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HYPERHOMOCYSTEINEMIA - RISK AND ITS MANAGEMENT

M .Preeth[2], J. Shobana [1]*, Narmatha Swaminathan[3], B.Prasanthi[1]
[1]Department of Hospital and Clinical Pharmacy, Bharat Institute of Technology-Pharmacy Mangalpally, Ibrahimpatnam, RR Dist, AP, India.
[2]Department of Pharmacology, JKK Muniyaraja Medical Research Foundation – College of Pharmacy, Namakkal Dist, Tamilnadu, India.
[3]Department of Pharmacy Practice, Vivekananda College of Pharmacy, Trichengodu, Salem, Tamilnadu, India.
Email: john.shobana@gmail.com

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ABSTRACT

Homocysteine is a sulfur containing amino acid that is created in the body from Methionine, an essential amino acid derived solely from dietary intake. Methionine is metabolized into Homocysteine via an intermediate, S-adenosyl Methionine. Homocysteine can be metabolized to produce cysteine, a nonessential sulfur-containing amino acid, or it can be remethylated to Methionine. Whether the body needs cysteine or Methionine will dictate which path Homocysteine metabolism will take. Homocysteinemia, or elevated plasma Homocysteine, is a major, independent risk factor of cardiovascular disease. High plasma levels of Homocysteine appear to injure the vasculature, impairing the functional abilities of endothelial and smooth muscle cells. Elevated Homocysteine also appears to be thrombogenic. Suboptimal intake of several B vitamins, renal failure, and genetic defects in Homocysteine metabolism can all contribute to abnormal Homocysteine levels. In the present review we have summarized the Homocysteine and its relationship with other diseases and Management of these complications.

Key words: Homocysteine, Hyperhomocysteinemia, Vitamin B, Methionine

INTRODUCTION

Homocysteine (Hcy) is an intermediate formed during the catabolism of sulfur containing essential amino acid, Methionine.[1,2,3] It is found either as free Homocysteine, cysteine, Homocysteine mixed disulfide or protein bound Homocysteine. The one that is bound with protein in plasma reflects total plasma Homocysteine (tHcy) [4]. Main etiological factors are Transsulfuration abnormalities, Cystathione synthase deficiency, Remethylation abnormalities, Defective vitamin B_{12} transport, Defective B_{12} coenzyme synthesis, Defective Methionine synthase, 5, 10 methylene tetrahydrofolate reductase deficiency or defects. Some diseases are also responsible for Hyperhomocysteinemia e.g. chronic renal failure, acute lymphoblastic leukemia, Psoriasis and vitamin deficiency (Vitamin B_{12} deficiency, Folate deficiency, Vitamin B_6 deficiency), drugs like Methotrexate (inhibits dihydrofolate reductase), Nitrous oxide (inactivates Methionine synthase) 6-azauridine triacetate (a vitamin B6 antagonist), Anticonvulsants, e.g., phenytoin and carbamazepine (folate antagonists) are also involved in increase formation of Homocysteine

Risk factors for Hyperhomocysteinemia

Smoking

Smoking is one of the important etiological factors for HHcy. 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 B_{12} and plasma pyridoxal 5Õ-phosphatein smokers might be related with HHcy.

Various studies that have been done in different part of the world in this aspect, it was noted that the serum tHcy concentrations were significantly increased in smoking as compared with nonsmoking pregnant women ($p < 0.001$). The folate and vitamin B_{12} concentrations were lower in smoking than in nonsmoking pregnant women, but only the differences in folate concentrations were statistically significant ($p < 0.001$). In the light of their

findings, they have proposed that smoking might enhance the vasoconstrictor capacity in pregnant women by increased tHcy concentrations and by a simultaneous decrease in the production of NO which is a vasodilator compound[5].

In another trial, they have been studied that the, plasma Hcy levels were significantly higher in smoking patients than in control subjects. Additionally, they found out that the potential effect of cigarette smoking on plasma Hcy levels was found to be clearly dose dependent. In one of the case control trial, they have been suggested that smokers with high plasma Homocysteine are at greatly increased risk of cardiovascular disease and should therefore be offered intensive advice to help them cease smoking. They also have reduced levels of those B-vitamins (folate, vitamin B_6 and vitamin B_{12}) that modulate Homocysteine metabolism. While this finding may reflect a direct effect of smoking or reduced B-vitamin intake, supplementation of these nutrients may be appropriate in smokers with high Homocysteine levels[6].

Food

Vegetarians who do not supplement their diet with vitamin B_{12} tend to have elevated Homocysteine levels. Elevated Homocysteine is associated with early mortality, heart disease, stroke, dementia, and birth defects. Vegetarians who get 3 to 100 µg of B_{12} per day through fortified foods or supplements will minimize any elevated Homocysteine problems due to a low B_{12} intake. It is clear that most people with slightly elevated (or higher) Homocysteine levels can lower them through taking folate and vitamin B_{12}. In 1998, the British Medical Journal published an analysis of 12 studies and concluded that folic acid in the range of 500-5,000 µg/day reduced Homocysteine by 25%, and that B_{12} supplements (average intake of 500 µg /day) reduced it a further 7%. Vitamin B_6 supplements (average of 16.5 mg/day) did not reduce Homocysteine further. 500 µg B_{12}/day is a lot more than necessary.

In one study reported in the BMJ, only 100 µg B_{12}/day (combined with folate and B_6) was successful in reducing Homocysteine from 7.2 - 5.8 µmol/l. In another, only 20 µg B_{12}/day (combined with folate and B_6)

resulted in reducing Homocysteine from 11.9 - 7.8 µmol/l. Vitamin B_{12} deficiency were significantly higher in vegetarians than those in occasional vegetarians and non- vegetarians. Therefore, maintaining a good vitamin B_{12} status should be emphasized for vegetarian's subjects to avoid elevated Hcy levels. In addition, occasional vegetarians had the lowest prevalence of Hyperhomocysteinemia and lower prevalence of vitamin B_2 or B_{12} insufficiency compared to non- vegetarians.[7]

Alcohol

A number of observational studies have suggested an association between moderate alcohol consumption and tHcy concentrations, and an association between alcohol, folate and chronic disease risk has been observed. However, little randomized trial evidence is available for examining the effect of alcohol on tHcy, and, in particular, it remains to be conclusively determined whether the effect of alcohol on tHcy concentrations depends on the type of alcoholic beverage.

It was observed that the Total Homocysteine (tHcy) is recognized as a CVD risk factor. It is elevated in patients with chronic alcoholism and falls following alcohol withdrawal; therefore, alcohol may have a deleterious effect on health by raising tHcy levels. Homocysteine is regulated through a series of pathways, which are dependent on B vitamins, particularly folate[8].

In another study, it was assessed the effect of an 8-week intervention with vodka or red wine on plasma tHcy and B vitamin concentrations in healthy male volunteers. The intervention resulted in a decrease in folate and vitamin B_{12} status and an increase in plasma tHcy. The effect of alcohol intervention on tHcy, folate and vitamin B_{12} concentrations did not differ between the red wine and vodka intervention groups[9].

Genetic Variation

Some people have elevated Homocysteine levels caused by a deficiency of B vitamins and folate in their diets. High Homocysteine levels are also seen in people with kidney disease, low levels of thyroid hormones, psoriasis, and with certain medications (such as antiepileptic drugs and Methotrexate). It has been recognized that

some people have a common genetic variant (called methylenetetrahydrofolate reductase, abbreviated *MTHFR*) that impairs their ability to process folate. This defective gene leads to elevated levels of Homocysteine in some people who inherit *MTHFR* variants from both parents.

Genetic mutations in *MTHFR* are the most commonly known inherited risk factor for elevated Homocysteine levels. We all have 2 *MTHFR* genes, one inherited from each parent. Some people have a genetic mutation in one or both of their *MTHFR* genes. People with mutations in one *MTHFR* gene are called "heterozygous" for the *MTHFR* mutation; if mutations are present in both genes, the person is said to be "homozygous" for the mutation. The most common *MTHFR* mutation is called the *MTHFR* C677T mutation, or the "thermo labile" *MTHFR* mutation. Another common mutation is called *MTHFR* A1298C. To have any detrimental effect, mutations must be present in both copies of a person's *MTHFR* genes.

Studies have been conducted to investigate whether having 2 *MTHFR* mutations increases the risk of blood clots in the arteries, blood clots in the veins, or CAD. This result suggested that the, so long as the Homocysteine level is normal, *MTHFR* mutations do not significantly increase the risk of heart attack or stroke[10, 11]

Complications of Hyperhomocysteinemia

Endothelial damage

Increased Hcy is associated with endothelial dysfunctions in healthy human. Hyperhomocysteinemia is considered to be a stronger risk factor for CHD in woman than men. An elevated blood level of Homocysteine is strongly related to an increased risk of atherosclerosis and cardiovascular disease. 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. 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-nitroso cysteine, a more potent vasodilator than endothelium-derived

relaxing factor. In addition Hcy may directly impair the NO pathway reducing NO elaboration by endothelial cells and increase oxidative degradation of NO[12].

Hypertension

The 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. However, studies which examine the association of hypertension and plasma Hcy levels do not seem adequate to reveal this relation clearly[13].

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demylinating disease of central nervous system (CNS), with an onset typically between 20 and 40 years of age and more prevalent in women. Homocysteine may have a neurotoxin that activates N-methyl-D.aspartate receptor which leads to cell death. It may be converted into homocysteic acid which also has a toxic effect on the neurons of cerebral cortex. So increased plasma level of total Homocysteine (tHcy) has a neurodegenerative effect and may be a risk factor for progression of disability in MS.

In one of the case control clinical trial, tHcy was compared between MS and Control group. It was observed that high serum tHcy is more in MS patients than healthy controls and significantly higher in the patients with severe disability (EDSS≥3). So, serum tHcy may have a positive effect on Pathophysiology of MS[14]

Coagulation System

Hcy causes thrombotic tendency. Elevation of thromboxane A_2 formation (which may reflect platelet activation), reduction of anti thrombin 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 Hcy. A clot in the veins is called a venous thrombosis. Most often, venous thrombosis occurs in the legs; however, the clot can break away from the wall of the vein and travel to the lung, leading to a potentially fatal complication called pulmonary embolism. Venous

blood clots occur in approximately 1 in 1000 individuals per year. Certain studies have suggested that elevated Homocysteine levels roughly double the risk of developing venous thrombosis[15].

Renal Failure

HHcy is very frequent in renal failure, which suggests that the kidneys function is crucial for Hcy catabolism. Hcy is ultra filtrated in glomeruli, almost completely absorbed in tubules, and degraded in kidney tissue by Transmethylation and Transsulphuration in the activated methyl cycle[16]. 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.

Diabetes Mellitus, Vascular Complications

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. There are still controversial studies with respect to the association between plasma Hcy and macro vascular complications or micro vascular complications.

Hoogeveen et, al[17] found that diabetic patients with HHcy had an increased risk for developing cardiovascular disease compared with those with normohomocysteinemia. Moreover one of the prospective studies 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 non diabetic subjects. For each 5µmol/l increase in Hcy, the risk of 5- year mortality rose by 17% in the non diabetic and by 60% in the diabetic subjects. Faisal I. Mohammad et al., have concluded that plasma level of Homocysteine is significantly elevated in diabetic coronary heart disease female patients above 50 years old and significantly elevated in non diabetic coronary heart disease males and female patients, thus non diabetic coronary heart disease male and female patients and diabetic coronary female patients are at high risk of vascular diseases. It is recommended that these patients may take supplementation of folate and vitamin B12 to reduce the level of Homocysteine[18].

Pregnancy and Birth Defects

Pre-eclampsia and eclampsia are common obstetrical problem causing adverse effects on pregnancy outcome. Elevated Homocysteine level is associated with pre-eclampsia and Eclampsia and the higher Homocysteine concentration in eclampsia compared to preeclampsia indicates its subtle association with the severity of disorder as well. So, maternal Hyperhomocysteinemia seems to have causal role in the etiopathogenesis of pre-eclampsia/eclampsia. Management of Hyperhomocysteinemia in antenatal period taking into account the B-vitamin supplementation might help substantially to reduce the adverse pregnancy outcome[19].

Folic acid intake in the weeks before and after conception has been shown to decrease the number of neural tube defects (NTD), such as spina bifida. Molloy et al[20]. conducted three separate case-control studies and found that women with a serum B_{12} level of less than 300pg/ml were significantly more likely to have a baby born with neural tube defects. In another trial, the researcher found out that the low levels of a particular measure of B_{12} activity increased the risk of having a baby with a NTD by 5 times.

Alzheimer's diseases

Research has shown that an elevated blood level of the sulphydryl amino acid Homocysteine termed Hyperhomocysteinemia is an independent risk factor for vascular disease. Accordingly, the hypothesis that Hyperhomocysteinemia may also play a role in the pathogenesis of AD has been proposed. Bell and team examined several elderly patients who were hospitalized for acute depression and found a statistically significant negative correlation between tHcy levels and cognitive ability[21].

Postmenopausal Women

Reiss *et al*., 1999[22], found basal Homocysteinemia is significantly higher in men than women. After menopause basal Homocysteinemia increases significantly in women, approaching those in men. Premenopausal women are protected from CHD by having favorable lipid profile and plasma tHcy level. After menopause this protection is lost most probably due to estrogen deficiency. In another trial, they have studied the effect of folic acid

supplements for six months, on Hcy level in postmenopausal women. The result has shown an Significant (p<0.001) decrease in Hcy level after six months of folic acid supplements[23].

Sports

Regular physical activity is associated with a reduction of cardiovascular morbidity and mortality; however, evidence of unfortunate cardiovascular events accompanying elite sport involvement continues to accumulate. To date, no information is available on possible peculiarities of the cardiovascular risk profile in athletes.

P Borrione and his group[24] has evaluated plasma Homocysteine levels in a group of athletes and to search for relationship with vitamin status and other metabolic variables in order to confirm the existence of a "sport-related Hyperhomocysteinemia" and to explain its clinical significance. They have suggested that it would represent an adaptation to training but the possibility of a secondary vascular damage cannot be excluded.

Management of Hyperhomocysteinemia

Blood levels of folate, vitamin B_{12} and vitamin B_6 are inversely related to tHcy. Even in a generally healthy population consuming a typical western diet, anyone with a nutritional deficiency that leads to low blood levels of folate, vitamin B_{12}, or vitamin B_6 is at increased risk for Hyperhomocysteinemia. It has been suggested that inadequate blood levels of one or more of these vitamin co-factors are responsible for approximately two-thirds of the cases of Hyperhomocysteinemia. According to these data, Hyperhomocysteinemia might be a sensitive marker of B_{12} and folate deficiency, as was found by Nilsson et al. consuming optimal levels of B_{12}, B_6 and folic acid on a daily basis, and lowering Homocysteine levels. Lowering of tHcy may slow the progression of AD. We recommend that AD patients take B vitamin supplements in order to lower their tHcy. 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.

Simply folic acid supplements can be beneficial to postmenopausal women in protecting them from CHD. So interference to lower it with medication with least side effects will be a great help to postmenopausal women to whom Hormone Replacement Therapy should no more be prescribed due to its harmful effects. This study favors the view that after menopause Hcy level increases significantly and a simple non Toxic and relatively inexpensive vitamin (folic acid) intervention might be useful in primary cardiovascular prevention in this high risk group because Hcy is a stronger risk factor for CHD in postmenopausal women than men.

Folate supplementation with 0.5 – 5mg/day significantly reduce total Hcy concentration by 25% in patients with mild to moderate Hyperhomocysteinemia. A decrease of total Hcy by 34-52% was observed in healthy volunteers consuming folic acid in dose 0.6-10mg/ day and a 27% decreases in patients with an acute myocardial infarction who were supplemented with 2.5mg of folic acid daily. Supplementation with Vit B12 produces a small additional effect 5-15% except the vitamin B12 deficient vegetarians. In these subjects supplemented by vitamin B12 in the total dose 2.2mg, the total Hcy concentration decreased by 42%[25].

Recently Schroecksnadel K et al. studied the influence of aspirin and atorvastatin on homocysteine production in human peripheral blood mononuclear cells (PBMC) obtained from healthy donors. Treatment of PBMC with aspirin (1-5 mM) as well as atorvastatin (5-100 μM) suppressed homocysteine production in a dose-dependent way. Their Data has suggested that the aspirin and atorvastatin may prevent homocysteine accumulation in the blood by suppressing immune activation cascades and proliferation of mitogen-driven T-cells. The influence of drugs on homocysteine production appears to be independent of any direct effect on homocysteine biochemistry[21].

SUMMARY

In recent years the amino acid Homocysteine has achieved the status of an important factor in vascular disease, diseases of aging, and other fundamental processes in biology and medicine. Homocysteine has also implicated abnormal Homocysteine metabolism in a wide range of other important disease processes, including

developmental birth defects, neurodegenerative diseases like Alzheimer's disease, autoimmune diseases like rheumatoid arthritis, hormonal imbalances, renal failure, cancer, and degenerative diseases of aging. In the future the biomedical significance of Homocysteine will become extraordinarily important for prevention and therapy of a wide range of major diseases.

From a preventive and therapeutic point of view, the biomedical significance of Homocysteine is extraordinarily important. Since the implications of the Homocysteine theory are primarily in the field of improved nutrition and preventive therapy, the benefits of the approach will follow improvements in food preservation, fortification of processed foods, and widespread use of vitamin B_6, folic acid, and vitamin B_{12} to prevent vascular disease. These benefits will be increased by improved understanding of the genetic basis of abnormal Homocysteine metabolism, such as thermo labile methylenetetrahydrofolate reductase, and the interaction of folic acid and other nutrients to prevent Hyperhomocysteinemia.

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Corresponding Author:

J. Shobana*

Email: *john.shobana@gmail.com*