Demystifying Relevance of Homocysteine Hypothesis in Native Asian Indian Population

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The homocysteine “hypothesis of arteriosclerosis” was first proposed by McCully in 1969, when he observed on autopsy premature atherothrombosis of the peripheral, coronary, and cerebral vasculature in children with homocystinuria, an inborn error in methionine metabolism. It was only in 1976, Wilcken and Wilcken provided the first evidence of a relationship between abnormal homocysteine metabolism and coronary artery disease (CAD) in the general population. Since these observations from several studies implied a pathogenetic role for homocysteine in atherosclerotic cardiovascular disease (CVD) though cause-effect relationship was still not conclusively proven.1

Currently since last few years, the utility of homocysteine in predicting risk for atherothrombotic vascular disease has been evaluated in several observational studies in a large number of patients. These studies show that the overall risk for vascular disease is small, with prospective, longitudinal studies reporting a weaker association between homocysteine and atherothrombotic vascular disease compared to retrospective case-control and cross-sectional studies.1 Furthermore, randomized controlled trials of homocysteine-lowering therapy have failed to prove a causal relationship. On the basis of these results, there is currently insufficient evidence to recommend routine screening and treatment of elevated homocysteine concentrations with folic acid and other vitamins to prevent atherothrombotic vascular disease.1

Homocysteine is a sulfur-containing amino acid produced in the metabolism of the essential amino acid methionine. Homocysteine is metabolized through two vitamin-dependent pathways viz. remethylation (requiring folate and vitamin B12), which converts homocysteine back to methionine, and transsulfuration (pathway requiring vitamin B12), which converts homocysteine to cysteine and taurine and a second remethylation pathway in the liver and kidney utilizes betaine instead of folate (folate independent).1 The total plasma (or total serum) homocysteine (tHcy) reflects the combined pool of free, bound, reduced, and oxidized forms of homocysteine in the blood. Normal tHcy levels range between 5 and 15 µmol/l (12 mmol/l being the upper reference limit for populations on a folic-acid-fortified diet, as in North America, similar cut off for Indian population does not exist) with elevations of 16 to 30 mmol/l, 31 to 100 mmol/l, and >100 mmol/l classified as mild, moderate, and severe hyperhomocysteinemia, respectively. Blood levels of tHcy are optimally measured during fasting. However, measurement after methionine load may be more sensitive in identifying mild disturbances in homocysteine metabolism and is ideal for research but is rarely used.1

Several dietary and lifestyle factors, genetic defects, nutritional deficiencies, and other etiologies can cause elevations in homocysteine (Genetic enzyme polymorphisms MTHFR, methionine synthase, cystathionine β synthase, dietary deficiency, folic acid, vitamin B12, vitamin B6, methionine, lifestyle factors, chronic alcohol intake, smoking, high coffee intake, renal failure, end-stage diabetes, systemic lupus erythematosus, hyperproliferative disorders, medications [methotrexate, sulfonamides, antacids]). A thermolabile variant of methylene tetrahydrofolate reductase (MTHFR) with reduced enzymatic activity (C677T mutation) is the most common form of genetic hyperhomocysteinemia (5% to 14% of the general population is homozygous for this mutation). However, an association of this mutation with increased CVD risk is manifest only in populations characterized by low baseline folate levels. Deficiency of folic acid, vitamin B6, and vitamin B12 accounts for the majority (two-thirds) of cases of elevated homocysteine in the general population.1

A typical Asian Indian diet is predominantly vegetarian is often deficient in B12 and folate nor is food fortified with folate. The diet rich in folate are Green Leafy Vegetables like Amaranth, Ambat Chukka, Mint, Spinach (120 mcg/100% of edible portion); Pulses – Bengal gram, Black gram, Green gram, Red gram (120 mcg); Oil Seeds – Gingelly, Soya bean (180 mcg); Fruits – Orange. The vitamin B12 Content of Food/100 gm of Edible Portion: Fishes (Mrigal [1.4 mcg], Shrimp [Fresh] [9.0 mcg]); Flesh Foods: (Buffalo Meat [1.7 mcg], Egg Hen [whole] [1.8 mcg], Egg White [0.2 mcg], Egg Yolk [4.4 mcg], Goat Meat [2.8 mcg], Goat Liver [90.4 mcg], Sheep

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family history of premature atherosclerotic disease. This manifest atherothrombotic disease that is out of screening may be advisable for individuals who homocysteine is not yet recommended. However, disease burden. Routine screening for elevated cardiovascular risk factors or is a marker of existing homocysteine is related to other confounding variables though the MAITREYI's cohort of Vaidya³ is more homogenous, the findings are typical and similar for both. The both studies encourage the need for better nutritional evaluation of subjects and converting them by simple food or even fortification or simple economic supplementation.

The therapeutic options for lowering elevated homocysteine are Folic acid: 500-5000 mcg, vitamin B6: 10-500 mg, vitamin B12: 1000-3000 mcg, trimethylglycine (TMG): 500-9000 mg, choline: 250-3000 mg, Inositol: 250-1000 mg, zinc: 30-90 mg, S-adenosyl-methionine: 200-800 mg. Folate supplementation (0.5 to 5 mg/day) significantly reduces tHcy concentration by 25% in patients with mild to moderate hyperhomocysteinemia. Supplementation with vitamin B12 produces a small additional effect (7%), whereas vitamin B6 treatment alone only reduces post-methionine load concentrations. Betaine (trimethylglycine) reduces fasting homocysteine by 12% to 20% without altering folate levels. Choline, a precursor to betaine, decreases fasting and post-methionine load homocysteine levels. Both betaine and choline can have an adverse impact on lipid profile.¹

Severe elevation of homocysteine concentration in patients with homocystinuria leads to a high incidence of premature atherothrombotic events. In vitro and in vivo studies demonstrate a plethora of biologically plausible mechanisms that implicate homocysteine in promoting atherosclerotic and thrombotic vascular disease. Numerous observational studies have also reported on the association between mild to moderately elevated homocysteine levels and vascular risk in both the general population and in those with pre-existing vascular disease. The overall risk for vascular disease is small, with prospective studies reporting weaker association compared to retrospective studies. It is unclear whether a causal relationship exists between homocysteine and cardiovascular risk, or if homocysteine is related to other confounding cardiovascular risk factors or is a marker of existing disease burden. Routine screening for elevated homocysteine is not yet recommended. However, screening may be advisable for individuals who manifest atherothrombotic disease that is out of proportion to their traditional risk factors or who have a family history of premature atherosclerotic disease. This can be done via measurement of fasting homocysteine concentrations or by evaluation of post-methionine load levels. Vitamin supplementation with folate, B6, and B12 significantly lowers homocysteine concentration and has also been shown to alter surrogate cardiovascular end points. Currently, there is no evidence that vitamin B supplementation reduces cardiovascular risk, and there may even be a suggestion of potential harm with treatment with high-dose vitamin B. These findings have brought renewed scrutiny to homocysteine's role in atherothrombotic vascular disease. Whether homocysteine is causative in the pathogenesis of atherothrombotic vascular disease will have to await the completion of a number of large, randomized controlled trials currently studying the effect of homocysteine-lowering vitamins on cardiovascular end points. Until then, the status of homocysteine as a risk factor for vascular disease remains unvalidated.¹

The cardiometabolic burden of Native Asians Indians is epidemic and the phenotype is rapidly evolving though natural history studies are few and rare. Exciting epigenetic work may suggest that maternal B12 and folate may be critical in the future. Even in current JAPI work done by two groups from western India on Homocysteine² and B12³ level correlation is attempted. They both represent heterogeneity within their respective cohorts though the Bhavan's cohort is in the post menopausal females. Homocysteine research in India always poses more questions than answers. A large number of women from the MAITREYI's study had hyperhomocysteinemia and were deficient in vitamin B12. A significant negative correlation between vitamin B12 and plasma Hcy levels was found in these older women.³ The CRISIS Cohort of Dr. Yajnik's group finding showed low vitamin B12 concentration and hyperhomocysteinemia are common in Indian men, particularly in vegetarians and urban middle class residents. Further studies are needed to confirm these findings in other parts of India.³ Yet both the studies are significant and are still showing directionality in an ill-researched area. Both make an attempt to reform the homocysteine debate in the predominantly vegetarian, non fortified Native Asian Indian Subjects.

REFERENCES