HOMOCYSTEINE AND ATHEROSCLEROSIS: POTENTIAL MECHANISMS AND CLINICAL IMPLICATIONS

W.G. Haynes, Assistant Professor of Internal Medicine, University of Iowa, Iowa City, Iowa, USA

INTRODUCTION

Homocysteine is a sulfur-containing amino acid which circulates at concentrations of ~10 μM in healthy human subjects. Homocystinuria is a disorder of metabolism of homocysteine, caused most frequently by deficiency of cystathionine ß-synthase (CBS), and associated with plasma homocyst(e)ine concentrations above 100 μM. It is characterised by CNS, skeletal and ocular complications.[1] In 1969, McCully reported two cases of homocystinuria which were notable for premature atherosclerosis at the ages of two months and eight years respectively.[2] Subsequent studies have shown that 60% of patients with homocystinuria experience thromboembolism or events related to atherosclerosis before the age of 40 years.[1] Premature atherosclerosis also occurs with deficiency of other homocysteine-metabolising enzymes, including 5,10-methylenetetrahydrofolate reductase (MTHFR) and methylenetetrahydrofolate-homocysteine methyltransferase. This implies that elevated concentrations of homocyst(e)ine predispose to atherosclerosis rather than increased concentrations of its precursor, methionine.[1,3] In recent years, evidence has accumulated that even modest elevations in plasma homocyst(e)ine may be an independent risk factor for atherosclerosis in the general population.

BIOCHEMISTRY AND METABOLISM

Homocysteine is formed during the metabolism of the essential amino acid, methionine, the major methyl-group donor in mammals. Homocysteine is disposed of either by remethylation to methionine or by transsulphuration to cystathionine (Figure 1). Remethylation can occur (1) by methionine synthase (vitamin B_{12} dependent), the methyl donor being 5-methyl-tetrahydrofolate (5-MTHF, a derivative of folic acid); or (2) by betaine-homocysteine methyltransferase, the methyl donor in this instance being betaine. Transsulphuration of homocysteine occurs by the enzyme CBS (Vitamin B_6 dependent) and forms cystathionine, which is converted to cysteine (Figure 1).[4,5] Remethylation and transsulphuration each account for ~50% of homocysteine disposal. Remethylation is the major determinant of fasting plasma homocyst(e)ine levels, whereas impaired transsulphuration causes increased homocysteine levels when methionine levels are elevated (such as post-prandially). Homocysteine is present in the plasma as free homocysteine (1%), as a homocysteine disulfide (homocystine, 10%), homocysteine-cysteine mixed disulfide (10%) or as the protein-bound form (80%) (Figure 2).[6] Current assays measure the sum of all four forms (plasma 'homocyst(e)ine'). Fasting plasma concentrations of homocyst(e)ine are regulated by genetic and environmental factors and are usually ~10 μM, with the ninety-fifth percentile at ~15 μM.[7]

Causes of hyperhomocysteinemia

Plasma homocyst(e)ine concentrations are increased in males, and with increasing age and the menopause.[8-10]

Genetic factors

Inherited deficiencies of enzymes in the methionine-homocysteine pathway can lead to hyperhomocyst(e)-inaemia, the two commonest enzymes affected being CBS and MTHFR.[1] Complete deficiency of CBS is an autosomal recessive disorder and produces marked hyperhomocyst(e)inaemia and homocystinuria.[1] Parents of children with homocystinuria are heterozygote carriers of CBS mutations and have abnormally potentiated increases in plasma homocyst(e)ine following oral methionine. However, heterozygotes are rare (<1%), so mutations in CBS do not contribute importantly to moderate hyperhomocyst(e)inaemia in the general population.[1] The enzyme MTHFR is responsible for the reduction of 5,10-methylene-tetrahydrofolate to 5-methyl-tetrahydrofolate, which is required for the remethylation of homocysteine by methionine synthase (Figure 1).[3] Thus, deficient activity of MTHFR indirectly blocks remethylation of homocysteine. The most common alteration in the MTHFR gene is a point mutation ($C_{677}T$) that causes an alanine-to-valine substitution.[11] The allele frequency of the MTHFR $C_{677}T$ mutation is 35% with a homozygous rate of 12%.[11] Homozygosity for the $C_{677}T$ mutation is characterised by MTHFR thermolability, which decreases the specific activity of the enzyme by 50% and modestly increases plasma homocyst(e)ine.[11] Several studies have shown a positive association between MTHFR thermolability, and coronary heart disease and stroke.[12-15] However, other studies have not demonstrated this association.[16-19] In subjects homozygous for the $C_{677}T$ mutation, low levels of both folate and B_{12} lead to a relatively large increase in homocyst(e)ine levels.[20] This interaction may explain the conflicting data on MTHFR genotype and atherosclerosis. A recent meta-analysis has concluded that although the $C_{677}T$ mutation is a major cause of mild hyperhomocyst(e)inaemia, the mutation does not increase cardiovascular risk.[21]

Environmental factors

Plasma homocyst(e)ine levels are elevated by cigarette smoking and coffee consumption.[8,22,23] A diet rich in green leafy vegetables, fruits, orange juice and cereal is associated with higher folate and lower homocyst(e)ine levels.[24] Consumption of animal protein increases plasma homocyst(e)ine for up to 24 hours, presumably through increased dietary methionine intake.[25] However, subjects with chronic high protein intake tend to have lower plasma homocyst(e)ine concentrations,[23] though this association may merely reflect higher dietary intake of folate and other B-vitamins.

Deficient intake of certain B-vitamins is probably the commonest cause of moderate hyperhomocyst(e)-inaemia.[26,28] Folic acid and vitamin B_{12} are required for remethylation of homocysteine, and even subclinical deficiency of these vitamins can increase plasma

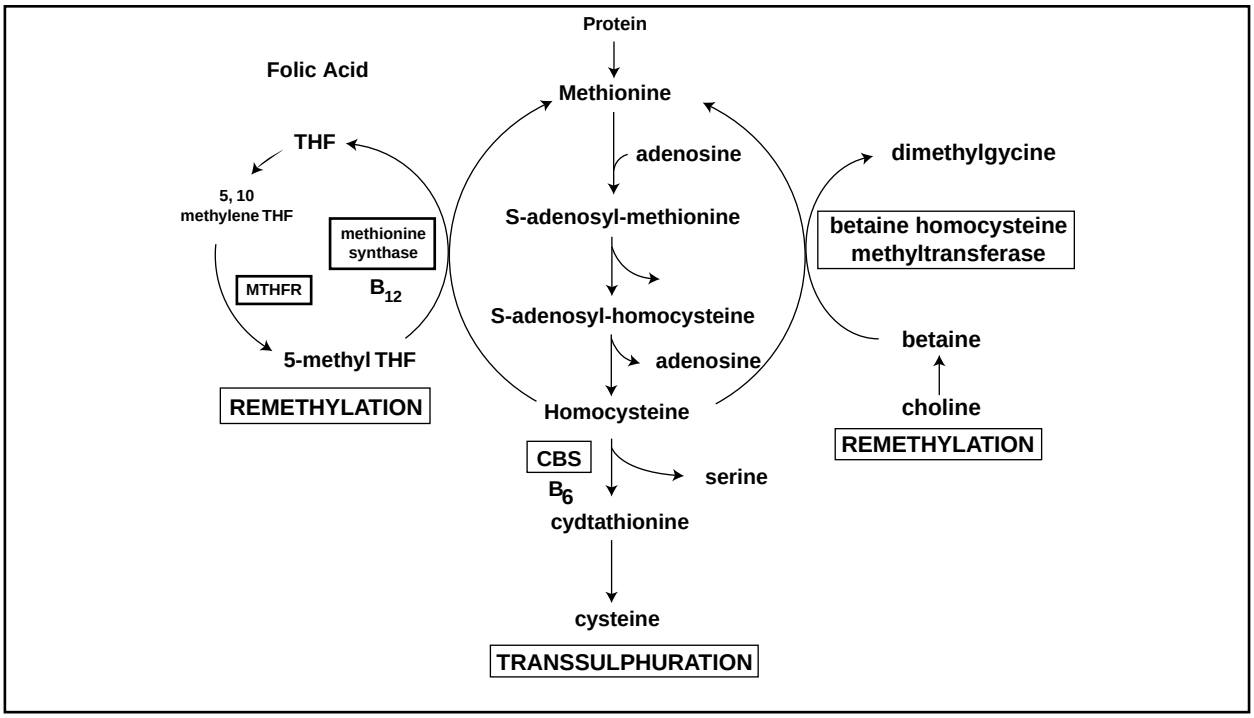

FIGURE 1

Metabolism of homocysteine. Homocysteine is formed following the use of methionine as a methyl-group donor. Homocysteine is disposed of through remethylation to methionine (using methionine synthase or betaine homocysteine methyltransferase) or by transsulphuration to cystathionine (using cystathionine ß-synthase; CBS). Methionine synthase requires the folic acid derivative 5-methyl tetrahydrofolate (THF) as a substrate. The rate-sensitive enzyme in the formation of 5-methyl THF is 5,10-methyltenetrahydrofolate reductase (MTHFR). Methionine synthase requires vitamin B_{12} as a cofactor; CBS requires vitamin B_6 as a cofactor.

homocyst(e)ine.[28] Vitamin B_6 is necessary for transsulphuration of homocysteine by CBS and its deficiency also causes moderate hyperhomocyst(e)inaemia particularly in high methionine states.[1, 28] The elderly are particularly susceptible to the development of subclinical vitamin deficiencies and 30-35% of elderly subjects have moderate hyperhomocyst(e)inaemia.[28,29]

Raised circulating homocyst(e)ine levels are observed in a number of systemic disorders (Table 1). Renal impairment is an important cause of hyperhomocyst(e)-inemia, with plasma homocyst(e)ine concentrations elevated two- to three-fold to 40-50 μM. Plasma homocyst(e)ine is increased by a number of drugs including anticonvulsants and nicotinic acid (Table 1).

HOMOCYSTEINE AND ATHEROSCLEROSIS

Ischaemic heart disease

Moderate hyperhomocyst(e)inaemia is associated with ischaemic heart disease (IHD) in both men and women in cross-sectional studies.[30,33] A meta-analysis of such studies performed up to 1995 suggested that a 5 μM increment in plasma homocyst(e)ine is associated with a 60% higher prevalence of IHD, similar to the effect of a 20 mg/dl increment in cholesterol.[30] In a more recent large-scale cross-sectional study, the relative risk of IHD was 2.0 for both fasting (>12 μM) and post-methionine hyperhomocyst(e)inemia (>38 μM; top quintile), after correction for conventional risk factors.[31] Hyperhomocyst(e)inemia is associated with more severe and more diffuse coronary atherosclerosis.[34] A few cross-sectional studies have not demonstrated an association between homocysteine and IHD, though this may be because of differential survival bias.[35]

Importantly, the findings in cross-sectional studies have been confirmed in at least seven prospective studies, including the US Physicians Health Study, in which homocyst(e)ine concentrations above 16 μM predicted a 3.4-fold increased incidence of myocardial infarction.[7] In the relatively short-term Rotterdam Study, IHD risk was increased 2.4-fold among subjects with homocyst(e)ine concentrations in the upper quintile.[36] In the recent British United Provident Association (BUPA) prospective study, the risk of IHD among men in the highest quartile of serum homocyst(e)ine was 2.9 times the risk among men in the lowest quartile.[37] A Dutch prospective study demonstrated that elevated homocyst(e)ine levels were strongly associated with prevalence of IHD and risk of dying of IHD, but not with an increased risk of first ever myocardial infarction.[38] In the Scottish Heart Health Study, plasma total homocyst(e)ine levels were independently predictive of the incidence of coronary heart disease in Scottish women and men.[39] The US Nurses Health Study showed an association between plasma total homocyst(e)ine concentrations and incident of total cardiovascular disease among middle-aged US women.[40] Plasma homocyst(e)ine levels were the strongest predictor of mortality in a prospective study of patients with angiographically confirmed coronary artery disease and previous myocardial infarction, with the risk of death increased 4.5-fold for homocyst(e)ine >20 μM as compared to <9 μM.[41] Homocyst(e)ine was more closely associated with complications of atherosclerosis than with angiographic extent of atherosclerosis, whereas the opposite held for cholesterol.[41] Prospective follow-up of the European

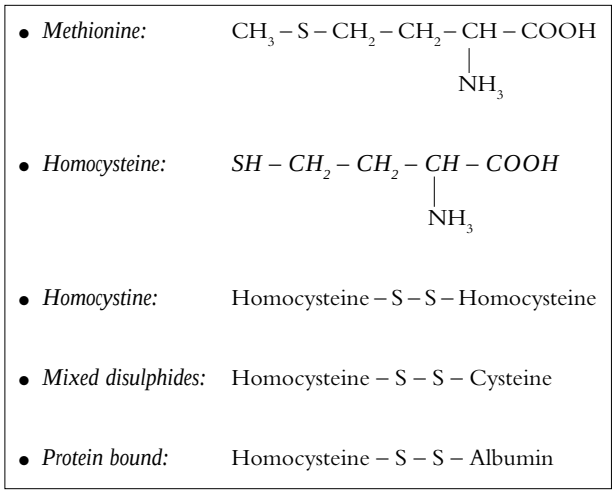

FIGURE 2
Chemical forms of methionine and homocysteine found in plasma.

Concerted Action Project on vascular disease and homocysteine indicates that post-methionine hyperhomocyst(e)inaemia is an independent predictive factor for cardiovascular death.[42] In the Bogalusa Heart Study, children with a positive family history of coronary heart disease had significantly higher age-adjusted plasma homocyst(e)ine levels.[43]

However, at least three prospective studies have not demonstrated that homocysteine is an independent predictor of IHD.[19,44,45] In the ARIC study, plasma homocyst(e)ine was predictive of IHD in women but not men; however, this association disappeared when B-vitamins were included in the analysis.[19] Indeed, the only association with IHD that remained was a negative one for vitamin B_6 levels.[19] These and other studies emphasise that it is still possible that homocysteine is acting merely as a marker for an as yet unknown risk factor for IHD, such as B-vitamin deficiency.[19,27,46]

Other manifestations of atherosclerosis

Several cross-sectional case-control studies have shown an increased risk of cerebrovascular disease with elevated fasting or post-methionine homocyst(e)ine concentrations.[30,31] Recent prospective studies have confirmed the association found in the cross-sectional studies.[38,47] In the Rotterdam Study, follow-up has shown an odds ratio of 2.5 of developing stroke with homocyst(e)ine levels in the top quintile.[36] Furthermore, a positive association has been found between plasma homocyst(e)ine and extracranial carotid arterial atherosclerosis.[48]

Cross-sectional studies have also shown an association between elevated homocyst(e)ine and peripheral arterial disease, with relative risks of 1.7 for fasting and 1.2 for post-methionine hyperhomocyst(e)inaemia.[31,49-51] However, some prospective studies have not been able to demonstrate a significant association between homocyst(e)ine levels and peripheral arterial disease.[52,53] This may reflect bias by the exclusion of subjects with elevated homocyst(e)ine who die prematurely. One recent study has shown that progression of symptomatic peripheral arterial disease and mortality from cardiovascular disease is more frequent in patients with elevated plasma homocyst(e)ine levels.[54]

TABLE 1

Genetic

- Cystathionine β-synthase deficiency
- $C_{677}T$ mutation of MTHFR
- Methionine synthase deficiency
- Methylenetetrahydrofolate homocyst(e)ine methyltransferase deficiency
- Male gender

Environmental

Physiological
- Age
- Menopause

Lifestyle factors
- Tobacco
- Coffee

Vitamin deficiencies
- Folic acid deficiency
- Cobalamin (vitamin B_{12}) deficiency
- Pyridoxine (vitamin B_6) deficiency

Systemic disorders
- Hepatic impairment
- Renal impairment
- Systemic lupus erythematosus
- Psoriasis
- Anorexia nervosa
- Hypothyroidism
- Malignancies: carcinoma breast, ovary, pancreas, acute lymphoblastic leukemia
- Solid organ transplantation

Drugs
- Methotrexate, phenytoin, azathioprine, theophylline, metformin, thiazide diuretics, colestipol, nicotinic acid, oral contraceptives

Venous thromboembolism

Hyperhomocyst(e)inaemia is also a risk factor for venous thromboembolism. One meta-analysis demonstrated a significantly increased risk of developing venous thrombosis with an odds ratio of 2.2 which increased to 4.4 when subjects aged more than 60 years were excluded.[55] Another meta-analysis of data from case-control studies gave a pooled odds ratio of 2.5 for venous thrombosis by hyperhomocyst(e)inaemia.[56] Homocysteine may also interact synergistically with other risk factors to cause venous and arterial thromboembolism. In a prospective study of patients with SLE, hyperhomocyst(e)inaemia (>14 μM) was associated with a 2.4 and 3.5 increased risk of venous and arterial thromboses, with more than 25% of strokes in this population caused by this modifiable risk factor.[57] Risk of thrombosis in children with homocystinuria is strongly dependent on the presence of the factor V Leiden mutation.[58] In the general population, the risk of idiopathic venous thromboembolism among individuals with both the factor V Leiden mutation and hyperhomocyst(e)inaemia is far greater (RR = 22) than the sum of the individual risks for homocysteine (RR = 3.4) or factor V Leiden (RR = 3.6).[59]

Chronic renal failure

Patients with end-stage renal disease are at high risk of cardiovascular events and frequently have quite marked hyperhomocyst(e)inaemia (20-50 μM). Cross-sectional studies have suggested an association between homocyst(e)ine concentrations and cardiovascular events in such patients. These findings are further strengthened by data from recent prospective studies. Patients with end-stage renal disease and plasma total homocyst(e)ine levels in the upper quartile (>27 μM) have a ~four-fold increased risk of nonfatal and fatal cardiovascular events as compared to the lower three quartiles.[60] Another prospective study demonstrated that ESRD patients with homocyst(e)ine concentrations in the top quartile (>34 μM) had a four-fold higher risk of dying (absolute risk: 18% over 18 months) than the remaining three quartiles (4%).[61]

PATHOPHYSIOLOGICAL MECHANISMS

The adverse cardiovascular effects of homocysteine appear to occur through induction of three interlinked pathological processes: thrombosis, atherosclerosis and high blood pressure.

Thrombosis

Homocysteine increases production and activation of procoagulant factors and inactivation of anticoagulant substances. *In vitro*, high concentrations (300 μM) of homocysteine induce endothelial cell tissue factor expression and activity, which may initiate coagulation.[62] Homocysteine also indirectly activates the procoagulant endothelial cell factor V,[63] and inactivates the anticoagulant substances, protein C and thrombomodulin, aiding formation of thrombin.[64] Homocysteine stimulates platelet generation of thromboxane A_2, which is a vasoconstrictor and pro-aggregant.[65] Physiologic concentrations of homocysteine (8 μM) promote binding of lipoprotein(a) to fibrin, thereby preventing plasminogen activation and fibrinolysis.[66] Homocysteine increases platelet and monocyte adhesion to endothelial cells *in vitro*.[67] Recent data shows that homocyst(e)ine also directly blocks the tissue plasminogen activator binding domain of annexin II, which would be expected to inhibit thrombolysis and thereby promote thrombosis.[68] In rat models, hyperhomocyst(e)inaemia induced by methionine supplementation or folate depletion enhances platelet aggregation, thromboxane biosynthesis, and macrophage-derived tissue factor activity.[69,70]

Atherosclerosis

Endothelial cytotoxicity. Infusion of high doses of homocysteine causes endothelial cytotoxicity in animals.[71] Endothelial cells with deficient CBS activity are more sensitive than normal cells to damage by exposure to high concentrations of methionine (10 mM).[72] Homocysteine can inhibit DNA synthesis in vascular endothelial cells and arrest their growth at the G1 phase of the cell cycle.[73] Hyperhomocyst(e)inaemia induced by methionine loading in rats increases neutrophil adhesion to endothelial cells.[74] This results in neutrophil migration across the endothelium, with concurrent damage and detachment of endothelial cells.

Endothelial mediators. High concentrations of homocysteine (5 mM) impair generation of nitric oxide by cultured endothelial cell.[75] Although endothelium-derived nitric oxide appears to modulate the deleterious effects of homocysteine by formation of a vasodilatory, anti-aggregatory S-nitrosothiol adduct, homocysteine-induced endothelial damage ultimately prevents formation of sufficient nitric oxide to protect endothelial cells.[75] Lentz and colleagues used a diet enriched in methionine and depleted in folate to induce moderate hyperhomocyst(e)inaemia (10 μM) in non-human primates.[76] In animals receiving this diet for four weeks, without evidence of atherosclerosis, there was clear impairment of endothelium-dependent vasodilatation both *in vitro* and *in vivo*. Interestingly, monkeys rendered atherosclerotic through diet-induced hypercholesterolaemia exhibit hyperhomocyst(e)inaemia that can be reversed by B-vitamin supplementation.[77] However, normalisation of homocyst(e)ine concentrations does not improve endothelial dysfunction in this model, implying that hypercholesterolaemia or atherosclerosis may modify the effects of homocysteine.[77]

In humans, flow-mediated dilatation of the brachial artery (a marker of conduit vessel endothelial function) is significantly impaired in patients with homocystinuria,[78] and in elderly subjects with moderate hyperhomocyst(e)-inaemia.[79] One preliminary report suggests that reduction of plasma homocyst(e)ine using B-vitamin supplementation normalises brachial artery flow-mediated dilatation.[80] Recent studies have delineated the relationship between homocysteine and endothelial dysfunction by using methionine administration to experimentally induce moderate hyperhomocyst(e)inaemia. Oral methionine load increases plasma homocyst(e)ine by four-fold to ~25 μM in young subjects and impairs flow-mediated endothelium-dependent vasodilatation of conduit arteries.[81-83] The time course of the impairment of flow-mediated vasodilatation mirrors the time course of increase in plasma homocyst(e)ine concentrations, suggesting that endothelial dysfunction is not caused by changes in plasma methionine. Methionine loading also impairs endothelial function in human forearm resistance vessels.[81] Endothelial dysfunction produced by methionine loading can be reversed by high dose folate and vitamin C, suggesting a pathophysiologic role for increased oxidant stress.[81,84]

Oxidant effects. Homocysteine can undergo auto-oxidation, forming hydrogen peroxide in the presence of copper or ceruloplasmin.[85] Hydrogen peroxide generated from homocysteine can lyse cultured endothelial cells, and this process is prevented by catalase.[85] Homocysteine also oxidises low-density lipoprotein,[86] and may therefore promote cellular uptake of modified LDL, an important step in the atherosclerotic process. Homocysteine also generates superoxide radicals, which inhibit NO-related cerebrovascular responses and endothelial-dependent relaxation of blood vessels, perhaps by peroxynitrite formation.[87,88] In addition to increased generation of peroxide and superoxide radicals, homocysteine has recently been shown to inhibit intracellular antioxidant enzymes, including glutathione peroxidase, thus decreasing the cell's ability to neutralise oxidant radicals.[89,90] Intracellular glutathione, which is an endogenous anti-oxidant, is significantly decreased by homocysteine.[91]

Vascular growth. Homocysteine stimulates the growth

promoting MAP kinase signal transduction pathway in vascular smooth muscle cells (VSMC), and enhances VSMC DNA synthesis, and cell proliferation and collagen expression.[92-94] Homocysteine also increases the mitogenic response of VSMC to platelet-derived growth factor four-fold, possibly by disturbing the activity of antioxidant enzymes.[95] In addition, homocysteine induces c-fos and c-myb, and increases DNA synthesis and cell proliferation 12-fold in neural crest-derived VSMC.[96] Furthermore, homocysteine stimulates aortic cyclin dependent kinase, which may contribute to VSMC growth.[97,98] Finally, homocysteine causes deterioration of the elastic structure of the arterial wall, probably through changes in metalloprotease activity.[99] These *in vitro* data are confirmed by *in vivo* studies. In rat carotid endarterectomy models, experimental elevation of plasma homocyst(e)ine increased intimal hyperplasia four-fold.[100] In humans, patients with homocystinuria have marked carotid artery wall hypertrophy.[101]

Hypertension. Homocysteine may also cause atherothrombotic events by increasing systemic blood pressure. In minipigs, experimental hyperhomocyst(e)inaemia due to chronic methionine administration increases systolic and diastolic arterial pressure.[102] This is accompanied by vascular wall thickening, disruption of the elastic component of the vessel wall and endothelial cell hypertrophy and disruption.[102] A recent analysis of the Systolic Hypertension in the Elderly Program Trial demonstrated a significant association between plasma homocyst(e)ine levels and isolated systolic hypertension.[103] In a separate study, patients with elevated homocyst(e)ine levels had significantly higher diastolic and mean arterial pressure than normohomocyst(e)inemic subjects.[104] It is possible that resistance vessel endothelial dysfunction contributes to the hypertensive effects of homocysteine.[81]

SCREENING AND TREATMENT

1. Should hyperhomocyst(e)inaemia be treated?

The balance of epidemiological evidence strongly supports a role for homocysteine in the pathogenesis of atherosclerosis and hypertension.[7,30-34,36-43] However, randomised controlled trials testing the effects of reducing homocyst(e)ine levels on cardiovascular endpoints have not yet been completed. One non-controlled study has demonstrated that treatment of hyperhomocyst(e)inaemia reduces progression of atherosclerosis, as assessed by ultrasound.[105] Indeed, most regulatory bodies appear to have accepted the safety of folic acid, which is widely-used antenatally and now added to all flour products in the USA.[106] Precipitation of neurological complications of undiagnosed B_{12} deficiency by folate supplementation can be prevented by administration of orally-absorbed doses of vitamin B_{12}. Given that treatment of hyperhomocyst(e)inaemia using B-vitamins is innocuous and cheap, it seems reasonable to screen and treat hyperhomocyst(e)inaemia in certain high-risk groups of patients.

2. Who should be screened?

Screening for hyperhomocyst(e)inaemia should be considered for patients with: unexplained atherosclerosis (≤1 conventional risk factor); progression of atherosclerosis despite optimal control of conventional risk factors; chronic renal failure or renal transplant; unexplained thrombosis or pulmonary embolism; and systemic lupus erythematosus.

3. How should screening be done?

Screening should include both fasting and post-methionine load homocyst(e)ine levels. Methionine is administered in a dose of 100 mg/kg with blood obtained four hours later. Many large-scale epidemiological studies have used only fasting homocyst(e)ine concentrations and the additional information to be gained from post-methionine homocyst(e)ine concentrations has been unclear. However, several recent studies have suggested that post-methionine hyperhomocyst(e)inaemia is independently associated with a ~two-fold increased risk of atherosclerotic complications.[31,42,107-109] Importantly, the two forms of hyperhomocyst(e)inaemia were not concordant, such that 30-50% of cases would not be detected if only fasting homocyst(e)ine concentrations were measured.

4. What is the threshold homocyst(e)ine concentration for initiation of treatment?

Methionine loading impairs endothelial function at plasma homocyst(e)ine levels greater than 10 μM, with the majority of impairment occurring in the range of 10-20 μM.[81,82] In epidemiological studies, plasma homocyst(e)ine values of 10-20 μM appear to confer a graded increased risk of atherosclerotic vascular disease.[30,41] In the European Concerted Action Project, fasting plasma homocyst(e)ine >12 μM or post-methionine homocyst(e)ine >38 μM (top 20% of population) were each associated with a two-fold increased risk of cardiovascular events.[31] Thus, it would seem appropriate to start treatment if fasting or post-methionine homocyst(e)ine concentrations are elevated to this degree.

5. How should hyperhomocyst(e)inemia be treated?

Treatment depends on the cause of hyperhomocyst(e)-inaemia, fasting and post-methionine load homocyst(e)ine levels, and coexistent medical conditions. Fasting hyperhomocyst(e)inaemia is usually sensitive to folate treatment, which reduces homocyst(e)ine concentrations by about 25%.[110,111] Vitamin B_{12} reduces fasting homocyst(e)ine levels by an additional 7%.[110,111] Vitamin B_6 has no effect on fasting homocyst(e)ine levels,[110] but will decrease post-methionine homocyst(e)ine levels by 20-30%.[112] Thus, if fasting levels are greater than 12 μM and post-methionine levels are less than 38 μM, folate may be started with 400 μg, increasing to 5,000 μg and vitamin B_{12} added in a dose of 1 mg, if homocysteine remains high. If the levels of fasting homocyst(e)ine are less than 12 μM and post-load levels greater than 38 μM, pyridoxine (vitamin B_6) 250 μg is indicated. With fasting levels greater than 12 μM and post-methionine levels greater than 38 μM, combined treatment with folate, vitamin B_6 and vitamin B_{12} is needed. If homocyst(e)ine concentrations remain high (as in renal insufficiency), treatment with betaine may be useful. Anti-oxidant therapy with vitamin C may help to prevent the adverse vascular effects of homocysteine, even if levels remain above 20 μM.[81] If treatment with folate is being considered, it is essential to either measure vitamin B_{12} levels, or supplement with adequate oral doses of vitamin B_{12}, to prevent neurological complications due to undiagnosed B_{12} deficiency.

Recent studies have shown that fortification of food

with small amounts of folic acid (130-670 μg/day) can decrease plasma homocyst(e)ine levels by 4-11%.[113-115] In 1996, the Food and Drug Administration mandated that all enriched grain products in the USA be fortified with folic acid (140 μg/100 g) with the aim of preventing neural tube defects. This intervention has had a rapid and large effect on population homocyst(e)ine concentrations. Since 1996, plasma folate concentrations have increased by 60-100%, depending on prior vitamin intake, in the Framingham cohort of middle-aged adults.[106] Plasma homocyst(e)ine concentrations have decreased by 7-10%, and the number of hyperhomocyst(e)inaemic subjects (homocyst(e)ine >13 μM) has fallen from 19% to 10%.[106] Thus, this intervention, designed to prevent neural tube defects, may have major cardiovascular benefits.

CONCLUSION

There is increasing observational evidence from epidemiological studies that homocyst(e)ine is an independent risk factor for cardiovascular diseases. Homocysteine may predispose to atherosclerosis and hypertension by producing endothelial dysfunction in both conduit and resistance arteries. The underlying fundamental pathophysiological process appears to be interference with endogenous anti-oxidant mechanisms, though homocysteine may also have direct mitogenic effects on vascular smooth muscle and prothrombotic actions. Randomised controlled trials, aimed at testing the effects of lowering plasma homocyst(e)ine on cardiovascular events in primary and secondary prevention settings, are underway. While waiting for the results of such trials it may be appropriate to screen for and treat hyperhomocyst(e)inaemia in patients at high risk of atherothrombotic events.

- Homocysteine is a sulphhydryl amino acid formed during metabolism of methionine. Plasma homocyst(e)ine levels are increased by rare genetic diseases, B-vitamin deficiency, certain drugs and renal impairment.
- Increasing epidemiological evidence suggests that homocyst(e)ine may act as an independent risk factor for the progression and complications of atherosclerosis.
- Homocyst(e)ine appears to promote atherosclerosis by causing endothelial dysfunction, increasing oxidant stress and promoting vascular smooth muscle growth.
- Recent human studies using methionine loading to experimentally induce moderate hyperhomocyst(e)inemia have demonstrated rapid and profound impairment of both resistance and conduit artery endothelial function.
- There are currently no data available from randomized, controlled trials of the effects of lowering plasma homocyst(e)ine on atherosclerotic vascular events. However, treatment of hyperhomocyst(e)inemia should be considered in individuals with progressive and unexplained atherosclerosis.

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