



FEMARGIN SACHETS – A Potent immunomodulator helps to regulate metabolic functions.

Govind Shukla*, C. Subrahmanyam, C.J Sampath Kumar

Lactonova Nutrition Research centre Hyderabad,

A unit of Lactonova Nutripharm (P) Ltd, Makers of Femargin Sachets

81/3, IDA Mallapur, Hyderabad, Telangana, India-500 076.

ABSTRACT

L-Arginine is a semi-essential amino acid involved in numerous areas of human physiology, including production of nitric oxide (NO) – a key messenger molecule involved in vascular regulation, immune activity, and endocrine function. Arginine is also involved in protein production, wound healing, erectile function, and fertility. Arginine 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. The present paper reviews the role of femargin Sachets developed by R&D cell of Lactonova Nutripharm Pvt Ltd. Hyderabad for overall successful Pregnancy outcome.

Keywords: Semi-essential amino acid, nitric oxide (NO), L-Arginine, femargin sachets.

INTRODUCTION

L-Arginine is a semi-essential amino acid involved in numerous areas of human physiology, including production of nitric oxide (NO) – a key messenger molecule involved in vascular regulation, immune activity, and endocrine function. Arginine is also involved in protein production, wound healing, erectile function, and fertility. Arginine 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 compensate for depletion or inadequate supply.^{1,2} Arginine is the most abundant nitrogen carrier in humans, containing four nitrogen atoms per molecule. Arginine is not a major inter-organ nitrogen shuttle; instead, it plays an important role in nitrogen metabolism and ammonia detoxification as an intermediate in the urea cycle.³

Biochemistry

Arginine is synthesized in mammals from glutamine via pyrroline 5-carboxylate (P5C) synthase and proline oxidase in a multi-step metabolic conversion.⁴

In adults, most endogenous arginine is produced from citrulline, a by-product of glutamine metabolism in the gut and liver. Citrulline is released into the circulation and taken up primarily by the kidney for conversion into arginine.⁵ Supplemental arginine is readily absorbed.⁶ About 50-

percent of ingested arginine is rapidly converted in the body to ornithine, primarily by the enzyme arginase.⁷ Because of this fast turnover, sustained-release preparations are being investigated as a way to maintain a steadier blood level over time. 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, arginine is a precursor for the synthesis of nitric oxide, proteins, urea, creatine, vasopressin, 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 is the biological precursor of nitric oxide (NO), an endogenous gaseous messenger molecule involved in a variety of endothelium-dependent physiological effects in the cardiovascular system.¹⁰ Much of arginine influence on the cardiovascular system is due to endothelial NO synthesis, which results in vascular smooth muscle relaxation and subsequent vasodilation, as well as inhibition of monocyte

adhesiveness, platelet aggregation, and smooth muscle proliferation. A great deal of research has explored the biological roles and properties of nitric oxide,^{11,12} which is also of critical importance in maintenance of normal blood pressure,¹³ myocardial function,¹⁴ inflammatory response,¹⁵ apoptosis,¹⁶ and protection against oxidative damage.¹⁷

Arginine is a potent immunomodulator. Supplemental arginine appears to up-regulate immune function and reduce the incidence of postoperative infection. Significant decreases in cell adhesion molecules and pro-inflammatory cytokine levels have also been observed. Arginine supplementation (30 g/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^{18,19}. Arginine has significant effects on endocrine function—particularly adrenal and pituitary secretion in humans and animals. Arginine administration can stimulate the release of catecholamines, ²⁰ insulin and glucagon, ²¹ prolactin,²² and growth hormone (GH);^{23,24} however, little is known about the specific mechanism(s) by which arginine exerts these effects.

Clinical Indications

Cardiovascular Conditions

Arginines effects on cardiovascular function are due to arginine-induced endothelial NO production. Endothelial nitric oxide synthase (eNOS) catalyzes this reaction, which produces NO and ornithine.

Nitric oxide diffuses into the underlying smooth muscle and stimulates guanylyl cyclase, producing guanosine-3,5-cyclic monophosphate (cGMP), which in turn causes muscle relaxation and vasodilation. Arginine supplementation has been shown to increase flow-mediated brachial artery dilation in normal individuals as well as those with hyperlipidemia and hypertension.^{25,26}

Nitric oxide is also responsible for creating an environment in the endothelium that is anti-atherogenic. Adequate NO production inhibits processes at the core of the atherosclerotic lesion, including platelet aggregation, monocyte adhesion and migration, smooth muscle proliferation, and vasoconstriction. Asymmetrical dimethylarginine (ADMA) competes with arginine for binding with eNOS, subsequently down-regulating activity of this vital enzyme. Increased plasma ADMA has been shown to be an independent risk factor for cardiovascular disease because of its inhibitory activity on eNOS. Oral arginine supplementation overrides the inhibitory effect of ADMA on eNOS, and improves vascular function in those with high ADMA levels.²⁷⁻²⁹

Angina Pectoris

Arginine supplementation has been effective in angina treatment in some, but not all, clinical trials. In 36 patients with chronic, stable angina given 6 g arginine daily for two weeks, significant improvement was noted in flow-mediated vasodilation, exercise time, and quality of life, compared to placebo.

No improvement was seen in ischemia markers on ECG or in time-to-onset of angina.³⁰

In a small, uncontrolled trial, seven of 10 people with intractable angina improved dramatically after taking 9 g arginine daily for three months.³¹

A double-blind trial in 22 patients with stable angina and healed myocardial infarction showed oral supplementation with 6 g arginine daily for three days increased exercise capacity.³²

However, in men with stable angina, oral supplementation with arginine (15 g/day) for two weeks was not associated with improvement in endothelium-dependent vasodilation, oxidative stress, or exercise performance.³³ In patients with coronary artery disease, oral supplementation of arginine (6 g/day for three days) did not affect exercise-induced changes in QT interval duration, QT dispersion, or the magnitude of ST-segment depression;³⁴ 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.³⁵

Congestive Heart Failure

Six weeks of oral arginine supplementation (5.6-12.6 g/d) significantly improved blood flow, arterial compliance, and functional status in patients with congestive heart failure (CHF), compared to placebo, in a randomized, double-blind trial.³⁶ Another double-blind trial found arginine supplementation (5 g three times daily) improved renal function in people with CHF.³⁷

After a one-week oral dosing with 6 g arginine daily in 30 males with stable CHF, significant improvements were seen in exercise duration, anaerobic threshold, and VO₂.³⁸

African Americans are at significantly greater risk for development of CHF than Caucasians. However, the improvement in endothelial function seen with arginine dosing may be more pronounced in African Americans compared to Caucasians, as was seen in a study of 52 CHF patients treated with an intra-coronary infusion of arginine.³⁹

Hypertension

Administration of arginine prevented hypertension in salt-sensitive rats, but not in spontaneously hypertensive rats.⁴⁰ If arginine was provided early, hypertension and renal failure could be prevented. In healthy human subjects, intravenous (IV) administration of arginine had vasodilatory and antihypertensive effects.⁴¹ In a small, controlled trial, hypertensive patients refractory to enalapril and hydrochlorothiazide responded favorably to the addition of oral arginine (2 g three times daily).⁴²

Small, preliminary trials have found oral ⁴³ and IV ⁴⁴ arginine significantly lowers blood pressure in healthy volunteers. IV 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.⁴⁵

Intermittent Claudication Intravenous arginine injections significantly improved symptoms of intermittent claudication in a 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.⁴⁶

Preeclampsia

Endothelial dysfunction appears to be involved in the pathogenesis of preeclampsia.⁴⁷

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.⁴⁸ Intravenous infusion of arginine (30 g) in preeclamptic women has reportedly increased systemic NO production and reduced blood pressure.⁴⁹

Human Immunodeficiency Virus (HIV) Infection and Acquired Immunodeficiency Syndrome (AIDS)

Arginine may be of benefit in individuals with HIV/AIDS. In a small pilot study of arginine supplementation in individuals with HIV, 11 patients were given 19.6 g/day arginine or placebo for 14 days. NKcell cytotoxicity increased 18.9 lytic units, compared to an increase of 0.3 lytic units with placebo. This was not statistically significant, most likely due to the small number of patients in the study.⁵⁰ A 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, 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.⁵¹ A six-month, randomized, double-blind trial of an arginine/essential fatty acid combination was undertaken in patients with HIV.⁵² Patients received a daily oral nutritional supplement (606 kcal supplemented with vitamins, minerals, and trace elements). In addition, half of the patients were randomized to receive 7.4 g arginine plus 1.7 g omega-3 fatty acids daily. 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.

Growth Hormone Secretion and Athletic Performance

In rats, NO stimulates secretion of GH-releasing hormone (GHRH), thereby increasing 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.⁵³ At high doses (approximately 250 mg/kg body weight), arginine aspartate increased GH secretion,⁵³ an effect of interest to body builders wishing to take advantage of the anabolic properties of the hormone.⁵⁴

In a controlled clinical trial, arginine and ornithine (500 mg of each, twice daily, five times per week) produced a significant decrease in body fat when combined with exercise.⁵⁵ Acute dosing of arginine (5 g taken 30 minutes before exercise) did not increase GH secretion, and may have impaired release of GH in young adults.⁵⁶

Longer-term, lowdose supplementation of arginine and ornithine (1 g each, five days per week for five weeks) resulted in higher gains in strength and enhancement of lean body mass, compared with controls receiving vitamin C and calcium.⁵⁷

Growth hormone has been observed to be lower in older males than young men; however, data suggest oral arginine/lysine (3 g each daily) is not a practical means of enhancing long-term GH secretion in older men.⁵⁸

Burns and Critical Trauma

Burn injuries significantly increase arginine oxidation and can result in depletion of arginine reserves. Total parenteral nutrition (TPN) increases conversion of arginine to ornithine and proportionally increases irreversible arginine oxidation, which, coupled with limited de novo synthesis from its immediate precursors, makes arginine conditionally essential in severely burned patients receiving TPN.⁵⁹

Several trials have demonstrated reduced length of hospital stay, fewer acquired infections, and improved immune function among burn⁶⁰ and trauma⁶¹.

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.⁶²

Short-term arginine supplementation may assist in maintenance of immune function during chemotherapy. Arginine supplementation (30 g/day for three days) reduced chemotherapy-induced suppression of lymphokine-activated killer cell cytotoxicity and lymphocyte mitogenic reactivity in patients with locally advanced breast cancer. In another study, arginine supplementation (30 g/day for three days prior to surgery) significantly enhanced the activity of tumor-infiltrating lymphocytes in human colorectal cancers in vivo.⁶³ Arginine, RNA, and fish oil have been combined to improve immune function in cancer patients.⁶⁴⁻⁶⁶ On the other hand, arginine has also promoted cancer growth in animal and human research.⁶⁷ 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 Syndrome

Endothelium-dependent vascular relaxation is impaired in type 1 and type 2 diabetes mellitus (DM), and endothelial NO deficiency is a likely explanation.⁶⁸ Diabetes is associated with reduced plasma levels of arginine,⁶⁹ and evidence suggests arginine supplementation may be an effective way to improve endothelial function in individuals

with diabetes. An IV bolus of 3-5 g arginine reduced blood pressure and platelet aggregation in patients with type 1 diabetes. 70

Low-dose IV arginine improved insulin sensitivity in obese patients and type 2 DM patients as well as in healthy subjects. 71 Arginine may also counteract lipid peroxidation and thereby reduce microangiopathic long-term complications of DM. 72 After one week of oral arginine supplementation (9 g daily), 10 women with type 2 DM showed significant improvement in endothelial function, noted by a 50-percent increase in flow-mediated brachial dilation. 73 A double-blind trial found oral arginine supplementation (3 g three times daily) significantly improved, but did not completely normalize, peripheral and hepatic insulin sensitivity in patients with type 2 diabetes. 74 In young patients with type 1 DM however, oral arginine (7 g twice daily for six weeks) failed to improve endothelial function. 75

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. 76,77 No clinical trials have yet explored the efficacy of arginine supplementation as a treatment for gastritis or peptic ulcer in humans.

Gastroesophageal Reflux (GERD) and Sphincter Motility Disorders

A small, double-blind trial 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. 78 However, in another study, arginine infusions (500 mg/kg body weight/120 min) failed to affect lower esophageal sphincter motility. 79

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 daily for two weeks. Forty percent of men in the treatment group experienced improvement, compared to none in the placebo group.

80 In a larger double-blind trial, men with ED were given 1,670 mg arginine daily or a matching placebo for six weeks. 81 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 daily for 17 days) found the amino acid no more effective than placebo. 82

Infertility, Female

Supplementation with oral arginine (16 g/ day) in poor responders to in vitro fertilization improved ovarian response, endometrial receptivity, and pregnancy rate in one study. 83

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. 84 Oral administration of 500 mg arginine-HCl per day to infertile men for 6-8 weeks markedly increased sperm count and motility in a majority of patients, and resulted in successful pregnancies. 85

Similar effects on oligospermia and conception rates have been reported in other preliminary trials. 86-89 However, when baseline sperm counts were less than 10 million/mL, arginine supplementation produced little or no improvement. 90,91

Interstitial Cystitis (IC)

In an uncontrolled trial, 10 patients with IC took 1.5 g arginine 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 also significantly decreased. 92

In a five-week uncontrolled trial, however, arginine supplementation was not effective, even at higher doses of 3-10 g daily. 93 In a randomized, double-blind trial of arginine for IC, patients took 1.5 g arginine daily for three months. Twenty-nine percent of patients in the arginine group and eight percent in the placebo group experienced 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. 94

Two controlled trials have demonstrated increased lymphocyte mitogenesis and improved wound healing in experimental surgical wounds in volunteers given 17-25 g oral arginine daily. 95,96 Similar results have been obtained in healthy elderly volunteers. 97

Preterm Labor and Delivery

Evidence from human and animal studies indicates nitric oxide inhibits uterine contractility and may help maintain uterine quiescence during pregnancy. 98 IV arginine infusion (30 g over 30 min) in women with premature uterine contractions transiently reduced uterine contractility. 99

Senile Dementia

Arginine (1.6 g/day) in 16 elderly patients with senile dementia reduced lipid peroxidation and increased cognitive function. 100

Side Effects and Toxicity

Significant adverse effects have not been observed with arginine supplementation. 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.

Dosage

Doses of arginine used in clinical research have varied considerably, from as little as 500 mg/day for oligospermia to as much as 30 g/day for cancer, preeclampsia, and premature uterine contractions.

Typical daily doses fall into either the 1-3g or 7-15g range, depending on the condition being treated. Because of the pharmacokinetics of L-arginine, use of a sustained-release preparation may be preferable, in order to keep blood levels more constant over time.

Warnings and Contraindications

It has been postulated, on the basis of older in vitro data¹⁰¹ and anecdotal reporting, that arginine supplementation might be 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.¹⁰² 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.¹⁰³ In fact, it is unclear whether NO acts as a protective or a stimulatory factor in airway hyper-responsiveness. 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.

DHA in Femargin.

polyunsaturated fatty acid) is found in every cell in our bodies. It is critical for brain, eye and central nervous system development and functioning.

During pregnancy, developing babies rely on their mothers to get needed DHA. Since DHA is derived from the foods DHA (Docosahexaenoic acid, an omega-3 long chain

we eat, the content of DHA in a mother's diet determines the amount of DHA passed on to her developing baby. Unfortunately, the majority of pregnant women fail to get the recommended amount of DHA in their diets and DHA is not found in most prenatal vitamins.

The DHA intake from an average diet during pregnancy is only 80 mg DHA per day, based on a paper in the Journal of Nutrition, 2005 (Denomme et al. 135: 206-211).

A minimum 300 mg DHA daily is suggested, based on a 1999 NIH body of experts recommending needed levels to support fetal brain development and visual acuity benefits.

- A 2003 study published in the journal *Pediatrics* showed children whose mothers took a DHA supplement during pregnancy scored higher on intelligence tests at four years of age than children of mothers not taking DHA supplements.
- A 2004 study published in *Child Development* found that babies whose mothers had high blood levels of DHA at delivery had advanced attention spans into their second year of life. During the first six months of life these infants were two months ahead of babies whose mothers had lower DHA levels.
- Other research studies suggest breastfed babies have IQs of six to 10 points higher than formula-fed babies. Medical and nutritional experts attribute this difference to the DHA infants receive while nursing. (*Obstetrics & Gynecology*, 2003).
- In a trial of women receiving DHA supplementation during the third trimester, the average length of gestation increased six days (*Obstetrics & Gynecology*, 2003).
- Research has found low levels of DHA in mother's milk and in the red blood cells of women with postpartum depression. (*Journal of Affective Disorders*, 2002). Some scientists believe increasing levels of maternal DHA may reduce the risk of postpartum depression

The Benefits of DHA for Adult Health: DHA is important for brain, eye and heart health throughout life. In fact, a growing body of research continues to support the role that DHA plays throughout adulthood including Brain health. DHA is necessary for the development and maintenance of optimal structure and function of nerve cells in the brain and eyes.

DHA plays a significant role in the maintenance of normal neurological function.

A recently published large, randomized, placebo-controlled nutritional study published in *Journal of the Alzheimer's Association* has demonstrated the benefits of algal DHA in improving memory in older adults.

Heart Health: The American Heart Association (AHA) has established the following guide containing recommended intakes for omega-3 fatty acids.

Population	Recommendation
Patients without documented coronary heart disease (CHD)	Eat a variety of (preferably fatty) fish at least twice a week. Include oils and foods rich in alpha-linolenic acid (flaxseed, canola and soybean oils; flaxseed and walnuts).
Patients with documented CHD	Consume about 1 g of DHA per day.
Patients who need to lower triglycerides	2 to 4 grams of DHA per day provided as capsules under a physician's care

Source: American Association	Heart	
------------------------------	-------	--

In 2005, the USDA Dietary Guidelines recognized an association between the omega-3 fats and good cardiovascular health.

Proanthocyanidin in Femargin

Proanthocyanidin (PAorPAC), also known as procyanidin, oligomeric proanthocyanidin (OPC), leucocyanidin, leucoanthocyanin and condensed tannins, is a class of flavanols. Proanthocyanidins are essentially polymer chains of flavonoids such as catechins.

Studies show that proanthocyanidins antioxidant capabilities are 20 times more powerful than vitamin C and 50 times more potent than vitamin E. OPCs may help protect against the effects of internal and environmental stresses as well as supporting normal body metabolic processes. The effects may include depressing blood fat, emolliating blood vessels, lowering blood pressure, preventing blood vessel sclerosis, dropping blood viscosity and preventing thrombus formation. Proanthocyanidins suppress production of a protein endothelin-1 that constricts blood vessels.

Methylcobolamin in femargin

Methylcobalamin is one of the two coenzyme forms of vitamin B12 (the other being adenosylcobalamin). It is a cofactor in the enzyme methionine synthase which functions to transfer methyl groups for the regeneration of methionine from homocysteine.

Clinical Applications Homocysteinemia

Elevated levels of homocysteine can be a metabolic indication of decreased levels of the methylcobalamin form of vitamin B12. Therefore, it is not surprising that elevated homocysteine levels were reduced from a mean value of 14.7 to 10.2 nmol/ml following parenteral treatment with methylcobalamin.

Dosage

The dosage for clinical effect is 1500-6000 mcg per day. No significant therapeutic advantage appears to occur from dosages exceeding this maximum dose. Methylcobalamin has been administered orally, intramuscularly, and intravenously; however, positive clinical results have been reported irrespective of the method of administration. It is not clear whether any therapeutic advantage is gained from the non-oral methods of administration.

Safety, Toxicity, and Side Effects

Methylcobalamin has excellent tolerability and no known toxicity.

Folic acid in femargin

Folic acid (also known as vitamin B₉, vitamin B_c or folacin) and folate (the naturally occurring form), as well as pteroyl-L-glutamic acid, pteroyl-L-glutamate, and pteroyl-

monoglutamic acid are forms of the water-soluble vitamin B₉. Folic acid is itself not biologically active, but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver. Adequate folate intake during the periconception period, the time right before and just after a woman becomes pregnant, helps protect against a number of congenital malformations, including neural tube defects (which are the most notable birth defects that occur from folate deficiency). Neural tube defects produce malformations of the spine, skull, and brain including spina bifida and anencephaly. The risk of neural tube defects is significantly reduced when supplemental folic acid is consumed in addition to a healthy diet prior to and during the first month following conception. Supplementation with folic acid has also been shown to reduce the risk of congenital heart defects, limb defects, and urinary tract anomalies. Folate deficiency during pregnancy may also increase the risk of preterm delivery, infant low birth weight and fetal growth retardation, as well as increasing homocysteine level in the blood, which may lead to spontaneous abortion and pregnancy complications, such as placental abruption and pre-eclampsia. The RDA for folate equivalents for pregnant women is 600–800 micrograms, twice the normal RDA of 400 micrograms for women who are not pregnant.

Fertility

Folate is necessary for fertility in both men and women. In men, it contributes to spermatogenesis. In women, on the other hand, it contributes to oocyte maturation, implantation, placentation, in addition to the general effects of folic acid and pregnancy. Therefore, it is necessary to receive sufficient amounts through the diet to avoid subfertility.

Vitamin B6 in Femargin

Vitamin B₆ is a water-soluble vitamin and is part of the vitamin B complex group. Several forms of the vitamin are known, but pyridoxal phosphate (PLP) is the active form and is a cofactor in many reactions of amino acid metabolism, including transamination, deamination, and decarboxylation. PLP also is necessary for the enzymatic reaction governing the release of glucose from glycogen. Vitamin B₆ has been used to treat nausea and vomiting in early pregnancy for decades. The intake of vitamin B₆, from either diet or supplements, could cut the risk of Parkinson's disease by half.

Vitamin B₆ has long been publicized as a cure for premenstrual syndrome (PMS). Study results conflict as to which symptoms are eased, but most of the studies confirm that women who take B₆ supplements have reductions in bloating, breast pain, and premenstrual acne flare, a condition in which pimples break out about a week before a woman's period begins. There is strong evidence that pyridoxine supplementation, starting ten days before the menstrual period, prevents most pimples from forming. This

effect is due to the vitamin's role in hormone and prostaglandin regulation. Skin blemishes are typically caused by a hormone imbalance, which vitamin B₆ helps to regulate. It is also suggested that ingestion of vitamin B₆ can alleviate some of the many symptoms of an alcoholic hangover and morning sickness from pregnancy. This might be due to B₆'s mild diuretic effect.

CONCLUSION

However, dietary intake remains the primary determinant of plasma arginine levels. The present paper reviews the role of femargin Sachets developed by R&D cell of Lactonova Nutripharm Pvt Ltd. Hyderabad for overall successful Pregnancy outcome.

REFERENCES

- Castillo L, Chapman TE, Sanchez M, Yu YM, Burke JF, Ajami AM, Vogt J, Young VR. Plasma arginine and citrulline kinetics in adults given adequate and arginine-free diets. *Proc Natl Acad Sci U S A*. 1993;90(16):7749-53. doi: 10.1073/pnas.90.16.7749, PMID 8356080.
- Castillo L, Ajami A, Branch S, Chapman TE, Yu YM, Burke JF, Young VR. Plasma arginine kinetics in adult man: response to an arginine-free diet. *Metabolism*. 1994;43(1):114-22. doi: 10.1016/0026-0495(94)90166-x, PMID 8289668.
- Abcouwer SF, Souba WW. Glutamine and arginine. In: Shils ME, Olson JA, Shike M, Ross AC, editors *Modern nutrition in health and disease*. 9th ed. Baltimore: Williams & Wilkins; 1999. p. 559-69.
- Wu G, Davis PK, Flynn NE, Knabe DA, Davidson JT. Endogenous synthesis of arginine plays an important role in maintaining arginine homeostasis in postweaning growing pigs. *J Nutr*. 1997;127(12):2342-9. doi: 10.1093/jn/127.12.2342, PMID 9405584.
- Dhanakoti SN, Brosnan JT, Herzberg GR, Brosnan ME. Renal arginine synthesis: studies in vitro and in vivo. *Am J Physiol*. 1990;259(3 Pt 1):E437-42. doi: 10.1152/ajpendo.1990.259.3.E437, PMID 1975989.
- Preiser JC, Berré PJ, Van Gossum A, Cynober L, Vray B, Carpentier Y, Vincent JL. Metabolic effects of arginine addition to the enteral feeding of critically ill patients. *JPEN J Parenter Enter Nutr*. 2001;25(4):182-7. doi: 10.1177/0148607101025004182, PMID 11434648.
- Castillo L, Sánchez M, Vogt J, Chapman TE, DeRojas-Walker TC, Tannenbaum SR, Ajami AM, Young VR. Plasma arginine, citrulline, and ornithine kinetics in adults, with observations on nitric oxide synthesis. *Am J Physiol*. 1995;268(2 Pt 1):E360-7. doi: 10.1152/ajpendo.1995.268.2.E360, PMID 7864114.
- Wu G, Morris SM Jr. Arginine metabolism: nitric oxide and beyond. *Biochem J*. 1998;336(1):1-17. doi: 10.1042/bj3360001, PMID 9806879.
- Meijer AJ, Lamers WH, Chamuleau RA. Nitrogen metabolism and ornithine cycle function. *Physiol Rev*. 1990;70(3):701-48. doi: 10.1152/physrev.1990.70.3.701, PMID 2194222.
- Wu G, Meininger CJ. Arginine nutrition and cardiovascular function. *J Nutr*. 2000;130(11):2626-9. doi: 10.1093/jn/130.11.2626, PMID 11053497.
- Gross SS, Wolin MS. Nitric oxide: pathophysiological mechanisms. *Annu Rev Physiol*. 1995;57:737-69. doi: 10.1146/annurev.ph.57.030195.003513, PMID 7539995.
- Wink DA, Hanbauer I, Grisham MB, Laval F, Nims RW, Laval J, Cook J, Pacelli R, Liebmann J, Krishna M, Ford PC, Mitchell JB. Chemical biology of nitric oxide: regulation and protective and toxic mechanisms. *Curr Top Cell Regul*. 1996;34:159-87. doi: 10.1016/s0070-2137(96)80006-9, PMID 8646847.
- Umans JG, Levi R. Nitric oxide in the regulation of blood flow and arterial pressure. *Annu Rev Physiol*. 1995;57(1):771-90. doi: 10.1146/annurev.ph.57.030195.004011.
- 1995;57:771-90.
- Hare JM, Colucci WS. Role of nitric oxide in the regulation of myocardial function. *Prog Cardiovasc Dis*. 1995;38(2):155-66. doi: 10.1016/s0033-0620(05)80004-0, PMID 7568904.
- Lyons CR. The role of nitric oxide in inflammation. *Adv Immunol*. 1995;60:323-71. doi: 10.1016/s0065-2776(08)60589-1, PMID 8607373.
- Brüne B, Messmer UK, Sandau K. The role of nitric oxide in cell injury. *Toxicol Lett*. 1995;82-83:233-7. doi: 10.1016/0378-4274(95)03481-1, PMID 8597059.
- Wink DA, Cook JA, Pacelli R, Liebmann J, Krishna MC, Mitchell JB. Nitric oxide (NO) protects against cellular damage by reactive oxygen species. *Toxicol Lett*. 1995;82-83:221-6. doi: 10.1016/0378-4274(95)03557-5, PMID 8597056.
- Brittenden J, Heys SD, Ross J, Park KG, Eremin O. Natural cytotoxicity in breast cancer patients receiving neoadjuvant chemotherapy: effects of L-arginine supplementation. *Eur J Surg Oncol*. 1994;20(4):467-72. PMID 8076711.
- Brittenden J, Park KGM, Heys SD, Ross C, Ashby J, Ah-See Ak, Eremin O. L-arginine stimulates host defenses in patients with breast cancer. *Surgery*. 1994;115(2):205-12. PMID 8310409.
- Imms FJ, London DR, Neame RL. The secretion of catecholamines from the adrenal gland following arginine infusion in the rat. *J Physiol*. 1969;200(1):55P-6P. PMID 5761977.
- Palmer JP, Walter RM, Ensink JW. Arginine-stimulated acute phase of insulin and glucagon secretion. I. In normal man. *Diabetes*. 1975;24(8):735-40. doi: 10.2337/diab.24.8.735, PMID 1158037.
- Rakoff JS, Siler TM, Sinha YN, Yen SS. Prolactin and growth hormone release in response to sequential stimulation by arginine and synthetic TRF. *J Clin Endocrinol Metab*. 1973;37(5):641-4. doi: 10.1210/jcem-37-5-641, PMID 4201417.
- Knopf RF, Conn JW, Fajans SS, Floyd JC, Guntsche EM, Rull JA. Plasma growth hormone response to intravenous administration of amino acids. *J Clin Endocrinol Metab*. 1965;25:1140-4. doi: 10.1210/jcem-25-8-1140, PMID 14328387.

24. Merimee TJ, Lillicrap DA, Rabinowitz D. Effect of arginine on serum-levels of human growth-hormone. *Lancet*. 1965;2(7414):668-70. doi: 10.1016/s0140-6736(65)90399-5, PMID 4158217.
25. Lekakis J, Papathanasiou S, Papamichael C, et al. Oral L-arginine improves endothelial dysfunction in patients with essential hypertension. *J Am Coll Cardiol*. 2001;260A.
26. Boger GI, Maas R, Schwedhelm E, Bierend A, Benndorf R, Kastner M, Steenpaß A, Boger RH. 865-3 Improvement of endothelium-dependent vasodilation by simvastatin is potentiated by combination with L-arginine in patients with elevated asymmetric dimethylarginine levels. *J Am Coll Cardiol*. 2004;43(5). doi: 10.1016/S0735-1097(04)92228-0.
27. Böger RH, Vallance P, Cooke JP. Asymmetric dimethylarginine (ADMA): a key regulator of nitric oxide synthase. *Atheroscler Suppl*. 2003;4(4):1-3. doi: 10.1016/s1567-5688(03)00027-8, PMID 14664896.
28. Böger RH. Asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, explains the "L-arginine paradox" and acts as a novel cardiovascular risk factor. *J Nutr*. 2004;134(10);Suppl:2842S-2847S; discussion 2853S. doi: 10.1093/jn/134.10.2842S, PMID 15465797.
29. Böger RH, Ron ES. L-arginine improves vascular function by overcoming deleterious effects of ADMA, a novel cardiovascular risk factor. *Altern Med Rev*. 2005;10(1):14-23. PMID 15771559.
30. Maxwell AJ, Zapien MP, Pearce GL, MacCallum G, Stone PH. Randomized trial of a medical food for the dietary management of chronic, stable angina. *J Am Coll Cardiol*. 2002;39(1):37-45. doi: 10.1016/s0735-1097(01)01708-9, PMID 11755284.
31. Blum A, Porat R, Rosenschein U, Keren G, Roth A, Laniado S, Miller H. Clinical and inflammatory effects of dietary L-arginine in patients with intractable angina pectoris. *Am J Cardiol*. 1999;83(10):1488-90, A8. doi: 10.1016/s0002-9149(99)00129-0, PMID 10335768.
32. Ceremuzyński L, Chamiec T, Herbaczynska-Cedro K. Effect of supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. *Am J Cardiol*. 1997;80(3):331-3. doi: 10.1016/s0002-9149(97)00354-8, PMID 9264427.
33. Walker HA, McGing E, Fisher I, Böger RH, Bode-Böger SM, Jackson G, Ritter JM, Chowienczyk PJ. Endothelium-dependent vasodilation is independent of the plasma L-arginine/ADMA ratio in men with stable angina: lack of effect of oral L-arginine on endothelial function, oxidative stress and exercise performance. *J Am Coll Cardiol*. 2001;38(2):499-505. doi: 10.1016/s0735-1097(01)01380-8, PMID 11499744.
34. Bednars B, Wolk R, Chamiec T, Herbaczynska-Cedro K, Winek D, Ceremuzyński L. Effects of oral L-arginine supplementation on exercise-induced QT dispersion and exercise tolerance in stable angina pectoris. *Int J Cardiol*. 2000;75(2-3):205-10. doi: 10.1016/s0167-5273(00)00324-7, PMID 11077135.
35. Egashira K, Hirooka Y, Kuga T, Mohri M, Takeshita A. Effects of L-arginine supplementation on endothelium-dependent coronary vasodilation in patients with angina pectoris and normal coronary arteriograms. *Circulation*. 1996;94(2):130-4. doi: 10.1161/01.cir.94.2.130, PMID 8674170.
36. Rector TS, Bank AJ, Mullen KA, Tschumperlin LK, Sih R, Pillai K, Kubo SH. Randomized, double-blind, placebo controlled study of supplemental oral L-arginine in patients with heart failure. *Circulation*. 1996;93(12):2135-41. doi: 10.1161/01.cir.93.12.2135, PMID 8925582.
37. Watanabe G, Tomiyama H, Doba N. Effects of oral administration of L-arginine on renal function in patients with heart failure. *J Hypertens*. 2000;18(2):229-34. doi: 10.1097/00004872-200018020-00015, PMID 10694193.
38. Yousufuddin M, Flather M, Shamim W, et al. A short course of L-arginine improves exercise capacity and endothelial function in chronic heart failure: a prospective, randomised, double blind trial. *J Am Coll Cardiol*. 2001;211A.
39. Houghton JL, Toresoff MT, Kuhner PA, et al. African American race predicts improvement in coronary microvascular endothelial function after L-arginine. *J Am Coll Cardiol*. 2001;258A.
40. Sanders PW. Salt-sensitive hypertension: lessons from animal models. *Am J Kidney Dis*. 1996;28(5):775-82. doi: 10.1016/s0272-6386(96)90265-6, PMID 9158221.
41. Calver A, Collier J, Vallance P. Dilator actions of arginine in human peripheral vasculature. *Clin Sci (Lond)*. 1991;81(5):695-700. doi: 10.1042/cs0810695, PMID 1661657.
42. Pezza V, Bernardini F, Pezza E, Pezza B, Curione M. Study of supplemental oral L-arginine in hypertensives treated with enalapril + hydrochlorothiazide. *Am J Hypertens*. 1998;11(10):1267-70. doi: 10.1016/s0895-7061(98)00153-8, PMID 9799047.
43. Siani A, Pagano E, Iacone R, Iacoviello L, Scopacasa F, Strazzullo P. Blood pressure and metabolic changes during dietary L-arginine supplementation in humans. *Am J Hypertens*. 2000;13(5 Pt 1):547-51. doi: 10.1016/s0895-7061(99)00233-2, PMID 10826408.
44. Maccario M, Oleandri SE, Procopio M, Grottoli S, Avogadri E, Camanni F, Ghigo E. Comparison among the effects of arginine, a nitric oxide precursor, isosorbide dinitrate and molsidomine, two nitric oxide donors, on hormonal secretions and blood pressure in man. *J Endocrinol Invest*. 1997;20(8):488-92. doi: 10.1007/BF03348006, PMID 9364253.
45. Schulze-Neick I, Penny DJ, Rigby ML, Morgan C, Kelleher A, Collins P, Li J, Bush A, Shinebourne EA, Redington AN. L-arginine and substance P reverse the pulmonary endothelial dysfunction caused by congenital heart surgery. *Circulation*. 1999;100(7):749-55. doi: 10.1161/01.cir.100.7.749, PMID 10449698.
46. Böger RH, Bode-Böger SM, Thiele W, Creutzig A, Alexander K, Frölich JC. Restoring vascular nitric oxide formation by L-arginine improves the symptoms of intermittent claudication in patients with peripheral arterial occlusive disease. *J Am Coll Cardiol*. 1998;32(5):1336-44. doi: 10.1016/s0735-1097(98)00375-1, PMID 9809945.

47. Roberts JM. Objective evidence of endothelial dysfunction in preeclampsia. *Am J Kidney Dis.* 1999;33(5):992-7. doi: 10.1016/s0272-6386(99)70439-7, PMID 10328745.
48. Helmbrecht GD, Farhat MY, Lochbaum L, Brown HE, Yadgarova KT, Eglinton GS, Ramwell PW. L-arginine reverses the adverse pregnancy changes induced by nitric oxide synthase inhibition in the rat. *Am J Obstet Gynecol.* 1996;175(4 Pt 1):800-5. doi: 10.1016/s0002-9378(96)80002-0, PMID 8885725.
49. Facchinetti F, Longo M, Piccinini F, et al. L-arginine infusion reduces blood pressure in pre-eclamptic women through nitric oxide release. *J Soc Gynecol Investig.* 1999;6:202-7.
50. Swanson B, Keithley JK, Zeller JM, Sha BE. A pilot study of the safety and efficacy of supplemental arginine to enhance immune function in persons with HIV/AIDS. *Nutrition.* 2002;18(7-8):688-90. doi: 10.1016/s0899-9007(02)00786-4, PMID 12093460.
51. Clark RH, Feleke G, Din M, et al. Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy beta-methylbutyrate, glutamine, and arginine: a.
4. Clark RH, Feleke G, Din M, Yasmin T, Singh G, Khan FA, Rathmacher JA. Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy beta-methylbutyrate, glutamine, and arginine: a randomized, double-blind, placebo-controlled study. *JPEN J Parenter Enter Nutr.* 2000;24(3):133-9. doi: 10.1177/0148607100024003133, PMID 10850936.
52. Pichard C, Sudre P, Karsegard V, Yerly S, Slosman DO, Delley V, Perrin L, Hirschel B. A randomized double-blind controlled study of 6 months of oral nutritional supplementation with arginine and omega-3 fatty acids in HIVinfected patients. *Swiss HIV Cohort Study. AIDS.* 1998;12(1):53-63. doi: 10.1097/00002030-199801000-00007, PMID 9456255.
53. Besset A, Bonardet A, Rondouin G, Descomps B, Passouant P. Increase in sleep related GH and Prl secretion after chronic arginine aspartate administration in man. *Acta Endocrinol.* 1982;99(1):18-23. doi: 10.1530/acta.0.0990018, PMID 7058674.
54. Macintyre JG. Growth hormone and athletes. *Sports Med.* 1987;4(2):129-42. doi: 10.2165/00007256-198704020-00004, PMID 3299611.
55. Elam RP. Morphological changes in adult males from resistance exercise and amino acid supplementation. *J Sports Med Phys Fitness.* 1988;28(1):35-9. PMID 3398508.
56. Marcell TJ, Taaffe DR, Hawkins SA, Tarpenning KM, Pyka G, Kohlmeier L, Wiswell RA, Marcus R. Oral arginine does not stimulate basal or augment exercise-induced GH secretion in either young or old adults. *J Gerontol A Biol Sci Med Sci.* 1999;54(8):M395-9. doi: 10.1093/gerona/54.8.m395, PMID 10496544.
57. Elam RP. Effect of arginine and ornithine on strength, lean body mass and urinary hydroxyproline in adult males. *J Sports Nutr.* 1989;29:52-6.
58. Corpas E, Blackman MR, Roberson R, Scholfield D, Harman SM. Oral arginine-lysine does not increase growth hormone or insulin-like growth factor-I in old men. *J Gerontol.* 1993;48(4):M128-33. doi: 10.1093/geronj/48.4.m128, PMID 8315224.
59. Yu YM, Ryan CM, Castillo L, Lu XM, Beaumier L, Tompkins RG, Young VR. Arginine and ornithine kinetics in severely burned patients: increased rate of arginine disposal. *Am J Physiol Endocrinol Metab.* 2001;280(3):E509-17. doi: 10.1152/ajpendo.2001.280.3.E509, PMID 11171607.
60. Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, Van Buren CT, Rothkopf MM, Daly JM, Adelsberg BR. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized clinical trial. *Crit Care Med.* 1995;23(3):436-49. doi: 10.1097/00003246-199503000-00006, PMID 7874893.
61. Weimann A, Bastian L, Bischoff WE, Grotz M, Hansel M, Lotz J, Trautwein C, Tusch G, Schlitt HJ, Regel G. Influence of arginine, omega-3 fatty acids and nucleotide-supplemented enteral support on systemic inflammatory response syndrome and multiple organ failure in patients after severe trauma. *Nutrition.* 1998;14(2):165-72. doi: 10.1016/s0899-9007(97)00429-2, PMID 9530643.
62. Takeda Y, Tominga T, Tei N, et al. Inhibitory effect of L-arginine on growth of rat mammary tumors induced by 7, 12, dimethylbenz(a)anthracene. *Cancer Res.* 1975;35:390-6.
63. Heys SD, Segar A, Payne S, Bruce DM, Kernohan N, Eremin O. Dietary supplementation with L-arginine: modulation of tumour-infiltrating lymphocytes in patients with colorectal cancer. *Br J Surg.* 1997;84(2):238-41, PMID 9052446.
64. Kemen M, Senkal M, Homann HH, Mumme A, Dauphin AK, Baier J, Windeler J, Neumann H, Zumtobel V. Early postoperative enteral nutrition with arginineomega-3 fatty acids and ribonucleic acidsupplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact. *Crit Care Med.* 1995;23(4):652-9. doi: 10.1097/00003246-199504000-00012, PMID 7536138.
65. Gianotti L, Braga M, Fortis C, Soldini L, Vignali A, Colombo S, Radaelli G, Di Carlo V. A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNAenriched enteral diet: effect on host response and nutritional status. *JPEN J Parenter Enter Nutr.* 1999;23(6):314-20. doi: 10.1177/0148607199023006314, PMID 10574478.
66. van Bokhorst-De Van Der Schueren MA, Quak JJ, von Blomberg-van der Flier BM, Kuik DJ, Langendoen SI, Snow GB, Green CJ, van Leeuwen PA. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. *Am J Clin Nutr.* 2001;73(2):323-32. doi: 10.1093/ajcn/73.2.323, PMID 11157331.
67. Park KGM. The Sir David Cuthbertson Medal Lecture 1992. The immunological and metabolic effects of L-arginine in human cancer. *Proc Nutr Soc.* 1993;52(3):387-401. doi: 10.1079/pns19930080, PMID 8302881.

68. Pieper GM. Review of alterations in endothelial nitric oxide production in diabetes: protective role of arginine on endothelial dysfunction. *Hypertension*. 1998;31(5):1047-60. doi: 10.1161/01.hyp.31.5.1047, PMID 9576113.
69. Pieper GM, Siebeneich W, Dondlinger LA. Shortterm oral administration of L-arginine reverses defective endothelium-dependent relaxation and cGMP generation in diabetes. *Eur J Pharmacol*. 1996;317(2-3):317-20. doi: 10.1016/s0014-2999(96)00831-x, PMID 8997616.
70. Giugliano D, Marfella R, Verrazzo G, Acampora R, Nappo F, Ziccardi P, Coppola L, D'Onofrio F. L-arginine for testing endothelium-dependent vascular functions in health and disease. *Am J Physiol*. 1997;273(3 Pt 1):E606-12. doi: 10.1152/ajpendo.1997.273.3.E606, PMID 9316452.
71. Wascher TC, Graier WF, Dittrich P, Hussain MA, Bahadori B, Wallner S, Toplak H. Effects of low-dose L-arginine on insulin-mediated vasodilatation and insulin sensitivity. *Eur J Clin Invest*. 1997;27(8):690-5. doi: 10.1046/j.1365-2362.1997.1730718.x, PMID 9279534.
72. Lubec B, Hayn M, Kitzmüller E, Vierhapper H, Lubec G. L-arginine reduces lipid peroxidation in patients with diabetes mellitus. *Free Radic Biol Med*. 1997;22(1-2):355-7. doi: 10.1016/s0891-5849(96)00386-3, PMID 8958162.
73. Regensteiner JG, Popylisen S, Bauer TA, Lindenfeld J, Gill E, Smith S, Oliver-Pickett CK, Reusch JE, Weil JV. Oral L-arginine and vitamins E and C improve endothelial function in women with type 2 diabetes. *Vasc Med*. 2003;8(3):169-75. doi: 10.1191/1358863x03vm489oa, PMID 14989557.
74. Piatti PM, Monti LD, Valsecchi G, Magni F, Setola E, Marchesi F, Galli-Kienle M, Pozza G, Alberti KG. Long-term oral L-arginine administration improves peripheral and hepatic insulin sensitivity in type 2 diabetic patients. *Diabetes Care*. 2001;24(5):875-80. doi: 10.2337/diacare.24.5.875, PMID 11347747.
75. Mullen MJ, Wright D, Donald AE, Thorne S, Thomson H, Deanfield JE. Atorvastatin but not L-arginine improves endothelial function in type I diabetes mellitus: a double-blind study. *J Am Coll Cardiol*. 2000;36(2):410-6. doi: 10.1016/s0735-1097(00)00743-9, PMID 10933350.
76. Brzozowski T, Konturek SJ, Sliwowski Z, Drozdowicz D, Zaczek M, Kedra D. Role of L-arginine, a substrate for nitric oxide synthase, in gastroprotection and ulcer healing. *J Gastroenterol*. 1997;32(4):442-52. doi: 10.1007/BF02934081, PMID 9250889.
77. Brzozowski T, Konturek SJ, Drozdowicz D, Dembiński A, Stachura J. Healing of chronic gastric ulcerations by L-arginine. Role of nitric oxide, prostaglandins, gastrin and polyamines. *Digestion*. 1995;56(6):463-71. doi: 10.1159/000201277, PMID 8536815.
78. Bortolotti M, Brunelli F, Sarti P, Miglioli M. Clinical and manometric effects of L-arginine in patients with chest pain and oesophageal motor disorders. *Ital J Gastroenterol Hepatol*. 1997;29(4):320-4. PMID 9476184.
79. Straathof JW, Adamse M, Onkenhout W, Lamers CB, Masclee AA. Effect of L-arginine on lower oesophageal sphincter motility in man. *Eur J Gastroenterol Hepatol*. 2000;12(4):419-24. doi: 10.1097/00042737-200012040-00009, PMID 10783995.
80. Zorngiotti AW, Lizza EF. Effect of large doses of the nitric oxide precursor, L-arginine, on erectile dysfunction. *Int J Impot Res*. 1994;6(1):33-5; discussion 36. PMID 8019615.
81. Chen J, Wollman Y, Chernichovsky T, Iaina A, Sofer M, Matzkin H. Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized study. *BJU Int*. 1999;83(3):269-73. doi: 10.1046/j.1464-410x.1999.00906.x, PMID 10233492.
82. Klotz T, Mathers MJ, Braun M, Bloch W, Engelmann U. Effectiveness of oral L-arginine in first-line treatment of erectile dysfunction in a controlled crossover study. *Urol Int*. 1999;63(4):220-3. doi: 10.1159/000030454, PMID 10743698.
83. Battaglia C, Salvatori M, Maxia N, Petraglia F, Facchinetti F, Volpe A. Adjuvant L-arginine treatment for in vitro fertilization in poor responder patients. *Hum Reprod*. 1999;14(7):1690-7. doi: 10.1093/humrep/14.7.1690, PMID 10402369.
84. Holt LE Jr, Albanese AA. Observations on amino acid deficiencies in man. *Trans Assoc Am Phys*. 1944;58:143-56.
85. Tanimura J. Studies on arginine in human semen. Part II. The effects of medication with L-arginineHCl on male infertility. *Bull Osaka Med Sch*. 1967;13:84-9.
86. De Aloysio D, Mantuano R, Mauloni M, Nicoletti G. The clinical use of arginine aspartate in male infertility. *Acta Eur Fertil*. 1982;13(3):133-67. PMID 6820754.
87. Scibona M, Meschini P, Capparelli S, Pecori C, Rossi P, Menchini Fabris GF. L-arginine and male infertility. *Minerva Urol Nefrol*. 1994;46(4):251-3. PMID 7701414.
88. Schachter A, Goldman JA, Zukerman Z. Treatment of oligospermia with the amino acid arginine. *J Urol*. 1973;110(3):311-3. doi: 10.1016/s0022-5347(17)60199-x, PMID 4725736.
89. Schachter A, Friedman S, Goldman JA, Eckerling B. Treatment of oligospermia with the amino acid arginine. *Int J Gynaecol Obstet*. 1973;11(5):206-9. doi: 10.1002/j.1879-3479.1973.tb00901.x, PMID 4803052.
90. Pryor JP, Blandy JP, Evans P, Chaput De Saintonge DM, Usherwood M. Controlled clinical trial of arginine for infertile men with oligozoospermia. *Br J Urol*. 1978;50(1):47-50. doi: 10.1111/j.1464-410x.1978.tb02765.x, PMID 343863.
91. Miroueh A. Effect of arginine on oligospermia. *Fertil Steril*. 1970;21(3):217-9. doi: 10.1016/S0015-0282(16)37384-8, PMID 5435745.
92. Smith SD, Wheeler MA, Foster HE Jr, Weiss RM. Improvement in interstitial cystitis symptom scores during treatment with oral L-arginine. *J Urol*. 1997;158(3 Pt 1):703-8. doi: 10.1097/00005392-199709000-00005, PMID 9258064.
93. Ehrén I, Lundberg JO, Adolfsson J, Wiklund NP. Effects of L-arginine treatment on symptoms and bladder nitric oxide levels in patients with interstitial cystitis. *Urology*. 1998;52(6):1026-9. doi: 10.1016/s0090-4295(98)00343-4, PMID 9836549.

94. Evoy D, Lieberman MD, Fahey TJ 3rd, Daly JM. Immunonutrition: the role of arginine. *Nutrition*. 1998;14(7-8):611-7. doi: 10.1016/s0899-9007(98)00005-7, PMID 9684265.
95. Barbul A, Rettura G, Levenson SM, Seifter E. Wound healing and thymotropic effects of arginine: a pituitary mechanism of action. *Am J Clin Nutr*. 1983;37(5):786-94. doi: 10.1093/ajcn/37.5.786, PMID 6846217.
96. Barbul A, Lazarou SA, Efron DT, Wasserkrug HL, Efron G. Arginine enhances wound healing and lymphocyte immune responses in humans. *Surgery*. 1990;108(2):331-6; discussion 336. PMID 2382229.
97. Kirk SJ, Hurson M, Regan MC, Holt DR, Wasserkrug HL, Barbul A. Arginine stimulates wound healing and immune function in elderly human beings. *Surgery*. 1993;114(2):155-9; discussion 160. PMID 8342121.
98. Buhimschi IA, Saade GR, Chwalisz K, Garfield RE. The nitric oxide pathway in pre-eclampsia: pathophysiological implications. *Hum Reprod Update*. 1998;4(1):25-42. doi: 10.1093/humupd/4.1.25, PMID 9622411.
99. Facchinetti F, Neri I, Genazzani AR. L-arginine infusion reduces preterm uterine contractions. *J Perinat Med*. 1996;24(3):283-5. doi: 10.1515/jpme.1996.24.3.283, PMID 8827578.
100. Ohtsuka Y, Nakaya J. Effect of oral administration of L-arginine on senile dementia. *Am J Med*. 2000;108(5):439. doi: 10.1016/s0002-9343(99)00396-4, PMID 10759111.
101. Tankersley RW. Amino acid requirements of herpes simplex virus in human cells. *J Bacteriol*. 1964;87:609-13. doi: 10.1128/jb.87.3.609-613.1964, PMID 14127578.
102. Ricciardolo FL, Geppetti P, Mistretta A, Nadel JA, Sapienza MA, Bellofiore S, Di Maria GU. Randomised double-blind placebo-controlled study of the effect of inhibition of nitric oxide synthesis in bradykinin-induced asthma. *Lancet*. 1996;348(9024):374-7. doi: 10.1016/s0140-6736(96)04450-9, PMID 8709736.
103. de Gouw HW, Verbruggen MB, Twiss IM, Sterk PJ. Effect of oral L-arginine on airway hyperresponsiveness to histamine in asthma. *Thorax*. 1999;54(11):1033-5. doi: 10.1136/thx.54.11.1033, PMID 10525564.

1.