Homocysteine and Risk of Cardiovascular Disease

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J. Auer, R. Berent, B. Eber

Homocysteine is a sulfur-containing amino acid derived from the metabolic demethylation of dietary methionine, which is abundant in animal protein. Homocysteine is metabolized by one of two pathways: remethylation and transulfuration. It is present in plasma in four forms: as circulating free thiol (1%); disulfide-bound to plasma proteins, chiefly albumin (70–80%); and combinations with itself to form the dimer homocysteine or with other thiols, including cysteine, with which it forms the homocysteine-cysteine mixed disulfide (20–30%). The term “total plasma homocysteine” (tHcy) refers to the combined pool of all four forms of homocysteine.

Homocysteine and Vascular Disease – Introduction

In 1969, McCully [1] made the clinical observation linking elevated plasma homocysteine concentrations with vascular disease. Subsequent investigations have confirmed this hypothesis. For about two decades, moderately raised concentrations of total homocysteine (tHcy) have been correlated with increased risk of atherothrombotic vascular events [2, 3], but only recently has evidence mounted to suggest that the association may be causal. The association is independent of other known risk factors and it is consistent across many studies. Furthermore, it is strong and dose-related, and it is biologically plausible. Although the molecular mechanism by which homocysteine or a related metabolite promotes atherothrombosis is unknown, the epidemiologic evidence of the association of hyperhomocysteinaemia with atherothrombotic vascular disease seems to be convincing. However, the evidence needs to be strengthened by a systematic review of all comparable studies and the demonstration, in randomised trials, that lowering tHcy is followed by a significant reduction in atherothrombotic vascular disease. In addition, the measurement of tHcy needs to be standardised. If these can be achieved then tHcy measurement will become another useful marker of vascular risk, multivitamin therapy will be another therapeutic option for people at risk of atherothrombotic vascular disease, and fortification of food with folic acid will rise high on the political and public health agenda.

Definition of Hyperhomocysteinaemia and Measurement of Plasma Homocysteine

An abnormal “total plasma (or serum) homocysteine” (tHcy) is defined by an arbitrary cut-off in the distribution of concentrations found in the “normal population”, in much the same way as other more common vascular risk factors like hypertension and hypercholesterolaemia have been defined. For example, after methionine-loading, hyperhomocysteinaemia is defined as a tHcy of more than 2 standard deviations (SD) above the mean [7]. Among fasting individuals, “normal” tHcy commonly ranges from 5 to 15 µmol/L [8, 9] and higher fasting values are classified as moderate (16–30), intermediate (31–100), and severe (>100 µmol/L) hyperhomocysteinaemia [10] on the basis of concentrations measured during fasting.

The majority of the clinical studies involving homocysteine have relied on the measurement of total plasma homo-
Homocysteine Metabolism

Homocysteine is a sulphydryl-containing amino acid derived from the metabolic demethylation of methionine. Homocysteine is metabolized by remethylation or transsulfuration. In the remethylation cycle, homocysteine is salvaged by the acquisition of a methyl group in a reaction catalyzed by methionine synthase. Vitamin B12 (cobalamin) is an essential cofactor for methionine synthase. N-methyltetrahydrofolate is the methyl donor in this reaction, and N,N-methylenetetrahydrofolate reductase acts as a catalyst in the remethylation process [12] (Figure 1). Under conditions with an excess of methionine or when cysteine synthesis is required, homocysteine enters the transsulfuration pathway. In this pathway, homocysteine condenses with serine to form cystathionine in a reaction catalyzed by the vitamin B6-dependent enzyme cystathionine (beta)-synthase.

Nutritional Factors and Homocysteine Metabolism (Table 1)

Nutritional deficiencies in the vitamin cofactors (folic acid, vitamin B12, and vitamin B6) required for homocysteine metabolism may promote hyperhomocysteinemia. Markedly elevated homocysteine concentrations have been observed in patients with nutritional deficiencies of the essential cofactor vitamin B12 [13] and the cosubstrate folate [14]. It has been suggested that about two-thirds of hyperhomocysteinemia is due to inadequate blood levels of one or more of these vitamin cofactors [15, 16].

Inadequate plasma concentrations of one or more B vitamins are contributing factors in approximately two thirds of all cases of hyperhomocysteinemia. Vitamin supplementation can normalize high homocysteine concentrations; however, it remains to be determined whether normalizing homocysteine concentrations will improve cardiovascular morbidity and mortality.

Table 1. Factors influencing homocysteine metabolism (factors increasing homocysteine levels)

<table>
<thead>
<tr>
<th>Nutritional deficiencies in vitamin cofactors</th>
<th>Genetic defects in homocysteine metabolism</th>
<th>Medications/toxins</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate</td>
<td>CysJ</td>
<td>Folate antagonists (methotrexate, phenytoin, carbamazepine)</td>
<td>Malignancy: acute lymphoblastic leukaemia, carcinoma of the breast, ovary and pancreas</td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td>MTHFR</td>
<td>Vitamin B6 antagonists (theophylline, azarabine, oestrogen-containing oral contraceptives, cigarette smoking)</td>
<td>Pernicious anaemia</td>
</tr>
<tr>
<td>Vitamin B12 (cobalamin)</td>
<td>Methionine synthase</td>
<td></td>
<td>Renal impairment</td>
</tr>
</tbody>
</table>

Hyperhomocysteinemia Caused by Other Factors

Renal impairment commonly causes hyperhomocysteinemia. Fasting tHcy rises as serum creatinine rises, not because of impaired urinary excretion but because of impaired metabolism of homocysteine by the kidney, the major route by which homocysteine is cleared from plasma. In contrast, urinary excretion is a very minor route for direct homocysteine clearance [17]. Total homocysteine levels are considerably higher in patients with chronic renal disease than...
the moderately raised concentrations commonly found in patients with atherothrombotic vascular disease, and this may contribute to the high incidence of vascular complications in patients with chronic renal failure. Values are higher in patients undergoing haemodialysis compared to peritoneal dialysis. The exact mechanisms for the raised levels of the amino acid seen in these patients remain unclear but reduced systemic clearance of homocysteine, lower circulating folate, and folate inhibition are probably major determinants.

A number of reports have linked hyperhomocysteinaemia to hypothyroidism, suggesting a potential mechanism for the higher incidence of vascular disease observed in patients with hypothyroidism. Hyperhomocysteinaemia has also been reported in patients with pernicious anaemia and it is unclear whether these patients are at increased risk for vascular events.

Elevated homocysteine concentrations have been reported in association with several types of carcinoma, including breast, ovarian, and pancreatic cancer [18]. Several drugs and toxins increase plasma homocysteine concentrations. Methotrexate depletes folate, the cosubstrate for methionine synthase, and causes a transient increase in plasma homocysteine concentrations. Phenytin, Theophylline (interfering with the synthesis of pyridoxal phosphate) and cigarette smoking interact with homocysteine metabolism. Cyclosporin may impair renal function and it has been associated with hyperhomocysteinaemia.

It has been reported that smokers have significantly lower pyridoxal phosphate concentrations than non-smokers [19]. These results suggest another important mechanism whereby smoking may promote atherogenesis. Homocysteine concentrations rise with age in both sexes. Women in general have lower concentrations than men, and concentrations rise after menopause. A high intake of caffeine or alcohol, and a sedentary lifestyle are associated with raised homocysteine.

Pathophysiologic Mechanisms of Association Between Hyperhomocysteinaemia and Atherosclerosis

Clinical and experimental studies suggest that high homocysteine concentrations may cause the atherogenic and thrombotic tendencies of homocystinuric and hyperhomocysteinaemic patients. Experimental evidence suggests that the atherogenic propensity associated with hyperhomocysteinaemia results from endothelial dysfunction and injury followed by platelet activation and thrombus formation [20, 21]. Although the exact mechanism of endothelial dysfunc tion is unknown, there is growing evidence that homocysteine exerts its effects by promoting oxidative damage. Superoxide-dependent formation of the hydroxyl radical has been shown to initiate lipid peroxidation [22], an effect that occurs at the level of the endothelial plasma membrane and within lipoprotein particles [23]. Homocysteine auto-oxidation has been shown to support the oxidation of low-density lipoprotein through the generation of the superoxide anion radical [24]. Homocysteine alters the normal anti-thrombotic phenotype of the endothelium by enhancing the activities of factor XII and factor V and depressing the activation of protein C [25]. All of these effects ultimately facilitate the formation of thrombin and create a prothrombotic environment. The production of endothelial-derived nitric oxide is also adversely affected by homocysteine [26]. In conclusion, it is clear that there is no one unifying hypothesis of the mechanism, if any, of homocysteine induced vascular damage although at present the endothelium is the most likely candidate.

Homocysteine as a Risk Factor for Vascular Disease

In an European multicentre investigation of 750 cases and a similar number of controls, a high homocysteine concentration conferred a risk equal to that of hypercholesterolaemia, smoking or hypertension [27]. Some, but not all, prospective (or nested case control) studies have confirmed these findings. In the multiple risk factor intervention trial (MRFIT), for example, the homocysteine concentrations in serum samples from men who subsequently suffered a myocardial infarction were not different from those in controls [28].

In another recent prospective study by Folsom and colleagues, higher homocysteine concentrations added to the risk of incident coronary artery disease in women but not in men [29]. In patients with coronary disease, higher homocysteine concentrations are related to lower circulating B vitamin concentrations. Indeed, in one study, as the concentration of folate fell, the levels of both homocysteine and cardiovascular risk rose [30]. Similarly, there is an increased vascular risk associated with lower levels of vitamin B6 [31].

Therapeutic Considerations of Hyperhomocysteinaemia

The treatment of hyperhomocysteinaemia varies with the underlying cause; however, vitamin supplementation (with folic acid, pyridoxine (vitamin B6), and vitamin B12) is generally effective in reducing homocysteine concentrations. The minimal effective doses of folic acid and pyridoxine have not yet been determined. In most patients, small doses of folate (0.4 to 5 mg per day) rapidly decrease homocysteine concentrations [32]. Whether doses lower than 400 µg are effective has not been adequately explored. Patients with renal impairment require much higher doses. A meta-analysis of data from 1114 individual participants in 12 randomised controlled trials of the effects of folic-acid-based supplements on basal tHcy found that the proportional and absolute reductions in tHcy produced by folic acid were greater at higher pretreatment tHcy and at lower pretreatment blood folate levels [33]. Folic acid alone, folic acid combined with vitamins B12 and B6, and vitamins B6 and B12 have all been shown to reduce homocysteine concentrations [34]. Because the response to homocysteine-lowering therapy is not uniform, and is dependent on factors such as genotype for enzymes involved in the metabolism of homocysteine, vitamin status, and nutritional needs [13], multivitamin doses required for the treatment of hyperhomocysteinaemia may vary according to individual patient requirements.

Normalization of the plasma homocysteine concentration usually occurs within four to six weeks after the initiation of therapy, but may occur in as little as two weeks. Interestingly, the reduction in mortality from cardiovascular causes since 1960 has been correlated with the increase in vitamin B6 supplementation in the food supply [11]. A potential hazard of folic acid therapy is progressive neurological damage (subacute combined degeneration of the spinal cord) in people with subclinical vitamin B12 deficiency in whom folic acid therapy may mask the development of the haematological manifestations of the B12 deficiency.

This can be avoided by either excluding B12 deficiency before starting folic acid or by supplementing folic acid therapy with vitamin B12. At least 400 µg per day of vitamin B12 is suggested as a supplement because the recommended daily intake of this vitamin is about 2 µg per day but only 1–3 % of oral vitamin B12 is absorbed by simple diffusion.
The major potential hazard of vitamin B6 is a sensory peripheral neuropathy with use over months to years at doses of vitamin B6 usually at least 400 mg daily. However, most doses for the treatment of moderate hyperhomocysteinaemia are only 10–50 mg per day. In patients with severe hyperhomocysteinaemia due to CBS deficiency effective homocysteine-lowering therapy does reduce the risk of cardiovascular disease during long-term follow-up [35]. However, although the combination of folic acid 25 mg, vitamin B6 25 mg, and vitamin B12 250 μg per day reduces the progression of atherosclerosis, as measured by carotid plaque area [36], it remains to be confirmed that homocysteine-lowering therapy will prevent important atherosclerotic vascular events in patients with moderate hyperhomocysteinaemia. Several large randomised clinical trials are addressing this issue (Table 2).

**Remaining Questions**

Many important questions remain – for example, is a high circulating homocysteine concentration causal in the pathogenesis of coronary disease and other atherosclerotic and thrombotic vascular diseases, or is it merely an epiphenomenon? Is the high homocysteine level a reflection of lower B vitamin status which is itself (directly or indirectly) linked to atherosclerosis? Or is it a reflection of diminished renal function so often seen in patients with vascular disease [37]? What, if any, is the mechanism by which homocysteine may induce atherosclerosis? In other clinical circumstances such as following organ transplantation, or in the presence of hypothyroidism or inflammatory bowel disease, does high homocysteine predict increased vascular risk?

### References

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