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PLASMA HOMCYSTEINE, VITAMINS B AND RISK FOR CARDIOVASCULAR DISEASE

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ABSTRACT

An elevated homocysteine (HCY) levels can be caused by a number of factors, including folate and B-vitamin deficiency, pre-existing atherosclerotic disease, diabetes and various drugs. Epidemiological evidence, as well as data from retrospective and prospective studies, supports an association between elevated HCY levels and increased risk of cardiovascular disease (CVD).Although the major studies that have reported to date show that vitamin supplementation was associated with a decrease in HCY levels, this failed to have any significant effect on cardiovascular risk. Epidemiological studies long ago identified age, gender, smoking, lipids, hypertension and diabetes along with psychological factors, lack of exercise and a low fruit and vegetable diet as cardiovascular disease (CVD) risk factors. Among the dietary risk factors, inadequate vitamin intakes have long been suspected to be CVD risk factors.The public health implications of homocysteine as a cardiovascular risk factor are particularly far-reaching, because homocysteine can be lowered effectively, inexpensively and safely by treatment with folic acid and other B vitamins.

The cardiovascular disease (CVD) burden of India is expected to double in the next two decades, making it the single largest cause of death and the second largest cause of disability by the year 2020 (Murray and Lopez , 1997).

The growing burden of CVD is due to the increasing prevalence of cardiovascular risk factors such as diabetes, hypertension, dyslipidaemia, overweight or obesity, physical inactivity and use of tobacco. India also perhaps suffers the highest loss in potentially productive years of life, as deaths due to CVD in persons in the age group of 35-64 years is high. It is predicted that by the year 2015, India will have the largest burden of CVD in the world (Sanderson et al; 2007).

Cardiovascular Disease Includes Two Major Sub-types Which are Discussed Below

1. Coronary heart disease (CHD)
2. Cerebrovascular disease (stroke)

Each year CVD causes an estimated 17 million deaths worldwide, Accounting for one-third of all deaths worldwide. More than one-third of these deaths occur in middle-aged adults. In developed countries heart disease and stroke are the first and second leading cause of death among adult men and women. The significance of any association between cardiovascular disease and circulating homocysteine concentration is attracting considerable attention. The normal activities of the trans-sulfuration and remethylation pathways maintain intracellular homocysteine levels within a narrow range, and the controlled release of homocysteine into blood results in blood measurements that provide an accurate index of homocysteine status.

Homocysteine

Homocysteine (HCY), a sulphur amino-acid first described by Butz and duVigneaud (1932), has been linked to atherosclerosis and CAD, tHcy might induce atherosclerosis by impairing coronary micro-vascular dilator function by smooth muscle proliferation, platelet activation, thrombogenesis , endothelial dysfunction, and collagen synthesis (Tawakol et al.; 2002).

Homocysteine is an amino acid with the formula $HSCH_2CH_2CH(NH_2)COOH$. It is a homologue of the amino acid cysteine, differing by an additional methylene ($-CH_2-$) group.The cysteine thiol group is nucleophilic and easily oxidized. The reactivity is enhanced when the thiol is ionized, due to the ability of thiols to undergo redox reactions, cysteine has antioxidant properties. Homocysteine exists at neutral pH values as a zwitterion: Betatine form of (S)-Homocysteine and (R)-Homocysteine.

A significant difference in total Homocysteine levels between patients with ischemic and hemorrhagic stroke, suggesting that elevated total Homocysteine is not only a reaction to attack illness but also a risk factor for recurrent stroke. Elevated Homocysteine levels also generates Homocysteine thiolactone which is known to be toxic (Boysen et al.;2003). Hyper-homocysteinemia is one of the major and independent risk factor for the development of atherosclerosic coronary artery disease. For about two decades moderately raised concentration of total

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homocysteine has been correlated with an increased risk of atherothrombotic vascular events. The process of identifying homocysteine as a possible risk factor for vascular disease already started in 1964.The accumulation of homocysteine in blood, and consequently in urine leading to homocysteinuria, was due to deficiency of the enzyme cystathionine beta-synthase. Mechanism by which total homocysteine may cause vascular disease include propensity for thrombosis, impaired thrombolysis, increased production of hydrogen peroxide (Ueland and Refsum 2000).

Metabolism of Homocysteine

HCY is a sulphur-containing amino acid in the body produced by conversion of methionine, an essential amino acid present in foods regularly consumed within the diet. However,to understand the potential relevance of HCY to CVD, it is important first briefly to review pathways involved in HCY metabolism (Selhub 1999). Some of these studies reported a statistically significant positive association between elevated HCY and coronary heart disease (CHD) and stroke. In contrast, other studies failed to demonstrate a significant association between plasma HCY and CHD. Homocysteine is not obtained from the diet. Instead, it is biosynthesized from methionine via a multi-step process (Champe et al.; 2008). First, methionine receives an adenosine group from ATP, a reaction catalyzed by S-adenosyl-methionine synthetase, to give S-adenosyl methionine (SAM). SAM then transfers the methyl group to an acceptor molecule, (i.e,nor-epinephrine as an acceptor during epinephrine synthesis, DNA methyl-transferase as an intermediate acceptor in the process of DNA methylation). The adenosine is then hydrolyzed to yield L-homocysteine. L-Homocysteine has two primary fates: conversion via tetra-hydrofolate (THF) back into L-methionine or conversion to L-cysteine (figure - 1).

The American Heart Association released an advisory statement classifying total homocysteine plasma concentrations as follows: 5-15 ìmol/L homocysteine as normal, 16-30 ìmol/L homocysteine as moderate, 31-100 ìmol/L homocysteine as inter mediately elevated and total Homocysteine levels above 100 ìmol/L as severely elevated concentrations. Hyper-homocysteinemia is defined as total Homocysteine concentration elevated above 15 micro mol/L. Hyper-homocysteinemia has been strongly associated with the pathogenesis of coronary vascular disease and correspondingly has been identified as a contributing factor in four main disease mechanisms including thrombosis, vascular oxidative stress, apoptosis and cellular proliferation.

Homocysteine appears to alter the anticoagulant properties of endothelial cells to a pro-coagulant phenotype. Mildly increased homocysteine causes dysfunction of the vascular endothelium Multiple prospective and case control studies suggested that a moderately elevated homocysteine concentration is an independent risk factor for atherothrombotic vascular disease. Homocystine

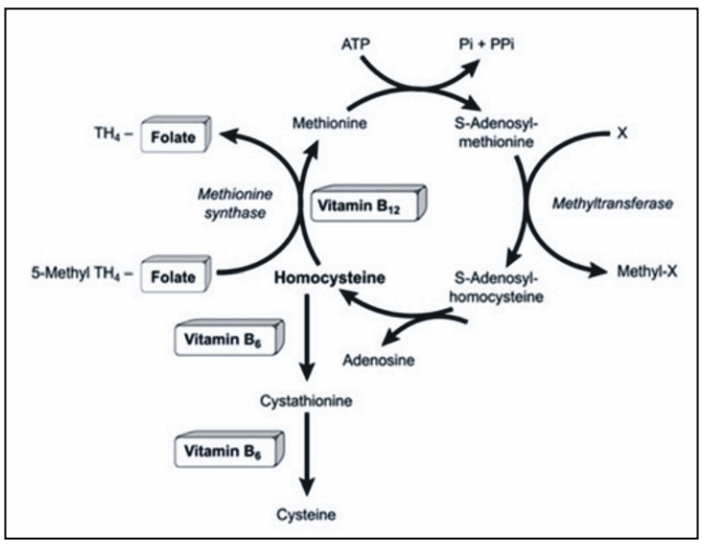

Figure 1 : Metabolism of Homocysteine

concentrations are consistently higher in patients with peripheral, cerebrovascular and coronary artery disease than in those without such disease. Elevated plasma total Homocysteine levels have been positively associated with ischemic stroke risk.

Homocysteine may induce cardiac remodeling in which the elastin/collagen ratio is reduced, causing cardiac stiffness and diastolic heart failure in hyperhomocysteinemia (Sundstrom and Vasan 2005). Plasma Homocysteine level is the strongest predictor of mortality in a prospective study of patient with angiographically confirmed coronary artery disease and previous myocardial infarction. The risk of death was increased 4.5 fold when Homocysteine was>20 micro mol as compared to <9 micro mol. An elevated plasma Homocysteine level is an important risk factor for recurrent ischemic cardiovascular events.

Correlation of Homocysteine, Folic Acid,Vitamin B_6 and B_{12} in CVD

An elevated levels of plasma tHcy is a marker of both vitamin B12 and folate deficiency. A border line vitamin B6 deficiency (plasma PLP concentration < 30 nmol/L) is strongly associated with the risk of CAD(Lin and Cheng, 2006).

A statically significant inverse relationship between serum folate level and risk of folate CHD. A previous case control study of early onset coronary artery disease noted a reduction in risked with increased serum folate level. Folate determinant of Homocysteine related carotid artery thickening arterial thickening has been associated with both stroke and CHD .Folic acid and vitamin B6 lower the grossly elevated tHcy concentration observed in these patients and significantly reduce cardiovascular events.

A high circulating tHcy concentration is a risk factor , the result of this prospective cohort study do not support that hypothesis however they do suggest that moderate to high serum folate concentration are associated with a greatly reduced incidence of acute coronary events. Folic acid effectively lowers homocysteine concentration in the plasma. Intervention studies are urgently need to determine if lowering Homocysteine is effective in decreasing the morbidity and mortality of cardio vascular disease. According to Blacher and Czerrichow et al.; (2005), that there is a high degree of proof relating plasma homocysteine levels to cardiovascular risk, the role of homocysteine as a casual cardiovascular risk factor remains controversial,

According to Susanna and Larsoon et al.; (2008), a meta analysis of randomized trides estimated that folic acid supplementation could be expected to reduce homocysteine concentration by 13.25% and that vitamin B_{12} produced 7 percent further reduction in homocysteine concentrations, Whereas vitamin B_6 had no significant additional effect.

Vitamin $_s$upplementation (Folic Acid, Vitamin B_6 and Vitamin B_{12})

A decrease in folic acid or B_{12} and B_6 is the primary cause of the increased risk of vascular disease. Elevated levels of homocysteine may just be a marker of low vitamin levels. Treatment with folic acid would decrease the risk of vascular disease and concurrently reduce homocysteine levels. Serum folate but not vitamin B_6 or B_{12} was a strong Predictor of Plasma homocysteine while all subject had adequate B-vitamin status. folate should be considered as a routine supplementation for individual who have risk for CAD, even for individuals with adequate folate status. Indicate that vitamin B_6 supplementation alone is less effective than folic Acid Combined with Vitamin B_{12}. The observational data suggest that even mild-to-moderate elevations in homocysteine increase cardiovascular risk; this observation is important, because such increases are common and can easily be corrected with safe and inexpensive therapy. Folic acid is the most important dietary determinant of homocysteine; daily supplementation with 0.5 to 5.0 mg typically lowers plasma homocysteine levels by about 25 percent. Vitamin B_{12} supplementation of at least 0.4 mg daily further lowers levels by about 7 percent, and vitamin B_6 supplements may be particularly important in lowering homocysteine after methionine loading. In conclusion, combined daily administration of 2.5 mg of folic acid, 50 mg of vitamin B_6, and 1 mg of vitamin B_{12} for five years had no beneficial effects on major vascular events in a high-risk population with vascular disease. (Natios and Savopuulos, 2009).

Summary

Prolonged follow-up from the Physicians Health Study also demonstrated a lack of association between for other cardiovascular risk factors. Studies of the general population have suggested that high homocysteine levels are associated with cardiovascular morbidity and mortality.Homocysteine levels can be lowered with folate, vitamin B6 and vitamin B12. Three large, randomized, controlled trials of patients with pre-existing cardiovascular disease In the present paper, the following are reviewed: possible biological mechanisms underlying the role for homocysteine as a cardiovascular risk factor; observational studies examining the association between elevated homocysteine and cardiovascular risk in the general population ; interventional studies of homocysteine-lowering therapy; possible reasons for the largely negative results from these trials; and the ongoing trials of homocysteine-lowering therapy. Along with this supplementation of folic acid and vitamin B6 and vitamin B12 to CVD showed beneficial effect.

CONCLUSION

At present, the totality of evidence does not refute or support any of the above-mentioned hypotheses, the wonders of folic acid and folic acid supplementation and reduction of homocysteine levels to prevent heart attacks may be counterproductive by offering yet another false promise to the public, who may become less responsive to more proven methods of reducing coronary heart disease such as lowering LDL cholesterol, ceasing smoking, and controlling high blood pressure. But it is suggestive that supplementation of above mentioned vitamins play role in lowering Homocysteine blood level which is one of the marker of CVD disorder. Regular intake of vitamin B complex might delay the onset of cardiovascular disorder. You can get these vitamins by taking a multivitamin each day and eating foods such as lentils and other legumes, nuts, and vegetables as well as fortified breads and cereals. It must be concluded that the jury is still out and that we still do not know whether an elevated level of homocysteine in plasma is a cause of cardiovascular disease or whether it is an epiphenomenon.

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