Homocysteine and Risk of Cardiovascular Disease

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J. Auer, R. Berent, B. Eber

Homocysteine is a sulphydryl-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 transsulfuration. 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 an increased risk of atherothrombotic vascular events [2,3], but only recently has evidence mounted to suggest that the association is 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 hyperhomocysteinemia 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.

Only about two-thirds of all episodes of symptomatic atherothrombotic vascular disease in developed countries can be attributed to established genetic and environmental vascular risk factors [4]. An additional causal vascular risk factor may be raised plasma levels of homocysteine (hyperhomocysteinemia). Mild hyperhomocysteinemia occurs in approximately 5 to 7 percent of the general population [5,6]. Patients with mild hyperhomocysteinemia are typically asymptomatic until the third or fourth decade of life when premature coronary artery disease develops, as well as recurrent arterial and venous thrombosis. Although 30 years have elapsed since hyperhomocysteinemia was first associated with an increased risk of atherothrombotic vascular disease, it is only recently that sufficient evidence has mounted to suggest that the association is independent and dose-related, and it remains to be established whether it is causal and modifiable.

Key words: homocysteine, cardiovascular disease, folate, pathophysiology, therapy

Definition of Hyperhomocysteinemia 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, hyperhomocysteinemia 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) hyperhomocysteinemia [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 homocysteine.
Homocysteine, which includes homocysteine, mixed disulfides involving homocysteine, homocysteine thiolactone, free homocysteine, and protein-bound homocysteine. Protein-bound homocysteine accounts for 70 to 80 percent of the total pool. An oral dose of methionine (100 mg per kilogram of body weight) can be given to persons with suspected hyperhomocysteinaemia who have normal homocysteine concentrations during fasting.

Plasma homocysteine concentrations are determined before the methionine challenge and between four and eight hours afterward.

Hyperhomocysteinaemia is considered to be present if the homocysteine concentration after methionine challenge is more than 2 SD above the mean [11]. The prognostic value of the methionine-challenge test has recently been discussed controversially [8]. In contrast to a weak association between plasma homocysteine concentrations after methionine challenge and premature coronary heart disease in persons with the thermolabile variant of N,N-methylenetetrahydrofolate reductase, there was a significant association between plasma homocysteine concentrations during fasting and premature coronary heart disease. In conclusion, this enzyme regulates basal homocysteine concentrations, and thus, its activity cannot be adequately assessed by a methionine-challenge test. By contrast, however, enzymes in the transsulfuration pathway are responsible for reversing transient, postprandial increases in the homocysteine concentration, and their activities can be evaluated by a methionine-challenge test.

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 (folate, vitamin B6, and vitamin B12) required for homocysteine metabolism may promote hyperhomocysteinaemia.

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 hyperhomocysteinaemia 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 hyperhomocysteinaemia. Vitamin supplementation can normalize high homocysteine concentrations; however, it remains to be determined whether normalizing homocysteine concentrations will improve cardiovascular morbidity and mortality.

Hyperhomocysteinaemia Caused by Other Factors

Renal impairment commonly causes hyperhomocysteinaemia. 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

Figure 1. Pathways of homocysteine metabolism (CBS = cystathionine-beta-synthase; Cbl = cobalamin; THF1 = monoglutamated form of tetrahydrofolate; B6 = vitamin B6; CH3 = Methyl).

Homocysteine is metabolized either by transsulfuration to cysteine (in a reaction catalyzed by cystathionine-beta-synthase [(CBS) with vitamin B6 as cofactor] or by remethylation to methionine. Remethylation is catalyzed by methionine synthase (and 5,10-methylenetetrahydrofolate reductase). Methionine synthase is dependent upon cobalamin (vitamin B12) as cofactor and folate as cosubstrate. An alternative remethylation pathway (not shown in the figure) uses the cobalamin independent betain-homocysteine methyltransferase.

<table>
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<tr>
<th>Nutritional deficiencies in vitamin cofactors</th>
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<tr>
<td>Folate</td>
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<td>Vitamin B6 (pyridoxine)</td>
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<td>Vitamin B12 (cobalamin)</td>
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<th>Genetic defects in homocysteine metabolism</th>
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<td>MTHFR</td>
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<td>Methionine synthase</td>
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<th>Medications/toxins</th>
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<td>Folate antagonists (methotrexate, phenytoin, carbamazepine)</td>
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<td>Vitamin B6 antagonists (theophylline, azarabine, oestrogen-containing oral contraceptives, cigarette smoking)</td>
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<th>Diseases</th>
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<td>Malignancy: acute lymphoblastic leukaemia, carcinoma of the breast, ovary and pancreas</td>
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<td>Pernicious anaemia</td>
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<td>Renal impairment</td>
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<td>Hypothyroidism</td>
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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 pa-
tients undergoing haemodialysis compared to peritoneal di-
alysis. 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 hyperhomocysteinemia to
hypothyroidism, suggesting a potential mechanism for the
higher incidence of vascular disease observed in patients with
hypothyroidism. Hyperhomocysteinemia has also been re-
ported in patients with pernicious anaemia and it is unclear
whether these patients are at increased risk for vascular events.

Elevated homocysteine concentrations have been re-
ported in association with several types of carcinoma, includ-
ing 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 homo-
cysteine concentrations. Phenytoin, Theophylline (interfer-
ence with the synthesis of pyridoxal phosphate) and cigarette
smoking interact with homocysteine metabolism. Cyclo-
sporin may impair renal function and it has been associated
with hyperhomocysteinemia.

It has been reported that smokers have significantly lower
pyridoxal phosphate concentrations than non-smokers [19].
These results suggest another important mechanism where-
by smoking may promote atherogenesis. Homocysteine con-
centrations 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 homo-
cysteine concentrations may cause the atherogenic and throm-
botic tendencies of homocystinuric and hyperhomocyst-
einaemic patients. Experimental evidence suggests that the
atherogenic propensity associated with hyperhomocystein-
emia results from endothelial dysfunction and injury fol-
lowed by platelet activation and thrombus formation [20,
21]. Although the exact mechanism of endothelial dysfunc-
tion is unknown, there is growing evidence that homo-
cysteine 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-oxida-
tion has been shown to support the oxidation of low-density
lipoprotein through the generation of the superoxide anion
radical [24]. Homocysteine alters the normal antithrombotic
phenotype of the endothelium by enhancing the activities of
factor XII and factor V and depressing the activation of pro-
tein C [25]. All of these effects ultimately facilitate the for-
mation of thrombin and create a prothrombotic environ-
ment. 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 hypo-
thesis of the mechanism, if any, of homocysteine induced vas-
cular 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 concentra-
tion 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 find-
ings. In the multiple risk factor intervention trial (MRFIT),
for example, the homocysteine concentrations in serum sam-
pleS from men who subsequently suffered a myocardial inf-
arction were not different from those in controls [28].

In another recent prospective study by Folsom and col-
leagues, 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 homo-
cysteine concentrations are related to lower circulating B vi-
tamin concentrations. Indeed, in one study, as the concen-
tration of folate fell, the levels of both homocysteine and cardio-
vascular risk rose [30]. Similarly, there is an increased vascu-
lar 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 gen-
erally effective in reducing homocysteine concentrations.
The minimal effective doses of folate 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 re-
nal 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 supple-
ments on basal tHcy found that the proportional and absolute
reductions in tHcy produced by folate were greater at
higher pretreatment tHcy and at lower pretreatment blood
tolate 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 uni-
form, and is dependent on factors such as genotype for en-
zymes involved in the metabolism of homocysteine, vitamin
status, and nutritional needs [13], multivitamin doses re-
quired 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 sup-
plementation in the food supply [11]. A potential hazard of
folic acid therapy is progressive neurological damage (sub-
acute 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 be-
fore 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).

### Table 2. Trials of homocysteine-lowering therapy in vascular disease

- Vitamins in Stroke Prevention (VISP) Trial, Bowman Gray School of Medicine, USA
- Norwegian Study of Homocysteine Lowering with B-vitamins in Myocardial Infarction (NORVIT), University of Tromso, Norway
- Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH); Clinical Trial Service Unit, Oxford, UK
- Women’s Antioxidant and Cardiovascular Disease Study (WACS); Harvard Medical School, USA
- Bergen Vitamin Study; University of Bergen, Norway
- Cambridge Heart Antioxidant Study (CHAOS-2); University of Cambridge, UK
- Heart Outcomes Prevention Evaluation (HOPE-2) Study; McMaster University, Canada
- Prevention with A Combined Inhibitor and Folate in Coronary Heart Disease (PACIFIC) Study; University of Sydney, Australia
- Vitamins TO, Prevent Stroke (VITATOPS) Study; Stroke Unit, Royal Perth Hospital, Western Australia

### 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 epidemiologic phenomenon? 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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