Selections from current literature: homocysteine: a modifiable risk factor for cardiovascular disease

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Cardiovascular diseases are the major causes of mortality in developed nations. Despite significant progress in our understanding of conventional risk factors, such as hypertension, hyperlipidaemia, diabetes, and cigarette smoking, these risk factors do not account for all cases of cardiovascular disease. Family history is a known risk factor, but the reasons for the increased risk are often obscure. Homocysteine, a sulphur-containing amino acid produced by the demethylation of dietary methionine, has recently received considerable attention as another potentially modifiable risk factor for atherosclerotic cardiovascular disease. Several enzyme deficiencies which lead to elevated plasma homocysteine levels may account for some of the genetic predisposition to cardiovascular disease.

Individuals with homocystinuria, a rare autosomal recessive condition most often caused by a deficiency of the enzyme cystathionine β-synthase, develop widespread premature atherosclerosis and thromboembolic venous 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. Since that time, several biological mechanisms for a role of homocysteine in the pathogenesis of atherosclerosis have been elucidated. Homocysteine induces the synthesis of procoagulant factors by vascular endothelium, potentiates the auto-oxidation of low density lipoprotein (LDL) cholesterol, promotes vascular thrombosis by reducing the activation of protein C, causes platelet aggregation, is directly toxic to vascular endothelium, and stimulates the proliferation of smooth muscle cells. Epidemiological studies consistently show that hyperhomocysteinaemia is an independent risk factor for coronary artery, cerebrovascular, and peripheral vascular disease. In 1992, Stamper et al. published the first prospective study showing that high levels of plasma homocysteine are associated with subsequent risk of myocardial infarction (MI) independent of other coronary risk factors. A 1994 Finnish study found no increased risk for atherosclerotic disease associated with serum homocysteine level. The authors, however, believe that the low incidence of hyperhomocysteinaemia in the Finnish population may have accounted for the lack of association.

Within the past 2 years additional studies have been released supporting an aetiologic role for homocysteine in atherosclerotic cardiovascular disease. This selection from the current literature reviews some of the recent literature on homocysteinaemia.


These authors demonstrated in a prospective nested case-control study the risk between homocysteine and coronary heart disease (CHD). They studied over 21 600 subjects drawn from the general population of Tromso, Norway, aged 12–61 years, who were free from MI at the initial survey (1986–1987). At follow up (mean 4 years), CHD had developed in 118 patients and five had died suddenly after the onset of chest pain. For each of the 123 cases, four controls were selected after matching for sex, age, and number of hours since last meal.

The cases had a 1.4 μmol/l higher mean level of serum homocysteine than controls (P = 0.0002). This corresponds to a relative risk of 1.41 (95% CI 1.16–1.71) for each 4 μmol/l increase (about 1 SD) in serum homocysteine. The authors performed a logistic regression analysis to assess the independent predictive value of homocysteine by including conventional cardiac risk factors such as serum total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, cigarette use, history of diabetes and angina pectoris. In this model, the estimated relative risk due to homocysteine decreased to 1.32 (95% CI 1.05–1.65). The authors also found an adjusted RR of 1.42 (95% CI 1.05–1.92) for those younger than 53 and an adjusted RR of 1.66 (95% CI 0.67–4.12) for women.

Comment

These data support the theory that hyperhomocysteinaemia is an independent risk factor for coronary heart disease in the general population. Interestingly,
homocysteine may be more important in early onset CHD and in women. The importance of this study, however, is that the investigators observe a graded association between the risk of MI and increasing homocysteine levels. Thus, even within the normal range, homocysteine levels were consistently higher among cases than controls. This is in contrast to the US Physicians’ Health Study, in which the risk for MI showed no increase until the 95th percentile level for homocysteine was reached. The present study supports the theory that there is no threshold level of homocysteine below which it is not associated with increased risk of MI. Therefore, a significant proportion of the population with ‘normal’ serum homocysteine may be at increased risk of MI.


This 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 also studied nutritional determinants of hyperhomocysteinaemia, including folate, vitamin B12, and pyridoxal-5’-phosphate (the coenzyme form of vitamin B6). Carotid artery stenosis was measured by ultrasonography. This was a cross-sectional study of 418 men and 623 women aged 67–96 years. The subjects were divided into two groups: those with a maximal carotid stenosis of 0–24% and those with a 25–100% carotid artery stenosis.

The odds ratio for stenosis of >24% was 2.0 (95% CI 1.4–2.9) for subjects with the highest quartile of plasma homocysteine concentration (>14.3 μmol/l) compared with those with the lowest quartile concentrations (<9.2 μmol/l) after adjustment for age, sex, plasma high density lipoprotein (HDL) cholesterol, systolic blood pressure, and smoking status (P < 0.001 for trend). In addition, plasma concentrations of folate and pyridoxal-5’-phosphate, and the level of folate intake were inversely associated with carotid artery stenosis after adjustment for age, sex, and other risk factors. The authors conclude that high plasma homocysteine levels and low concentrations of folate and vitamin B6 are associated with an increased risk of extracranial carotid artery stenosis in a population-based cohort of elderly people.

Comment
This cross-sectional study provides convincing evidence of a causative role for homocysteine in the pathogenesis of cerebrovascular disease. It complements the results of Arnesen et al., which implied a positive relationship between homocysteine and coronary heart disease, and gives further credence to the link between homocysteine and atherosclerosis. The authors chose a 25% stenosis as a cutoff because of studies which demonstrate a significantly increased prevalence of both stroke and coronary heart disease among persons with similar degrees of carotid artery stenosis. However, this study did not use a clinical endpoint.

Interestingly, the risk of carotid artery stenosis appeared to be elevated in subjects with homocysteine concentrations between 11.4 and 14.3 μmol/l—levels which have previously been believed to be normal. This is consistent with data from Arnesen et al., in which a graded relation between homocysteine and CAD was demonstrated. The clinical relevance of this result is that people with ‘normal’ homocysteine levels may still benefit from dietary treatments aimed at reducing homocysteine levels.

In addition, the authors indicated that nearly two-thirds of individuals with elevated plasma homocysteine had inadequate concentrations of one or more of the vitamins studied. I agree with the authors’ statement that randomized controlled trials of the effects of homocysteine-lowering vitamin therapy on morbidity and mortality from vascular disease in elderly people with hyperhomocysteinaemia are needed. However, I would suggest that these trials incorporate people of all age groups with hyperhomocysteinaemia. The Food and Drug Administration (FDA) recently mandated that US cereal-grain products be fortified with folic acid at 140 μg/100 g of cereal grain product, in an effort to reduce the incidence of neural tube defects. It will be interesting to observe what effect this mandate has on homocysteine levels and cardiovascular mortality. A recent review article on homocysteine and folic acid intake estimated that nearly 40 000 lives could be saved annually if cereal-grain products were fortified with folic acid at 140 μg/100 g. Tucker et al. estimated a 3% reduction in risk of carotid artery stenosis and a 5% reduction in CAD risk with this level of fortification.


This prospective, population-based study examined the association between serum total homocysteine concentration (tHcy) and stroke. Using a nested case-control study design within the British Regional Heart Study cohort, the investigators follow 5661 men, aged 40–59 years, from entry (1978–1980) to December 1991. The men were randomly selected from 18 general practice populations throughout the UK. More than 99% of study participants were followed for morbidity and mortality to December 1991, with an average length of follow-up of 12.8 years. By December 1991, 141 incident cases of stroke had developed among men with no history of
stroke at screening. Using serum saved from the time of initial entry into the study, the authors measured, tHcy in 107 of the 141 cases and in 118 age- and practice-matched controls. Total serum homocysteine concentrations were significantly higher in cases than controls (13.7 versus 11.9 μmol/l; P = 0.004). The authors also found a graded increase in the relative risk of stroke in the second, third, and fourth quarters of tHcy concentration relative to the first (odds ratios 1.3, 1.9, 2.8; trend P = 0.005). Adjustment for conventional cardiovascular risk factors as well as town, social class, forced expiratory volume, packed cell volume, and serum creatinine did not lessen the association. The authors conclude that tHcy is a strong and independent risk factor for stroke.

Comment
Strokes are one the leading causes of mortality and disability in the Western world. Over the past 20 years, there has been a substantial decline in the incidence of stroke, largely attributable to better diagnosis and treatment of hypertension, a well known risk factor. The evidence presented in this study supports the theory that homocysteine is another risk factor for stroke and may be synergistic with hypertension. Evidence exists that elevated homocysteine levels can be reduced by inexpensive vitamin therapy. Whether this will lead to a reduction in the incidence of cardiovascular disease remains to be seen and randomized control trials are needed.

Importantly, this study has a clinical endpoint, stroke, as opposed to the study reported by Selhub et al., which measured only carotid artery stenosis. Unfortunately, it did not include women, which would have made it even more generalizable.


This article studied the effect of treating mild hyperhomocysteinemia in young (<51 years) patients with peripheral arterial occlusive disease. Forty-eight hyperhomocysteinaemic patients were treated with folic acid (5 mg daily) and pyridoxine (250 mg daily). Endothelial dysfunction was studied in 18 patients who were treated for 1 year. As there is no gold standard for endothelial dysfunction, the investigators measured plasma levels of three endothelium-derived proteins involved in haemostasis: von Willebrand factor (vWF), thrombomodulin (TM) and tissue-type plasminogen activator (tPA). Numerous studies suggest that endothelial damage and preclinical atherosclerosis are associated with increased plasma levels of these proteins. The authors defined hyperhomocysteinaemia as an abnormal homo-
cysteine level following a methionine load. They began by testing 205 consecutive patients (age <51 years) with peripheral arterial occlusive disease and found that 48 of these patients (23%) had hyperhomocysteinaemia.

At baseline, the investigators elevated fasting homocysteine levels were present in 24 of the 48 patients. After 12 weeks of treatment with folic acid and pyridoxine, fasting and post-load homocysteine levels were normal in 98% and 100% of patients, respectively. Also, at baseline, median vWF and TM levels were above normal and both were significantly reduced after 1 year of folic acid/pyridoxine treatment. tPA levels were normal at baseline and did not change.

Patients reported no adverse effects of the folic acid and pyridoxine treatment. No new vascular events occurred during follow-up, either in the 48 patients followed for 6–12 weeks or in the subgroup of 18 patients followed for 1 year.

Comment
Peripheral vascular disease (PVD), while not a leading cause of mortality, is a leading cause of morbidity in developed countries. Furthermore, it is associated with the same conventional risk factors as MI and stroke. Thus, it is noteworthy that 23% of young patients with PVD had hyperhomocysteinaemia. Interestingly, fasting plasma homocysteine levels identified only half of the hyperhomocysteinaemic patients as defined by methionine loading. Should clinicians define hyperhomocysteinaemia by fasting levels or after a methionine load? According to a recent review article, studies using fasting levels have similar results to those using methionine loading to define hyperhomocysteinaemia. Thus, given time and cost considerations, the fasting plasma homocysteine level is probably the most appropriate test to define hyperhomocysteinaemia.

This is one of the first prospective studies that shows significant improvement in both homocysteine levels and endothelial dysfunction in hyperhomocysteinaemic patients treated with vitamin therapy. Unfortunately, as the authors point out, the study was neither randomized nor placebo-controlled. I agree, however, that chance alone is unlikely to account for the dramatic effects on homocysteine metabolism. The true benefit of such vitamin therapy can only be measured by a reduction in the number of clinical events. Are randomized, prospective trials of vitamin therapy versus placebo (with the outcome being reduction of clinical events) needed before widespread treatment of hyperhomocysteinaemia is undertaken?

Family history of early coronary artery disease is regarded as a significant risk factor for cardiovascular disease. Is homocysteine metabolism responsible for some of the genetic susceptibility to atherosclerosis? The investigators measured plasma concentrations of homocysteine, vitamins $B_6$, $B_12$, and folate as well as other coronary risk factors in 120 male and 42 female patients with early familial CAD and in 155 controls (85 men and 70 women) of the same age range. The authors define ‘early CAD’ as an MI, a percutaneous transluminal angioplasty (PCTA), or a coronary artery bypass graft (CABG) before age 55 in men or 65 in women. ‘Familial CAD’ was defined as having had a sibling confirmed as having early CAD by the same criteria. The age range for both cases and controls was 38–68 years.

The authors found, as expected, that conventional cardiac risk factors such as male sex, age, smoking, hypertension, diabetes, cholesterol, and higher body mass index (BMI) were all significantly more common in cases than controls. Plasma homocysteine was also significantly higher in patients with CAD than controls. They noted a progressive increase in risk among both men and women as fasting homocysteine levels rose above 9 $\mu$mol/l. Furthermore, homocysteine levels above 13 $\mu$mol/l were associated with significantly increased risk among all cases. Relative odds for CAD were >8 for both men and women with homocysteine levels of 19 $\mu$mol/l compared with those with homocysteine levels of 9 $\mu$mol/l or less ($P < 0.0001$), after adjustment for other risk factors. The authors also observed that no vitamin concentration approached clinical significance as a risk factor after plasma homocysteine was entered into the model. The strongest correlation between vitamins and homocysteine was with folate. Finally, the investigators found that subjects with early familial CAD and low plasma folate levels had exaggerated elevations in plasma homocysteine, which may suggest a possible genetic sensitivity to the harmful effects of lower folate intake.

**Conclusion**

Cardiovascular diseases are the main cause of mortality in developed countries. Conventional risk factors do not explain all occurrences. The studies reviewed in this article indicate that homocysteine is an independent risk factor for coronary artery, cerebrovascular, and peripheral vascular disease. Vitamin therapy can reduce plasma homocysteine levels; however, further studies are needed to determine whether lowering homocysteine levels will reduce the incidence of cardiovascular diseases. In patients with homocystinuria, lowering the serum homocysteine concentration reduces the risk of adverse cardiovascular events. It makes empirical sense that lowering homocysteine levels will decrease cardiovascular mortality and morbidity, just as treatment of hypertension and hypercholesterolaemia have been shown to be beneficial. With those risk factors, however, pharmacological therapies are both expensive and potentially dangerous. Thus, there is a need to show clear benefit before using such medication. However, with homocysteine, the situation is different because the treatments are inexpensive and relatively innocuous. The potential risk of masking the haematological signs of vitamin $B_6$ deficiency might be reduced by adding vitamin $B_12$ to the folic acid supplements and closer monitoring of these patients.

Plasma homocysteine levels are currently available from many laboratories in the USA. The patient should be fasting (preferably overnight) to ensure optimal results. I have started asking for these measurements for anyone with a personal or family history of early atherosclerotic disease. I believe there is now enough evidence to make the fasting plasma homocysteine level a routine cardiovascular risk factor. A convenient time to order the test is when ordering a cholesterol or lipid panel. If a patient has an elevated fasting plasma homocysteine level, he or she should be treated with folic acid. A safe dose for most patients would be...
400 µg to 1 mg per day. The homocysteine measurement could be repeated at 6-month intervals initially, then every 1–2 years, thereafter. If a patient has a borderline high or high normal result in the setting of other cardiac risk factors (especially family history of early cardiovascular disease), then he or she should probably also be treated with folic acid. The risks are far outweighed by the potential benefits. Unfortunately, without the pharmaceutical push, clinical trials of folic acid therapy for hyperhomocysteinaemia may still be years away. In the face of all the recent evidence, I do not believe we can afford to wait.

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References