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Lipoprotein (A) In Type 2 Diabetes Mellitus as A Marker of Atherosclerotic Cardiovascular Disease

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ABSTRACT

Background: One of the most important complications of Type 2 diabetes mellitus (T2DM) is atherosclerotic cardiovascular disorders (ASCVD), a disease that affects a large percentage of the population and considered a healthcare burden. **Objective:** Our aim to establish a probable relationship between lipoprotein (a) [Lp (a)] and T2DM and to demonstrate it as a marker of (ASCVD).

Patients and Methods: This case-control study included 200 subjects; 150 diabetic patients and 50 age and gender matched healthy subjects. Thorough history taking of T2DM with assessment of vascular diabetic complications was done. The fasting plasma glucose, HbA1c, lipid profile, s. creatinine and Lp (a) level were performed to all participants.

Results: Lp (a) levels were significantly low in diabetic patients (19.8 ± 13.4 mg/dl) compared to control group (32.6 ± 20.8 mg/dl) ($p < 0.001$). Lp (a) level was significantly higher in diabetics with macro-vascular complications (22.7 ± 14.4 mg/dl) than diabetics with micro-vascular complications (11.7 ± 6.5 mg/dl). Lp (a) level among diabetics with macro-vascular complications was insignificant higher than diabetics without vascular complications ($p= 0.08$).

Conclusion: Lp (a) is strongly associated with T2DM and its vascular complications that needs further research especially genetic study.

Keywords: Lipoprotein (a), Diabetes Mellitus, HbA1c, ASCVD, case control study.

INTRODUCTION

The number of persons with diabetes was expected to reach 463 million in 2019, that prevalence was estimated by International Diabetes Federation (IDF). By 2030 cases could reach 578 million and by 2045, over one half of the world's population could be affected [(1)]. Diabetics could experience two folds risk of developing cardiovascular diseases (CVD). Dyslipidemia as well as hypertension as known risk factors of to develop CVD are usually present in type 2 diabetes mellitus (T2DM) patients, however they are not directly related for the population-specific higher risk of CVD [(2,3)].

Nontraditional risk factors have been extensively studied to be identified and correlated with macrovascular consequences among diabetic patients. Extensive study has been devoted to the lipoprotein (a) [Lp (a)], is considered one among the many potential risk factors. Apolipoprotein (a) is covalently connected to apoB-100 by bond pf disulfide type, making Lp (a) a particle like low-density lipoprotein (LDL). LPA gene, with location on chromosome 6q26-27, is the primary factor in determining plasma Lp (a) concentration. Apo (a) proteins come in a range of sizes because the Lp (a) gene contains an arbitrary number of kringle IV repeats. Different versions of the protein apo(a) exist, and these variants are referred to as isoform (a) [(4,5)].

Lp (a) levels are inversely proportional to the size of the apo(a)isoform because the endoplasmic reticulum of hepatocytes sequesters bigger molecules, resulting in lower plasma levels [(6)]. Since the precursor protein for Lp (a) does not leave the cell until the final stages of protein synthesis are complete, the quantity of Lp (a) in the plasma is capped by the much slow rate of production of the larger isoforms[(7)].

Our study aimed to establish a probable relationship between Lp (a) and T2DM and to demonstrate it as a marker of (ASCVD).

PATIENTS AND METHODS

Our study was a cross-sectional case control analysis of 150 subjects having T2DM and 50 healthy controls of matched age and gender. Participants were selected from the clinic population at Banha University Hospital between August 2021 and February 2022. The age of studied subjects ranged between 40 and 70 years with normal lipid profile.

Patients with one or more of the following characteristics were excluded; Patients with Type 1 DM, gestational diabetes, patients receiving estrogens or progesterone, patients receiving drugs affecting metabolism of Lp (a) like long time using of steroids as well as niacin and other diseases that might affects Lp (a) level as liver cirrhosis, heart failure, thyroid disease, acute illness, severe infection, or malignancy.

Subjects were grouped as; the control group (**group A**), constituting 50 apparently healthy volunteers, and the case group (**group B**) with 150 T2DM patients. The diabetic group were further subdivided into the following 3 subgroups; 1) Subgroup *B*: it involved 50 patients of T2DM without complications, 2) Subgroup *C*: it involved 50 patients of T2DM who had macro-vascular complications (one or more of cerebrovascular disease, peripheral vascular disease as well as coronary artery disease), and 3) Subgroup *D*: it involved 50 patients of T2DM who had micro-vascular complications (one or more of retinopathy, neuropathy and nephropathy).

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Demographic and anthropometric data were collected, additionally, treatment and vascular consequences from diabetes.

Laboratory data: At the Clinical Pathology Department, we tested fasting plasma glucose (FPG), lipid profile, serum creatinine, as well as glycated hemoglobin (HbA1c) at Benha University Hospital, according to the laboratory's standard procedures. For Lp (a) measurement; the laboratory received whole blood collected in tubes containing separating gel for analysis then centrifuged, the serum was collected and kept at -80C. (ELISA) was used for the analysis. When Lp (a) was below 14 mg/dL, it was considered desirable; and when between 14 and 30 mg/dL, it was considered at risk; and when between 31 and 50 mg/dL, it was considered high risk; and beyond 50 mg/dL, it was considered extremely high risk [(8)].

Ethical consideration:

All procedures done on human participants in this study have been approved by the Ethics Committee of Benha University, Egypt, in accordance with the principles described in the Declaration of Helsinki by the World Medical Association. Before being enrolled, every patient gave written consent.

Statistical analysis

Investigation report forms were used to document the collected information. The analysis was performed in SPSS (Statistical Package for the Social Sciences) version 26. Means and standard deviations (SD) were used for summarization of quantitative data, and frequencies and related percentages were used to present qualitative data. For the statistical significance of difference, means of two sets of numerical data had been compared by the Student's t-test. The Mann-Whitney U-test was employed for comparing the two groups, as it is appropriate for non-parametric continuous data. We used the chi-square test to compare means across groups in our categorical data analysis (X^2). When the p value of a statistical test was equals or less than 0.05, it was considered to be significant.

RESULTS

Our study consisted of 50 healthy control individuals (**group A**) (28 males and 22 females) and 150 Patients with T2DM **group B** (64 males and 86 females) that was further subdivided into three subgroups; *subgroup B* (diabetic patients without vascular complications), *subgroup C* (diabetes with macro-vascular complications), and *subgroup D* (diabetic with micro-vascular complications).

Table (1) demonstrated that systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, FPG, s. creatinine, triglyceride (TG) level, Low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) were significantly higher in all diabetic patients than the control group (p<0.001). However, body mass index (BMI) was insignificantly higher in diabetic patients (32.23 ± 5.52 kg\m2) than control group (30.60 ± 5.51kg\m2) (p= 0.07). The mean duration of DM was 10.25 years (SD 2.12).

Table (1): Subjects' sociodemographic and laboratory data.

Variable (Quantitative Data)		Cases (n=150)		Control (n=50)		p-value
		Mean	SD	Mean	SD	
Age (years)		54.88	8.50	53.1	8.8	0.2
BMI(Kg\m^2)		32.23	5.52	30.60	5.51	0.07
SBP (mmHg)		139.92	15.72	121.24	10.53	<0.001
DBP (mmHg)		84.23	9.08	76.94	5.68	<0.001
HbA1c %		8.38	1.83	5.20	0.24	<0.001
FPG(mg\dl)		130.26	4.76	82.84	6.77	<0.001
S. Creatinine (mg \dl)		1.38	0.14	0.83	0.14	<0.001
TG level(mg \dl)		137.17	15.56	118.66	18.27	<0.001
LDL-C (mg \dl)		89.67	9.36	85.38	7.11	0.003
HDL-C (mg \dl)		42.31	7.46	44.16	5.18	0.1
Total-Cholesterol (mg\dl)		178.15	17.41	158.06	17.79	<0.001
Duration of DM (years)		10.25	2.12	---	---	---
Variable (Qualitative Data)		**No.**	**%**	**No.**	**%**	
Sex	Female	86	57.3%	28	56.0%	0.9
	Male	64	42.7%	22	44.0%	
Smoking	No	98	65.3%	32	64.0%	0.9
	Yes	52	34.7%	18	36.0%	
DM Treatment	Insulin	48	32%	---	---	---
	OAD	102	68%	---	---	---

SD= standard deviation, BMI= Body mass index ,SBP=systolic blood pressure DBP=diastolic blood pressure, HbA1c= hemoglobin A1C, FPG=fasting plasma glucose, TG =triglycerides ,LDL,C=low density lipoprotein cholesterol, HDL,C=high density lipoprotein cholesterol ,DM =diabetes mellitus ,OAD=oral anti diabetic drugs .

Table (2) shows that SBP, DBP, HbA1c, FPG, TG level, HDL–C and TC were significantly higher in the diabetic patients without complications compared to the control group. Lp (a) level was significantly higher in the control than the diabetic groups without complications (p <0.001).

Table (2): Clinical and laboratory data of group (A) and subgroup (B).

Variable	Group (A) (n=50)		Subgroup (B) (n=50)		T test	p-value
	Mean	SD	Mean	SD		
SBP (mmHg)	121.24	10.53	133.36	14.42	4.8	<0.001*
DBP (mmHg)	76.94	5.68	80.96	8.14	2.8	0.003*
HbA1C %	5.20	0.24	7.70	0.79	21.4	<0.001*
FPG (mg/dl)	82.84	6.77	125.20	31.70	9.2	<0.001*
S. Creatinine (mg/dl)	0.83	0.14	0.86	0.15	0.9	0.2
TG level (mg/dl)	118.66	18.27	128.64	20.46	2.6	0.02*
LDL-C (mg/dl)	85.38	7.11	85.52	8.65	0.1	0.5
HDL-C (mg/dl)	44.16	5.18	40.68	8.16	2.5	0.006*
T-Cholesterol	158.06	17.79	168.28	17.10	2.9	0.002*
Lp (a) (mg/dl)	32.6	7.38	19.8	13.4	3.31	<0.001*

Table (3) demonstrated that SBP, DBP, HbA1c, TG, TC were significantly higher in macro-vascular diabetic complications in comparison to subgroup (B). Mean Lp (a) levels were insignificant higher in macrovascular diabetic complications (22.7 ± 4.64 mg/dl) than subgroup (B) (19.8 ± 3.84 mg/dl) (p value 0.08).

Table (3): Clinical and laboratory data of subgroups (B) and (C).

Variable	Subgroup *B* (n=50)		Subgroup *C* (n=50)		T test	p-value
	Mean	SD	Mean	SD		
SBP (mmHg)	133.36	14.42	145.4	15.3	4.03	<0.001*
DBP (mmHg)	80.96	8.14	85.5	8.9	2.6	0.005*
HbA1c %	7.70	0.79	9.3	2.5	4.3	<0.001*
FPG (mg/dl)	125.20	31.70	134.3	30.4	1.5	0.07
S. Creatinine (mg\dl)	0.86	0.15	0.8	0.16	1.8	0.04*
TG level(mg\dl)	128.64	20.46	139.1	10.3	3.2	<0.001*
LDL-C(mg\dl)	85.52	8.65	87.2	8.4	1.01	0.2
HDL-C(mg\dl)	40.68	8.16	40.6	5.8	0.1	0.5
T-Cholesterol (mg\dl)	168.28	17.10	176.1	14.9	2.4	0.008*
Lp (a) (mg/dl)	19.8	3.84	22.7	4.64	1.7	0.08

Table (4), lipid profile was significantly higher in subgroup (D) than subgroup (C). The levels of Lp (a) were significantly higher in subgroup (C) than subgroup (D).

Table (4): Clinical and laboratory data of subgroups (C) and (D).

Variable	Subgroup (C) (n=50)		Subgroup (D) (n=50)		T test	p-value
	Mean	SD	Mean	SD		
SBP (mmHg)	145.4	15.3	141.1	15.3	1.4	0.1
DBP (mmHg)	85.5	8.9	86.2	9.4	0.4	0.3
HbA1C %	9.3	2.5	8.1	1.3	3.1	0.003*
FPG (mg/dl)	134.3	30.4	131.3	4.2	0.4	0.3
S. Creatinine	0.8	0.16	2.5	0.2	9.9	<0.001*
TG level(mg\dl)	139.1	10.3	143.8	9.5	2.3	0.01*
LDL-C(mg\dl)	87.2	8.4	96.2	7.4	5.7	<0.001*
HDL-C(mg\dl)	40.6	5.8	45.7	7.2	3.9	<0.001*
T-Cholesterol (mg\dl)	176.1	14.9	190.1	12.6	5.04	<0.001*
Lp (a) (mg/dl)	22.7	4.84	11.7	1.75	4.9	<0.001*

DISCUSSION

For better clinical diagnosis and treatment of high-risk individuals, it is essential to have a better understanding of the underlying causes of CVD and T2DM. Our findings showed that Lp (a) was significantly lower in diabetic patients than in the control group. These findings corroborated those of a European population study that found an inverse relationship between Lp (a) levels and the development of T2DM [(9)].

Our results are supported by the results of a prospective research that looked at the connection between plasma Lp (a) levels and the onset of T2DM in 26,746 women from the Women's Health Services (WHS) and the Copenhagen City Heart Study (CCHS). Results from the WHS and CCHS studies showed that patients with diabetes had lower Lp (a) levels than those without diabetes [(9)]. The San Antonio Heart Study found no significant difference in Lp (a) levels between the diabetes and non-diabetic populations, while we found the opposite to be true [(10)]. Some reasons for decreased Lp (a) in diabetic people could include; The LPA gene encodes Lp (a), and studies have demonstrated that the kringle IV type 2 (KIV-2) variant is critical to the size of the Lp (a) isoform. Low Lp (a) levels are associated with an increased risk of developing T2DM, which is in turn linked to large isoform size (indicated by a high number of KIV-2 repetitions in the gene). Hence, it is not just Lp (a) concentrations that mediate the link between Lp (a) and T2DM; rather, the high isoform size of Lp (a) molecules plays a role as well. Genetic study revealed a correlation between increasing isoform size and an increased chance of acquiring T2DM [(11)].

Low Lp (a) concentrations may be a sign of insulin resistance, as indicated in one study, which found an inverse relationship between Lp (a) and insulin and 2-hour postprandial glucose levels [(12)]**.** Another study showed that Insulin blocks the function of apolipoprotein(a) in hepatocytes, which may explain why Lp (a) concentrations are lower in type 2 DM and higher in type 1 DM [(13)].

Our findings suggest a weak association between Lp (a) and the onset of ASCVD in diabetics, with Lp (a) levels being insignificantly higher in the group of patients with macrovascular problems compared to those without such complications. However, Lp (a) levels were considerably higher in the group of diabetics who experienced macro-vascular difficulties as opposed to those who experienced micro-vascular complications. Increased risk of CVD was found to correspond with greater plasma levels of Lp (a) in the Copenhagen Cardiovascular Health Study (CCHS), the Copenhagen Ischemic Heart Disease Study (CIHDS), and the Copenhagen General Population Study (CGPS) [(14)]. In addition, **Clarke *et al.*** found a significant association between high Lp (a) levels and CHD risk in their case control genetic study [(15)]**.** Two Mendelian randomization studies have found an association between Lp (a) and the risk of atherosclerosis and CVD [(16)].

Patients having coronary angiography (including those with diabetes) were studied, and researchers found that whereas Lp (a) was a robust and independent predictor of CVD events among those without diabetes, it was not among those with diabetes [(17)]. According to a study conducted by the European Society of Cardiology, there was a linear correlation between Lp (a) and CVD occurrences. With the following clinical scenarios, it is recommended that Lp (a) be measured: (i) premature CVD, (ii) Familial hypercholesterolemia (FH), (iii) increased Lp (a) levels or a family history of CVD, and (iv) CVD recurrence despite excellent statin therapy; 10-year mortality risk of less than 5%[(18)]. However, one study revealed no association between plasma Lp (a) levels and CVD risk in patients with T2DM [(19)]. After 13 years of follow-up, patients with T2DM who had high or low Lp (a) levels did not differ significantly in their risk of CHD or stroke, according to a study conducted by **Abu-Lebdeh *et al.*** [(20)] **.** Another study identified a modest connection between plasma Lp (a) levels and the incidence of CVD and death in age-adjusted diabetics, using data from the NHS and Health Professional Follow up Study (HPFS) trials [(21)].

A general population study with a 10-year follow-up found no significant difference in the association between Lp (a) and CHD between those with and without diabetes [(22)]**.** The association of Lp (a) with ASCVD could be explained as follow; Firstly, Cholesterol is deposited in the expanding atherosclerotic lesions because Lp (a) is more tightly confined than LDL by binding to the extracellular matrix via apo lipoprotein(a) and apo lipoprotein B component[(23)]. Wound healing is aided by Lp (a) because the apo(a) molecule has an affinity for fibrin, stimulates cell proliferation, and transports cholesterol. Lipid buildup in the arterial wall is caused by Lp (a), binding to fibrinogen, proteoglycans, and fibronectin among other components of the subendothelial matrix [(24)]. Secondly, Oxidative modification of Lp (a) creates a substrate for macrophage absorption and promotes foam cell formation, just as it does for low-density lipoprotein (LDL) [(25)]**.**

As oxidized Lp (a) was discovered to have an inflammatory impact by increasing monocyte chemotaxis and inducing the formation of vascular adhesion molecules [(26)]. Thirdly, Because of its similarities to plasminogen, Apo(a), which is present in Lp (a), may reduce the activity of plasminogen and raise the risk of thrombosis. To rephrase, Plasminogen activation may be inhibited by Lp (a) because of competition for fibrin binding [(27)]**.** Evidence suggests that apo(a) interacts with tissue plasminogen activator (tPA) and plasminogen to alter the kinetics of plasmin generation within the fibrinolytic complex [(28)]. As Lp (a) promotes synthesis of plasminogen activator inhibitor-1, less tPA is available for plasminogen activation (PAI-

1) [29]. Additional thrombogenic properties of Lp (a). include the ability to enhance platelet aggregation and the inactivation of tissue factor pathway inhibitor [30]. Lastly, Lp (a) is a member of the same family as apoE and has been demonstrated to stimulate the formation of endothelium and smooth muscle cells in laboratory experiments (a).

Ichikawa *et al.* [31] supported proliferation of smooth muscle cells in regions of Lp (a) deposition in transgenic rabbits. Smooth muscle cell proliferation, regulated negatively by transforming growth factor-, was shown to be reduced by Lp (a)[32]. The actin cytoskeleton of cultured endothelial cells has been demonstrated to rearrange itself in response to the apo(a) component of Lp (a). The development of atherosclerosis is preceded by the endothelium being damaged and more permeable due to a lack of cell-to-cell interaction [33].

Limitation of the study: In a retrospective case-control study, the possibility of an artefact, like cause effect bias, could not be excluded. In general, hospital-based studies are considered methodologically suspect by many investigators. Our study was conducted at Benha University Hospitals, so it did not represent the whole Egyptian populations. In addition to the level of Lp (a), we need to evaluate the size of the molecule and to identify the isoforms responsible for ASCVD.

CONCLUSION

Lp (a) screening may be recommended for atherosclerotic patients with DM as secondary preventive tool because atherosclerosis is the most common cause of morbidity and mortality among diabetics that places a massive burden on Egypt's healthcare resources. Further prospective study is needed with a large number of populations for better assessment of Lp (a) as an indicator of CVD.

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