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Review article

Current Knowledge on the Prevention of Hyperhomocysteinemia as a Risk Factor for Cardiovascular Diseases

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SUMMARY

Introduction. Homocysteine is an amino acid that is formed in the metabolism of methionine as the quantitatively most important metabolite. Its chemical structure has been known for 90 years and its biological roles are still being investigated. Under normal conditions, homocysteine is present in plasma at the concentration of 5 - 9 μmol/l. When the cell capacity for homocysteine is reached, it is transported to the extracellular space, until the intracellular level is normalized. If the cell is unable to reach the required levels of homocysteine, it accumulates in the blood and hyperhomocysteinemia occurs.
Discussion. It has been determined that many factors, such as congenital enzyme deficiency, age, sex, inadequate diet (vitamin B complex deficiency) increase the level of homocysteine in the blood. Impaired kidney function, diabetes, hyperthyroidism, as well as many medications, can have an effect on homecysteinemia. Increased concentration of homocysteine in the blood accelerates the process of atherosclerosis by several different mechanisms and represents an independent risk factor for the occurrence of cardiovascular diseases and adverse cerebral events. The prevalence of hyperhomocysteinemia is estimated at 5% in the general population and 13 - 47% among patients with symptomatic atherosclerotic vascular disease.
Conclusion. For these reasons, the level of homocysteine in the blood should be monitored and corrective measures should be implemented, which include sufficient intake of folic acid, vitamins B12 and B6, in doses that depend on fasting homocysteine levels and after the methionine load test.

Keywords: **homocysteine, prevention, atherosclerosis, chronic noncommunicable diseases**

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INTRODUCTION

Cardiovascular diseases have a great socio-medical significance and their prevention, early detection and treatment are one of the biggest current challenges for health care professionals and society. Nowdays cardiovascular diseases are responsible for approximately one-third of all-cause mortality worldwide. The etiology of these diseases is multifactorial with a number of variable risk factors, so that many scientific studies have been focused on them and their prevention (1 - 4).

Diet is associated with the incidence of ischemic heart disease and its role is considered as functional in the prevention or health promotion (5, 6). A detailed analysis of the current evidence shows that the relationship between food ingredients and cardiovascular health is much more complex than the hypothesis that dyslipidemia is an important cause of atherosclerosis (7, 8).

Numerous metabolic risk factors associated with ischemic heart disease, beside diet, have been considered (9).

Homocysteine is a sulfur-containing amino acid, not found in food, but produced in the body during normal methionine and cysteine metabolism. The chemical structure of homocysteine has been known since 1932. Thirty years later, the study was published (10) describing two young people with severe mental retardation and elevated urinary homocysteine levels. A few years later, attention was drawn to the importance of elevated levels of homocysteinemia in the pathogenesis of atherosclerosis (11), which was even better metabolically explained at the end of the last century (12, 13).

The aim of this paper is to present current knowledge regarding the prevention of hyperhomocysteinemia as a risk factor for cardiovascular disease. The understanding of homocysteine metabolism, the factors that lead to hyperhomocysteinemia, as well as the mechanisms through which hyperhomocysteinemia causes cardiovascular disease, enable us to devise the means of the prevention and therapeutic possibilities for its correction.

Homocysteine is an amino acid, but exclusively from the chemistry aspect and it is not found in food proteins. Together with glutathione and cysteine, it is one of the characteristic amino thiol compounds in mammals (14). In the body, homocysteine exists in the free form, or in the form of disulfides and proteins. Free or reduced homocysteine represents 1 - 2% of total homocysteine. About 80% of plasma homocysteine is bound to proteins, mainly albumin (15). B-complex vitamins are cofactors of enzymes involved in homocysteine metabolism.

THE METABOLISM AND PATHOLOGY OF HOMOCYSTEIN

Hyperhomocysteinemia represents an increase in total homocysteine (bound and free) in the body and the definition differs depending on the study (16). When the cell capacity for homocysteine is reached, it is transported to the extracellular space until the level in the cell normalizes. If the cell is unable to keep appropriate levels of homocysteine, as a consequence of any disorder in the intracellular metabolism of homocysteine, transport to the extracellular fluid continues and homocysteine accumulates in the blood, leading to hyperhomocysteinemia (17). Plasma concentrations of homocysteine in healthy subjects range between 5 and 15 μmol/l, and the upper limit of the reference values may differ depending on the analytical method used (15). Moderate hyperhomocysteinemia involves blood homocysteine concentrations between 16 - 30 μmol/l, intermediate hyperhomocysteinemia ranges between 31-100 μmol/l, and values over 100 μmol/l indicate a severe form of hyperhomocysteinemia.

Mild and moderate hyperhomocysteinemia occurs as a result of genetic factors (methylenetetrahydrofolate reductase deficiency), side effects of medicines, lifestyle and chronic diseases (18). Severe forms of homocysteinemia, where homocysteine levels can reach 400 μmol/l, are caused by a mutation in the enzyme cystation beta synthetase, which leads to homocysteinuria (19). However, people with this deficiency represent a very small percentage of the world population (approximately 1 in 200 000), with the clinical symptoms of mental retardation, ectopia lentis, and bone abnormalities, and their premature death is usually the result of thromboembolism (20).

The connection between hyperhomocysteinemia and coronary artery occlusion, cerebrovascular disease, peripheral circulatory disease and venous thrombosis has been demonstrated in many studies, so hyperhomocysteinemia can be considered as the independent risk factor for ischemic heart disease (21). The prevalence of hyperhomocysteinemia is estimated at 5% in the general population, and between 13% and 47% among patients with

symptomatic atherosclerotic vascular disease (22). Possible mechanisms by which hyperhomocysteinemia causes vascular damage include endothelial toxicity, increased smooth muscle cell proliferation, free radical-mediated cell damage, platelet activation, and thrombosis (23).

LIFESTYLE FACTORS AND HOMOCYSTEINE

Physiological factors that affect the level of homocysteine in the body are age, sex and lifestyle. Total homocysteine concentrations in the plasma increase during life by about 1 μmol/l per decade and almost double from childhood to old age, especially in women (24), probably due to decreased renal function and insufficient intake of vitamins.

The concentration of total homocysteine in men is about 25% higher than in women, but this difference decreases after menopause (25).

Coffee consumption, insufficient physical activity and alcoholism increase the concentration of total homocysteine in the body, probably due to changes in folate metabolism and vitamin depletion (26). However, moderate alcohol consumption lowers the concentration of total homocysteine in plasma. Regular intake of vegetables and fruits and physical activity are inversely proportional to the level of homocysteine in the blood, and therefore prevent adverse effects on the cardiovascular system (27, 28).

Lack of vitamins B (folic acid, vitamin B12, vitamin B6, vitamin B2) is probably the most common cause of moderate hyperhomocysteinemia (29), therefore prevention of these deficits is important for the prevention of adverse health effects. Inadequate diet or malabsorption of these vitamins increases the risk of hyperhomocysteinemia.

The most common nutritional cause of elevated plasma homocysteine levels in the healthy population is folate deficiency (30). Supplementation of folic acid, vitamin B6 and vitamin B12 significantly reduces the level of homocysteine in the blood, but the effects on reducing the development of cardiovascular disease are still not clear enough (31, 32). A meta-analysis (1,114 subjects in twelve randomized trials) showed (33) that folic acid supplementation (0.5 – 5.0 mg/day) reduced total homocysteine levels in the blood approximately by a quarter (95% CI 23, 28, $P < 0.001$).

In addition, folic acid supplementation is more effective than supplementation with other B vitamins and should be recommended to any patient who has hyperhomocysteinemia. Blood homocysteine levels should be measured and treated at an early age, which is likely to reduce the incidence of vascular disease and other pathological processes in high-risk populations (30).

DIETARY HABITS THAT CAN AFFECT THE LEVEL OF HOMOCYSTEINE

There are many foods that are a good natural source of folic acid (33) and one large plate of dark green vegetables can satisfy almost all daily folic acid needs (Table 1).

Folic acid is also found in beans and peas, mostly in colorful ones. A small bowl of any type of lens will give optimal daily amount of folic acid. The amount of folic acid in some fruits is given in Table 2.

Table 1. *Folic acid content in green leafy vegetables (mg/1 cup)*

Vegatable	Amount of folic acid	Daily needs
Spinach	263	65%
Kale	177	44%
Soy	170	42%
Lettuce	76	19%
Broccoli	85	25%
Brussels sprout	85	25%

Table 2. *Folic acid content in fruits (mg)*

Fruit	Amount of folic acid	Daily needs
Papaya (one)	115	29%
Orange (one)	40	10%
Grapefruit (one)	30	8%
Strawberries (1 cup)	25	6.5%
Raspberries (1 cup)	14	4%

Table 3. *Folic acid content in seeds (mg)*

Seed	Amount of folic acid	Daily needs
Sunflower seeds (¼ cup)	82	21%
Peanuts (¼ cup)	88	22%
Almonds (1 cup)	46	12%

Sunflower seeds, flax seeds and peanuts are especially rich in folic acid, and one cup contains about 300 mg of folic acid (Table 3).

Folic acid is also found in some animal foods (egg yolks). The minimal daily intake for folic acid is 50 μg, the recommended daily intake (RDI) for the average adult is 400 μg/day and 600 μg/day during pregnancy. Normal folic acid depots in healthy individuals are only 5 - 20 mg.

In many countries, daily folate intake is increased by supplementation with folic acid, folinic acid or 5-methyltetrahydrofolate or by fortification of foods, primarily to prevent thrombosis (34).

The effect of vitamin B6 on the level of homocysteine in the blood is the least pronounced and only severe and long-term deficiency of vitamin B6 can lead to hyperhomocysteinemia (35). Deficiencies of water-soluble vitamin B6 are rare, because of its presence in many foods (whole grains, legumes, chicken, fish, bananas, egg yolks, nuts, vegetables), as well as in most multivitamin supplements. Deficiencies can occur due to hereditary disorders, poor absorption in the digestive system, malnutrition or due to the use of drugs that reduce vitamin B6 depots.

According to recent research (36), there were no differences between effects of homocysteine-lowering interventions in the form of vitamin B6, B9, or B12 supplements given alone or in combination and placebo on myocardial infarction, death from any cause, or side effects. Regarding stroke, a small difference was found in the effect that favors homocysteine-lowering interventions with vitamin B6, B9 or B12 supplementation given alone or in combination compared to placebo.

Vitamin B6 therapy has no effects on the total fasting homocysteine level, but lowers the total homocysteine concentration after the methionine loading test by 20 - 30%. In severe forms of hyperhomocysteinemia, pyridoxal phosphate intake reduces the level of homocysteinemia, but never to normal values.

Vitamin B12 in the form of methylcobalamin is needed for the successful action of the folate-dependent enzyme, methionine synthase. Methionine synthase plays a role in the synthesis of the amino acid methionine from homocysteine, and this biochemical process takes place in the cytosome of the cell. For this reason, the therapy of hyperhomocysteinemia often includes supplements of both folic acid and cobalamin, and this combination provides sufficient reserves of the cofactor for methionine synthase, thus enabling normal metabolism of tetrahydrofolate and remethylation of homocysteine to methionine.

Vitamin B12 is found in animal source foods exclusively, so vegetarians are at risk of this deficiency (37, 38). In addition, diseases that inhibit the absorption of the food in the intestines (lack of digestive enzymes) can lead to vitamin B12 deficiency. People older than 65 years are also at risk for cobalamin deficiency. Vitamin B12 (in a dose of 0.2 to 1 mg per day, average value 0.5 mg) reduces fasting homocysteine levels by additional 7% with

already given folic acid, which can lower 25% of homocysteine in the blood.

Animal foods are rich in methionine. Meat and fish contain 2.7 g/100 g, eggs 3.2 g/100 g, cow's milk 2.9 g/100 mL, and human milk only 1.4 g/100 mL of methionine. Fruits and vegetables contain 0.9 – 1.2 g methionine/100 g, with the exception of peaches and grapes, which contain 3.6 g/100 g (39).

HYPERHOMOCYSTEINEMIA AND CARDIOVASCULAR DISEASES

Some pathological conditions such as renal failure, diabetes, psoriasis, hyperthyroidism, neurological diseases, etc. may be accompanied by an increase in the total concentration of homocysteine in the body.

A few pharmacologically active compounds also increase the level of homocysteine, such as antifolates, methotrexate, nitrogen oxides, L-DOPA, hormone therapy, antiepileptics, bile acid derivatives, etc. There are also pharmacologically active compounds that lower the level of homocysteine, like adenosine and related compounds, sulfhydryl compounds, etc.

The molecular basis of the association between hyperhomocysteinemia and cardiovascular disease has not been completely clarified, although increased blood homocysteine levels are considered to be the risk factor for atherosclerosis (40). Endothelial dysfunction is an initial event of atherosclerosis and occurs in hyperhomocysteinemia for a number of reasons.

Previous research has demonstrated an association between homocysteine and the lipid profile. Regression analysis conducted in China showed that hyperhomocystinemia was associated with hypertriglyceridemia, hypercholesterolemia, and high LDL-cholesterol (41).

Fasting hyperhomocysteinemia and hyperhomocysteinemia after an oral methionine loading test have a similar risk of cardiovascular disease occurrence by hyperlipidemia or smoking, but less impact towards hypertension (21). In patients with acute coronary syndrome (over 1300 patients were followed) who were followed for many years, higher homocysteine levels were identified in individuals with a higher risk of recurrent myocardial infarction (42). Elevated homocysteine levels were associated with an increased risk of serious adverse cardiovascular events and overall mortality among patients with acute coronary syndrome (43). Studies have also shown a positive correlation between hyperhomocysteinemia and the coronary slow flow phenomenon (CSFP) and cardiovascular adverse events (44). Elevated homocysteine levels also represent the independent risk factor for congestive heart failure in adults without myocardial infarction in the history of the disease: the risk was 1.9 times higher in men and 1.8 times higher in women (45).

Treatment of hyperhomocysteinemia depends on the cause, the presence of another risk factor, fasting homocysteine levels and levels after the methionine loading test (46). Treatment of hyperhomocysteinemia should be approached analytically and nutrient doses of folic acid, 5-methylethrahydrofolate and betaine should be applied gradually or in combination based on clinical and laboratory evaluations.

In addition, betaine can remethylate homocysteine to methionine and a dose of 6 g/day betaine can reduce fasting homocysteine by 1.8 μM (46). Choline, as a precursor of betaine, may act as a second mechanism in reduction of fasting serum homocysteine concentrations and concentrations after methionine loading test (47).

CONCLUSION

Hyperhomocysteinemia is considered toxic to cells and is associated with a variety of health problems such as cardiovascular disease, ischemic stroke, neurological disorders, diabetes, cancer, hypothyroidism, conditions associated with renal dysfunction, and vitiligo. Numerous research have shown that homocysteine acts on the cardiovascular system through various mechanisms, encouraging the development of atherosclerosis and thrombosis, leading to coronary artery occlusion, cerebrovascular diseases, peripheral circulation diseases and venous thrombosis. Therefore, it is necessary to monitor the level of homocysteine in the body and control hyperhomocysteinemia regarding prevention of cardiovascular diseases.

Many factors such as congenital enzyme deficiency, age, sex, diet and others can increase the level of homocysteine in the blood.

Treatment of hyperhomocysteinemia includes folic acid, vitamins B12 and B6, in doses that depend on fasting homocysteine levels and levels after the methionine loading test.

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Značaj prevencije hiperhomocisteinemije kao faktora rizika za kardiovaskularne bolesti

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SAŽETAK

Uvod. Homocistein je amino-kiselina koja predstavlja glavni metabolit metionina. Njegova hemijska struktura poznata je već 90 godina, a biološke uloge se i dalje istražuju. U normalnim uslovima, homocistein se nalazi u plazmi u koncentraciji 5 – 9 μmol/l. Kada se popune ćelijski kapaciteti za homocistein, on se transportuje u ekstracelularni prostor, do normalizacije intracelularnog nivoa. Ukoliko ćelija nije u stanju da obezbedi potrebne nivoe homocisteina, homocistein se nagomilava u krvi i nastaje hiperhomocisteinemija.
Diskusija. Utvrđeno je da mnogi faktori, kao što su urođeni nedostatak enzima, uzrast, pol, neodgovarajuća ishrana (nedostatak posebno vitamina B grupe) povećavaju nivo homocisteina u krvi. Takođe, oslabljena funkcija bubrega, dijabetes, hipertireoza, kao i mnogi lekovi, mogu uticati na homocisteinemiju. Povećana koncentracija homocisteina u krvi ubrzava proces ateroskleroze pomoću nekoliko različitih mehanizama i predstavlja nezavisan faktor rizika za pojavu kardiovaskularnih bolesti i neželjenih cerebralnih događaja. Prevalencija hiperhomocisteinemije procenjena je na 5% u opštoj populaciji i 13 – 47% među pacijentima sa simptomatskom aterosklerotskom vaskularnom bolešću.
Zaključak. Iz navedenih razloga treba pratiti nivo homocisteina u krvi i sprovoditi korektivne mere koje uključuju dovoljan unos folne kiseline, vitamina B12 i B6, u dozama koje zavise od nivoa homocisteina natašte i nakon testa opterećenja metioninom.

Ključne reči: **homocistein, prevencija, ateroskleroza, hronične nezarazne bolesti**