

THE REVIEW OF

NATURAL PRODUCTS

TOPIC:

L-ARGININE

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COMMON NAME(S): L-arginine

SOURCE: Amino acids are the major components of protein. Animal and plant products contain several amino acids, including arginine. Some of these sources are meats, milk, and eggs.¹ The physiologically active form, L-arginine, is the natural product obtained by hydrolysis of proteins. In the laboratory, arginine can be precipitated from gelatin hydrolysate. L-arginine also can be synthesized from L-ornithine and cyanamide in aqueous solution in the presence of Ba(OH)₂.² Because L-arginine can be synthesized endogenously from L-citrulline, it is classified as a nonessential amino acid in adults. However, in children and in certain conditions (eg, trauma, infection), L-arginine synthesis may become compromised and then may be considered "semi-essential."³

HISTORY: L-arginine is commonly sold as a health supplement claimed to be capable of improving vascular health and enhancing sexual function in men.

PHARMACOLOGY: Nitric oxide is produced by a variety of animal and human cells and is involved in many physiological and pathophysiological processes.⁴ Nitric oxide is a free radical, generated from L-arginine by the enzyme nitric oxide synthase.⁵ L-arginine supplementation to raise nitric oxide levels has been suggested to be beneficial in many areas.

Nutritional/Metabolic/Immunostimulatory: Arginine is classified as a nonessential amino acid but may become essential in stressful situations, including periods of growth (during childhood or pregnancy) or trauma to the body (eg, severe sepsis, wound healing, liver disease).⁶⁻⁸ L-arginine is a human growth stimulant and has been used in bodybuilding.⁹ In jaundiced rats, L-arginine supplementation demonstrated anabolic and immunostimulatory properties.¹⁰ Anabolic actions also can be confirmed in many studies concerning L-arginine supplementation and improved wound healing,^{4,11-13} including healing of burns,¹⁴ tendons,⁵ GI tract,¹⁵ and bone.¹⁶ One mechanism suggested may be because of the enzyme arginase, which produces a favorable environment for fibroblast and collagen production.¹⁷ L-arginine has also exhibited protective effects in spinal cord injury in animals¹⁸ and in cortical impact injury in rats.¹⁹ In another

report, exogenous L-arginine produced nitric oxide, resulting in a decrease of hepatic ischemia/reperfusion injury.²⁰

Cardiovascular health: Many cardiovascular diseases originate in the vascular endothelial cells, which, if unhealthy, can cause vasoconstriction, inflammation, thrombolytic activity, and cell proliferation. These abnormalities are due in part to enhanced degradation of nitric oxide. By having increased concentrations of L-arginine available to maintain nitric oxide, it may improve certain vascular disease states.²¹⁻²³ Several articles are available on this topic and include the following findings: 1) Increased flow-induced vasodilation in isolated guinea pig hearts was dependent on L-arginine to maintain nitric oxide concentrations;²⁴ 2) Coronary blood flow was restored after L-arginine was administered in diabetic dogs;²⁵ 3) L-arginine produced nonstereo-specific peripheral vasodilation and improves endothelium-dependent vasodilation in coronary heart disease (CHD) patients;²⁶ 4) Patients with peripheral artery disease experienced a 150% improvement in walking distance with L-arginine supplementation of 8 g twice daily for 14 days;²⁷ 5) An intermediate compound of L-arginine was found to be reduced in plasma concentrations of patients with cardiovascular risk factors, including impairment of endothelial function;²⁸ 6) L-arginine has improved cardiac performance in severe congestive heart failure (CHF) patients;²⁹ 7) CHD patients with angina demonstrated improvement after L-arginine supplementation,³⁰ as have angina patients who experienced improved exercise tolerance with L-arginine.³¹ In one clinical trial, oral L-arginine therapy was ineffective in improving nitric oxide bioavailability in coronary artery disease (CAD) patients.³²

L-arginine also has been beneficial in similar disease states including hypertension and hypercholesterolemia. It has enhanced vasodilation and has lowered systolic blood pressure in rats.³³⁻³⁵ According to one report, L-arginine supplementation in humans significantly lowered blood pressure in 6 patients.³⁶ Certain mechanisms in this area have been investigated, suggesting that nitric oxide-mediated vasodilator tone is deficient in hypertension³⁷ and salt-sensitive patients with mild essential hy-

hypertension reduce the ability of L-arginine to produce nitric oxide in vascular endothelium.³⁸ Nitric oxide possesses antithrombotic and antiatherosclerotic actions in the vasculature. A report on hypercholesterolemic rabbits demonstrated a direct inhibitory effect on leukocyte adhesion from L-arginine. This effect was found to be beneficial in cardiovascular health, to slow the development of atheromatous lesions, to reduce vascular superoxide anion production, and to improve endothelium-dependent relaxation.³⁹ In human microvascular endothelial cells, nitric oxide (with L-arginine substrate) regulates tissue factor as well, reducing endotoxin and cytokine-induced expression of tissue factor.⁴⁰

L-arginine supplementation in other vascular disease states has been beneficial. L-arginine's ability to increase nitric oxide availability has improved transplantation diabetes, renal disease, and other perfusion-type injuries. IV infusion of L-arginine into animals undergoing liver transplantation improved cardiac output, liver blood flow, and pulmonary vascular resistance, and reduced portal hypertension and reperfusion injury.^{41,42} L-arginine supplementation to piglets with chronic hypoxia-induced pulmonary hypertension has increased nitric oxide production.⁴³

The substrate for nitric oxide synthesis by the endothelium is limited in diabetes but can be overcome with L-arginine supplementation.⁴⁴ L-arginine counteracts lipid peroxidation, reducing damage to the blood vessels.⁴⁵ Hyperglycemia in patients with type 2 diabetes causes hemodynamic changes (eg, reduction of blood pressure), which can be reversed by L-arginine.⁴⁶ Endoneurial ischemia in animals may be improved by L-arginine.⁴⁷ L-arginine also may play a role in insulin resistance.⁴⁸

L-arginine is a precursor for polyamines required for proliferative responses characteristic of many renal diseases. It is also the nitric oxide precursor that is a vasodilator in the endothelium, which is beneficial in reducing intraglomerular pressure and disease.⁴⁹ L-arginine has been proven effective in nephrosclerosis and progressive renal failure.⁵⁰ L-arginine's ability to raise nitric oxide levels relaxes bladder muscle spasms, as well, and controls the pain in interstitial cystitis.⁵¹

Relaxation of cavernous smooth muscle in the penis requires nitric oxide synthesized by L-arginine. This sug-

gests that L-arginine may be beneficial in erectile dysfunction. In rats, increased nitric oxide concentrations demonstrated erectile response and altered vascular tone, suggesting possible benefit in men with Peyronie disease.⁵² In humans, it has been advertised that L-arginine in the form of dietary supplements improves sexual performance in men. However, in a clinical, controlled, crossover study no statistical difference in impotence scores was found in 32 patients administered 3 × 500 mg L-arginine/day vs placebo.⁵³

Other effects of L-arginine include increasing quantity and cytotoxic capability of lymphokine activated and natural-killer T-cells in breast cancer.⁵⁴ Another source suggests that individuals with genital herpes should decrease their intake of arginine (while increasing lysine). Arginine assists herpes simplex in multiplying, while lysine breaks down arginine.⁵⁵

TOXICOLOGY: Parenteral administration of L-arginine in high doses has caused metabolic acidosis including elevated potassium levels due to effects on intra- and extracellular potassium balance.³ Oral administration of L-arginine in humans has not caused any major adverse effects. L-arginine may exacerbate sickle cell crisis. Doses up to 30 g/day are well tolerated, with infrequent reports of nausea and diarrhea.⁵⁶ No adverse effects were reported with 9 g/day L-arginine over 6 months.³⁰ Arginine may trigger onset of herpes infection, although there is no solid evidence to confirm this.⁵⁶

SUMMARY: L-arginine is the physiologically active form of the nonessential amino acid arginine. However, it may become "essential" in stressful situations, including growth periods or wound healing. L-arginine plays an important role in healing by providing a favorable environment for fibroblast and collagen production. In addition, L-arginine increases nitric oxide concentrations (low concentrations are typical of cardiovascular disease). L-arginine has been beneficial in cardiovascular diseases (eg, CHD, hypertension, renal disease, diabetic vascular disease). It has become popular because of claims that it improves erectile dysfunction, but human studies have not yet confirmed this effect. In standard dosages, L-arginine appears to have little or no adverse effects.

PATIENT INFORMATION – L-arginine

Uses: L-arginine has been beneficial in several cardiovascular diseases. It plays an important role in healing and increases nitric oxide concentrations.

Side Effects: L-arginine has few reported side effects. Nausea and diarrhea have been reported infrequently. Parenteral administration at high doses has caused metabolic acidosis or electrolyte alterations.

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