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Research Article

Study of Pattern of Dyslipidemia and Lipoprotein Abnormalities among Siblings of Young Acute Myocardial Infarction Patients

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Abstract

Introduction: Coronary heart disease (CHD) represents the leading cause of death in adults worldwide. Familial clustering in young MI may be due to common genetic pool, to the common family environment, or a mixture of both.

Methods: This is a case control prospective study in which total 110 siblings of young Indian patients who suffered from myocardial infarction and 50 healthy young controls were studied over a period of 2 years. The primary objective was to study the pattern of dyslipidemia and lipoprotein abnormalities and secondary objective was to study the prevalence of conventional risk factors among siblings of young Indian patients (age < 45 years) with acute myocardial infarction (MI).

Results: Age and sex distribution were well matched. On studying conventional risk factors in groups A and B, it was seen that the history of smoking (72% vs 52% p-0.021), hypertension (62% vs 30% p-0.0003), diabetes mellitus (38% vs 12% p-0.001) and increased waist circumference (60% vs 32% p0. 001) were more in group A in comparison to group B. On analyzing lipid profile in group A and B, it was found that total cholesterol (210.09 ± 0.09 vs 186.62 ± 31.67, p-0.0001), triglyceride (162.82 ± 25.08 vs 145.36 ± 27.83 p-0.0002, LDL (140.31 ± 39.27 vs 115.82 ± 32.46, p-0.0002), HDL (37.90 ± 8.16 vs 42.56 ± 6.45, p-0.0002), ApoB100 (152.17 ± 51.09 vs 122.32 ± 18.79, p-0.003), ApoA1 (134.92 ± 55.61 vs 172.42 ± 49.84, p-0.0001), ratio of ApoB/ApoA1 (1.45 ± 0.93 vs 0.76 ± 0.32, p-0.004) and LP (a) (27.36 ± 16.24 vs 16.70 ± 5.93, p < 0.0001) were different in both groups.

Conclusion: Conventional atherosclerotic risk factors, lipid and lipoprotein abnormalities were significantly more common in sibling of young acute MI in comparison to the general population.

Keywords: *Acute Coronary Syndrome; Myocardial Infarction; Dyslipidemias; Apolipoproteins; Lipoprotein (a)*

Introduction

Coronary heart disease (CHD) represents the leading cause of death in adults globally [1,2]. Although myocardial infarction (MI) mainly occurs in patients older than 45 years, young men or women can suffer acute MI. Fortunately, its incidence is not common in patients younger than 45 years [3]. However, the disease carries a significant morbidity, psychological effects, and financial constraints for the person and the family when it occurs at a young age. The protection offered by young age has been slowly taken away by the increased prevalence of risk factors for CHD in adolescents such as smoking, obesity, and lack of physical activity [4]. The cut off age of 45 has been used in most studies to define young patients with MI and the same age criteria was used in this study [5].

Family history in young MI

Family and twin studies are consistent with premature CAD being strongly influenced by genetic factors [6,7]. Several prospective studies [8-10] indicate that a family history of premature CHD is an independent risk factor even when other risk factors are taken into account. The relative risk for CHD in first-degree relatives has been reported to range from two to as high as twelve times that of the general population [11-13].

Familial clustering may be due to genetic resemblance between members of the family, to the common family environment or, as is probably the case where both factors contribute. Members of a family will tend to share similar environmental factors such as occupational classification, diet, smoking, exercise habits and psychosocial stress, which have been shown to be related to the incidence of ischemic heart disease. This will perhaps be true of siblings rather more than of parent and child [14].

Dyslipidemia and lipoprotein abnormalities in siblings of young myocardial infarction patients

A large US study of persons developing CHD before the age of 60 years showed that an LDL cholesterol concentration of > 130 mg/deal was more than twice as common in their asymptomatic siblings under the age of 60 years as in the population at large (38% v 16%) [15]. Analogous but much less pronounced differences were observed in the European Atherosclerosis Research Study (EARS) which investigated young adults with a paternal history of myocardial infarction before the age of 55 [16]. In this study the best lipoprotein discriminants were plasma apoB100 and triglyceride concentrations, which were higher in those with a positive family history of premature CHD than in age and sex matched controls.

Pattern of dyslipidemia and lipoprotein abnormalities in Indians

Indians tend to have higher levels of triglycerides, lower HDL levels and higher levels of LP (a). In addition, higher CHD risk in this population may be related to a higher prevalence of metabolic syndrome, insulin resistance, and diabetes. The metabolic syndrome has become increasingly common in India. Therefore, Indians with dyslipidemia should be treated as aggressively as if they had a CHD risk equivalent-similar to the treatment of patients with diabetes or heart disease. Lipoprotein (a) is still considered an emerging risk factor. A high level of LP (a) is in the prevalent dyslipidemia in patients with premature CHD.

Despite all available theoretical assumptions, there are very few studies defining the role of lipid and lipoprotein abnormalities among siblings of acute myocardial infarction patients. High risk families such as these account for > 50% of coronary heart disease before the age of 45 years, intensive efforts should be made to identify and alter modifiable risk factors. Therefore, this study was planned with the primary objective to study the pattern of dyslipidemia and lipoprotein abnormalities among siblings of Young patients (age <45 years) with acute myocardial infarction and secondary objective to study the prevalence of conventional risk factors smoking, diabetes, hypertension, abdominal obesity among siblings of Young patients with acute myocardial infarction.

Methods

This study was conducted in the department of Cardiology of Dr. Ram Manohar Lohia Hospital, New Delhi. It is a case control prospective study. A total of 123 siblings of young Indian patients who suffered from myocardial infarction at less than 45 years of age and 62 healthy young controls were screened over the period of 2 years. Out of 123 cases, 110 siblings were finally recruited in the study (Group A) and out of 62 healthy controls, 50 (Group B) were selected for study based on different inclusion and exclusion criteria.

Inclusion criteria

1. Siblings of young Indian patients (age < 45 years) with acute myocardial infarction

2. The subject who had provided written informed consent.

Exclusion criteria

1. Acute inflammatory illness (within the last month)
2. Individuals with valvular heart disease
3. Acute or chronic liver disease
4. Acute or Chronic Renal Failure
5. Acute Infectious diseases
6. Patients inability or unwillingness to comply with study protocol
7. The subject is already taking anti-hyperlipidemia drugs.

Procedures of measurement

Venous blood was collected from the ante cubital vein of the subjects after overnight fasting. Individuals were seated for at least five minutes prior to phlebotomy to avoid hemoconcentration. 4 ml of blood was collected in plain vial for routine biochemical investigations and extended lipid profile. Serum sample was stored in aliquots at -20°C and not thawed till batch analyzed for serum APO A1, APO B and Lpa is complete. Analysis was done within 6 months as per their stability suggested in the literature provided with kit. Lipid profile, APO A1 and APO B and Lipoprotein (a) test, measurement was done by auto analyzer. APO A1, APO B measurement was done by Roche Tina-quaint Apolipoprotein A 1 reagent and Roche Tina-Quant Apolipoprotein B reagent using an Immunoturbidometric assay on Roche/ Hitachi 917 analyzer.

Study definitions

Baseline clinical characteristics of siblings of young MI patients were evaluated. Clinical profiles include age, sex, smoking history, hypertension, diabetes mellitus and abdominal obesity.

Smoking: Both cases and controls were classified as smoker and non-smoker. A smoker [21] is defined as a patient who had smoked cigarettes regularly, at least 1 cigarette/day within 2 years before study inclusion. A non-smoker is defined as a person who has not smoked a cigarette in his or her life or her life or quit smoking at least two years before inclusion in the study.

Participants were diagnosed as hypertensive [22] if they are using anti-hypertensive medication, or if either systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg was recorded at least twice during standard examination.

Diabetes mellitus [23] was diagnosed as a fasting blood glucose of ≥ 126 mg/dl at least two times in admission or 2-hour plasma glucose ≥200 mg/dl during an OGTT (75g); or random plasma glucose ≥ 200 mg/dl with symptoms of hyperglycemia or if they are treated with hypoglycemic agents or insulin.

Central obesity [24] was defined on the basis of waist circumference (WC). Men and women with WC values ≤ 102 and ≤ 88 cm, respectively, were considered to have a normal WC, whereas men and women with WC values > 102 and > 88 cm, respectively, were considered to have a high WC.

Dyslipidemia [25] was diagnosed according to ATPIII criteria IE dyslipidemia was diagnosed if plasma lipid analysis shows one or more of the following: hypercholesterolemia [total cholesterol (TC) ≥ 200 mg/dl and/or hyper triglyceridemia [triglycerides (TGs) ≥ 150 mg/dl] and low levels of high-density lipoprotein (HDL-C) [HDL-C ≤ 40 mg/dl in males and HDL-C ≤ 50 mg/dl in females.

LDL values were said to be increased if they were:

- ≥ 100 mg/dl in presence of CAD or CAD risk equivalent
- ≥ 130 mg/dl in presence of 2+ risk factors
- ≥ 160 mg/dl in presence of 0-1 risk factors

Myocardial infarction

Criteria for acute, evolving, or recent MI [26]

Either of the following criteria satisfies the diagnosis for acute, evolving, or recent MI:

1. Typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following:
    a. Ischemic symptoms.
    b. Development of pathologic Q waves in the electrocardiogram.
    c. Electrocardiographic changes indicative of ischemia (ST-segment elevation or depression).
    d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
2. Pathologic findings of an acute myocardial infarction.

Lipoprotein abnormalities

Lipoprotein abnormalities were considered if APO B100 was found to be > 130 mg/dl, APO A1 was found to be < 120 mg/dl in male and < 140 mg/dl in females. The ratio of ApoB100/ApoA1 > 0.6 and Lpa > 14 mg/dl were considered to be significantly associated with increased risk of coronary heart disease.

Statistical analysis

Statistical quantitative data were analyzed using the Unpaired "t" test/Mann-Whitney U test for comparisons of data between the different patient groups. For qualitative variables Chi-Square Test/Fischer's Exact Test was applied. $P < 0.05$ was considered significant. Graph pad Instat 3 software system was used for statistical analysis.

Observation and Results

There was no significant difference in age and gender between Group A and Group B. Mean age of study population in Group A and Group B were 38.20 ± 5.7 years and 35.76 ± 7.9 years, respectively (p value 0.06, SD 7.97,95% CI 33.49 - 38.02). Total number of male subjects in group A were 77 (70%) and in group B were 36 (71%) (p value of 0.87) while the number of female subjects in group A were 33 (30%) and in group B were 14 (29%) (p value of 0.86).

Conventional risk profile

On studying conventional risk factors, it was seen that these were statistically more prevalent in group A in comparison to group B (Table 1).

S No	Risk factors	Group A	Group B	P value
1	Smoking	80 (72%)	26 (52%)	0.021
2	Hypertension	69 (62%)	15 (30%)	0.0003
3	Diabetes mellitus	42 (38%)	6 (12%)	0.001
4	Increased Waist Circumference	67 (60%)	16 (32%)	0.001

Table 1: *Conventional risk factor distribution in both groups.*

Lipid profile abnormalities

On analyzing lipid profile among subjects in both the groups A and B, as per defined methods and criteria in our study. It was found that mean values for total cholesterol, triglycerides, LDL and HDL of siblings (group A) were significantly different from those of controls (group B) (Table 2).

It was found that total cholesterol were raised on 54% of siblings in comparison to 36% in controls, triglycerides were raised on 64% of siblings in comparison to 32% in controls, LDL was on the high side in 54% of siblings in comparison to 36% in controls and HDL values were lower than normal in 73% of siblings in comparison to 44% in controls.

The mean value for total cholesterol among siblings (group A) were 210.09 ± 38.11 mg/dl (p 0.0001, SD 38.11, 95% CI 202.88 - 217.30) which was significantly more than the controls (group B) which was 186.62 ± 31.67 mg/dl (p value 0.0001, SD 31.67, 95% CI 177.61 - 195.63). Similarly, the mean value for triglyceride in siblings (group A) was 162.82 ± 25.08 mg/dl (p value 0.0002, SD 25.08, 95% CI 158.07 - 167.56) which was more from those of controls (group B) which was 145.36 ± 27.83 mg/dl (p value 0.0002, SD 27.83, 95% CI 137.44 - 153.28), the difference between the two groups were highly significant. On the same line, mean values for LDL cholesterol between the two groups were significantly different, with higher values for LDL cholesterol among siblings of young MI patients. The mean values of LDL cholesterol in group A were 140.31 ± 39.27 mg/dl (p value 0.0002, SD 39.27, 95% CI 132.88 - 147.74) in comparison to group B which were 115.82 ± 32.46 mg/dl (p value 0.0002, SD 32.46, 95% CI 106.58 - 125.06). Protective lipid IE HDL profile was significantly higher in group B (controls) in comparison to group A (siblings). The mean values for HDL cholesterol among group B were 42.56 ± 6.45 mg/dl (p value 0.0002, SD 6.45, 95% CI 40.72 - 44.39) while in group A (siblings) the mean values for HDL were 37.90 ± 8.16 (p value 0.0002, SD 8.16, 95% CI 40.72 - 44.39) (Table 2).

Apolipoproteins

The estimation of apolipoproteins was done as per described method and increased values were decided as per established criteria adopted in this study (Table 3). It was found that the mean values of apolipoprotein B100 (APO B100) and apolipoprotein A1 (APO A1) were significantly different in group A and group B. The ratio of APO B100/Apo A1 was higher in group A (siblings) for young Indian, MI patients in comparison to group B (controls) and the difference is highly significant (p value 0.004) (Figure 1). APO B 100 and increased ratio of the APO B100/Apo A1 which were associated with an increased risk of future cardiovascular events were raised in 54% and 57% of the siblings in comparison to 32% and 39% in controls respectively. APO A1 which was found to be protective for cardiovascular events was lower than normal in 52% of siblings in comparison to 32% in controls.

S No	Lipid profile (mg/dl)	Group A	Group B	P value
1	Total cholesterol	210.09 ± 0.09	186.62 ± 31.67	0.0001
2	Triglyceride	162.82 ± 25.08	145.36 ± 27.83	0.0002
3	LDL	140.31 ± 39.27	115.82 ± 32.46	0.0002
4	HDL	37.90 ± 8.16	42.56 ± 6.45	0.0002

Table 2: *Lipid profile distribution among groups A and B.*

Lipoprotein a

LP (a) estimation was done among both groups A and B as per described method in the study and cut off values were selected as increased according to study guidelines. LP (a) were significantly found to be increased in group A as compared to group B (p value 0.01) (Table 3). LP (a) were found to above normal range in 60% of siblings in comparison to 38% in controls.

Correlation analysis between APO B100/Apo A1 and Lpa

Similarly, ratio of APO B100/Apo A1 was found to highly correlated to Lpa values IE with increasing values of ratio of APO B100/Apo A1 the Lpa values also rises and the results were highly significant (p value < 0.0001, r = 0. 77, 95% CI 0.68 - 0.84).

Correlation analysis between Lpa and LDL

Similarly, among group A Lpa was highly correlated to LDL levels, which was found to be statistically significant (p value < 0.0001, r = 0.74, 95% CI 0.63 - 0.81).

Correlation analysis, among ratio of APO B100/APO A1 to LDL

Correlation analysis, among ratio of APO B100/APO A1 to LDL in group A, it was found that the ratio of APO B100/Apo A1 was found to be highly correlated to LDL values IE with increasing values of rationality of APO B100/Apo A1 the LDL values also rises and the results were highly significant (p value < 0.0001, r = 0. 75, 95% CI 0.66 - 0.83) (Figure 2).

S No	Lipoprotein	Group A	Group B	P value
1	Apo B-100	152.17 ± 51.09	122.32 ± 18.79	0.003
2	Apo A-1	134.92 ± 55.61	172.42 ± 49.84	0.0001
3	Ratio ApoB100/ApoA1	1.45 ± 0.93	0.76 ± 0.32	0.004
4	Lpa	27.36 ± 16.24	16.70 ± 5.93	< 0.0001

Table 3: *Apolipoprotein profile distribution among groups A and B.*

Discussion

In this study, index patients up to 45 years of age were selected, according to the criterion in the literature, which consider a patient with acute myocardial infarction young if he or she is ≤ 45 years old [5]. To determine the actual prevalence of conventional risk factors, including lipid and lipoprotein abnormality, 110 apparently coronary disease free sibling in 100 Indian patients who had documented acute myocardial infarction before 45 years of age were studied. To compare the results with general population 50 apparently healthy controls were selected. In this study, to minimize the bias, both age and sex distribution was kept equal without statistically significant differences among cases and control. Number of male subjects were more in comparison to female subjects in both the groups, approximately in 2:1 fashion.

In this study among risk factors, smoking continues to be a predominant risk factor among siblings in comparison to healthy controls. The majority of male siblings (brothers) were smoker in comparison to female siblings (sisters). Among other risk factors hypertension, diabetes mellitus and increased waist circumference were also significantly present more in siblings than controls.

In this study, smoking was present in 72% of siblings, 42% siblings were hypertensive, 30% siblings were diabetic and 41% of siblings had an increased waist circumference. Among siblings 66% of brothers and 6% of the sisters were smoked. In siblings 20% of sisters and 42% of brothers were hypertensive, 8% of sisters and 30% of brothers were diabetic. Adiposity was present in 20% of sisters and 41% of brothers. These findings were similar to some studies done in the past. In a study done by Diane m. Becker., *et al.* [17] to determine the actual prevalence of hyperlipidemia, hypertension and diabetes, and the awareness of these coronary risk factors in unaffected family members, 150 apparently coronary disease free sibling of 86 people who had documented coronary disease before 60 years of age were studied. With the use of nationally established recommendations for blood pressure and lipids, which are based on coronary disease risk curves, screening revealed that 48% of brothers and 41% of the sisters were hypertensive, 45% of brothers and 22% of the sisters had a lipid abnormality, 38% of siblings were current cigarette smokers and 4.7% were diabetic.

In contrary to this study the few prior family studies [18,19] done by Gudmund-son S., *et al.* and Hamsten A., *et al.* concluded that measured blood pressure in siblings reported a lower prevalence of hypertension (approximately 20%). In this study too siblings were found to be significantly more hypertensive than control.

On analysis of lipid profile among siblings and control it was found that dyslipidemia was significantly more common in sibling in comparison to general population (controls). It was found that total cholesterol were raised in 54% of siblings in comparison to 36% in controls, triglycerides were raised in 64% of siblings in comparison to 32% in controls, LDL was on higher side in 54% of siblings in comparison to 36% in controls and HDL values were lower than normal in 73% of siblings in comparison to 44% in controls. Triglyceride and HDL abnormalities were markedly different in siblings and controls. The mean values of total cholesterol, triglyceride, LDL and HDL were also significantly different between the siblings and control. These findings were well matched with other studies mainly done by Hamsten A., *et al.* (Am J Cardiol 1987), Goldstein JL., *et al.* (J Clin Invest 1973) and Shucker B (JAMA 1987) which concluded that in siblings of acute MI coronary heart disease risk curves demonstrate a sharp increase in the slope of risk at total cholesterol levels of 240 mg/dl, which correspond approximately to an LDL cholesterol cut point of 160 mg/dl. "High risk" LDL cholesterol was the most frequent abnormality observed in both men and women. As with hypertension, abnormal lipids were more common in brothers than in sisters with 54% and 78%, respectively, exhibiting desirable lipid patterns on screening. The awareness of elevated lipid levels was low in both brothers and sisters with 73% unaware.

On further analysis of apolipoprotein and Lpa in siblings and control in this study it was found that values of APO B100, APO A1, APO B100/Apo A1 ratio and Lpa were significantly different in siblings in comparison to general population (controls). APO B 100 and increased ratio of the APO B100/Apo A1 which were associated with an increased risk of future cardiovascular event were raised in 54% and 57% of the subjects in comparison to 32% and 39% in controls respectively. APO A1 which found too protective for cardiovascular events was lower than normal in 52% of siblings in comparison to 32% in controls.

Similarly, Lpa values were also significantly raised in siblings in comparison to controls. Lpa was found to above normal range in 60% of siblings in comparison to 38% in controls. Mean values of these parameters were too significantly different in siblings than controls. Surprisingly, there was no significant difference among male and female siblings in relation to these parameters signifying that both sexes are equally at risk for future cardiovascular event in case of history of acute MI in their sibling at a young age and both of brothers and sisters need equal attention in relation to risk factor modification and change in life style. These findings are in accordance with the study done by Aila M, Rissanen and Esko A, Nikkila., *et al.* [20] in (1979) who concluded that familial hyperlipidemia was twice and familial hypertension three times as common in case as in reference families; other risk factors were equally common in both. It is concluded that most of the familial aggregation of coronary heart disease is mediated by familial aggregations of hyperlipidemia and hypertension.

Study Limitations

This study has a few limitations and the important one which deserve mention are as follows:

1. This was a case control nonrandomized study.
2. Incidence of risk factors for atherosclerosis were higher in siblings as compared to controls, which may adversely affect the lipid and lipoprotein abnormalities in them. So, a randomized study with matching atherosclerotic risk factor profile in siblings and control is needed to draw a definite conclusion.
3. More number of cases are required to draw a definite conclusion on this point.

Conclusion

Lipid and lipoprotein abnormalities in the form of raising levels of total cholesterol, LDL cholesterol, triglyceride, decreased levels of HDL cholesterol, increased APO B/APO A1 ratio and Lpa were significantly more common in sibling of young acute MI in comparison to the general population. Among conventional atherosclerotic risk factors, smoking, hypertension, diabetes mellitus and increased abdominal obesity were also found to be significantly more prevalent in siblings of young acute MI than the general population.

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