Homocysteinemia: New Information about an Old Risk Factor for Vascular Disease
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Abstract
Objective: To determine the importance of homocysteinemia as a risk factor for atherosclerotic vascular disease.

Design: Literature review of published studies homocysteine as risk factor for atherosclerotic vascular disease.

Methods: MEDLINE search from 1969 to 1998 using homocysteine and vascular disease as search terms, from which 13 articles were selected for review.

Results: Homocysteine is a sulfur containing amino acid derivative formed during methionine metabolism. Inherited deficiencies of cystathionine B synthase or MTHF reductase result in markedly elevated plasma homocysteine levels and homocystinuria. Although rare, hereditary homocystinuria results in a variety of life threatening vascular complications occurring at a young age. Lesser degrees of homocysteinemia may result from vitamin B12, folate and pyridoxine deficiencies as well as a recently described mutation of the MTHF reductase gene. Homocysteinemia from these causes has been shown to increase the risk of coronary artery disease, peripheral artery disease, stroke, and venous thrombosis. Postulated mechanisms for this association are discussed.

Conclusion: Homocysteinemia is a risk factor for premature vascular disease. The strength of this association is similar to that due to hyperlipidemia and tobacco use. Although vitamin supplementation with folic acid, B12, and B6 is able to reduce homocysteine levels in many persons, proof of the effectiveness of vitamin treatment in preventing or halting the progression of vascular disease is not yet available.

Homocysteine is a compound formed during the metabolism methionine, an essential amino acid present in dietary protein. In 1969, Kilmer McCully described extensive arterial vascular disease occurring in two children with homocystinuria. He hypothesized that homocysteine or a metabolite of homocysteine caused the arterial damage and suggested that lesser degrees of plasma homocysteine elevation may be a risk factor for arteriosclerosis in otherwise normal individuals. Over the 29 years since McCully's initial report, the role of homocysteine in the development of premature vascular disease has been clarified. Over 75 studies have shown a relationship between total homocysteine levels and coronary artery disease, peripheral artery disease, stroke, and venous thrombosis.

Chemistry
Homocysteine is a sulfur-containing amino acid derivative that is formed during the metabolism of the amino acid, methionine (see figure 1). Once formed, homocysteine can be converted back into methionine or transformed into cysteine, another essential amino acid used for protein synthesis. Conversion of homocysteine to methionine requires the enzyme methionine synthase to catalyze the reaction, a methyl group derived from the metabolism of the folic acid, and vitamin B12 (cobalamin). Conversion of homocysteine to cysteine requires the enzyme cystathionine B synthase and vitamin B6 (pyridoxine). Deficiencies of folic acid, vitamin B12, vitamin B6, or the enzymes cystathionine B synthase or methionine synthase can...
result in elevated plasma levels of homocysteine. Homocysteine exists in various forms in plasma: homocysteine, itself, and various disulfide derivatives of homocysteine. Traditionally, normal total plasma homocysteine levels have been defined to be those in the range from 5 to 15 micromol/liter. However, recent studies indicate that the risk of vascular disease may be increased in the presence of homocysteine concentrations lower than 15 micromol/liter.

Hereditary Homocystinuria
Inherited deficiencies of the enzymes cystathionine B synthase or MTHF reductase result in very high plasma levels of homocysteine. High plasma levels of homocysteine result in the accumulation of homocysteine in tissues and its appearance in the urine (homocystinuria). The most common cause of homocystinuria is cystathionine B synthase deficiency.

Cystathionine B synthase deficiency is inherited as an autosomal recessive disorder. Individuals who have inherited mutations of the gene coding for cystathionine B synthase from both parents (homozygous individuals) have low or undetectable levels of cystathionine B synthase and very high plasma levels of homocysteine (>100 micromol per liter). Homocystinuria due to cystathionine B synthase deficiency is uncommon; the prevalence among newborns is estimated to range from 1/100,000 to 1/400,000. Individuals with homocystinuria due to cystathionine B synthase deficiency have mental retardation, osteoporosis, and dislocated ocular lenses. Life threatening vascular complications occur at a rate of approximately 4% per year. Another autosomal recessive disorder, MTHF reductase deficiency, also causes homocystinuria. MTHF reductase deficiency is rare; only isolated cases have been reported. Individuals with this disorder demonstrate a variety of abnormalities including mental retardation, muscle weakness, psychoses, paraparesis as well as vascular complications.

Homocysteinemia
Homocysteinemia refers to an elevation in plasma homocysteine concentration. Although homocysteinemia can be used to describe any degree of plasma homocysteine elevation, usually the term is used to indicate...
lesser degrees of elevation than that seen in homocystinuria. Although homocystinuria is rare, homocystinemia is fairly common. Recently a specific mutation in the MTHF reductase gene, termed the C677T mutation, has been shown to result in the production of a thermolabile form of MTHF reductase having decreased function, mildly to moderately elevated plasma homocysteine levels (12.3 to 16.3 micromol per liter) and low serum folic acid levels. It has been estimated that 5% of Caucasians may be homozygous for this mutation. The prevalence of the homozygous C677T state may be 12-15% in European, Middle Eastern, and Japanese populations. The frequency of this mutation is increased among persons with premature coronary artery disease and other cardiovascular disorders.\textsuperscript{4,5,6}

Homocystinemia may result from other causes as well. Because the vitamins, B6, B12, and folic acid, are necessary to convert homocysteine into methionine and cysteine, dietary deficiencies of these vitamins can result in homocysteinemia. It has been estimated that up to 40% of the general population does not consume enough folate to maintain homocysteine levels in the normal range. The fact that homocysteine levels increase with age has been attributed to decreased vitamin consumption and impaired vitamin absorption by the elderly. Renal failure, psoriasis, hypothyroidism, and medications that interact with folic acid metabolism (eg phenytoin, methotrexate) or vitamin B6 (theophylline) may all cause homocystinemia. Homocysteine is also seen in association with a variety of malignancies including lymphoblastic lymphoma and breast, ovarian, and pancreatic cancers.

**Homocysteine and vascular damage**

The mechanisms by which homocysteine produces vascular damage are as yet unknown. Evidence seems to indicate that vascular damage results from injury to the vascular endothelium. Endothelial damage may occur as homocysteine is oxidized in the plasma thereby releasing superoxide radicles and hydrogen peroxide which are toxic to endothelial cells. Homocysteine also promotes the formation of blood clots by causing platelet aggregation, increasing the activity of clotting factors V and XI, and inhibiting protein C activation. Homocysteine is also thought to promote the formation of atherosclerotic plaques by reacting with LDL-cholesterol causing these particles to aggregate and to be taken up macrophages and incorporated in foam cells, the precursors of atherosclerotic plaques. Homocysteine has also been shown to inhibit endothelium-dependent arterial dilation and to promote the proliferation of endothelial smooth muscle. All these effects result in an increased risk for the development of coronary artery disease, cerebral vascular disease, peripheral vascular disease, and venous thromboembolic disease.

**Quantifying the risk of vascular disease in homocystinemia**

Recently, the European Concerted Action Project published the results of a retrospective case-controlled study investigating the relationship between plasma homocysteine levels and vascular disease.\textsuperscript{7} Seven hundred fifty patients with vascular disease and 800 control subjects free from known vascular disease were evaluated for the presence of conventional risk factors and plasma homocysteine levels. All were younger than age 60. Males comprised 72.5% of those with vascular disease and 71.3% of controls. There were 383 persons with coronary artery disease, 211 persons with a cerebral vascular disease, and 156 persons with peripheral vascular disease. An elevated total homocysteine level was defined as that in the top quintile of the plasma homocysteine distribution occurring in the control population (>12 micromol/liter). The relative risk of vascular disease was estimated using a conditional regression model. After adjusting for the presence of other risk factors, elevated plasma homocysteine levels was found to be strongly related to the presence of vascular disease (see table 1). The risk of vascular dis-
Relative Risk for the presence of: 

<table>
<thead>
<tr>
<th>All vascular disease</th>
<th>CAD</th>
<th>CVD</th>
<th>PVD</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Concerted Action Project</td>
<td>1.9 (1.4-2.4)</td>
<td>2.0 (1.4-2.8)</td>
<td>1.7 (1.1-2.7)</td>
<td>1.7 (1.0-2.9)</td>
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<tr>
<td>Physicians Health Study</td>
<td>3.4 (1.38.8)</td>
<td></td>
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<tr>
<td>Framingham Study</td>
<td>1.6 (1.1-2.4)</td>
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<tr>
<td>Boushey, et al</td>
<td>1.8 (1.6-2.0)</td>
<td>2.3 (1.8-2.9)</td>
<td>6.8 (2.9-15.8)</td>
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</tr>
<tr>
<td>Leiden Thrombophilia Study</td>
<td>1.9 (1.1-3.3)</td>
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CAD: coronary artery disease; CVD: cerebral vascular disease; PVD: peripheral vascular disease; DVT: deep venous thrombosis. (95\% confidence intervals)

Homocysteinemia was also found to increase the risk of acute myocardial infarction or death due to coronary artery disease in the Physicians’ Health Study, a prospective study of 22,071 US physicians between the ages of 40 and 84. For individuals having total plasma homocysteine levels above the 95th percentile (>15.8 micromol/liter), the relative risk of myocardial infarction was 3.4 after adjusting for the presence of other risk factors including diabetes, angina, body mass index, total cholesterol/HDL ratio, and aspirin use.

A cross-sectional study of 1,041 elderly subjects between the ages of 67 to 96 drawn from the Framingham study who were evaluated for the presence of cerebral vascular disease with carotid doppler ultrasonography demonstrated that the risk of extracranial carotid stenosis was significantly increased when plasma homocysteine concentrations exceeded 11.3 micromol/liter after adjusting for age, sex, and the presence of other risk factors.

Boushey et al performed a meta-analysis of 27 studies that related plasma homocysteine concentrations to the presence of arteriosclerotic vascular disease. They concluded that an elevated fasting plasma homocysteine concentration is associated with a 1.8 fold increased risk of coronary artery disease, a 2.3 fold increased risk of cerebrovascular disease, and a 6.8 fold increased risk of peripheral vascular disease. They also concluded that the risk of cardiovascular disease was increased 1.6 fold for men and 1.8 fold for women for every 5 micromol per liter increase in total plasma homocysteine concentration above 10.

In the Leiden Thrombophilia study, 269 patients having their first episode of deep venous thrombosis were evaluated for inherited and acquired factors predisposing to thrombosis. A plasma homocysteine level above the 90th percentile (>16.6 micromol per liter) was associated with a two fold increase risk of deep venous thrombosis after adjust-
ment for other risk factors such as antithrombin or protein C or S deficiency. A plasma homocysteine level above the 95th percentile (21.1 micromol/liter) was associated with a four-fold increased risk.

Recently, Nygard et al investigated the relationship between mortality and plasma homocysteine concentration among 587 patients with angiographically confirmed coronary artery disease. At four years of follow-up, mortality for patients having total homocysteine levels below 9 micromol/liter was 3.8%; mortality rates were 8.6% for those having total plasma homocysteine levels of 9 to 14.9 micromol/liter and 24.7% for those having total plasma homocysteine levels \( \geq 15 \) micromol/liter. After adjusting for the severity of coronary artery disease, total cholesterol, serum creatinine, left ventricular ejection fraction, age and sex, a total plasma homocysteine concentration between 9 and 14.9 micromol/liter conveyed a relative mortality risk of 1.84 compared to individuals having total plasma homocysteine levels <9 micromol/liter. The relative mortality risk was 2.83 for total plasma homocysteine levels between 15 and 19.9 micromol/liter and 5.52 for levels \( \geq 20 \) micromol/liter.

**Risk Modification**

Numerous studies have shown that total plasma homocysteine concentrations vary inversely with plasma concentrations of folic acid, vitamin B12 and vitamin B6 and that the prevalence of cerebral and cardiovascular disease vary inversely with plasma folic acid concentrations. Of the three vitamins mentioned, folic acid has been found to be the most effective agent in reducing plasma homocysteine levels. These observations have lead to the recommendation that high risk individuals having homocysteine levels above 12 micrograms per liter be evaluated for the presence of B12 deficiency. If B12 deficiency is present, it should be treated. If vitamin B12 levels are normal or if homocysteine levels remain elevated after B12 treatment, folic acid supplementation should be given beginning at a dose of 400 micrograms per day and increasing to 1.2 to 2 mg or even up to 5 mg per day if necessary.

Since plasma homocysteine concentrations have been shown to rise following ingestion of methionine and since vitamin B6 has been shown to reduce this “post-load” increase in homocysteine, vitamin B6 supplementation has also been recommended for persons at high risk for developing vascular disease even if fasting plasma homocysteine concentrations are normal.

Unfortunately no studies are yet available to indicate that these treatments are effective in preventing the development or progression of the homocysteine induced vascular disease.

**Summary**

Severe elevations in plasma homocysteine concentrations such as those seen in hereditary homocystinuria have long been recognized as a cause of premature atherosclerotic vascular disease. In recent years, lesser degrees of homocysteinemia have also been shown to be associated with premature vascular disease. The strength of this association has been shown to be similar to that due to hyperlipidemia and tobacco use. Accordingly, homocysteinemia may be one of the risk factors deserving consideration when assessing the risk of atherosclerotic vascular disease or when underwriting for preferred risk products. Many questions remain, however, including the following:

Does the risk of homocysteinemia differ between persons with established vascular disease and those with no known indication of vascular disease or those having a family history of premature vascular disease?

How effective will lowering plasma homocysteine be in preventing the development of vascular disease in individuals with or without other risk factors?
To what degree does normalization of previously elevated plasma homocysteine levels modify the risk of morbidity and mortality in persons with established atherosclerotic vascular disease?

Hopefully, studies now in progress will soon provide information to answer these and other similar questions.

References