INHERITED DYSLIPIDAEMIC DISORDERS CONTRIBUTING TO CORONARY HEART DISEASE

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Background: Lipoprotein (a) [Lp (a)] is an established independent risk factor for premature myocardial infarction (MI)/coronary artery disease (CAD). The study was conducted to determine the value of Lp (a) in prediction of CAD or MI in the offspring at risk. **Methods:** A total of 160 subjects were investigated. Serum Lp (a) was measured by ELISA, serum total cholesterol, triglycerides (TG) and HDL-Cholesterol by enzymatic colorimetric methods using standard kits. **Results:** Differences in levels of total Lp (a) and cholesterol were observed between patients and controls. Both Lp (a) (16.23±1.95 mg/dL) and cholesterol (175.00±7.60 mg/dL) of group A (patients) were higher than the corresponding controls. However an opposite trend in results was noted for serum HDL-Cholesterol in patients vs. controls. **Conclusion:** Persons found to have elevated levels of Lp (a) should focus on controlling the known modifiable risk factor for heart disease, especially smoking, hypercholesterolemia, obesity, hypertension and sedentary life style.

Keywords: Dyslipidaemia, Coronary Artery Disease, CAD, Lipoprotein (a), Myocardial Infarction, MI, Cholesterol, HDL-Cholesterol, LDL-Cholesterol, Triglycerides

INTRODUCTION

Coronary artery disease (CAD) is now classified as one of the genetic diseases attributed to numerous gene-environmental interactions, since the risk of heart disease is in large part inherited. It is important to screen family members of the inherited trait found in the patients with heart diseases. The inheritance of gene from particular parent is generally a 50% chance due to separation and recombination of gene during meiosis.[1–2] It is now realized that the most important mode of action of certain genetic factors is through their interaction with environmental factors.[3] With the recognition of the importance of genetic factor in the aetiology of premature CAD, several studies have come forward in the recent past, highlighting the role of various risk factors and their association with inheritance[1,4]

Serum lipoprotein (a) [Lp (a)] level proves to be valuable in the assessment of CAD risk early in life.[5] A significant positive relation was found between Lp (a) concentrations and number of parental risk factors. Children whose grand parents had history of CAD had Lp (a) concentrations shifted towards higher values. Measurements of Lp (a) in children may help to identify those at an increased risk of atherosclerotic disease, especially when their parents have at least two relative risk factors.[6] CAD remains a common cause of morbidity and mortality through out the world. According to the American Heart Association cardiovascular disease is the leading cause of death in United States. Premature CAD with myocardial infarction (MI) can occur in as young as 18 years, which is the youngest reported case in Pakistan.[7] The risk factor concept has been extremely useful because it permits one to assess the importance not only of the aforementioned risk factors but also of genetic trait in given individuals, such as family history of premature coronary artery disease. Using such information, it has become possible to determine whether modification of a given risk factor will result in modification of the risk for a particular disease.[8] The prevention of coronary artery disease is based on control of several factors associated with a disease or clinical condition and suspected to play a pathogenic role, defined as risk factors. These include smoking, hyperlipidaemia, hypertension, obesity, Type-1 and Type-2 diabetes mellitus and postmenopausal status.[9] For more than 40 years since the discovery of this abnormal lipoprotein by Berg in 1963; this has been the source of more than insight.[6,10]

Lp (a) is like a recalcitrant, untruly stepchild in the family of lipoproteins. Lp (a) is a cholesterol rich lipoprotein resembling low-density lipoprotein (LDL) to which large polymorphic glycoprotein, apoprotein (a) [Apo (a)], is covalently bonded and exists as free standing particle in normolipidaemic subjects, however it can associate covalently with triglycerides (TG) rich lipoprotein in hyper-triglyceridemic subjects.[11–13] Lp (a) displays strong atherothrombotic properties; it plays a pivotal role in the genesis and progression of thrombosis in the arteries.[14] Apo (a) present in atherosclerotic but not normal vessel walls suggests that Lp (a) may play a role in the atherosclerotic process, after lesion have developed. In the early plaque, most of the Lp (a) is located within endothelial cells.[15] Several epidemiologic studies have shown that Lp (a) is a risk factor for cardiovascular disease.[16]

The present study is aimed at the role of lipoprotein (a) with serum cholesterol in offspring of patients suffering from myocardial infarctions.

MATERIAL AND METHODS

A total of 160 consecutive subjects were included in the present study from Cardiac Care Unit (CCU), Cardiology Department, and Outpatient Department of Cardiology Units of Lady Reading Hospital, and Khyber Teaching Hospitals, Peshawar, Pakistan.

The subjects were divided in to four (4) groups, A, B, C and D respectively. Group A (n=40) and group B (n=40) were comprised of patients and their offspring respectively who had myocardial infarction (Proven hospital record). They were cross-matched with individuals and their offspring having no personal or family history of CAD or hypercholesterolemia, group C (n=40) and group D (n=40) respectively. Information regarding variables viz. age, sex, body mass index (BMI), blood pressure, smoking habit and family history hypertension were recorded on a standard proforma. Subjects having endocrinological disorder were excluded from the study. Fasting blood was drawn from the antecubetal vein of all the subjects in sitting position and serum separated was stored at -20 °C till further analysis.

Serum Lipoprotein (a) and cholesterol were determined by standard kits (Cat. No. 1107020 and 1001092). Similarly serum triglycerides and HDL-cholesterol were determined by enzymatic colorimetric methods using kits (Cat. No. 1001312 and 1001095 respectively) supplied by Spinreact, Spain. Whereas LDL-cholesterol was calculated using Friedwald formula.[17]

RESULTS

The Mean±SEM age among the patients and their offspring was found to 55.30±2.20 and 18.20±1.03 years, whereas in controls and their offspring it was found to be 46.85±1.60 and 17.51±0.90 years respectively. Male outclass the female among the patients and their ratio was 2:1 whereas an opposite trend was found in group B offspring in whom it was 1:1.85. Similarly male to female ratio among the controls and their offspring was equal (1:1) respectively. Body mass index among the patients and their offspring was noted to be 24.80±1.00 and 21.40±1.10 Kg/m^2 respectively and in normal healthy individuals and their offspring it was observed to be 26.01±1.37 and 22.50±0.73 Kg/m^2 respectively. The highest numbers of smokers (37%) were found in-group A followed by controls in whom only 7 (17.5%) were found to be smokers. Similarly 31 (77.5%) individuals among the patients were reported to have a strong family history of hypertension whereas 21 (52.5%) of their offspring were having family history of hypertension (Table–1).

The general statistical calculations for the understudy population are shown in Table–2. Lp (a) for patients (Group A) was observed to be 23.86±2.50 mg/dL and in controls (Group C) it was found to be 11.20±1.26 mg/dL while Lp (a) among the offspring of patients (Group B) and controls (Group D) were observed to be 16.23±1.99 and 7.17±1.60 mg/dL respectively. Serum cholesterol among patients was 216.30±16.90 mg/dL whereas in normal healthy individuals it was found to be 170.46±10.60 mg/dL. Similarly it was noted to be 175.00±1.95 mg/dL and 145.50±7.60 mg/dL for their offspring respectively. The data further revealed that the values of serum triglycerides were significantly higher ($p<0.01$) for both the patients and their offspring when compared with normal healthy individuals and their offspring respectively. On the other hand serum HDL-Cholesterol were found to be lower for patients (Group A) and their offspring (Group B) when compared with normal healthy individuals (Group C) and their offspring (Group D) respectively (Table–2).

Table–1: General Characteristics of Patients, Normal Healthy Individuals and their Offspring

Characteristics	Parents		Offspring	
	Patient (Group A)	Control (Group C)	Patient (Group B)	Control (Group D)
Age (Years)	55.30±2.20	46.85±1.60	18.20±1.03	17.51±0.90
Male: Female	27:13	20:20	14:26	20:20
BMI (Kg/m^2)	24.80±1.00	26.01±1.37	21.40±1.10	22.50±0.73
Systolic B (mmHg)	137.30±2.99	126.00±2.90	110	100
Diastolic B (mmHg)	87.10±1.58	80.66±1.14	80	75
Smoking Habit (%)	15 (37%)	7 (17.5%)	–	–
FH HTN (%)	31 (77%)	–	21 (52.5%)	–

(Values are expressed as Mean±SEM)

BMI=Body Mass Index, Group A= Abnormal Patients, Group C= Normal Parents, Group B= Abnormal Offspring of A, Group D= Normal Offspring of C, FH HTN= Family History of Hypertension

Table–2: Serum Lipid Profile in Patients, Controls and their Offspring

Group	Lp (a) (mg/dL)	T. Cholest. (mg/dL)	TG (mg/dL)	HDL–C (mg/dL)	LDL–C (mg/dL)
A	23.86±2.50*	216.30±16.90‡	190.06±18.62‡	40.80±3.22$^{\infty}$	138.56±15.90†
C	11.20±1.26	170.46±10.60	158.03±13.19	42.86±3.70	96.93±9.98
B	16.23±1.99‡‡	175.00±1.95‡‡	161.00±18.27	32.80±1.30§	110.00±10.49
D	07.17±1.60	145.00.50±7.60	137.70±9.99	38.13±7.10	99.56±6.12

*p<0.005 when compared with Controls Parents (Group C), **p<0.01 when compared with Controls Offspring (Group D)
$^{\ddagger}p$<0.01 when compared with Controls Parents (Group C), $^{\ddagger\ddagger}p$<0.001 when compared with Control Offspring (Group D)
$^{\infty}p$<0.05 when compared with Controls Parents (Group C), $^{\S}p$<0.05 when compared with Control Offspring (Group D)
$^{\dagger}p$<0.005 when compared with Controls Offspring (Group D)

DISCUSSION

Heart disease is a condition of diverse aetiology.[18] Elevated levels of cholesterol have a high incidence of atherosclerosis, many studies published since 1950's have shown that plasma cholesterol is strongly and independently related to the development of coronary artery disease and that there is a gradient of risk from lowest to highest plasma cholesterol.[9, 19,20] CAD in elderly is likely to depend not only on the concentration of cholesterol at an older age but the length of lifetime exposed to an increased cholesterol level.[21] The importance of early detection of hyperlipidaemia lies in the possibility of delaying or arresting the progression of early atherosclerotic lesion by lowering serum cholesterol level. A strong and consistent difference of cholesterol concentration was observed between case and control (53%) in the studies conducted elsewhere in the world.[1,4] The results of present study are in accordance with the above-cited studies (p<0.05).

Lipoprotein (a) is the only major lipid risk factor whose levels generally remains fairly constant throughout our life, but are presumably modulated by sex hormone and it shows a strong heritibility.[1] Lp (a) concentration greater than 30 mg/dL has been reported to be associated with two folds increased risk for developing CAD.[22] Elevated levels of plasma Lp (a) is now considered a major risk factor for atherosclerosis and cardiovascular disease.[23,24] Significant positive relation was observed between Lp (a) concentration and the number of parental risk factors, children whose grand parents had a history of CAD had Lp (a) levels shifted towards higher values.[6,24] Craig *et al* (1998) reporting on a meta-analysis of prospective studies have documented that Lp (a) is an independent prospective risk factor for CAD and that its measurement may be useful to guide management of individuals with family history of CAD.[25] Elevated levels of Lp (a) have been reported in children with familial hypercholesterolemia. It was further suggested that Lp (a) is not only important risk factor for CAD but also more strongly related to the risk of CAD than are HDL-C and LDL-C.[26,27]

The present work provides information regarding Lp (a), TC, TG, and HDL-C in offspring and examines the relation of Lp (a) concentration and cholesterol levels to parental MI. It was further concluded from the present work that there is a strong positive evidence of higher Lp (a) and cholesterol concentration in the offspring of parents with premature MI than in the normal healthy individuals, suggesting that Lp (a) is a strong lipid variable predisposing to CAD. The familial environment may account for this but the genetic predisposition is stronger as Lp (a) levels are strongly and genetically determined.

CONCLUSION

As lipoprotein (a) concentrations are primarily under genetic control and does not respond measurably to diet or drug treatment, so persons found to have elevated levels of Lp (a) should focus on controlling the known modifiable risk factor for heart disease, especially smoking, hypercholesterolemia, obesity, hypertension and sedentary life style.

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