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Hyperhomocysteinemia and Coronary Artery Disease in the Asian Indian Population

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Introduction

The increased prevalence of coronary artery disease (CAD) among migrant Asian Indians and individuals in the subcontinent of India is partly attributed to elevated plasma levels of homocysteine (Hcy). Hcy, a sulfur-containing amino acid, is derived from the metabolic demethylation of dietary methionine (1,2,3). Four different forms of Hcy exist: 1% is present as free thiol; 70-80% circulates as a disulphide-bound to albumin; and the remaining 20-30% forms a dimer with itself or other thiols (1). The grouping of these four forms is referred to as total plasma Hcy (tHcy) and it is the elevation of this serum component that has been noted as an independent risk factor for CAD. Total plasma Hcy within the normal range is 5 to 15 µmol/L and hyperhomocysteinemia (HHC) is categorized as moderate (16-30 µmol/L), intermediate (31-100 µmol/L), and severe (>100 µmol/L) HHC (4). The concentration of tHcy is determined by genetic and nutritional factors, such as levels of dietary folate and cobalamin. Since these nutrients are essential co-factors in the metabolic pathway of Hcy, deficiencies of folate and cobalamin result in elevated Hcy levels in the Asian Indian population (2,4,5,6,7,8).

The risk of CAD for individuals living in the subcontinent of India is forty percent higher than compared to Europeans (4). Asian Indians residing in America have a four fold higher risk than Caucasians and a twenty fold higher risk than Japanese people. In addition, Indians are prone to this disease five to ten years earlier than other ethnicities and the disease progression is more severe (7). It is important to note that a majority of the other risk factors for CAD, such as cigarette smoking, blood pressure, and cholesterol, are not consistently higher in Indians, compared to other cultures (2,7,8). This indicates that the increased mortality from CAD in Indians is not due to these conventional risk factors. Diabetes and insulin resistance, however, are more prevalent in the Asian Indian population, but their exact contribution to CAD risk still needs to be determined (2,5). This paper seeks to determine the effects and causes of hyperhomocysteinemia in the Asian Indian population and provide support on the need to initiate a food fortification program in India to decrease the threatening rates of CAD.

Atherogenic Properties of Hyperhomocysteinemia

Elevated plasma levels of Hcy promotes atherogenesis by several mechanisms including the increase of oxidative injury to the arterial endothelium, thrombotic effects of the coagulation system, and impaired vasodilator properties of the endothelium (1,9,10,11,12). Although the exact mechanism is unknown, it has been postulated that the free thiol group on Hcy may interact with nitric oxide or disulfide bonds in endothelial molecules resulting in the formation of reactive oxygen species. The endothelial injury caused by this process may then alter the release of the vasodilator, nitric oxide, leading to abnormal interactions among the arterial wall and components of blood, such as leukocytes and platelets (9). A study by Chambers et al. studied the relationship between levels of plasma Hcy and vascular endothelial dysfunction. After supplying low-dose oral methionine or dietary animal protein to patients with no history of vascular disease, flow-mediated dilatation was measured over a period of twenty-four hours. It was concluded that concentrations of Hcy found in patients with premature vascular disease results in a rapid and dose-related impairment of dilatation (3). The graded, inverse relationship between Hcy levels and endothelial function is an important indicator of the causal role of Hcy in atherogenesis (2).

A linear, graded relationship has been demonstrated between tHcy levels and risk for CAD, venous thrombosis, myocardial infarction, and mortality (10). From this graded relationship, it has been estimated that the mortality ratio for a tHcy level between 10 and 15 µmol/L is 1.6 while it increases to 2.5 if the tHcy level is between 15 and 20 µmol/L (10). Similarly, the relationship between tHcy and CAD risk results in an odds ratio of 1.7 (1,11). A study by Refsum et al. concluded that 77% of the total population of India has elevated tHcy levels, with a median of almost 20 µmol/L (4). Indians living in America were found to have significantly elevated tHcy levels (9.4 µmol/L) as compared to other cultural groups (8.0 µmol/L) (7). Based on the mortality and odds ratios, Asian Indians are at a heightened risk of CAD and mortality. Nutritional and Genetic Causes of Hyperhomocysteinemia in Asian Indians

Folate Deficiency

Folate, a naturally occurring form of water-soluble B vitamins, is found in leafy greens, dry beans, fruits, and vegetables. It reduces Hcy levels by acting as an essential co-factor increasing the rate of recycling of Hcy to methionine (9). For this reason, several studies demonstrated a strong inverse relationship between Hcy levels and folate levels in Asian Indians (2,6,8,13,14). The recommended dietary allowance (RDA) of folic acid is 100 µg/day for Asian Indians (6). A study conducted by Misra et al. examined the prevalence of folate deficiency in areas of India. By asking individuals to complete a 24-hour food recall, it was determined that 95% of the population consumed insufficient levels of folate (63.1 µg/day). Vegetarians consistently had lower folate intake then non-vegetarians; however, both groups were significantly deficient (6). Carmel et al. identified a distinction between migrant Asian Indians and native Indians since their study did not find evidence of folate deficiency in Asian Indians living in America. It was concluded that supplement use, folic acid fortification, and a more varied diet results in adequate folate intake. Increased Hcy levels in this migrant population are therefore attributed to cobalamin deficiency (7).

Low folic acid levels may be caused by malabsorption due to gastrointestinal infections and dietary deficiencies. In fact, folate deficiency among Asian Indians is mostly attributed to prolonged cooking of vegetables which destroys over ninety percent of the folate content (2). An alteration in the intestinal bacterial composition may also lead to folate deficiency since bacterial metabolism is a major source of reabsorbed folic acid. Interestingly, fructose malabsorption accelerates gastrointestinal transit time allowing less contact time for efficient absorption of nutrients. In addition, it causes a change in the colon's composition of bacteria (13,15). For these reasons, management of HHC in Asian Indians should not only focus on supplementation of vitamins, but also target the issues of malabsorption and intestinal bacterial composition.

Cobalamin Deficiency

Cobalamin, also known as Vitamin B12, is a co-factor in the metabolic pathway of Hcy, thus its levels are inversely related to Hcy concentrations (1,4,6). Due to the fact that this nutrient is only present in animal foods such as milk, meat, poultry, and eggs, one needs to be concerned about cobalamin deficiency in the large Indian vegetarian population. Since non-vegetarian Indians consume a substantially lower amount of animal-derived products than individuals on a Western diet, they are also susceptible to cobalamin deficiency (4). The RDA of cobalamin in Asian Indians is 1 µg/day (6,8). Multiple studies have demonstrated that native and migrant Indians receive lower levels of cobalamin than recommended. In India, Refsum et al. researched

cobalamin deficiency by measuring levels of total cobalamin and holotranscobalamin (holoTC), an effective marker of deficiency. It was determined that 52% of the subjects were deficient in cobalamin and 73% had low holoTC levels. Although more vegetarians were cobalamin deficient than non-vegetarians, the concentrations of this nutrient did not differ significantly between the two groups (4). According to a study conducted by Carmel et al., cobalamin deficiency in the United States occurs in 46.7% of Indians and only 10.5% of other individuals (7). Since cobalamin is the main determinant of Hcy levels (6,16), measures need to be taken to assure that Indians receive an adequate intake of this essential nutrient.

Cobalamin deficiency results in megaloblastic anemia, thrombocytopenia, and neurological deficits due to cobalamin's involvement in DNA synthesis and myelin maintenance. In most cases the presence of cobalamin deficiency is due to dietary deficiency of animal products. However, the fact that non-vegetarian Indians also experience low levels of cobalamin is important. Genetic mechanisms may have caused Indians to adapt to a chronic low cobalamin concentration. This is due to the possibility that the low prevalence of the methylenetetra-hydrofolate reductase 677C?T polymorphism in Indians protects against the adverse effects of cobalamin deficiency (4). Another explanation is that dietary restriction in childhood of cobalamin may have a greater impact on cobalamin levels than intake during adulthood (7). Malabsorption or alterations in intestinal bacteria composition may contribute to cobalamin deficiency as well (4). Since none of the Indians in the study conducted by Carmel et al. suffered from cobalamin-absorption, reduced amounts of dietary animal products is most likely the principal cause of cobalamin deficiency in migrant Asian Indians.

Genetic Mutations

The methylenetetrahydrofolate reductase (MTHFR) 677C?T mutation impairs this enzyme's function in the remethylation of Hcy to methionine. For this reason, the MTHFR 677T mutation contributes to elevated Hcy concentrations; however, this mutation does not influence Hcy levels in Asian Indians (2,17). In fact, the prevalence of homozygous MTHFR 677T in Indians was less than a third of that in Europeans. In Asian Indians, unlike in Europeans, there were no significant differences in Hcy concentrations between subjects with the TT genotype compared to subjects with the CT or CC genotype. One explanation is that this mutation was lost during evolution in the Asian Indian population to protect against the negative metabolic effects of low cobalamin levels (17). Overall, nutritional factors are more critical than genetic mutations in the development of HHC in Asian Indians.

Food Fortification for the Future

The fact that Asian Indians have elevated levels of Hcy raises significant concern due to the relationship between Hcy and mortality from CAD. In order to reduce the incidence of CAD among Asian Indians, folic acid fortification of foods such as grains and flour needs to be implemented in India. In fact, folic acid fortification was implemented in the United States in 1998 resulting in a decline in folate deficiency and tHcy levels (16). It is too early to determine whether fortification will lower rates of CAD; however, its advantageous effect on lowering tHcy levels may benefit Indians. In fact, a randomized, placebo-controlled trial studied the effect of folic acid treatment on the progression of atherosclerosis. The findings indicated that treatment with folic acid decreases the rate of abnormal exercise electrocardiographic tests signifying a reduced risk of atherosclerosis (18). Folic acid supplementation is hypothesized to decrease the risk by improving endothelial function such as nitric-oxide mediated dilatation (9).

Since cobalamin is the main determinant of Hcy levels, it is also beneficial to raise awareness about cobalamin supplementation. Increasing levels of folic acid and cobalamin through supplementation results in significantly lower Hcy levels than fortification alone (19); thus, it important for migrant Asian Indians with HHC to take vitamin supplements.

The prevalence of CAD is steadily increasing among Asian Indians and contributing to a significant number of deaths in this population. Elevated plasma Hcy levels are consistently higher in Indians than other individuals even though a majority of the various risk factors for CAD are comparable to other groups. Unfortunately, research on the relationship between Hcy and CAD has been carried out mostly on North American and European populations, thus, there is a dire need for attention to be placed on the Asian Indian population. Future studies should comprehensively analyze the different causes of HHC in the Indian population to determine if dietary patterns, sanitation, or other diseases, such as malabsorption and gastrointestinal disorders, are the culprit in these increasing rates of CAD incidence. Government nutrition agencies in India need to consider implementing nationwide programs of folic acid fortification and cobalamin supplementation. In the mean time, however, Asian Indians worldwide should receive health education about this vital issue. By doing so, Asian Indians can immediately alter their dietary patterns, cooking methods, and usage of vitamin supplements. Most importantly, individuals will learn that the devastating rates of CAD in this culture can be modified by their personal lifestyle choices and it no longer has to be an inevitable outcome.

REFERENCES

1. Hankey G, Eikelboom, J. Homocysteine and vascular disease. Lancet. 1999;354:407-412.
2. Chambers J and Kooner J. Homocysteine: a novel risk factor for coronary heart disease in
UK Asian Indians. Heart. 2001;86:121-122.
3. Chambers J, Obeid O, Kooner J. Physiological increments in plasma homocysteine induce vascular endothelial dysfunction in normal human subjects. Arterioscler Thromb Vasc Biol. 1999;19:2922-7.
4. Refsum H, Yajnik C, Gadkari M, et al. Hyperhomocysteinemia and elevated methylmalonic
acid indicate a high prevalence of cobalamin deficiency in Asian Indians. Am J Clin Nutr. 2001;74:233-241.
5. Chambers J, Obeid O, Refsum H, et al. Plasma homocysteine concentrations and risk of coronary heart disease in UK Indian Asian and European men. Lancet.2000;355:523-7.
6. Misra A, Vikram N, Pandey RM, et al. Hyperhomocysteinemia, and low intakes of folic acid
and vitamin B12 in urban North India. Eur J Nutr. 2002;41:68-77.
7. Carmel R, Mallidi PV, Vinarskiy S, et al. Hyperhomocysteinemia and cobalamin deficiency
in Asian Indians in the United States. Am J Hematol. 2002;70:107-114.
8. Lakshmi AV, Maniprabha C, Krishna TP. Plasma homocysteine level in relation to folate and
vitamin B6 status in apparently normal men. Asia Pacific J Clin Nutr. 2001;10:194-196.
9. Woo KS, Chook P, Lolin Y, et al. Folic acid improves arterial endothelial function in

adults
with hyperhomocystinemia. J Am Coll Cardiol. 1999;34:2002-6.
10. Nygard O, Nordrehaug JE, Refsum H, et al. Plasma homocysteine levels and mortality in
patients with coronary artery disease. N Engl J Med. 1997;227:230-6.
11. Boushey C, Beresford SA, Omenn G, et al. A quantitative assessment of plasma
homocysteine as a risk factor for vascular disease. JAMA. 1997;274:1049-1057.
12. Bamji M, Lakshmi AV. Less recognized micronutrient deficiencies in India. Nutrition
Foundation of India, April 1998.
13. Ledochowski M, Bernhard W, Fuchs D. Homocysteine and heart disease in Indian
Asians.
Lancet. 2000;355:2248-50.
14. Ghosh P, Khan SA. Coronary heart disease in Indian Asians. Lancet. 2000;355:1727-8.
15. Martyn C. Serum homocysteine and risk of coronary heart disease in UK Indian Asians.
Lancet. 2000;355:512-3.
16. Quinlivan EP, Gregory JF. Effect of food fortification on folic acid intake in the United
States. Am J Clin Nutr. 2003;77:221-5.
17. Chambers J, Ireland H, Thompson E, et al. Methylenetetrahydrofolate reductase 677
C?T
mutation and coronary heart disease risk in UK Indian Asians. Arterioscler Thromb
Vasc Biol. 2000;20:2448-2456.
18. Vermeulen E, Stehouwer C, Twisk JW, et al. Effect of homocysteine-lowering
treatment
with folic acid plus vitamin B6 on progression of subclinical atherosclerosis: a randomized,
placebo-controlled trial. Lancet. 2000;355:517-522.
19. Jacques P, Selhub J, Bostom A, et al. The effect of folic acid fortification on plasma
folate
and total homocysteine concentrations. N Engl J Med. 1999;340:1449-1454.