LE Magazine March 2003

REPORT

Creatine: More than a sports nutrition supplement

Although creatine offers an array of benefits, most people think of it simply as a supplement that bodybuilders and other athletes use to gain strength and muscle mass. Nothing could be further from the truth.

A substantial body of research has found that creatine may have a wide variety of uses. In fact, creatine is being studied as a supplement that may help with diseases affecting the neuromuscular system, such as muscular dystrophy (MD). Recent studies suggest creatine may have therapeutic applications in aging populations for wasting syndromes, muscle atrophy, fatigue, gyrate atrophy, Parkinson's disease, Huntington's disease and other brain pathologies. Several studies have shown creatine can reduce cholesterol by up to 15% and it has been used to correct certain inborn errors of metabolism, such as in people born without the enzyme(s) responsible for making creatine. Some studies have found that creatine may increase growth hormone production.

What is creatine?

Creatine is formed in the human body from the amino acids methionine, glycine and arginine. The average person's body contains approximately 120 grams of creatine stored as creatine phosphate. Certain foods such as beef, herring and salmon, are fairly high in creatine. However, a person would have to eat pounds of these foods daily to equal what can be obtained in one teaspoon of powdered creatine.

Creatine is directly related to adenosine triphosphate (ATP). ATP is formed in the powerhouses of the cell, the mitochondria. ATP is often referred to as the "universal energy molecule" used by every cell in our bodies. An increase in oxidative stress coupled with a cell's inability to produce essential energy molecules such as ATP, is a hallmark of the aging cell and is found in many disease states. Key factors in maintaining health are the ability to: (a) prevent mitochondrial damage to DNA caused by reactive oxygen species (ROS) and (b) prevent the decline in ATP synthesis, which reduces whole body ATP levels. It would appear that maintaining antioxidant status (in particular intra-cellular glutathione) and ATP levels are essential in fighting the aging process.

It is interesting to note that many of the most promising anti-aging nutrients such as CoQ10, NAD, acetyl-l-carnitine and lipoic acid are all taken to maintain the ability of the mitochondria to produce high energy compounds such as ATP and reduce oxidative stress. The ability of a cell to do work is directly related to its ATP status and the health of the mitochondria. Heart tissue, neurons in the brain and other highly active tissues are very sensitive to this system. Even small changes in ATP can have profound effects on the tissues' ability to function properly. Of all the nutritional supplements available to us currently, creatine appears to be the most effective for maintaining or raising ATP levels.

How does creatine work?

In a nutshell, creatine works to help generate energy. When ATP loses a phosphate molecule and becomes adenosine diphosphate (ADP), it must be converted back to ATP to produce energy. Creatine is stored in the human body as creatine phosphate (CP) also called phosphocreatine. When ATP is depleted, it can be recharged by CP. That is, CP donates a phosphate molecule to the ADP, making it ATP again. An increased pool of CP means faster and greater recharging of ATP,

which means more work can be performed. This is why creatine has been so successful for athletes. For short-duration explosive sports, such as sprinting, weight lifting and other anaerobic endeavors, ATP is the energy system used.

To date, research has shown that ingesting creatine can increase the total body pool of CP which leads to greater generation of energy for anaerobic forms of exercise, such as weight training and sprinting. Other effects of creatine may be increases in protein synthesis and increased cell hydration.

Creatine has had spotty results in affecting performance in endurance sports such as swimming, rowing and long distance running, with some studies showing no positive effects on performance in endurance athletes. Whether or not the failure of creatine to improve performance in endurance athletes was due to the nature of the sport or the design of the studies is still being debated. Creatine can be found in the form of creatine monohydrate, creatine citrate, creatine phosphate, creatine-magnesium chelate and even liquid versions. However, the vast majority of research to date showing creatine to have positive effects on pathologies, muscle mass and performance used the monohydrate form. Creatine monohydrate is over 90% absorbable. What follows is a review of some of the more interesting and promising research studies with creatine.

Creatine and neuromuscular diseases

One of the most promising areas of research with creatine is its effect on neuromuscular diseases such as MD. One study looked at the safety and efficacy of creatine monohydrate in various types of muscular dystrophies using a double blind, crossover trial. Thirty-six patients (12 patients with facioscapulohumeral dystrophy, 10 patients with Becker dystrophy, eight patients with Duchenne dystrophy and six patients with sarcoglycan-deficient limb girdle muscular dystrophy) were randomized to receive creatine or placebo for eight weeks. The researchers found there was a "mild but significant improvement" in muscle strength in all groups. The study also found a general improvement in the patients' daily-life activities as demonstrated by improved scores in the Medical Research Council scales and the Neuromuscular Symptom scale. Creatine was well tolerated throughout the study period, according to the researchers.1

Another group of researchers fed creatine monohydrate to people with neuromuscular disease at 10 grams per day for five days, then reduced the dose to 5 grams per day for five days. The first study used 81 people and was followed by a single-blinded study of 21 people. In both studies, body weight, handgrip, dorsiflexion and knee extensor strength were measured before and after treatment. The researchers found "Creatine administration increased all measured indices in both studies." Short-term creatine monohydrate increased high-intensity strength significantly in patients with neuromuscular disease.2

There have also been many clinical observations by physicians that creatine improves the strength, functionality and symptomology of people with various diseases of the neuromuscular system.

Creatine and neurological protection/brain injury

If there is one place creatine really shines, it's in protecting the brain from various forms of neurological injury and stress. A growing number of studies have found that creatine can protect the brain from neurotoxic agents, certain forms of injury and other insults. Several in vitro studies found that neurons exposed to either glutamate or beta-amyloid (both highly toxic to neurons and involved in various neurological diseases) were protected when exposed to creatine.3 The researchers hypothesized that "… cells supplemented with the precursor creatine make more phosphocreatine (PCr) and create larger energy reserves with consequent neuroprotection against stressors."

More recent studies, in vitro and in vivo in animals, have found creatine to be highly neuroprotective against other neurotoxic agents such as N-methyl-D-aspartate (NMDA) and malonate.4 Another study found that feeding rats creatine helped protect them against tetrahydropyridine (MPTP), which produces parkinsonism in animals through impaired energy production. The results were impressive enough for these researchers to conclude, "These results further implicate metabolic dysfunction in MPTP neurotoxicity and suggest a novel therapeutic approach, which may have applicability in Parkinson's disease."5 Other studies have found creatine protected neurons from ischemic (low oxygen) damage as is often seen after strokes or injuries.6

Yet more studies have found creatine may play a therapeutic and or protective role in Huntington's disease7, 8 as well as ALS (amyotrophic lateral sclerosis).9 This study found that "… oral administration of creatine produced a dose-dependent improvement in motor performance and extended survival in G93A transgenic mice, and it protected mice from loss of both motor neurons and substantia nigra neurons at 120 days of age. Creatine administration protected G93A transgenic mice from increases in biochemical indices of oxidative damage. Therefore, creatine administration may be a new therapeutic strategy for ALS." Amazingly, this is only the tip of the iceberg showing creatine may have therapeutic uses for a wide range of neurological disease as well as injuries to the brain. One researcher who has looked at the effects of creatine commented, "This food supplement may provide clues to the mechanisms responsible for neuronal loss after traumatic brain injury and may find use as a neuroprotective agent against acute and delayed neurodegenerative processes."

Creatine and heart function

Because it is known that heart cells are dependent on adequate levels of ATP to function properly, and that cardiac creatine levels are depressed in chronic heart failure, researchers have looked at supplemental creatine to improve heart function and overall symptomology in certain forms of heart disease. It is well known that people suffering from chronic heart failure have limited endurance, strength and tire easily, which greatly limits their ability to function in everyday life. Using a double blind, placebocontrolled design, 17 patients aged 43 to 70 years with an ejection fraction <40 were supplemented with 20 grams of creatine daily for 10 days. Before and after creatine supplementation, the researchers looked at:

1) **Ejection fraction of the heart (blood present in the ventricle at the end of diastole and expelled during the contraction of the heart)**

2) **1-legged knee extensor (which tests strength)**

3) **Exercise performance on the cycle ergometer (which tests endurance)**

Biopsies were also taken from muscle to determine if there was an increase in energy-producing compounds (i.e., creatine and creatine phosphate). Interestingly, but not surprisingly, the ejection fraction at rest and during the exercise phase did not increase. However, the biopsies revealed a considerable increase in tissue levels of creatine and creatine phosphate in the patients getting the supplemental creatine. More importantly, patients getting the creatine had increases in strength and peak torque (21%, $P < 0.05$) and endurance (10%, $P < 0.05$). Both peak torque and 1-legged performance increased linearly with increased skeletal muscle phosphocreatine ($P < 0.05$). After just one week of creatine supplementation, the researchers concluded: "Supplementation to patients with chronic heart failure did not increase ejection fraction but increased skeletal muscle energy-rich phosphagens and performance as regards both strength and endurance. This new therapeutic approach merits further attention."10

Another study looked at the effects of creatine supplementation on endurance and muscle metabolism in people with congestive heart failure.11 In particular the researchers looked at levels of ammonia and lactate, two important indicators of muscle performance under stress. Lactate and ammonia levels rise as intensity increases during exercise and higher levels are associated with fatigue. High-level athletes have lower levels of lactate and ammonia during a given exercise than non-athletes, as the athletes' metabolism is better at dealing with these metabolites of exertion, allowing them to perform better. This study found that patients with congestive heart failure given 20 grams of creatine per day had greater strength and endurance (measured as handgrip exercise at 25%, 50% and 75% of maximum voluntary contraction or until exhaustion) and had lower levels of lactate and ammonia than the placebo group. This shows that creatine supplementation in chronic heart failure augments skeletal muscle endurance and attenuates the abnormal skeletal muscle metabolic response to exercise.

It is important to note that the whole-body lack of essential high energy compounds (e.g. ATP, creatine, creatine phosphate, etc.) in people with chronic congestive heart failure is not a matter of simple malnutrition, but appears to be a metabolic derangement in skeletal muscle and other tissues.12 Supplementing with high energy precursors such as creatine monohydrate appears to be a highly effective, low cost approach to helping these patients live more functional lives, and perhaps extend their life spans.

Conclusion

Creatine is quickly becoming one of the most well researched and promising supplements for a wide range of diseases. It may have additional uses for pathologies where a lack of high energy compounds and general muscle weakness exist, such as fibromyalgia. People with fibromyalgia have lower levels of creatine phosphate and ATP levels compared to controls.13 Some

studies also suggest it helps with the strength and endurance of healthy but aging people as well. Though additional research is needed, there is a substantial body of research showing creatine is an effective and safe supplement for a wide range of pathologies and may be the next big find in anti-aging nutrients. Although the doses used in some studies were quite high, recent studies suggest lower doses are just as effective for increasing the overall creatine phosphate pool in the body. Two to three grams per day appears adequate for healthy people to increase their tissue levels of creatine phosphate. People with the aforementioned pathologies may benefit from higher intakes, in the 5-to-10 grams per day range.

Find out more about Creatine from Life Extension

References

1. Walter MC, et al. Creatine monohydrate in muscular dystrophies: A double blind, placebo-controlled clinical study. Neurology 2000 May 9; 54(9): 1848-50.

2. Tarnopolsky M, et al. Creatine monohydrate increases strength in patients with neuromuscular disease. Neurology 1999 Mar 10; 52(4): 854-7.

3. Protective effect of the energy precursor creatine against toxicity of glutamate and beta-amyloid in rat hippocampal neurons. J Neurochem 1968-1978; 74(5).

4. Malcon C, et al. Neuroprotective effects of creatine administration against NMDA and malonate toxicity. Brain Res 2000; 860(12): 195-8.

5. Matthews RT, et al. Creatine and cyclocreatine attenuate MPTP neurotoxicity. Exp Neurol 1999; 157(1): 142-9.

6. Balestrino M, et al. Role of creatine and phosphocreatine in neuronal protection from anoxic and ischemic damage. Amino Acids Abstract 2002; 23(1-3): 221-229.

7. Matthews RT, et al. Neuroprotective effects of creatine and cyclocreatine in animal models of Huntington's disease. J Neurosci 1998; 18(1): 156-163.

8. Ferrante RJ, et al. Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. J Neurosci 2000; 20
(12): 4389-97.

9. Klivenyi P, et al. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. Nat Med 1999; 5(3): 347-50.

10. Gordon A, et al. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. Cardiovasc Res 1995 Sep; 30(3): 413-8.

11. Andrews R, et al. The effect of dietary creatine supplementation on skeletal muscle metabolism in congestive heart failure. Eur Heart J 1998 Apr; 19(4): 617-22.

12. Broqvist M, et al. Nutritional assessment and muscle energy metabolism in severe chronic congestive heart failure-effects of long-term dietary supplementation. Eur Heart J 1994 Dec; 15(12): 1641-50.

13. Park JH, et al. Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. Arthritis Rheum 1998 Mar; 41(3): 406-13.

Additional References of Interest

Earnest CP, Almada AL, Mitchell TL. High-performance capillary electrophoresis-pure Creatine monohydrate reduces blood lipids in men and women. Clin Sci Colch 1996 Jul; 91(1): 113-8.

Field ML .Creatine supplementation in congestive heart failure. Cardiovasc Res 1996 Jan; 31(1): 174-6.

Kreider, RB, Ferreira M, et al. Effects of creatine supplementation on body composition, strength, and sprint performance. Med Sci Sports Exerc 1998; 30(1): 73-82.

Odland LM, MacDougall JD, Tarnopolsky MA, Elorriaga A, Borgmann A. Effect of oral Creatine supplementation on muscle [PCr] and short-term maximum power output. Med Sci Sports Exerc 1997 Feb; 29(2): 216-9.

Pearson DR, Hamby DG, Russel W, Harris T. Long-term effects of Creatine monohydrate on strength and power. J Strength Cond Res 1999; 13(3); 187-192.

Peeters BM, Lantz CD, Mayhew JL. Effect of oral creatine monohydrate and creatine phosphate supplementation on maximal strength indices, body composition, and blood pressure. J Strength Cond Res.

Back to the Magazine Forum