

Arginine: Clinical Potential of a Semi-Essential Amino Acid

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Abstract

Arginine, a semi-essential amino acid, is involved in numerous areas of human biochemistry, including ammonia detoxification, hormone secretion, and immune modulation. Arginine is also well known as a precursor to nitric oxide (NO), a key component of endothelial-derived relaxing factor, an endogenous messenger molecule involved in a variety of endothelium-dependent physiological effects in the cardiovascular system. Because of arginine's NO-stimulating effects, it can be utilized in therapeutic regimens for angina pectoris, congestive heart failure, hypertension, coronary heart disease, preeclampsia, intermittent claudication, and erectile dysfunction. In addition, arginine has been studied in the treatment of HIV/AIDS, athletic performance, burns and trauma, cancer, diabetes and syndrome X, gastrointestinal diseases, male and female infertility, interstitial cystitis, immunomodulation, and senile dementia. Toxicity, dosage considerations, and contraindications are also reviewed.

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Introduction

Arginine is a semi-essential amino acid involved in multiple areas of human physiology and metabolism. It is not considered essential because humans can synthesize it *de novo* from glutamine, glutamate, and proline. However, dietary intake remains the primary determinant of plasma arginine levels, since the rate of arginine biosynthesis does not increase to compensate for depletion or inadequate supply.^{1,2}

Arginine contains four nitrogen atoms per molecule, making it the most abundant nitrogen carrier in humans and animals (Figure 1). Although it is not a major inter-organ shuttle of nitrogen, arginine nevertheless plays an important role in nitrogen metabolism as an intermediate in the urea cycle, making it essential for ammonia detoxification.³

Arginine Biochemistry

Arginine is synthesized in mammals from glutamine via pyrroline 5-carboxylate (P5C) synthetase and proline oxidase in a multi-step metabolic conversion.⁴ In adults, most endogenous arginine is derived from citrulline, a by-product of glutamine metabolism in the gut or liver. Citrulline is released into the circulation and taken up primarily by the kidney for conversion into arginine.⁵

Supplemental arginine in enteral feeding is readily absorbed.⁶ About half of ingested arginine is rapidly converted in the body to ornithine, primarily by the enzyme arginase.⁷ Ornithine, in turn, can be metabolized to glutamate and proline, or through the enzyme ornithine decarboxylase into the polyamine pathway for degradation into compounds such as putrescine and other polyamines.

In addition to the above-mentioned metabolic activity, arginine is a precursor for the synthesis of proteins, as well as nitric oxide, urea,

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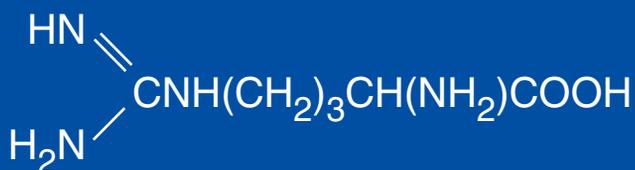
creatinine, and agmatine.⁸ Arginine that is not metabolized by arginase to ornithine is processed by one of four other enzymes: nitric oxide synthase (to become nitric oxide); arginine:glycine amidinotransferase (to become creatine); arginine decarboxylase (to become agmatine); or arginyl-tRNA synthetase (to become arginyl-tRNA, a precursor to protein synthesis). Arginine is also an allosteric activator of N-acetylglutamate synthase, which synthesizes N-acetylglutamate from glutamate and acetyl-CoA.⁹

Mechanisms of Action

Arginine has significant effects on endocrine function – particularly adrenal and pituitary secretion – in humans and animals. Arginine administration has long been known to stimulate the release of catecholamines,¹⁰ insulin and glucagon,¹¹ prolactin,¹² and growth hormone (GH).^{13,14} Little is known, however, about the exact mechanism by which arginine exerts these effects.

Arginine is the biologic precursor of nitric oxide (NO), an endogenous messenger molecule involved in a variety of endothelium-dependent physiological effects in the cardiovascular system¹⁵ (Figure 2). As the precursor to nitric oxide, many of arginine's clinical effects are thought to be mediated by its effects on endothelial-derived relaxing factor. An immense quantity of research has explored the biological roles and properties of nitric oxide,^{16,17} which appears to be of critical importance in maintenance of normal blood pressure,¹⁸ myocardial function,¹⁹ inflamma-

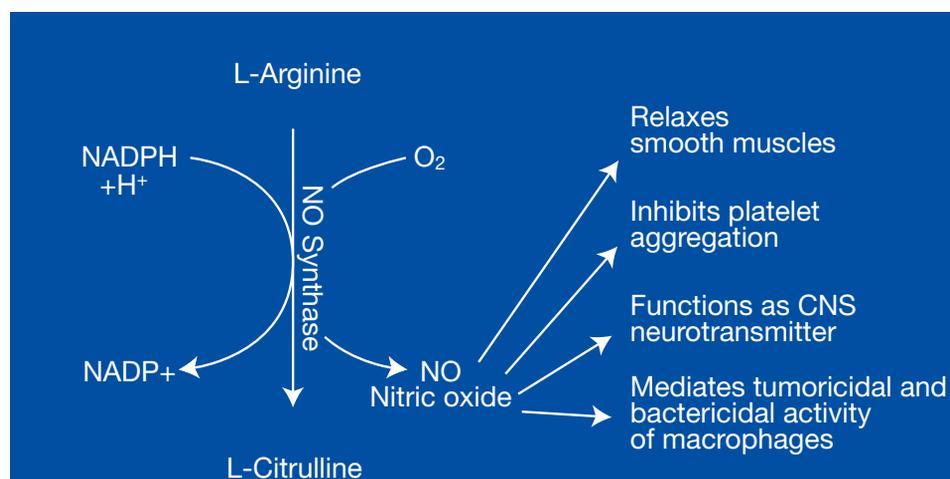
Figure 1. Structure of Arginine



tory response,²⁰ apoptosis,²¹ and protection against oxidative damage.²² Arginine is also a critical component of vasopressin (anti-diuretic hormone).

Arginine is a potent immunomodulator. Supplemental arginine appears to up-regulate immune function and reduces the incidence of post-operative infection. A significant decrease in cell adhesion molecule and pro-inflammatory cytokine levels has also been observed. Arginine can positively influence aspects of immunity under some circumstances and influence cytokine balance.

Figure 2. Synthesis and Functions of Nitric Oxide



Adapted from: Champe P, Harvey R. *Lippincott's Illustrated Reviews: Biochemistry, Second Edition*. Philadelphia, PA: J. B. Lippincott Company; 1994.

Arginine supplementation (30 g per day for three days) has been shown to significantly enhance natural killer (NK) cell activity, lymphokine-activated killer cell cytotoxicity, and lymphocyte mitogenic reactivity in patients with locally advanced breast cancer.^{23,24}

Clinical Applications of Arginine ***Human Immunodeficiency Virus*** ***(HIV) and Acquired*** ***Immunodeficiency Syndrome (AIDS)***

Arginine may be of benefit in individuals with HIV/AIDS. In a small pilot study of arginine supplementation in persons with HIV, 11 individuals were given 19.6 g per day arginine or placebo for 14 days. NK-cell cytotoxicity increased 18.9 lytic units, compared to +0.3 lytic units with placebo. This was not statistically significant, most likely due to the small number of patients.²⁵

The combination of glutamine, arginine, and hydroxymethylbutyrate (HMB) may prevent loss of lean body mass in individuals with AIDS cachexia. In a double-blind trial, AIDS patients with documented weight loss of at least five percent in the previous three months received either placebo or a combination of 3 g HMB, 14 g L-glutamine, and 14 g arginine given in two divided doses daily for eight weeks. At eight weeks, subjects consuming the mixture gained 3.0 ± 0.5 kg of body weight, while those supplemented with placebo gained only 0.37 ± 0.84 kg ($p = 0.009$). The weight gain in the supplemented group was predominately lean muscle mass, while the placebo group lost lean mass.²⁶

A six-month, randomized, double-blind trial of an arginine/essential fatty acid combination was undertaken in patients with HIV.²⁷ All patients received a daily oral nutritional supplement (606 kcal supplemented with vitamins, trace elements, and minerals). In addition, half of the patients were randomized to receive 7.4 g arginine plus 1.7 g omega-3 fatty acids per day. Body weight increased similarly in both groups and there was no change in immunological parameters. Clinical trials evaluating the effect of arginine as monotherapy for AIDS patients have yet to be conducted.

Cardiovascular Conditions

Angina Pectoris

Arginine supplementation has been effective in the treatment of angina in some, but not all, clinical trials. In an uncontrolled trial, seven of ten people with intractable angina improved dramatically after taking 9 g arginine per day for three months.²⁸ A significant decrease in cell adhesion molecule and pro-inflammatory cytokine levels was also observed. A double-blind trial in 22 patients with stable angina and healed myocardial infarction showed oral supplementation with 6 g arginine per day for three days increased exercise capacity.²⁹

In men with stable angina, two-week oral supplementation with arginine (15 g per day) was not associated with improvement in endothelium-dependent vasodilation, oxidative stress, or exercise performance.³⁰ In patients with coronary artery disease, oral supplementation of arginine (6 g per day for three days) did not affect exercise-induced changes in QT-interval duration, QT dispersion, or the magnitude of ST-segment depression;³¹ however, it did significantly increase exercise tolerance. The therapeutic effect of arginine in patients with microvascular angina is considered to be the result of improved endothelium-dependent coronary vasodilation.³²

Congestive Heart Failure

Patients with congestive heart failure (CHF) have reduced peripheral blood flow at rest, during exercise, and in response to endothelium-dependent vasodilators. Nitric oxide formed from arginine metabolism in endothelial cells contributes to regulation of blood flow under these conditions. A randomized, double-blind trial³³ found six weeks of oral arginine supplementation (5.6-12.6 g per day) significantly improved blood flow, arterial compliance, and functional status compared to placebo. Another double-blind trial found arginine supplementation (5 g three times per day) improved renal function in people with CHF.³⁴

Atherosclerosis and Coronary Heart Disease

Impairment of the NO synthase pathway may be one of the earliest events in atherogenesis.³⁵ Animal studies have suggested anti-atherogenic effects of supplemental arginine, including improved endothelium-dependent vasodilation, inhibition of plaque formation,³⁶ and decreased thickening of the aortic tunica intima.³⁷ In humans, arginine supplementation normalized platelet aggregation in hypercholesterolemic adults.³⁸ However, increased dietary arginine has not been consistently associated with decreased mortality from coronary heart disease,³⁹ and arginine supplementation (a single intravenous dose of 16 g) failed to affect maximal working capacity, indices of myocardial ischemia, or blood flow in hypercholesterolemic patients.⁴⁰

Hypertension

Administration of arginine prevented hypertension in salt-sensitive rats, but not in spontaneously hypertensive rats.⁴¹ If arginine was provided early, hypertension and renal failure could be prevented. In healthy human subjects, IV administration of arginine had vasodilatory and anti-hypertensive effects.⁴² In a small, controlled trial, hypertensive patients refractory to enalapril and hydrochlorothiazide responded favorably to the addition of oral arginine (2 g three times per day).⁴³ Small, preliminary trials have found oral⁴⁴ and IV⁴⁵ arginine significantly lowers blood pressure in healthy volunteers.

Intravenous infusion of arginine (15 mg/kg body weight/min for 35 min) improved pulmonary vascular resistance index and cardiac output in infants with pulmonary hypertension.⁴⁶

Intermittent Claudication

Intravenous arginine injections significantly improved symptoms of intermittent claudication in one double-blind trial. Eight grams of arginine, infused twice daily for three weeks, improved pain-free walking distance by 230 ± 63 percent and the absolute walking distance by 155 ± 48 percent (each $p < 0.05$) compared to no improvement with placebo.⁴⁷ To date, this is the only trial of arginine for intermittent claudication.

Preeclampsia

Endothelial dysfunction appears to be involved in the pathogenesis of preeclampsia.⁴⁸ In an animal model of experimental preeclampsia, IV administration of arginine (0.16 g/kg body weight/day) from gestational day 10 until term reversed hypertension, intrauterine growth retardation, proteinuria, and renal injury.⁴⁹ Intravenous infusion of arginine (30 g) in preeclamptic women has reportedly increased systemic NO production and reduced blood pressure.⁵⁰ Clinical trials are needed to validate the role of supplemental arginine in prevention and treatment of preeclampsia.

Growth Hormone (GH) Secretion and Athletic Performance

In rats, NO stimulates secretion of growth hormone-releasing hormone (GHRH) and thereby increases secretion of GH. However, GHRH then increases production of NO in somatotroph cells, which subsequently inhibits GH secretion. In humans, arginine stimulates release of GH from the pituitary gland in some populations, but the mechanism is not well understood. Most studies suggest inhibition of somatostatin secretion is responsible for the effect.⁵¹

At high doses (approximately 250 mg/kg body weight), arginine aspartate has increased GH secretion,⁵² an effect of interest to body builders wishing to take advantage of the anabolic properties of the hormone.⁵³ In a controlled clinical trial, arginine and ornithine (500 mg of each, twice per day, five times weekly) produced a significant decrease in body fat when combined with exercise.⁵⁴ Acute, low-dose arginine (5 g taken 30 minutes before exercise) did not increase GH secretion, and may have impaired release of GH in young adults.⁵⁵ Longer-term, low-dose supplementation of arginine and ornithine (1 g each, five days per week for five weeks) yielded higher gains in strength and enhancement of lean body mass when compared with controls receiving vitamin C and calcium.⁵⁶

Growth hormone has been observed to be lower in older males than young men; however, data suggest oral arginine/lysine (3 g each per day) is not a practical means of enhancing long-term GH secretion in older men.⁵⁷

Burns and Critical Trauma

Burn injuries significantly increase arginine oxidation and fluctuations in arginine reserves. Total parenteral nutrition (TPN) increases conversion of arginine to ornithine and proportionally increases irreversible arginine oxidation. Elevated arginine oxidation, coupled with limited *de novo* synthesis from its immediate precursors, make arginine conditionally essential in severely burned patients receiving TPN.⁵⁸ Several trials have demonstrated reduced length of hospital stay, fewer acquired infections, and improved immune function among burn⁵⁹ and trauma⁶⁰ patients supplemented with various combinations of fish or canola oil, nucleotides, and arginine.

Cancer

Animal research has shown large doses of arginine may interfere with tumor induction.⁶¹ Short-term arginine supplementation may assist in maintenance of immune function during chemotherapy. Arginine supplementation (30 g per day for three days) reduced chemotherapy-induced suppression of NK-cell and lymphokine-activated killer cell cytotoxicity, and lymphocyte mitogenic reactivity in patients with locally advanced breast cancer.^{23,24} In another study,⁶² arginine supplementation (30 g per day for three days prior to surgery) significantly enhanced the activity of tumor-infiltrating lymphocytes in human colorectal cancers *in vivo*. Arginine, RNA, and fish oil have been combined to improve immune function in cancer patients.⁶³⁻⁶⁵

On the other hand, arginine has also promoted cancer growth in animal and human research.⁶⁶ Polyamines act as growth factors for cancers. In several types of cancer, drugs are being investigated to inhibit ornithine decarboxylase (ODC), and hence inhibit polyamine formation. The possibility of arginine stimulating polyamine formation might be a concern in chronic administration, since both arginase and ODC appear to be up-regulated in some cancers.

Diabetes and Insulin Resistance

Endothelium-dependent relaxation is impaired in humans with both type 1 and type 2 dia-

betes mellitus (DM), as well as in animal models of diabetes. Endothelial nitric oxide deficiency is one likely explanation.⁶⁷ Diabetes is associated with reduced plasma levels of arginine,⁶⁸ and evidence suggests arginine supplementation may be an effective way to improve endothelial function in individuals with diabetes. An intravenous (IV) bolus of 3-5 g arginine reduced blood pressure and platelet aggregation in patients with type 1 diabetes.⁶⁹ Low-dose IV arginine improved insulin sensitivity in obese and type 2 DM patients as well as in healthy subjects.⁷⁰ Arginine may also counteract lipid peroxidation and thereby reduce microangiopathic long-term complications of DM.⁷¹

A double-blind trial found oral arginine supplementation (3 g three times per day) significantly improved, but did not completely normalize, peripheral and hepatic insulin sensitivity in patients with type 2 diabetes.⁷² In young patients with type 1 DM, however, oral arginine (7 g twice per day for six weeks) failed to improve endothelial function.⁷³

Gastrointestinal Conditions

Gastritis and Ulcer

Preliminary evidence suggests arginine accelerates ulcer healing due to its hyperemic, angiogenic, and growth-promoting actions, possibly involving NO, gastrin, and polyamines.^{74,75} No clinical trials have yet explored the safety or efficacy of arginine supplementation as a treatment for gastritis or peptic ulcer in humans.

Gastroesophageal Reflux Disease (GERD) and Sphincter Motility Disorders

A small, double-blind trial⁷⁶ found oral arginine supplementation significantly decreased the frequency and intensity of chest pain attacks, as well as the number of nitroglycerin tablets taken for analgesia, in patients with esophageal motility disorders. However, in another study,⁷⁷ arginine infusions (500 mg/kg body weight/120 min) failed to affect lower esophageal sphincter motility. No studies have yet explored the efficacy of arginine supplements for GERD.

Genitourinary Conditions

Erectile Dysfunction (ED)

In a small, uncontrolled trial, men with ED were given 2.8 g arginine per day for two weeks. Forty percent of the men in the treatment group experienced improvement, compared to none in the placebo group.⁷⁸ In a larger double-blind trial, men with ED were given 1,670 mg arginine per day or a matching placebo for six weeks.⁷⁹ Arginine supplementation was effective at improving ED in men with abnormal nitric oxide metabolism. However, another double-blind trial of arginine for ED (500 mg three times per day for 17 days) found the amino acid no more effective than placebo.⁸⁰ Further double-blind research in large groups is needed to confirm the efficacy of arginine for ED.

Infertility, Female

Supplementation with oral arginine (16 g per day) in poor responders to *in vitro* fertilization improved ovarian response, endometrial receptivity, and pregnancy rate in one study.⁸¹

Infertility, Male

Arginine is required for normal spermatogenesis. Over 50 years ago, researchers found that feeding an arginine-deficient diet to adult men for nine days decreased sperm counts by approximately 90 percent and increased the percentage of non-motile sperm approximately 10-fold.⁸² Oral administration of 500 mg arginine-HCl per day to infertile men for 6-8 weeks markedly increased sperm counts and motility in a majority of patients, and resulted in successful pregnancies.⁸³ Similar effects on oligospermia and conception rates have been reported in other preliminary trials.⁸⁴⁻⁸⁷ However, when baseline sperm counts were less than 10 million/mL, arginine supplementation produced little or no improvement.^{88,89}

Interstitial Cystitis

In an uncontrolled trial,⁹⁰ 10 patients with interstitial cystitis (IC) took 1.5 g arginine orally daily for six months. Supplementation resulted in a significant decrease in urinary voiding discomfort, lower abdominal pain, and vaginal/urethral

pain. Urinary frequency during the day and night was also significantly decreased. In a five-week uncontrolled trial, however, arginine supplementation was not effective, even at higher doses of 3-10 g per day.⁹¹ In a randomized, double-blind trial of arginine for IC, patients took 1.5 g arginine per day for three months. Twenty-nine percent of patients in the arginine group and eight percent in the placebo group had clinical improvement (i.e., decreased pain and urgency) by the end of the trial ($p = 0.07$). The results fell short of statistical significance, most likely because of the small sample size ($n = 53$).

Perioperative Nutrition

Arginine is a potent immunomodulator. Evidence is mounting for a beneficial effect of arginine supplementation in catabolic conditions such as sepsis and postoperative stress. Supplemental arginine appears to up-regulate immune function and reduce the incidence of postoperative infection.⁹² Two controlled trials have demonstrated increased lymphocyte mitogenesis and improved wound healing in experimental surgical wounds in volunteers given 17-25 g oral arginine per day.^{93,94} Similar results have been obtained in healthy elderly volunteers.⁹⁵

Preterm Labor and Delivery

Evidence from human and animal studies indicates nitric oxide inhibits uterine contractility and may help maintain uterine quiescence during pregnancy.⁹⁶ Intravenous arginine infusion (30 g over 30 min) in women with premature uterine contractions transiently reduced uterine contractility.⁹⁷ Further research is needed to confirm the efficacy and safety of arginine in prevention of preterm delivery.

Senile Dementia

Arginine (1.6 g per day) in 16 elderly patients with senile dementia reduced lipid peroxidation and increased cognitive function.⁹⁸

Side Effects, Potential Toxicity, and Contraindications

Significant adverse effects have not been observed with arginine supplementation. However, long-term studies are needed to confirm its apparent safety. People with renal failure or hepatic disease may be unable to appropriately metabolize and excrete supplemental arginine and should be closely monitored when taking arginine supplements.

It has been postulated, on the basis of older *in vitro* data⁹⁹ and anecdotal reporting, that arginine supplementation is contraindicated in persons with herpes infections (i.e., cold sores, genital herpes). The assumption is that arginine might stimulate replication of the virus and/or provoke an outbreak; however, this caution has not been validated by controlled clinical trials.

Bronchoconstriction is reportedly inhibited by the formation of NO in the airways of asthmatic patients, and a bronchoprotective effect of NO in asthma has been proposed.¹⁰⁰ Airway obstruction in asthma might be associated with endogenous NO deficiency caused by limited availability of NO synthase substrate (i.e., arginine). However, oral arginine (50 mg/kg body weight) in asthmatic patients triggered by a histamine challenge produced only a marginal, statistically insignificant improvement of airway hyper-responsiveness to histamine.¹⁰¹ In fact, it is unclear whether NO acts as a protective or a stimulatory factor in airway hyper-responsiveness. Current data suggest modulating NO synthesis by giving oral arginine supplements has no significant benefit on airway response to exercise in asthmatic subjects,¹⁰² and may even induce bronchoconstriction when nebulized and inhaled.¹⁰³ Until more is known, arginine should not be used to treat asthma.

Since polyamines act as growth factors for cancers, and arginine may stimulate polyamine synthesis, chronic administration of arginine in cancer patients should probably be avoided until information arises regarding the safety of this practice.

Recommended Dosage

Doses of arginine used in clinical research have varied considerably, from as little as 500 mg per day for oligospermia to as much as 30 g per day for cancer, preeclampsia, and premature uterine contractions. Typical doses fall into either the 1-3 g per day range, or the 7-15 g per day range, depending on the condition being treated.

Conclusion

Arginine appears to be a safe and effective therapy for many health conditions, particularly cardiovascular diseases responsive to modulation of endothelial-derived relaxing factor. Although double-blind trials of arginine have been conducted to evaluate its efficacy (i.e., for AIDS cachexia, congestive heart failure, endothelial function in type 1 diabetes, and erectile dysfunction), more studies are needed to confirm the efficacy of this semi-essential amino acid in the treatment of other health conditions. Healthcare practitioners should exercise caution in recommending arginine to any patient with a history of genital or oral herpes, asthma, or cancer. Otherwise, the amino acid is safe in typically recommended doses of 1-15 g per day.

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