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Relation of Serum Lipoprotein (a) and Severity of Coronary Artery Disease in Type 2 Diabetic Patients

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ABSTRACT

Background: For coronary artery disease, lipoprotein (a), or Lp (a), is a well-established risk marker.
Objectives: The aim of the current work was to determine the correlation between the severity of coronary artery disease and the serum lipoprotein (a) level in diabetic patients.
Subjects and methods: At the National Heart Institute, Cairo, we conducted this cross-sectional observational study. From July 2021 to January 2022. 114 Type 2 diabetic individuals qualified for coronary angiography were enrolled in the study. All the participants in the trial were subjected to full history taking, clinical examination, ECG, Echocardiography, complete blood count, liver enzymes and serum creatinine, Lipoprotein (a) measurement and coronary angiography.
Results: According to the results of our research, patients with high levels of lipoprotein (a) also had higher Syntax scores (p-value < 0.001). On the contrary, patients' lipoprotein (a) levels did not correlate statistically with any of the other measurements taken (p-value > 0.05).
Conclusion: It could be concluded that patients with diabetes may have an increased risk of cardiovascular disease if their Lp (a) level is elevated, and the Lp (a) level is an essential clinical marker in both the general population and those with diabetes. A higher Lp (a) level in type 2 diabetics, according to our findings, is of great clinical significance.
Keywords: Coronary artery disease, Diabetes, Lipoprotein (a).

INTRODUCTION

LDL particles include apolipoprotein B-100 (apoB100), which has had another protein, apolipoprotein a (apo a), covalently attached to it. Lipoprotein (a) is a circulating lipoprotein that contains this modified form of apoB100 [(1)].

Low density lipoprotein cholesterol (c-LDL) is bound to the glycosylated protein known as apoprotein (a) in the formation of Lp (a), bridged by a disulphide. Because it is determined genetically, the plasma concentration of Lp (a) in each person is nearly constant throughout their lifetime. Plasma apo (a) isoform size and Lp (a) levels have an anti-parallel relationship [(2)].

An elevated cardiovascular disease risk development has been linked to the presence of apoB-containing lipoproteins. Lp (a) was defined to be promising valuable marker used aiding in treatment modalities of heard diseases [(3)].

Macrovascular coronary artery disease, microvascular nephropathy, retinopathy, and cerebral vasculopathy all occur often in diabetics: Lower-limb artery atherosclerotic lesions and/or intermittent claudication are both linked to atherosclerosis. Increased Lp (a) levels in the blood was positively correlated with higher incidence of coronary heart disease development. In particular, two Lp (a) variants have been found to be substantially related with elevated Lp (a) levels in the blood and a higher risk of CHD [(2)].

Worldwide, cardiovascular disease has risen to the position of a leading cause of death. Cardiovascular disease (CVD) mortality and morbidity are significantly reduced when plasma levels of LDL-C, a kind of low-density lipoprotein cholesterol, are reduced [(4)].

According to European Society of Cardiology recommendations, patients with intermediate or high CVD risk should have their Lp(a) levels checked, and readings beyond the cutoff of 50 mg/dL are indicative of an extremely high cardiovascular risk. To lower LDL cholesterol and improve the prognosis of patients presenting with acute coronary syndromes, it is imperative that patients get extensive lipid lowering therapy.

CVD events recur after an ACS in patients with familial hypercholesterolemia, who have an increased risk due to their genetic predisposition [(5)].

This study goal was determining the correlation between the severity of coronary artery disease and the serum lipoprotein (a) level in diabetic patients.

PATIENTS AND METHODS

This cross-sectional observational study included a total of 114 diabetic patients who were eligible for coronary angiography, attending at National Heart Institute, Cairo. This study was conducted between July 2021 till January 2022.

Inclusion criteria:

- Age ≥ 18 years old.
- Diabetes mellitus, diagnosis based on (Fasting Glucose Levels equal or higher than 126mg/dl or plasma glucose 2 hours post prandial equals or higher than 200 mg/dl or Hemoglobin A1C to be more than 6.5% or hyperglycemia or hyperglycemic crises in a patient with the basic signs and characteristics, random blood sugar more than 200 mg/dl [(6)].
- Indication for coronary angiography as +ve cardiac enzymes, ECG changes, +ve stress ECG and +ve Myocardial Perfusion Imaging (MPI).

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Exclusion criteria:

Patients who had any of the following conditions were not allowed to participate in the study:

- Renal impairment.
- Severe liver disease.
- Sepsis.
- Coagulopathy.

A detailed medical history was obtained from all participants in this study (age, sex, risk factors (smoking, HTN, dyslipidemia), duration and medication of DM), general examination (pulse, blood pressure, neck vein, lower limb edema, etc,), local examination (auscultation was done to detect additional sounds and murmurs). 12 leads ECG (to detect ischemic changes (T wave inversion, ST segment changes) and arrhythmia as AF), Echocardiography: using vivid 55 machine with the patient in the left lateral position according to recommendation of American Society of Echocardiography, M-mode: to measure LVEDD, LVESD and EF, 2D: to assess wall motion abnormalities, Laboratory tests: complete blood count, liver enzymes and serum creatinine, Lipoprotein (a) measurement and Coronary angiography.

Ethical Consideration:

An approval of the study was obtained from Menoufia University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

In order to analyze the data acquired, Statistical Package of Social Services version 24 was used to execute it on a computer (SPSS). In order to convey the findings, tables and graphs were employed. The quantitative data was presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (T) is used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X2) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined. As a rule of thumb, Kruskal Whitney test is employed when the predicted count is fewer than five in more than 20% of cells. Measurement on a regular basis More than two normally distributed variables were compared using the Anova test.

RESULTS

In terms of the study's participants' demographics, patients average age was (57.4 ± 7.9) ranged from 40-75 years. Among the study patients, there were 64 males (56.1 percent) and 50 females (43.9 percent). (Table 1).

Table (1): Demographics of the studied patients

		Studied patients (N = 114)	
Sex	**Male**	**64**	**56.1%**
	Female	**50**	**43.9%**
Age (years)	**Mean ±SD**	**57.4 ± 7.9**	
	Min – Max	**40 – 75**	

For risk factors of the study patients, there were 102 hypertensive (89.5%), 112 dyslipidemic (98.2%), 38 patients (3.3%) with positive family history, 48 smokers (42.1%) and 14 X-Smokers (12.3%) (Table 2).

Table (2): The patients' risk factors were analyzed.

Parameters		Studied patients(N = 114)	
Hypertension		**102**	**89.5%**
Dyslipidemia		**112**	**98.2%**
Family history		**38**	**33.3%**
Smoking	**Non-smoker**	**52**	**45.6%**
	Smoker	**48**	**42.1%**
	X-Smoker	**14**	**12.3%**

The presentation of the studied patients. There were ST elevation in 10 patients (8.8%), non ST elevation in 9 patients (7.9%) and chronic stable angina (elective) in 95 patients (83.3%) (Table 3).

Table (3): Presentation of the studied patients

Studied patients (N = 114)		Studied patients (N = 114)	
ECG	**ST elevation**	**10**	**8.8%**
	Non ST elevation	**9**	**7.9%**
	Chronic stable angina (elective)	**95**	**83.3%**

Classification of the studied patients according to Syntax score. There were 58 patients (50.9%) with mild Syntax score (≤ 22) CAD, 31 patients (27.2%) of moderate Syntax score (23-32) CAD and 25 patients (21.9%) of severe Syntax score (>32) CAD (Table 4).

Table (4): Classification of the studied patients according to Syntax score

Studied patients (N = 114)		N	%	mean ±SD
Syntax score	**Mild (≤ 22) CAD**	**58**	**50.9%**	**12.9 ± 6.5**
	Moderate (23 – 32) CAD	**31**	**27.2%**	**27.2 ± 2.3**
	Severe (> 32) CAD	**25**	**21.9%**	**39.2 ± 4.8**

Patients' lipoprotein (a) levels and Syntax scores had a highly significant positive relationship (p-value <

0.001) on the contrary, Patients' lipoprotein (a) levels did not correlate statistically with any of the other measurements taken (p-value > 0.05) (Table 5).

Table (5): Lipoprotein (a) and other variables in the patients under investigations

Parameters	Lipoprotein (a)	
	(r)	p-value
Age	**-0.01**	**0.925 NS**
Duration of smoking	**0.00**	**0.967 NS**
Serum creatinine	**-0.08**	**0.397 NS**
EF	**-0.13**	**0.177 NS**
Syntax Score	**0.59**	**< 0.001 HS**

EF= ejection fraction (r): Pearson correlation coefficient. HS: p-value < 0.001 is considered highly significant**.**

DISCUSSION

The major cause of death in developed countries is cardiovascular disease. Improvements in cardiac revascularization procedures have significantly reduced mortality, but results in high-risk patient subgroups remain unsatisfactory despite these advancements in revascularization and antithrombotic medicines for coronary artery disease (CAD) treatment. A great deal of attention has been given to finding risk factors for coronary artery disease that can be avoided or at least minimized. Patients with diabetes mellitus are more susceptible to cardiovascular disease, especially coronary artery disease, than the general population [(7)].

Diabetes mellitus consequences are mostly caused by dyslipidaemia, which is the disease's fundamental metabolic imbalance. These three factors were believed to be atherogenic in patients with type 2 diabetes mellitus: hypertriglyceridemia, low HDL, and high LDL. Dyslipidaemia is a primary contributor to insulin resistance [(8)].

Diabetic complications have been linked to an increased risk of CAD and mortality. Diabetes mellitus (DM) is associated with a 2-to-3-fold increase in the risk of cardiovascular disease compared to persons who are not diabetic. Type 2 diabetes patients have a distinct lipid and lipoprotein profile than the general population, with a high triglyceride level and low HDL-C levels [(9)].

Atherosclerosis and thrombosis are both caused by the interference of the fibrinolytic system with the lipid metabolism of Lp (a), an independent macromolecular lipoprotein that has a very high degree of homology and specific antigenicity. Lp (a) is distinct from other apolipoproteins in that it has a high degree of homology and specific antigenicity [(10)].

Murase *et al.* [(11)] found that; diabetics who had coronary heart disease tend to have greater Lp (a) levels than diabetics who do not have coronary heart disease, however it is not clear if elevated Lp (a) levels in diabetics are associated to an increased risk of cardiovascular events. Also, **Mora *et al.*** [(12)] stated that their group's increased risk for cardiovascular disease is complicated further by the fact that their Lp(a) levels are lower than those of non-diabetics.

In diabetic patients, we looked at the link between serum lipoprotein (a) and the severity of coronary artery disease. 114 patients from the National Heart Institute, Cairo participated in this cross-sectional study. Cardiovascular angiography was performed for all patients to determine the extent of coronary artery disease and the Syntax score was determined. All patients had their serum Lp (a) levels checked.

Regarding smoking in our study, there were 48 smokers (42.1%) and 14 X-smokers (12.3%). **Turfana *et al.*** [(13)] found that there is no significant difference between smokers and nonsmokers as regard the severity of coronary artery disease, this may be explained by they include all patients with history of smoking and didn't differentiate between Ex-smokers and current smokers.

Acute endothelial dysfunction triggered by nicotine leads to atherosclerotic plaque formation, and chronic carbon monoxide damage results in irreversible narrowing and thrombi, reducing coronary lumen patency. Both of these hypotheses are based on evidence from studies of coronary artery disease in smokers, which shows a consistent and repeatable response to nicotine exposure[(14)].

When the endothelium loses its integrity, it becomes thrombogenic due to numerous mechanisms that stimulate platelet aggregation, adhesiveness, inflammatory cell movement, and lipid material precipitation. Smoking cigarettes activates the adrenaline and parasympathetic nervous systems, which might lead to these side effects [(15)].

Regarding hypertension in our study, there were 102 hypertensives (89.5%). **Su *et al.*** [(16)] found that there were more older, male, and nonsmokers with diabetes with CAD than there were without CAD.

Wei and colleagues [(17)] found that the coronaries of diabetics are more complicated. More widespread atherosclerosis caused by increased necrotic core size and macrophage and T lymphocyte infiltrates may explain this association between diabetic coronary artery disease and these factors. In diabetic patients, a higher incidence of recurrent plaque ruptures with subsequent repair is expected to result in an increased incidence of obstructive lesions.

Wei *et al.* [(17)] found also that when compared to healthy people with normal systolic and diastolic blood pressure, hypertensive patients have more severe coronary artery disease and more complicated coronary artery lesions. Including a huge sample size of more than 1500 patients, as well as diverse inclusion criteria, they included the patients with unstable angina.

Diabetic complications, such as hyperglycemia-induced oxidative stress, endothelial dysfunction, mineral metabolism changes caused by renal

dysfunction, and elevated levels of inflammatory cytokines in the bloodstream, all lead to blood vessel calcification[18]. People with coronary artery disease are more likely to acquire diabetes mellitus, according to these data.

Turfana *et al.* [13] found no substantial difference in coronary heart disease between diabetics and non-diabetics was identified in a separate investigation, and this could be due to their vastly differing patient populations.

As regard serum creatinine, the mean serum creatinine of the studied patients was 0.96± 0.3 mg/dl. As regard lipoprotein (a), the mean lipoprotein (a) of the studied patients was 65.6 ± 28.7. **Kwon *et al.*** [19] found that overall, the median Lp(a) level was 13.5 mg/dl.

Syntax score, the most modern and reliable angiographic instrument for quantifying severity and complexity of coronary artery disease and predicting results of coronary intervention,, was used in our present study and was significantly higher in those with high Lp (a) compared to those with normal Lp (a) levels with cut off value 22 for mild and 34 for high risk scores [20].

According to Syntax score, there were 58 patients (50.9%) with mild Syntax score (≤ 22) CAD, 31 patients (27.2%) of moderate Syntax score (23-32) CAD and 25 patients (21.9%) of severe Syntax score (>32) CAD. Serum lipoprotein (a) was significantly higher in the patient with severe Syntax score (>32) CAD than other groups.

Our investigations demonstrated a statistically significant association between lipoprotein (a) and Syntax score in patients investigated (p-value < 0.001). On the contrary, Patients' lipoprotein (a) levels did not correlate statistically with any of the other measurements taken (p-value > 0.05). **Kwon *et al.*** [19] found that older patients were more likely to have increased Lp (a) levels than younger ones (p < 0.0001), non-smoking personnel (p = 0.002), and females (p = 0.004)

Diabetes and low-density lipoprotein (Lp(a)) cholesterol (DLC) are two of the most important risk factors for cardiovascular disease that should be evaluated while treating people at high risk. A high level of lipoprotein(a) (Lp (a)) has been identified in the general population as a risk factor for cardiovascular disease [21]. Furthermore, **Erqou *et al.*** [22] strengthened the possible causal role of higher Lp (a) levels in the general population's development of cardiovascular disease.

Mora and colleagues [12] reported the inverse relationship between development of type 2 diabetes and values of LP (a). Diabetic people have lower Lp (a) levels than non-diabetics. A higher Lp (a) level in diabetics does not rule out the possibility of cardiovascular disease.

A high Lp (a) level in diabetics, whether they have CAD, has been implicated in a number of investigations. **Mohan and colleagues** [23] The Lp (a) levels of people with type 2 diabetes and CAD are higher than those of those with type 2 diabetes without CAD and of healthy controls.(non-diabetic patients without CAD). **Gazzaruso *et al.*** [24] found that among patients with coronary artery disease, type 2 diabetics are more likely than non-diabetic patients to have lower levels of Lp (a). Type 2 diabetics with CAD, on the other hand, have higher levels of Lp (a) than diabetics without CAD.

According to **James *et al.*** [25], Lp (a) tends to be elevated more among diabetics who suffer from coronary heart problems than from other diabetics who don't have any cardiac issues. Diabetes type 2 patients with higher Lp(a) levels, according to **Pedreno *et al.*** [26], have an elevated risk of coronary artery disease.

In diabetic individuals, the predictive significance of increased Lp (a) remains a matter of debate. **Kwon *et al.*** [27] found that in general populations, an increased Lp (a) level has been linked to a poorer prognosis. Additionally, **Pencina *et al.*** [28] study results demonstrated a poorer outcome for people with type 2 diabetes who had elevated Lp (a) levels. Also, **Hernandez *et al.*** [29] in type 2 diabetes patients, a high Lp (a) level has been shown to be a risk factor for cardiovascular disease. In contrast, **Qi *et al.*** [30] study suggested that type 2 diabetics with raised Lp (a) had no increased risk of cardiovascular disease.

Toro *et al.* [31] examined aged T2DM cohort's micro- and macro-vascular problems to see if Lp (a) plasma concentrations had any bearing on their development, and found that greater levels of Lp (a) were associated with an increased risk of CHD and DN.

Anuurad *et al.* [32] have proposed that Lp (a) may be an independent risk factor for cardiovascular disease, and have observed that serum Lp (a) level is positively linked with both incidence and severity of cardiovascular disease. **Kwon *et al.*** [33] demonstrated increased Lp (a) is linked to worse outcomes for type 2 diabetes patients with symptoms of coronary artery disease. Furthermore, patients with type 2 diabetes and symptomatic CAD who have a higher Lp (a) level have a better prognosis.

In Chinese patients with stable coronary artery disease a study was conducted by **Dai *et al.*** [34]. Lp (a) basic levels tend to be more among persons who had more severe coronary heart problems . In 166 patients (10.1 percent), Major cardiac heart problems occurred, with a mean follow-up period of 39.6 months. Event-free survival rates differed significantly between Lp groups after adjusting for (a). Hazard ratio for MACEs was 1.291 per standard deviation in log transformed Lp (a) levels after accounting for known cardiovascular risk factors. The risk of getting major cardiac consequences was higher in patients with stable CAD who had OMT and Lp (a). Greater levels of Lp (a) in blood were linked to more severe coronary artery disease in those who had higher levels of Lp (a).

Gudbjartsson *et al.* [35] determined the relationship between very low molar concentrations of Lp (a) and

high T2D risk. CAD and other cardiovascular diseases risk was influenced by Lp (amolar)'s concentration. For individuals who had Lp (a) levels in the 79th percentile, the odds of developing coronary artery disease rose from an OR of 1.11 to an OR of 2.01 when compared to those who had Lp (a) levels in the demographic median range. To reduce cardiovascular disease risk, persons with Lp (a) concentrations over the 79th percentile (50 nM) should lower their levels to the population median of 14 nM.

A high Lp (a) level may increase the risk of cardiovascular disease in diabetics, according to our findings. A greater Lpa level in type 2 diabetics is of major clinical significance.

The current study had some limitations including Further research with larger sample sizes are recommended following the outcomes of this study at Menoufia University Hospitals, Menoufia. Addition of Lp (a) as a routine laboratory work up in diabetic patients is recommended, Good control of diabetic mellitus is recommended, Lipoprotein (a) reflects the presence and extent of angiographically documented coronary artery disease, Lp (a) tends to be higher in advanced cases of coronary heart diseases among diabetics. So, we recommended SYNTAX score as an important and reliable tool for quantification of severity and complexity of coronary lesions in coronary angiography. Also, to better understand the predictive relevance of high Lp (a) in type 2 diabetes patients, larger cohort-based studies are needed. A bigger sample size is recommended for future research. In addition, future follow-up should be carefully considered. Such technologies are supported by multi-center sampling, which increases validity.

CONCLUSION

It could be concluded that patients with diabetes may have an increased risk of cardiovascular disease if their Lp (a) level is elevated, and the Lp (a) level is an essential clinical marker in both the general population and those with diabetes. A higher Lp (a) level in type 2 diabetics, according to our findings, is of great clinical significance.

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Author contribution: Authors contributed equally in the study.

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