

The Longwood Herbal Task Force
(<http://www.mcp.edu/herbal/default.htm>) and
The Center for Holistic Pediatric Education and Research
(<http://www.childrenshospital.org/holistic/>)

Creatine

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Principal Proposed Use: Enhancement of athletic performance

Other Proposed Uses: Treatment of rare metabolic and neuromuscular disorders, treatment of chronic heart failure

Overview

Creatine gained prominence in the 1990's as a natural way to enhance athletic performance and build lean body mass. Other uses include the treatment of rare metabolic and neuromuscular disorders and the treatment of chronic heart failure. Creatine is naturally synthesized in the human body, primarily in the kidney and liver, and transported by the blood for use in the muscles. It is metabolized and excreted renally. Overall, it appears to have modest benefits for intense, repetitive exercise lasting less than 30 seconds. It has no significant benefits on prolonged (endurance) aerobic exercise. Creatine and creatine analogs are under investigation in animal studies of cancer. Additional study is needed to clarify creatine's role in treating metabolic and neuromuscular disorders and chronic heart failure. Creatine is very safe, although there is a report of renal failure in a patient taking high doses over a prolonged period and a similar report in a patient with pre-existing renal disease. Caffeine may counteract creatine's benefits on acute intermittent exercise performance. There are no data evaluating the safety of creatine supplements during pregnancy, lactation or childhood.

Historical and Popular Uses

Creatine is a relative newcomer to the dietary supplement scene. It is not part of Traditional Chinese Medicine, Ayurveda, or Naturopathic Medicine. It gained prominence in the early 1990's as a natural way to increase lean body mass and enhance athletic performance. It

has not been banned by the International Olympic Committee, the International Amateur Athletic Federation or the National Collegiate Athletic Association.

Creatine is one of the supplements most commonly used by adult and adolescent athletes; teen athletes frequently exceed the recommended loading and maintenance doses¹. Anecdotes suggest that approximately 25% of professional baseball players and up to 50% of professional football players take creatine supplements². In 1998, the creatine market in the US was estimated to be \$200 million³.

Common Names

Creatine is also called creatine citrate, creatine monohydrate, and creatine phosphate. Creatine was named after the Greek word for “flesh”.

Biochemistry and Physiology

Creatine is normally found in meat and fish; the typical adult omnivore consumes approximately 1 – 2 grams daily. It is also synthesized in the human body from dietary amino acids⁴. Synthesis begins in the kidney when arginine and glycine form guanidoacetic acid. This product is methylated in the liver, forming creatine, technically known as methylguanidine-acetic acid. Creatine is transported through the blood to muscles where it is highly concentrated as creatine phosphate (CrP). About 95% of body stores are found in muscle; creatine is also found in the liver, kidney, sperm, brain, eyes and nerves.

Normal creatine plasma levels are 40 –100 micromoles/liter; levels are about 25 mcM/L in vegetarians⁵. The total adult body pool is approximately 120 –140 grams, of which approximately 95% is stored in muscle⁶.

Myocytes use creatine to make phosphocreatine (PCr) via the enzyme creatine kinase (CK). Phosphocreatine is used to convert adenosine diphosphate (ADP) to adenosine triphosphate (ATP). Phosphocreatine also buffers intracellular hydrogen ions associated with lactate production and muscle fatigue during exercise. Thus, creatine may increase both the force of muscle contraction (by boosting ATP levels) and the duration of anaerobic exercise. During the first ten seconds of intense exercise, creatine levels are markedly depleted.

Creatine is well absorbed after oral administration; absorption appears to be enhanced by taking it with a high carbohydrate diet⁷. Typically, a loading dose of 20 grams daily for 5 days is used to rapidly increase muscle creatine levels, followed by a maintenance dose of 2 - 5 grams daily; muscle levels can also be increased more gradually with a daily maintenance dose of 5 grams^{7,8}. After oral dosing, maximum creatine levels are reached in approximately 90 minutes⁹. Creatine is metabolized to creatinine and excreted renally as creatine and creatinine; 40% is excreted within ten hours of administration. Dosing is typically twice daily.

Experimental Studies

Creatine: Potential Clinical Benefits

1. Cardiovascular: Chronic heart failure
2. Pulmonary: none
3. Renal and electrolyte balance: none
4. Gastrointestinal/hepatic: none
5. Neuropsychiatric: none
6. Endocrine: none
7. Hematologic: none
8. Rheumatologic: none
9. Reproductive: none
10. Immune modulation: none
11. Antimicrobial: none
12. Antineoplastic: Antiproliferative effect on tumors
13. Antioxidant: none
14. Skin and mucus membranes: none
15. Other/miscellaneous: Enhancement of athletic performance, treatment of rare metabolic defects and neuromuscular disorders

1. **Cardiovascular:** Chronic heart failure: Based on its effects in building skeletal muscle mass and improving high intensity athletic performance, researchers have begun evaluating the effects of creatine supplementation in patients with chronic heart failure^{10,11}.
 - i. *In vitro data*: See Miscellaneous: Enhanced athletic performance.
 - ii. *Animal data*: In rats, data on the effects of creatine supplementation on cardiac energy reserves have been conflicting: one study suggested improved reserves and another failed to show any impact^{12,13}.
 - iii. *Human data*: Both case series and randomized trials support the use of creatine supplementation in patient with heart failure.

Among fifteen patients with NYHA Class II-III heart failure, treatment with creatine phosphate (6 grams i.v. daily for five days) was associated with an improvement

in ejection fraction and improved clinical symptoms¹⁴. In patients with acute myocardial infarction, creatine phosphate plus nifedipine was more effective than nifedipine alone in increasing stroke index¹⁵.

A randomized controlled trial of 17 patients with chronic heart failure who were given either creatine (20 grams daily) or placebo for ten days showed no significant improvement in cardiac function with creatine supplementation; however, those treated with creatine had a significant increase in skeletal muscle strength and endurance¹⁶. These findings were replicated in a randomized, double-blind study of 20 patients with chronic heart failure; those taking creatine supplements for six days had significantly improved skeletal muscle endurance in laboratory tests compared with patients assigned to placebo¹⁷.

In a double-blind, placebo controlled trial, 13 patients hospitalized with NYHA class II-III heart failure and treated with conventional therapy were also given either creatine phosphate (6 grams) or placebo intravenously daily for four days; those given creatine had a significant improvement in cardiac ejection fraction and percent fractional shortening¹⁸. In a large randomized, controlled multi-center trial of 1007 patients with chronic heart failure who were treated with conventional therapy, 508 were randomized to receive creatine phosphate (1 gram twice daily intravenously for two weeks) and 499 to receive conventional therapy only. The creatine-treated group improved significantly more than the placebo group in terms of symptoms of heart failure (dyspnea, edema), signs of ischemia (angina, need for sublingual nitroglycerin) and the incidence of ventricular premature beats¹⁹.

2. **Pulmonary:** none
3. **Renal and electrolyte balance:** none
4. **Gastrointestinal/hepatic:** none
5. **Neuropsychiatric:** See Miscellaneous: Neuromuscular disorders.
6. **Endocrine:** none.
7. **Hematologic:** none
8. **Rheumatologic:** none
9. **Reproductive:** none

10. **Immune modulation:** none

11. **Antimicrobial:** none

12. **Antineoplastic:** Antiproliferative effect on tumors: Some researchers speculate that creatine, like antioxidants, upregulates apoptosis in preneoplastic and neoplastic cells²⁰.

- i. *In vitro data:* Cyclocreatine, a creatine kinase substrate analog, is cytotoxic to a broad spectrum of solid tumors²¹. Several synthetic creatine kinase analogs are cytotoxic to the human ME-180 cervical carcinoma, the MCF-7 breast adenocarcinoma and the HT-29 colon adenocarcinoma cell lines and delay the growth of a rat mammary adenocarcinoma by six to eight days, which is comparable to effects seen with standard regimens of currently used anticancer drugs²².
- ii. *Animal data:* Nude mice transplanted with human colon adenocarcinoma who were given creatine supplements demonstrated significant inhibition of tumor growth; the growth inhibition was directly correlated with creatine tissue concentrations²³. When rats with mammary carcinoma were treated with the intravenously administered creatine analogs cyclocreatine, beta-guanidinopropionic acid or creatine phosphate, there was significant tumor growth delay²⁴.
- iii. *Human data:* none

13. **Antioxidant:** none

14. **Skin and mucus membranes:** none

15. **Other/miscellaneous:** Enhancement of athletic performance, treatment of rare metabolic defects and neuromuscular disorders

a. Enhancement of athletic performance

- i. *In vitro data:* none
- ii. *Animal data:* Rats given creatine supplements had no change in glycogen resynthesis in liver or skeletal muscle²⁵. Rats given creatine supplements chronically had a down regulation in the expression of creatine transporter protein, which is responsible for creatine uptake into cells²⁶. These results have uncertain implications for the chronic use of creatine supplements by either athletes or patients with metabolic or neuromuscular defects.

iii. *Human data:*

- a. **Physiology: increased muscle phosphocreatine levels.** In a pilot study of eight adults who took creatine supplements and then performed dynamic knee extension inside a magnetic resonance imaging system, there was a significant increase in the muscle levels of phosphocreatine, but no effect on muscle ATP levels or the energy costs of muscle contractions²⁷.

In young healthy men, creatine supplementation for two to five days increased resting muscle levels of phosphocreatine (by 11% to 16%), but had no effect on phosphocreatine breakdown or resynthesis during isometric muscle contractions²⁸.

In middle-aged men (mean age 58 years), creatine supplementation increased resting phosphocreatine levels in the muscle by 30%, increased phosphocreatine resynthesis rates and improved strength during single knee extension²⁹.

- b. **Physiology: increase in lean body mass.** In young men (average age 20 years), creatine supplements increased lean body mass by approximately two kg over nine weeks³⁰. In older men (60 –82 years), creatine supplements taken daily for nine weeks did not change body composition or strength, but did reduce muscle fatigue³¹. These results were replicated in a Scandinavian study of 32 elderly subjects (67 – 80 years old, half of whom were women), for whom eight weeks of creatine supplementation failed to enhance maximum strength or endurance³².
- c. **Physiology: other.** Creatine supplementation for five days significantly increased the maximal accumulated oxygen deficit (MAOD), one measure of anaerobic exercise capacity, in young men⁶. In healthy young men, creatine supplementation facilitated the rate of muscle relaxation between periods of isometric muscle contractions, but did not affect torque production³³. Among untrained, college aged men, creatine supplementation for five days led to a significant improvement in maximal isometric strength during knee extension (large muscle strength), but no improvement in handgrip strength (small muscle strength)³⁴.

- d. **Exercise performance.** Data on effectiveness are mixed. Most studies have had small sample sizes and short follow-up periods. Most support creatine's use in enhancing performance during short bursts of anaerobic muscle activity (less than 30 seconds duration), but do not support its use to enhance sustained aerobic activities³⁵.
- i. *Weight lifting:* Randomized controlled trials studies suggest that creatine supplements enhance performance in repetitive lifting exercises³⁶. For example, in double-blind randomized, controlled trials in both football players and women beginning a weight training program, creatine supplementation significantly improved weight lifting performance^{37,38}. In other small randomized, controlled trials in adult men, creatine supplementation (for 1- 50 weeks) increased maximum voluntary contraction of knee extensors, maximal bench press weight lifted and static vertical jump power^{39,40,41}.
- ii. *Sprinting:* Creatine's ability to enhance performance during sprints, whether these are running, bicycling, swimming or kayaking is much more modest than its effect on weight training performance.

For running performance, two studies showed benefits^{42,43} and three did not^{44,45,46}. For example, in male handball players randomized to receive either creatine (15 grams daily) or placebo for five days, the creatine-supplemented group had significantly improved sprint times⁴³. On the other hand, in a placebo controlled trial of 18 competitive sprinters, creatine supplements had no impact on 60-meter sprint time⁴⁶.

Studies of creatine's impact on bicycling sprints have also had mixed results. In an open trial of nine men, creatine (20 grams daily for five days) produced a four percent increase in work production during 30-second bouts of maximal cycling⁴⁷. Two open trials showed no impact on maximal bicycling performance^{48,49}. In a randomized, controlled trial, those who received creatine supplementation significantly increased their total maximal cycling work (time to exhaustion)⁵⁰. In another double-blind study, cyclists who received creatine supplements had increased peak and mean sprint power

output by eight to nine percent, but they had no improvement in endurance time to exhaustion⁵¹.

Studies of creatine supplementation in swimmers yielded mixed results. In two double-blind, randomized controlled trials among competitive swimmers, creatine supplementation significantly improved swim times during one or two of three sets of sprints^{52,53}. However, in a third study creatine supplementation did not improve single sprint times⁵⁴.

Finally, in a randomized controlled trial of 16 highly trained men, creatine supplementation significantly increased the amount of work performed on a kayak ergometer during periods of 90 to 300 seconds⁵⁵.

There are no studies evaluating creatine's effect on sprint performance in elderly athletes or children, and no studies evaluating its long-term effects

iii. Endurance activities: Randomized trials have failed to show any impact of creatine supplementation on performance during endurance exercise testing in competitive athletes. For example, among triathletes who took 6 grams of creatine daily for five days, there was no significant impact on endurance performance, despite an improvement in interval power performance⁵⁶. Similarly, among elite bicyclists, creatine supplementation had no impact on time to cycling to exhaustion (endurance test)^{9,51}. Six weeks of creatine supplementation did not benefit ten female members of a university swim team in terms of performance during endurance exercise⁵⁷. Nor did it help competitive rowers in a 1000-meter rowing performance⁵⁸.

- b. Treatment of rare metabolic defects and neuromuscular disorders, e.g. guanidinoacetate methyltransferase (GAMT) deficiency, hyperornithinemia, and muscular dystrophy.
 - i. *In vitro data:* Dystrophic skeletal muscle cells from mice and Duchenne muscular dystrophy (DMD) patients that were treated with creatine exhibited increased intracellular phosphocreatine and increased myotubular formation and survival⁵⁹; the authors concluded that creatine might be a useful therapy for patients with DMD.

- ii. *Animal data:* In animals with experimentally induced Parkinsonism, creatine supplementation produced significant protection against loss of Nissl and tyrosine hydroxylase immunostained neurons in the substantia nigra⁶⁰.

Oral administration of creatine to G93A transgenic mice (who have significant mitochondrial dysfunction which leads to symptoms similar to amyotrophic lateral sclerosis, ALS) led to dose-dependent improvement in motor performance and extended survival⁶¹; this has led to speculation that creatine supplementation may be useful for patients with ALS.

In animal models of Huntington's disease, induced by malonate poisoning, creatine supplements were neuroprotective, increasing brain concentrations of creatine and phosphocreatine⁶².

- iii. *Human data:*

- a. **GAMT deficiency:** Hepatic guanidinoacetate methyltransferase (GAMT) deficiency was first described in two children with severe developmental delay and extrapyramidal symptoms^{63,64}. This condition is diagnosed by a deficiency of creatine in the brain measured by magnetic resonance imaging; it has been treated with oral creatine supplementation^{65,66}. A four-year-old girl with dystonic-dyskinetic syndrome, developmental delay and epilepsy was diagnosed as having GAMT deficiency, leading to low tissue creatine levels; creatine supplementation of 400 –500 mg/kg daily led to significant clinical improvements^{67,68}. No randomized controlled trials have been reported.
- b. **Hyperornithinemia:** Gyrate atrophy of the choroid and retina with hyperornithinemia is caused by an autosomal recessive deficiency of ornithine-delta-aminotransferase activity; patients have decreased muscular and brain stores of creatine. Symptoms include blindness and muscle weakness. In one case series, nine patients with hyperornithinemia were given supplemental creatine, which helped correct creatine tissue levels^{69,70}.
- c. **Neuromuscular diseases:** Creatine has also been used to treat a broad range of neuromuscular diseases (eg., mitochondrial cytopathy, neuropathic disorders, muscular dystrophy, congenital myopathy and inflammatory myopathy). In two

pilot studies of patients with a variety of neuromuscular diseases, creatine supplementation (10 g daily for five days and then 5 g daily for five days) increased all measured indices of high-intensity strength by 10 - 15% and increased lean body mass⁷¹.

In a randomized, cross-over study, seven patients with mitochondrial cytopathy were treated with creatine supplements (10 g daily for 14 days followed by 4 g daily for seven days); creatine treatment resulted in significantly ($P < 0.05$) increased handgrip strength, with no changes in the other measured variables such as lower intensity aerobic activities⁷².

There are no randomized trials evaluating the chronic use of creatine supplements in the treatment of neuromuscular disorders in terms of toxicity or effectiveness in improving the ability to perform activities of daily living. The Muscular Dystrophy Association has funded a multi-center, placebo-controlled trial evaluating creatine's effects in persons with amyotrophic lateral sclerosis (ALS) (<http://www.mdausa.org:80/research/creatine.html>).

Toxicity and Contraindications

All food supplements carry the potential for contamination with herbs, heavy metals, incipients and pharmaceuticals.

Allergic reactions can occur to any natural product in sensitive persons

Allergic reactions to creatine have been reported.

Potentially toxic compounds in creatine: Creatine itself

Acute toxicity: In 1997, three collegiate wrestlers who took creatine died; although creatine supplementation was initially thought to be the cause of death, investigation did not confirm this. A moderate decline in renal function developed in a 25-year-old man with nephrotic syndrome who took creatine to enhance soccer performance; his renal function improved within a month of stopping the supplements⁷³; critics of this report noted that the patient had a history of recurring renal failure⁷⁴. A previously healthy 20-year-old man developed acute interstitial nephritis after taking 20 grams of creatine daily for four weeks; apparently he had stopped the creatine before being seen by a physician, yet his

creatinine level rose from 1.4 to 2.3 mg/dL during his hospitalization, returning to normal within a month after his diagnosis. It is not clear that the creatine was the cause of his renal problems⁷⁵.

In adults given 20 grams daily of creatine, urinary creatinine excretion increased from 1.1 to 1.2 grams per 24 hours; urinary creatine excretion was four times greater than baseline one week after three weeks of oral creatine supplementation, suggesting enhanced clearance with exposure³⁸. In a study of five healthy men, a five-day loading regimen of 20 grams daily of creatine supplementation had no adverse effect on any measure of renal function (creatinine, creatinine clearance, or glomerular filtration rate)⁷⁶. In a larger study of 20 men who were given 21 grams of creatine daily for five days and then 3 grams daily for 58 days, there were no adverse effects on creatinine clearance, urea clearance or albumin excretion⁷⁷.

There is often initial weight gain of one or two kg during the five day loading period, which may interfere with mass-dependent activities such as running and swimming^{36,78}. Undissolved creatine powder may cause gastroenteritis⁷⁴. Diarrhea, heat intolerance and muscle cramps have also been reported with oral creatine supplementation^{1,4,7}.

Chronic toxicity: Impaired renal function has been reported^{74,77}. Most studies have been less than 12 weeks in duration; little is known about the long-term effects of creatine supplementation⁷⁸.

Limitations during other illnesses or in patients with specific organ dysfunction: Contraindicated for patients with impaired renal function or dehydration.

Interactions with other herbs or pharmaceuticals: Contraindicated for patients taking diuretic medications. Cimetidine competes with creatinine for renal tubular secretion and may increase the risk of adverse renal effects; similar interactions may be found with probenecid which blocks renal tubular transport. Because non-steroidal anti-inflammatory drugs (NSAIDs) may impair renal function, patients using these medications should be cautious in taking creatine supplements.

Caffeine apparently antagonizes creatine's ergogenic effects, leading to a complete loss of creatine's benefits on intense intermittent exercise performance^{79,80}.

Safety during pregnancy, lactation and/or childhood: Unknown

Typical dosages

Provision of dosage information does NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used..

Doses may be adjusted when using supplements in combinations.

Doses may also vary according to the type and severity of the condition treated and individual patient conditions.

Adult doses: Studies valuating creatine's effect on athletic performance have used a loading dose of 20 grams daily for five to seven days, then 5 grams daily. Absorption appears to be enhanced by concurrent carbohydrate ingestion^{7,55,79,81,82,83}.

Pediatric doses: To treat guanidinoacetate methyltransferase deficiency: 2 grams/kilogram daily

Availability of standardized preparations: Yes

Dosages used in supplement combinations: Variable

Proprietary names: Creatine Booster, Creatine Citrate, Creatine Monohydrate Powder, Creatine Xtreme Punch, Creatine Xtreme Lemonade, Creatine Powder Drink Mix, Creavescent, Total Creatine Transport, Hardcore Formula Creatine Powder, Power Creatine, Phosphagen, HPCE Pure Creatine Monohydrate, Phosphagen Pure Creatine Monohydrate

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