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Lipoprotein (a) In Type 2 Diabetes Mellitus: Relationship of Glycemic Control and LDL to HDL Ratio

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Abstract

Background: Lp(a) evaluation may have the potential to improve cardiovascular risk prediction when used in addition to traditional lipid profiles. The present study was undertaken to evaluate the Lp(a) levels in healthy control and type 2 diabetic patients, also evaluate their association with the degree of glycemic control and LDL: HDL ratio.
Method: Fifty types 2 diabetic patients and age and sex-matched fifty non-diabetic controls were enrolled in the study. Fasting venous blood sample was collected from all the patients and analyzed for fasting blood glucose (FBS), glycated hemoglobin (HbA1c), lipid profile, and serum Lp(a). The Lp(a) levels were compared between two groups and association between the Lp(a) levels and LDL: HDL ratio was evaluated.
Results: Lp(a) levels were found to be significantly increased in the diabetic group (28.64±4.93) as compared to the control group (25.08±3.43). There was a significant elevation in the levels of BMI, FBG, total triglyceride, LDL: HDL ratio, TC/LDL ratio in the diabetic group as compared to the control group. Lp(a) levels showed an association with and degree of glycemic control in diabetic patients, but there was no association found between the level of Lp(a) and LDL: HDL ratio.
Conclusion: Type-2 diabetes mellitus is strongly associated with increased Lp (a) levels, and elevated Lp(a) levels reflect the glycemic status and are also independent of an increase in LDL: HDL ratio. Serum Lp (a) associated with lipid abnormalities high triglyceride, high LDL, TC/LDL ratio, and low HDL makes people with diabetes prone to coronary artery disease (CAD).
Keywords: Diabetes mellitus, Dyslipidemia, Lipoprotein, Hemoglobin, Glycemic control, Triglyceride.

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1. Background

In India, diabetes is no more an epidemic. Still, it became pandemic, according to the International Journal of Diabetes in developing countries, which called India as the diabetes capital of the world. Diabetes is frequently associated with dyslipidemia and increased percentages of glycated hemoglobin. Patient with type 1 DM is generally not hyperlipidemic if they are under good glycemic control. But patients with type-2 DM are usually dyslipidemic even if under relatively good glycemic control.

They have several lipid abnormalities, including elevated plasma triglycerides, elevated Low-Density Lipoprotein-Cholesterol (LDL-C), and decreased High-Density Lipoprotein-Cholesterol (HDL-C) [1]. Moreover, type II diabetes mellitus is associated with a cluster of interrelated plasma lipid and lipoprotein abnormalities, including reduced plasma levels of HDL and elevated plasma levels of TG, total cholesterol, VLDL, and LDL cholesterol. Triglyceridaemia has been associated with the risk of

coronary heart disease both in type II diabetic and non-diabetic subjects [2].

Generally, patients with diabetes tend to have a higher proportion of smaller and denser LDL particles, which are more susceptible to oxidation and may thereby increase the risk of cardiovascular events [3,4]. Diabetic is prevalent in the local area day by day. The number is increasing at the same time the complication of a person with diabetes has been realized with ever-increasing frequency adverse cardiovascular events as the complication of the disease may be lethal; hence early detection is the need of time. Lp(a) is the important Bio-Chemical markers of cardiovascular disorders, and this newer parameter has not been studied so well in this Vidarbha Region relating to Type-2 diabetic mellitus. Lp(a) along with other parameters like LDH: HDL ratio, which helps in early diagnosis of pre-diabetic and Type-2 diabetic patient. Keeping this in mind, the present study was carried out to evaluate the level of Lp(a) with the degree of LDL: HDL ratio and glycemic control besides evaluating an independent risk factor for cardiovascular anarchy.

2. Materials and Methods

After obtaining Institutional Ethical Committee approval, this case-control study was carried out in the Department of Biochemistry, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Science (Deemed University) Sawangi, Wardha, Maharashtra, India. Total 100 adult subjects of either sex, age between 45-65years were enrolled-

Study Group:

Fifty diagnosed patients of Type -2 diabetes mellitus (a combination of both good and poor glycemic control T2D patients) under antidiabetic treatment.

Control Group:

Fifty adult patients were Non-diabetic healthy controls. Patients suffering from thyroid disease, protein-losing enteropathy, nephrotic syndrome, liver failure, and hemolytic jaundice were excluded from the study. A proforma and questionnaire were given to all the participants regarding their family history of type-2 DM, duration of DM in patients, and any other major disease such as cardiovascular, as well as on their lifestyle characteristics, e.g. physical activity, dietary habits, hypertension, smoking, economic status, etc.

One day before sample collection, all the subjects were instructed not to take anything after dinner. On the next morning, after assuring 12 hours fasting, written consent was taken. Then 5.0 ml of venous blood was drawn from the Cubital vein and analyzed for various biochemical parameters on the same day (Table 1). The remaining serum sample was aliquot and stored at -20^{o} C until used for lipoprotein (a) detection. Participants were also evaluated for various anthropometric parameters such as blood pressure, waist circumference (WC), and body mass index (BMI). The Lp(a) levels in the diabetic group were compared with the control group, and the association between the Lp(a) levels and LDL: HDL ratio was evaluated.

2.1 Statistical analysis

Data analysis was done by using descriptive statistics, proportion, and Student‘t’ statistic at a 5% level of significance. Also, we compared the observation of control and experimental group using diagrammatic tools. We find an association between two variables using the Chi-Square test.

3. Observations and Results

Total fifty types 2 diabetic patients and age and sex-matched fifty non-diabetic controls were enrolled in the study. The majority of patients were in the age group of 45-50 years, followed by 60-65 years with male predominance in both the groups. In the study group, most of the patients (20; 40%) suffering from diabetes only, 10 (20%) patients were suffering from diabetes and hypertension, 10 (20%) were from diabetes and cardiovascular diseases, 10 (20%) patients who have diabetes and some other diseases while in the control group, 10 (20%) patients were suffering from hypertension and 40 (80%) from other diseases. The socio-demographic profile of patients and family history are shown in table 2.

Table 3 shows the mean values of anthropometric and biochemical parameters. Also, showed Lp(a) levels were found to be significantly increased in the diabetic group as compared to the control group. There was a significant elevation in the levels of BMI, FBG, total triglyceride, but not the total cholesterol and LDL cholesterol and TC/HDL-cholesterol ratio in type2 diabetics compared to the control group($p<0.05$). LDL: HDL ratio, TC/LDL ratio was also increased in the diabetic group as compared to the control group.

Lp(a) levels showed an association with and degree of glycemic control in diabetic patients, but there was no association between the level of Lp(a) with LDL: HDL ratio (Table 4). Thus, the results of the present study suggest that Lp(a) levels are increased in type 2 diabetic patients. The elevated Lp(a) levels reflect the glycemic status. They are also independent of an increase in LDL: HDL ratio suggesting different metabolic pathways and the genetic connection for LDL and Lp(a).

Table 1: Different Biochemical parameters along with methods

Test	Method
Fasting plasma glucose (FPG)	GOD-POD method [5]
PPPG	GOD-POD method [5]
Glycosylated Hb	Latex agglutination inhibition assay [6]
TG	GPO-POD Enzymatic method[7,8]
Cholesterol	Enzymatic CHOD- POD method[8, 9]
HDL	Enzymatic endpoint method [10]
VLDL	Indirect method- Friedewald Equation [11]
LDL	Indirect method- Friedewald Equation [11]
Lipoprotein (a)	Turbidimetric method [12]

Table 2: Socio-demographic profile and history of patients

Parameters		Study group	Control group
Age	45-50	23 (46%)	28 (56%)
	50-55	08 (16%)	05 (10%)
	55-60	07 (14%)	06 (12%)
	60-65	12 (24%)	11 (22%)
Sex	Male	26 (52%)	30 (60%)
	Female	24 (48%)	20 (40%)
BMI	Not at risk	20 (40%)	23 (46%)
	At risk of overweight	27 (54%)	24 (48%)
	Overweight	03 (6%)	06 (12%)
Resident	Rural	23 (46.94%)	20 (40%)
	Urban	26 (53.06%)	30 (60%)
Social Economic Status	Medium	30 (60%)	31 (62%)
	Poor	12 (24%)	11 (22%)
	Rich	08 (16%)	08 (16%)
Physical Activity	Maximum	17 (34%)	13 (26%)
	Minimum	12 (24%)	12 (24%)
	Moderate	21 (42%)	25 (50%)
Dietary habit	Mixed	35 (70%)	36 (72%)
	Non-Veg	02 (4%)	01 (02%)
	Veg	13 (26%)	13 (26%)
Addiction	Smoking	05 (10%)	08 (16%)
	Tobacco Chewing	19 (38%)	10 (20%)
	Alcoholic	16 (32%)	09 (18%)
	Not addicted	10 (20%)	23 (46%)
Family history of the previous disease	Diabetes	16 (32%)	19 (38%)
	Hypertension	21 (42%)	18 (36%)
	Cardiovascular disease	13 (26%)	13 (26%)

Table 3: Comparison of mean of anthropometric and Biochemical parameters between two groups

Parameters		Study group	Control group	P-value
Anthropometric parameters	SBP	134.16±7.82	123.84±6.69	0.000
	DBP	86.88±6.44	81.24±4.02	0.000
	WC	78.68±9.76	74.12±7.83	0.012
	BMI	26±3.61	25.27±3.64	0.159
Biochemical parameters	HBA1c level	8.04±1.34	5.55±0.396	0.000
	T. CHOL (mg/dl)	190.08±50.01	191.7±35.01	0.917
	TG (Mg/dl)	168±81.4	130.02±34	0.003
	HDLc (mg/dl)	35.88±9.27	45.27±4.09	0.000
	LDLc (mg/dl)	77.7±55.4	120.04±30.06	0.000
	VLDLc (mg/dl)	33.6±16.3	26.04±6.79	0.003
	TC/LDL (Ratio)	5.61±1.55	4.25±0.76	0.000
	LDL:HDL Ratio	3.60±1.28	2.679±0.691	0.000
	Lp (a)(mg/dl)	28.64±4.93	25.08±3.43	0.000

Table 4: Association of Lp(a) with glycosylated hemoglobin and LDLc: HDLc Ratio

Groups	HbA1c	Lp (a)			
		Frequency	<25mg/dl	>25mg/dl	Total
Study group	≤8%	Observed	19	5	24
		Expected	14.88	9.12	
	>8%	Observed	12	14	26
		Expected	16.12	9.88	
Control group	4.5 to 5.5%	Observed	10	05	15
		Expected	7.50	7.50	
	5.6 to 6	Observed	15	20	35
		Expected	17.50	17.50	
Groups	**LDLc: HDLc Ratio**	**Lp (a)**			
		Frequency	**<25mg/dl**	**>25mg/dl**	**Total**
Study group	<3.5	Observed	18	8	26
		Expected	16.12	9.88	
	>3.5	Observed	13	11	24
		Expected	14.88	9.12	
Control group	<2.5	Observed	10	10	20
		Expected	10	10	
	>2.5	Observed	15	15	30
		Expected	15	15	

In both the groups, there was no correlation found between LP(a)and LDLc, as depicted in Figures 1 and 2.

Figure 1: Scatterplot between Lp(a) and LDLc for Experimental Group

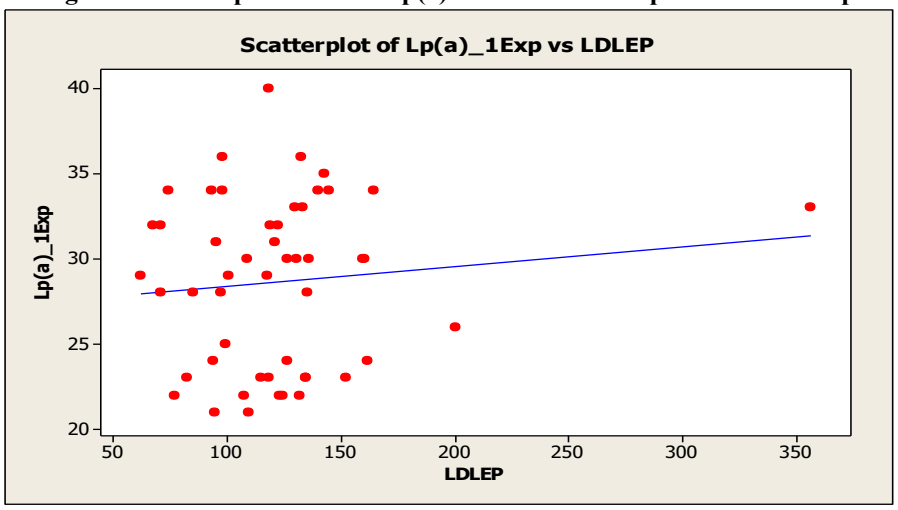
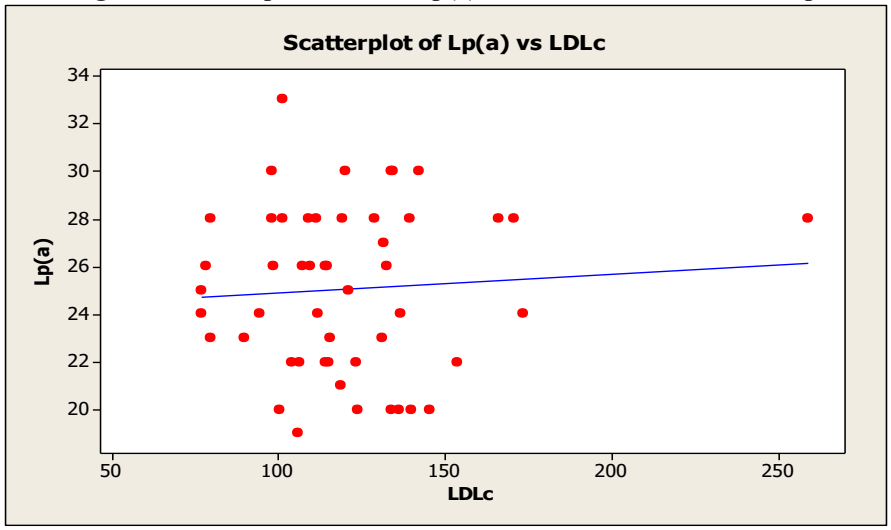


Figure 2: Scatterplot between Lp(a) and LDLc for Control Group



4. Discussion

Achievement of precise glycemic control is the main aim of the management of diabetes mellitus. Based on glycemic control, the diabetic subjects were assessed in the present study with the anthropometric and certain biochemical parameters as similar to a study done by Patil *et al* [13] and Patel *et al* [14]. Previous studies [15,16] attempted to measure the adverse cardiovascular outcome of poor glycemic control in diabetic subjects, but they have not considered the anthropometric parameters. In the current study, the adverse cardiovascular outcome in the form of ischemic heart disease or atherosclerosis has not been measured due to limitations in the protocol. One of the essential anthropometric parameters was bodyweight of the individual, and the prevalence of obesity observed was 6 % as per the criteria of BMI in both gender was considered as the parameter measuring obesity. There was a statistically significant difference found in mean systolic and diastolic blood pressure between the two groups.

We observed that in diabetic subjects, the lipid parameters are adversely affected. The levels of high-density lipoprotein cholesterol (HDL) were low, and the level of triglyceride (TG), LDL, and VLDL cholesterol was significantly high in the study group, which is comparable with the study done by Patil *et al* [13]. The family history of type 2 DM was associated with dyslipidemia. Serum HDL levels were reported significantly low in diabetic subjects. TC/HDL ratio was significantly increased in the diabetic group as compared to the control group; this finding is correlated with the previous studies [17-19]. Solfrizzi *et al* [20] reported that TC/HDL-C ratio was a sensitive and specific index of cardiovascular risk and should be considered a predictor of CHD risk, with which our study favorably matches.

One of the essential constituents of the LDL cholesterol family is Lipoprotein (a), which was separately measured in the present study. The mean value of the Lp-a level was high in the study group as compared to the age-matched control group, which is in agreement with the research done by Chandani and Kollengode [21]. As same as other studies [22-24], the glycemic control in the study group was measured by glycosylated haemoglobin (Hb-A1c) levels rather than estimations of fasting or postprandial blood glucose levels. We took HbA1c as the indicator of glycemic control and tried to correlate the association of HbA1c with levels of Lp(a). The cut-off value for HbA1c was ≤ eight as good glycemic control, and >8 was considered as an indicator of inadequate glycemic control following the standard protocol [25]. The subjects were grouped in two based on Lp(a) levels ≤ 25 and above 25, and association with Lp(a) levels was observed. The positive association of two parameters, i.e., the poor glycemic control with high HbA1c individuals are likely to have higher levels of Lp(a) levels, as indicated in the present study. These results are in agreement with prior work [16, 26].

Schmitt *et al* [27] suggested that LDL uptake by fibroblasts might be impaired in people with type-II diabetes leading to an increase in LDL: HDL ratio. The present study did not indicate any association of Lp(a) levels with the LDL: HDL ratio, which was comparable with the research done by Singla *et al* [15]. Also, there was no correlation found between LDL cholesterol and Lp(a) levels as the mean Lp(a) levels did vary significantly between two groups, this result is in agreement with the study done by Ramirez *et al* [28]. We have not attempted to resolve subgroups of lipoproteins such as Apolipoprotein A and B due to limitations of the protocol. LDL: HDL ratio significantly differed between controlled and uncontrolled diabetics (P>0.05) similar results have also been reported by Schmitt *et al* [27]. The present study might be extended with consideration of few facts such as the ratio of Apolipoprotein A and B; a retrospective observation of any adverse cardio-vascular events to the subjects enrolled in the study; measures to find any role played by oxygen-derived free radicals/ reactive oxygen species to assess the tissue damage and increasing the sample size to reach a substantial conclusion.

5. Conclusion

From the results of the present study, it can be concluded that type-2 diabetes mellitus is strongly associated with increased Lp(a) levels. We have found a significant association between the levels of Lp(a) and glycated hemoglobin. No significant correlation could be established between Lp(a) and LDL: HDL ratio. Serum Lp (a) associated with lipid abnormalities high triglyceride, high, LDL TC/LDL ratio, and low HDL makes people with diabetes prone for CAD.

As the present study was performed on a population confined to a particular Vidarbha area, the results do not necessarily apply to the other racial groups. The small sample size is also another limitation of the study. Further prospective studies will be required to establish these findings. Lipoprotein (a) In Type 2 Diabetes Mellitus: Relationship of Glycemic Control and LDL to HDL Ratio

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