

Isolated cases have implicated creatine supplementation in direct renal toxicity.[3,4,5] However, no large scale studies have shown a pattern of renal or other toxicity in healthy humans.[6] Researchers agree that longer term studies are necessary before the possibility of a pattern of toxicity can eliminated. However, most striking in the literature is a general discord among researchers as to whether current studies suggest that creatine represents a serious risk to tissue injury. Direct and indirect evidence exists to support both the argument for its potential toxicity as well as that for its innocuousness. In Nutrition Bytes 2002, Der Hovanessian commented that studies failed to show evidence for toxicity due to short and medium term use of CrM, but he reserved caution for the potential for toxicity due to long term use.[10] This caution stemmed from the lack of reliable studies, with only the 5 year study by Poortmans et al., qualifying as long term.[11] While this study reported no major toxicity, among other problems, it only had 9 study subjects. The fact that the Poortmans et al. might be considered a substantial study highlights the paucity of reliable evidence on creatine use. The major limitations of research to date are small sample size and short length of studies. If toxicity is rare, large scale studies are required to capture the effect. Additionally, if the effects are insidious and slow in onset, only longer term studies will sufficiently recognize the deleterious effects. It cannot be argued that studies to date offer strong evidence-based artillery either to the industry proponent nor the frank critic of creatine use.

In terms of indirect evidence, the results of animal studies are mixed. Taes et al. report that 28 day treatment of both healthy and partially nephrectomized rats with creatine supplementation did not impair renal function.[7] A study by Edmunds et al. challenges this conclusion. It examined creatine supplementation in rats with cystic kidney diseases and showed that creatine may exacerbate the progression of kidney disease.[14] Meanwhile, Tarnopolsky et al. report mixed results after 159 day treatment of mice and 365 day treatment of rats. While histological examination of rat livers revealed no abnormalities, that of the mice livers showed areas of hepatitis.[8] Also, studies of creatine metabolism suggest that its breakdown may lead to mutagenic metabolites.[9] The implication of an increased carcinogenic load due to creatine and its metabolites cannot be overlooked, notwithstanding the lack of specific studies confirming the causal or contributory relation between creatine and certain cancers.

Results from direct studies are equally mixed and not of sufficient quality to address the concern of potential long term toxicity. Two recent studies of moderate length argue for the intermediate term lack of severe toxicity of creatine. Kreider et al examined a 69 item panel of serum, whole blood and urinary markers of clinical health, including metabolic markers, muscle and liver enzymes, electrolytes, lipid profiles, hematological markers and lymphocytes, in college athletes in a 21 month non-blinded trial.[12] This trial failed to show significant differences in clinical markers between creatine takers and controls. In a companion study, Greenwood et al. compared the incidence of cramping, dehydration, muscle tightness, and injuries in creatine takers and controls among college athletes in a 3 year non-blinded trial.[13] This study found fewer or similar rates of the above problems among creatine takers when compared to controls.

The second major risk category is lack of quality control. Creatine supplementation remains relatively unregulated. According to the Dietary Supplement Health and Education Act of 1994, much less stringent oversight exists for nutritional supplements, such as creatine, than for pharmaceuticals, allowing food supplements producers to make structure and function claims without FDA approval or comprehensive scientific backing. Equally alarming is the lack of assurance for integrity of concentration and purity, leaving open the possibilities of toxicity due to overdosing and contamination.[15]

Conclusion:

The use of creatine supplementation continues to be a hotly debated and relevant topic for health care professionals, amid its widespread use among young people and the mass of research with inconclusive or questionable outcomes. While the argument that creatine is an effective anaerobic ergogenic aid has a wealth of evidence, the case for the safety of its long term use does not. This fact is worrisome given the cavalier manner in which many use the supplement, as considerations of genetic predispositions to kidney disease, underlying occult or known disease states, or even metabolically competing medications are often excluded from the decision of whether, how much and for how long to use the creatine supplement. While evidence to date does not suggest a widespread pattern of severe side effects from its use, the research is silent regarding risks in the context of disease, such as impaired glomerular filtration. In an era where the burden of proof lies with the health care professional, who operates under the principle of evidence based

medicine, physicians should work to communicate this lack of clarity, to urge caution and to demand more comprehensive research.

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