

HOMOCYSTEINE

Homocysteine, a sulfur containing amino acid, is in the forefront as a cardiovascular risk factor. Though its role in atherosclerosis and atherothrombosis is confirmed, it should be noted that most naturally occurring substances have a purpose in physiology; homocysteine is not the exception.

The American Academy of Family Physicians explains that homocysteine is normally changed into other amino acids for use in the body's normal functions. For example, homocysteine is an intermediate in the biosynthesis of L-cysteine, a non-essential amino acid and metabolic precursor to cystine. Cysteine is important in fatty acid synthesis and energy metabolism, but its most important role takes place in the liver where it assists glutathione in the detoxification of carcinogens and dangerous chemicals. (Braverman, 1987) Once cysteine is generated, it can be directed into several pathways, including synthesis of glutathione and taurine. Amino acids play strategic roles in cardiac function, cholesterol excretion, and bile salt formation. (Lehninger et al., 1993)

Some researchers believe that the residuals of homocysteine may support the adrenal glands, contribute to neurotransmitter synthesis and the regeneration of bones and cartilage. It should be strongly emphasized that homocysteine must be detoxified in order for its by-products to offer bio-chemical advantage. If disposal systems (remethylation and transsulfuration) are nonfunctional, allowing homocysteine to accumulate, the results can be deadly.

Experiments have demonstrated if high levels of homocysteine accumulate in the cell, this can inhibit DNA repair. Without DNA repair, mutations and breakage can occur: an effect closely linked to aging. Also, the liver depends upon methylation to perform the rites of detoxification. This action is inhibited by high homocysteine levels. If homocysteine is not detoxified and begins to accumulate, plaque builds up in the endothelial cells lining the arteries. This occurs as homocysteine reacts with LDL-cholesterol to form small, dense particles. Macrophages use these particles to form foam cells, that like to "swell," protruding into the space of the artery, obstructing blood flow. Elevated levels of homocysteine, also, block production of nitric oxide in the cells of the blood vessel walls, making the vessels less pliable and even more susceptible to plaque buildup. Dr. Kilmer McCully, crusader for the homocysteine theory of heart disease, says that homocysteine plays a key role in every pathophysiological process that leads to arteriosclerotic plaque. (McCully, 1996)

A heart attack or stroke is more likely to occur as homocysteine inhibits the production of tissue plasminogen activators, a substance produced naturally by cells in the walls of blood vessels that prevents clotting. Blood flow, as demonstrated by numerous studies, is significantly impaired, particularly among middle aged and senior subjects with high levels of homocysteine.

The European Journal of Clinical Investigation reported that **40% of all stroke victims have elevated homocysteine** levels compared to only 6% of controls. (Brattstrom et al., 1992) Other studies chronicled similar findings, i.e., elevations in homocysteine in 16 out of 38 patients with cerebrovascular disease (42%), 7 of 25 with peripheral vascular disease (28%), and 18 of 60 with coronary vascular disease (30%), but in none of the 27 normal subjects. (Clarke et al., 1991) A team from Massachusetts General reported even more incriminating data, announcing that **mild-moderately elevated homocysteine independently increased the risk of stroke by 86%**. (Results collected through meta-analysis of 15 studies and reported by Kelly, 2001) High concentrations of homocysteine and low levels of folate and vitamin B6 are, also, associated with an increased risk of carotid-artery stenosis in the elderly. (Selhub et al., 1995) Higher levels of homocysteine predispose for blood clots in the legs, deep venous thrombosis (DVT), as well. (den Heijer et al., 1996)

Because homocysteine encourages free radical activity, genes are also involved in the homocysteine attack. This has significant impact upon the cardiovascular system, as homocysteine activates genes in blood vessels, encouraging the coagulation process and the proliferation of smooth muscles. Since homocysteine wields such a powerful cardiovascular blow from so many different directions, it is estimated that **a 3-unit increase in homocysteine equates to a 35% increase in heart attack risk**. (Verhoef et al., 1996) The risk becomes even greater if elevated

homocysteine occurs with other risk factors. For example, a hypertensive woman with elevated homocysteine levels has a 25-fold increased risk of vascular disease.

Though the dangers imposed by elevated homocysteine are not a new finding, most of the medical community has (until recently) ignored homocysteine, as a cardiovascular risk. Craig Cooney, Ph.D., says that excessive homocysteine is now widely recognized by scientists, as the single greatest biochemical risk factor for heart disease, estimating **that homocysteine may be a participant in 90% of cardiovascular problems.**

Homocysteine levels should be kept as low as possible, i.e., below 7 micromolar per liter of blood plasma. Laboratories usually regard levels up to 15 micro mol/L as normal, but epidemiological data reveal that homocysteine levels above 6.3 reflect a progressive increase in the risk of a heart attack. (Robinson et al., 1995) Though the incidence of hypertension, thrombotic stroke, peripheral vascular disease (gangrene), blood vessel toxicity, and the risk of heart attack escalate as homocysteine levels increase, tests to measure homocysteine are not routinely ordered in a cardiovascular workup.

While the focus of this article is on cardiovascular disease, it should be noted that individuals suffering with Alzheimer's disease, depression, eye problems, liver damage, kidney disease, several types of malignancies, i.e., acute lymphoblastic leukemia, breast, pancreatic, and ovarian cancer, Crohn's disease, ulcerative colitis, and irritable bowel disease, often, present with elevated homocysteine levels. (Clarke et al., 1998) (Cattaneo et al., 1998) (Mayer et al., 1997) (Refsum et al., 1991) (Romagnuolo et al., 2001)

Because of homocysteine's role in sulfur and methyl group metabolism, elevated levels of homocysteine would be expected to negatively impact the biosynthesis of SAME, carnitine, chondroitin sulfate, coenzymeQ10, creatine, cysteine, dimethylglycine, epinephrine, glucosamine sulfate, glutathione, melatonin, pantethine, phosphatidylcholine, and taurine. Short supply of these nutrients could severely disable cardiac performance.

HOMOCYSTEINE LOWERING NUTRIENTS

Published literature emphasizes that folic acid, vitamin B12, vitamin B6, zinc, (nutrient co-factors) and trimethylglycine (a methyl donor) are critical to the reduction of homocysteine.

Folic Acid in conjunctions with B vitamins is the initial therapy of choice.

A Polish study showed that administering folic acid (5 mg/day), vitamin B6 (300 mg/day), and B12 (1000 microgram/day) over an 8-week period reduced benchmark homocysteine levels by one-half (from 20 to 10 micromoles/liter) and also reduced thrombin, an intermediate in the production of fibrinogen. (Undas, et al., 1999) It has been theorized that **properly administered folate might prevent as many as 30,000 premature deaths**, annually. Individuals with low folate status, regardless of age or sex, have a 69% increase in the risk of fatal coronary heart disease compared to individuals with higher levels, i.e., > 13.6 nanomoles per liter.

The New England Journal of Medicine reported that treatment with a combination of folic acid, vitamin B12, and pyridoxine significantly reduced homocysteine levels and decreased the rate of restenosis and the need for revascularization of the target lesion after coronary angioplasty. The researchers concluded that this inexpensive treatment, with minimal side effects, should be considered as adjunctive therapy for patients undoing coronary angioplasty. (Schnyder et al., 2001)

Vitamin B6 is the second means of homocysteine disposal via the transsulfuration pathway, a sequence dependent upon vitamin B6. This pathway converts homocysteine to the powerful antioxidants cysteine and glutathione. Chronic mega dose vitamin B6 supplementation (300 to 500 mg daily) can result in neurological symptoms that, typically, fade when the dosage is reduced or discontinued. Careful monitoring to determine the lowest vitamin B6 dose capable of controlling homocysteine levels is essential. Note: Vitamin B6 is, also, a reliable diuretic, making it of particular advantage to patients with high blood pressure and congestive heart failure.

Researchers selected 421 patients with mildly elevated homocysteine to determine their response to vitamin B6 (250 mg daily). After 6 weeks of vitamin B6 supplementation, 56% of the patients had normal homocysteine levels. Non-normalized homocysteine concentrations were treated with a combination of supplements, i.e., vitamin B6 (250 mg daily) and/or folic acid (5 mg daily) and/or TMG (6 gm daily) solely or in combination. The more aggressive treatment normalized homocysteine levels in 95% of the remaining cases.

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Trimethylglycine (TMG), also, called **betaine**, emerges as one of the most important nutrients to prevent and reverse existing heart disease. TMG delivers its cardiac advantage by acting as a potent remethylation agent. Betaine supplementation (TMG) usually causes a substantial lowering of homocysteine but regular dosing must continue to sustain the improvement.

Choline, another methyl donor, can act independently to lower homocysteine levels, but it only influences remethylation in the liver and kidneys, leaving the heart and brain less protected. Methylating factors, as vitamin B12 and folic acid, add additional protection.

Magnesium reduces blood pressure, is a calcium antagonist and beta blocker, tempers sympathetic nervous system, is beneficial in arrhythmias and mitral valve prolapse, increases the number and sensitivity of insulin receptors, has anti-diabetic properties, encourages the methylation process, prevents toxic buildup of homocysteine, reduces iron and calcium levels, is a vasodilator, opposes platelet aggregation.

READERS GUIDE TO FOOD SOURCES, ENHANCERS and ANTAGONISTS TO HOMOCYSTEINE-LOWERING NUTRIENTS

The American Journal of Clinical Nutrition reported that a chemical component of coffee and black tea (chlorogenic acid) could raise serum homocysteine levels. (Olthof et al., 2001) Individuals with elevated homocysteine may wish to restrict high intake of these beverages. Conversely, **a diet rich in fruits and vegetables may reduce the risk of heart disease (7% to 9%) by reducing blood levels of homocysteine.** Foods not exposed to the milling process i.e. whole grains, have a more reliable nutrient bank and are capable of delivering more homocysteine-lowering vitamins and minerals.

FOLIC ACID rich foods are liver, kidney beans, lima beans, and fresh, green leafy vegetables (especially, spinach, asparagus, and broccoli). Other sources include most fish, beets, cabbage, eggs, whole grains, and citrus fruits. Fortification of enriched grain products with folic acid was associated with a substantial improvement in folate status in a population of middle aged and older adults. (Jacques et al., 1999)

Folic acid is most efficient when combined with vitamin B12, biotin, pantothenic acid, and vitamin C. According to the Committee on Dietary Allowances, heat and oxidation (occurring during cooking and storage) can destroy as much as half of the folate in foods.

Sulfa drugs interfere with the bacteria in the intestines that manufacture folic acid. Methotrexate (an anti-cancer drug) depletes folate, causing a transient elevation in homocysteine and phenytoin (an anti-epileptic drug) interferes with folate metabolism. Oral contraceptives, alcohol, coffee, and smoking are, also, considered folic acid antagonists.

VITAMIN B6 appears in most foodstuffs but the best sources are brewer's yeast, wheat germ, pork, organ meats (especially liver), whole grain cereals, legumes, potatoes, bananas, and oatmeal. Other sources include most beans and fish, avocados, and egg yolk.

Complimentary nutrients in regard to vitamin B6 absorption are all other B vitamins, vitamin C, magnesium, potassium, zinc, and high-quality protein.

Antidepressants, alcohol, coffee, exercise (to excess), estrogen therapy, and oral contraceptives appear to either increase the need for vitamin B6 or reduce its status. Diuretics and cortisone drugs block its absorption. (Ubbink et al., 1996)

AGE-MANAGEMENT MEDICINE ♦ FOR A LIFETIME OF HEALTH

VITAMIN B12, the most complex of the B vitamins, should be of special interest to vegetarians who, after chronic abstinence from animal products, can become seriously deplete in this nutrient. Most vitamin B12 deficiencies occur, however, not because of inadequate dietary consumption but rather because of poor absorption. It is important to note that neither man nor animal is able to synthesize or manufacture vitamin B12 in the body. Production of B12 is dependent upon simpler forms of plant life, such as fungi and bacteria. Animal derivatives, i.e., eggs, fish/marine life, beef/pork, and milk/dairy products are good sources of vitamin B12, but liver and kidney represent the very best sources.

Nutrients considered B12 enhancers are others of the B complex (especially folic acid and vitamin B6), vitamin C, iron, potassium, sodium, and calcium.

Medications to treat gout, anticoagulant drugs and potassium supplements may block the absorption of vitamin B12 from the digestive tract. For optimal B12 utilization, also, avoid coffee, alcohol, and laxatives.

MAGNESIUM is found in many foods but particularly in nuts, grains, legumes, dark-green vegetables, and most fish. Good sources are spinach, broccoli, tomato juice, navy and pinto beans, sunflower seeds, tofu, halibut, cashews, artichoke and black-eyed peas. (Whitney et al., 1998)

Magnesium enhancers include the B-complex (especially vitamin B6), vitamin C, calcium, essential fatty acids and amino acids.

The body's requirement for magnesium increases if using alcohol, taking higher levels of zinc and vitamin D, or exposed to fluoride, unrelenting stress, or tobacco. Dietary fats and fat-soluble vitamins, cod liver oil, calcium (large amounts), iron, and excesses of protein decrease magnesium absorption. Oxalic acid foods, as rhubarb, spinach, tea, almonds, chard, and cocoa, also, hinder its absorption. Diuretics and chronic diarrhea can seriously deplete many minerals, including magnesium.

SUPPLEMENT DOSING

The following daily supplements (used alone or in combination) are effective in lowering homocysteine levels:

FOLIC ACID	800 – 5000mg
B6	100 – 500mg
TMG	500 – 9000mg
B12	250 – 3000mg
CHOLINE	250 – 3000mg
INOSITOL	250 – 100mg
SAMe	200 – 800mg

NOTE:Administering homocysteine-lowering nutrients is so individualized that blood testing is essential to determine adequate dosages. To assume that homocysteine is not a threat (because you are taking folic acid and B vitamins) is not a guarantee that the dosage is appropriate to render protection. In addition inappropriately high levels of some of these substances can result in serious side-effects. You should proceed with therapy only under the direct supervision of you doctor.

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**Portions of this protocol have been excerpted from The Life Extension Foundation's "Cardiovascular Disease Protocol"*