Homocysteine – is it the end of the line?

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For nearly 40 years it has been suggested that high levels of homocysteine are associated with an increased risk of cardiovascular disease and that lowering these levels might be beneficial. On the basis of recently-published evidence, however, it appears that this hypothesis no longer holds and it is, perhaps, now time to move on in the search for non-conventional cardiovascular risk factors and other markers of disease risk.

Epidemiologically, causation must follow a strict set of criteria, the most important of which is probably that reducing or removing the potential risk factor will prospectively reduce the incidence of new disease. Cholesterol fulfils this criterion brilliantly and there is little doubt now that high levels of cholesterol result in a higher incidence of coronary heart disease. Similarly, there is strong and consistent epidemiological evidence that homocysteine is related to cardiovascular disease. The Homocysteine Studies Collaboration Meta-analysis[1] showed the relative risk of ischaemic heart disease was 0.89 for a 3 µmol/L reduction in homocysteine level (95% confidence interval [CI] 0.83–0.96), and the relative risk of stroke for the same reduction in homocysteine was 0.81 (95% CI 0.69–0.95). However, unlike lowering cholesterol with statins, for example, there is now growing evidence that lowering homocysteine with varying combinations of vitamins B6 and B12 and folic acid is not associated with a significant reduction in cardiovascular risk. It seems that homocysteine is falling at the final hurdle and that the whole hypothesis is in doubt.

Until recently, there have been prospective data on using vitamins to lower homocysteine only on soft surrogate end points, such as carotid intimal: medial thickness. These data have been conflicting. Over the last five years, large multicentre prospective trials giving various doses of folic acid, vitamin B12 and vitamin B6 to subjects with mildly elevated homocysteine levels have been initiated on several continents. These appear to provide consistent but negative results.

Homocysteine studies

The Vitamin Intervention for Stroke Prevention[2] trial shows that in 3,680 patients with stroke, two years of treatment with vitamins lowers homocysteine levels significantly but does not reduce the rate of future vascular events. The Norwegian Vitamin[3] trial shows that in 3,749 survivors of acute myocardial infarction who were treated with combinations of folic acid, vitamin B12 and vitamin B6, there was no significant effect of vitamins on the risk of the composite primary end point of recurrent myocardial infarction, stroke or sudden death from coronary heart disease.

Finally, the Heart Outcomes Prevention-2[4] trial treated 5,522 patients with vascular disease or diabetes with a combination of folic acid, vitamin B12 and vitamin B6 or placebo for five years. There was a significant reduction in total plasma homocysteine but no significant reduction in the composite end point of myocardial infarction, stroke or death from cardiovascular disease. There was a marginally significant reduction in stroke among the patients receiving vitamins compared to those receiving placebo in the trial but the real significance of this is unclear. These data appear to provide strong, consistent evidence that there is no clinical benefit to lowering plasma homocysteine with vitamins, particularly vitamin B12 and folic acid.

What is the link?

What is considerably less clear is the exact nature of the apparently consistent association between homocysteine and cardiovascular disease. It is unlikely that the reproducible and apparently robust association between homocysteine and dis-

ease is purely due to chance. There are also demonstrable *in vitro* and *in vivo* mechanisms whereby homocysteine might exert an atherogenic effect. Homocysteine may be a surrogate for another process or atherogenic pathway and we could be oversimplifying the complex metabolic pathways that link homocysteine to the atherosclerotic plaque.

Several potential reasons have been postulated in recent months to account for the lack of clinical effect of the B vitamins and folic acid, including a potential effect of folic acid on thymidine synthesis in the methylation process, adverse effects on the methylation cycle caused by introducing excess folic acid and vitamin B12 to the cycle, and increased production of asymmetrical dimethylargine (ADMA) at the level of the endothelium, which may negate the effect of homocysteine lowering.

Regardless of these arguments, there is a consensus emerging that the hypothesis that homocysteine lowering with vitamins can reduce future cardiovascular events is incorrect. If we must accept that the epidemiologically reproducible relationship between homocysteine and vascular disease is genuine, as it appears to be, then it is potentially far more complex than previously believed and will require further thought. Clinically, there is now little justification for using folic acid or B vitamins in patients with established cardiovascular disease, whether or not they have elevated homocysteine levels.

Conflict of interest

None declared.

References

1. The Homocysteine Studies Collaboration. Homocysteine and risk of ischaemic heart disease and stroke. A meta-analysis. *JAMA* 2002;**288**: 2015-22.
2. Toole JF, Malinow MR, Chambless LE *et al*. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 2004;**291**:565-75.
3. Bønaa KH, Njølstad I, Ueland PM *et al*. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006; **354**:1578-88.
4. The Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;**354**:1567-77.

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