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Title of Thesis : Biochemical And Genetic Studies On Hyperhomocysteinemia In Relation To Vascular Diseases And Role Of Homocysteine Lowering Agents On Vascular Risk Factors

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Findings

1. Homocysteine conforms to "Hill's Criteria of Causality", thereby establishing it as a risk factor for vascular disease, and not just a risk marker.
2. The mean homocysteine in normal North Indian urban population was 10.78 ± 0.21 μmol/L and the range was 2.6 – 15.0 μmol/L. This was comparable to worldwide data.
3. Mean homocysteine was not significantly different in males and females, even when females were segregated into those who were pre-menopausal and those who were menopausal.
4. Mean plasma homocysteine concentration in occlusive vascular disease was significantly higher than that in controls.
5. The association of homocysteine with vascular disease was greater in North Indian urban population than in other populations.
6. Multivariate analysis revealed that when all the parameters were considered in association with each other, causality (as per Hill's criteria) of all three types of vascular disease (i.e. coronary artery disease, cerebrovascular disease and peripheral vascular disease) was attributable only to homocysteine. Also, the association of hyperhomocysteinemia exceeded manifold the association of the other "conventional" risk factors with vascular disease.
7. The prevalence of homocysteine>10.0 μmol/L was higher than the prevalence of homocysteine>15.0 μmol/L in all categories of vascular disease patients (i.e. coronary artery disease, cerebrovascular disease and peripheral vascular disease), indicating an absence of threshold beyond which homocysteine is pathogenic, and a dose-response relationship between homocysteine and vascular disease.
8. Arteries and veins both were susceptible to the effects of hyperhomocysteinemia.

9. In cases of venous occlusion, the highest homocysteine levels were seen in the patients of deep vein thrombosis especially if it was complicated with pulmonary embolism. Thus, it was also demonstrated that homocysteine levels could have a prognostic or predictive role in patients with deep vein thrombosis.
10. The frequency of the C allele at MTHFR 677 was significantly higher in controls than in patients. Conversely, the frequency of the T allele was significantly higher in patients as compared to controls. The prevalence of the TT genotype of the MTHFR C677T polymorphism in patients (11.43%) was higher than in controls (2.86%), and, correspondingly, the prevalence of the CC genotype was lower in patients (58.57%) than in controls (71.43%).
11. As per the Hardy Weinberg calculations, it was ascertained that the observed prevalence of CC, CT and TT genotypes differed significantly from that expected in subjects of coronary artery disease and peripheral vascular disease.
12. Higher plasma homocysteine concentrations were associated with the 'TT' genotype of this polymorphism in patients of vascular disease.
13. Total antioxidant level were significantly lower in patients, especially those of cerebrovascular disease ($p=0.001$) and peripheral vascular disease ($p=0.005$), when compared to controls. Homocysteine levels did not bear a significant correlation with TAS.
14. The role of lipid peroxides, as a mechanism of perpetuation of vascular pathology due to hyperhomocysteinemia was demonstrated by its association with coronary artery disease and cerebrovascular disease, and its significant positive correlation with plasma homocysteine concentrations in patients of vascular disease.
15. Homocysteine concentrations bore a significant correlation with vitamin B_{12}, folate and lipid peroxides, thus suggesting lipid peroxides as a mechanism of vascular pathology (due to hyperhomocysteinemia), and vitamin B_{12} and folate as a means of reduction of homocysteine levels.
16. Whatever the cause of hyperhomocysteinemia, therapy with high dose (5mg) of folic acid alone, or a combination of 1.5mg of folate and 500 μg of vitamin B_{12} were equally effective in lowering homocysteine concentration even in the absence of a deficient state.

Thus, homocysteine has emerged as an easily modifiable risk factor of vascular disease.