ORIGINAL ARTICLE

Lipids and lipoprotein(a) concentrations in Pakistani patients with type 2 diabetes mellitus

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Aim: The aim of the present study was to analyze serum lipoprotein(a) [Lp(a)] levels in Pakistani patients with type 2 diabetes mellitus (DM) and to find correlations between clinical characteristics and dyslipidaemias in these patients.
Methods: Fasting blood samples were analyzed for Lp(a), total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), glucose and glycosylated haemoglobin (HbA1c) in 68 Pakistani patients with type 2 DM and 40 non-diabetic healthy control subjects.
Results: Lp(a) levels were significantly raised in diabetics as compared to the control group. No correlation of Lp(a) was seen with age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and fasting glucose. There was a positive correlation of BMI to SBP and DBP. There was a significant positive correlation between Lp(a) and total cholesterol and LDL-c. No correlation of Lp(a) was observed with HDL-c, triglycerides and glycosylated haemoglobin (HbA1c).
Conclusion: The present study led us to conclude that serum Lp(a) levels are significantly raised in type 2 DM and have a positive correlation with serum total and LDL-c levels.

Keywords: diabetes mellitus, dyslipidaemias, lipoprotein(a), lipoproteins glycosylated haemoglobin
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Introduction

Patients with diabetes mellitus (DM) have a high prevalence of coronary artery disease (CAD) [1]. The major risk factors in DM are hyperglycaemia, dyslipidaemia and hypertension. Diabetic dyslipidaemia is characterized by elevated levels of very low-density lipoproteins cholesterol (VLDL-c), low-density lipoprotein cholesterol (LDL-c) and=lower levels of high-density lipoprotein cholesterol (HDL-c), often referred to as the lipid triad [2]. Lipid abnormalities in diabetic patients are likely to play an important role in the development of atherogenesis and so are called atherogenic dyslipidaemia [3]. An issue of considerable interest is the relative contribution of each component of atherogenic dyslipidaemia to CAD risk. Growing evidence suggests that all the components of lipid triad are independently atherogenic [4].

Studies of Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) have come up with favourable outcomes of glycaemic control in diabetics [2]. DCCT revealed that in patients with type 1 DM the risk of microvascular complications reduced by 50–75% in intensively treated patients. The benefits were observed with an average HbA1c of 7.2% in the intensively treated group of patients compared with 9.0% in conventionally treated groups of patients [5]. The UKPDS conclusively demonstrated that improved blood glucose control in type 2 diabetics reduced microvascular complications by 25% [6,7].

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The exact mechanism by which atherosclerosis occurs in DM is still not known. It was found in early studies that atherosclerotic plaques in arterial walls contained large amounts of cholesterol, thus giving a clue that serum cholesterol might be an independent factor in the development of atherosclerotic plaques [8]. Later on, raised levels of LDL-c was considered to be a primary risk factor for CAD. It has been found that LDL-c-lowering therapy reduces the risk for subsequent coronary events even in patients with advanced atherosclerotic disease [9]. In another study, small dense LDL particles have been suggested to be associated with an increased risk of CAD [10]. Despite these evidences showing the possible role of LDL in atherosclerosis, the precise mechanism by which LDL promotes atherosclerosis still remains unknown.

The role of raised levels of LDL and of lower levels of HDL in pathogenesis of atherosclerosis in DM has not been adequately proven. Lipoprotein(a) [Lp(a)] may be one of the links to accelerated atherogenesis in DM patients, because its raised levels are associated with premature CAD. It is stucturally similar to plasminogen and competes with it for its receptors thus decreasing its fibrinolytic activity by decreasing formation of plasmin. This leads to a procoagulant state in the body [11]. It is not fully established whether Lp(a) levels are raised in DM. The aim of the present study was to analyze serum Lp(a) levels in Pakistani patients with type 2 DM and to find correlations between clinical characteristics and dyslipidaemias in these patients.

Patients and methods

This study was carried out at the Department of Chemical Pathology, Armed Forces Institute of Pathology (AFIP), Rawalpindi. This study was approved by the Army Medical College Ethics Review Board. As per selection criteria, 68 patients were finally selected from a group of 187 type 2 DM patients. For control group, 40 non-diabetic, age- and sex-matched healthy individuals were selected from a group of 48 subjects.

The patients participating in the study were diagnosed cases of type 2 DM. Thirty-nine patients were males and 29 were females. Their height was measured in centimetres with shoes off and weight was measured in kilograms in indoor clothing. Body mass index (BMI) was calculated by the following formula:

$$\text{BMI} = \text{Body weight in kilograms/Height in metres}^2$$

Clinical information, date of diagnosis and medical history were obtained by chart review and patient interview by one of the authors (SSH). All the patients were in stable metabolic condition. Patients having any disease that could affect the metabolic status of the body and the parameters studied like nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, stroke, diabetic ketoacidosis and non-ketotic hyperosmolar diabetes were excluded [12,13]. Those patients giving history of familial hypercholesterolaemias, ischaemic heart disease or myocardial infarction were also excluded from the study [14,15]. The history of medication was recorded, and the patients taking lipid-lowering agents, oral contraceptives and steroids were also excluded [16,17].

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was recorded in sitting position in the right arm in mmHg, by mercury sphygmomanometer. Pulse and respiratory rate per minute and temperature were also recorded by one of the authors (SSH).

The subjects included in the control group were age- and sex-matched healthy individuals selected from the staff members of AFIP and Army Medical College. They were not suffering from any acute infection or any metabolic or psychological disorder. They had no family history of hypercholesterolaemias or DM. Their lipid profiles and fasting blood glucose levels were measured. They had normal lipid profile and fasting blood glucose levels less than 6.1 mmol/l (110 mg/dl).

Fasting blood samples were taken from the antecubital vein, serum was separated, aliquoted and then frozen at $-70\,^{\circ}\text{C}$. 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 colourimetric method with the kit supplied (Linear Chemicals, Barcelona, Spain). Total Cholesterol was measured by CHOD-PAP (Cholesterol Oxidase Phenol Ampyrone), an enzymatic colourimetric kit (Linear Chemicals). GPO-PAP (Glycerol Phosphate Oxidase), an enzymatic colourimetric kit was used for serum triglycerides estimation (Linear Chemicals). The instrument used was Selectra 2 autoanalyser. CHOD–PAP method was used for HDL-c and LDL-c measurement (Merck Systems, San Antonio, TX, USA). Serum Lp(a) levels were measured immunochemically with a Sandwich ELISA that uses a mouse monoclonal anti-apo(a) antibody as the solid phase antibody and a sheep anti-apo B-100 polyclonal antibody (antibody against B-100) as the detection antibody. The antibodies used in this assay identify all known isoforms of apo(a). There was no cross-reactivity with plasminogen and LDL. The kits used were supplied by Innogenetics Biotechnology for Health Care, Gent, Belgium. Ion exchange resin separation method was used for estimation of glycosylated haemoglobin (Stanbio Glycohemoglobin, Boerne, TX, USA) for which ethylenediaminetetraacetic acid (EDTA)-added whole blood was used.

Analysis

The data was analyzed by computer software program Statistical Package for Social Sciences (SPSS Version 10). Data was expressed as mean and standard error of the mean (SEM). The tests applied for statistical analysis were Student's *t*-test and Spearman's correlation coefficient. A p value of 0.05 was taken as statistically significant and all tests were two tailed.

Results

Clinical characteristics

Clinical characteristics of the control group and diabetics are shown in table 1. SBP, DBP, fasting plasma glucose and HbA1c are significantly higher in diabetics ($p < 0.001$) as compared to non-diabetic healthy subjects. There was an insignificant difference in age and BMI between diabetic and control group ($p > 0.05$).

Lipid and Lp(a) profile

Comparison of lipid profile and Lp(a) levels between DM patients and controls are summarized in table 2. The serum levels of total cholesterol and triglycerides were significantly higher in diabetics (<0.05, respectively). LDL-c levels were higher in diabetics but the difference did not reach statistical significance. There were significantly lower levels of HDL-c in diabetics ($p < 0.001$). The mean levels of Lp(a) were 47.65 ± 6.22 mg/dl (Mean ± SEM) in diabetics, and there was a significant difference when compared with control group in which levels were 20.8 ± 3.54 ($p < 0.05$).

Table 1 Clinical characteristics and glycaemic status of control and DM patients (Mean ± SEM)

	Control (n = 40)	DM patients (n = 68)
Gender (n)	Male (16), female (14)	Male (39), female (29)
Age (years)	49.26 ± 1.13	50.38 ± 1.43
BMI (kg/m^2)	25.82 ± 0.38	26.11 ± 0.58
SBP (mmHg)	125.66 ± 1.53	144.57 ± 2.60*
DBP (mmHg)	78.10 ± 1.19	87.11 ± 1.60*
Fasting plasma glucose (mmol/l)	5.07 ± 0.09	9.89 ± 0.39*
HbA1c percentage	4.81 ± 0.08	7.31 ± 0.14*

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
*$p < 0.001$ as compared to control.

Table 2 Fasting serum lipid and lipoprotein(a) [Lp(a)] profile of control and DM patients (Mean ± SEM)

	Control (n = 40)	DM patients (n = 68)
Total cholesterol (mmol/l)	4.35 ± 0.11	4.97 ± 0.13*
LDL cholesterol (mmol/l)	2.69 ± 0.11	3.12 ± 0.15
HDL cholesterol (mmol/l)	1.21 ± 0.02	1.00 ± 0.04†
Triglycerides (mmol/l)	1.35 ± 0.07	1.88 ± 0.15*
Lp(a) mg/dL	20.8 ± 3.54	47.65 ± 6.22*

LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*$p < 0.05$ as compared to control.
†$p < 0.001$ as compared to control.

Correlation coefficients

Spearman's correlation coefficients were determined for diabetic patients by the computer software SPSS. No correlation of Lp(a) is seen with age, BMI, SBP, DBP or fasting glucose. There was a positive correlation of BMI to SBP and DBP ($r = 0.431$ and 0.522, respectively). A weak positive correlation of HbA1c was seen with DBP ($r = 0.30$) (table 3). The correlations were also calculated for serum Lp(a), lipid profile and HbA1c (table 4). There was a significant positive correlation between Lp(a) and total cholesterol ($r = 0.552$) and LDL-c ($r = 0.520$). No correlation of Lp(a) was observed with HDL-c, triglycerides or HbA1c. There was a significant weak negative correlation between serum HDL-c and total cholesterol ($r = -0.261$), while a strong negative correlation with LDL-c ($r = -0.435$). There was a significant correlation between total cholesterol and triglycerides ($r = 0.466$) and LDL-c ($r = 0.266$). A strong negative correlation was observed between HDL-c and HbA1c ($r = -0.705$) and a weak positive correlation with LDL-c ($r = 0.316$).

Discussion

The major risk factors in DM are glycaemic status, dyslipidaemia and hypertension. The present study was an effort to provide an insight into some of the risk factors in DM. We observed a significantly higher BMI, SBP and DBP in diabetic patients as compared with healthy individuals.

The results of the present study are in accordance to Ramirez *et al.* [18] who found elevated Lp(a) levels in a combined group of type 1 and type 2 diabetic subjects relative to non-diabetic subjects. Ramirez *et al.* hypothesized that a defect in the clearance of Apo-B 100 may be responsible for this change in diabetics. Similarly, glycosylation of LDL particle and its receptor may lead to prolongation of its half life in the plasma. But they did

Table 3 Spearman's correlations between age, BMI, SBP, DBP, fasting glucose, HbA1c, Lp(a) and duration of DM in DM patients (n = 68)

	Age	BMI	SBP	DBP	Fasting glucose	HbA1c	Lp(a)	Duration of DM
Age	1.000	−0.183	0.188	−0.113	−0.028	0.193	0.016	0.260*
BMI	−0.183	1.000	0.431†	0.522†	0.031	−0.211	−0.087	−0.232
SBP	0.188	0.431†	1.000	0.695†	0.133	−0.020	0.163	0.018
DBP	−0.113	0.522†	0.695†	1.000	0.171	0.030	0.193	−0.093
Fasting glucose	−0.028	0.031	0.133	0.171	1.000	0.624†	0.155	0.105
HbA1c	0.193	−0.211	−0.020	0.030	0.624†	1.000	0.135	−0.044
Lp(a)	0.016	−0.087	0.163	0.193	0.155	0.135	1.000	−0.114
Duration of DM	0.260*	−0.232	0.018	−0.093	0.105	−0.044	−0.114	1.000

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure, Lp(a), lipoprotein(a).
*Correlation is significant at the 0.05 level.
†Correlation is significant at the 0.01 level.

not find any correlation between serum Lp(a) and lipid profile in DM patients. In the present study, there was a significant positive correlation between serum Lp(a), total cholesterol and LDL-c. This positive association between Lp(a), total cholesterol and LDL-c is not surprising because dyslipidaemias are very common in DM. One possibility for increased concentration of Lp(a) in diabetics could be explained by understanding the assembly of Apo(a) with Apo-B 100 moiety of LDL Apo(a) is primarily synthesized in the liver and is entered into the circulation, where the LDL moiety is attached to it [19]. Thus, if higher number of LDL particles are present in the circulation, there would be more union between LDL and Apo(a) and thus higher concentrations of Lp(a). But this cannot be the sole explanation for this association because the metabolic pathways of LDL and Lp(a) are quite different. Further studies are needed in this regard.

In a study by Parhofer *et al.* [20], it was observed that Lp(a) production and not catabolism determined plasma concentrations, and the inverse association of Lp(a) concentrations with size of Apo(a) isoforms was due to difference in production rate and not catabolism. The differences in Lp(a) concentrations among individuals with the same Apo(a) isoform were due to differences in production and not catabolism. The level of LDL is primarily regulated by its rate of catabolism while synthetic rate is the main determinant of Lp(a) concentration. Moreover, it has been found that LDL receptors are not utilized for catabolism of Lp(a) [21,22].

Table 4 Spearman's correlation coefficient between lipid profile, Lp(a) and HbA1c of DM patients (n = 68)

	T Chol	LDL-c	HDL-c	Trig	Lp(a)	HbA1c
T Chol	1.000	0.929†	−0.261*	0.466†	0.552†	0.219
LDL-c	0.929†	1.000	−0.435†	0.266*	0.520†	0.316*
HDL-c	−0.261*	−0.435†	1.000	−0.265*	0.016	−0.705†
Trig	0.466†	0.266*	−0.265*	1.000	0.236	0.245
Lp(a)	0.552†	0.520†	0.016	0.236	1.000	0.135
HbA1c	0.219	0.316*	−0.705†	0.245	0.135	1.000

T Chol, total cholesterol; Trig, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a).
*Correlation is significant at the 0.05 level.
†Correlation is significant at the 0.01 level.

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 glycated Lp(a) is increased in the circulation in diabetic subjects [23]. It is evident that glycation prolongs the half life of lipoproteins and so would be for Lp(a). This may lead to raised levels of Lp(a) in diabetics. This may be because glycation may be affecting Lp(a) concentrations apart from genetics which is the major determinant of Lp(a) concentrations. There is a wide variation in the concentrations of Lp(a) among individuals [24]. Therefore, in every individual, the rise may be different. The effect of different environmental factors like insulin, exercise, oestrogens and niacin may be additive enough to affect Lp(a) levels significantly [25].

In another study, no difference in Lp(a) concentrations was observed between diabetics and non-diabetic controls. Moreover, there was no association between Lp(a), age, sex, total cholesterol, triglycerides, LDL-c, HDL-c, albuminuria, type of treatment and presence of CAD [26].

Kronenberg and colleagues found that in subjects with high LDL levels (3.3 mmol/l), plasma Lp(a) concentrations were predictive of risk of development of early atherogenesis in a dose-dependent manner [27]. However, the risk was not correlated with Apo(a) isoform size and was not present when LDL levels were <3.3 mmol/l.

In a case control study by Chih-Jen Chang and colleagues [28], serum Lp(a) levels and lipid profile were compared between type 2 DM patients and age- and sex-matched non-diabetics. Diabetics had higher triglycerides and Apo B levels and lower levels of HDL. However, no difference in Lp(a) levels was noted between diabetics and non-diabetic controls. Most probably the cause would be occurrence of large size isoforms in diabetics. There was no correlation of Lp(a) levels with total cholesterol, LDL-c, HDL-c and triglycerides. In another study in Chinese patients [29], no significant difference was seen in Lp(a) levels between diabetics and non-diabetics similar to the above mentioned study. This shows that population difference are present in Lp(a) levels. Moreover, the same study did not reveal any significant correlation of Lp(a) levels with total cholesterol, LDL-c, HDL-c and triglycerides. We have observed a significant positive correlation of Lp(a) levels with total cholesterol and LDL-c levels. The positive correlation between serum Lp(a) and total cholesterol levels is supported by the findings of Rainwater [30]. The author mentioned that correlation of Lp(a) with total cholesterol levels was not surprising, because many enzymes and pathways of lipoprotein metabolism are likely to influence Lp(a) particles once they are in circulation. This is because the author observed a significant variation in genetically specified Lp(a) concentration and measured Lp(a) concentrations. However, Rainwater *et al.* [31] found lower levels of Lp(a) in type 2 DM patients. The authors attributed their findings to the presence of large size Apo(a) isoforms responsible for lower concentrations of Lp(a) in type 2 DM subjects. The author presumed that non-enzymatic glycosylation of Apo(a) is responsible for larger size of Apo(a) and each allele in diabetic subjects averaged 4.1 kDa larger than the same allele in non-diabetic subjects, which may be responsible for lower levels of Lp(a) in type 2 diabetics. Another reason of their differential findings could be the inclusion of newly diagnosed diabetics in the NIDDM group, i.e. 24 out of 81 DM patients were diagnosed at the time of sampling for Lp(a). They did not have previous history of DM.

These results are in line with other studies that suggested that CAD risk may be dependent on additional lipid risk factors and indicate that LDL-c may not be an independent risk factor for the development and progression of atherogenesis in type 2 DM. Lp(a) has been suggested to be a new member of metabolic syndrome and it may be used in routine clinical practice in future as a cardiovascular risk marker [32].

Conclusions

The present study led us to conclude that serum Lp(a) levels are significantly raised in type 2 DM and have a positive correlation with serum total cholesterol and LDL-c levels but not with triglyceride levels. It is suggested that Lp(a) may be an additive factor for accelerated atherogenesis in type 2 DM patients.

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