Homocysteine: A new coronary heart disease risk factor

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The issue of homocysteine is at present at the center of attention of those interested in preventive cardiology.

What is Homocysteine?

Homocysteine is a sulfur-containing amino acid formed during the processing of methionine. Of no known biological role, it can be re-methylated to methionine or sulfoconjugated with serine to form cysteine in a series of enzymatic reactions. The former steps use vitamin B12 and folic acid while the latter uses vitamin B6 as a co-factor.

Under normal conditions, methionine is derived from food protein. Thus, the higher the meat consumption, the higher the methionine supply. To smoothly run the methionine transformation, the body requires a sufficient supply of the above listed vitamins. If there is a dearth of these vitamins, and if there is a high intake of protein, e.g. excessive meat intake, the intermediary product, homocysteine, starts to accumulate. Accumulation of homocysteine in the blood has a direct toxic effect on the endothelium by impairing EDRF-NO production as well as stimulating smooth cell proliferation. All these effects have a strong atherogenic potential.

Serum homocysteine is measured from a blood sample taken after a twelve hour fast. A normal homocysteine level is between 5 and 15 micromoles per liter (µmol/L). Abnormal levels are classified as moderate (16 to 30 µmol/L), intermediate (31 to 100 µmol/L) and severe (> 100 µmol/L). Severely elevated levels of homocysteine can be caused by either genetic or dietary factors.

History of Homocysteine

In the mid 1960s a Harvard physician, Dr. McCully, treated an eight year old girl with the rare inherited metabolic condition (homocystinuria) that causes homocysteine levels to rise. The autopsy of this patient showed massive generalized atherosclerosis. Dr. McCully speculated the cause of atherosclerosis to be high homocysteine levels and wondered if the same was true for atherosclerosis in adults. Dr. McCully hypothesized that even slightly elevated homocysteine levels could cause atherosclerosis in older individuals, but his hypothesis failed to get acceptance.

Recent studies are now confirming Dr. McCully's work of more than 20 years ago. Mild to moderate elevations (15-30 µmol/L) of plasmatic homocysteinemia have been associated with cardiovascular diseases, including ischemic heart disease, cerebrovascular disorders and ischemic disorders of the lower limbs. The association is stronger between homocysteine and peripheral vascular disease and cerebrovascular disorders, than the association between homocysteine and ischemic heart disease (1). Multiple case-control studies have demonstrated that the homocysteine level is higher among patients with proven ischemic heart disease and premature CAD as compared to a clinically healthy population (1). In the Physicians Health Study (2) a threefold increase risk of MI was observed with plasma homocysteine levels above 15.8 nmol/mL as compared with those having lower plasma levels of this amino acid. A cross sectional analysis done on the Framingham study respondents found that those with homocysteine levels greater than 14.4 nmol/mL had a twofold increase in carotid stenosis. This study was included subjects 65 years of age or older. Similar findings were reported concerning aortoiliac occlusive disease. On the basis of recent retrospective, prospective and epidemiological studies from Europe, the United States and Canada, it is now widely accepted that mild hyperhomocysteinemia is an independent risk factor for cardiovascular disease even after taking
into account the presence of other traditional risk factors. Evidence from these studies has shown the association between homocysteine and cardiovascular disease to be equally valid in both men and women.

Several lines of evidence suggest that homocysteine obviously plays a causal role in atherothrombotic disease. Repeated observations suggest that homocysteine may affect the coagulation system and the resistance of the endothelium to thrombosis (3), and as mentioned above, it may interfere with the vasodilator and anti-coagulation functions of nitric oxide (NO) (4). Several authors emphasize the ability of homocysteine to increase production of intracellular free radicals in endothelial cells. With increased production of free radicals and a decreased ability of endothelial cells to scavenge these radicals, molecules of NO become vulnerable to oxidative stress (5,6).

The role homocysteine plays in atherogenesis is complicated by its binding to plasma protein carriers and the fact that several factors are involved in its metabolism. The majority of homocysteine (up to 80%) is in the bound form (7), and the other 20 % consists of i) free homocysteine, ii) homocystin, reduced form or iii) homocystein-cystein mixed disulfide.

From the population perspective, the mild hyperhomocysteinemia is of greater concern than the more symptomatic homocystinuria because of its increased prevalence and initially asymptomatic clinical course (8). It is estimated that approximately 20% of Canadians may have elevated homocysteine levels. Population-based studies to date have confirmed that nutritional intake and plasma levels of vitamins B12, B6 (and its metabolite pyridoxal 5-phosphate, PLP) and folic acid, are important determinants of plasma levels of homocysteine. Studies involving analysis of family members have also shown that genetic factors are involved in the determination of homocysteine levels (9). The recent characterization of a common mutation at the methylene tetrahydrofolate reductase gene (MTHRF, a key enzyme in the conversion of homocysteine to methionine) shed light on the mechanism of genetic predisposition.

A large, case control, multi-centre European trial, involving men and women younger than 60 years of age, found that the overall risk of coronary and other vascular disease risk was 2.2 times higher in those with plasma total homocysteine levels in the top fifth of the normal range as compared to those in the bottom four-fifths. This risk was independent of other risk factors, but was notably higher in smokers and individuals with high blood pressure (10).

A Norwegian study published in 1997, found that among 587 patients with coronary heart disease, the risk of death after four to five years was proportional to plasma total homocysteine levels. The risk rose from 3.8 percent in those with the lowest levels (below 9 µmol/L) to 24.7% with the highest levels (greater than 15 µmol/L) (11).

There have been several intervention studies illustrating that supplementation with vitamin B6, B12 and folic acid effectively reduce plasma homocysteine levels (12,13), however, the therapeutic influence of this reduction of homocysteine on cardiovascular mortality and morbidity did not yield unequivocal results. The topic is fueled by controversy and there is no definitive evidence one way or the other. A well designed randomized controlled trial to determine whether or not vitamin supplementation effectively decreases cardiovascular disease morbidity and mortality in individuals with elevated homocysteine is urgently needed.

**Conclusion**

To date, a massive database exists which confirms the importance of plasma homocysteine as a powerful predictor of future risk of coronary heart disease and other complications of atherosclerosis. Elevated homocysteine levels can be reduced through adequate intake of folic acid, vitamin B6 and vitamin B12. On the other hand we do not have any evidence from randomized clinical trials that supplementation of these vitamins would reduce the probability of atherosclerotic complications. It is unwise to make therapeutic recommendations based on substitute indicators.
However, avoidance of excessive meat intake and increased consumption of vegetables and fruits is a dietary measure which has many health benefits, including a potential to reduce elevated homocysteine levels.

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- graduated from Charles University in Prague (M.D.) in 1951 and received his Ph.D. (Cardiology and Preventive Medicine) from the Institute for Cardiovascular Research in Prague in 1958;
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References


