Raised Plasma Homocysteine: an Emerging Risk Factor for Ischaemic Heart Disease: A Review

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One half to two thirds of atherosclerotic vascular diseases can be explained by classical risk factors like smoking, diabetes mellitus, hypertension, dyslipidaemia, family history of premature atherosclerotic vascular diseases, physical inactivity, obesity etc. Some other variables appear to contribute to the development of atherosclerotic vascular diseases which include estrogen deficiency, lipoprotein (a), plasma fibrinogen, plasminogen-activator inhibitor type I, endogenous tissue plasminogen activator (tPA), C-reactive protein and homocysteine. Over the last several years, investigators undertook extensive research work, in home and abroad, to determine the contribution of plasma homocysteine in the pathogenesis of atherosclerotic vascular diseases. So far the research work indicates, raised plasma homocysteine appears to be a potential risk factor for ischaemic heart disease.

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Introduction

Despite steady progress in treatment of cardiovascular diseases, people are still dying of these diseases, although at later ages.[1] By the year 2020, Coronary heart disease (CHD) and stroke will hold first and fourth places respectively in the World Health Organization's list of leading causes of disability.[2] Smoking, obesity, hypercholesterolaemia, family history, physical inactivity, diabetes mellitus, hypertension are established risk factors of IHD. In recent years, it has been suggested that one half to two thirds of risk for atherosclerotic vascular disease can be explained by classic risk factors.[3] Other variables that have come under scrutiny for their potential contribution include estrogen deficiency, lipoprotein (a), plasma fibrinogen, plasminogen-activator inhibitor type I, endogenous tissue plasminogen activator (tPA), C-reactive protein and homocysteine.[4]

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First suspicion on homocystine as a risk factor:
High level of homocysteine (Hcy) is now considered associated with heart disease. In the late 1960s a pathologist in Boston encountered two children with homocysteinuria, who despite being very young, had advanced atherosclerosis. The pathologist concerned, Kilmer McCully, opined about possible link between homocysteine and the formation of atheromatous plaque.[5]

Definition of hyperhomocysteinaemia and Determination:
Normal levels of fasting plasma homocysteine are considered to be between 5 and 15 μmol/L. Moderate, intermediate and severe hyperhomocysteinaemia refer to fasting concentrations between 16 and 30, between 31 and 100, and >100 μmol/L, respectively.[6] A single fasting sample is accepted as the most cost effective test.[7]

Patho-physiologic mechanisms of vascular disease:
Both clinical and experimental evidence suggests that the atherogenic propensity associated with hyperhomocysteinaemia is caused by endothelial dysfunction and injury which in turn is followed by platelet activation and thrombus formation. Figure-2 shows postulated adverse effects of homocysteine. The postulated effects involve oxidative damage to vascular endothelial cells and increased proliferation of vascular smooth muscle cells after oxidative metabolism of Hcy to homocystine and homocysteine thiolactone. Oxidative modification of LDL promotes the formation of foam cells which in turn yields another source of reactive oxygen species.[8-10]

Cross sectional and Retrospective case control studies:
Many cross-sectional and retrospective observational studies have examined the association between plasma Hcy level and cardiovascular risk and most support the existence of such an association. Boushey et al., reported a meta-analysis of 27 observational studies including about 4000 patients. A raised t-Hcy (usually defined as above the 90th or 95th percentile of controls) was associated with an increased risk of fatal and nonfatal atherosclerotic vascular disease in the coronary (Odds ratio (OR) 1.7; 95% Confidence Interval (CI) 1.5-1.9), cerebral (OR 2.5, CI, 2.0-3.0), and peripheral (OR 6.8, CI, 2.9-15.8) circulations.[12] The magnitude of risk was similar to that for other risk factors, such as hypercholesterolaemia and smoking, and it was estimated that about 10% of coronary heart disease in the general population might be attributable to Homocysteine.[11] Boushey et al.(1995) also observed a 5 μmol/L increase in t-Hcy was associated with an increase in vascular risk of about one-third, which is of similar magnitude to an increase in plasma cholesterol of 19 mg/dl. Since publication of this meta-analysis, many additional observational studies have been done.

Prospective cohort studies:
Prospective longitudinal studies provided a strong and consistent association between a risk factor and disease is found. However, the results of prospective cohort studies that

evaluated the association between hyperhomocysteinaemia and vascular risk remained inconclusive.

A large prospective cohort study from Tröms**ø**, Norway, reported a relative risk for coronary artery disease of 1.41 (CI, 1.16 to 1.71) for each increase of 4 μmol/L in serum Hcy level.[12] After 5 years of follow up, the physicians Health Study found an adjusted relative risk for fatal or nonfatal myocardial infarction of 3.4 (CI, 1.3 to 8.8; p=0.01) for persons whose Hcy levels were in the highest 5% compared with those whose Hcy levels were in the lowest 90%.[12] The British United Provident Association study reported a risk for fatal coronary heart disease of 2.9 (CI, 2.04 to 4.12) among men whose Hcy level was in the highest quarter compared with those whose Hcy level was in the lowest quarter, after adjustment for other risk factors.[13] The British Regional Heart Study found an independent, graded, positive association between hyper-homocysteinemia and the risk for stroke.[14] Plasma Hcy levels seemed to be the strongest predictor of mortality in a prospective study of patients with angiographically confirmed coronary artery disease and previous myocardial infarction. The risk of death (compared with a plasma Hcy level of < 9 μmol/L) was 1.9 for patients with Hcy level between 9 and 14.9 μmol/L, and 4.5 for Hcy levels of more than 20 μmol/L.[15] A smaller prospective study from Zutphen, Netherlands, reported a positive association between Hcy levels and risk for myocardial infarction and stroke.[16] The Rotterdam study reported odds ratio of 2.53 (CI, 1.19 to 5.35) for stroke and 2.43 (CI, 1.11 to 5.35) for myocardial infarction in patients whose plasma Hcy level was in the highest fifth.[17]

Schnyder et al observed significant association of t-Fcy with the severity of CAD (p <0.05) along with other established risk factors.[18] A study conducted in 2001 in Bangladeshi population showed that plasma homocysteine level is significantly higher in CAD patients than control subjects (p = 0.001).[19]

In a recent study (in 2003) at National Institute of Cardiovascular Diseases (NICVD), Dhaka, an attempt was made to find out the association between plasma total homocysteine level and the number of major epicardial coronary arteries severely narrowed. A total of 100 patients admitted for coronary angiography, with the diagnosis of ischaemic heart disease, in National Institute of Cardiovascular Diseases, Dhaka, Bangladesh, in 2003, were included in this study. Amongst them 50 patients were taken as cases (Fasting plasma total homocysteine level > 15 μmol/ l) and 50 patients were taken as control (Fasting plasma total homocysteine level < 15 μmol/l). The patients in both study and control groups were similar in respect to their age, gender and BMI, and had similar distribution of risk factors for CAD. Only tHcy was heigher in study group. Coronary angiogram was reviewed to identify culprit lesions and >50% stenosis was regarded as significant. Disease severity was evaluated by counting the major epicardial coronary arteries with significant stenosis. This study showed significant association of homocysteine level with the severity of CAD (p < 0.001). In our study homocysteine level levels were 10.6 ± 1.82 (μmol/l) in the group with 0-vessel disease and 17.62 ± 4.8

(µmol/l) in the group with 3-vessel disease.[20]

Conclusion

Raised plasma total homocysteine level seems to have a significant positive correlation with the pathogenesis of ischaemic heart disease. It may also be regarded as an independent risk factor for this disease. Raised plasma total homocysteine level also seems to have significant positive correlation with the number of vessel involvement in established coronary artery disease. Hyperhomocysteinaemia thus may predict whether early interventional or a more conservative approach of therapy would provide maximum benefit to the patient. However, further research involving a large number of participants is expected to substantiate the pathophysiologic findings of the current studies.

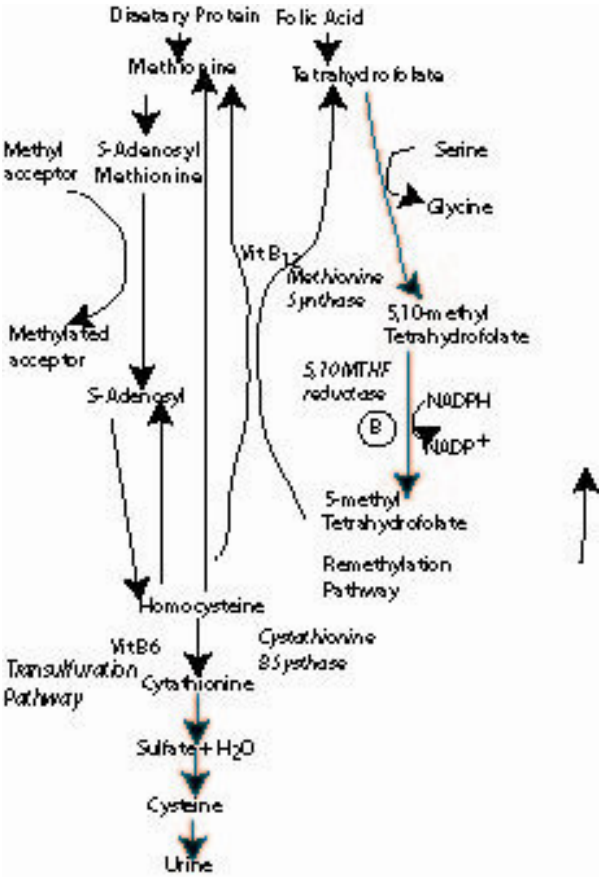

Figure 1. Pathways of homocysteine metabolism.

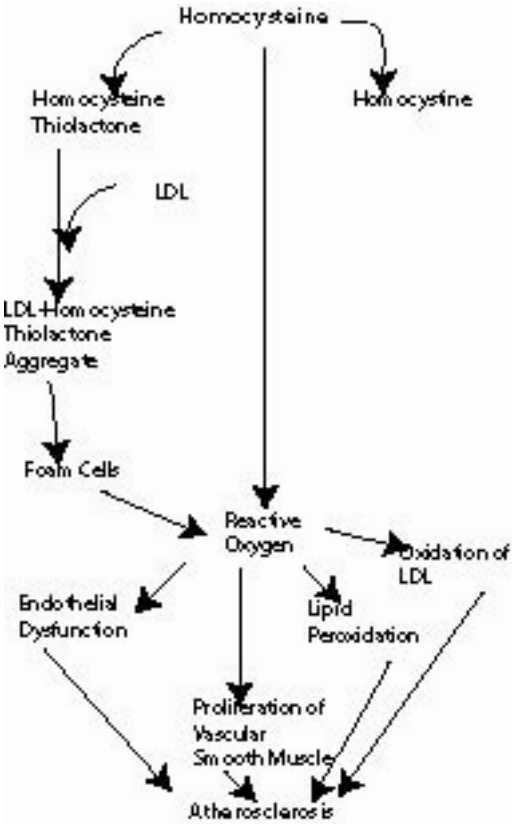

Figure 2. Postulated adverse vascular effects of homocysteine

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