Homocysteine, B vitamins, and risk of cardiovascular disease

Homocysteine is a sulphur containing amino acid that plays an important role in methionine and folate metabolism. By receiving a methyl group from 5'-methyltetrahydrofolate, it is reconverted to methionine (fig 1), which is essential for many biochemical reactions critical to the formation of protein, nucleic acids, and creatinine. Reconversion of homocysteine to methionine also contributes to the maintenance of intracellular stores of tetrahydrofolate.

Homocysteine has become a target for many basic and clinical investigators because of a clinical syndrome described almost 40 years ago. The syndrome, homocystinuria, is an autosomal recessive disorder characterised by abnormalities of the long bones, ocular lens dislocation, mental retardation, and aggressive vascular disease, in particular venous thromboembolism. The underlying enzymological abnormality, a deficit of cystathionine $\beta$ synthase, results in impairment of homocysteine transsulfuration. As a consequence, the concentrations of the amino acid in plasma may rise 20-fold from the normative range of 5–15 µmol/l. About 10 years after the discovery of homocystinuria it was hypothesised by McCully that high plasma homocysteine might be causally related to the vascular complications of the disease. In 1976, Wilcken and Wilcken studied patients without homocystinuria but with angiographically proved coronary artery disease. Using the methionine loading test, in which 0.1 mg/kg body weight of this amino acid is administered orally, they found that the prevalence of high circulating homocysteine concentrations, or hyperhomocysteinaemia, was higher than in normal controls. They concluded that people with a genetic susceptibility, namely carriers of the genetic mutation for cystathionine $\beta$ synthase deficiency, might be at greater risk of coronary artery disease.

Figure 1  Pathways for the metabolism of homocysteine. Normal transsulfuration requires cystathionine $\beta$ synthase with vitamin B6 as cofactor. Remethylation requires 5,10-methylenetetrahydrofolate reductase and methionine synthase. The latter requires folate as cosubstrate and vitamin B12 (cobalamin) as cofactor. An alternative remethylation pathway also exists using the cobalamin independent betaine–homocysteine methyltransferase.
Nutritional disorders

Genetic
Cystathionine \(\beta\) synthase deficiency (the cause of classic homocystinuria)
5,10-Methylene-tetrahydrofolate reductase deficiency (rare) or
thermolability (common)
Methionine synthase deficiency (rare)

Nutritional disorders
Folate deficiency
Vitamin B12 deficiency
Vitamin B6 deficiency

Systemic disease
Renal failure
Malignant diseases
Puerperia
Hyperthyroidism

Drug
Cholestyramine and colestipol (decrease cobalamin and folate absorption)
Methotrexate (inhibits dihydrofolate reductase)
Phenytoin and carbamazepine (antagonise folate)
Nitrous oxide (inactivates methionine synthase)
Niacin and theophylline (decrease pyridoxal kinase)
Androgens (increase muscle mass and serum creatinine)
Cyclosporin A (decreases renal function)
Metformin (may decrease cobalamin absorption)
Fibrac acid derivatives (may interfere with renal function)

Hyperhomocysteinaemia: result of a gene–nutrient interaction

For some years, attention focused on the role of heterozygos-
ity for homocystinuria as a possible cause of the high homo-
cysteine concentrations that are seen in up to 30–40% of
patients with coronary artery disease. This cause is now felt
unlikely. Indeed, a glance at the biochemical pathways of
homocysteine metabolism shows that abnormalities of other
critical enzymes and several cofactors could also lead to high
homocysteine concentrations. For example, transsulfuration
of homocysteine also requires vitamin B6, an essential cofac-
cor for cystathionine \(\beta\) synthase. It is no surprise, therefore,
that plasma concentrations of this vitamin correlate nega-
atively with those of homocysteine. In addition, the remethyla-
ion of homocysteine, which results in the reconstitution of
methionine and tetrahydrofolate, also requires the enzymes
methionine synthase and methylenetetrahydrofolate reduct-
ase (MTHFR). Deficiencies of these enzymes, although rare,
have been described. Predictably, they are associated with
hyperhomocysteinaemia and notably they are also associated
with vascular disease. Two relatively common variant
polymorphisms in the gene coding for MTHFR have been
described. One of these, the C677T mutation, may also be
associated with hyperhomocysteinaemia especially in the
presence of lower folate concentrations. Its relation to coro-
ary artery disease remains controversial although a recent
meta-analysis has shown the same prevalence in patients with
cardiovascular disease as in controls. Methionine synthase
requires cobalamin (vitamin B12) and folate as cosubstrate,
and deficiencies of both of these vitamins are well known
causes of hyperhomocysteinaemia (table 1).

Other factors affecting plasma homocysteine

AGE, SEX, AND LIFESTYLE
Homocysteine concentrations rise with age in both sexes.
Women in general have lower concentrations than men, and
concentrations rise after menopause. Cigarette smoking, a
high intake of caffeine or alcohol, and a sedentary lifestyle
are associated with raised homocysteine. At a population
level, however, the most important causes are probably lower
concentrations of folic acid and vitamins B12 and B6.

SYSTEMIC ILLNESSES
Creatinine correlates strongly with plasma homocysteine.
In end stage renal disease homocysteine concentrations
increase two- to threefold. 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 sys-
temic clearance of homocysteine, lower circulating folate,
and folate inhibition are probably major determinants.
Homocysteine may also rise with various cancers,
hypothyroidism, inflammatory bowel disease, and folate
absorption such as colestipol and cholestyramine. Nitrous
oxide acts as a cobalamin antagonist. Theophylline and
niacin may result in vitamin B6 deficiency. Cyclosporin
may impair renal function and it has been associated with
hyperhomocysteinaemia. Homocysteine concentrations
fall with the use of B vitamins: folic acid, vitamin B12, and
betaine encourage remethylation whereas vitamin B6 pro-
motes increased transsulfuration. The aminothiols peni-
cillamine and acetylcysteine may also reduce plasma
homocysteine as may exogenous oestrogen.

Table 1 Causes of hyperhomocysteinaemia

<table>
<thead>
<tr>
<th>Cause</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Male sex</td>
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<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
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<tr>
<td>Lifestyle factors including smoking, heavy intake of coffee, and alcohol</td>
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Homocysteine as a risk factor for vascular disease

Since the early study of Wilcken and Wilcken many case
control studies have shown that homocysteine is an
independent risk factor for atherosclerotic vascular disease
and for venous thrombosis. Broadly similar findings are
found irrespective of whether the homocysteine is measured
in the fasting state or following the methionine loading test.
For example, in a European multicentre investigation of 750
cases and a similar number of controls, a high homocysteine
concentration conferred a risk equal to that of hypercholes-
teraemia, smoking or hypertension. 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 myo-
cardial infarction were no different from those in controls.
In another recent prospective study by Folsom et al higher
homocysteine concentrations added to the risk of incident
coronary artery disease in women but not in men.
In patients with coronary disease, higher homocysteine concen-
trations are related to lower circulating B vitamin concen-
trations. Indeed, in one study, as the concentration of folate fell,
the levels of both homocysteine and cardiovascular risk
rose. Similarly, there is an increased vascular risk associated
with lower levels of vitamin B6 both in case control and
prospective studies. Hyperhomocysteinaemia has also been
associated with increased atherothrombotic risk in end stage
renal disease and systemic lupus erythematosus.

Possible pathophysiological mechanism of vascular injury

IN VITRO STUDIES
Clinical and experimental studies suggest that high homo-
cysteine concentrations may cause the atherogenic and
thrombotic tendencies of homocystinuric and hyperhomocy-
steinaemic patients. A single discrete mechanism, however,
remains unproved. Homocysteine may have adverse effects on platelet function, clotting factors and
may also promote vascular smooth muscle cell migration
and proliferation. It may also exert important negative influences on endothelial function and result in either
prooxidant or prothrombotic effects. For example, homo-
cysteine auto-oxidises readily and forms potentially
noxious hydrogen peroxide and superoxide anion in the
process. Endothelium derived nitric oxide may protect
Treatments and trials

FOLIC ACID SUPPLEMENTS

Folic acid is the treatment of choice for reduction of high homocysteine concentrations. Most patients only require doses of 0.4 mg, the current recommended dietary allowance for this vitamin in the USA. Such amounts are inexpensive, highly effective, and safe. A meta-analysis of 12 randomised controlled trials involving 1114 patients showed that daily supplementation with 0.5–5 mg of folic acid and 0.5 mg of vitamin B12 decreases homocysteine concentrations by a quarter to a third.29 In another study, the effects of daily doses of 0.1, 0.2, and 0.4 mg folic acid were compared; and 0.2 mg was as effective as 0.4 mg.30 Although usually innocuous, it should be emphasised that the use of folic acid alone may predispose to neurological damage in those who are also deficient in vitamin B12. This is of particular importance in the elderly in whom it may be prudent to check vitamin B12 levels if long term folic acid treatment is considered. In some clinical situations, dose requirements may rise. In patients with end stage renal disease, for example, folic acid doses as high as 15 mg/day have been used31 and may still not normalise the raised homocysteine concentrations typically seen in this clinical condition. Larger doses than 0.4 mg may also be needed in patients on drugs that antagonise the actions of folate.

These homocysteine lowering effects of folic acid may translate into favourable clinical outcomes. Woo et al have shown that folic acid supplementation may improve endothelium dependent vasodilatation.32 Similar findings have been reported in patients with familial hypercholesterolaemia using 5-methyltetrahydrofolate, the active form of folic acid.33 Even more provocative are the findings of Peterson and Spence who, in a small uncontrolled study, showed that supplemental folic acid may decrease the progression of carotid atherosclerosis.34

Clinical trials

Several large secondary prevention trials using folic acid either alone or combined with vitamins B6 or B12 are now in progress in patients with vascular diseases. In the USA, the vitamin intervention for stroke prevention (VISP) study is assessing the effect of B vitamins on the recurrence of stroke in patients with established cerebrovascular disease. In Scandinavia, the Norwegian Study of homocysteine lowering with B vitamins in myocardial infarction (NORVIT) and the western Norwegian study on the effect of homocysteine reduction with B vitamins in patients with angiographically verified coronary artery disease (WEN-BIT) are also underway. The study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH) is in progress in the UK and the prevention with a combined inhibitor and folate in coronary heart disease (PACIFIC) trial is ongoing in Australia. Other studies in similar patient populations and in patients with end stage renal disease are being performed in Europe, Canada, and the USA, and the results are expected in the next several years. Hopefully, they will determine if the use of B vitamin supplements leads to improved outcomes in these patients.

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? What, if any, is the mechanism by which homocysteine may induce atherosclerosis? In other clinical circumstances such as smoking, organ transplantation, or in the presence of hypothyroidism or inflammatory bowel disease, does high homocysteine predict increased vascular risk?

For the clinician in practice, the routine measurement of homocysteine concentrations, although advocated by some, remains speculative until the results of the current intervention trials become known.35 Similarly, the use of pills containing low dose B vitamins as a primary or secondary preventive measure against vascular disease remains unproved, although they are definitely cheap, probably innocuous, and may help prevent acute vascular episodes.

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**Health campaigns**

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