Hyperhomocystenemia is a Risk Factor For Coronary Artery Disease in Patients of Diabetes Mellitus in India

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ABSTRACTS:

Background: Prevalence of coronary artery disease (CAD) is very high amongst the people of Indian sub-continent. Among the Indians more than 60% of the CAD remains unexplained by conventionally risk factor. Recently a number of new cardiovascular risk factors have been identified & homocysteine is one of them. Various clinical studies have shown that higher homocysteine level is a risk factor for atherosclerotic vascular disease. Studies on the association of hyperhomocysteinemia as a cardiovascular risk factor in Indian patients have shown conflicting results. Hyperhomocysteinemia has been reported both in type-1 and type-2 Diabetes mellitus & has been correlated with macro vascular complication in western population. There is very limited number of studies of hyperhomocysteinemia as a cardiovascular risk factor in Indian Diabetic patients. So we undertook this study.

Methods: We studied 80 patients of diabetes mellitus with 20 healthy control subjects. Out of 80 patients, 40 patients of diabetes mellitus with CAD (Group-C)and their homocysteine level compared with 40 patients of diabetes mellitus without CAD (Group-B) and 20 controls (Group-A).

Results: The mean homocysteine level in Group-A is found to be 10.2 ± 1.4 µmol/L, in Group-B is 12.75 ± 4.2 µmol/L where as in Group-C is 19.4 ± 7.5 µmol/L. The mean homocysteine level was significantly high in patients of diabetes mellitus with coronary artery disease in comparison to patients of diabetes mellitus without coronary artery disease and healthy controls at $p < 0.01$.

Conclusion: Increased level of homocysteine is a risk factor for coronary artery disease in patients with of diabetes mellitus.

Keywords :- Coronary artery disease-diabetes mellitus-homocystein-Indian population

INTRODUCTION:

Prevalence of coronary artery disease (CAD) is known to be very high amongst people of Indian subcontinent [1]. Moreover CAD in Asian Indian occur prematurely and at least a decade or two earlier than that of the Europeans [2]. In Indian population more than 60% of the CAD remains unexplained by conventional risk factors like obesity, hypertension, smoking, dyslipidemia, and diabetes mellitus. Recently a number of new

cardiovascular risk factors have been identified in these subgroups of patients. They are upper body obesity, higher C-Reactive Protein (CRP), Plasminogen activator inhibitor-1(PAI-1) and homocystine level [3-5].

Homocystine, a sulphur containing amino acid is a product of methionine metabolism. A high level of this amino acid is injurious to vascular endothelium as it promotes LDL oxidation and thrombus formation. Observations in more than 80 clinical studies, mostly done in western countries have suggested that homocystine is a risk factor for atherosclerotic vascular disease and arterial and venous thromboembolism [6, 7]. Serum homocystine levels are dependant on age, renal function, dietary intake of folic acid and vitamin B_{12}. A number of studies have shown inverse relationship with blood homocystine level and serum folic acid, vitamin B_6 and vitamin B_{12} [8]. Epidemiologic studies conducted in Indian population have reported the prevalence of hyperhomocysteinemia in 52% to 84%. The mean homocysteine are also very high ranging from 19.5 to 23.2 μmol/l [9, 10]. This is in contrast to the studies in western population. This is attributed to the low dietary intake of vit B_{12} and folic acid as majority of Indians are vegetarian and the food they take are cooked for prolonged periods [11]. In view of this finding hyperhomocysteinemia could be an important cardiovascular risk factor in Indian population.

However studies on the association of hyperhomocysteinemia as a cardiovascular risk factor in Indian population has shown conflicting results, with some studies providing association [12], while others have found none [13-16].

Diabetes mellitus is another important risk factor for CAD. Results of epidemiological study indicate that it is associated with 2 to 4 times greater risk of CAD [17]. With 41 million people suffering from diabetes, India is regarded as the diabetes capital of the world. The number is slowly increasing and by 2025 the number is expected to be 68 million [18]. The risk of vascular disease in diabetes is dependant on hyperglycaemia and other risk factors like dyslipidemia, hypertension and obesity. However these known risk factors cannot explain all the risk for atherosclerosis in diabetes and new metabolic risk factor like hyperhomocystenemia may play a significant role [19].

Hyperhomocystenimia has been reported in type 1 and type 2 diabetes mellitus [20]. Multivariant regression analysis has shown an independent relationship between homocysteine and macro vascular complication in type 2 diabetes mellitus of western population [21]. There have been very few studies of hyperhomocysteinemia as a cardiovascular risk factor in Indian diabetes patients and they have shown mixed results. Munshi et al reported that hyperhocysteinemia is associated with macrovascular disease in a significant proportion of patients with type 2 diabetes mellitus [22]. However Deepa et al reported lack of association of homocysteine and CAD in urban south Indian male diabetic and non-diabetic subjects [23].

From the above facts it can be said that although the prevalence of hyperhomocysteinemia is very high in Indian population, few studies which have been conducted regarding the association between serum homocysteine level and CAD in both diabetic and nondiabetc subjects are inconclusive and there is a need for further study in this area.

MATERIALS AND METHODS:

The present study was conducted at Department of Medicine, V.S.S. Medical College, Burla, Odisha, India from the period of May 2007 to December 2010 and involved 80 patients of diabetes mellitus and 20 healthy control subjects. The study was approved by the Institutional Ethical Committee. A total of 100 cases were studied and categorized into three groups as follows.

Group-A: consisted of 20 healthy controls with normal fasting blood sugar and absence of evidence of ischemic heart disease both clinically and with normal 12 lead ECG.

Group-B: consisted of 40 patients of type-2 diabetes mellitus without CAD attending to the OPD or admitted to the indoor. They were diagnosed by revised ADA criteria 2011 i.e. fasting plasma glucose ≥126mg/dl and/or 2 hour plasma glucose ≥ 200mg/dl

Group-C: consisted of 40 patients of type-2 diabetes mellitus with CAD. Type-2 diabetes was diagnosed as per group-B criteria. CAD was diagnosed by history of typical angina associated with electro-cardigraphic evidence of Ischemic heart disease in 12 lead ECG or by trade mill test. Patients of type-2 diabetes mellitus with acute myocardial infraction were excluded. Other exclusion criteria were renal failure, proteinuria, and use of medications like digoxin, metformin, smoking, and cardiomyopathy.

Routine biochemical and hematological tests were done by automated analyzer and cell counter. Plasma homocysteine was measured by chemiluminescence method.

Statistical analysis: results are presented as means and standard deviations. Data were analyzed with SPSS version 11.0. Differences between groups were evaluated by using student's t test. Two sided p values < 0.5 were considered statistically significant**.**

RESULTS:

A total 100 cases were included in this study with a mean age of 57.8 ± 6.9. There was no statistical significant in the age of the three groups studied $(p>0.05)$. The percentage of male cases was 60, 56 and 58 in group A, B and C respectively. There was no statistical significance observed in the gender distribution in the three groups $(p>0.05)$. There was no statistical difference in fasting blood sugar level, serum urea, serum creatinine, and total cholesterol level (including TG, HDL, LDL) between the three groups $(p>0.05)$. The mean homocysteine level in group-A $(10.2\pm1.4~\mu mol/L)$ was comparable to group-B *i.e* diabetes mellitus without coronary artery disease patients $(12.75\pm4.2~\mu mol/L)$. However the mean homocysteine level in group-C *i.e.* Diabetes mellitus with coronary artery disease patients $(19.4\pm7.5~\mu mol/L)$ was significantly high in comparison to group-A & B $(p<0.01)$. Comparison of all biochemical parameters has been depicted in table-1.

DISCUSSION:

Recent observation in large number of clinical studies suggests that homocysteiene is an independent risk factor for atherosclerotic vascular disease including CAD and stroke especially in western population [24]. There are very few studies on homocysteiene level and its predictive value in vascular disease of Indian population. A study of plasma homocysteine level amongst immigrant Indians in the UK demonstrated association of plasma homocysteine levels with CAD [14]. But in a similar study conducted at Singapore the homocysteine level was similar in three ethinic groups namely Indians, Malayas and Chinese [25]. Many studies conducted at developed countries like USA and Japan have reported that there is an increase frequency of elevated homocysteine in patients of diabetes mellitus with CAD.

Limited number of studies has been undertaken regarding the association of serum homocysteine level with CAD in Indian diabetic patients. Das et al reported that the plasma homocysteine level concentration was lower in lean type 2 diabetes mellitus patients [26]. The study by Munshi et al reported that hyper homocysteinemia is associated with macrovascular disease in a significant proportion of patients with NIDDM [22]. In a recent study conducted by Deepa et al there was no association between serum homocysteine level and CAD in south Indian male patients with or without diabetes mellitus [15]. Also there was no significant increase of homocysteiene level in diabetes per se or in diabetic patients with CAD. In the present study, there was no significant increase of homocysteine level in patients with diabetes mellitus in comparison to control. However in patients with diabetes mellitus with CAD the homocysteine level was significantly high in comparison with patients of diabetes mellitus without coronary artery disease and that of the controls.

Our results are in contrast to that of Deepa et al, This could be explained by the fact that the mean homocysteine level in these study population was less in comparison of ours. Higher homocysteine level in the present study is in accordance with that of various epidemiological reports conducted in Indian population which showed that almost $2/3^{rd}$ have hyperhomocysteinemia. High homocysteine levels in our study subjects could be due to poor intake of dietary vit B_{12}, B_6 and folic acid and low serum levels of these nutrients. This could not be confirmed as we have not estimated serum B_{12} and folic acid level. Our finding of raised homocysteine level in type-2 diabetes mellitus with CAD suggests that homocysteine may contribute to identify patients for screening of CAD in addition to other recognized cardiovascular risk factors. If hyperhomocysteinemia is associated with type-2 diabetes mellitus further evaluation for CAD should be undertaken in these patients. Other larger and prospective studies are needed in Indian subjects to confirm our findings and to establish whether homocysteine level can be used as a suitable marker for CAD screening in type-2 diabetes patients.

CONFLICT OF INTEREST:

The authors declare there is no any conflicting interest

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Table-I. Comparison of various biochemical parameters in three groups of patients.

	Group-A (control)	Group-B (DM without CAD)	Group-C (DM with CAD)	*p* value
Number	20	40	40	
Age(in years)	52.0±5.26	58.0±6.24	64.0±5.14	
Diabetes age (in years)	-	6.8±4.3	8.2±6.8	>0.05
BMI kg/m^2	30.1±3.52	30.2±5.5	29.8±4.5	
FBS	82.6±17.6	170.2±44.98	180.2±50.2	
PPBS	105±21.5	210.2±60.38	220.6±58.1	
Urea	24.6±7.4	28.4±5.9	32.2±9.6	
Creatinine	0.78±0.24	0.98±0.24	1.2±0.26	
Total Cholesterol	204.4±32.85	228±47.39	236±30.46	
TG	108.6±57.92	162.3±79.1	158.4±79.3	
HDL	43.7±9.24	44.2±9.38	40.2±6.92	
LDL	120.6±20.5	130.6±39.1	136.2±28.4	
Hb A$_1$C	5.1±1.34	8.2±1.42	7.8±1.82	
Microalbuminuria	84±59.3	86±67.9	110±57.1	
Homocysteine	10.2±1.4	12.75±4.2	19.4±7.5	<0.01