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RISK PREDICTION – HOMOCYSTEINE IN CORONARY HEART DISEASE

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ABSTRACT

Majority of patients who experience a Coronary Heart disease event have one or more of the conventional risk factors for atherosclerosis and so do many people who have not yet experienced such an event. Thus predictive models based on conventional risk factors have lower than the desired accuracy, providing a stimulus to search for new factors to predict accurately the risk of CHD. In this regard newer risk factors like homocysteine, Lp(a), insulin resistances are the important ones and are called as 'novel risk factors'. The study was undertaken to find the prediction of CHD risk by homocysteine in comparison with other conventional risk factors. The data obtained suggests a very high sensitivity, specificity and accuracy with above 90% positive prediction value for homocysteine in CHD patients when compared to commonest conventional risk factors.

KEY WORDS

Coronary Artery Disease, homocysteine, Conventional risk factors, Novel Risk factors.

INTRODUCTION

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the modern society. The cost of management of CHD is a significant economic burden and so prevention of coronary artery disease is very important step in the management. Prevention of CHD can be approached in many ways including health promotion campaigns, specific protection strategies, life style modification programs, early detection and good control of risk factors and constant vigilance of emerging risk factors (1). The concept of cardiovascular risk factors arose from the Framingham Heart Study a landmark study in cardiovascular disease epidemiology. The version of Framingham risk point scores by NCEP (ATP III) is based on the traditional risk factors of age, sex, dyslipidemia, blood pressure and smoking (2). By contrast, in the more recent Prospective cardiovascular Munster (PROCAM) simple scoring scheme, 8 risk variables are identified: age, family history of premature myocardial infarction, Diabetes mellitus, Systolic blood pressure, smoking, LDL-cholesterol, HDL-cholesterol, and triglycerides (3). Despite the lack of agreement, however, continued focus on newer factors is warranted as they may further improve our ability to predict future risk and determine treatment when they are included along with the classic risk factors. The study of these risk factors is important since the ability to accurately predict the CHD risk of a specific individual based on his or her conventional risk factor profile is limited (4). These newer risk factors are called 'novel risk factors' which includes Lp(a), homocysteine, fibrinogen, and hsCRP.

Elevated plasma homocysteine may be an important cause for atherosclerosis formation (5). The adverse effects of homocysteine, involve oxidative damage to vascular endothelial cells, increased proliferation of smooth muscle cells, and oxidative modification of low density lipoprotein, all leading to atherosclerosis (6).

Chamber's et al reported that plasma homocysteine is an independent risk factor for coronary artery disease (CAD) in Asian Indian compared to Europeans (7). In a recent study Nair et al reported that methylenetetra hydrofolate reductase (MTHFR) gene mutation causing hyperhomocysteinemia as a risk for increased risk of CAD in Indians (8). However, the result on hyperhomocysteinemia in CAD has been conflicting as several other studies have failed to demonstrate an association between homocysteine and CAD in Indians (9, 10). Thus the evidence for plasma homocysteine, as an

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independent risk factor in Indian community is not clearly understood. Therefore this study was done to evaluate the relationship between the total homocysteine levels and CAD in south Indians urban population. We compared the modifiable conventional risk factors with homocysteine in CAD patients to find the prediction rate of CHD risk.

MATERIALS AND METHODS

The patients were selected randomly from the Department of Cardiology, Sri Jayadeva Institute Cardiology, Bangalore, who had come for cardiac evaluation during October 2004 to August 2005. The study group consisted of 273 patients who had undergone coronary angiogram test, of which 117 had normal coronary arteries (control group) and 156 had stenosis (>50%) in one or more major epicardial coronary arteries (patients group). The study was approved from the ethics committee of the Institute and informed consent were obtained from patients.

The diagnosis of diabetes was based on past medical history and drug treatment for diabetes and, or fasting blood glucose level >126mg/dl or postprandial glucose >150mg/dl WHO criteria (11). The diagnosis of hypertension was based on drug treatment for hypertension and, or blood pressure >140/90mm of Hg WHO criteria (12). Persons who smoke (10 or more cigarettes/day) for the past one-year or more and also the persons who had quiet smoking in the past three months were included as smokers. If any one of parents had experienced premature CHD, then they were considered as patients having family history of premature CHD.

Biochemical Methods : A fasting blood sample was taken from all the patients and controls for the estimation of homocysteine. Homocysteine was assayed by using high pressure liquid chromatography apparatus equipped with electrochemical detector as described by J.L.D'Eramo et al (13). Here sodium borohydride ($NaBH_4$) was used as a reductant and 0.1M monochloroacetic acid and 3.6mM sodium octylsulfate adjusted to pH 3.2 was used as the mobile phase. All the reagents used were of HPLC grade.

Statistical analysis : All the values calculated as mean ± standard deviation. The two groups were analyzed by comparing each parameter by students- t test. The diagnostic statistics namely, sensitivity, specificity, positive predictive value, negative predictive value, accuracy, odds ratio and kappa were calculated for finding the diagnostic values of CHD risk factors. P values were computed using 'chi square' distribution.

RESULTS

The basic characteristics of the CAD patients and controls were given in table 1. There were 117 controls with 74 (63%) males and 43 (37%) females. The control group had 32 diabetic, 38 hypertensive and 38 with habit of smoking. The mean homocysteine (± SD) was 11.69 ± 2.8 μmol/L. In CAD patients 71 were diabetic, 118 were hypertensive and 91 were smokers. The mean homocysteine (± SD) was 18.59 ± 2.63 mmol/L. Statistically significant increases in number of patients having common risk factors are seen in CAD patients. Homocysteine was also increased significantly ($p<0.001$) in plasma of CAD patients when compared to controls.

Table 1 : Risk factors distribution in CAD patients and controls

Risk factors of CAD	Group 1 Controls (n=117)	Group 2 CAD patients (n=156)	P Value
Age in years (mean ± SD)	46.54± 8.18	51.12 ± 7.04	<0.001
Males (%)	74 (63.3%)	127 (81.4%)	—
Females (%)	43 (36.6%)	29 (18.6%)	
Family history of Premature CAD	18 (15.4%)	37 (23.7%)	0.089
Diabetes	32 (27.6%)	71 (45.5%)	0.002
Hypertension	38 (32.5%)	118 (75.6%)	<0.001
Smokers	38 (32.5%)	91 (58.3%)	<0.001
Homocysteine (μmol/L) (mean ± SD)	11.69 ± 2.80	18.59 ± 2.63	<0.001

Table 2 : Comparison of diagnostic values for CAD with different risk factors

Diagnostic Values for CAD	Diabetes	HTN	Smokers	F/H of premature CAD	Homocys-teine
Sensitivity (%)	45.51	75.64	58.33	23.72	92.95
Specificity (%)	72.65	67.52	67.52	84.62	86.32
PPV (%)	68.93	75.64	70.54	67.22	90.06
NPV %	50.00	67.52	54.86	45.41	90.18
Accuracy %	57.14	72.16	62.27	49.82	90.00
Odds Ratio	2.22	6.46	2.29	1.71	83.21
Kappa value	0.17	0.43	0.25	0.08	0.79
P value	0.002	<0.001	<0.001	0.09	<0.001

HTN – hypertension, PPV – positive prediction value, NPV – negative prediction value.

The diagnostic values for CAD patients for each of these conventional risk factors along with Homocysteine were calculated statistically and shown in table 2. Homocysteine showed the highest sensitivity (92.95%), specificity (86.32%), positive prediction value (90.06%), negative prediction value (90.18%) and accuracy (90%) when compared to other risk factors. The odds ratio for homocysteine was 83.21 which are highest when compared to diabetes (2.22), hypertension (6.46), smokers (2.29) and family history of premature CAD (1.71). Kappa values (0.79) show a substantial agreement of CAD patients with respect to Homocysteine.

DISCUSSION

Homocysteine a sulphur containing amino acid, which is derived from the dietary methionine, has been associated with cardiovascular events. Several studies show that the sites of adverse effect of homocysteine include endothelial surface, vascular smooth muscle cells, connective tissue, interaction with plasma lipoprotein, clotting factor and platelets (14). The association between raised homocysteine and thrombosis was reported by McCully (15), who demonstrated thrombovascular abnormality in homocystinuria patients. In the last three decades several studies (16, 17) showed an association between homocysteine and CAD.

Several recent studies investigated the contribution of homocysteine to CAD risk both among immigrant Indians (7, 18) and those living in India (10, 19). Chambers et al (7) reported that elevated plasma homocysteine levels were independently associated with CAD in UK Indians. A population study from Canada (18) reported that South Asians had higher plasma homocysteine than European counterparts. Boushy et al (20) showed homocysteine as an independent graded risk predictor for atherosclerotic disease in coronary, cerebral and peripheral vessels.

Recently Nair et al (8) reported that methylenetetrahydrofolate reductase (MTHFR) gene mutation causing hyperhomocysteinemia as a risk factor for CAD. There are other studies from south India (21, 22) showing the association of homocysteine with CAD risk. In contrast to these studies there are also few studies (10, 23) showing negative relation. The limitations in these studies could be the numbers, to detect the significant differences between the studied populations.

In our study the main modifiable risk factors considered were diabetes, hypertension and smoking. Other constitutional risk factors like age, male sex and family history of premature CAD were also compared between CAD and control group. Our data show a statistically significant increase in homocysteine in CAD patients when compared to controls (table 1). Patients with diabetes, hypertension and smokers are significantly more in CAD group in comparison to controls. When diagnostic values like sensitivity, specificity, positive prediction value and accuracy were compared (table 2) between these risk factors in CAD patients, homocysteine with highest sensitivity and accuracy emerged as the best predictor (with odds ratio 83.2) of CAD risk.

In conclusion our data suggests that plasma homocysteine levels were increased significantly in CAD patients when compared to controls. And also homocysteine is the best predictor of CHD risk amongst other conventional risk factor in CAD patients.

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