Hotline Editorial

Homocysteine — an innocent bystander in vascular disease?

Homocysteine is derived from the metabolism of methionine, an essential amino acid primarily found in dietary animal protein. Homocysteine concentrations are determined by genetic and nutritional factors; mutations in the genes for enzymes involved in homocysteine metabolism, such as the common 5,10-methylenetetrahydrofolate reductase (MTHFR) 677C→T mutation, and deficiencies of vitamins B6, B12, and folic acid, are associated with hyperhomocysteinaemia.[1]

Homocysteine and risk of vascular disease

In 1969, McCully reported that children with the rare metabolic disorder homocystinuria, who have severe hyperhomocysteinaemia, develop widespread, premature atherosclerosis.[2] The relationship between elevated homocysteine and vascular disease in adults has now been evaluated in more than 30 cross-sectional and prospective studies, and approximately 10,000 subjects.[3,4] The results have been remarkably consistent, with few exceptions. Elevated plasma homocysteine is an independent risk factor for peripheral vascular, cerebrovascular, and coronary heart disease, and in prospective studies, homocysteine concentrations of 9, 15 and 20 μmol l−1, predict total mortality ratios of 1.9, 2.8, and 4.5, respectively.[5] Homocysteine concentrations exceeding the upper limit of normal (15 μmol l−1) are common, and are found in almost 30% of patients with vascular disease. In North American and European populations, it is estimated that elevated homocysteine may contribute to 10% of population coronary heart disease risk[3].

Differences in homocysteine between populations

The observations that homocysteine concentrations vary from 7 to 11 μmol l−1 between European countries,[6] and are closely related to national age-standardized cardiovascular disease mortality rates, suggest that homocysteine is an important factor underlying the variation in cardiovascular disease between these populations. Few studies have been undertaken in non-white subjects. Recent data show that plasma homocysteine concentrations are higher in Indian Asians, and contribute to their increased coronary heart disease mortality rates, compared to European whites[7]. Amongst Indian Asians, elevated homocysteine is accounted for by reduced levels of vitamins B12 and folate, suggesting that nutritional factors underlie their raised homocysteine concentrations. Unlike Europeans, the common MTHFR 677T mutation does not influence homocysteine levels in Asians, despite their lower folate concentrations[8]. In fact, the frequency of homozygosity for MTHFR 677T amongst Indian Asians is less than one-third that in European whites, excluding a role for this mutation underlying increased coronary heart disease risk in Indian Asians.

Homocysteine and vascular endothelial function

A crucial question is whether homocysteine has a causal role in the development of atherosclerosis, or is simply a marker for increased vascular risk.[9] Evidence to support a direct role for homocysteine in the pathogenesis of vascular disease has emerged from studies demonstrating that there is a dynamic and inverse relationship between plasma homocysteine and vascular endothelial function. An acute elevation in homocysteine is associated with rapid onset vascular endothelial dysfunction, an early manifestation of atherosclerosis.[10–14] These observations are consistent with in vitro reports of a dose- and time-dependent effect of homocysteine on endothelial cellular function,[15,16] and may help to explain the incremental risk of vascular events with increasing homocysteine concentrations.[5,8] Rapid onset endothelial dysfunction can also be demonstrated following physiological increments in plasma homocysteine induced by low-dose oral methionine, or dietary animal protein.[12] These findings suggest
that even diet related increments in plasma homocysteine may contribute to the development and progression of atherosclerosis.

The mechanisms linking homocysteine to endothelial dysfunction are not clear. There is growing evidence that homocysteine exerts its effects by promoting oxidative damage in endothelial cells, with the generation of superoxide anion radicals (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$). Generation of free-radical superoxide anions may promote oxidation of low-density-lipoprotein (LDL), and deactivation of nitric oxide. Deactivation of nitric oxide, the major endothelium derived vasodilator, may lead to vaso-constriction, platelet aggregation, and monocyte adhesion, all of which promote atherosclerosis. In vivo studies have confirmed the presence of oxidan stress during hyperhomocysteaemia, through measurement of lipid peroxides, and by reversal of homocysteine-induced endothelial dysfunction using the antioxidant vitamin C.

**Effects of homocysteine lowering**

Plasma homocysteine concentrations can be reduced by 25–30% through oral supplementation with B vitamins (folate, B$_12$ and B$_6$). Recent studies have examined the effects of homocysteine lowering, through B vitamin supplementation, on surrogate markers of atherosclerosis. In healthy volunteers, and in patients with coronary heart disease, B vitamin supplementation is associated with an improvement in endothelium dependent dilatation, and in serum markers of endothelial injury. Amongst healthy siblings of patients with premature atherosclerosis, homocysteine-lowering reduces the occurrence of abnormal exercise tests, consistent with a decreased risk of future atherosclerotic coronary events. Vitamin treatment had no effect on ankle–brachial pressure index, or on carotid and peripheral arterial outcome variables, although these tests may not be sufficiently sensitive to detect modest changes in subclinical atherosclerosis. More conclusive evidence to support a causal role for homocysteine in vascular disease may emerge from the results of the large scale randomized, placebo-controlled intervention trials investigating whether homocysteine lowering will reduce cardiovascular events in patients with coronary heart disease. These studies are expected to report within the next 5 years.

**Conclusions**

Epidemiological studies provide convincing and consistent evidence that elevated homocysteine is a risk factor for vascular disease, including coronary heart disease, in adults. Physiological studies show that elevated homocysteine induces vascular endothelial dysfunction, lending support to the hypothesis that the relationship between homocysteine and vascular disease is causal. However at present, there are no data to show that lowering homocysteine will reduce major cardiovascular end-points. The results of large-scale intervention studies with hard end-points are keenly awaited.

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**References**


