

Name of Supplement

Creatine

Scientific Name/Common Names

N-amidinosarcosine, N- (aminoiminomethyl)-N methyl glycine¹

Creatine is also known as creatine monohydrate, creatine phosphate, creatine citrate^{1,2}

Description of Active Ingredient

Creatine is a naturally occurring nitrogen compound synthesized by the liver, kidneys and pancreas from the amino acids arginine, glycine, and methionine. One to two grams of creatine is endogenously produced per day with the remaining supply coming from dietary sources. Exogenous sources rich in creatine include fish and meats. The majority of the creatine pool is found in skeletal muscle tissue (95%), with the remaining pool located in the brain, heart, retina, and testes. Creatine is irreversibly converted to the creatinine metabolite and excreted in urine.³

⁴ Serum creatinine is used to estimate glomerular filtration rate and should not be confused with creatine. Creatine can also be metabolized to methylamine, which can be deaminated to form formaldehyde.^{2,3}

Mechanism of Action

ATP is the immediate source of energy for muscle contraction. However, ATP stores in muscle are low, lasting only a few seconds. Creatine can be phosphorylated to form phosphocreatine (PCr). PCr acts as an energy buffer to indirectly provide energy in the form of phosphoryl groups. PCr concentrations are about four times greater than ATP concentrations in skeletal muscle. PCr lends phosphoryl groups back to ADP, thus regenerating ATP during anaerobic activity. It is hypothesized that increasing the PCr concentration through creatine supplementation will provide enhanced energy/performance during short repeated bouts of energy expenditure such as weight lifting, repeated jumping and sprinting.^{3,4} Enhanced energy is the basis for creatine's use in other disease states such as heart failure and rheumatoid arthritis (RA). Creatine is also proposed to enhance hepatic insulin sensitivity and thus decrease serum triglyceride levels making it useful in dyslipidemia.⁵

Uses/Efficacy

- Primary use is as an ergogenic aid to enhance athletic performance
 - Creatine 5g qid for four days ("loading" phase) followed by 5g qd (maintenance dose) thereafter was shown to enhance physical performance during short-term, high-intensity exercise. Maximal muscle strength measured by leg presses, leg extensions and squats was 20-25% greater (P<0.05) while using creatine

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compared to placebo. Creatine was shown to increase arm torque by up to 25% (P<0.05) versus placebo.⁶ An absolute maximum bench press strength difference of 6.85kg (95% confidence interval [CI], 5.24-8.47) was seen between the creatine and placebo groups, with the creatine group benefiting.⁷ Large amounts of data are available.

- Heart failure
 - Creatine 5g qid for ten days, used in patients with New York Heart Association (NYHA) functional Class II/III heart failure was shown to enhance muscle function. Total creatine, PCr, and free creatine significantly increased after creatine supplementation versus placebo (P<0.05). Physical endurance measured by cycle ergometer exercise increased by 10-21% compared to placebo (P<0.05). Muscle strength measured by peak torque during two-legged cycle ergometry was 5% greater in the creatine group compared to the placebo group (P<0.05). However, there was no difference in ejection fraction at rest and during exercise between the creatine group and placebo group.⁸ Limited data are available.
- Dyslipidemia
 - The use of creatine 5g qid for five days followed by 5g bid for 51 days in 34 patients with total cholesterol greater than 200 mg/dl was shown to significantly decrease triglycerides (TG's) and very-low-density-lipoprotein (VLDL) at 4, 8, and 12 week follow-up compared to placebo.⁵ TG's and VLDL values were decreased by 22-26% while using creatine. However, confounding variables such as diet and exercise were not considered. The proposed mechanism of action is enhanced hepatic insulin sensitivity caused by creatine.⁵ Limited data are available.
- Rheumatoid arthritis
 - The use of creatine 5g qid for 5 days followed by 2g qd for 16 days was shown to significantly increase muscle strength index in 12 RA patients. Disease activity measured by the disease activity score significantly decreased with the use of creatine. However, patients showed no improvement in physical function measured by the Health Assessment Questionnaire.⁹ Limited data are available.

Contraindications/Allergies

- Hypersensitivity to creatine²
- Active renal impairment or disease states which increase the risk of renal impairment such as diabetes.^{1,2}

Dosage Forms

The most common form is powder, which can be mixed with water or juice. One teaspoonful yields five grams of creatine. Other dosage forms include capsules, tablets, gum, sports drinks, and liquid sub-lingual forms.¹⁰

Recommended Dose/Duration

Most studies used regimens consisting of a loading dose (LD) phase followed by a maintenance dose (MD). Doses greater than 20 grams per day are not recommended because the creatine muscle saturation is exceeded and higher doses may lead to increased adverse effects.^{3,4}

- Ergogenic aid to enhance athletic performance:
LD of 5g qid for 5 days with a MD of 2-5g.^{1-4,6,7} An alternative is 3g qd for 30 days.³
- Heart Failure (NYHA functional classes II and III):
5 grams qid for 10 days.^{3,8}
- Dyslipidemia:
LD of 5g qid for five days with a MD of 5g bid for 51 days.⁵
- Rheumatoid Arthritis:
LD of 5g qid for 5 days with a MD of 2g qd for 16 days.^{3,9}

Drug Interactions

- Caffeine antagonizes the ergogenic effect of creatine. This effect may be mediated through the inhibition of PCr re-synthesis.¹¹
- Cimetidine may cause increased serum creatinine (metabolite) concentrations by competing for renal tubular secretion, which could lead to an increased risk of adverse events.²
- Diuretics may cause dehydration and renal impairment leading to increased serum concentrations of creatinine.²
- Ma huang serum concentrations may be increased while using creatine leading to increased adverse effects. This effect may be mediated by creatine induced renal impairment.¹²
- Nephrotoxic drugs in combination with creatine may cause additional kidney dysfunction, since creatine has been associated with renal impairment.¹
- NSAIDS can cause renal impairment leading to increased serum creatinine concentrations.²
- Probenacid could increase serum levels of creatinine because probenacid blocks renal tubular secretion.²
- Trimethoprim may increase creatinine concentrations by interfering with creatinine excretion.²

Drug Food Interactions

- Foods containing caffeine may antagonize the ergogenic effects of creatine.^{1,2,11}
- Carbohydrates appear to enhance uptake into muscle cells. The proposed mechanism of action is through carbohydrate mediated insulin secretion. Insulin is proposed to enhance creatine muscle uptake by stimulating sodium/potassium pump activity.^{4,13}

Drug Disease Interaction

- Active renal impairment or disease states that increase the risk of renal impairment such as diabetes.^{1,2}

Laboratory Interactions

- Serum creatinine levels have been shown to increase acutely during the loading dose phase and increase chronically with long-term use.⁶
- A small but significant increase in blood urea nitrogen (2mg/dL) was shown after using creatine for 9 weeks in females.⁵

Safety Issues/Adverse Events

- One case study reported that a young male suffered an ischemic stroke while using caffeine and ma huang.¹²
- Avoid using in pregnancy and lactation. No data are available.²
- GI distress, nausea, diarrhea^{1,2}
- Dehydration, muscle cramping, renal dysfunction^{1,2}
- Weight gain^{1,2}

References

1. Jellin JM, Gregory PJ, Batz F, Hitchens K, et al. Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database. 4th ed. Stockton, CA: Therapeutic Research Faculty; 2002:423-25.
2. AltMedDex® System: Abt L & Hammerly M (Eds): AltMedDex® System. MICROMEDEX, Greenwood Village, Colorado (Edition expires [3/2003]).
3. Persky AM, Brazeau GA: Clinical pharmacology of the dietary supplement creatine monohydrate. *Pharmacol Rev* 2001; 53(2):161-76.
4. Stricker PR: Other ergogenic agents. *Clin Sports Med* 1998; 17(2):283-97.
5. Earnest C, Almada AL, and Mitchell TL: High-performance capillary electrophoresis-pure creatine monohydrate reduces blood lipids in men and women. *Clin Sci* 1996; 91(1):113-18.
6. Vandenberghe K, Goris M, Van Hecke P, et al: Long-term creatine intake is beneficial to muscle performance during resistance training. *J Appl Physiol* 1997; 83(6):2055-63.
7. Dempsey RL, Mazzone MF, Meurer LN: Does oral creatine supplementation improve strength? A meta-analysis. *J Fam Pract* 2002; 51(11):945-51.
8. Gordon A, Hultman E, Kaijser L, Kristjansson S, Rolf CJ, Nyquist O, and Sylvén C: Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. *Cardiovasc Res* 1995; 30:413-18.
9. Willer B, Stucki G, Hoppeler H, Brühlmann P, and Krähenbühl S: Effects of creatine supplementation on muscle weakness in patients with rheumatoid arthritis. *Rheumatology* 2000; 39(3):293-98.

10. Anderson RA, advisory board. Integrative Medicine Access – Professional Reference to Conditions, Herbs & Supplements. Massachusetts: Integrative Medicine Communications; 2000.
11. Vandenberghe K, Gillis N, Van Leemputte M, Van Hecke P, Vanstapel F, and Hespel P. Caffeine counteracts the ergogenic action of muscle creatine loading. *J Appl Physiol* 1996; 80(2): 452-7.
12. Vahedi K, Domigo V, Amerenco P et al: Ischaemic stroke in a sportsman who consumed MA HUANG extract and creatine monohydrate for body-building. *J Neurol Neurosurg Psychiatry* 2000; 68(1):112-113.
13. Steenge GR, Simpson EJ, and Greenhaff PL. Protein and carbohydrate-induced augmentation of whole body creatine retention in humans. *J Appl Physiol* 2000; 89: 1165-71.