

Lipoprotein(a) is a feature of the presence, diffuseness, and severity of coronary artery disease in Saudi population

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ABSTRACT

الأهداف: تركيز مادة الليبوبروتين-أ [Lp(a)] في مرضى سعوديين ممن يعانون من أمراض الشرايين التاجية والذي أثبت تشخيصهم بتصوير الأوعية لمعرفة العلاقة بين تركيز الليبوبروتين وبين الشدة وانتشار المرض.

الطريقة: أجريت دراسة مقطعية عرضية في مستشفى الملك خالد الجامعي - الرياض - المملكة العربية السعودية، خلال عامي 2006م و 2007م، وشملت الدراسة 147 مريضاً مصابون بأمراض في الشرايين التاجية (CAD)، و 49 فرداً من الأصحاء، متناسقين بالعمر. تمت دراسة مؤشر كتلة الجسم (BMI)، ثم تصوير الأوعية في 133 ممن هم مصابين بأمراض في الشريان التاجي (CAD). تم أخذ عينات من الدم وحللت لمعرفة نسبة الكوليسترول (TC)، الأحماض الدهنية الثلاثية (TG)، لليبوبروتين المنخفض الكثافة (LDL)، لليبوبروتين العالي الكثافة (HDL)، و لليبوبروتين-أ [Lp(a)].

النتائج: تبين أن المرضى المصابين بأمراض الشريان التاجي (CAD) لديهم نسبة عالية من مادة لليبوبروتين-أ متوسط التركيز بالمقارنة مع مجموعة الأصحاء ($25.78 \pm 25.09 \text{ mg/dl}$) مقابل (14.57 ± 11.81) $p=0.0030$. أما بالنسبة للمرضى الذين ليس لديهم ضيق ($10.97 \pm 8.06 \text{ mg/dl}$) أو ضيق في وعاء تاجي واحد ($19.67 \pm 17.33 \text{ mg/dl}$) كان مستوى تركيز الليبوبروتين-أ أقل بالمقارنة بالذين لديهم ضيق في وعائين ($31.88 \pm 32.17 \text{ mg/dl}$) أو ثلاث أوعية ($29.70 \pm 28.12 \text{ mg/dl}$). كانت نسبة الليبوبروتين-أ ذات علاقة مباشرة بنتائج الشريان التاجي ($r=0.234$ $p=0.033$) ونتائج جنسيني ($r=0.256$ - $p=0.02$). التدخين (OR: 1.86، 95% CI: 1.020-2.510، $p=0.04$) ومستوى الأحماض الدهنية الثلاثية (TG) ($r=0.234$ $p=0.033$) ومستويات مادة لليبوبروتين-أ ($1.251-4.932$ ، $p=0.03$ OR: 2.04، 95% CI: 1.033-3.687، $p=0.025$) أثبتت دقة تنبئة بشدة الإصابة بمرض الشرايين التاجية (CAD). المستويات العالية الخطورة من مادة لليبوبروتين-أ أكبر من أو يساوي 30 mg/dL كانت موجودة في 66.7% من مرضى الشرايين التاجية (CAD).

خاتمة: مستويات مادة لليبوبروتين-أ عالية في المرضى السعوديين المصابين بأمراض الشرايين التاجية (CAD) بالمقارنة بالأصحاء، ومرتبطة بمدى شدة وانتشار الانسداد في الشرايين التاجية.

Objectives: To study lipoprotein(a) [Lp(a)] levels in Saudi patients with angiographically defined coronary artery disease and to see its relationship with its severity and diffuseness.

Methods: This cross sectional study was carried out at King Khalid University Hospital, Riyadh, Saudi Arabia in 2006-2007. One hundred and forty-seven individuals with coronary artery disease (CAD) and 49 healthy individuals matched for age and body mass index were studied. Among CAD patients, 133 underwent angiography. Blood samples were analyzed for total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL) and Lp(a).

Results: Coronary artery disease patients had higher Lp(a) levels than controls ($25.78 \pm 25.09 \text{ mg/dl}$ versus $14.57 \pm 11.81 \text{ mg/dl}$, $p=0.0030$). Patients without stenosis ($10.97 \pm 8.06 \text{ mg/dl}$) and one vessel involvement ($19.67 \pm 17.33 \text{ mg/dl}$) had significantly lower levels of Lp(a) compared to double ($31.88 \pm 32.17 \text{ mg/dl}$) and triple ($29.70 \pm 28.12 \text{ mg/dl}$) vessel disease. Lipoprotein(a) levels correlated significantly with coronary vessel score ($r=0.234$, $p=0.033$) and Gensini score ($r=0.256$, $p=0.02$). Smoking (odds ratio [OR]: 1.86; 95% confidence interval [CI]: 1.020-2.510; $p=0.04$), TG levels (OR: 2.04; 95% CI: 1.251-4.932; $p=0.03$) and Lp(a) levels (OR: 1.56; 95% CI: 1.033-3.687; $p=0.025$) significantly predicted CAD severity. High risk levels of Lp(a) $\geq 30 \text{ mg/dL}$ were present in 66.7% of CAD patients.

Conclusion: Lipoprotein(a) levels are significantly higher in Saudi patients with CAD compared to healthy individuals, and are associated with more severe and diffuse blockage of the coronary vessels.

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Lipoprotein(a) Lp(a) has emerged as a powerful genetic risk factor for coronary artery disease (CAD).¹⁻³ It is a complex molecule of low-density lipoprotein (LDL) to which a large hydrophilic glycoprotein, apolipoprotein(a), is covalently linked via disulfide bonds. Based on its structure Lp(a) has both atherogenic and prothrombotic properties.⁴ In the general population, Lp(a) has been reported to be a well-established, independent cardiovascular risk factor.⁵ In those patients who already have a history of CAD, most of the researchers suggest that Lp(a) increases the risk of future cardiovascular events,⁶⁻⁹ but some of them have shown negative results.¹⁰⁻¹³ Recent data indicate that the apoB/apoAI ratio, apoB and Lp(a) are independent risk factors for CAD and are superior to any of the cholesterol ratios in prediction of cardiovascular risk.¹⁴ Because of the complex origin of CAD, it is important to target the full array of risk factors for modification, rather than focusing on a single factor or treatment.¹⁵ Non-traditional risk markers may prove to be better predictors of first or recurrent coronary events.¹⁶ The aim of this paper is to study the Lp(a) levels in Saudi patients with angiographically defined CAD, and to determine its relationship with CAD severity.

Methods. This study was conducted in the Departments of Physiology and Cardiology, College of Medicine, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia. The project was carried out from June 2006 to August 2007, and was funded by the College of Medicine Research Center (CMRC). The study protocol was approved from ethical and formal standpoints by the Research Ethics Committee of College of Medicine Research Center. The selected individuals were informed on the objectives and procedures of the study, and those patients who agreed to participate signed the consent form. The consent form was typed both in English and Arabic language. A clinical record of each individual including personal data, demographic data, family history and result of the coronary angiography was completed in a predesigned proforma. Inclusion criteria included: Saudi adult patients of any gender with ischemic heart disease who had attacks of angina or myocardial infarction (MI) and underwent coronary angiography. Exclusion criteria included: diseases that could affect the metabolic status of the body and the parameters under study such as nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, stroke, diabetic ketoacidosis, and non-ketotic hyperosmolar diabetes. The history of medication was recorded, and the patients taking oral contraceptives and steroids were also excluded.^{17,18} Patients with history of MI in the last 2 months were also excluded from the study. We studied 147 individuals with CAD among

whom 133 patients underwent coronary angiography. Overnight fasting blood samples were collected; serum was separated within 2-3 hours after collection and was stored at -70°C in all subjects. Control group included gender, age, and body mass index (BMI) matched individuals who were free of clinical manifestations of coronary, peripheral or cerebral artery disease by history, physical examination and electrocardiographic findings. In addition, the female subjects were matched for menopausal status because 71.4% (n=30) of CAD females were menopause. Therefore, we selected 68.4% (n=13) post menopausal females. Fasting venous blood samples were analyzed for lipids comprising total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and Lp(a). Total cholesterol, TG, LDL, and HDL were analyzed by enzymatic colorimetric method. The instrument used was Autoanalyser Dimension (Dade Behring, Inc., Deerfield, IL, USA) and the kits were also provided by the same company. Lipoprotein(a) was analyzed by turbidimetric immunoassay with the kits quantex Lp(a) supplied by biokit Spain. The measurement in our study was traceable to the International Standardization Reagent SRM2B, which is accepted by the World Health Organization (WHO) Expert Committee on Biological Standardization as the First WHO/International Reference Reagent for Lipoprotein(a) Immunoassay (IFCC).¹⁹ Lipoprotein(a) was measured on a Hitachi 911, manufactured by Roche diagnostics, USA. For Lp(a), the limit of quantification (LOQ) was 1.3 mg/dL and the limit of detection (LOD) was 0.4 mg/dL. Patients were divided into 4 groups on the basis of coronary vessel involvement into normal coronaries, single vessel disease, double vessel disease, and triple vessel disease. All patients underwent left ventriculography and selective coronary angiography via the right femoral approach. Coronary arteries were seen by utilizing right and left oblique views with cranial and caudal positions. Evidence of CAD presence was defined on the basis of at least 50% stenosis in a major coronary vessel. Each lesion in the coronary arteries was regarded as significant due to premature atherosclerosis. Gensini scoring system was used to determine the CAD severity. This scoring system considers the percentage of blockage in different coronary vessels as well as the site of blockage, and a score was obtained for each vessel under consideration. By assessing percentage of luminal narrowing and localization, we graded the CAD severity.²⁰ Left main coronary artery, left anterior descending artery, circumflex, and right coronary arteries were assessed. Multiple lesions in the same vessel were regarded as one-vessel disease.

Statistical analysis. The data was analyzed using computer software program Statistical Package for Social Sciences (SPSS version 10, Chicago). Descriptive

characteristics and lipid profile of the study patients were calculated as mean \pm SD and median (range) for continuous variables and as percentages for categorical variables. To assess differences in age, blood pressure, TC, LDL, HDL, TG, and BMI the analysis of variance was utilized. Lipoprotein(a) data, due to its extreme skewness, was analyzed by non-parametric statistical test Mann-Whitney U test and Wilcoxon (Kruskal-Wallis) test when comparing 2 or more groups, respectively. A p -value of <0.05 was considered as statistically significant. The relative percentage distribution of individuals in different groups with desirable and high risk levels of Lp(a) was determined. Categorical variables were compared between various groups using Chi square test. Multiple logistic regression analysis and Spearman's correlation coefficients were applied where necessary.

Results. Clinical and demographic data of control subjects and all CAD patients are given in Table 1. There were non-significant differences between age and BMI in the control and CAD groups. Coronary artery disease patients had significantly higher levels of TG ($p<0.012$) and Lp(a) ($p<0.003$) compared to control

subjects. While HDL levels were significantly higher in the control subjects ($p<0.0000$). The non-significant difference in TC and LDL is not surprising because most of these patients are receiving statins. The prevalence of risk factors is as follows diabetes mellitus 66.2% ($n=88$), hypertension 54.9% ($n=73$), smoking 34.6% ($n=46$), and dyslipidemia 27.8% ($n=37$). This shows that the highest prevalence was of diabetes mellitus in these cases, followed by hypertension. Table 2 shows the clinical and biological data in normal coronaries, single vessel, double vessel, and triple vessel disease patients. Lipids, Lp(a), and Gensini scores were compared between single vessel, double vessel and triple vessel disease patients (Table 3). Patients with no stenosis had significantly lower levels of TC and LDL compared to all other CAD groups. While the difference was not significant for TC, TG, LDL and HDL among other sub-groups (Table 3). Patients with no stenosis (10.97 ± 8.06) and one vessel (19.67 ± 17.33) involvement had significantly lower levels of Lp(a) compared to those with double (31.88 ± 32.17) and triple (29.70 ± 28.12) vessel disease. It shows that in individuals with higher levels of Lp(a) there is a tendency for more diffuse involvement of coronary atherosclerosis. Lipoprotein(a)

Table 1 - Clinical and biological data of control and all coronary artery disease (CAD) patients.

Clinical and biological data	Control (n=49)	All CAD (n=147)	P-value
Gender M/F	30/19	105/42	
Age	52.40 \pm 8.62	57.55 \pm 11.84	0.2883
Body mass index	26.41 \pm 3.58	28.18 \pm 6.29	0.2646
Systolic blood pressure mm Hg	125.31 \pm 15.48	132.35 \pm 20.71	0.1352
Diastolic blood pressure mm Hg	75.67 \pm 10.91	76.86 \pm 15.90	0.1948
Total cholesterol mmol/L	4.48 \pm 0.60	4.30 \pm 1.39	0.7492
Triglycerides mmol/L	1.11 \pm 0.49	1.83 \pm 1.09	0.0120
Low density Lipoprotein mmol/L	2.76 \pm 0.53	2.74 \pm 1.18	0.8423
High density lipoprotein mmol/L	1.07 \pm 0.32	0.72 \pm 0.25	0.0000
Lipoprotein(a) mg/dl	14.57 \pm 11.81	25.78 \pm 25.09	0.0030
Lipoprotein(a) median	11.3	19.5	
Lipoprotein(a) range	0.9 - 53.2	2.3 - 151.7	

Differences were studied by Mann-Whitney -test for lipoprotein(a) and Student's t-test for other parameters.

Table 2 - Clinical and biological data in normal coronaries, single vessel, double vessel and triple vessel disease patients.

Clinical and biological data	No stenosis (n=14)	Single vessel (n=29)	Two vessel (n=33)	Triple vessel (n=56)
Age years (mean \pm SD)	51.50 \pm 15.69	57.10 \pm 14.38	77.06 \pm 11.75	57.76 \pm 11.09
Body mass index clinical and biological data (mean \pm SD)	27.67 \pm 4.21	30.40 \pm 4.80	28.94 \pm 2.87	27.62 \pm 5.46
Hypertension (%)	7 (50.0)	17 (58.6)	18 (54.5)	31 (55.3)
Diabetes (%)	9 (64.2)	16 (55.1)	24 (72.7)	39 (69.6)
Dyslipidemia (%)	3 (21.4)	9 (32.1)	7 (21.2)	18 (32.1)
Smoking (%)	6 (42.8)	14 (48.3)	10 (30.3)	16 (28.6)

Differences were studied by Analysis of Variance for numerical data and Chi Square for percentages.

levels did not differ significantly between double vessel disease and triple vessel disease patients. Patients with Gensini ≥ 40 had significantly higher value of Lp(a) (33.30 ± 30.47) compared to those with Gensini < 40 (23.45 ± 23.15 , $p < 0.05$). Lipoprotein(a) levels were correlated significantly with coronary vessel score ($r = 0.234$, $p = 0.033$) as well as severity scoring ($r = 0.256$, $p = 0.02$) based on Gensini scoring system. There was a positive correlation of Lp(a) with TC ($r = 0.254$, $p = 0.008$) and LDL ($r = 0.237$, $p = 0.041$) levels. (Table

4). No correlation of Lp(a) was observed with age, BMI, SBP and DBP (Table 5). A multiple logistic regression analysis was performed with CAD severity (Gensini score < 40 or ≥ 40) as a dependent variable, and the following as predictive variables: gender, age, hypertension, diabetes, smoking, BMI, Lp(a), TC, TG, LDL and HDL. Analysis showed that smoking (OR: 1.86; 95% CI: 1.020–2.510; $p = 0.04$), TG levels (OR: 2.04; 95% CI: 1.251–4.932; $p = 0.03$) and Lp(a) levels (OR: 1.56; 95% CI: 1.033–3.687; $p = 0.025$) were

Table 3 - Lipids, Lp(a), and Gensini score in single vessel, double vessel and triple vessel disease patients (N=133).

Lipids and lipoprotein(a) levels	No stenosis (n=14)	Single vessel (n=29)	Two vessel (n=33)	Triple vessel (n=56)
Total cholesterol mmol/L (mean \pm SD)	3.89 \pm 1.57*	4.32 \pm 1.25	4.17 \pm 0.94	4.32 \pm 1.59
Triglycerides mmol/L (mean \pm SD)	2.02 \pm 1.09	1.98 \pm 0.90	1.69 \pm 0.53	1.76 \pm 1.29
Low density lipoprotein mmol/L (mean \pm SD)	2.34 \pm 1.13*	2.55 \pm 1.03	2.73 \pm 0.82	2.87 \pm 1.36
High density lipoprotein mmol/L (mean \pm SD)	0.53 \pm 0.27	0.71 \pm 0.24	0.71 \pm 0.13	0.73 \pm 0.28
Lipoprotein(a) mg/dl	10.97 \pm 8.06*	19.67 \pm 17.33†	31.88 \pm 32.17	29.70 \pm 28.12
Lipoprotein(a) median	8.85	16.6	22.9	22.95
Gensini Score	9.86 \pm 2.91	31.58 \pm 32.12‡	55.14 \pm 51.26	76.86 \pm 40.87

* $p < 0.05$ compared to single, double and triple vessel disease, † $p < 0.05$ compared to double and triple vessel disease
‡ $p < 0.0001$ compared to triple vessel disease. Differences were studied by Wilcoxon (Kruskall Wallis) for Lp(a) and ANOVA for all other parameters.
Data is expressed as mean \pm SD.

Table 4 - Spearman's correlation's between lipoprotein(a) [Lp(a)], coronary vessel scoring, severity scoring and lipid profile in all coronary artery disease (CAD) patients.

Parameters	Vessel Score	Gensini score	Lp(a)	Total cholesterol	Triglycerides	Low density lipoprotein	High density lipoprotein
Vessel Score	1.000	0.334†	0.234*	0.018	-0.160	0.166	-0.076
Gensini score		1.000	0.256*	0.010	0.053	0.061	0.037
Lp(a)			1.000	0.254†	0.048	0.237*	0.116
Total cholesterol				1.000	0.422	0.913	0.469
Triglycerides					1.000	0.128	0.080
Low density lipoprotein						1.000	-0.385†
High density lipoprotein							1.000

*Correlation is significant at the 0.05 level. †Correlation is significant at the 0.01 level.

Table 5 - Spearman's correlation's between lipoprotein(a) [Lp(a)], coronary vessel scoring, severity scoring, age, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) in all coronary artery disease (CAD) patients.

Parameters	Vessel Score	Gensini score	Lp(a)	Age	BMI	SBP	DBP
Vessel score	1.000	0.334†	0.234*	-0.055	-0.284*	0.181	0.175
Gensini score		1.000	0.256	0.031	-0.011	0.141	0.032
Lp(a)			1.000	-0.105	-0.050	0.009	0.029
Age				1.000	-0.234*	0.140	-0.064
BMI					1.000	-0.105	-0.042
SBP						1.000	0.552†
DBP							1.000

*Correlation is significant at the 0.05 level. †Correlation is significant at the 0.01 level.

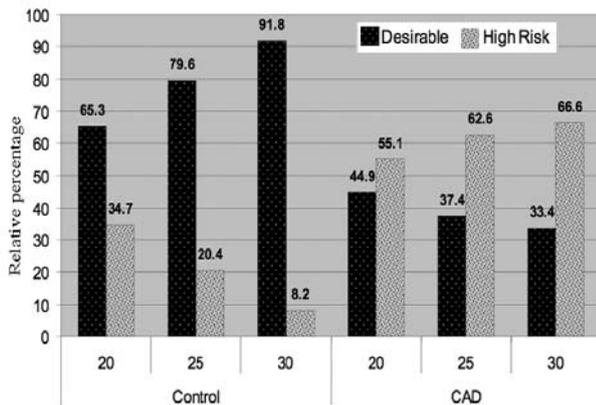


Figure 1 - Relative percentage distribution of control and CAD patients into desirable and high risk level categories considering 20 mg/dl, 25 mg/dl and 30 mg/dl as the cutoff point for high risk levels of lipoprotein(a). CAD - coronary artery disease

significant predictors for CAD severity. The relative percentage distribution of subjects falling into desirable and high risk level categories was calculated in control and all CAD patients (Figure 1). We analyzed the data by taking 20 mg/dL, 25 mg/dL and 30 mg/dL as the cut off levels for desirable and high risk levels. The prevalence of high risk levels of Lp(a) was significantly higher in CAD patients compared to control subjects. It was observed that when you take series levels of higher values for risk levels you will obtain a lower percentage of control subjects falling into high risk category, and for CAD patients it is the other way round. For example at 30 mg/dL, 91.8% control subjects are in desirable category while only 8.2% subjects in high risk category. While at the same level being considered in CAD patients, the prevalence of desirable levels was 33.4 % and 66.6% patients had high risk levels (Figure 1). When we considered 25 mg/dL as the cutoff value, we observed that in CAD patients the prevalence of desirable levels was 37.4% and 62.6% patients had high risk levels. At 20 mg/dL it was 44.9% and 55.1%. Therefore, the best cutoff level in CAD patients was considered to be 30 mg/dL.

Discussion. This study is the first report of Lp(a) levels in Saudi population with CAD. There are some interesting observations in this study. We observed that Lp(a) levels are raised in CAD patients compared to matched healthy subjects. Moreover, Lp(a) levels are related to CAD severity in these individuals. Similar findings have been reported from other parts of the world and state that the serum Lp(a) level is associated with the angiographic severity of CAD after myocardial

infarction.^{21,22} Lipoprotein(a) has also been reported to have a positive correlation with total and low density lipoprotein cholesterol levels.²³ Therefore, it is less strongly associated with vascular events when LDL cholesterol is low, and lowering LDL with statins might be an effective approach at decreasing the cardiovascular risk conferred by high Lp(a).²⁴ The non-significant difference in TC and LDL between CAD and controls is not surprising as most of these patients are receiving statins. There are some conflicting results also regarding severity of Lp(a) with CAD severity.²⁵⁻²⁷ These differences are due to variations in study design, population, measurement methods, and sometimes even due to statistical methods of analysis. In a recent study, elevated levels of Lp(a) have been regarded as an independent risk factor of CHD in carriers of other important CHD risk factors.²⁸ Zorio et al²⁹ reported that Lp(a) levels and small isoforms are markers of early MI and that Lp(a) levels ≥ 30 mg/dL are associated with severe patterns of coronary atherosclerosis. Our observations are in line with their findings. Lipoprotein(a) and oxidized phospholipid:apo B-100 ratio and CAD are strongly associated. Lipoprotein(a) was predictive of coronary artery obstruction. Lipoprotein(a) levels were weakly associated with LDL-C.³⁰ We also found that Lp(a) levels correlated positively with TC and LDL levels. Gazzaruso et al³¹ reported that Lp(a) levels and apo(a) are reliable predictors of CAD severity in type 2 diabetes and CAD patients with more severe CAD exhibit higher Lp(a) levels. We have similar observation that patients with Gensini >40 had significantly higher value of Lp(a) compared to those with Gensini <40 .³¹ At present, elevated levels of Lp(a) indicate higher risk of cardiovascular events, regardless of the fact whether it is only a marker or an active factor of pathophysiologic process. Increased Lp(a) concentration may refer to the need for therapy, frequent monitoring and determination of even stricter aims for high risk cases by selecting metabolically neutral and best tolerated drugs. According to currently prevailing attitude of most authors, routine determination of Lp(a) is not justified. Rather its determination is useful in patients who had a cardiovascular incident under 55 years of age, in those with recurrent coronary stenosis, or those with positive family history of such incidents.³² Lipoprotein(a) continues to be the focus of intense research and new exciting data have been continuously documented. Therefore, both the prothrombic and atherogenic mechanisms of Lp(a) may be elucidated in the near future, thus providing more defined indications for the determination of Lp(a) values and Apo (a) isoforms in clinical practice.³³ A possible limitation of our study is its cross sectional design. Long term prospective trials are

needed to determine the exact predictive value of Lp(a) as an atherogenic and prothrombotic risk marker.

In conclusion, Lp(a) levels are higher in Saudi patients with CAD compared to healthy individuals and are associated with more severe and diffuse blockage of coronary vessels due to atherosclerosis. Moreover, Lp(a) levels may be used as predictor and optional marker for presence of CAD and its severity in Saudi population.

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