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Lipoprotein (a) and Glycaemic control in Pakistani Subjects with Diabetes Mellitus

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Introduction

Among the most common chronic disorders of modern time, diabetes mellitus (DM) remains unique because of its multisystem ramifications. DM is the most common cause of secondary dyslipidemias. People with DM have 2-4 fold increase in the risk of developing cardiovascular disease. The major risk factors in DM are hyperglycaemia, dyslipidemias and hypertension. Diabetic dyslipidemia is characterized by elevated levels of very low density lipoproteins (VLDL), low density lipoproteins (LDL) and lower levels of high density lipoproteins (HDL). Atherogenic dyslipidemia in diabetic patients is often called diabetic dyslipidemia or lipid triad.1 An issue of considerable interest is the relative contribution of each component of atherogenic dyslipidemia to coronary artery disease (CAD) risk. Growing evidence suggests that all the components of lipid triad are independently atherogenic.2

Epidemiologic studies have shown that an increased risk exists in diabetics, even when total plasma cholesterol, HDL, arterial pressure and smoking are corrected . The explanation for the excess macrovascular complications is not yet readily apparent. There are different views regarding these complications in DM like qualitative abnormalities in plasma proteins, hyperinsulinemia, platelet abnormalities and impairment in coagulation system.3

Despite intense research in the field of risk factors for coronary heart disease (CHD) and other thromboembolic disorders it is yet difficult to define the independent contribution of several interrelated abnormalities in lipoproteins to atherogenesis. For example the association between LDL levels and CHD is well accepted but yet a relatively high proportion of cases with CHD have LDL in the normal range.4 Beyond the lipid parameters provided by the lipoprotein profile, several additional components of the lipoprotein system have been identified and are under evaluation. Some of the more important of these include apo B, apo A1, HDL subclasses, small dense LDL particles, remnants of chylomicrons & VLDL, IDL and Lp (a). At present, the knowledge is insufficient to recommend that they may be used in routine clinical practice.5,6 Because accurate and reliable measurements of these various fractions are not widely available and because we lack definitive data showing their contributory role as risk factors for CHD more research is required to determine their clinical usefulness. In the coming years a new member may be added to atherogenic dyslipidemias and that is lipoprotein (a). Lp (a) has now been identified as an independent risk factor for premature CAD and aggravates the atherogenic effect of diabetes mellitus.7

Lipoprotein (a) [Lp (a)] was first identified by Kare Berg in 1963 as an LDL variant.8 It is formed by an LDL moiety and a unique protein, apolipoprotein (a) [Apo (a)], linked to apolipoprotein B-100 [Apo-B100] of LDL.5 The structural gene for Apo (a) is located on chromosome number 6 with the gene for plasminogen, giving a clue that both may have arisen from a common ancestral gene.9 The most

intriguing feature of Apo (a) is that it shares an extensive structural homology with plasminogen, a key proenzyme of the fibrinolytic cascade. Kringle V and the protease domain of Apo (a) share >85% amino acid identity with the corresponding plasminogen domains, even though the protease domain of Apo (a) does not appear to have a catalytic function.5

Lp (a) is believed to contribute to lipid induced atherogenesis similar to LDL particles.10 Within a population the plasma levels can vary from less than 0.5 mg/dl to over 200 mg/dl.11 The cutoff Lp (a) value to classify subjects as being at
increased risk for CAD varies greatly among studies and ranges from 20 to 40 mg/dl. Given the uncertainty related to Lp (a) cutoff value, it has been suggested that clinicians use a conservative Lp(a) value of 30 mg/dl, particularly in patients with concomitantly elevated LDL cholesterol.12,13

The purpose of the present study was to measure Lp(a) levels in patients with DM and to see that whether there is any difference in Lp (a) levels between diabetics with good glycaemic control and poor glycamic control.

Subjects and Method

This cross sectional study was carried out at the Chemical Pathology, Department of Armed Forces Institute of Pathology (AFIP), Rawalpindi. Sixty subjects with Diabetes Mellitus (DM) and thirty healthy individuals were studied. Fifty three of these were of type 2 DM and seven were type 1 DM.

The individuals participating in the study were diagnosed cases of DM based on the criteria proposed by American Diabetes Association.14 Diagnosis of DM was carried out by either two fasting plasma glucose (FPG) levels >7.0 mmol/l (126 mg/dl) on two different occasions or one FPG >7.0 mmol/l plus one random blood glucose >11.1 mmol/l (199 mg/dl). Subjects were included in the study voluntarily after they signed the consent Performa. They were allotted study numbers. Thirty four were males and twenty six females. Their height was measured in centimeters and weight in kilograms. BMI was calculated by the following formula:

BMI = Body Weight in Kilograms / Height (square meters)
History and clinical examination was recorded on a separate Performa. All the subjects were in stable metabolic condition. History was taken regarding any disease that could affect the metabolic status of the body like nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, diabetic ketoacidosis and non ketotic hyperosmolar diabetes.15,16 Any person having a positive history of the above mentioned disorders were excluded from the study. Those giving a history of familial hypercholesterolemia, ischaemic heart disease or myocardial infarction were also excluded from the study.17,18 The history of medication was recorded and those taking lipid lowering agents, oral contraceptives and steroids were also excluded.19,20

Blood pressure (SBP/DBP) was recorded in sitting position in the right arm as mmHg, by mercurial sphygmomanometer. Pulse and respiratory rate per minute and temperature were also recorded. In general physical examination any finding relevant to hyperlipidemias like xanthomas or xanthelasma were noted.

The percentage of glycosylated haemoglobin (HbA1c) was taken as the marker of glycaemic control.21 The subjects were divided into two groups on the basis of glycaemic control into good glycaemic control (HbA1c <7.5%) and poor glycaemic control (HbA1c > 7.5%).

The subjects included in the control group were healthy individuals with mean age of 44.6 years. They were not suffering from any acute infection or any metabolic or psychological disorder. They had no family history of hypercholesterolemias or DM. They had normal lipid profile and fasting blood glucose level less than 6.1 mmol/l (110 mg/dl). All the tests were run in duplicate and the average of the two readings was taken as the final result.

Glucose was estimated by GOD-PAP (Glucose Oxidase Phenyl Ampyrone) method, an enzymatic colorimetric method with the kit supplied by Linear Chemicals (Cat No.GL-5083). Total Cholesterol was measured by CHOD-PAP (Cholesterol Oxidase Phenol Ampyrone), an enzymatic colorimetric method, using kits of Linear Chemicals, Spain (Cat No. CH 5054). The instrument used was Selecta 2 autoanalyzer as for glucose. GPO-PAP (Glycerol Phosphate Oxidase), an enzymatic colorimetric method was used for serum triglycerides estimation. The kit was supplied by Linear chemicals (Cat No TR 5046). The instrument used was Selectra 2 autoanalyzer as for glucose. CHOD - PAP Method was used for HDL-C estimation with the kit was supplied by Merck Systems (Cat No;28248). CHOD PAP, an enzymatic colorimetric method was used for LDL-C estimation using kits of Merck System (Cat No 28248). Lp (a) was estimated by enzyme linked immunoabsorbant assay.The kit used was supplied by Innogenetics Biotechnology for Health Care, Belgium (Cat. No. 000703A). Ion exchange resin separation method was used for estimation of Glycosylated Haemoglobin.The kit was supplied by Stanbio Glycohemoglobin (Pre-Fil).

The data was analyzed by computer program "Microsoft Excel" and Statistical Package for Social Sciences (SPSS). The tests applied for statistical analysis were Student's t test and a p value < 0.05 was taken as significant.

Results

Sixty subjects with diabetes mellitus (DM) and thirty healthy individuals participated in this study. Fifty three were of type 2 DM and seven were of type 1 DM. The diabetics were divided into Group A and B on the basis of glycaemic control. Group A consisted of diabetics with good glycaemic control (HbA1c $< 7.5\%$) and group B with poor glycaemic control (HbA1c $>7.5\%$). Group C was healthy control group. Each group consisted of 30 subjects. In group A 18 were males and 12 females. In group B, 17 were males and 13 females. Group C consisted of 16 males and 14 females.

The clinical characteristics and glycemic status of subjects in group A, B and C are summarized in table 1. A significant difference was present between BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of both well controlled and poorly controlled diabetics when compared with controls ($p<0.05$). A significant difference was observed in fasting glucose and glycosylated hemoglobin (HbA1c) values between the two groups. Fasting lipid profile and Lp (a) values of group A, B and C are summarized in table 2. The difference in levels of serum total cholesterol, low density lipoprotein cholesterol (LDL-C) and triglyceride was not significant between group A and C while serum high density lipoprotein cholesterol (HDL-C) levels were significantly lower in group A ($p<0.05$). When compared with the controls there are significantly higher levels of serum total cholesterol ($p< 0.05$), triglycerides ($p<0.01$) and LDL-C ($p<0.01$) in group B while serum levels of HDL-C
were significantly lower (<0.001).The mean levels of Lp(a) in control are 20.8 ± 3.54 mg/dl i.e., significantly less than in well controlled diabetics (40.11 8.9 ± mg/dl, $p<0.05$). Mean Lp(a) levels in group B were 55.19 ± 8.55 mg/dl i.e., significantly higher than in group C ($p < 0.001$).

The difference in duration of diabetes was also non-significant in the two groups. The mean levels of fasting plasma glucose were 8.12 ± 0.43 mmol/l in well controlled diabetics and 11.67 ± 0.48 mmol/l in poorly controlled diabetics ($p<0.001$) (table 2).

Similarly mean levels for HbA1c were 6.12 ± 0.14% in well controlled diabetics and 8.51 ± 0.19% in poorly controlled diabetics ($p<0.001$) (table 1). In lipid profile (table 2) serum total cholesterol ($p<0.02$) and LDL-C ($p<0.01$) levels were significantly higher in poorly controlled diabetics than those who were well controlled and serum HDL-C ($p<0.001$) was significantly lower. Serum triglyceride levels were higher in the poor control group but the difference was non-significant (table 2). As far as Lp (a) levels are concerned there was a non-significant difference in the two groups. The mean levels of Lp(a) were higher in poorly controlled diabetics (55.19 ± 8.55mg/dl) than their well controlled counterparts (40.11 ± 8.9 mg/dl); the difference was not significant ($p>0.05$) (table 2).

Discussion

The major risk factors in DM are glycaemic status, dyslipidemia and hypertension.1 The present study was an effort to provide an insight into some of the risk factors in DM. We have observed a significantly higher BMI, SBP and DBP in diabetics as compared to healthy individuals. These findings are in line with many studies showing an increased prevalence of DM in obese persons22-24 and of hypertension in diabetics.25

It has been observed in many studies that improvement in glycaemic control in diabetic people modifies lipoprotein levels positively. An interesting observation in our study was seen when we compared the lipid profile of healthy controls with diabetics having a good glycaemic control. Serum total cholesterol, LDL-C and triglycerides were in upper normal ranges of desired levels. This evidence is in support of many cross-sectional studies and clinical trials, which reveals the positive improvement in lipid profile with better metabolic control.26-29 Furthermore, achievement of good glycaemic control may lead to near normalization of lipid levels in the blood.30 The levels of HDL-C were significantly lower in diabetics even in well controlled diabetics when compared with control. There are different results quoted by various studies regarding Lp(a) levels in diabetics. The major reasons for the discrepant results of the prospective studies have been attributed to the variation in study design, collection and storage of samples, methods used for statistical analysis and population differences that reflect the known ethnic variability in the distribution of Lp (a) levels and Apo (a) size isoforms.

The mechanism of raised Lp (a) levels in DM is not clear. It has been hypothesized that a defect in clearance of apoprotein B-100 lipoproteins exists in diabetic persons. Glycosylation and other modifications of the LDL particle and glycosylation of the LDL receptor has been proposed to cause a decrease in LDL cellular metabolism in diabetes.31 Despite the presence of LDL, Apo (a) imparts unique properties with respect to synthesis and catabolism. In fact, apo B-100 in Lp (a) particles does not appear to mediate the catabolism of this lipoprotein via the LDL receptor thus suggesting that the attachment to Apo (a) produces hindrance and/or conformational change of apo B-100.32 Whereas the rate of removal from the circulation determines the level of LDL, evidence has been provided that the rate of synthesis is the primary determinant of Lp (a) levels.33,34 Increased apo B100 production would provide a higher number of apo B-100 molecules to be attached to Apo (a) because in diabetes LDL levels are raised.35

Wolfeenbuttel BH and colleagues found elevated levels of Lp (a) in type 2 diabetics. No significant change was observed in Lp (a) levels after improved glycaemic control with insulin although

significant decrease in total and LDL cholesterol, triglycerides, apolipoprotein B and free fatty acids were observed with concomitant rise in HDL levels. Our findings are in conformity with the data reported by the peers.36

Ritter et al did not find a significant effect of improved metabolic control in 9 Type 1and 9 Type 2 DM subjects.37 The authors analyzed these subjects together, and the degree of improvement in glucose control was not associated with significant lowering of Lp (a) levels.

Lp (a) level has also been determined in African Americans with Type 2 DM by W. Douglas Sheer and his colleagues38 found no significant difference in Lp (a) levels between diabetics and non diabetics. The mean levels of Lp (a) in the study were lower in the diabetics when compared with the control. These findings are in contrast to our results which show higher Lp (a) level in diabetics. The possible reason could be the large size of apo (a) isoforms leading to lower Lp(a) levels.39 However, no association was found between glycaemic control and Lp (a) levels.
In a study by Wester Louis et al40 no statistical difference could be established between Lp (a) levels in Type 1and Type 2 DM and healthy controls. They proposed that Lp (a) concentrations in Type 1 and Type 2 DM were independent of short-term and long-term glycometabolic control or the occurrence of microalbuminuria, neuropathies or retinopathies. However, poor glycometabolic control affected the elevated Lp (a) levels insignificantly beyond the threshold of 25 mg/dl in Type 1 DM. The reason for their findings could be the same size of isoforms in diabetics and controls. The non significant effect of glycaemic control on Lp (a) levels is in agreement to our data.

Durlach et al41 did not find any significant difference in Lp (a) concentrations in Type 2 DM and control subjects. In line with our study, there was no association with glycaemic control. In another study42 subjects with Type 2 DM had significantly higher Lp(a) levels than control subjects and no association was found between Lp(a) levels and glycaemic control or CAD. Type 2 DM subjects had higher triglycerides and lower HDL levels. These findings also support our data. No correlation was observed in between insulin levels and Lp(a) in a study on Nigerian population.43 We also did not observe any correlation between insulin and Lp(a). Nigerians have higher median levels of Lp (a) than habitats of other areas.

The findings of Francis et al44 were similar to our study. They observed increased levels of Lp(a) in type 2 diabetics with raised prevalence of high risk levels of Lp(a) (>25 mg/dl) and the effect of glycaemic control had a positive trend on Lp(a) levels but it did not reach the level of significance. Moreover, similar to our findings they also observed positive correlation of Lp(a) with total cholesterol and LDL-C but not with triglycerides and HDL-C.

Plasma lipoprotein (a) levels in Turkish type 2 DM patients with and without vascular diabetic complications were studied. The plasma Lp (a) levels were found to be significantly increased in the type 2 diabetics compared with the healthy subjects. Plasma Lp (a) levels in type 2 diabetics with diabetic vascular complications were significantly higher than those of the type 2 patients without diabetic vascular complications and healthy subjects. There were significant correlations between plasma Lp (a) levels and apolipoprotein B (apo B) in all Type 2 DM patients. No correlation was observed between Lp (a) levels and age, sex, duration of diabetes, fasting blood glucose, HbAlc, the mode of treatment, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and apolipoprotein Al levels in all patients.45 Martinez- Triguero and his colleagues46 found significantly raised levels of Lp (a) in diabetics with poor metabolic control when compared with diabetics with good metabolic control. This is in contrast to our findings. A significant difference in their study and our study is that they selected diabetics irrespective of the presence or

absence of cardiovascular disease (CVD). They studied 88 Type 2 diabetics, out of which 23 had CVD. As is evident from many studies that Lp (a) is a cause of premature coronary artery disease and any level >30 mg/dl is related to premature heart disease and other thromboembolic disorders. Therefore, the CAD could be present in those patients before the diabetes was diagnosed and the raised levels of Lp (a) may not be due to the poor metabolic control.

In a study on type 1 diabetic children comparisons of Lp (a) concentrations were made between the non-diabetic and diabetic children with good to fair glycemic control. Significantly higher levels were found in children with poor metabolic control when compared with good glycemic control group or normal children. However the cutoff value of glycosylated hemoglobin for good and bad glycemic control was 11% in this study as compared to our study in which it was 7.5%.47
To what extent the rate of synthesis, transcription and translation of apo (a) are affected by hyperglycaemia is still not exactly known. The concentration of glycosylated Lp (a) is increased in the circulation in diabetic subjects.48 It is evident that glycosylation prolongs the half life of lipoproteins and so would be for Lp (a). This may lead to raised levels of Lp (a) in diabetics. In the present study Lp (a) levels were higher in poorly controlled diabetics than well controlled diabetics but the difference was non significant. This may be because glycation may be affecting Lp (a) concentrations to a little extent while genetics would be the major determinant of Lp (a) concentrations. There is a wide variation in the concentrations of Lp (a) among individuals.5 Therefore, in every individual the rise may be different. The effect of different environmental factors like insulin, exercise,estrogens and niacin may be additive enough to affect Lp (a) levels significantly.49 In a recent study by Alagozlu et al50 the non obese type 2 DM patients were studied. They were divided into 3 groups according to the type of treatment administered i.e. insulin, sulphonylureas and an untreated group. There was no significant difference in Apo A I, Apo B and triglyceride levels in different groups of diabetics. HDL levels were significantly lower in the untreated group. Lp (a) levels were significantly higher in the untreated group. However, HbA1c levels were not measured in the study. It was concluded that gaining metabolic control may also have favorable effects on Lp (a) level.

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