Genes, greens, and homocysteine

Over the past 20 years evidence has emerged from many scientific disciplines to support the hypothesis that a raised serum concentration of the amino acid homocysteine is a risk factor for atherosclerotic vascular disease. Studies of such novel risk factors are important given that the classic risk factors fail to account for all of the existing prevalence of vascular disease. Novel factors may also provide insights into the aetiology of vascular disease. We review the current status of homocysteine as a risk factor for cardiovascular disease.

Homocysteine metabolism: genetics and environment
Homocysteine is a sulphur amino acid derived from methionine, an essential amino acid found in abundance in a typical western diet. Serum homocysteine exists as the pure disulphide, homocystine (homocysteine-homocystine), or as the mixed disulphide, homocystine-cysteine. Each of these species is 70% protein-bound while 30% is in the free form. In this article, the abbreviation Hcy is used to refer to all such species collectively and the total Hcy (tHcy) refers to combined free and protein-bound forms. The accompanying figure shows the methionine metabolic pathway. Cystathionine synthase (CS), methylene tetrahydrofolate reductase (MTHFR), and methionine synthase regulate two key stages in this pathway, namely demethylation (or transsulphuration) and re-methylation by which Hcy is "recycled" to methionine. Vitamins B12 and B6 are essential cofactors and folic acid is an essential co-substrate for these processes. A less important pathway uses betaine as a cofactor for the enzyme betaine homocysteine methyltransferase. Deficiencies of these nutrients or genetically determined enzymatic defects lead to disturbed Hcy metabolism. A methionine "load" can be given to identify subjects with defective transsulphuration in a manner analogous to that of a glucose tolerance test, and fasting or basal tHcy can be measured to assess the activity of the re-methylation pathway. The classic but rare homozygous defects of CS, MTHFR, and cobalamin result in homocystinuria but the frequency of defective alleles is insufficient to explain the prevalence of raised plasma Hcy in those with vascular disease. Though a defective (thermolabile) variant of MTHFR has a much higher reported frequency (17%) among patients with coronary artery disease, the relevance of such functionally defective alleles to coronary risk in healthy unselected populations remains uncertain. Subclinical deficiencies of nutrients that modulate Hcy metabolism, already known to be causally related to raised plasma Hcy concentrations, may be of greater importance in those with functional enzymatic defects. Plasma concentrations of homocysteine were high in 12–14% of families with siblings affected by early coronary heart disease. Whether or not this represents a shared environmental-nutritional deficiency rather than a purely genetic defect remains unclear. Drawing an analogy with serum cholesterol may be useful given that it too is determined by both genetic and nutritional influences.

Homocysteine and coronary risk
Subjects with untreated homocystinuria are at greatly increased risk of atherothrombotic events. The observation by McCully of accelerated atherosclerosis in two cases of homocystinuria known to have different enzyme defects but who in common had greatly raised plasma Hcy concentrations, focused attention on whether more moderately raised plasma Hcy is a risk factor for vascular disease in those lacking well defined genetic defects.

MECHANISMS OF VASCULAR DAMAGE
Numerous mechanisms by which Hcy may act to promote atherothrombosis have been proposed. These include altered platelet function, endothelial cell damage, a reduction in the protective effect of endothelial derived...
relaxing factor, and enhancement of the binding of lipoprotein (a) to fibrin. Many of these experiments were carried out in vitro using endothelial cell cultures in the presence of unphysiological concentrations of Hcy but the data support the biological plausibility of Hcy being an agent that can damage endothelial cells and promote atherosclerosis.

EPIDEMIOLOGICAL STUDIES

Epidemiological data supporting Hcy as a risk factor for coronary heart disease were reviewed by Ueland et al. and, more recently, in a meta-analysis. Consistently, in studies of patients with coronary heart disease, plasma Hcy concentrations were significantly higher in cases than controls. Adjustment for the presence of other cardiovascular risk factors supports the independence of Hcy as a risk factor for cardiovascular disease. In a single large multicentre case-control study, raised fasting and post-load plasma Hcy concentrations matched in strength conventional cardiovascular risk factors such as raised serum cholesterol. Analysis of the nutrient status of subjects assessed by vitamin intake or by plasma nutrient concentration supports the biological plausibility of Hcy as a risk factor with an inverse relation between plasma Hcy concentration and nutrient level. Pachpanun and colleagues suggested that the inverse relation between plasma Hcy and serum folate concentration accounts for the homocysteine-associated risk of coronary heart disease.

Perhaps the strongest evidence is that from prospective studies, which are not susceptible to the same inherent biases as case-control studies. Most prospective studies support the strength and independence of homocysteine as a risk factor and point to a likely dose-response relation across the plasma homocysteine distribution or at least to a threshold phenomenon in the upper half of the distribution. The Physicians' Health Study showed a relative risk of subsequent myocardial infarction of 3.4 (95% CI: 1.3 to 8.8) for the top 5th percentile of the plasma Hcy distribution compared with the bottom 90th percentile after adjustment for other risk factors. Although open to interpretation, the data are consistent with a gradient in risk with increasing plasma Hcy concentration. Stronger evidence for a dose-response effect in an unselected population has come from the Tromsø study. Epidemiological data may also point to mechanisms of action of Hcy. In the Physicians' Health Study of subjects with angina, a weakly positive relation between plasma Hcy and risk of angina was found with an adjusted odds ratio of 1.6 (95% CI 0.7 to 3.5) for subjects in the upper one fifth compared with the bottom fifth of plasma Hcy. Hcy may therefore act primarily to promote thrombosis and myocardial infarction rather than atherosclerosis and angina.

THERAPEUTIC IMPLICATIONS

Treatment of classic homocystinuria involves administration of betaine and of vitamins B6 and B12 or folic acid and a diet low in methionine. Raised plasma Hcy concentrations in subjects with coronary heart disease who do not have homocystinuria may also be treated successfully with folic acid, vitamin B12, or vitamin B6. Of the available treatments, folic acid in doses as low as 1mg seems to be the most effective in terms of Hcy-lowering. However, the benefit of any such treatment in reducing morbidity and mortality endpoints is currently unknown and randomised controlled trials are required.

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