The Prevalence Of Hyperhomocysteinemia And Its Correlation With Conventional Risk Factors In Young Patients With Myocardial Infarction

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Abstract: Background: Ischemic heart disease is a leading cause of death throughout the world. Indians are more prone to premature coronary artery disease. About 20% patients with CAD have no identifiable risk factors. Thus the importance of homocysteine as a risk factor for CAD in Indian patients needs to be recognized. Objective: The present study was designed to find out association between the plasma homocysteine and traditional risk factors in young acute myocardial infarction patients. Materials And Methods: The study included 50 male patients of less than 40 years old, who were fulfilling the WHO criteria for acute myocardial Infarction presenting within 48 hours. Plasma homocysteine levels were studied in addition to the traditional risk factors. RESULTS: The mean age of the patients was 34.1 ±4.2years. The mean homocysteine level was 23.58 ±6.2 µmol/L. The prevalence of hyperhomocysteinemia was 70% in the study subjects. Plasma homocysteine levels were significantly increased in patients with smoking. ($p \leq 0.001$),alcoholism($p \leq 0.003$) and dyslipidemia($p \leq 0.006$) . Elevation of homocysteine levels in patients with Diabetes mellitus, Hypertension and family history of CAD (coronary artery disease) was not significant. Conclusion: Our results showed that homocysteine levels are elevated in young patients with AMI. In the present study significantly higher level of homocysteine was found in smokers, patients with alcoholism and dyslipidemia. However, there was no significant elevation was found in Diabetes mellitus, Hypertension and family history of CAD. Plasma homocysteine has emerged as a significant independent risk factor for young MI patients. Therefore, plasma homocysteine should be evaluated in all young patients with myocardial infarction especially in the absence of traditional risk factors. [Suthar H et al NJIRM 2013; 4(1) : 72-77]

Key Words: Acute myocardial infarction, young adults, homocysteine, conventional risk factors.

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Introduction: Coronary artery disease (CAD) is a most common cause of mortality and morbidity throughout the world[1]. Acute myocardial infarction (AMI) in the young, defined as being less than 40-45 years of age in most studies, accounts for 3-12% of total AMI[2]. It mostly afflicts men[3]. It strikes an individual during the most productive years of life. People in our part of the world suffer from CAD at relatively younger age, i.e., about half of MI occurs under the age of fifty years[4]. The incidence of CAD in the young has been reported to be 12%–16% in Indians[5, 6]. About 50% of the CAD-related deaths in India occur below the age of 50 years, and about 25% of acute myocardial infarction in India occurs under the age of 40 years[4, 7].

Although traditional risk factors such as hyperlipidemia, smoking, hypertension, and diabetes mellitus are thought to explain most CAD, 15% to 20% of those with CAD have no identifiable risk factors and therefore miss the opportunity for primary prevention[8]. The cause of atherosclerosis which is the primary pathologic basis of CAD still remains elusive. In the context of atherogenesis, we continue to examine the role of several precursors of atherogenesis[9]. Evaluation of major coronary risk factors in Indian patients undergoing angiography has shown that in about one-third of the patients no major risk factors are detectable, yet suffer from the disease[10]. Therefore, the role of newer risk factors is being identified.

Homocysteine is a novel atherosclerosis risk factor; it derives from the metabolism of methionine, an essential amino acid found primarily in dietary animal protein. Less than 1% circulates as free thiols; 70-80% is bound to plasma protein chiefly albumin and remaining 20-30% combines with itself or with other thiols to from dimers[11]. Normal levels of plasma homocysteine usually range from 5 to15 mmol/L. Higher fasting values are classified as moderate (16 to 30 mmol/l), intermediate (31 to 100 mmol/L) and severe (>100 mmol/L) hyperhomocysteinemia.

Homocysteine concentrations are determined by genetic and nutritional factors, and deficiencies of vitamin B6, B12 and Folic acid are associated with

hyperhomocysteinemia[12].Low blood levels of folate appear to be a particularly strong environmental determinant of homocysteine levels in many populations. studies have found increased risk of myocardial infarction among patients with moderate hyperhomocysteinemia[13]. Elevated levels of homocysteine are associated with vascular disease[14, 15]. Factors which influence the level of homocysteine include age, genetic and nutrition.

This study was carried out to assess the homocysteine levels in CAD patients and to compare these with conventional risk factors such as hypertension, smoking, diabetes, obesity, family history and abnormal lipid profile. The present study was conducted in the younger age group of patients.

Material and Methods : Total 50 patients with first acute myocardial infarction were studied. All patients from 16–40 years of age presenting with first acute myocardial infarction were included in the study. All patients detail history was taken including occupation, any past history of ischemic heart disease, hypertension, diabetes mellitus or cerebrovascular accident.

The diagnosis of AMI was confirmed based on WHO criteria i.e. at least two of the three elements (1)history of ischemic chest pain (2) serial electrocardiogram changes of ST- segment elevation of >1 mm with or without T wave inversion and Q wave in more than two consecutive limb leads or chest leads in standard 12 lead electrocardiogram (3) cardiac enzymes elevation. A young patient was defined as one aged 40 years or less upon admission.

Exclusion Criteria

1. Patients aged more than 40 years.
2. Patients with BMI > 25 kg/m^2 were considered as obese.
3. Patients on drugs such as methotrexate, anticonvulsants.
4. Patients with hyper/hypothyroidism, liver and renal disorder.
5. Patients with stable or unstable angina, or patients having old MI

Risk factors of CAD were defined as:

1. Overweight (body mass index >25kg/m^2)
2. Smoking (more than 10 cigarettes daily for at least 5 years)
3. Family history (any first-degree relatives with confirmed CAD)
4. Diabetes mellitus (FBS >126mg/dl, using insulin or oral hypoglycemic agents or newly detected Diabetes Mellitus cases satisfying WHO criteria.)
5. Hypertension (Known hypertensive using antihypertensive drugs or newly detected hypertensive according to JNC VIII criteria)
6. Dyslipidemia - According to US National Cholesterol Education Program Expert Panel (NCEP-ATP III) guidelines, patients were considered to have dyslipidemia when (a). Total cholesterol > 200 mg%, (b). HDL < 40 mg %, (c). LDL > 100 mg% (d). Triglycerides > 150 mg%.

Fasting plasma homocysteine : Plasma homocysteine level >15 µmoles/L was considered as hyperhomocysteinemia.

Amount, duration and the type of alcohol in the form of Rum, Whisky, Brandy, Vodka, Gin, etc consumed was enquired, those subjects who consumed more than half bottles of these spirits daily (or intermittently with abstinence of 2-3 days), for more than 5 years were considered as alcoholics The female patients were asked about the current use of Oral contraceptive pills or left less than 3 months of diagnosis of myocardial infarction. The patients walking 4 Km/day for 5 times a week were labeled as physically active and patients walking less than that as physically inactive or sedentary. Patients were examined for cardiovascular system, measurement of height and weight, examinations for clinical signs of hyperlipopreteinemia such as arcus corneae, xanthomata, yellow deposits over palmer creases, yellow papules on skin and mucosa, lipaemia retinalis and hepatosplenomegaly.

In every patient CBC, ESR, WBC, plasma proteins, Serum lipid profile, S. Troponine –I and S. Homocystine level were done " FBS is more than 100mg% or if there is family history of diabetes mellitus in first degree relatives, oral GTT was done. Fasting lipid profile was

investigated within 48 hours of acute MI, because lipid profile is altered by acute MI, it tends to lower the HDL-C and raises triglycerides.

Results: In present study, out of 50 patients, 47(94%) were male and 3(6%) were female. The mean age of the patients was 34.1 ±4.2years ranging from 22 to 39 years. The youngest male and female was 22 and 39 years of age respectively. Male to Female ration in our study was 16: 1. Chest pain was the most common symptom present in all patients (100%), followed by sweating (62%), and dyspnoea (36%). Vomiting was present in 12% and palpitation in 6%.

Table No. 1 : Age and Sex distribution

Age in Years	Male	Female	Total	Percentage (%)
16-25	2	-	2	4
26-30	11	-	11	22
31-35	13	-	13	26
36-40	21	3	24	48
Total	47	3	50	100

In present study, most common site of MI is anterior wall 27(54%), followed by inferior wall15 (30%), lateral wall6 (12%) and posterior wall 2(4%) patients. In our study STEMI was found 41(82%) of patients, while NSTEMI was found in 9(18%) of patients.

In present study Smoking (72%) was the predominant risk factor followed by dyslipidemia(66%), alcoholism(40%) Hypertension (36%) and Sedentary life style (28%).Thirty-three patients (66%) had LDL >100 mg/dl while TG>150mg/dl was present in 15(30%) of patients and low LDL (<40mg/dl) was present in 14(28%) patients.

Table: 2: Risk factors in young patients with myocardial infarction

No.	Risk factors	Number of Cases	Percentage
1	Smoking	36	72
2	Dyslipidemia	33	66
3	Alcoholism	20	40
4	Hypertension	18	36
5	Sedentary lifestyle	14	28
6	Family H/O CAD	8	16
7	Diabetes Mellitus	11	22
8	Obesity	5	10

The mean homocysteine level was 23.58 ±6.2 µmol/L. Smokers had significantly higher level of plasma homocysteine than non smokers (28.15±6.1vs19.92±5.12, p< 0.001), which was statistically significant. In patients with STEMI plasma homocysteine level (25.41±5.12) was higher than NSTEMI patients (23.43±6..65). The mean homocysteine level in vegetarians was 27.11±6.78 µmol/l and in non-vegetatians it was 20.23±6.67 µmol/l.

Table 3: Homocysteine levels with relation to risk factors among patients

No	Risk Factor		(%) Percentage	Homcysteine Level	P value
1	Smoking	Present	72	28.15±6.1	<0.001
		Absent	28	19.92±5.12	
2	Diabetes Mellitus	Present	22	19.91±5.23	0.872
		Absent	78	20.28±5.12	
3	Dyslipidemia	Present	66	28.76±5.45	0.006
		Absent	34	19.73±5.12	
4	Hypertension	Present	36	23.15±4.13	0.059
		Absent	64	19.31±4.12	
5	Family H/O CAD	Present	16	23.12±4.32	0.510
		Absent	84	19.46±3.12	
6	Obesity	Present	10	21.69±5.34	0.089
		Absent	90	20.45±5.89	
7	Alcoholism	Present	40	24.34±5.78	0.003
		Absent	60	19.56±4.23	

There was significant elevation of homocysteine in patients with smoking followed by alcoholism and dyslipidemia. There was no significant elevation of homocysteine in patients having risk factors like Diabetes mellitus, Hypertension and family history of CAD.

Table No. : 4: Biochemical Parameters in Dyslipidemic and Normolipidemic patients

	Total patients	Dyslipidemic patients	Normolipidemic patients
No	50	36	14
Age	34.1 ±4.2	32.1±1.6	35. 9±3
% Male	94	94.44	92.85
S. Homocysteine (nmol/ml)	23.58 ± 6.2	28.76± 5.45	19.73± 5.12
S. Cholesterol (mg/dl)	191.9± 40.12	212.7± 52.1	178.0± 27.6
S. Triglycerides (mg/dl)	163.4± 52.1	189.2± 56.6	139.2± 33.2
S. HDL (mg/dl)	38.4± 15.2	36.8± 12.6	42.7± 9.5
S. LDL (mg/dl)	123.9± 20.7	136.8± 19.1	113.8± 16.9

Discussion : Young patients, in most populations are characterized by less extensive disease and relatively favorable prognosis, as compared to older patients. In contrast young Asian Indians with CAD usually have a poorer prognosis because of extensive atherosclerosis and multivessel disease. In the present study the mean age of the patients was 34.1 ±4.2 years. In the Indian subcontinent CAD occurs about a decade earlier, as compared to the western world. The sex distribution in this study was 94% males and 6% females. The study was predominantly a male oriented, as CAD affects young males more severely and commonly than females. This can also be attributed to the protective effect of estrogen in premenopausal females.

The prevalence of hyperhomocysteinemia was 70% in our study. It is comparable with study done by Puri et al[16], in which it was 72.5 % and Kumar et al[17] 83.3%. Smoking as a most common risk factor was present in 72% of our patients. This correlates with studies done by Mohammad masoomi et al[18] (66.3%), Puri et al[16] (52.94%). Smoking accounts for approximately 20% of all deaths of CAD in the US as described by the Washington office technology assessment group study. Diabetes mellitus was seen in 22% patients in our patients which correlates with Puri et al[16].

Table No.5:
Prevalence of hyperhomocysteinemia in India

Study	Age of participant	Prevalance
Kumar A et al[21]	<45 yrs	83.3 %
Puri A et al[16]	<45 yrs	72.5 %
Yashwant K et al[17]	<40 yr	58.0%
Our Study	<40 yr	70%

The relation between diabetes and CAD is not uniform in all population. Connor[19] described the relative risk of diabetes in CAD and has shown an incidence of diabetes in CAD ranging from 32 to 67%. Family history was present in 16% of our patients. It has been classified in category IV (nonmodifiable) in the classification given by Pearson[20]. Its presence significantly increases the risk of future development of CAD and it has a multiplying effect in the presence of other risk factors.

Table No.5
Comparison of Homocysteine levels with other studies

Studies	S. Homocysteine Level
T Angeline et al[23]	24.59±6.14
Kumar A et al [21]	26.9±6.2
Puri et al[16]	27.8±13.11
Abraham et al[22]	22.81±13.9
Harish Rao B et al [24]	18.59 ± 2.63
Our study	23.58 ±6.2

In our study the mean level of homocysteine in patients was23.58 ±6.2 µmol/L which correlates with studies done by T Angeline et al[23], Kumar A et al[21] and Abraham et al[22]. Hyperlipidemia was seen in 36 % of the patients in our study. In the hyperlipidemic patients S. homocysteine level was 28.76±5.45while in the normolipidemic patients it was 19.73±5.12 µmol/L (p=0.006). Thus there was

a significant difference in the homocysteine levels in relation to the lipid profile. Elevated serum cholesterol is causally associated with increased risk of CAD. Specifically a 10% increase in serum cholesterol is associated with a 20 to 30% increased risk of CAD and elevations earlier in life may be associated with higher risk of CAD as given by Larosa et al[25]. A low HDL and high triglycerides along with LDL can occur alone or in combination and multiply the risk of CAD. In our study no significant difference in mean homocysteine level between patients having ST elevation myocardial infarction as compared to patients with non-ST elevation myocardial infarction.

Boushey et al reported a meta-analysis of 27 observational studies in which it was estimated that about 10% of coronary heart disease in the general population might be attributed to homocysteine[26]. Graham et al in the large European collaborated study (ECAP) concluded that homocysteine was an independent risk factor for atherosclerotic disease[27]. A study by Chambers et al suggested plasma homocysteine as an independent risk factor in Indian migrants to UK[28]. Population studies have shown that plasma homocysteine concentrations are higher in immigrant ethnic Indians compared to North Americans and European Whites [28]. Reduced intake of vitamin B12 has been reported in Indians and cooking may further destroy folate content . This may account for higher homocysteine levels in Indians. Prolonged lowering of homocysteine by 3-4 µmol/L was associated with a 30-40% reduction in risk of CAD[29.]

Conclusion: In the present study significantly higher level of homocysteine was found in smokers, patients with alcoholism and dyslipidemia. However, there was no significant association between hyperhomocysteinemia and other conventional risk factors like Diabetes mellitus, Hypertension and family history of CAD. Thus, plasma homocysteine should be evaluated in all young patients of myocardial infarction especially in the absence of traditional risk factors and it should be considered as an independent risk factor for development of future CAD. The sex distribution in this study was 94% males and 6 % females. The study was predominantly a male oriented, as CAD affects young males more severely and commonly than females. This can also be attributed to the protective effect of estrogen in premenopausal females.

Identification of these individual risk factors have not only created a new challenge to the understanding of pathology of MI but have also opened up different approaches other than simply modifying the conventional risk factors in primary prevention of MI. Therefore, the roles of newer risk factors have to be identified. This observation needs further validation with large scale studies to justify for early screening of Homocysteine levels as it is a potentially modifiable risk factor with little economic burden.

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