Review Article

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FEMARGIN SACHET - FOR OVERALL SUCCESSFUL HEALTHY OUTCOME

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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 for overall success ful out comes.

Key words: Semi-essential Amino acid, L-Arginine, Femargin.

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]

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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 with hyperlipidemia & 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 $\pm$ 63 percent and the absolute walking distance by 155 $\pm$ 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 (0.16g/kgbody-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 hydroxymethyl -butyrate (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 $\pm$ 0.5 kg, while those supplemented with placebo gained only 0.37 $\pm$ 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 burn[60] and trauma.[61] 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.[18,19] 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 diabete.[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] 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 fiveweek 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.

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] Further researches are needed to confirm the efficacy and safety of arginine in prevention of preterm delivery.

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 1-3 g or 7-15 g 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 data[101] 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 broncho-protective 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.

Role of DHA in femargin.

DHA (Docosahexaenoic acid, an omega-3 long chain 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 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's 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 in *Alzheimer's & Dementia: the 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 Heart Association**

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

Proanthocyanidin in Femargin

Proanthocyanidin (PA o rPAC) also known asprocyani din, oligomericproanthocyanidin (OPC),leukocyanidin, leucoanthocyanin and condensed tannins, is a class of flavanol. Proanthocyanidin are essentially polymer chains of flavonoids such as catechins. (Ref; www.herbalchem.net. Retrieved 2008-03-17).

Studies show that proanthocyanidins antioxidant capabilities are 20 times more powerful than vitamin C and 50 times more potent than vitamin E (Ref: *Journal of Medicinal Food* 6 (4): 291–9). 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 scleroses, dropping blood viscidity and preventing thrombus formation.(Ref: *The American journal of clinical nutrition* 77 (6): 1466–73.). Proanthocyanidins suppress production of a protein endothelin-1 that constricts blood vessels.(Ref; *Nature* 444 (7119: 566.)

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

Bell's Palsy: Evidence suggests methylcobalamin dramatically increased the recovery time for facial nerve function in Bell's palsy.(Ref; Jalaludin MA. Methylcobalamin treatment of Bell's palsy. Methods Find Exp Clin Pharmacol 1995;17:539-54)

Cancer: Cell culture and in vivo experimental results indicated methylcobalamin inhibited the proliferation of malignant cells.(Ref; Int J Vitam Nutr Res 1997;67:164-170). Research indicated that methylcobalamin enhanced survival time andreduced tumor growth following inoculation of mice with Ehrlich ascites tumor cells.(Ref: Shimizu N, Hamazoe R, Kanayama H, et al. Experimental study of antitumor effect of methyl-B12. Oncology 1987;44:169-173). Methylcobalamin has been shown to increase survival time of leukemic mice. Under the same experimental conditions, cyanocobalamin was inactive.(Ref; Tsao CS, Myashita K. Influence of cobalamin on the survival of mice bearing ascites tumor. Pathology 1993;61:104-108)

Diabetic Neuropathy: Oral administration of methylcobalamin (500 mcg three times daily for four months) resulted in subjective improvement in burning sensations, numbness, loss of sensation, and muscle cramps. An improvement in reflexes, vibration sense, lower motor neuron weakness, and sensitivity to pain was also observed.(Ref; Yaqub BA, Siddique A, Sulimani R. Effects of methylcobalamin on diabetic neuropathy. Clin Neurol Neurosurg 1992;94:105-111).

Eye-Function: Experiments indicated chronic administration of methylcobalamin protected cultured retinal neurons against N-methyl-D- aspartate-receptor-mediated glutamate neurotoxicity. Deterioration of accommodation following visual work has also been shown to improve in individuals receiving methylcobalamin.(Ref; Invest Ophthalmol Vis Sci 1997;38:848-854).

Heart Rate Variability: Heart rate variability is a means of detecting the relative activity and balance of the sympathetic/parasympathetic nervous systems. Methylcobalamin produces improvements in several components of heart rate variability, suggesting a balancing effect on the nervous system.(Ref; Horm Metab Res 1995;27:43-44)

HIV: Under experimental conditions, methylcobalamin inhibited HIV-1 infection of normal human blood monocytes and lymphocytes.(Ref; Blood 1995;86:1281-1287)

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. (REF; Atherosclerosis 1993;103:149-15)

Male Impotence: In one study, methylcobalamin, at a dose of 6 mg/day for 16 weeks, improved sperm count by 37.5 percent.(ref; Hinyokika Kiyo 1987;33:151-156.) In a separate investigation, methylcobalamin, given at a dose of 1,500 micrograms per day for 4-24 weeks, resulted in sperm concentration increases in 38 percent of cases, total sperm count increases in 54 percent of cases, and sperm motility increases in 50 percent of cases.(Ref; Clinical experience with methylcobalamin (CH3-B12) for male infertility. Hinyokika Kiyo 1984;30:581-586.)

Sleep Disturbances: The use of methylcobalamin in the treatment of a variety of sleep-wake disorders is very promising. Although the exact mechanism of action is not yet elucidated, it is possible that methylcobalamin is needed for the synthesis of melatonin, since the biosynthetic formation of melatonin requires the donation of a methyl group. Supplementation appears to have a great deal of ability to modulate melatonin secretion, enhance light-sensitivity, normalize circadian rhythms, and normalize sleep-wake rhythm.(Ref; Neurosci Lett 1995;192:1-4).

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 B_9, vitamin $B_c$or folacin) and folate (the naturally occurring form), as well as pteroyl-L-glutamic acid, pteroyl-L-glutamate, and pteroylmonoglutamic acid are forms of the water-soluble vitamin B_9. 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 (Ref; *Journal of the American Medical Association* 262 (20): 2847–2852). Supplementation with folic acid has also been shown to reduce the risk of congenital heart defects,cleft lips (Ref; *BMJ (Clinical research ed.)* 334 (7591): 464) 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.(Ref; Health Professionals Recommendations, Folic Acid, NCBDDD, CDC)

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. (Ref; *Hum Reprod Update*13 (2): 163–74).

Heart disease

An estimated 13,500 deaths occur annually due to folate deficiency's effect on coronary artery disease and the risk of ischemic heart disease, and stroke has been reduced by 15% since folate fortification regulations were enforced. Adequate concentrations of folate, vitamin B_{12}, or vitamin B_6 may decrease the circulating level of homocysteine, an amino acid normally found in blood. There is evidence an elevated homocysteine level is an independent risk factor for heart disease and stroke. The evidence suggests high levels of homocysteine may damage coronary arteries or make it easier for blood platelets to clump together and form a clot.(Ref; Refsum H, Ueland PM, Nygard O, Vollset SE (1998). "Homocysteine and cardiovascular disease".*Annual Review of Medicine* 49 (1): 31–62).

Vitamin B6 in Femargin

Vitamin B_6 is a water-soluble vitamin and is part of thevitamin 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 acidmetabolism, including transamination, deamination, and decarboxylation. PLP also is necessary for the enzymatic reaction governing the release of glucose from glycogen. Vitamin B_6 has been used to treat nausea and vomiting in early pregnancy for decades.(Ref; Sheehan P. Hyperemesis gravidarum--assessment and management. Aust Fam Physician. 2007 Sep;36(9):698-701). The intake of vitamin B_6, from either diet or supplements, could cut the risk of Parkinson's disease by half (Ref; Increased intake of vitamin B6Sheet". Retrieved 2006-08-11).

Vitamin B_6 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 B_6supplements 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 B_6 helps to regulate. It is also suggested that ingestion of vitamin B_6 can alleviate some of the many symptoms of an alcoholic hangover and morning sickness from pregnancy. This might be due to B_6's mild diuretic effect. (Ref; THE MYSTERIOUS VITAMIN B6. By Dr. Russ Ebbets. Off The Road Column).

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