Editorial

Homocysteine: the new player in the field of coronary risk

The recently published trials of lipid lowering[1 2] showing a significant reduction in acute events and mortality have emphasised the causal role of high plasma low density lipoproteins (LDL) in coronary atherosclerosis. Health policy on screening blood cholesterol has changed as a result. In contrast, though epidemiological studies over the past 20 years have shown that high fibrinogen concentrations are also an independent risk factor,[3 4] and indeed are a stronger predictor than plasma LDL, there has been little interest in either measuring or reducing plasma fibrinogen. This is because there is no consensus on how to measure plasma fibrinogen, no established normal ranges, and no interventional studies to show benefit from lowering fibrinogen. Drugs that specifically lower fibrinogen are not available: ticlopidine and fibrates do lower fibrinogen concentrations but have additional effects.

Homocysteine has emerged as another risk factor for the development of ischaemic heart disease.[5] It will be some time before its status is established and decisions on whether therapeutic attempts should be made to lower blood concentrations. Homocysteine, like fibrinogen, may become ignored in the management of individual patients.

There are two metabolic steps in homocysteine degradation on which plasma concentrations depend. These involve transsulphuration and re-methylation by the enzymes cystathionine-β-synthase and methylene tetrahydrofolate reductase. Folic acid, vitamin B6, and B12 act as cofactors for these enzymes. Genetic abnormalities in these pathways can cause raised plasma homocysteine concentrations to which deficiencies of folic acid and vitamins B6/B12 also contribute. High homocysteine concentrations may fall after vitamin supplementation of the diet.[5 6] A study in this issue (page 117) reports that Chinese patients with high plasma homocysteine concentrations had normal folate concentrations, suggesting that in this population genetic factors predominate.[7] None the less, it would be interesting to study the effect of administering folate to these patients.

One cause of hyperhomocysteinaemia involves a defect of cystathionine-β-synthase. One in 70 of the general population are heterozygous for this defect. Some heterozygous carriers have normal or even subnormal plasma concentrations but they can be identified by a methionine load test or by measuring the activity of the enzyme in fibroblasts cultured from the skin. All the methods of identifying heterozygous gene carriers are, however, relatively insensitive and expensive. Even allowing for this insensitivity, abnormalities of the cystathionine-β-synthase gene do not explain the prevalence of hyperhomocysteinaemia in subjects with proven coronary disease. The gene for a thermolabile form of the methylene tetrahydrofolate reductase enzyme has recently been identified and may prove to be responsible for high blood concentrations of homocysteine in many subjects.[8]

Currently hyperhomocysteinaemia caused by genetic defects is diagnosed by the simple measurement of blood concentrations. Seventy to eighty percent of plasma homocysteine is bound to protein: the remainder is free as a disulphide. This ratio can change after storage of the plasma sample but there are reliable methods to measure total plasma homocysteine. There is no generally accepted normal range of blood concentrations, however. In the Framingham Heart Study 14 μmol/l corresponded to the 90th percentile for subjects with normal folate and B6/12 concentrations. The same study showed that the increased level of risk for vascular disease started at a concentration of 11·4 μmol/l.[9] In the United States Physicians' Health Study 95% of healthy controls had concentrations below 15·8 μmol/l.[10] Other studies suggest that 15 μmol/l or 15·7 μmol/l define the "normal" plus 2SD populations.[11 12] Gender makes considerable differences to the concentration of homocysteine that can be regarded as normal. In our study[10] of 463 individuals the normal range in men was 13·5 (0·4) μmol/l and in women it was 11·3 (0·3) μmol/l ($P < 0·0001$).

Many studies have not taken this gender difference into account. It has become clear that many non-genetic influences such as smoking, physical activity, blood pressure, and even cholesterol impinge on homocysteine concentrations in the plasma.[11] At present the status of plasma homocysteine as a risk factor resembles that of fibrinogen rather than LDL plasma.

Magnitude of risk associated with hyperhomocysteinaemia

The small number of prospective studies that measured plasma homocysteine concentrations before ischaemic heart disease appeared are the best evidence for regarding a raised homocysteine concentration as a risk factor.[10 13 14] Only one study did not identify homocysteine as an independent predictor of myocardial infarction and stroke.[15] Homocysteine concentrations appear to be independent of geographic, dietary, and racial influences.[7] Patients with coronary heart disease in France have concentrations of homocysteine that are raised to a similar extent as those in other European countries.[13] A low frequency of genetic defects in homocysteine metabolism does not explain the paradox of a low incidence of ischaemic heart disease in France compared with the United Kingdom. Other explanations such as an increased consumption of red wine and olive oil are more plausible.[16 17]

How to treat hyperhomocysteinaemia

Currently measurement of plasma homocysteine is indicated only when ischaemic heart disease has developed in the absence of other risk factors such as a high plasma LDL. The challenge is what to do when concentrations are high. Folic acid and vitamins may lower plasma homocysteine but they are not recognised treatments and will not be paid for by, for example, the French Social Security system. It is thought that up to 17% of coronary disease subjects may have hyperhomocysteinaemia caused by

genetic defects in one of the enzymes responsible for its metabolism. There is a temptation to give folate and vitamins because side effects are unlikely. There are, however, no data on how long treatment would have to continue or whether the risk would be reduced. One potential risk of giving folic acid indiscriminately is that it will mask the haematological manifestations of B12 deficiency. For this reason cobalamin would have to be added to folic acid and vitamins B6 and B12. Before embarking on such polypharmacy, we need trials to establish a reduction in risk. These trials would have to be funded by health authorities and national scientific bodies because it is unlikely that the pharmaceutical industry will do so.

G MONTALESCOT

Cardiology Department,
Hôpital Pitié-Salpetrièré,
Paris,
France

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