Homocysteine and cardiovascular disease: time to routinely screen and treat?

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Abstract

Modest elevations in plasma homocysteine from either genetic or acquired causes appear to relate to cardiovascular disease on the basis of strong epidemiological evidence. We know that homocysteine can be lowered with varying doses of folic acid, with or without vitamins B_6 and B_{12}, although we do not yet know the potential cardiovascular benefit of vitamin supplementation in these subjects. Several multicentre interventional trials are underway to address this question and, until these are complete, we recommend a healthy diet high in folate replete foodstuffs. We also recommend oral folic acid supplements in some subjects with cardiovascular disease and high homocysteine, mindful that definitive evidence of benefit is lacking.

Key words: homocysteine, cardiovascular disease prevention, vitamins.

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Introduction

Total plasma homocysteine is a derivative of dietary methionine, an essential amino acid found in a wide variety of foodstuffs. Modest elevations in plasma homocysteine, between 12 and 20 µmol/L – either from genetic or acquired causes such as vitamin deficiency – are common and may affect between 10–20% of Caucasians with a slightly higher prevalence in some ethnic subgroups, i.e. West Indians. Higher elevations, of the order of > 100 µmol/L, are considerably rarer and are due to homozygous genetic mutations (see figure 1). Hyperhomocysteinaemia strongly but, as yet, incompletely fulfils the epidemiological criteria necessary to be considered a risk factor for cardiovascular disease. Whether to screen for and treat the relatively common phenomenon of modestly raised homocysteine in both primary and secondary prevention settings remains the subject of considerable debate and a strong consensus has not been reached.

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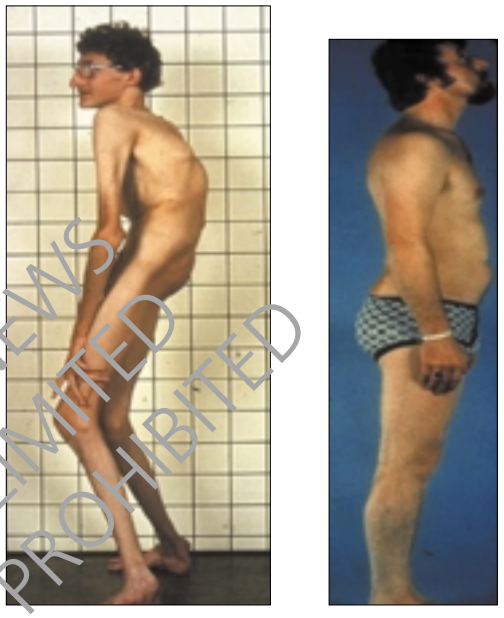
Figure 1. Subject with congenital homocysteinuria (left) – one of 50 patients with classical homocysteinuria due to Cystathionine Beta Synthase deficiency – compared with normal subject



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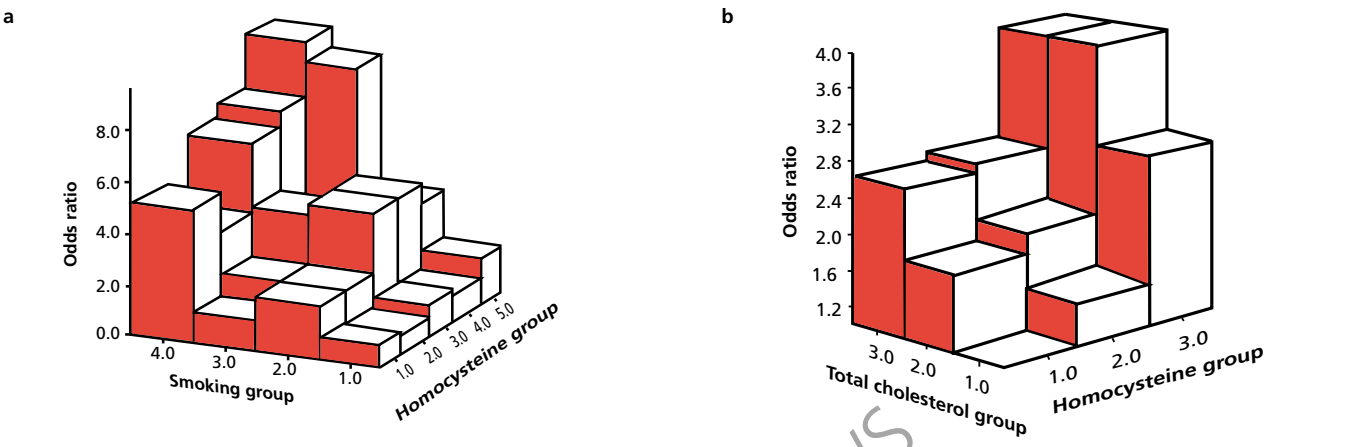
Relationship between homocysteine and cardiovascular disease

A strong graded relationship exists between homocysteine and coronary, cerebrovascular and peripheral vascular disease.[1-4] The relationship has been demonstrated both retrospectively and prospectively and is weaker in prospective than case-control studies. A meta-analysis of 4,000 cases by Danesh and Lewington in 1998 estimated an odds ratio of 1.9 per 5 µmol increase in plasma homocysteine for case-control studies with volunteer controls, an odds ratio of 1.6 for case-control studies with population-based controls, and an odds ratio of 1.3 for prospective studies.[5] Our own European Concerted Action Project case-control study of 750 cases of vascular disease and 800 controls has demonstrated an odds ratio of 2.1 for men and 2.2 for women and has noted significant interactions between

Figure 2. Relationship between **a**) homocysteine and smoking and **b**) homocysteine and total cholesterol in The European Concerted Action Project on Homocysteine



homocysteine and conventional risk factors.[6] For example, figure 2a shows that current heavy smokers with a homocysteine level greater than 12.5 µmol/L have a 13 times greater risk of vascular disease than never smokers with normal homocysteine levels.[7] Significant interactions are also seen between homocysteine, hypertension and hyperlipidaemia (figure 2b).

The temporal nature of the relationship between homocysteine and disease is evident from subjects with congenital homocysteinuria resulting from an inherited deficiency of cystathionine β synthase. This is one of several enzyme defects leading to severe hyperhomocysteinaemia in childhood – vascular events in early adulthood are almost inevitable in the absence of homocysteine-lowering treatment in these subjects.

Several biologically plausible mechanisms exist whereby homocysteine may initiate or promote atherosclerotic damage at the level of the endothelium. The most likely pathways are the ability of homocysteine to oxidise low density lipoprotein cholesterol particles[8] and to inhibit the enzyme DDAH which breaks down asymmetric dimethylarginine (ADMA), a potent endogenous inhibitor of endothelial nitric oxide synthase.[9] There is also evidence of effects on endothelial cell function, smooth muscle proliferation, collagen accumulation within the vessel wall and an effect on platelet aggregation, all of which are key steps in the pathogenesis of the atheromatous plaque.[10]

Evidence for causative role

We know that we can lower total plasma homocysteine levels using folic acid supplements with or without varying doses of cobalamin and vitamin B_6. The Homocysteine Lowering Trialists Collaboration in 1998 showed that 0.5 mg to 5 mg of folic acid will lower homocysteine levels by 25%, adding 0.5 mg of vitamin B_{12} will reduce homocysteine by a further 7%, while adding B_6 produced no further reduction. What is not known, however, is whether lowering homocysteine will lead to a reduced rate of progression or onset of cardiovascular disease? Without fulfilling this final criterion of causality we cannot say with any great degree of certainty that raised homocysteine causes vascular disease, and to do so would seem imprudent.

To attempt to answer this, several multicentre interventional trials are underway which are outlined in the next article by Dr Jennifer Bexley (see table 1, page 120). Combined, more than 40,000 subjects are enrolled in randomised trials supplementing folic acid at doses up to 5 mg with and without varying doses of vitamins B_6 and B_{12}. Studies are encompassing both primary and secondary prevention of cardiovascular disease. We are two to three years away from any published findings and recommendations must be issued and interpreted with caution until then.

On the assumption that lowering plasma homocysteine with folate will reduce the progression of atherosclerosis, it is estimated that increasing dietary folic acid via fruit and vegetables alone would be sufficient to greatly improve cardiovascular morbidity and mortality. It has been estimated that a 40% increase in dietary folic acid via fruit and vegetables would reduce total cardiovascular deaths by 2%, while adding folic acid supplements would reduce deaths by 4%. In public health terms, food fortification with folic acid would probably yield the greatest benefit, particularly when we consider the evidence that folic acid supplementation also reduces the risk of neural tube defects. Based on these estimates, folic acid supplementation has become mandatory in some countries, notably the USA, but not the European Union including the UK, where a more conservative approach has been taken to date.

Screening

Until we know more from current interventional trials, the question of whether to routinely screen for and treat modest hyperhomocysteinaemia remains problematic. Given the likelihood of homocysteine having a significant causative role in atherosclerotic cardiovascular disease, it would seem prudent to recommend a healthy diet high in fruit and vegetables for

Key messages

- Hyperhomocysteinaemia appears to relate causally to cardiovascular disease
- Hyperhomocysteinaemia can be reversed by supplementation with vitamins B_6, B_{12} and folic acid
- There is no definite evidence that homocysteine lowering improves cardiovascular outcomes although interventional trials are underway
- High folate fruit and vegetables are recommended in subjects at high cardiovascular risk with elevated homocysteine. As yet there is insufficient evidence to recommend folic acid supplementation in these subjects

anyone with risk factors for cardiovascular disease. Screening tests for total plasma homocysteine have become widely available and relatively inexpensive, costing approximately the same as a full lipoprotein profile assay when a critical turnover number is reached. We do not recommend, as some centres do, measuring homocysteine only in those whose cardiovascular disease cannot be explained by conventional risk factors since there is considerable evidence that the effect of homocysteine is as strong in those with established risk factors as it is in those without, given its interaction with these factors. We would therefore recommend screening subjects with cardiovascular disease, mindful that the arguments in favour of causality are persuasive but not yet conclusive, and recommend oral folic acid supplements of at least 500 µg once-daily in those patients with raised plasma homocysteine > 12.5 µmol/L.

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