Title
Homocysteine and Cardiovascular Disease

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Cardiovascular Risk Factors

There are currently at least nine risk factors that are useful in predicting the likelihood of an individual to suffer from a heart attack or stroke. These include: heredity, being male, advancing age, cigarette smoking, high blood pressure, diabetes, obesity (especially excess abdominal fat), lack of physical activity, and abnormal blood cholesterol levels. The more of these risk factors an individual has, the more likelihood there is of that individual becoming ill. Although factors such as heredity, gender, and age cannot be changed, all other influences can be strongly affected by changes in an individual's behavior. By changing behavior, one can modify these factors and subsequently reduce their risk of having a heart attack.

Recently, elevated levels of an amino acid, homocysteine, have been linked to increased risk of premature coronary artery disease and stroke. Fortunately, it is also a modifiable risk factor:

Figure 1. Pathways of methionine and homocysteine metabolism. Methionine is converted to S-adenosylmethionine; the methyl group of methionine is thereby "activated" and can be transferred to different acceptor molecules by a variety of transferases. S-adenosylhomocysteine is the other reaction product, and is hydrolyzed to adenosine and L-homocysteine. The latter has two fates: First, it can be condensed with serine to form cystathionine by the pyridoxal phosphate (vitamin B6)-requiring enzyme cystathionine synthase; the cystathionine can be hydrolyzed to alpha-ketobutyrate and cysteine by another B6-requiring enzyme, cystathionase. Second, homocysteine can accept a methyl group from N5-methyltetrahydrofolate for the resynthesis of methionine, regeneration free tetrahydrofolate for other metabolic activities. The reaction is catalyzed by homocysteine methyltransferase, and requires methylcobalamin, a coenzyme derived from vitamin B12. Actually, the N%'-methyl-THF recharges the cobalamin after the homocysteine accepts the methyl group from the B12 derivative. (Adapted by Dr. Patrice Zamenhof, Biological Chemistry Department, UCLA)
What is homocysteine?

Homocysteine is an intermediate in the interconversion of the amino acids methionine and cysteine, a process requiring at various stages, activated folic acid (tetrahydrofolate and N-methyl-tetrahydrofolate) and enzymes containing the cofactors vitamin B6 (pyridoxal phosphate) and vitamin B12 (methyl-cobalamin). Homocysteine is toxic to the vascular endothelium but undergoes rapid enzymatic metabolism so it is not normally present in the bloodstream.

How do homocysteine levels become elevated?

A large number of individuals have elevated blood levels of homocysteine. This has been attributed to genetic inability to metabolize homocysteine as well as a deficiency of one or more of the vitamin cofactors required for its conversion.

Vitamin B12 Deficiency

Vitamin B12 deficiency results in serious disease. Vitamin B12 is not made by either plants or animals and can be synthesized by only a few species of microorganisms. It is required in only minute amounts, about 3mg/day, by healthy people, but the severe disease pernicious anemia results from failure to absorb vitamin B12 efficiently from the intestine, where it is synthesized by intestinal bacteria or obtained from digestion of meat in the diet. The pathology in pernicious anemia includes reduced production of erythrocytes, reduced levels of hemoglobin, and severe, progressive impairment of the central nervous system (1).

Vitamin B12 is an important cofactor in the metabolism of homocysteine. Therefore, vitamin B12 status is now commonly considered as a factor relating to plasma homocysteine concentration (2). Vitamin B12 deficiency is a common condition in the elderly. The metabolite homocysteine may be elevated in plasma deficiency of vitamin B12 [Figure 1]. This deficiency is also due to impaired absorption of B12 caused by gastric atrophy (damage to the lining of the stomach) which is common as people age.

Vitamin B6 Deficiency

Plasma/serum homocysteine may also be related to vitamin B6 status (2). Deficiencies of vitamin B6 intake and plasma levels are frequent in the population and associated with elevation of plasma homocysteine (3). Dietary deficiencies of vitamin B6 in the population are caused by insufficient intake of foods containing this nutrient and by loss of this nutrient in the processing, preservation, and marketing of foods, leading to a serious depletion from major sources of calories including flour, white rice, sugars, fats, and oils. Atherogenesis in the population is secondary to hyperhomocysteinemia caused by dietary deficiencies of vitamin B6 as well as genetic defects in enzymes affecting homocysteine metabolism (4).
Folic Acid Deficiency

In addition to its relation to vitamins B12 and B6, plasma/serum homocysteine may also be related to folate (folic acid) status. Abnormal elevation of homocysteine occurs among people whose diet contains inadequate amounts of folic acid. Folic acid is thought to protect against heart disease because it breaks down homocysteine and allows it to be cleared from the bloodstream. A University of Washington review referred to 11 studies of folic acid's effects on homocysteine levels. Among these was the Tufts research, which showed for the first time that inadequate intake of the vitamin is the main determinant of the homocysteine-related increase in the risk of carotid blockage (5). In 1996, Canadian investigators reported that among more than 5,000 men and women who participated in a national nutrition survey, those in the quarter of the group with the lowest folic acid were 69 percent more likely to die of a coronary problem that those in the quartile with the largest stores of the vitamin (6).

Homocysteine's link to cardiovascular disease

In 1969, Dr. Kilmer McCully, a Harvard pathologist, first proposed a link between elevated homocysteine and arterial damage after noting similar vascular changes in two patients with elevated homocysteine levels from different mechanisms (7). Since that time, several biological mechanisms for the role of homocysteine in the pathogenesis of atherosclerosis have been elucidated (8). Vascular damage to intimal cells by homocysteine has been related to oxidative stress, production of hydrogen peroxide and superoxide, inactivation of nitric oxide, and inhibition of glutathione peroxidase activity and synthesis (9). The increased propensity to thrombosis in hyperhomocysteinemia has been related to effects on multiple coagulation factors, including platelets, tissue factor, activated protein C, thrombomodulin, thromboxane, lipoprotein (a) binding to fibrin, and factors V, VII, and XII (10). Modification of low-density lipoprotein (LDL) by homocysteine thiolactone forms small, dense LDL particles that self-aggregate and are taken up by macrophages to form foam cells (11), leading to intimal damage, oxidative modification of LDL, deposition of cholesterol and lipids, thrombogenesis, and the connective alterations of developing arteriosclerotic plaques (12). Additionally, homocysteine is directly toxic to vascular endothelium and stimulates the proliferation of smooth muscle cell (8).

A recent study compared 131 patients with severe blockages in two coronary arteries, 88 patients with moderate blockage of one coronary artery, and another group of healthy individuals without heart disease. The researchers found a linear relationship between blood homocysteine levels and severity of the coronary blockages: For every 10% elevation of homocysteine, there was nearly the same rise in the risk of developing severe coronary heart disease (13).

In another study, the authors demonstrated in a prospective nested case-control study the risk between homocysteine and coronary heart disease (CHD). At the follow up (mean 4 years), CHD had developed in 118 patients and five had died suddenly after the onset of chest pain. These cases had a 1.4 mmol/l higher mean level of serum homocysteine than
controls. This along with other data supports the theory that hyperhomocysteinemia is an independent risk factor for coronary heart disease in the general population (14).

Yet another study examined the relationship between carotid artery stenosis and plasma homocysteine concentrations among 1041 members of the original Framingham Heart Study cohort, a prospective study of cardiac risk factors initiated in 1948. The authors concluded that high plasma homocysteine levels and low concentrations of folate and vitamin B6 are associated with an increase risk of extracranial carotid artery stenosis in a population-based cohort of elderly people (15). This cross-sectional study provided convincing evidence of a causative role for homocysteine in the pathogenesis of cerebrovascular disease (8).

A last population-based study examined the association between serum total homocysteine concentration and stroke using a nested case-control study design. The authors concluded that total homocysteine concentration in the serum is a strong and independent risk factor for stroke (16).

Overall, studies continuously support that homocysteine is an independent risk factor for coronary artery, cerebrovascular, and peripheral vascular disease (8) comparable with hypercholesterolemia, smoking, and hypertension (17).

Effectiveness of Vitamin Supplementation/Dietary Modification

Folic Acid

There is consistent evidence that dietary and supplemental folic acid can reduce homocysteine levels (5). Folate is essential for homocysteine metabolism, and sub-optimal status of the vitamin is the most frequently cited reason for the elevation of plasma homocysteine (18). Diet alone is unlikely to be sufficient to increase circulating folate levels and decrease serum total homocysteine. The bioavailability of folic acid from typical conjugated folates in the diet is one half that from supplements. Studies have shown significantly lower serum homocysteine levels in persons taking supplements containing folic acid than in those relying solely on diet (19). A dose as low as 200 mg/day of folic acid is effective in lowering plasma homocysteine concentrations (18). Major food sources of folate are ready-to-eat breakfast cereals, orange juice, leafy green vegetables and fruit.

Vitamin B6

A large proportion of the population, especially the elderly, does not consume adequate amounts of B6 as judged by the RDA standards. Approximately 3 mg of vitamin B6 would be effective in reducing homocysteine levels and subsequently, risk for cardiovascular disease. Both multivitamins and ready-to-eat cereal are sources of crystalline vitamin B6. In a New Mexico Aging Process study, population food sources of vitamin B6 included ready-to-eat cereal 21.3%, total fruit 20.2%, total vegetables 17.7%, leafy vegetables 4.1%, and orange juice (2).
Vitamin B12

Marginal vitamin B12 status can be an important cause of high levels of homocysteine, particularly in the elderly. This condition can often be treated with oral vitamin B12 supplements (20). An additional reason for giving vitamin B12 is that folic acid supplements can mask vitamin B12 deficiencies, which are not uncommon in the elderly and may cause neurologic damage if left untreated as mentioned previously. 200-1000 mg of B12 should be included in supplements that contain 400 mg of folic acid (5).

Conclusion

Elevated homocysteine levels have recently been identified as a modifiable risk factor for cardiovascular disease. While there is a negative correlation between homocysteine levels and amounts of vitamins B12, B6 and folic acid, there is a proven linear relationship between homocysteine levels and coronary artery disease. Such observations suggest that alterations in levels of vitamins may help to reduce the toxic levels of homocysteine, which has adverse affects on vascular endothelium, coagulation, and smooth muscle simulation. Taking B vitamins can lower homocysteine levels. Although lowering the serum concentration of homocysteine has been proven to reduce the risk of adverse cardiovascular events among people with homocystinuria, studies have not yet determined whether lowering mildly elevated blood homocysteine levels reduce the incidence of heart attacks or strokes; most experts believe that scientific studies will soon prove that it does. In the meantime, vitamin supplementation is harmless and inexpensive. It is highly encouraged that all individuals increase their dietary intake of fruits and vegetables to maintain adequate levels of these vitamins that have been proven to lower the levels of this new cardiovascular disease risk factor.

REFERENCES


