Cardiovascular disease (CVD) is the commonest cause of death globally. Previously considered a disease of the affluent, the last decade has seen an epidemic increase in the burden of CVD in India and the developing world. Asian Indians are particularly prone to CVD as compared to all other ethnic groups. In Asians, the disease has been found to be more severe, diffuse and associated with more serious complications and higher mortality at younger age. Besides traditional risk factors like hypertension, diabetes mellitus, hyperlipidaemia and smoking, there has been growing interest in the role of newer risk factors such as homocysteine, C-reactive protein, lipoprotein(a), infections and inflammations in the pathogenesis of CVD.

Homocysteine is formed during the metabolism of the essential amino acid methionine. Plasma homocysteine levels are increased in males, aging, menopause, and in smokers. Deficient intake of folic acid, pyridoxine and cobalamin is the commonest cause of hyperhomocysteinaemia. Hereditary enzymatic abnormalities and systemic disorders like hepatic impairement, chronic renal failure and certain malignancies are also associated with elevated homocysteine concentrations. Drugs like phenytoin, metformin, thiazide diuretics, theophylline, oral contraceptives and cytotoxic drugs can cause an increase in homocysteine levels.

The incidence of hyperhomocysteinaemia in community based Indian studies has been reported to be much higher (52-84%) than in the west.2,3 The factors implicated are dietary deficiency of vitamins involved in homocysteine metabolism and genetic defect in methylenetetrahydrofolate reductase (MTHFR) enzyme.4

The association between homocysteinuria, an inborn error of metabolism, and premature atherosclerosis has been well described in literature.5 This has lead to the recent interest in the role of elevated plasma homocysteine as an independent risk factor for progression and complications of atherosclerosis.5 Hyperhomocysteinaemia increases the cardiovascular risk conferred by other commonly present risk factors like hyperlipidaemia and smoking as has been reported by several studies.7 To date there are no large randomized controlled trials to justify lowering homocysteine levels to retard atherosclerotic vascular events. In the HOPE 2 study vitamins failed to reduce the risk of new cardiovascular events.8 However, treatment of hyperhomocysteinemia maybe justified in subjects with unexplained atherosclerosis.

Type 2 diabetes mellitus is a well known risk factor for the development of atherosclerotic vascular disease. It has been suggested that insulin resistance, which is the fundamental biochemical defect in diabetics, is the major cause for this rather than hyperglycaemia per se.9 Ruige et al demonstrated that hyperinsulinaemia (an early marker of insulin resistance) was associated with an increased risk of cardiovascular disease.10 Insulin resistance plays a important role in the development of atherosclerosis and hypertension.7 Higher levels of plasminogen activator inhibitor-1 (PAI-1) and increased fibrinogen levels are related to insulin resistance. Dyslipidaemia with increased LDL cholesterol and reduced HDL cholesterol is also found in insulin resistant states like metabolic syndrome. Insulin resistance is also associated with endothelial dysfunction and microalbuminuria.

Even though both insulin resistance and hyperhomocysteinaemia are associated with atherosclerosis, the correlation between the two has not been extensively studied. The Framingham Offspring study demonstrated a modest association between hyperinsulinaemia and fasting homocysteine levels.11 Similarly in another study in Japanese diabetic patients, insulin resistance was an independent predictor of total homocysteine levels.12 Gillay et al also showed a positive association between homocysteine and insulin resistance.13 However, Tanrikulu-kilic et al found no correlation between plasma homocysteine and insulin resistance in healthy pre-menopausal women.14 Two other studies in large healthy populations reported a similar effect.15,16

In the present issue of this journal Sainani et al have observed that both insulin resistance and homocysteine were significantly and independently associated with CVD risk in 130 subjects. This is the first important study to assess the relationship between insulin sensitivity and homocysteine levels in the Indian population. Moreover, unlike the previously reported studies in healthy population, this study recruited patients with documented CVD and compared them with controls. This study could have been strengthened had the controls been selected on the basis of normal coronary angiography rather than normal Echo and stress test. Furthermore, there is a high prevalence of vitamin B12 deficiency in Indian subjects which could affect the homocysteine levels. It would have been interesting had the association of vitamin adjusted homocysteine levels and insulin resistance been analysed as was done in Framingham study. The prevalence of coronary artery disease is increasing in India and therapies targeted at reducing these newer risk factors could provide another therapeutic option. Larger trials are needed in Indian subjects to assess the beneficial effects of lowering homocysteine and insulin resistance on cardiovascular events.

References


8. The Heart Outcomes prevention evaluation (HOPE 2) investigators, homocysteine lowering with folic acid and B vitamins in vascular disease. NEJM 2006; 354: 1566-77.


**ANNOUNCEMENT**

**6th Infectious Disease Certificate Course - IDCC 2009**

6th September (Sunday) - 13th September (Sunday), 2009 • 8.30 am to 4.30 pm

VENUE: PD Hinduja National Hospital and Medical Research Centre, Mumbai, INDIA

ORGANISED BY

PD Hinduja National Hospital and Medical Research Centre, Mumbai, India in collaboration with Henry Ford Health Systems, Detroit, USA

Objective: Diagnosis, Management & Prevention of Infectious Diseases.

Focus: Acute Febrile Illnesses, Tuberculosis, HIV, Infections in ICU & Immunocompromised, Organ Specific Infections, Pharmacology, Microbiology.

Format: Ward and Microbiology Rounds, Archived Cases, Interactive Lectures, MCQs, Work Mats, Visit to Infectious Disease Hospital.

Eligibility: Post-graduates in Medicine and Microbiology (Final year postgraduates may also be considered).

Registered procedure: Candidates to send short bio-data with Demand Draft / Cheque of Rs.4,500/- in favour of PD Hinduja National Hospital and Medical Research Centre payable at Mumbai.

Candidate to make their own arrangement for accommodation.


Course Information / Detailed Programme: www.hindujahospital.com/IDCC 2009

Inquiries: 022-24447204 / 5, marketing@hindujahospital.com

Course Co-ordinators: Dr. F.D. Dastur • Dr. Rajeev Soman • Dr. Camilla Rodrigues