SUPPLEMENT MONOGRAPHS

PHARMACOKINETICS
Some pharmacokinetic data are available from animal studies. Human pharmacokinetic data are lacking. It is unclear as to how much of an ingested dose of alpha-GPC gets into the brain or, for that matter, how much choline from a dose of ingested alpha-GPC gets to the brain.

INDICATIONS AND USAGE
It has been claimed that alpha-GPC is indicated for situations in which increased human growth hormone secretion is desirable and for the treatment of cognitive disorders. Evidence is insufficient to warrant support for either of these claimed indications at this time.

RESEARCH SUMMARY
The claim has been made that this putative acetylcholine precursor encourages the body to secrete increased levels of human growth hormone. There is some preliminary evidence that this is so, but whether this has any therapeutic significance remains to be seen. Safety data are also lacking. Claims that alpha-GPC is helpful in the treatment of cognitive disorders in the elderly are based upon scant and preliminary findings which, nonetheless, may warrant further investigation.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS
Alpha-GPC is contraindicated in those who are hypersensitive to any component of the preparation.

PRECAUTIONS
Because of lack of long-term safety data, children, pregnant women and nursing mothers should avoid use of alpha-GPC.

ADVERSE REACTIONS
To date, no adverse reactions have been reported.

INTERACTIONS
There are no known drug, nutritional supplement, food or herb interactions.

OVERDOSAGE
There are no reports of overdosing.

DOSAGE AND ADMINISTRATION
Those who use alpha-GPC take 500 milligrams to 1 gram daily. About 40% of alpha-GPC is choline.

LITERATURE


L-Arginine

DESCRIPTION
L-arginine is a protein amino acid present in the proteins of all life forms. It is classified as a semi-essential or conditionally essential amino acid. This means that under normal circumstances the body can synthesize sufficient L-arginine to meet physiological demands. There are, however, conditions where the body cannot. L-arginine is essential for young children and for those with certain rare genetic disorders in which synthesis of the amino acid is impaired. Some stress conditions that put an increased demand on the body for the synthesis of L-arginine include trauma (including surgical trauma), sepsis and burns. Under these conditions, L-arginine becomes essential, and it is then very important to ensure adequate dietary intake of the amino acid to meet the increased physiological demands created by these situations.

L-arginine, even when it is not an essential amino acid as defined above, is a vital one. In addition to participating in protein synthesis, it plays a number of other roles in the body. These include the detoxification of ammonia formed during the nitrogen catabolism of amino acids via the formation of urea. In addition, L-arginine is a precursor in the formation of nitric oxide, creatine, polyamines, L-glutamate, L-proline, agmatin (a possible neurotransmitter in the brain) and the arginine-containing tetrapeptide tuftsin, believed to be an immunomodulator. L-arginine is a glycogenic amino acid; it can be converted to D-glucose and glycogen if needed by the body or it can be catabolized to produce biological energy.

L-arginine, when administered in high doses, stimulates pituitary release of growth hormone and prolactin and pancreatic release of glucagon and insulin. Intravenous L-arginine may be used as an aid in the evaluation of problems with growth and stature that may be due to growth hormone deficiency. Intravenous arginine hydrochloride may be used as a fourth-line agent in the treatment of severe metabolic alkalosis. L-arginine is also used as an immunonutrient in enteral and parenteral nutrition to help improve the immune status in those suffering from sepsis, burns and trauma.
L-arginine is predominately synthesized in the kidney. It is a key intermediate in the Krebs-Henseleit urea cycle. L-ornithine and L-citrulline are precursors in the synthesis of L-arginine, and L-arginine is converted to urea and L-ornithine via the enzyme arginase. The portion of L-arginine that is not converted to urea enters the circulation, and is distributed to the various tissues and metabolized as discussed above. A much smaller amount of L-arginine is produced in the liver.

The typical dietary intake of L-arginine is 3.5 to 5 grams daily. Most dietary L-arginine comes from plant and animal proteins. Small amounts of free L-arginine are found in vegetable juices and fermented foods, such as miso and yogurt. Soy protein and other plant proteins are richer in L-arginine than are animal proteins, which are richer in lysine. It is thought that the possible hypcholesterolemic effect of soy protein is due, at least in part, to the higher L-arginine content in this protein.

L-arginine is a basic amino acid with the molecular formula C6H14N4O2 and with a molecular weight of 174.20 daltons. It has 3 pKs: pK1=2.18, pK2=9.09 and pK3=13.2. Therefore, it carries a positive charge at physiological pH. The stereoisomer of L-arginine, D-arginine, does not have any biological activity, as far as we know. L-arginine is also known as 2-amino-5-guanidinovaleic acid and (S)-2-amino-5-[aminomethyl]amin] pentaneoic acid. Its one-letter abbreviation is R. It is also abbreviated as Arg. The terms L-arginine and arginine are frequently used interchangeably. The structural formula of L-arginine is as follows:

\[
\text{L-arginine}
\]

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

Supplemental L-arginine may have anti-atherogenic, antioxidant and immunomodulatory actions. It may also have wound-repair activity.

**MECHANISM OF ACTION**

Many of supplemental L-arginine's activities, including its possible anti-atherogenic actions, may be accounted for by its role as the precursor to nitric oxide or NO. NO is produced by all tissues of the body and plays very important roles in the cardiovascular system, immune system and nervous system. NO is formed from L-arginine via the enzyme nitric oxide synthase or synthetase (NOS), and the effects of NO are mainly mediated by 3',5'-cyclic guanylate or cyclic GMP. NO activates the enzyme guanylate cyclase, which catalyzes the synthesis of cyclic GMP from guanosine triphosphate or GTP. Cyclic GMP is converted to guanylic acid via the enzyme cyclic GMP phosphodiesterase.

NOS is a heme-containing enzyme with some sequences similar to cytochrome P-450 reductase. Several isoforms of NOS exist, two of which are constitutive and one of which is inducible by immunological stimuli. The constitutive NOS found in the vascular endothelium is designated eNOS and that present in the brain, spinal cord and peripheral nervous system is designated nNOS. The form of NOS induced by immunological or inflammatory stimuli is known as iNOS. iNOS may be expressed constitutively in select tissues such as lung epithelium.

All the nitric oxide synthases use NADPH (reduced nicotinamide adenine dinucleotide phosphate) and oxygen (O2) as cosubstrates, as well as the cofactors FAD (flavin adenine dinucleotide), FMN (flavin mononucleotide), tetrahydrobiopterin and heme. Interestingly, ascorbic acid appears to enhance NOS activity by increasing intracellular tetrahydrobiopterin. eNOS and nNOS synthesize NO in response to an increased concentration of calcium ions or in some cases in response to calcium-independent stimuli, such as shear stress.

**In vitro** studies of NOS indicate that the Km of the enzyme for L-arginine is in the micromolar range. The concentration of L-arginine in endothelial cells, as well as in other cells, and in plasma is in the millimolar range. What this means is that, under physiological conditions, NOS is saturated with its L-arginine substrate. In other words, L-arginine would not be expected to be rate-limiting for the enzyme, and it would not appear that supra-physiological levels of L-arginine—which could occur with oral supplementation of the amino acid—would make any difference with regard to NO production. The reaction would appear to have reached its maximum level. However, **in vivo** studies have demonstrated that, under certain conditions, e.g. hypercholesterolemia, supplemental L-arginine could enhance endothelial-dependent vasodilation and NO production.

The discordance between the **in vivo** results—increased NO production under certain conditions—and the **in vitro** enzyme studies described above is known as the “arginine paradox.” There are a few explanations for the “arginine paradox.” NOS may be inhibited by asymmetric dimethylarginine or ADMA, which is known to be elevated in hypercholesterolemia and which increases mononuclear cell (monocyte and T-lymphocyte) adhesiveness in hypercholesterolemics. ADMA is formed by post-translational methylation of L-arginine residues in proteins and is released from the proteins following their hydrolysis. The “arginine
paradox” may be explained in part by increasing levels of L-arginine overcoming the inhibition of NOS by ADMA. In addition to hypercholesterolemia, elevated levels of ADMA are associated with hypertension, diabetes, preeclampsia, smoking and aging. Elevation of ADMA may be due to altered metabolism of this substance by dimethylarginine dimethylaminohydrolase or DDAH. DDAH is the major enzyme involved in ADMA catabolism. Decreased levels of DDAH have been found in diabetic and hypercholesterolemic animal models.

Other explanations of the “arginine paradox” include the presence of other inhibitors of NOS yet to be discovered, impaired transport of L-arginine into or within endothelial cells and impaired regeneration of L-arginine from L-citrulline. There is another interesting possibility. A non-enzymatic pathway by which NO may be produced has recently been described. Endothelial dysfunction is associated with increased oxidative stress resulting in increased formation of such reactive oxygen species as hydrogen peroxide and superoxide anions. Further, during conditions of oxidative stress, enzymatic synthesis of NO may decrease, and NO reacts with superoxide anions to form the reactive nitrogen species peroxynitrite. Under these conditions, L-arginine can essentially scavenge hydrogen peroxide and superoxide to form NO non-enzymatically. Interestingly, in this non-enzymatic reaction, L-arginine, as well as the non-biological D-arginine, can both form NO.

NO formed from supplemental L-arginine can play a major role in the possible anti-atherogenic activity of L-arginine. NO inhibits mononuclear cell adhesion, platelet aggregation, proliferation of vascular smooth muscle, production of some reactive oxygen species, such as superoxide anions, and promotion of endothelium-dependent dilation. Leukocyte adhesion, platelet aggregation, smooth muscle proliferation, endothelial dysfunction and oxidative stress are all part of the process of atherogenesis. L-arginine may also have anti-atherogenic activity independent of its role in the enzymatic formation of NO.

L-arginine may itself have antioxidant activity. L-arginine has been found to inhibit the oxidation of low-density lipoproteins (LDL) to oxidized LDL (oxLDL). The oxidation of LDL to oxLDL is believed to be a pivotal early step in atherogenesis. L-arginine may also scavenge superoxide anions and hydrogen peroxide (see above), as well as inhibit lipid peroxidation.

L-arginine has been shown to have immunomodulatory activity. For example, in human breast cancer, supplementation with this amino acid has been reported to increase the quantity and cytotoxic activity of natural killer (NK) cells and lymphokine-activated-killer (LAK) cells. L-arginine is considered an immunonutrient and is added to enteral and parenteral feedings for burn, sepsis and trauma patients. The mechanism of L-arginine’s possible immunomodulating activity is not entirely clear. It may, at least in part, be again due to L-arginine’s role in the production of NO. Production of NO, with consequent decrease of the cyclic AMP/cyclic GMP ratio in NK cells, would favor the production of interleukin-1, which is known to activate NK cells and may directly enhance NK cell cytotoxicity. L-arginine is also a precursor in the synthesis of the tetrapeptide tuftsin, which itself appears to have immunomodulatory activity. Tuftsin’s activity appears to depend on two of the four amino acids present in its structure, L-arginine and L-proline. L-arginine also participates in the synthesis of L-proline.

L-arginine’s possible activity in wound repair may be due to its precursor role in the formation of L-ornithine and, ultimately, L-proline. L-proline is a key element in collagen biosynthesis.

PHARMACOKINETICS
Following ingestion, L-arginine is absorbed from the lumen of the small intestine into the enterocytes. Absorption is efficient and occurs by an active transport mechanism. Some metabolism of L-arginine takes place in the enterocytes. L-arginine not metabolized in the enterocytes enters the portal circulation from whence it is transported to the liver, where again some portion of the amino acid is metabolized. L-arginine not metabolized in the liver enters the systemic circulation, where it is distributed to the various tissues of the body. L-arginine participates in various metabolic activities, including the production of proteins, D-glucose, glycogen, L-ornithine, urea, nitric oxide, L-glutamate, creatine, polyamines, L-proline, agmatine and tuftsin. L-arginine is eliminated by glomerular filtration and is almost completely reabsorbed by the renal tubules. L-arginine produces peak plasma levels approximately one to two hours after oral administration.

INDICATIONS AND USAGE
L-arginine shows promise in the treatment and prevention of cardiovascular disease (including atherosclerosis, hypertension, hyperlipidemia and angina pectoris), in the treatment of some forms of male infertility and some kidney disorders and it is helpful in accelerating wound healing in some circumstances. It has demonstrated some positive immune-modulating and anticancer effects. There is preliminary evidence that it could be helpful in some men with erectile dysfunction and in some others with migraine, liver disease and primary ciliary dyskinesia. There is conflicting but mostly negative evidence related to claims that it can improve exercise performance and promote lean muscle mass.
Numerous *in vitro* experiments have shown that L-arginine has effects on endothelial cells that could be expected to inhibit cardiovascular disease. Inferences have been drawn from these studies suggesting that L-arginine, through its nitric oxide activity, especially in the endothelial cells of the blood vessels, inhibits vasoconstriction, thrombolytic activity, cell proliferation, inflammation and other activities that promote cardiovascular disease.

Some of the promise of these *in vitro* studies has been realized in animal and clinical studies. In hypercholesterolemic animal models, L-arginine helps normalize lipids and vasodilatory response, inhibits platelet aggregation and formation of intimal lesions. Further, it has been seen in some of these animal studies to cause pre-existing lesions to regress.

Similarly, L-arginine has had significant positive effects in hypercholesterolemic and hypertensive humans. It has also been helpful in those with angina pectoris. In a recent long-term study, supplemental L-arginine, given for six months, resulted in significant improvement in coronary small-vessel endothelial function associated with a decrease in plasma endothelin concentrations.

In a double-blind, placebo-controlled study of 22 subjects with stable angina, supplemental L-arginine (1 gram twice daily) significantly improved exercise capacity. L-arginine supplementation resulted in a 70% reduction in angina attacks in another study.

In other studies, L-arginine was credited with significantly reducing lipid peroxidation in patients with diabetes mellitus. Conflicting results were produced by two studies related to L-arginine's effects on vasomotor response in smokers. In one of these studies, L-arginine significantly reversed abnormal myocardial blood flow response to a cold pressor test; in the other small study, no significant positive effect was seen.

The treatment of oligosperma with L-arginine was first reported many years ago. In one of these early studies, 178 men with oligosperma were given 4 grams of L-arginine daily. Severe oligosperma was diagnosed in 93 of these subjects. Treatment ceased in subjects who showed no improvement after two months. A 100% increase in sperm count was achieved in 42 cases, resulting in 15 pregnancies. There was marked increase in sperm number and motility in an additional 69 patients, resulting in another 13 pregnancies.

Subsequent studies have shown that L-arginine improves sperm count and motility. A recent small study credited L-arginine with producing pregnancies, but larger clinical trials are needed to confirm the efficacy seen in the early work.

L-arginine is of benefit in some kidney diseases and shows some promise in interstitial cystitis. It helps improve kidney function in some diabetic animal models and prevents chronic renal failure in others. A recent study indicated that L-arginine facilitates renal vasodilatation and natriuresis in renal transplant patients. There was also the suggestion in this study that L-arginine counteracts the antinatriuretic effect of cyclosporin.

Several studies have found that L-arginine benefits some with interstitial cystitis. Other studies, however, have not reported benefit. It appears that L-arginine can decrease pain and urgency in some subsets of interstitial cystitis patients, but more research is needed to confirm this.

L-arginine has long been used following trauma and during sepsis. Studies have shown that L-arginine improves nitrogen balance and thus reduces protein catabolism. Animal studies have shown that L-arginine can be of significant benefit after severe burn injury, increasing survival, improving cardiac function and preventing bacterial translocation. Intravenous L-arginine has been helpful in some human traumas, helping to speed healing while inhibiting post-injury wasting and weight loss.

L-arginine shows many effects on immune function both *in vitro* and *in vivo*. In various animal studies, L-arginine has, reportedly, improved host immunity in a variety of conditions through its effects on the thymus and T-lymphocytes. It has also been reported to reduce the incidence of chemically induced tumors and to reduce the size of pre-existing tumors. It has significantly inhibited metastatic spread of some cancers in animal work.

In human work, oral L-arginine has increased the responsiveness of some immune components and has decreased the number and percent of T suppressor/cytotoxic cells (CD8) in healthy human volunteers. In a clinical trial involving patients undergoing abdominal surgery, intravenous L-arginine diminished postoperative reduction in the mitogenic responses of peripheral blood lymphocytes to ConA and PHA. Enhancement of these same responses was reported in a study in which L-arginine was given to HIV patients. L-arginine supplementation in this study, did not, however, alter T-lymphocyte subsets or ratios.

In a more recent study of L-arginine's effects in HIV-infected subjects, supplementation for six months (7.4 grams daily) failed to produce any improvement in immunological parameters measured, but body weight increased in L-arginine-supplemented subjects.
In healthy human volunteers, administering 30 grams of L-arginine daily for three days resulted in enhanced natural-killer (NK) and lymphokine-activated-killer (LAK) cell activity. A mean rise of 91% in NK cell activity and a mean rise of 58% in LAK cell activity were observed. The researchers concluded: “The substantial enhancement of human NK and LAK cell activity by large doses of L-arginine could be useful in many immunosuppressed states, including malignant disease, AIDS and HIV infection, in which depressed NK cell activity is an important component of the disease process.”

Supplementation with L-arginine has significantly increased the quantity and cytotoxic activity of NK cells and lymphokine-activated cells in patients with breast cancer in one study. Research is ongoing.

There is recent, preliminary evidence that oral L-arginine can help some men with erectile dysfunction. In a double-blind, placebo-controlled study, 50 men with this disorder were randomized to receive 5 grams of L-arginine daily or placebo for six weeks. Nine of 29 L-arginine-supplemented subjects and two of 17 controls reported significant subjective improvement in erectile function. All nine of the L-arginine responders had low urinary levels of stable metabolites of nitric oxide at baseline. These levels doubled by the end of the study. More research is needed.

In another recent study, L-arginine was found to be helpful in subjects suffering from primary ciliary dyskinesia, a genetic disorder characterized by impaired cilia motility and abnormally low levels of nasal nitric oxide. L-arginine, in combination with ibuprofen, also proved helpful in significantly reducing migraine pain intensity compared with placebo in another recent, preliminary, multi-center study of 40 migraine patients.

Research related to L-arginine’s claimed hepatoprotective effects is dated. The data, however, looked promising and deserve follow-up.

Claims that L-arginine enhances exercise performance and promotes development of lean body mass while burning fat in healthy individuals are poorly supported. Weight gain was decreased in obese mice fed L-arginine, but there are no human data to support anti-obesity claims for L-arginine.

There are hypothetical reasons to believe that L-arginine, popular with some body builders, might have ergogenic/anabolic effects but, so far, these effects have not been demonstrated. High dose oral L-arginine has, however, been shown to induce release of growth hormone and prolactin but, again, no studies have been conducted to see whether this could have any meaningful ergogenic or anabolic effect.

**CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS**

**CONTRAINDICATIONS**

Supplemental L-arginine is contraindicated in those with the rare genetic disorder argininemia. It is also contraindicated in those hypersensitive to any component of an arginine-containing preparation.

**PRECAUTIONS**

Because of absence of long-term safety studies, and because of the possibility of growth hormone stimulation, pregnant women and nursing mothers should avoid L-arginine supplementation.

Those with renal or hepatic failure should exercise caution in the use of supplemental L-arginine.

Proteins of the herpes simplex virus are rich in L-arginine, and there are a few reports (mainly anecdotal) of those taking supplemental L-arginine who have had recurrences of oral herpes lesions. Although it is unlikely that those with a history of herpes simplex virus infection will have recurrences if they use L-arginine supplements, they should nevertheless be aware of this possibility.

**ADVERSE REACTIONS**

Oral supplementation with L-arginine at doses up to 15 grams daily are generally well tolerated. The most common adverse reactions of higher doses — from 15 to 30 grams daily — are nausea, abdominal cramps and diarrhea. Some may experience these symptoms at lower doses.

**INTERACTIONS**

**DRUGS**

**Cyclosporine:** L-arginine may counteract the antinaturetic effect of cyclosporin.

**Ibuprofen:** L-arginine may increase the absorption of ibuprofen if taken concomitantly.

**Organic nitrates:** L-arginine supplements theoretically may potentiate the effects of organic nitrates if taken concomitantly.

**Sildenafil citrate:** Theoretically, L-arginine supplements taken concomitantly with sildenafil citrate, may potentiate the effects of the drug.

**HERBS**

**Yohimbe:** L-Arginine, if used concomitantly, may enhance the effect of yohimbe.

**DOSAGE AND ADMINISTRATION**

L-arginine is available in tablet, capsule and powder form and as L-arginine hydrochloride and free base L-arginine. It is also available in medical foods as an aid in the enhancement of immune function.
Various doses are used. For cardiovascular health reasons, doses from 8 to 21 grams daily have been used in divided doses. To help aid with sperm quantity and quality, doses of 10 to 20 grams daily have been used in divided doses. Doses of 5 grams daily have been used for erectile dysfunction. Doses of 1.5 to 2.4 grams daily have been used for interstitial cystitis.

**LITERATURE**


L-Aspartate

**DESCRIPTION**
L-aspartate is a protein amino acid naturally found in all life forms. L-aspartate is a dicarboxylic amino acid. Although most L-aspartate is in proteins, small amounts of free L-aspartate are found in body fluids and in plants. The normal diet contains about 2 grams of L-aspartate daily. L-aspartate is also in the alternative dipeptide sweetener aspartame; the amount of L-aspartate from the sweetener is a small fraction of total L-aspartate consumed.

L-aspartate is considered a non-essential amino acid, meaning that, under normal physiological conditions, sufficient amounts of the amino acid are synthesized in the body to meet the body’s requirements. L-aspartate is formed by the transamination of the Krebs cycle intermediate oxaloacetate. The amino acid serves as a precursor for synthesis of proteins, oligopeptides, purines, pyrimidines, nucleic acids and L-arginine. L-aspartate is a glycogenic amino acid, and it can also promote energy production via its metabolism in the Krebs cycle. These latter activities were the rationale for the claim that supplemental aspartate has an anti-fatigue effect on skeletal muscle, a claim that was never confirmed.

L-aspartate is also known as L-amino succinate. Its IUPAC abbreviation is Asp. Its one-letter abbreviation, used when spelling out protein structures, is D. It is a solid, with an acid form that is slightly soluble in water, and with salt forms that are more water-soluble. Available salts include magnesium, calcium, potassium, zinc and combinations thereof. L-aspartate is used interchangeably with the term aspartic acid. The biological form of this substance, however, is the anion of aspartic acid, L-aspartate. Aspartic acid has the following chemical structure:

![Aspartic acid](image)

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**
L-aspartate salts are delivery forms for cations such as magnesium, potassium, calcium and zinc.

**MECHANISM OF ACTION**
L-aspartates can form salts with cations such as magnesium, potassium, calcium and zinc.

**PHARMACOKINETICS**
Following ingestion, L-aspartate is absorbed from the small intestine by an active transport process. Following absorption, L-aspartate enters the portal circulation and from there is transported to the liver, where much of it is metabolized to protein, purines, pyrimidines and L-arginine, and is catabolized as well. L-aspartate is not metabolized in the liver; it enters the systemic circulation, which distributes it to various tissues of the body. The cations associated with L-aspartate independently interact with various substances in the body and participate in various physiological processes.

**INDICATIONS AND USAGE**
There is no support for the claim that aspartates are exercise performance enhancers, i.e. ergogenic aids.

**RESEARCH SUMMARY**
There are claims that L-aspartate is a special type of mineral transporter for cations, such as magnesium, into cells. Magnesium aspartate has not been found to be more biologically effective when compared with other magnesium salts.

There are also claims that L-aspartate has ergogenic effects, that it enhances performance in both prolonged exercise and short intensive exercise. It is hypothesized that L-aspartate, especially the potassium magnesium aspartate salt, spares stores of muscle glycogen and/or promotes a faster rate of glycogen resynthesis during exercise. It has also been hypothesized that L-aspartate can enhance short intensive exercise by serving as a substrate for energy production in the Krebs cycle and for stimulating the purine nucleotide cycle.

An animal study using injected aspartate failed to find any evidence of a glycogen-sparing effect or any ergogenic effects whatsoever. A more recent double-blind human study of male weight trainers similarly found aspartate supplementation to have no effect, and another study of the effect of aspartate on short intensive exercise again found no effect.

**CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS**

**CONTRAINDICATIONS**
L-aspartate supplementation is contraindicated in those hypersensitive to any component of the preparation.