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Lipoprotein (a) levels and their connection to insulin resistance and beta-cell function in coronary artery disease

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Abstract

Cardiovascular disease (CVD) remains a global health burden, claiming millions of lives every year. While traditional risk factors like cholesterol and blood pressure play a crucial role, emerging players like lipoprotein(a) (Lp(a)) and insulin resistance are gaining increasing attention. The study included 90 non-diabetic patients with coronary artery disease (CAD) as the case group and 90 controls. Fasting serum samples were collected to measure glucose, insulin, and lipid profile parameters, including triglycerides, total cholesterol, high-density lipoproteins (HDL), and lipoprotein (a) concentrations. Additionally, serum C-peptide levels were determined. The homeostatic model assessment of insulin resistance (HOMA-IR) was utilized to quantify insulin resistance. Poisson regression demonstrated that only LP(a) was significantly associated with the number of coronary artery lesions in CAD patients (IRR= 1.45, $p<0.001$), suggesting that increasing levels beyond 300 mg/dL is associated with a 45% increase in the number of lesions. Alternatively, neither LDL levels > 100 mg/dL ($p=0.5$) nor HDL levels < 40 mg/dL were associated with significant changes in the number of coronary lesions. This study contributes to the growing body of evidence supporting the critical association between Lp(a) and CAD. Identifying patients with elevated Lp(a) could improve CAD diagnosis, risk stratification, and guide personalized management. Furthermore, the association with insulin resistance in CAD patients suggests a potential role of Lp(a) in predicting the insulin resistance-related coronary disease prior to overt diabetes in nondiabetic patients.

Keywords: Lipoprotein (a), Insulin Resistance, Beta-Cell Function, Coronary Artery Disease.

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1. Introduction

Cardiovascular disease (CVD) remains a global health burden, claiming millions of lives every year. While traditional risk factors like cholesterol and blood pressure play a crucial role, emerging players like lipoprotein(a) (Lp(a)) and insulin resistance are gaining increasing attention. Therefore, it is important to delve into the intricate relationship between Lp(a) and insulin resistance within the context of CVD, exploring their individual and combined impacts on cardiovascular health. [1, 2]. Lp(a) is a lipoprotein particle that consists of a low-density lipoprotein (LDL) molecule bound to apolipoprotein(a). 3 It is similar in structure to LDL cholesterol but has an additional protein component. Elevated levels of Lp(a) have been identified as an independent risk factor for CVD, including coronary artery disease, stroke, and peripheral arterial disease. 4 Lp(a) promotes the formation of atherosclerotic plaques by several mechanisms, including its ability to bind to fibrin and inhibit fibrinolysis, leading to thrombus formation. [3, 5]. Insulin resistance, on the other hand, is a metabolic state where cells become less responsive to the hormone insulin, leading to impaired glucose uptake and utilization. 6 Insulin is a hormone produced by the pancreas that regulates glucose metabolism and homeostasis. Also, insulin resistance is closely associated with obesity, sedentary lifestyle, and metabolic syndrome – all of which are significant risk factors for CVD development and worsening. This metabolic dysregulation is a cardinal feature of type 2 diabetes and prediabetes, but also occurs in non-diabetic individuals. Insulin resistance significantly contributes to CVD through various pathological pathways, including hyperglycaemia, endothelial dysfunction, and pro-inflammatory state. [6, 7].

Recent studies have suggested a potential link between Lp(a) and insulin resistance in CVD patients. 1, 2, 8, 9 One possible mechanism involves oxidative stress and inflammation. Both Lp(a) and insulin resistance have been shown to promote oxidative stress and inflammation within blood vessels. Oxidative stress leads to the production of reactive oxygen species, which can damage endothelial cells lining the blood vessels. This damage triggers an inflammatory response that further contributes to plaque formation [10]. Furthermore, Lp(a) has been found to impair insulin signalling pathways within cells. Insulin normally binds to its receptor on cell surfaces, initiating a cascade of events that promote glucose uptake into cells [11]. However, elevated levels of Lp(a) can interfere with this process by inhibiting insulin receptor function or downstream signalling molecules such as Akt or GLUT4 transporters. This disruption in insulin signalling exacerbates insulin resistance and impairs glucose metabolism [12]. Additionally, both Lp(a) and insulin resistance are associated with dyslipidaemia – abnormal lipid profiles characterized by high levels of LDL cholesterol and triglycerides along with low levels of high-density lipoprotein (HDL) cholesterol. Dyslipidaemia plays a crucial role in the development of atherosclerosis by promoting lipid deposition within arterial walls. The combination of elevated Lp(a), insulin resistance, and dyslipidaemias creates a perfect storm for accelerated plaque formation and progression [13]. The interaction between Lp(a) and insulin resistance may also be influenced by genetic factors. Both conditions have been found to have strong heritability components, suggesting that certain genetic variations may predispose individuals to develop both conditions simultaneously or synergistically increasing their effects on CVD risk [14, 15]. In other words, both Lp(a) and insulin resistance play significant roles in the development and progression of cardiovascular disease. 5 Despite the complexities, understanding the interplay between Lp(a) and insulin resistance holds significant clinical implications. It can help refine risk stratification in CVD patients, identifying individuals at particularly high risk due to the combined effect of these factors. This knowledge can guide personalized preventive and therapeutic strategies. Therefore, a comprehensive study is needed to fully understand the underlying correlation linking the levels of Lp(a), insulin resistance, and CVD pathogenesis so that future targeted interventions can be developed for improved prevention and treatment strategies for patients at risk.

2. Materials and Methods

From March 2021 to October 2021, a total of 100 consecutive patients (Patient group) admitted with a diagnosis of acute coronary syndromes without any previous history of diabetes mellitus in the Al-Najaf Center for Cardiovascular Surgery and Cardiac Catheterization, were enrolled in this study. Eligibility criteria were a clinical history of ACS accompanied by at least one of the following: electrocardiographic changes consistent with ACS). The study protocol was approved by the ethics committee of University of Kufa. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Fasting blood samples were collected for the analysis of all routine investigations including blood sugar, serum insulin levels, lipid profiles and C-reactive protein (CRP) levels. Patients with fasting blood sugar level between 100-126 mg/dl were included in the study. Exclusion criteria included patients on insulin treatment or with diabetes mellitus (DM), as well as individuals with autoimmune diseases, cancer, rheumatoid arthritis, renal or liver diseases.

The subjects included in the control group were weight and height matched healthy individuals selected from the staff members of Al-Najaf Center, they did not present any acute infection or any metabolic or psychological disorder and had no family history of hypercholesterolemia or diabetes. Their lipid profiles and fasting blood glucose levels were measured, showing they had normal lipid profiles and fasting plasma glucose.

2.1 Blood Sample Collection

Approximately 5ml of blood was collected from each participant through peripheral venous puncture. The blood samples were divided into two parts. The first part (4ml) was placed in a gel tube and allowed to clot for about 15 minutes at body temperature before being centrifuged for 10-15 minutes at 2000 xg. The resulting serum was then stored at -20°C for subsequent analysis of different parameters. The second part (1ml) of the blood sample was mixed with EDTA and used for HbA1c measurement.

2.1.1. Biochemical Analysis

2.1.1.1. Measurement of lipid profile

Using the AU480 analyzer (Beckman Coulter), a spectrophotometric approach was used to test serum levels of TC, TG, LDL, and HDL cholesterol. Every parameter was tested using the typical assay procedure. It was possible to calculate the serum concentration of very low density lipoprotein (VLDL) cholesterol using reagents and reference intervals obtained from Beckman Coulter. The cholesterol oxidase-peroxidase method was used to measure blood cholesterol, and the glycerolphosphate oxidase-peroxidase method was used to measure serum total TG. Using an enzyme chromogen method, HDL cholesterol was measured by binding to lipoproteins other than HDL (LDL, VLDL, and chylomicrons) using an anti-human-β-lipoprotein antibody in the first reagent. The formation of antigen-antibody complexes impedes enzyme reactions with the addition of a second reagent. The LDL cholesterol estimate was carried by using a shielding substance that shields LDL from enzymatic processes. HDL, VLDL, and chylomicrons—all non-LDL lipoproteins—were degraded by an interaction with cholesterol esterase and cholesterol oxidase (CHO). This reaction produces hydrogen peroxide, which is broken down by the kit first reagent's catalase. Sodium azide inactivates catalase and releases the protective reagent from LDL when the second reagent was applied. After that, LDL level was quantified.

2.1.1.2. Measurement of glucose and HbA1c

Plasma glucose and HbA1c levels were measured spectrophotometrically using commercial kits (Beckman Coulter) according to manufacturer’s protocol.

2.1.1.3. Measurement of insulin, C-pepide and Lipoprotein (a) levels

The Sandwich Enzyme Linked Immunosorbent Assay (ELISA) technique was used for determination of the plasma Insulin, C-peptide, and Lipoprotein (a) levels using commercially available kits according to the manufacturer’s

protocol. Additionally, standard samples were used for each assay for construction of the standard curves. Finally, the concentration of the plasma samples was quantified after color measurement using ELISA micro-plate reader at 450 nm.

2.1.1.4. Determination of Fasting Resistance Of Insulin (IR)

Insulin resistance and beta-cell function were assessed using the homeostatic model assessment (HOMA). The HOMA-IR index was calculated using the formula: HOMA-IR = [Glucose (mg/dl) x Insulin (μU/milliliter) / 405]. The HOMA-B index, representing beta-cell function, was calculated using the formula: HOMA-B = 360 x insulin (μU/milliliter) / glucose(mg/dl) – 63.16

2.2. Statistical Analysis

Statistical analysis was performed using SPSS software version 25. Categorical variables were presented as percentages, while continuous variables were expressed as mean ± SD. The Student's t-test was utilized to compare the means between the patient and control groups. An ANOVA test was used to compare the means of parameters between Lp(a) quartile groups. Spearman correlation analysis was employed to study the correlation between parameters. Odds ratios of changes in markers of insulin resistance in the 4th quartile of Lp(a) compared to the 1st quartile were determined using binary logistic regression. A p-value < 0.05 was considered statistically significant.

3. Results and Discussion

3.1. Participants Selection and Baseline Characteristics

Initially, 100 adult patients with confirmed diagnosis of coronary artery disease (CAD) were screened for eligibility. Of these, 10 were excluded for reasons including a diagnosis of diabetes mellitus (N=6), concomitant renal or hepatic disease (N=3), and the need for urgent coronary artery bypass grafting (CABG, N=1). The remaining 90 patients constituted the CAD patient group for the study. A total of 90 healthy individuals were then matched to the CAD patient cohort based on weight and height criteria, ensuring comparability between the groups (

Figure **1**). To the best of our knowledge, this work is the first to investigate the association between lipoprotein (a) [Lp(a)] levels with insulin resistance and both the incidence and severity of coronary artery disease (CAD) in the nondiabetic population. The link between insulin resistance and coronary artery is well-established and related to multiple pathophysiologic factors. Insulin resistance can promote the development of atherosclerosis through mechanisms that involve dyslipidemia, hypertension, and inflammation [17]. The key findings from the current work suggested that Lp(a) could predict the diagnosis of CAD in our cohort of non-diabetic patients. Furthermore, Lp(a) demonstrated superior capability over age-adjusted LDL and HDL levels in predicting the disease severity in terms of the number of identified coronary lesions on coronary angiographic assessment. The mechanistic basis for the association between Lp(a) and atherosclerotic disease is unclear but may relate to its prothrombotic, proinflammatory, and proatherogenic properties. [18]A very recent study, including 100,000 individuals from the UK, suggested that Lp(a) has an approximately 6-fold greater atherogenicity compared to LDL per particle. **[**19]Among different lipid biomarkers, we found that Lp(a) was the only one that demonstrated a significant correlation with the markers of insulin resistance in CAD patients, suggesting a specific role in the pathophysiological consequences of insulin resistance in nondiabetic patients on the incidence and progression of CAD. In the current work, Lp(a) demonstrated comparable accuracy to age-adjusted LDL and HDL levels in predicting CAD diagnosis, with an AUC of 0.984 for Lp(a) alone. The optimal cut-off for Lp(a) estimated through the current study was 125.2 mg/dL, with levels above this threshold associated with a 98.3% accuracy for CAD diagnosis. In previous studies, the optimal cut-off of Lp(a) levels for predicting the risk of CAD was demonstrated to be highly variable and dependent on the population studied as well as the outcome measures assessed. [20]Matsushita et al. investigated the impact of serum Lp(a) levels on coronary plaque progression and cardiovascular events in statin-treated patients with acute coronary syndrome (ACS) in a prospective cohort study including 102 patients who underwent intravascular ultrasound. Their findings suggested that higher Lp(a) levels (>20 mg/dl) are associated with slight plaque progression and lower event-free survival rates. [21] Yurtseven et al., found that an Lp(a) level of 19.5 mg/dl served as the cut-off value for predicting CAD in 247 patients with LDL levels ≥ 190 mg/dL [22]. Consistently, our findings suggest that Lp(a) was the only parameter that significantly correlated with CAD severity, as assessed by coronary angiography lesion counts. Lp(a) levels greater than 300 mg/dL were associated with a 45% increase in the number of lesions. Similarly, a meta-analysis of 283,328 patients from 17 observational studies assessed the association of elevated lipoprotein (a) levels with various cardiovascular outcomes, including cardiac events, cardiovascular events, cardiovascular mortality, and all-cause mortality in CAD patients. [23] Kwon et al. suggested that elevated Lp(a) levels are a significant independent predictor of major adverse cardiovascular events (MACE), including cardiac death and non-fatal myocardial infarction in a study including 6252 subjects suspected of having CAD . [24]Consistent with our findings, Tamang et al. demonstrated that MI patients have elevated levels of serum Lipoprotein(a), which was a better predictor of coronary heart disease risk than traditional lipid profile and lipid ratios. [25]The association between elevated Lp(a) levels with adverse cardiovascular outcomes was also consistently shown in CAD patients undergoing PCI with [26,27]or without diabetes.28 Despite the agreement with the bulk of the current literature, different cut-offs for Lp(a) levels were reported in relation to the associated cardiovascular events. In a multi-ethnic Asian population consisting of 2025 patients with AMI, predominantly men (94.5%) and of Chinese ethnicity (61.4%), the median Lp(a) levels were highest in the CAD+AMI+ group, followed by CAD+AMI- and CAD-, with concentrations of 26.2, 20.1, and 15.8 nmol/L respectively. The study revealed significant ethnic variations in Lp(a) levels, with the highest levels found in Asian Indians, then Malays, and Chinese. The authors concluded Lp(a) ≥120 nmol/L was positively correlated with the severity of CAD (p = 0.020) [29]. Several observational studies argued that Lp(a) raises the risk of CVD only when LDL-C levels rise above a particular threshold. Elevated Lp(a) (>32 mg/dL) was only a predictor of CVD risk in

participants with LDL-C levels ≥3.3 mmol/L, out of 500 subjects without CVD in the Bruneck research [30]. Only those with LDL-C levels greater than 3.7 mmol/L had increased levels of Lp(a) (≥33 mg/dL) linked to coronary heart disease among the 9,133 patients in the PRIME research [31]. Only women with an LDL-C > 3.1 mmol/L, out of 27,791 participants in the Women's Health Study, had elevated Lp(a) levels (≥44 mg/dL), which were linked to future CV events [32]. A 1-SD rise in Lp(a) was linked to CVD in a meta-analysis of prospective trials involving 126,634 participants, however this association was limited to those whose non-HDL cholesterol was >3.8 mmol/L [33]

An important finding of our study was that increasing Lp(a) levels were significantly associated with insulin, C-peptide, and HOMA-IR in our population of non-diabetic patients. This suggests Lp(a) may be linked to insulin resistance and hyperinsulinemia prior to overt diabetes development. In contrast, several studies showing an inverse association in diabetic [34]and nondiabetic patients [35,36]. The proposed mechanisms linking Lp(a) and insulin resistance are multifactorial. Insulin may suppress Lp(a) production in the liver, autoimmune factors may reduce Lp(a) before diabetes onset [37]. The causal relationship between Lp(a) and insulin resistance was further suggested by the impact of drugs targeting Lp(a) on glycemic measures. For instance, alirocumab, an antihyperlipidemic agent that lowers Lp(a), increased risk of incident type 2 diabetes, suggesting Lp(a) lowering may increase diabetes risk [38]. In line with our findings, several studies suggested weak or absent correlation between Lp(a) levels and [39-41]. A study of 217 elderly patients with type 2 diabetes mellitus reported no differences in Lp (a) levels between patients with good vs. poor glycemic control [42]. We hypothesized that elevated Lp(a) promoted vascular inflammation which could directly contribute to peripheral insulin resistance. consequently, hyperinsulinemia itself may up-regulate Lp(a) production by the liver through unclear pathways. The conflicting findings of the association between Lp(a) and markers of insulin resistance in our study, as well as the existing literature, could be related to the inclusion of different population (nondiabetic vs diabetic), the existence of different isoforms of Lp(a) with varying metabolic characteristics which levels are affected by multiple genetic and dietary factors [43].

Importantly, we found that Lpa Levels was significantly higher in the patient group compared to the control group ($p<0.001$). This was consistent with the elevation of the lipid markers investigated, including, LDL, VLDL, and TG in the patient group, while HDL levels were significantly lower in patients ($p<0.001$). The positive association with LDL was concluded by many previous studies and is related to the inclusion of LDL with Lp(a) particles. Similarly, Elevated Lp(a) levels were significantly associated with unfavorable lipid profile, including higher LDL, TG, and total cholesterol in a case-control study including 47 down syndrome patients [44]. The association between Lp(a) levels and HDL concentration is presented with conflicting evidence. High Lp(a) levels were associated with significantly lower HDL concentrations in a cohort study consisting of a cohort of 142,611 diabetic patients [45]. The relationship between Lp(a) and HDL seems to depend on the overall lipid profile. For instance, one study found Lp(a) was associated with HDL only when the total/HDL cholesterol ratio was at least mildly elevated [46]. Notably, we found that the increase in Lp(a) in CAD patients was the most pronounced among the other lipid parameters, with around 5-fold increase (493%) compared to controls. Interestingly, the consistent pattern of association between LP (a) and lipid markers could not be reproduced when analyzing the patients data only, since we found no correlation between LP (a) and LDL, VLDL, TG, or HDL levels in CAD group ($p>0.5$). This aligns with the previously discussed body of evidence suggesting the strong link between CAD and elevated Lp(a) levels [18,29,31,47].

The current work has several implications on the clinical practice of CAD management. Our findings suggest that Lp(a) screening should be considered in non-diabetes patients with suspected CAD, especially those with premature onset or without other clear risk factors. Levels ≥125 mg/dL may warrant further diagnostic testing for CAD based on the high accuracy demonstrated in this study. Furthermore, Patients with established CAD and Lp(a) levels >300 mg/dL should be considered high risk for more extensive or severe disease. More intensive management with lower LDL targets may be reasonable for this subgroup. Incorporating Lp(a) measurement into standard lipid screening panels should be considered to better identify elevated CAD risk patients. This could lead to earlier intervention and prevention. At baseline, significant differences were observed between the healthy control group (N=90) and patients (N=90) in terms of the mean age, which was significantly higher for patients compared to controls (57.48±12.43 years vs. 36.32±4.63 years, respectively, $p<0.001$). However, no significant differences between both groups as regarding body weight ($p=0.074$) or height ($p=0.062$). We found a modest significant difference in body mass index (BMI), with patients having a higher mean BMI of 29.28±4.50 kg/m2 compared to 27.00±2.39 kg/m2 in the healthy group ($p=0.002$). A summary of baseline characteristics is depicted in Table 1.

3.2. Lipid parameters

Total cholesterol levels were significantly higher in patients (164.23±47.15 mg/dL vs. 111.26±11.88 mg/dL in the healthy cohort, $p<0.001$). Triglyceride levels also were significantly higher in patients (144.78±76.02 mg/dL vs. 96.58±23.63 mg/dL in healthy individuals, $p<0.001$). High-density lipoprotein (HDL) levels demonstrated lower levels in patients (32.79±7.45 mg/dL) compared to the healthy group (47.14±4.68 mg/dL, $p<0.001$). Low-density lipoprotein (LDL) levels were nearly double in patients (102.49±38.43 mg/dL) relative to healthy subjects (44.80±12.64 mg/dL, $p<0.001$). Very Low-Density Lipoprotein (VLDL) levels followed a similar trend, being higher in patients (28.96±15.20 mg/dL) than in healthy individuals (19.32±4.73 mg/dL, $p<0.001$). The most noticeable difference was observed in Lipoprotein(a) [Lp(a)] levels.

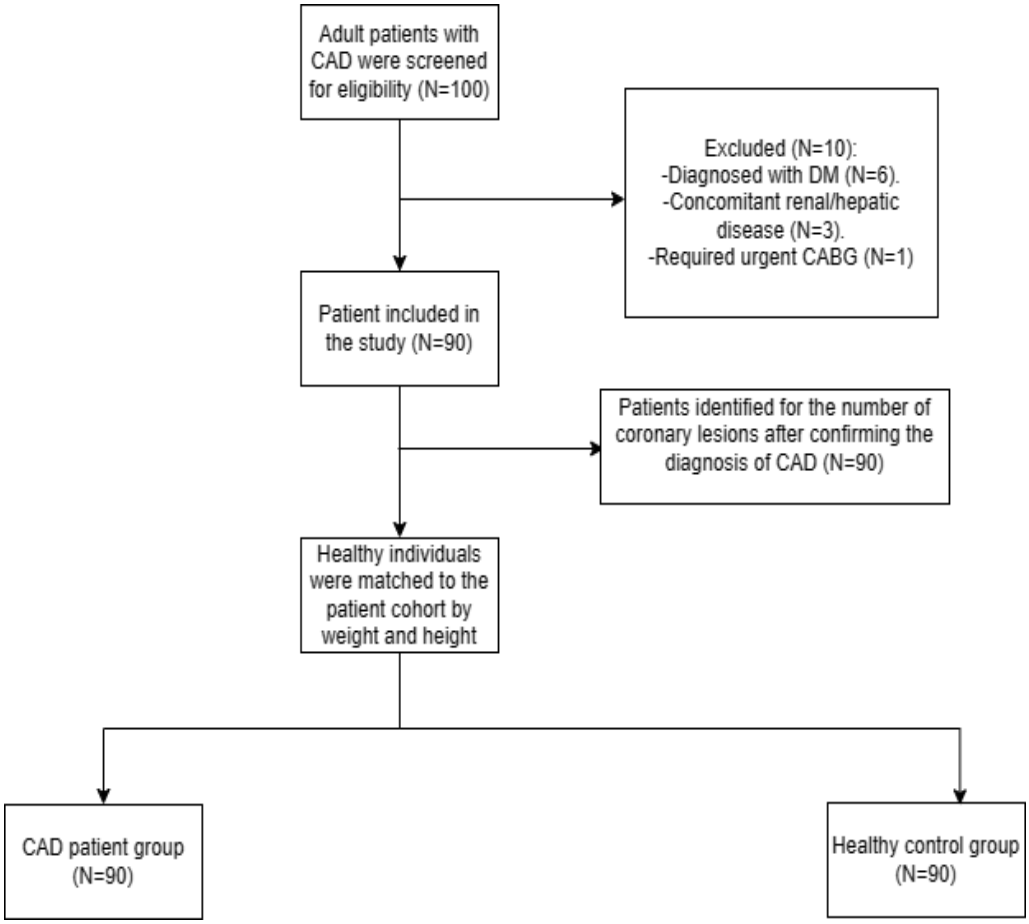

Figure 1: Study flow chart.

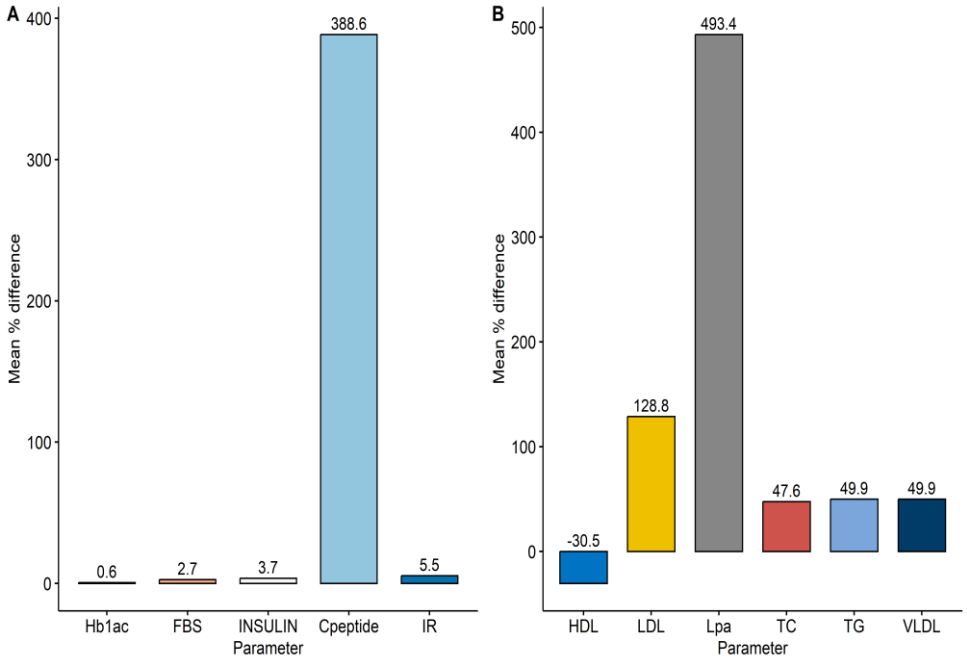

Figure 2: Assessment of percent differences of CAD patients relative to controls in terms of: A. glycemic indices and B. lipid parameters in the studies patients (N=90).

Table 1: Baseline Characteristics of Study Participants (N=90).

Characteristic	**Healthy**, N = 901	**Patients**, N = 901	**p-value**2
Age (years)	36.32±4.63	57.48±12.43	**<0.001**
Weight (kg)	75.08±10.88	79.07±11.94	0.074
Height (m)	1.66±0.08	1.64±0.06	0.062
Body Mass Index (kg/m2)	27.00±2.39	29.28±4.50	**0.002**

1Mean±SD
2Wilcoxon rank sum test

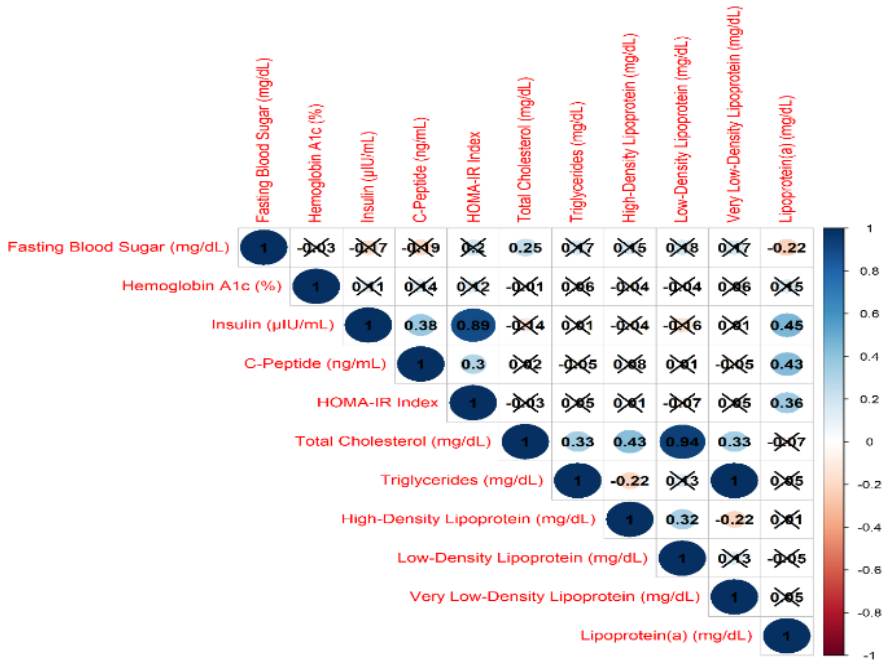

Figure 3: Heatmap summarizing the correlations between different glycemic indices and lipid parameters in patients diagnosed with coronary artery disease (N=90). The darker the blue circles, the higher the magnitude of correlations. Numbers within the circles represent correlation coefficients calculated using the Pearson correlation test. The symbols of "X" represent non-significant correlations, otherwise, all correlations are statistically significant at $p<0.05$.

Table 2: Lipid Profile Comparisons Between Healthy Individuals and Patients.

Characteristic	**Healthy**, N = 901	**Patients**, N = 901	**p-value**2
Total Cholesterol (mg/dL)	111.26±11.88	164.23±47.15	**<0.001**
Triglycerides (mg/dL)	96.58±23.63	144.78±76.02	**<0.001**
High-Density Lipoprotein (mg/dL)	47.14±4.68	32.79±7.45	**<0.001**
Low-Density Lipoprotein (mg/dL)	44.80±12.64	102.49±38.43	**<0.001**
Very Low-Density Lipoprotein (mg/dL)	19.32±4.73	28.96±15.20	**<0.001**
Lipoprotein(a) (mg/dL)	100.85±9.07	598.45±410.14	**<0.001**

1Mean±SD
2Wilcoxon rank sum test

Table 3: Glycemic Indices Comparisons Between Healthy Individuals and Patients.

Characteristic	**Healthy**, N = 901	**Patients**, N = 901	**p-value**2
Fasting Blood Sugar (mg/dL)	97.50±12.72	100.18±16.39	**0.020**
Hemoglobin A1c (%)	5.14±0.65	5.17±0.67	0.6
Insulin (µIU/mL)	7.73±2.22	8.02±5.47	0.065
C-Peptide (ng/mL)	8.38±1.64	40.93±29.75	**<0.001**
HOMA-IR Index	1.87±0.60	1.97±1.43	0.2

1Mean±SD
2Wilcoxon rank sum test

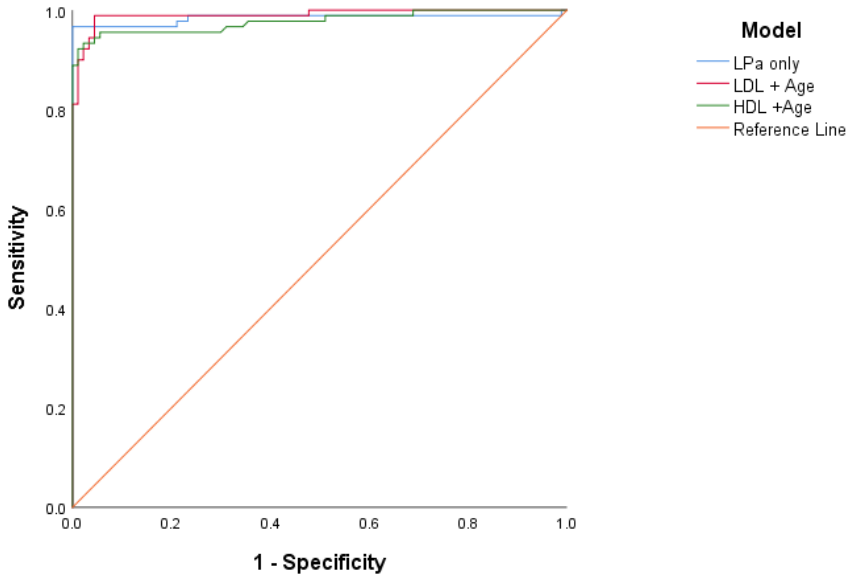

Figure 4: Receiver operating curves (ROCs) for predicting the diagnosis of coronary artery disease based on Lp(a), age-adjusted LDL, and age-adjusted HDL levels.

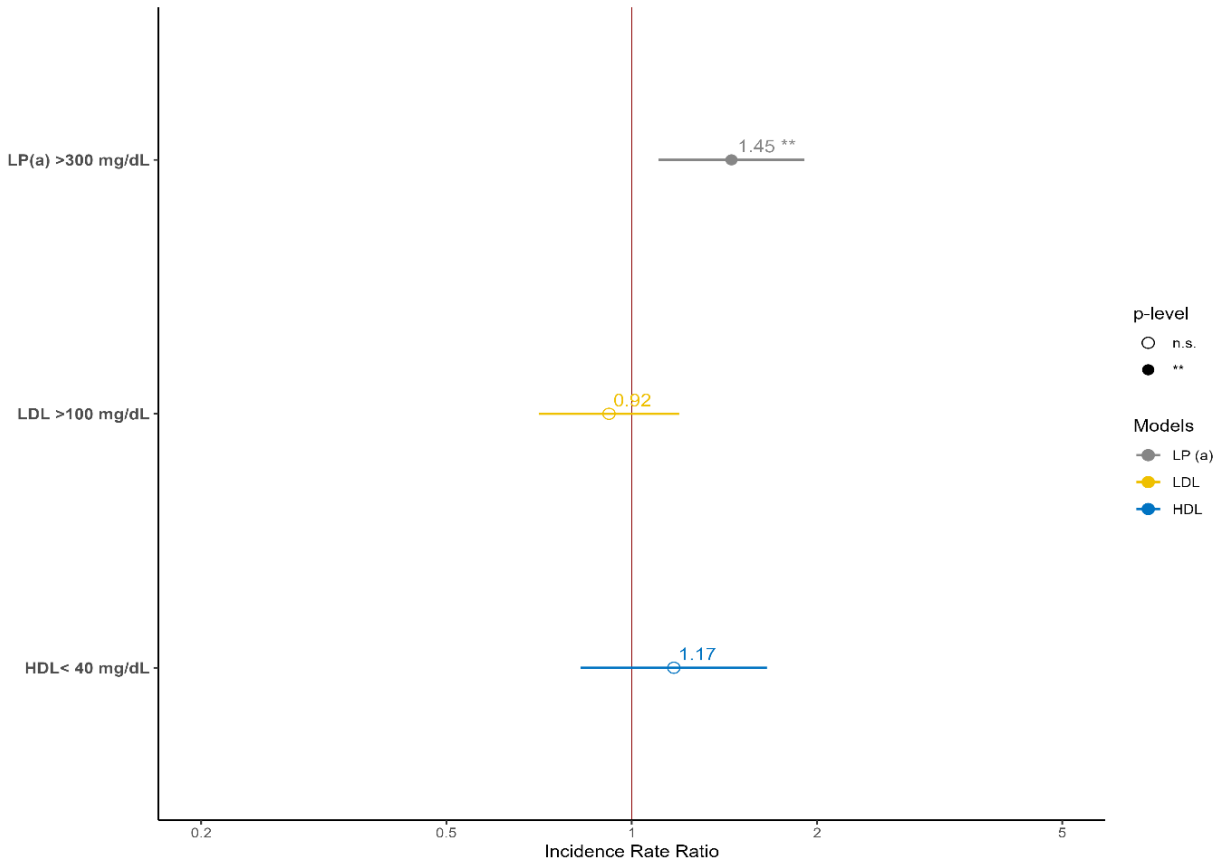

Figure 5: Forest plot demonstrating the coefficients of Poisson regression predicting the number of lesions in patients identified with coronary artery disease (N=90). The vertical red line corresponds to an incidence rate ratio of 1 (No effect). Horizontal lines represent the effects of LP (a), LDL, and HDL on predicting the number of lesions. Double asterixis (**) represents statistical significance at p<0.01.

Table 4: Logistic regression model results for the prediction of coronary artery disease diagnosis (N=180).

Model	AUROC	SE	*P*	95% Confidence interval
LP(a) only	**.984**	**.011**	**<0.001**	**.962 - 1.000**
LDL + Age	**.990**	**.006**	**<0.001**	**.979 - 1.000**
HDL +Age	**.978**	**.011**	**<0.001**	**.956 - .999**

Table 5: Comparing baseline characteristic, lipid parameters, and glycemic indices between CAD patients stratified based on the number of identified coronary lesions (N=90).

Characteristic	**<3 lesions**, N = 451	**≥3 lesions**, N = 451	p-value
No. of lesions	1.69±0.47	3.40±0.50	**<0.0012**
Age (years)	57.02±11.22	57.93±13.65	0.72
Body Mass Index (kg/m^2)	29.18±4.38	29.39±4.66	0.92
Hemoglobin A1c (%)	5.13±0.74	5.21±0.60	0.62
Fasting Blood Sugar (mg/dL)	102.46±17.80	97.90±14.68	**0.0412**
Total Cholesterol (mg/dL)	173.07±52.10	155.40±40.29	0.0842
Triglycerides (mg/dL)	151.54±81.27	138.02±70.66	0.52
High-density lipoprotein (mg/dL)	34.02±7.59	31.56±7.18	0.22
Low-density lipoprotein (mg/dL)	108.74±44.35	96.24±30.68	0.32

Table 6: Poisson regression analysis predicting the number of identified coronary lesions in patients diagnosed with coronary artery disease (N=45)

Characteristic	IRR1	95% CI1	p-value
LP(a) >300 mg/dL	1.45	1.11, 1.91	**0.007**
LDL> 100 mg/dL	0.92	0.71, 1.19	0.5
HDL< 40 mg/dL	1.17	0.84, 1.68	0.4

1IRR = Incidence Rate Ratio, CI = Confidence Interval

Patients exhibited significantly elevated average Lp(a) levels compared to controls (598.45±410.14 mg/dL vs.100.85±9.07 mg/dL in healthy controls, p<0.001) [**Table** 2]. Among the different lipid parameters, Lp(a) levels demonstrated the highest mean percent difference in patients relative to controls (493.4%) [

Figure 2b].

3.3. Glycemic indices

The mean fasting blood sugar (FBS) level was significantly higher in the patient group (100.18±16.39 mg/dL vs. 97.50±12.72 mg/dL in healthy individuals, p=0.020). However, the mean Hemoglobin A1c levels were comparable between the two groups (5.14±0.65% in healthy individuals vs. 5.17±0.67% in patients, p=0.6). A slight, statistically non-significant, increase in insulin levels was observed in patients (8.02±5.47 µIU/mL) compared to healthy controls (7.73±2.22 µIU/mL, p=0.065). Alternatively, there was a substantial elevation in C-Peptide levels in the patient group (mean 40.93±29.75 ng/mL vs. 8.38±1.64 ng/mL in healthy individuals, p<0.001). The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) Index was slightly higher in patients (1.97±1.43) compared to healthy individuals (1.87±0.60, p=0.2) [**Table** 3]. Among the different glycemic indices, C-peptide levels demonstrated the highest mean percent difference in patients relative to controls (388.6%) [

Figure 2a].

3.4. Association between LP (a) levels and glycemic indices

Among the different investigated lipid parameters, the correlation analysis suggested that only Lp(a) levels were significantly associated with the glycemic parameters

including insulin (r=0.45, p<0.001), C-peptide (r=0.43, p<0.001), and HOMA-IR index (r=0.36, p<0.001). The rest of the investigated lipid parameters, including total cholesterol, triglycerides, HDL, LDL, and VLDL showed a non-significant correlation with insulin, C-peptide, and HOMA-IR index (p>0.5) [Figure 3].

3.5. Prediction of coronary artery disease

LP(a) demonstrated comparable predictive capacity to predict the incidence of CAD (AUC = 0.984, p<0.001) to age-adjusted LDL levels (AUC = 0.990, p<0.001) and age-adjusted LDL levels (AUC = 0.978, p<0.001). The cut-off of LP(a) for diagnosis of CAD was estimated at 125.2 mg/dL with a 96.7% sensitivity, 100% specificity, and 98.3% accuracy (Table 4,

Figure 4).

3.6. Prediction of the number of coronary artery lesions

Comparing individuals with fewer than three coronary lesions to those with three or more lesions, no significant differences were observed in the majority of the cardiovascular and metabolic risk factors, including age, body mass index, hemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, insulin levels, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index (p>0.5) [**Table 5**]. However, the FBS levels were significantly lower in the group with three or more lesions (p = 0.0412). Moreover, C-peptide levels were significantly higher in the group with three or more lesions (p = 0.0122). The most notable finding was the significant difference in Lipoprotein(a) [Lp(a)] levels between the groups. Individuals with three or more lesions had significantly higher levels of Lp(a) (p < 0.0013), more than doubling the concentration found in those with fewer lesions. Furthermore, Lp(a) demonstrated a statistically significant correlation with the number of the identified lesions (r=0.52, p<0.001 using the Spearman correlation test). Poisson regression demonstrated that only LP(a) was significantly associated with the number of coronary artery lesions in CAD patients (IRR= 1.45, p<0.001), suggesting that increasing levels beyond 300 mg/dL is associated with a 45% increase in the number of lesions. Alternatively, neither LDL levels > 100 mg/dL (p=0.5) nor HDL levels < 40 mg/dL were associated with significant changes in the number of coronary

Figure 5].

3.7. Limitations

and

3.8. Limitations

However, several limitations should be acknowledged in the current work. The modest sample size from a single center may reduce generalizability of the findings. As this was an observational study, the potential effects of lowering Lp(a) levels on CAD outcomes could not be assessed. Furthermore, we did not investigate the impact of dietary and drug-related factors affecting the lipid profile among the included patients, which could potentially confound the association between Lp(a) levels and lipid markers. Future studies should be designed with larger sample sizes and longer follow up to investigate the association between Lp(a) and cardiovascular mortality. The validity of the concluded cut-offs for prediction of CAD as well as the number of coronary lesions should be further investigated on a large cohort of patients.

4. Conclusion

Taken together, this study contributes to the growing body of evidence supporting the critical association between Lp(a) and CAD. Identifying patients with elevated Lp(a) could improve CAD diagnosis, risk stratification, and guide personalized management. Furthermore, the association with insulin resistance in CAD patients suggests a potential role of Lp(a) in predicting the insulin resistance-related coronary disease prior to overt diabetes in nondiabetic patients.

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