

Editorial

Homocysteine: a novel risk factor for coronary heart disease in UK Indian Asians

The population of the UK includes approximately 1.6 million people of Indian Asian descent, most of whom are first or second generation migrants. In UK Indian Asians, mortality from coronary heart disease (CHD) is 40% higher,¹ and admission rates with myocardial infarction are twofold higher,² compared to the European white population. The increase in CHD risk is most striking in young men, among whom CHD mortality rates are twice those in Europeans.¹

The mechanisms underlying increased CHD mortality in UK Indian Asians are not well understood. Population studies show that levels of cigarette smoking, blood pressure, and cholesterol are not consistently raised in Indian Asians, compared to Europeans,³⁻⁴ indicating that these conventional risk factors do not account for the excess CHD mortality in Indian Asians.³ In contrast, diabetes and insulin resistance are more prevalent in Indian Asians than European whites,³⁻⁵ although their precise contribution to increased CHD risk in Asians remains to be determined.

Raised plasma homocysteine: an emerging risk factor for vascular disease

Homocysteine is a sulfur containing amino acid, derived from the metabolism of dietary methionine (fig 1).⁶ 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

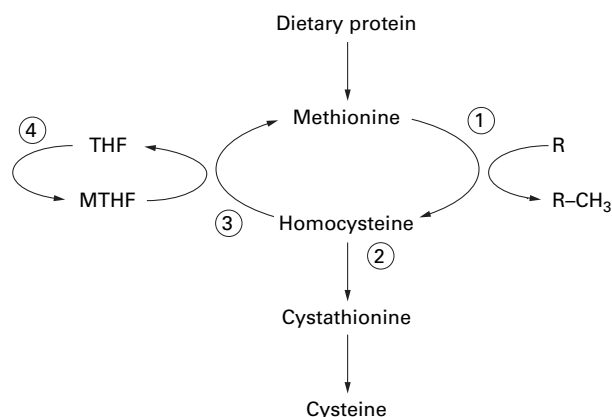


Figure 1 Outline of metabolic pathway for homocysteine.

(1) Transmethylation. Conversion of methionine to homocysteine, thereby transferring methyl group to other species (R). (2) Transsulfuration. Irreversible conversion of homocysteine to cysteine: via rate limiting enzyme cystathionine- β -synthase, with vitamin B₆ as essential co-factor. (3) Remethylation. Regeneration of methionine from homocysteine: catabolised by methionine synthase, with 5,10-methylene-tetrahydrofolate (MTHF, a form of folic acid) and vitamin B₁₂ as essential co-factors. (4) Regeneration of MTHF from tetrahydrofolate (THF), catabolised by enzyme 5,10-methylene-tetrahydrofolate reductase (MTHFR).

(MTHFR) 677C→T mutation, and deficiencies of vitamins B₆, B₁₂, and folic acid (essential co-factors for homocysteine metabolism) are associated with raised homocysteine concentrations.

Children with the rare metabolic disorder homocystinuria, who have severe hyperhomocysteinaemia, develop widespread, premature atherosclerosis.⁷ This observation led to the hypothesis that homocysteine might contribute to the development of atherosclerosis in adults. This possibility has now been evaluated in more than 30 studies, involving over 10 000 subjects.⁸⁻⁹ The results have been remarkably consistent, with few exceptions. Raised 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 $\mu\text{mol/l}$ predict total mortality ratios of 1.9, 2.8, and 4.5, respectively.¹⁰ Homocysteine concentrations exceeding the upper limit of normal (15 $\mu\text{mol/l}$) are common, and are found in almost 30% of patients with vascular disease. In North American and European populations, it is estimated that raised homocysteine may contribute to 10% of population CHD risk.⁸

Homocysteine concentrations in Indian Asians

Recent studies show that plasma homocysteine concentrations are higher in UK Indian Asians than European whites,¹¹⁻¹³ and also confirm that homocysteine is a risk factor for CHD in this racial group.¹¹ Based upon these findings, it is estimated that elevated homocysteine may contribute to twice as many CHD deaths in UK Asians compared to Europeans.¹¹ Among UK Indian Asians, raised homocysteine is accounted for by reduced concentrations of vitamins B₁₂ and folate, compared to Europeans,¹¹ and not by differences in renal function,¹⁴ suggesting that nutritional factors may underlie raised plasma homocysteine concentrations in Asians. Reduced intake of vitamin B₁₂ has been reported in Indian Asians, and prolonged cooking of vegetables, which is common practice in many Indian Asian households, may destroy up to 90% of folate content.¹⁵⁻¹⁷ These observations imply that the increased CHD risk in this racial group may be reduced by dietary supplementation with B vitamins. In contrast, unlike Europeans, the common MTHFR 677T mutation does not influence homocysteine concentrations in Asians, despite their lower folate concentrations.¹⁸ In fact, the frequency of homozygosity for MTHFR 677T among UK Indian Asians is less than one third that in European whites.¹⁸ These findings exclude a role for this mutation underlying increased CHD risk in UK Indian Asians, although do not discount the possibility that novel genetic defects, other than the MTHFR C677T mutation, influence homocysteine metabolism in this racial group.

Homocysteine: marker or causal agent in vascular disease?

It remains unknown whether homocysteine has a causal role in the development of atherosclerosis, or is simply a marker for increased vascular risk.⁶⁻¹⁹ Evidence to support the former has emerged from studies showing a dynamic and inverse relation between plasma homocysteine and vascular endothelial function. An acute increase in homocysteine is associated with rapid onset vascular endothelial dysfunction—an early manifestation of atherosclerosis—and this effect may be mediated by an increase in oxidation stress.²⁰⁻²² Rapid onset endothelial dysfunction can also be demonstrated following physiological increments in plasma homocysteine induced by low dose oral methionine, or dietary animal protein.²³ These findings are consistent with *in vitro* reports of a dose and time dependent effect of homocysteine on endothelial cellular function,²⁴⁻²⁶ and suggest that even diet related increments in plasma homocysteine may contribute to the development and progression of atherosclerosis.

Additional evidence to support a causal role for homocysteine in vascular disease comes from studies investigating the effects of homocysteine lowering through B vitamin supplementation. In healthy volunteers, and in patients with CHD, B vitamin supplementation is associated with an improvement in endothelium dependent dilatation, and in serum markers of endothelial injury.²⁷⁻³⁰ Furthermore, among 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.³¹ More conclusive evidence may emerge from the results of the large scale randomised, placebo controlled, intervention trials currently in progress, investigating whether homocysteine lowering will reduce cardiovascular events in patients with CHD. These studies are expected to report within the next five years.³²

Conclusions

CHD mortality is higher in UK Indian Asians than European whites, and is not accounted for by conventional coronary risk factors. Recent studies show that homocysteine concentrations are higher in Indian Asians than European whites,¹¹⁻¹² and suggest that homocysteine may contribute to their increased CHD mortality.¹¹ These observations imply that the increased CHD risk in this racial group may be reduced by dietary supplementation with B vitamins. 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 awaited with interest.

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