

Homocysteine and Atherosclerosis

Alev Eroğlu Altınova

İlhan Yetkin

Gazi University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey

Recently hyperhomocysteinemia has emerged as a new risk factor for atherosclerosis. In the present review we summarized metabolism, potential adverse effects of plasma homocysteine and its relationship with the other classical risk factors for cardiovascular diseases.

Key words: Homocysteine, Atherosclerosis, Diabetes Mellitus, Cardiovascular disease risk factor

Introduction

Atherosclerosis is a disease the precise mechanism of which is still being debated. It is the leading cause of mortality in developed countries. Conventional risk factors for atherosclerosis including advancing age, elevated blood pressure, hyperlipidemia, diabetes mellitus and cigarette smoking, do not explain this association completely. Recently, it has been recognized that mild to moderate increases in plasma homocysteine (Hcy) levels were shown to confer an independent risk factor for vascular disease in both clinical and experimental studies (1,2). It has also been suggested that hyperhomocysteinemia (HHcy) contributes to the accelerated atherosclerotic process in diabetes mellitus (3). The mechanisms by which HHcy promotes atherosclerosis are not fully understood. Among the possible causes: induction of cyclin A gene expression in vascular smooth muscle cells; endothelial dysfunction; reduction of protein C levels; inhibition of von Willebrand factor processing and secretion; enhancement of lipid peroxidation; direct endothelial damage caused by Hcy, due to accumulation in endothelial cells; interaction between nitric oxide (NO) and Hcy;

and finally reduction in serum antithrombin activity, with a reduction of thrombomodulin have been revealed (4).

Hcy is a sulphur-containing amino acid that is an intermediary product in methionine metabolism. As shown in Figure 1, Hcy is catabolized in two vitamin B₆ dependent reactions to cysteine. In most tissues Hcy can also be remethylated to methionine, a reaction requiring vitamin B₁₂ as a cofactor and 5-methylenetetrahydrofolate, the circulating form of reduced folate, as methyl donor. High performance liquid chromatography can be used to measure plasma total Hcy concentration, which usually ranges from 5 to 15 µmol/l (5).

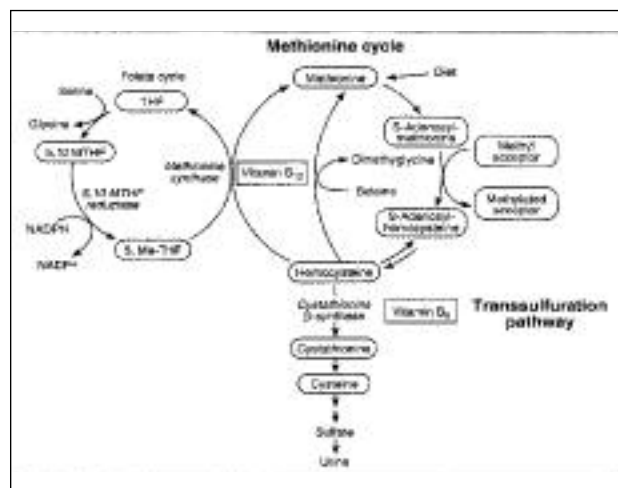


Figure 1. The metabolic pathways for the metabolism of plasma homocysteine. THF, tetrahydrofolate; MTHF, methylenetetrahydrofolate; Me-THF, methyltetrahydrofolate (6).

Correspondence address:

Alev Eroğlu Altınova
Ahmet Rasim Sok. 41/6 Çankaya
06460 Ankara / Turkey
E-mail: alevaltinova@yahoo.com
Telephone: +90 (312) 439 94 60

Plasma Hcy concentrations increase with age, and levels are higher in men than in women. This is determined by both genetic and nutritional factors. Table 1 summarizes the principal causes of HHcy (6).

Table 1. Causes of Hyperhomocysteinemia (6)

1) Inherited causes
a) Transsulfuration abnormalities
Cystathione synthase deficiency
b) Remethylation abnormalities
Defective vitamin B ₁₂ transport
Defective B ₁₂ coenzyme synthesis
Defective methionine synthase
5, 10 methylenetetrahydrofolate reductase deficiency or defects
2) Acquired causes
a) Diseases
Chronic renal failure
Acute lymphoblastic leukemia
Psoriasis
b) Deficiency states
Vitamin B ₁₂ deficiency
Folate deficiency
Vitamin B ₆ deficiency
c) Drugs
Methotrexate (inhibits dihydrofolate reductase)
Nitrous oxide (inactivates methionine synthase)
6-azauridine triacetate (a vitamin B ₆ antagonist)
Anticonvulsants, eg, phenytoin and carbamazepine (folate antagonists)

Endothel and Homocysteine

Although several explanations have been proposed for Hcy mediated vascular disease, there is growing evidence that endothelial dysfunction is an initiating event. Evidence that Hcy has a direct toxic effect on endothelial cells has been derived both from in vitro studies in human cell cultures and from in vivo animal models. Short-term intravenous infusion of Hcy results in desquamation of endothelial cells and has been associated with arterial damage similar to early human atherosclerosis (6).

The redox property of the sulfhydryl group of Hcy, leading to the formation of reactive oxygen species, such as superoxide and hydroxyl radicals, is believed to play a pivotal role (7).

On the other hand, increase in plasma Hcy leading to the transient decrease in plasma cysteine, which is a substrate for NO production, may decrease the availability of endothelium-derived relaxing factor and the function of S-nitrosocysteine, a more potent vasodilator than endothelium-derived relaxing

factor (8). In addition Hcy may directly impair the NO pathway reducing NO elaboration by endothelial cells and increase oxidative degradation of NO (9).

Coagulation System and Homocysteine

HHcy causes thrombotic tendency. Elevation of thromboxane A₂ formation (which may reflect platelet activation), reduction of antithrombin III activity (50% to 75% of normal) and activation of factor V, reduction of factor VII have been shown as the causes of increased coagulability in HHcy (6).

Lipids and Homocysteine

Available data suggest that elevated plasma Hcy concentrations lead to oxidation of LDL-cholesterol, potentially causing atherosclerosis. An interaction with lipoprotein (a) which promotes binding with fibrin has also been reported (6).

Hypertension and Homocysteine

It has been suggested that in conditions of reduced NO production, such as in diabetes mellitus, a slight increase in Hcy might scavenge residual endothelial NO and influence arterial regulatory tone. Recently a correlation between systolic blood pressure and plasma Hcy has been demonstrated in a hypertensive geriatric population (4). However, studies which examine the association of hypertension and plasma Hcy levels do not seem adequate to reveal this relation clearly (4,10).

Smoking and Homocysteine

In a study including type 1 diabetic patients, plasma Hcy levels were significantly higher in smoking patients than in control subjects. Additionally, when diabetic patients and control subjects were categorized according to the number of cigarettes smoked per day, the potential effect of cigarette smoking on plasma Hcy levels was found to be clearly dose-dependent (11). Although no straightforward explanation is available, it has been thought that smoking might directly inactivate enzymes of Hcy remethylation, such as methionine synthase. Smoking is also accompanied by changes in plasma thiol redox status, possibly due to a higher formation of reactive oxygen species. Furthermore, reduced intake of nutrients and vitamins and lower levels of plasma folate, vitamin B₁₂ and plasma pyridoxal 5'-phosphate in smokers might be related with HHcy.

Renal Failure and Homocysteine

HHcy is very frequent in renal failure, which suggests that the kidney's function is crucial for Hcy catabolism. Hcy is ultrafiltrated in glomeruli, almost completely absorbed in tubuli, and degraded in kidney tissue by transmethylation and trans-sulphuration in the activated methyl cycle. It has been shown that metabolism in kidney tissue accounts for a major fraction of total renal clearance of plasma Hcy and the loss of capacity for Hcy degradation might explain the increase in plasma Hcy seen in end-stage renal disease (12).

Diabetes Mellitus, Vascular Complications and Homocysteine

The possible role of mild HHcy in diabetes is not clear. HHcy may accelerate vascular damage related to diabetes. Some studies re-searching the relationship between plasma Hcy and diabetes have shown that type 2 diabetic patients have a higher prevalence of HHcy than control subjects (13,14). There is also debate concerning the association of HHcy and vascular complications in diabetes. There are still controversial studies with respect to the association between plasma Hcy and macrovascular complications (15,16) or microvascular complications (17-19).

Hoogeveen et al. found that diabetic patients with HHcy had an increased risk for developing cardiovascular disease compared with those with normohomocysteinemia (16). Moreover the Hoorn study, a prospective study, indicated that HHcy was related to 5-year mortality independent of other major risk factors and appeared to be a stronger (1.9-fold) risk factor for mortality in type 2 diabetic patients than in nondiabetic subjects. For each 5 µmol/l increase in Hcy, the risk of 5-year mortality rose by 17% in the nondiabetic and by 60% in the diabetic subjects (20).

In our study, not published yet, plasma Hcy levels in 116 patients with a diagnosis of type 2 diabetes and 31 non-diabetic control subjects were studied. We found that elevated plasma homocysteine levels were strongly associated with nephropathy and coronary artery disease in patients with type 2 diabetes mellitus (21).

Treatment of Hyperhomocysteinemia

Since HHcy is recognized as a risk factor for vascular disease, detecting HHcy in patients at high

risk of cardiovascular disease may be of clinical importance. Many studies have shown that there has been an inverse correlation between HHcy and vitamin B₁₂ (15,22) and folic acid levels (4,23,24) which is stronger for folic acid than vitamin B₁₂. One etiology of mild HHcy is insufficient intake of vitamins B₆, B₁₂ and folic acid, therefore an effective treatment of deficiency of these vitamins may be beneficial. The HHcy may be readily reversed by folic acid either alone, or in combination with vitamins B₁₂ and B₆ (3,25). Recently, folic acid supplementation to bread has been started in some countries. It has been suggested that if enhancing oxidative stress is an effect of HHcy on the endothelial cells, dietary antioxidants such as vitamin E may also help reduce the risk of vascular disease associated with Hcy (26). But further studies are needed to test the effect of such treatments on the primary and secondary prevention of cardiovascular diseases.

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