Can mild-to-moderate hyperhomocysteinaemia impair endothelial function in the absence of other risk factors for cardiovascular disease?

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ABSTRACT
The majority of clinical studies demonstrate that patients with hyperhomocysteinaemia have an increased risk of atherothrombotic events. However, there is a striking and poorly understood heterogeneity in the severity of clinical features in individuals with hyperhomocysteinaemia. This observation suggests that other factors must exist that modulate the relationship between hyperhomocysteinaemia and clinical disease. Therefore identifying factors that inhibit or enhance the vasculotoxic effects of homocysteine is important, as is elucidation of how homocysteine damages blood vessels. This comment discusses the study of Woodman and colleagues in this issue of Clinical Science in which they investigate the effects of hyperhomocysteinaemia on endothelial function.

In 1969, McCully [1] performed an autopsy on two children with severe hyperhomocysteinaemia caused by a distinct inborn error of metabolism and found extensive arterial thrombosis and atherosclerosis involving all large-, medium- and small-sized arteries. This observation led to the hypothesis that homocysteine causes atherothrombotic disease.

Homocysteine is a sulphur-containing amino acid formed during the metabolism of the essential amino acid methionine. Homocysteine can be metabolized by so-called remethylation and trans-sulphuration. In the remethylation cycle, methionine is regenerated by the transfer of a methyl group from N5-methyltetrahydrofolic acid (5-MTHF; the active form of folic acid) to homocysteine. In trans-sulphuration, which requires vitamin B6 as a cofactor, homocysteine is metabolized to cysteine [2]. Severe hyperhomocysteinaemia (≥70–100 µmol/l) is rare and is often caused by genetic defects in the enzymes involved in homocysteine metabolism, such as cystathionine β-synthase. In contrast, the most common known causes of mild-to-moderate hyperhomocysteinaemia (≥12–70 µmol/l) are nutritional deficiencies of folic acid, vitamin B12 and vitamin B6, and impaired renal function [3].

The clinical phenotype that accompanies severe (genetic) hyperhomocysteinaemia is fairly heterogeneous. Similarly, the association between homocysteine levels and risk of myocardial infarction and stroke is strong in some studies and weak in others [4]. This may, of course, be coincidental, but another possibility is that the vasculotoxic effects of homocysteine are strongly modulated by other (unknown) factors [5,6].

Homocysteine appears to be a vasculotoxic substance, promoting atherogenesis by causing endothelial damage through increasing oxidative stress and interfering with the antithrombotic properties of the endothelium [3,7,8]. Nevertheless, the association between hyperhomocysteinaemia and impaired endothelium-dependent nitric-oxide (NO)-mediated vasodilation is not consistent across studies [9,10]. Could it be that homocysteine is more vasculotoxic in an atherogenic environment caused by other risk factors for atherosclerosis?

In order to test further the hypothesis that homocysteine itself is vasculotoxic in humans, it is important to investigate the effects of hyperhomocysteinaemia on endothelial function in a clinical condition where no other known atherogenic risk factors are present. The study by Woodman et al. [11] in this issue of Clinical Science addresses this question. They critically reviewed prior studies that addressed the same topic and found that important uncertainty exists regarding the presence, in these studies, of other atherosclerotic risk factors besides hyperhomocysteinaemia. Therefore Woodman et al. [11] included healthy subjects with hyperhomocysteinaemia

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and used strict criteria to exclude subjects with any known atherosclerotic risk factors. Their main conclusion is that mild-to-moderate hyperhomocysteinaemia alone does not cause endothelial dysfunction in healthy subjects in the absence of other cardiovascular risk factors. These results are of importance as it helps us to hypothesize further on the mechanisms linking hyperhomocysteinaemia to atherothrombosis. For example, could it be that folic acid is the central determinant and that hyperhomocysteinaemia is, in part, a marker of intracellular folic acid deficiency?

Usui et al. [12] have demonstrated that methionine loading in healthy volunteers acutely impaired endothelial function. Pretreatment with folic acid did not prevent the rise in homocysteine, but prevented the impaired vascular response. These findings suggest that it may not be homocysteine itself which is responsible for the acute endothelial dysfunction in this setting, but the acute lowering of folic acid induced by methionine loading. Indeed, in vitro, 5-MTHF has intrinsic antioxidant actions, increases NO production by endothelial NO synthase (eNOS) and is a cofactor of tetrahydrobiopterin production, which is essential for an optimal functioning of eNOS [13,14]. Also, 5-MTHF restored endothelial function in patients with familial hypercholesterolaemia without influencing homocysteine levels [15]. In addition, Doshi et al. [16] have demonstrated that folic acid improved endothelial function in patients with coronary artery disease by a mechanism largely independent of homocysteine. Taken together, these data show that it is not clear whether the effect of folic acid on endothelial dysfunction is mediated by lowering of homocysteine, by other effects of folic acid or by both.

How to reconcile these findings? One might hypothesize that, in healthy subjects with hyperhomocysteinaemia only, a normal intake of folic acid is sufficient to protect the endothelium and to remethylate homocysteine. However, in subjects with hyperhomocysteinaemia and atherosclerotic risk factors, which impair endothelial function, the need for folic acid may be increased. Could differences in atherosclerotic burden (folic acid need) and differences in dietary folic acid intake between individuals explain, in part, the heterogeneity of the association of homocysteine levels with atherothrombotic disease? Against this hypothesis, perhaps, is the observation that the association between homocysteine levels and myocardial infarction and stroke is clearly not stronger in the presence of other risk factors (age, male sex, hypertension and hypercholesterolaemia) than in their absence, except for diabetes [4,17].

It thus remains unclear what variables (cardiovascular risk factors or otherwise) modulate the effect of homocysteine on the vessel wall. There is a clear need to study further the issue of what factors are capable of enhancing or inhibiting the pro-thrombotic and pro-atherogenic effects of homocysteine.

REFERENCES


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