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IS HYPERHOMOCYSTEINEMIA APPROACHING TRADITIONAL RISK FACTORS FOR CARDIOVASCULAR DISEASES?

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SUMMARY – Hyperhomocysteinemia is an independent risk factor for cardiac, cerebral and peripheral vascular disease as well as for venous thromboembolic disease. Its clinical relevance appears to approach the known, traditional risk factors such as hypercholesterolemia, diabetes mellitus, hypertension, and cigarette smoking. The benefit of homocysteine concentration reduction has been demonstrated in cardiovascular disease. The recommended drug dosage varies among clinical studies, depending on the etiology of hyperhomocysteinemia and on homocysteine and folic acid concentrations in patient serum; however, there is general consensus that folic acid and vitamin B_{12} are first line treatment. In addition, measurement of homocysteine concentration is advised in patient groups at risk, with an increased daily dietary vitamin intake in these patients.

Key words: *Hyperhomocysteinemia – complications; Hyperhomocysteinemia – physiopathology; Cardiovascular diseases – physiopathology; Cardiovascular diseases – complications*

Introduction

Cardiovascular disease remains the leading cause of death in the USA, Europe and most part of Asia[1]. Many pathophysiologic studies in humans and animals confirm the concept of endothelial response to injury in the form of endothelial dysfunction as the initial step in the atherosclerotic cascade of events. The possible cause implicated in endothelial dysfunction leads to atherosclerosis, including elevated and modified low-density lipoprotein (LDL), free oxygen radicals, hypertension, diabetes mellitus, genetic alterations, infection with microorganisms such as herpes viruses and *Chlamydia* pneumonia, elevated plasma homocysteine concentration, and combinations of these factors[2].

Homocysteine (Hcy) is an amino acid produced on methionine metabolism along the trans-sulfuration pathway. Mild to moderate increase in plasma Hcy concentration is found in 5% to 7% of the general population. Hyperhomocysteinemia is an independent risk factor for atherosclerotic vascular disease[3-6] and recurrent venous thromboembolism[7].

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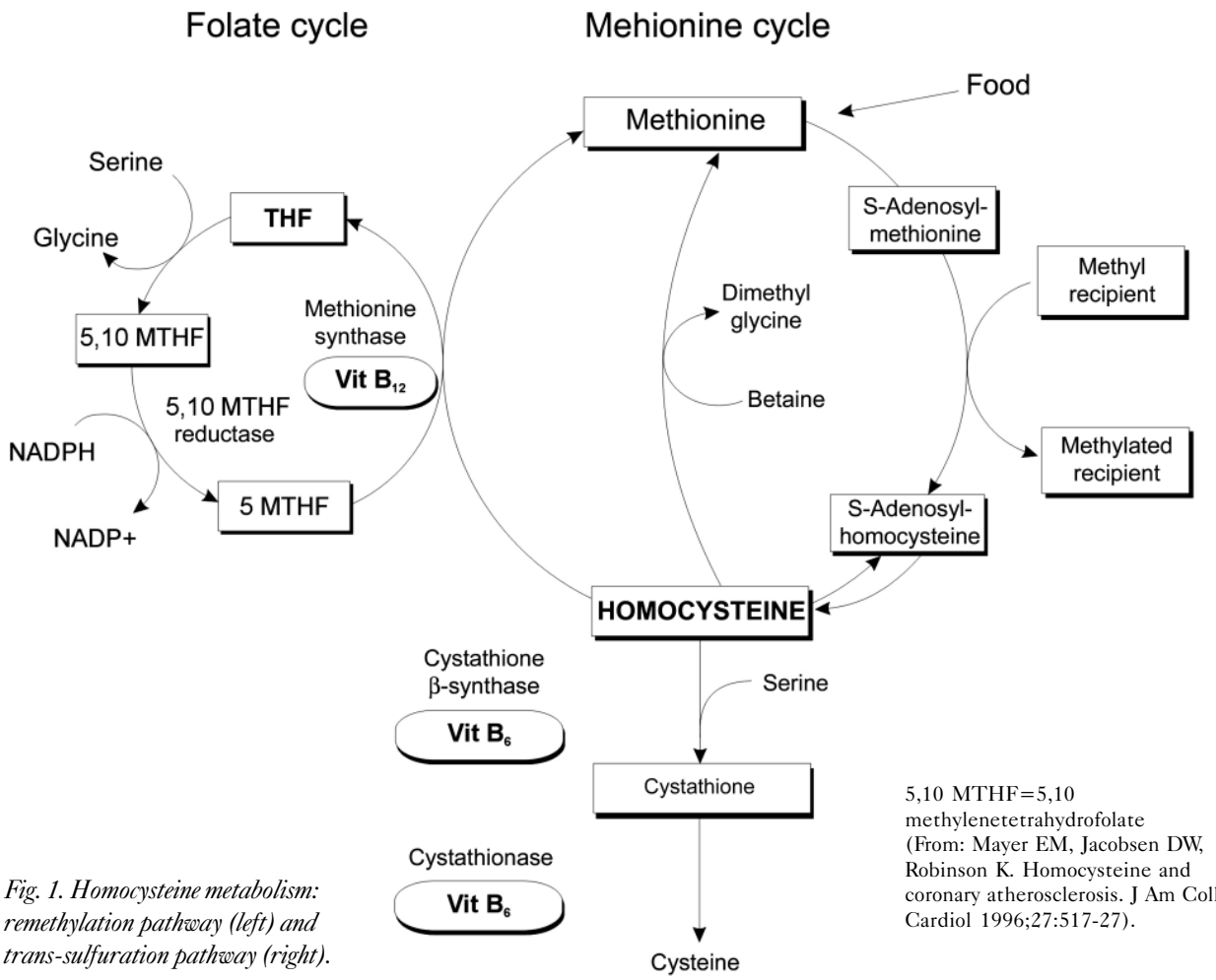
The Etiology of Hyperhomocysteinemia

Hcy is produced during the course of methionine metabolism (Fig. 1)[8]. Methionine is converted into S-adenosyl methionine, a reaction catalyzed by methionine adenosyltransferase. Then it is converted to S-adenosyl homocysteine that is metabolized into homocysteine, which then undergoes remethylation or transsulfuration. In the presence of an adequate amount of methionine, some 50% of homocysteine enter the transsulfuration pathway, which is regulated by cystathione β synthase (CBS), which requires vitamn B_6 as a cofactor (pyridoxal phosphate). Cystathione is converted to cysteine by the enzyme cystathionase, which also requires vitamin B_6. In case of the need of methionine, homocysteine is converted to methionine by remethylation. This process requires 5-methyltetrahydrofolate-



5,10 MTHF=5,10 methylenetetrahydrofolate (From: Mayer EM, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. J Am Coll Cardiol 1996;27:517-27).

Fig. 1. Homocysteine metabolism: remethylation pathway (left) and trans-sulfuration pathway (right).

homocysteine methyltransferase (methionine synthase) and 5,10-methylenetetrahydrofolate reductase (MTHFR). These reactions require adequate amounts of folic acid and vitamin B_{12}.

Methionine can also be formed from the addition of homocysteine remethylation by the reaction catalyzed by betaine-homocysteine methyltransferase. S-adenosyl methionine is a metabolic regulator of homocysteine flow between the trans-sulfuration and remethylation pathways. An elevated concentration of S-adenosyl methionine leads to methionine increase, inhibits MTHFR, and stimulates trans-sulfuration.

The factors influencing plasma concentration of Hcy include genetic abnormalities and vitamin deficiencies.

Genetic abnormalities

The thermolabile variant of MTHFR is a major determinant of the most common genetic form of mild to moderate hyperhomocysteinemia, resulting from alanine substitution for valine (C to T) in amino acid 677 (C677T). The prevalence of MTHFR in the general population is 5%-14%. Homozygosity for thermolabile MTHFR (TT genotype) is frequently associated with a decreased serum concentration of folic acid[9].

The lack of β-synthase is another genetic abnormality that may underlie severe hyperhomocysteinemia.

Vitamin deficiencies

Hyperhomocysteinemia can be caused by folate, vitamin B_{12} and vitamin B_6 deficiencies[10,11]. Strong causal relationship has been demonstrated between the concentrations of folate and vitamin $B_{12,}$ and the concentration of Hcy. A stable Hcy concentration is reflected in normal values if daily folate intake exceeds 400 mg[12]. The role of vitamin deficiency in the pathogenesis of hyperhomocysteinemia was assessed in 1041 elderly

patients[13]. Two-thirds of patients with increased Hcy concentration had the concentrations of folate, vitamin B_{12} and pyridoxal-5-phosphate (vitamin B_6 coenzyme) below the normal limits. In the Food and Drug Administration report, the intake of cereals fortified with folic acid resulted in higher plasma folate concentration and lower Hcy concentration in comparison with subjects on a different diet[14].

A number of factors influencing the level of Hcy have already been identified. Fasting determination of Hcy is preferred because a protein rich meal will increase Hcy level by 15%-20%[15]. The habits such as cigarette smoking[16] and alcohol consumption[17] contribute to the decrease of folate, vitamin B_{12} and vitamin B_6 while supporting hyperhomocysteinemia. Nygard *et al.*[16] report on positive correlation between the number of cigarettes and Hcy level. In this study, heavy smokers had by 12% (male) and 23% (female) higher plasma Hcy than nonsmokers. This could be explained by the fact that cigarette smoking is associated with changes in the thiol redox status, and that smokers have lower plasma concentrations of folate, vitamin B_{12} and vitamin B_6 than nonsmokers[18]. Studies have also pointed to the correlation between Hcy increase and age. The process of aging is associated with a declining bioavailability of essential cofactors, vitamin B_6, vitamin B_{12} and folic acid[19], and lower production of sex hormones. Age differences in the concentration of Hcy could be ascribed to the effect of sex hormones on its metabolism; e.g., Hcy increase in postmenopausal women[19,20]. An increased plasma concentration of 17β-estradiol can result in lower plasma Hcy in premenopausal women[19]. The level of Hcy is lower during pregnancy and estrogen therapy[21]. Plasma Hcy is also increased by some drugs and toxins. Methotrexate inhibits the action of folate, thus causing transient Hcy increase. Phenytoin also interferes with folate metabolism and can cause moderate hyperhomocysteinemia. Theophylline, a phosphodiesterase inhibitor, can cause hyperhomocysteinemia antagonizing pyridoxal phosphate synthesis (vitamin B_6). Therapy with cholestypol and niacin, lipid lowering agents, results in Hcy increase, possibly due to their interference with folate absorption[22]. Pathologic states associated with Hcy elevation are renal failure[23], carcinoma of the lungs, ovary and pancreas, colorectal carcinoma, and acute lymphoblastic leukemia[24,25]. The transformed cells in culture are unable to use Hcy in their metabolism, which is believed to also occur *in vivo*, in case of tumor cells[22].

The Pathophysiology of Hyperhomocysteinemia

Homocysteine is primarily characterized by atherogenic and prothrombotic properties. Hcy favors vascular injury through multiple mechanisms: 1) Hcy stimulates increased monocyte secretion of chemotactic protein 1 and interleukin 8[26]; 2) thiolactone, an Hcy metabolite, can form particles with LDL-cholesterol that are ingested by macrophages. Thus formed foam cells releases lipid into the atherosclerotic plaque; 3) the prothrombotic effect of Hcy, which has been confirmed in patients with acute coronary syndrome[27], includes tissue plasminogen activator weakening, Factor VIIa and Factor V activation, protein C and heparin sulfate inhibition, fibrinopeptide A and prothrombin fragments 1 and 2 increase, endothelial antithrombotic activity reduction, and modification of the thrombomodulin function[28,29]; 4) oxidative stress by free radicals formed during oxidation and reduction of Hcy can cause direct damage to endothelial cells[30]; 5) platelet aggregation may be secondary as a direct proaggregation Hcy effect or due to reduced endothelium mediated platelet inhibition; and 6) prolonged exposure of endothelial cells to Hcy reduces the activity of dimethylarginine dimethylaminohydrolase, which results in a decreased production of nitric oxide. This can contribute to the weakened, endothelium dependent vasodilation[31].

Endothelial dysfunction as the result of injury leads to compensatory response by modifying homeostatic properties of the endothelium, i.e. increased endothelial adhesiveness for leukocytes and platelet, and stimulation of procoagulant and anticoagulant endothelial properties by the formation of vasoactive molecules, cytokines and growth factors. Inflammatory response stimulates migration and proliferation of smooth muscle cells, leading to arterial wall thickening. The arterial compensatory response to the thickening is vasodilation, the phenomenon being known as "remodulation". Granulocytes as inflammatory cells are rarely present in any stage of atherogenesis. The response is mediated by monocyte-macrophages and a T lymphocyte subtype specific for each particular disease. Further macrophage and lymphocyte accumulation at the site of lesion results in the release of hydrolytic enzymes, cytokines, chemokines and growth hormones, which induce additional injury up to the possible focal necrosis of the blood vessel. This is followed by the cycle of mononuclear cell accumulation, smooth muscle cell migration and proliferation, and fibrous tissue formation, which leads to le-

sion reconstruction and fibrous formation with lipid and necrotic tissue in its center. In this stage, compensatory dilation of the artery becomes impossible, and the lesion progresses into the lumen changing the blood flow in the affected vessel, tending to its obstruction[32].

The role of Hcy in endothelial dysfunction is supported by the studies confirming that Hcy concentration is lowered by folic acid supplementation[33].

Clinical Evidence for the Role of Hyperhomocysteinemia in Cardiovascular Disease

Many studies[34-36] have indicated that hyperhomocysteinemia causes: 1) myocardial infarction and other acute coronary syndrome[27,37]; 2) premature coronary disease[38]; 3) increase in total and cardiovascular disease mortality[39]; 4) increased complication rate following angioplasty[40]; 5) carotid artery stenosis[41]; and 6) stroke[42]. Meta-analysis of 30 prospective and retrospective studies that included 5073 patients with ischemic heart disease and 1113 stroke patients[43] revealed strong correlation between Hcy concentration and cardiovascular events. Upon selection according to the known cardiovascular risk factors, an Hcy concentration lower by 25% (~3 mmol/L) was associated with a lower risk of ischemic heart disease (by 11%) and stroke (by 19%) in prospective studies. These results supported the next meta-analysis of 40 studies that included 11162 patients homozygous for the thermolabile form of MTHFR and 12758 cotrol subjects[44]. In patients with MTHFR TT genotype, the prevalence of coronary heart disease was by 16% higher as compared with control subjects. The studies conducted in Europe and North America showed significant differences, i.e. greater association of TT genotype and coronary heart disease in Europe than in America. The difference could be attributed to the different folate status because the studies in North America were performed after 1995 when recommendation on the higher dietary intake of folate and vitamin B had already been issued. A study in 750 patients with documented vascular disease and 800 control subjects found low folate and vitamin B_6 concentrations, and their association with an increased risk of atherosclerosis, irrespective of the traditional risk factors[10]. The risk associated with folate could be explained by the elevated serum Hcy concentration, while the relationship of vitamin B_6 and atherosclerosis does not depend on Hcy concentration. Besides elevated lipoprotein(a) levels and low total antioxidant status, hyperhomocysteinemia is an additional biochemical discriminating factor of serious cerebrovascular stenosis[45].

Percutaneous Transluminal Coronary Angioplasty

Hyperhomocysteinemia is associated with serious complications following percutaneous transluminal coronary angioplasty (PTCA), as demonstrated by a study in 549 patients undergoing PTCA of at least one coronary artery stenosis. The study confirmed the correlation between Hcy concentration and rate of severe postoperative complications such as cardiac death, nonfatal cardiac infarction, or most commonly lesion at the site of revascularization[40].

The exact cause of these events has not yet been fully explained, however, Hcy is known to inhibit the growth of endothelial cells, and was demonstrated to prevent re-endothelialization following balloon injury and to stimulate neointima formation in a rat model of hyperhomocysteinemia. This finding points to the role of Hcy in post-angioplasty restenosis[46]. Folate supplementation lowers Hcy concentration, thus diminishing its restenotic effect.

Laboratory Diagnosis of Hyperhomocysteinemia

Homocysteine is a sulfur-containing amino acid with a sulfhydryl group, which appears to be sensitive to oxidation in physiologic pH. Some 70%-75% of Hcy in blood is bound to protein, mostly albumin, with disulfide bond. The rest of 25%-30% occurs in three forms: dimer homocysteine (homocystine, oxidized form); mixed disulfide, mostly homocysteine-cysteine[47]; and about 2% of free homocysteine in reduced form (rHcy). Of total Hcy, the rHcy molecule is bioactive, its plasma concentration being 0.04-0.25 mmol/L. Some confusion might be provoked by a study reporting on normal rHcy concentration in spite of 2- to 3-fold total Hcy concentration[48]. This may suggest the possible erroneous interpretation according to which the plasma concentration of rHcy remains constant although the concentration of total Hcy and free and mixed homocysteine-disulfide are increased. In this case, the mechanism by which Hcy could mediate vascular pathology would be hard to understand. Therefore, a new method of gas spectrometry has been adopted for its superior sensitivity in comparison with previous methods for detection of rHcy in healthy subjects and patients with end-stage renal fail-

ure. It has shown that an increase in total Hcy concentration above the normal limits is accompanied by a proportional increase in rHcy[49].

The normal concentration of total homocysteine (tHcy) is >10 mmol/L (calculated and age- and sex-adjusted). In adults, the normal level is generally 5-15 mmol/L. Hyperhomocysteinemia is defined as a tHcy level greater than 15 mmol/L: mild 15-30 mmol/L, moderate 30-100 mmol/L, and severe >100 mmol/L[50].

The Treatment of Hyperhomocysteinemia

The treatment of hyperhomocysteinemia includes supplementation of folic acid, vitamin B_{12} and vitamin B_6[51]. Diet rich in fruit, vegetable, and low in fat and saturated acids also reduces Hcy concentration[52]. The effect of vitamin supplementation has been demonstrated in a meta-analysis of 12 studies including 1114 subjects[53]. Folic acid at a dose of 0.5-5 mg/day lowered Hcy concentration by 15%, vitamin B_{12} (0.5 mg/day) contributed to its decrease by another 7%, whereas the addition of pyridoxine had no additional effect on Hcy decrease. A similar effect of therapy with folic acid has also been reported from other studies[54,55]. The effect of folic acid was less pronounced in patients with a lower initial serum concentration of Hcy and higher initial concentration of folic acid[55]. In a study of 75 patients with coronary heart disease, the intake of food fortified with 127 mmol/L folic acid *per* day resulted in folic acid increase by 31% and Hcy decrease by 3.7%. Food enriched with 499 and 665 mmol/L folic acid *per* day increased the concentration of folic acid by 65% and 106%, and decreased the concentration of Hcy by 11% and 14%, respectively[54]. In another study including 723 patients with coronary heart disease, patients were administered 2 mg or 0.2 mg folic acid daily, or placebo. The decrease in serum concentration of Hcy was significantly greater at the higher dosage of folic acid (16% *vs* 11%)[55].

The treatment of patients with hyperhomocysteinemia and early atherosclerotic disease of coronary vessels by the administration of folic acid (1 mg/day), vitamin B_{12} (0.4 mg/day) and vitamin B_6 (10 mg/day) has shown that the dose of folic acid should be increased to 5 mg/day for efficient decrease of Hcy concentration. In patients with Hcy concentration >30 mmol/L or chronic renal failure, the initial dose of folic acid was 5 mg/day, resulting in normalization of Hcy concentration in two weeks, with additional decrease over the next six weeks[56]. The effect of dosage and duration of therapy was demonstrated by a study that included 37 healthy subjects with hyperhomocysteinemia administered folic acid at a dose of 0.2 mg/day. In all study subjects, a decrease of Hcy concentration was recorded in seven weeks. In 21 patients, the concentration of Hcy fell to normal values after 7 months of therapy. In the rest of patients, a folic acid dose >5 mg/day was needed for normalization of Hcy values[57].

Recommendations

There is no doubt that a decrease in Hcy concentration reduces the risk of the development of cardiovascular disease and venous thromboembolism. Therefore, it is advised to measure Hcy concentration in patients with other traditional risk factors, venous thrombosis of unknown etiology, or early development of atherosclerotic disease. The American Heart Association Science Advisory also recommend additional testing of Hcy concentration in patients with: malnutrition and malabsorption; hypothyroidism; renal failure; and systemic lupus erythematosus. Patients taking drugs such as nicotinic acid, theophylline, methotrexate and E-dopa should take food rich in vitamins or daily vitamin supplementation[58].

Conclusion

Hyperhomocysteinemia is an independent risk factor for vascular diseases of the heart, brain and periphery as well as for venous thromboembolic disease. Its clinical relevance appears to approach the known, traditional risk factors such as hypercholesterolemia, diabetes mellitus, hypertension, and cigarette smoking. The beneficial effect of Hcy concentration decrease in cardiovascular disease has been demonstrated. Although the conclusions of clinical trials on the recommended dose of the drug differ depending on the etiology of hyperhomocysteinemia, and the concentration of Hcy and folic acid in patient serum, there is general consensus that folic acid and vitamin B_{12} are the first-line therapy, with recommendation for Hcy measurement and supplemental dietary intake of vitamins in patient groups at risk.

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Sažetak

PRIBLIŽAVA LI SE HIPERHOMOCISTEINEMIJA TRADICIONALNIM ČIMBENICIMA RIZIKA ZA SRČANOŽILNE BOLESTI?

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Hiperhomocisteinemija je neovisan čimbenik rizika za bolesti krvnih žila srca, mozga, periferije i tromboembolijske bolesti vena. Po važnosti se približila dosadašnjim tradicionalnim čimbenicima rizika: hiperkolesterolemiji, šećernoj bolesti, hipertenziji i pušenju. Dokazana je korist sniženja koncentracije homocisteina u srčanožilnim bolestima. Zaključci kliničkih pokusa se razilaze u preporuci o dozi lijeka, ovisno o etiologiji hiperhomocisteinemije te koncentraciji homocisteina i folne kiseline u serumu bolesnika, no svi se slažu da je davanje folne kiseline i vitamina B_{12} osnova liječenja. Uz to se preporuča mjerenje koncentracije homocisteina u rizičnim skupinama bolesnika i savjetuje pojačan dnevni unos vitamina hranom u ovih bolesnika.

Ključne riječi: *Hiperhomocisteinemija – komplikacije; Hiperhomocisteinemija – fiziopatologija; Kardiovaskularne bolesti – fiziopatologija; Kardiovaskularne bolesti – komplikacije*