Original Article

Association of Serum Lipoprotein(a) with Fasting Lipid Profile in Type 2 Diabetic Patients

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Abstract:
Background: *Type 2 diabetes mellitus is a multifactorial metabolic disorder characterized by chronic hyperglycemia caused by decreased production or sensitivity to insulin. Dyslipidemia is most common complication of type 2 diabetes mellitus which is one of the major risk factors for coronary heart disease. Recent studies quite impressively suggest that, Lp(a)-a small dense LDL like particle is an emerging cardiovascular risk factor which is also associated with diabetes. The purpose of the present study is to find out the association of serum Lp(a) with fasting lipid profile in type 2 diabetes mellitus patients.* ***Methodology:*** *This was a hospital based cross-sectional study comprising hundred (100) diagnosed type 2 diabetic patients aged between 31 and 60 years. This study was carried out in the department of Biochemistry, Chittagong Medical College and inpatient & outpatient department of Endocrinology, Chittagong Medical College Hospital. Samples were taken by non-probability consecutive sampling. Important variables in this study were FPG, serum Lp(a)and fasting serum lipid profile (TC, TG, LDL & HDL).* ***Results:*** *The mean value of serum Lp(a) level was increased in type 2 diabetic patients (44.32 ± 2.6 mg/dl). Serum Lp(a) levels were positively and significantly correlated with total cholesterol and LDL-cholesterol but not correlated with fasting plasma glucose and serum triglyceride.* ***Conclusion:*** *The results of the present study suggest that Lp(a) levels were positively and significantly correlated with increased total cholesterol and LDL-cholesterol in type 2 diabetic subjects suggesting similar metabolic pathways and the genetic connection for LDL and Lp(a).*

Key words: Serum Lp(a), Type 2 DM, Fasting Lipid Profile

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Introduction:

Diabetes mellitus is a chronic metabolic disorder that is often associated with unacceptably high disease burden especially in developing countries[1]. Diabetes mellitus is the major cause of secondary dyslipidemia and diabetic dyslipidemia is characterized by the atherogenic triad of high serum triglyceride concentration, low serum HDL concentration and increased serum LDL concentration[2-3]. This pattern of dyslipidemia in diabetes mellitus leads to vascular complications[4].

Recent evidence suggests that, a small dense LDL like particle also known as Lp(a) is elevated in type 2 diabetes mellitus. This elevated level of Lp(a) is associated with the increased risk of cardiovascular diseases even more than any other lipids[5-6]. Many prospective epidemiological studies have reported the positive associations of Lp(a) concentration with atherosclerosis, coronary artery disease and stroke[7,8]. In human serum, Lp(a) was first identified by Kare Berg in 1963 as an LDL variant during a study of LDL antigenicity[9]. Lp(a) is LDL like particle that consist of one molecule of apolipoprotein(a) and another molecule of apolipoprotein B-100. Apo(a) covalently bound to apo B-100 by disulphide bond. Apo(a) proteins vary in size due to a size polymorphism, which is caused by a variable number of so-called kringle IV repeats in the LPA gene. This size variation at the gene level is expressed on the protein level. These variable apo(a) sizes are known as 'apo(a) isoforms'[10].

Lp(a) is synthesized by the liver and circulated in blood. Lp(a) plasma concentrations mainly controlled by the apolipoprotein(a) gene (LPA gene) located on chromosome 6q26-27 [11]. Lp(a) shares an extensive structural homology with plasminogen, a key pro-enzyme of fibrinolytic cascade. The gene for plasminogen is also located on chromosome six. Because of its structural similarity to plasminogen, Lp(a) competes with plasminogen binding sites on endothelial cell & fibrin thus prevent the conversion

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of plasminogen to plasmin. Plasmin is an important enzyme present in blood for fibrinolysis. So Lp(a) can play a role in thrombogenesis[11]. The serum level of Lp(a) is said to be increased when it is >14 mg/dl but the atherogenic properties of Lp(a) levels are expressed over 30 mg/dl[12]. The half-life of Lp(a) in the circulation is about 3-4 days[10]. The serum level of Lp(a) is mostly genetically determined and not very much influenced by gender, dietary habit, fasting state or physical activity[13].

Several studies have reported high serum concentration of Lp(a) in diabetic patients compared to nondiabetic people[14-15]. Serum Lp(a) is now considered as a new risk factor for cardiovascular disease and showed a genetic link to accelerate atherogenesis in diabetes mellitus[16]. Serum Lp(a) level has been found also to be associated with intermediate markers of CVD risk including obesity and hypertension[17,18].

Serum Lp(a) levels are generally not responsive to traditional lipid lowering drugs such as statins or fibrates. Beside that niacin (Vit B3) is the most effective agent that lowers the Lp(a) level by 30-40%[19]. Many studies showed that Lp(a) levels were also elevated in certain disease conditions such as renal failure and autoimmune disease but decreased in liver disease[20-22]. The present study was designed to find out the relationship among Lp(a) with other lipid parameters in type 2 diabetic patients in this part of our country.

Materials and Methods:
This cross-sectional study was carried out in the Department of Biochemistry, Chittagong Medical College and inpatient & outpatient department of Endocrinology, Chittagong Medical College Hospital. Study duration was one year from July 2017 to June 2018.

Data were collected by Pre-designed questionnaire containing all the variables of interest and fulfilling the exclusion & inclusion criteria for the study population. Hundred diagnosed type 2 diabetic patients with the age range of 31 to 60 years were selected by non-probability consecutive sampling. Permission for the study was taken from the Ethical Review Committee of CMC. Informed consent from each subject was taken before the collection of samples.

Under all aseptic precaution 5 ml of fasting venous blood sample was taken from each participant using sterile disposable syringe. While 2 ml venous blood samples were collected in sodium fluoride tube for measuring fasting plasma glucose and another 3 ml blood samples were taken in a red top tube and allowed to clot for the collection of serum. Serum was separated by centrifugation for 5 min at 4000 rpm and was taken into Eppendorf for measuring Lp(a) and fasting lipid profile.

Plasma glucose was measured by glucose oxidase-peroxidase method using multichannel auto analyzer. Serum Lp(a) level was measured by nephelometry in Siemens BN proSpec analyzer. Fasting serum lipid profile was measured by enzymatic kinetic method using an auto-analyzer.

All the data were processed and analyzed using Microsoft excel and IBM-SPSS v22.0 for Windows. Statistical inference was based on 95% confidence interval and p value ≤0.05 was considered statistically significant. Variables were expressed as mean ± standard error of means (SEM). To test the correlation among Lp(a) with FPG and lipid profile Pearson's correlation coefficient were used. The summarized data were presented in the form of tables and figure.

Results:
In this cross-sectional study, hundred diagnosed type 2 diabetic patients were taken. Out of 100 patients 43 were male and 57 were female. Mean age were 46.2±0.9 years. Data were expressed as mean±SEM. Confidence level was fixed at 95% and p-value of 0.05 or less was considered statistically significant.

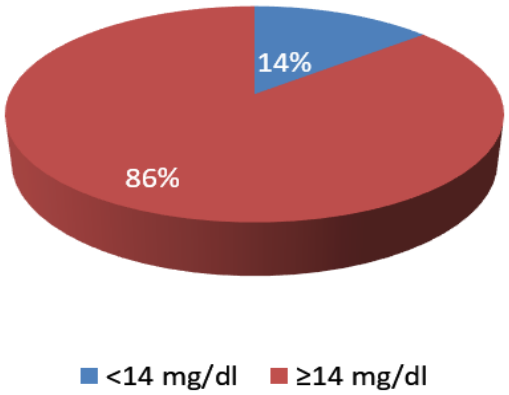

Figure-1: Pie chart shows that 86% cases had increased serum Lp(a) level in this study

Table-I shows the mean value of age, FPG, fasting lipid profile and serum Lp(a) level (44.32±2.6 mg/dl) in this study.

Table-II shows that total cholesterol and LDL-cholesterol were significantly associated with increased serum Lp(a) but serum TG was not associated with serum Lp(a) level in study subjects.

Table-III shows that there was positive significant correlation of Lp(a) with total cholesterol and LDL-cholesterol, whether negative correlation was

observed with serum HDL. But no significant correlation was observed among Lp(a) with FPG and TG.

Table-I: Baseline characteristics of the study subjects (n=100)

Characteristics	Mean ± SEM	Range
Age (years)	46.2 ± 0.90	31-60
Fasting plasma glucose (mmol/L)	8.66 ± 0.30	3.5-19.1
Lp(a) level (mg/dl)	44.32 ± 2.6	9-115
Total Cholesterol (mg/dl)	218.1 ± 4.4	120-316
Serum TG (mg/dl)	191.4 ± 7.03	67-510
Serum LDL (mg/dl)	132.4 ± 3.61	61-235
Serum HDL (mg/dl)	37.2 ± 0.6	24-55

Table-II: Association of serum Lp(a) with fasting lipid profile in the study subjects (n=100)

Variables (mg/dl)	Lp(a) <14	Lp(a) <14	p value (Significance)
TC <200	7	20	p <0.05 (Significant)
TC ≥200	7	66	
LDL <100	11	10	p <0.05 (Significant)
LDL ≥100	3	76	
TG <150	01	22	p >0.05 (Not Significant)
TG ≥150	13	64	

Table-III: Pearson's correlation among Lp(a) with FPG and fasting lipid profile in the study subjects (n = 100)

Pearson's Correlation	Correlation Coefficient (r)	P value (Significance)
Lp(a) with FPG	0.05	p>0.05 (Not Significant)
Lp(a) with total cholesterol	0.51	p<0.05 (Significant)
Lp(a) with LDL	0.52	p<0.05 (Significant)
Lp(a) with triglyceride	0.03	p>0.05 (Not Significant)
Lp(a) with HDL	-0.14	p>0.05 (Not Significant)

Discussion:

Diabetes mellitus is an iceberg disease. With an increasing incidence worldwide, diabetes mellitus will be a leading cause of morbidity and mortality for the foreseeable future[23]. Changes in lipid-profile are a consequential event in Diabetes mellitus. Components of lipid profile are well known risk factors for complications of diabetes mellitus like CHD[24]. In the present study, the mean values of serum total cholesterol, LDL-cholesterol and triglyceride levels were higher than the desired values and mean HDL values were lower than the desired value (Table-I).

In type 2 Diabetes mellitus, hypertriglyceridemia results from insulin resistance, hyperglycemia and hyperinsulinemia which accelerated lipolysis following insulin resistance increases the availability of free fatty acids, while hyperglycemia and hyperinsulinemia trigger triglyceride synthesis in the liver through the activation of ChREBP and SREBP1c respectively. As a result, the activity of CETP also increases which leads to the enrichment of HDL particles with triglycerides, while depleting them from cholesteryl esters, thus decreasing HDL cholesterol levels[25].

The increased level of total cholesterol in type 2 diabetes mellitus is due to reduction of plasma campesterol, a marker of cholesterol absorption and increase plasma levels of lathosterol, a marker of cholesterol synthesis[26]. In patients with type 2 diabetes, the number of LDL B/E cell-surface receptors is significantly reduced, which may be due to reduced insulin-mediated expression and could be responsible for observed decrease in LDL catabolism inducing a longer duration of LDL in plasma[27].

Lipoprotein(a) is a distinct class of lipoprotein that is structurally related to LDL. Different studies have shown that high Lp(a) in blood is a risk factor for atherosclerosis, thrombosis, coronary heart disease and cerebrovascular disease[28]. Present study showed that, there was increased serum Lp(a) levels in type 2 diabetic patients (44.32 ± 2.6 mg/dl). In the present study, considering the optimal cut off points at 14 mg/dl, 86% of type-2 diabetic patients had Lp(a) >14mg/dl. In a South-Asian study the percentage of elevated Lp(a) in type 2 diabetes mellitus was found 43.4%[29]. As Lp(a) values are different in various ethnic group populations, but in most of the studies revealed that South-Asians have higher level of Lp(a) concentrations[16].

The mechanism of elevated Lp(a) in Type 2 diabetes mellitus are peripheral resistance to the action of insulin with chronic hyperinsulinemia, increase in the rate of synthesis of Lp(a) than its catabolic rate and decrease rate of catabolism of LDL in diabetes

mellitus. As Lp(a) is constituted by apo(a) and LDL, decrease in the catabolism of the latter will be naturally reflected on the level of Lp(a)[30]. Glycation also prolongs the half-life of Lp(a), which may lead the higher plasma concentration of Lp(a) in diabetes mellitus[31].

In this study, serum Lp(a) levels were significantly associated and positively correlated with total cholesterol and LDL-cholesterol. As cholesterol and LDL are important components of Lp(a), so it can be explained such positive correlations with Lp(a). These correlations were consistent with previous studies[15,32-35]. But there were no correlations among Lp(a) with fasting plasma glucose and serum triglycerides. This similar finding was observed by Premkumar KS and Candido AP[15,34].

It is an established fact that type 2 diabetes mellitus is a strong risk factor for coronary artery disease[5,36]. Moreover many prospective epidemiological studies have reported the positive associations of serum Lp(a) with atherosclerosis, coronary artery disease and stroke[7-8]. The observations of the designed study are an adjunct to the finding of other studies where researchers raised the possibility of serum Lp(a) as an additional finding for cardiovascular and cerebrovascular risk assessment in type 2 diabetes mellitus patients.

Conclusion:

Type 2 diabetes mellitus is associated with atherogenic lipid disorders. Lp(a) is now considered as one of the cardiovascular risk factors in type 2 diabetic patients with longer duration of diabetes. So, additional data remain to be acquired on future studies as to clarify more comprehensively whether Lp(a) should play a role as a screening tool in the quotidian clinical practice.

Conflict of Interest:

The authors declare to have no conflicts of interest.

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