

# Lipoprotein(a) and SYNTAX Score Association with Severity of Coronary Artery Atherosclerosis in North India

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## ترابط البروتين الدهني (أ) ومقياس SYNTAX مع شدة تصلب الشريان التاجي في شمال الهند

فوزية أشفق، بي كي غويل، ناجراجا موورثي، ريشي سيثي، محمد إدريس خان، محمد ظفر إدريس

**المخلص:** الهدف: هذه الدراسة المقطعية دراسة الترابط بين مستويات البروتين الدهني (أ) كمؤشر لتصلب الشرايين وعلاقتها بشدة تصلب الشريان التاجي، الطريقة: تم تسجيل 360 مريضاً على التوالي في معهد سانجاي غاندي للدراسات العليا بمعهد العلوم الطبية ومستشفى جامعة الملك جورج الطبية، لكانوا، شمال الهند، من الذين كانوا يعانون من آلام في الصدر وأعراض تصلب الشريان التاجي وبنفس الوقت كانوا يتناولون علاج تخفيض دهون، بين يونيو 2009 وأكتوبر 2011. تم سحب الدم صباحاً قبل الفطور قبل تصوير الشريان التاجي لقياس مستويات الدهون والبروتين الدهني (أ). تم حساب التأزر بين التدخل التاجي عن طريق الجلد بتاكوس ومقياس جراحة القلب (SYNTAX) وفقاً لنتائج تصوير الشريان التاجي. تم تقسيم المرضى إلى 3 مجموعات بناءً على شدة إصابة الشريان التاجي ومقياس (SYNTAX). النتائج: كشف تصوير الأوعية الدموية إصابة الشريان التاجي في 270 مريضاً، وكانت مستويات البروتين الدهني (أ) أعلى عند المصابين بمرض الشريان التاجي مقارنةً بغيرهم ( $23.85 \pm 48.73$  ملجم / دل مقابل  $11.15 \pm 18.95$  ملجم / دل  $P < 0.0001$ ) كما كانت مستويات البروتين الدهني (أ) أقل عند المصابين بتضيق شريان واحد مقارنةً بالمصابين بتضيق شريانيين أو ثلاثة ( $18.41 \pm 39.28$  ملجم / دل مقابل  $22.98 \pm 58.01$  ملجم / دل، و  $24.13 \pm 69.22$  ملجم / دل  $[P < 0.05]$ ). كانت مستويات البروتين الدهني (أ) أعلى بكثير عند المصابين بمرض الشريان التاجي الشديد مع نقاط (SYNTAX) أكثر من 30 ( $24.35 \pm 88.16$  ملجم / دل). ارتبطت مستويات البروتين الدهني (أ) بشكل كبير مع مؤشر (SYNTAX) ( $r = 0.70$ ) ( $P < 0.0001$ ). الخلاصة: ثبت في هذه الدراسة الترابط الإيجابي بين مستويات البروتين الدهني (أ) ومؤشر (SYNTAX) في الأوعية المصابة. وعلاوة على ذلك، كان مستوى البروتين الدهني (أ) المرتفع عامل اختطار مسبب مستقل لأمراض القلب التاجية. تخفيض مستويات البروتين الدهني (أ) سوف تقلل الإصابة بأمراض القلب التاجية في الوقاية الأولية والثانوية. هناك حاجة ملحة لتحديد أي من المرضى ينبغي أن يُعالج، وأي منهم الذي يجب أن يُستهدف للتدخل المبكر.

**مفتاح الكلمات:** البروتين الدهني (أ): الشحوم الثلاثية؛ الأوعية التاجية؛ مؤشر كتلة الجسم؛ تصلب الشرايين.

**ABSTRACT: Objectives:** This cross-sectional study investigated the association of lipoprotein(a) [Lp(a)] levels as an atherosclerosis predictor and their relationship to the severity of coronary artery disease (CAD). **Methods:** 360 consecutive patients at Sanjay Gandhi Postgraduate Institute of Medical Sciences and King George's Medical University hospitals, Lucknow, North India, with chest pains, CAD symptoms and on lipid-lowering therapy were enrolled between June 2009 and October 2011. Before coronary artery angiography (CAG), a fasting blood sample was assessed for lipid and Lp(a) levels. The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score was calculated according to the CAG results. Patients were divided into 3 groups based on CAD severity and SYNTAX scores. **Results:** Angiography revealed CAD in 270 patients. Lp(a) levels were higher in CAD compared to non-CAD patients ( $48.7 \pm 23.8$  mg/dl versus  $18.9 \pm 11.1$  mg/dl [ $P < 0.0001$ ]). The levels of Lp(a) were lower in single than in double and triple vessels ( $39.3 \pm 18.4$  mg/dl versus  $58.0 \pm 23.0$  mg/dl, and  $69.2 \pm 24.1$  mg/dl, [ $P < 0.05$ ]). Lp(a) levels were significantly higher in severe CAD with SYNTAX score  $>30$  ( $88.0 \pm 24.0$  mg/dl). Lp(a) levels correlated significantly with SYNTAX scores ( $r = 0.70$ ,  $P < 0.0001$ ). **Conclusion:** In this study, Lp(a) levels were positively associated with a patient's SYNTAX score in diseased vessels. Furthermore, an elevated Lp(a) level was a causal, independent risk factor of CAD. Lowering Lp(a) levels would reduce CAD in primary and secondary prevention settings. There is an urgent need to define more precisely which patients to treat and which to target for earlier interventions.

**Keywords:** Lipoprotein (a); Triglycerides; Coronary vessels; Body mass index; Atherosclerosis.

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**ADVANCES IN KNOWLEDGE**

- This study establishes the level of lipoprotein (a) [Lp(a)] which could be a predictive factor for angiographic-proven coronary artery disease (CAD) in northern Indians.
- High levels of triglycerides (TG) are a contributing factor in atherosclerosis. An increase in atherogenic particles, especially small dense low-density lipoprotein (LDL) cholesterol, may be a causative factor for the initiation and precipitation of coronary atherosclerosis.
- Every region and race must have standardised cut-off levels for the early detection and prevention of CAD.

**APPLICATION TO PATIENT CARE**

- The study indicates that the presence of Lp(a) is strongly associated with the level of severity of coronary atherosclerosis even in the case of normal total cholesterol, moderately increased TG, and low high-density lipoprotein (HDL) cholesterol levels in patients.
- Intervention with Lp(a)-lowering agents are required to prevent progressive coronary disease.
- It may be helpful to estimate serum TG levels to identify the presence of CAD even in patients who are receiving treatments such as hypolipidemic drugs like statins.

Atherosclerosis is a disease of large and medium-sized arteries such as the carotid and coronary arteries, and arteries of the lower extremities. It is characterised by focal lesions of one of the following types: fatty streak, fibrous plaque, or complicated lesions. A great number of hypotheses have been published about the pathogenesis of atherosclerosis, such as the lipid hypothesis, thrombogenic hypothesis, and the endothelial cell injury hypothesis. Many epidemiological studies have revealed that chronically elevated lipid and cholesterol levels are associated with an increased incidence of atherosclerosis.<sup>1</sup> Approximately 20% of the general population has high circulating levels of lipoprotein(a) [Lp(a)].<sup>2</sup>

The presence of Lp(a) has emerged as a powerful genetic risk factor for coronary artery disease (CAD).<sup>3-5</sup> It is a complex molecule of low-density lipoprotein (LDL) to which a large, hydrophilic glycoprotein, apolipoprotein (a) [Apo(a)], is covalently linked via disulfide bonds. Based on its structure, Lp(a) has both atherogenic and prothrombotic properties.<sup>6</sup>

In advanced atherosclerosis, Lp(a) is an independent risk factor not dependent on LDL. Lp(a) represents a coagulant risk of plaque thrombosis.<sup>7</sup> Apo(a) contains domains that are very similar to plasminogen, whose main function is to dissolve fibrin blood clots. Lp(a) accumulates in the vessel wall and inhibits the binding of plasminogen to the cell surface. This inhibition of Lp(a) also promotes the proliferation of smooth muscle cells. This unique feature suggests it causes the generation of clots and atherosclerosis.

Triglyceride-(TG) rich lipoproteins, which originate both in the intestines and liver, are considered an atherogenic factor.<sup>8,9</sup> The aim of this

study was to evaluate, in judging the severity of CAD, the association between the level of Lp(a) as a biomarker, and lipid status.

## Methods

A cross-sectional study was conducted on 360 consecutive patients (300 male and 60 female) who underwent coronary angiography between June 2009 and October 2011 at the Sanjay Gandhi Postgraduate Institute of Medical Sciences and the King George's Medical University (KGMU) tertiary care hospitals in Lucknow, Uttar Pradesh, North India. The study was approved by KGMU's ethics committee. Subjects were informed of the objectives and procedure of the study and informed consent was taken with the consent form in both English and Hindi. The patients' demographic profiles, socioeconomic status, personal habits, and disease risk factor histories were recorded. Blood pressure (BP) was measured before the patients were sent to the catheterisation laboratory.

Patients with a history of chest pain, angina, acute myocardial infarction (AMI), non ST-segment elevation myocardial infarction (NSTEMI), unstable angina, and stable angina were included. All patients received long-term treatment with angiotensin-converting-enzyme (ACE) inhibitors, calcium (Ca) antagonists, or  $\alpha$ - and  $\beta$ -adrenergic blocking agents. Almost all cases received statin treatment—most frequently atorvastatin. Patients with nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, stroke, or diabetic ketoacidosis were excluded. Coronary angiography was performed using the Judkins technique, or a radial approach.<sup>10</sup> Coronary angiography results were evaluated by

**Table 1:** Comparison of clinical and biochemical parameters between coronary artery disease (CAD) and non-CAD patients as defined by angiography

Parameters	CAD (SYNTAX score > 0) (n = 270)	Non-CAD (SYNTAX score = 0) (n = 90)	P value
SBP (mmHg)	142 ± 18	138 ± 16	<0.001
DBP (mmHg)	86 ± 10	82 ± 11	<0.001
BMI (kg/m <sup>2</sup> )	26 ± 2.1	24.9 ± 2.7	<0.001
TC (mmol/l)	3.9 ± 0.8 (150.8 ± 30.2)	3.6 ± 0.8 (139.9 ± 30.3)	0.03
TG (mmol/l)	2.1 ± 0.5 (182.8 ± 43.9)	1.4 ± 0.5 (124 ± 44)	0.001
HDL-C (mmol/l)	0.8 ± 0.2 (30.9 ± 7.5)	1.3 ± 0.2 (40 ± 9)	<0.001
LDL-C (mmol/l)	2.2 ± 0.7 (83 ± 28.9)	1.9 ± 0.7 (75 ± 27)	0.02
VLDL-C (mmol/l)	0.9 ± 0.2 (36 ± 9.2)	0.6 ± 0.2 (24.7 ± 8.9)	<0.001
Atherogenic marker Lipoprotein(a) (mg/dl)	48.7 ± 23.8	18.9 ± 11	<0.001

All results expressed in mean and standard deviation (SD). All values are reported in mmol/l and mg/dl, respectively.

CAD = coronary artery disease; SYNTAX = synergy between percutaneous coronary intervention with taxus; SBP= systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; TC = total cholesterol; TG = triglycerides; HDL-C = high density lipoproteins cholesterol; LDL-C = low density lipoproteins cholesterol; VLDL-C = very low density lipoproteins cholesterol; Lp(a) = Lipoprotein(a).

interventional cardiologists, who were blinded to the serum Lp(a) analysis. In coronary angiography, the complexity of CAD was determined by an angiographic grading tool—the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score.<sup>11-12</sup> In principle, the SYNTAX score is the sum of the points assigned to each individual lesion identified in the coronary tree with >50% narrowing in the diameter of the vessels that measure greater than 1.5 mm. The percentage of stenosis was not a consideration. Only the presence of a stenosis from 50–99% in diameter, a narrowing of less than 50% in diameter, or a total occlusion were considered. The entire patient group was divided into two subgroups: subjects with CAD who had a SYNTAX score >0 and subjects without significant coronary artery stenosis with a SYNTAX score of 0.

Fasting blood samples were collected after a 10 to 12 hour fast and before cardiac catheterisation.

**Table 2:** Lipoprotein(a) levels in normal coronary and diseased vessels

Vessels grade	No. of patients	Lp(a) level (mg/dl) Mean ± SD (Min–Max)	95% CI of mean
Normal coronary*	90	18.9 ± 11 (3.00–40.0)	16.61–21.28
Single vessel disease†	163	39.3 ± 18 (21.4–104)	36.43–42.12
Double vessel disease‡	58	58 ± 23 (22.8–108)	51.97–64.05
Triple vessel disease	49	69 ± 24 (22.8–110)	62.29–76.76
<b>F and P values</b>		<b>95.72; &lt;0.001</b>	

Lp(a) = Lipoprotein(a); SD = standard deviation; CI = confidence interval; \*Significantly different from single, double and triple vessel disease ( $P < 0.0001$ ); †Significantly different from double and triple vessel disease ( $P < 0.0001$ ); ‡Significantly different from triple vessel disease ( $P = 0.01$ ) (Holm-Bonferroni multiple comparison test.).

Samples were taken in sterile tubes, centrifuged at 3000 rpm for 10 minutes at 4°C, and then stored at -80°C until assayed. Fasting blood glucose (FBG), serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), serum TG, and LDL-cholesterol (LDL-C) levels were estimated by standard methods. Lp(a) was measured by agglutination due to an antigen-antibody reaction between Lp(a) in a sample and anti-Lp(a) antibodies absorbed to latex particles. The assay range is approximately 3–90 mg/dl. Higher values of Lp(a) were rechecked by diluting the sample with normal saline. Results were then standardised.

The results are presented in mean ± standard deviation (SD) and percentage. The unpaired t-test was used to compare the two continuous variables and one way analysis of variance (ANOVA) was used to compare more than two continuous variables. The 95% confidence interval (CI) of means was also calculated. The Pearson correlation coefficient was calculated to find out the correlation between two variables. The  $P$  value <0.05 was considered significant. All the analysis was carried out by using the Statistical Package for the Social Sciences (SPSS), Version 15.0 (IBM, Chicago, IL, USA).

## Results

The mean age of the patients was 54.0 ± 8.0 years, ranging from 30–65 years. A total of 270 patients (75%) of the 360 patients had angiographically-

**Table 3:** Lipid parameters in normal coronary and diseased vessels of patients

Parameters Units: mmol/l (mg/dl)	Vessel Grades				P value
	NC	SVD	DVD	TVD	
TC	3.6 ± 0.8 (140 ± 30)	3.0 ± 0.7 (151 ± 28)	3.9 ± 0.9 (152 ± 35)	3.8 ± 0.8 (148 ± 31)	0.78
TG	1.4 ± 0.5 (124 ± 44)	1.9 ± 0.4 (177 ± 39)	2.1 ± 0.5 (187 ± 42)	2.2 ± 0.6 (197 ± 57)	<0.001
HDL-C	1.0 ± 0.2 (40 ± 9)	0.8 ± 0.2 (31 ± 7)	0.8 ± 0.2 (31 ± 8)	0.8 ± 0.2 (30 ± 6)	<0.001
LDL-C	1.4 ± 0.7 (75 ± 27)	2.2 ± 0.7 (84 ± 27)	2.2 ± 0.8 (83 ± 32)	2.0 ± 0.7 (79 ± 29)	0.08
VLDL-C	0.6 ± 0.2 (25 ± 9)	0.9 ± 0.2 (35 ± 8)	0.9 ± 0.2 (37 ± 8)	1.0 ± 0.3 (39 ± 12)	<0.001

NC = normal coronary; SVD = single vessel disease; DVD = double vessel disease; TVD = triple vessel disease; TC = total cholesterol; TG = triglycerides; HDL-C = high density lipoproteins cholesterol; LDL-C = low density lipoproteins cholesterol; VLDL-C = very low density lipoproteins cholesterol.

proven CAD and 90 (25%) had normal coronary arteries (non-CAD group). The systolic and diastolic blood pressure was significantly higher in CAD patients ( $P < 0.001$ ) as compared to the non-CAD patients. The body mass index (BMI) was significantly higher in CAD patients ( $P < 0.0001$ ) as compared to non-CAD patients. There was a highly significant difference ( $P < 0.0001$ ) in the level of TG between CAD ( $2.0 \pm 0.5$  mmol/l) and non-CAD ( $1.4 \pm 0.5$  mmol/l) patients. A highly significant difference was observed in the level of very low density lipoproteins (VLDL) between CAD ( $0.9 \pm 0.2$  mmol/l) and non-CAD ( $0.6 \pm 0.2$  mmol/l) patients. However, the HDL was significantly lower ( $P < 0.0001$ ) in CAD patients ( $0.8 \pm 0.2$  mmol/l) as compared to non-CAD ( $1.0 \pm 0.2$  mmol/l) patients. Lp(a) levels were significantly higher in CAD ( $49 \pm 24$  mg/dl) than non-CAD patients ( $19 \pm 11$  mg/dl) [Table 1].

Parameters were compared by vessel grades. Lp(a) levels were significantly different among normal and different grades ( $P < 0.0001$ ). The Holm-Bonferroni pairwise comparison test showed that lipoprotein levels were significantly higher in all diseased vessels than those categorised as normal ( $P < 0.0001$ ) [Table 2]. CAD subjects with diseased vessels had higher TG and VLDL levels, and lower HDL cholesterol concentrations in diseased vessels as compared to people with normal coronary status [Table 3].

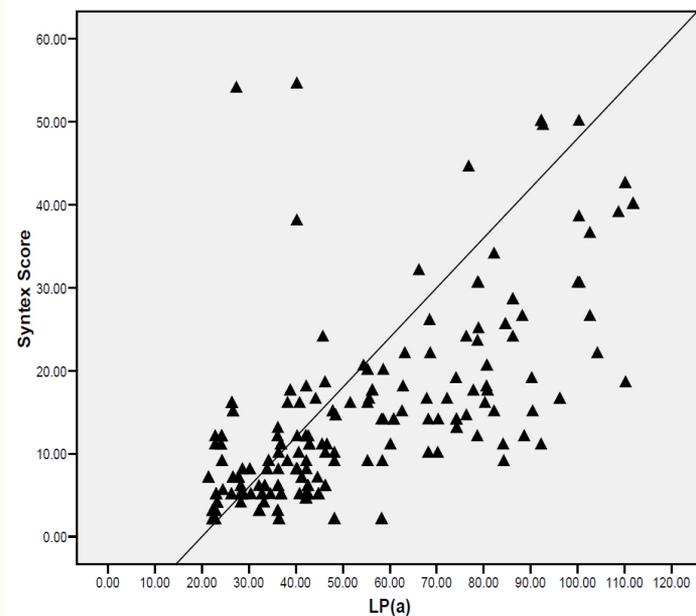
A subgroup analysis indicated that Lp(a) levels were significantly higher ( $P < 0.0001$ ) in patients with TG levels  $\geq 150$  mg/dl ( $47.6 \pm 25.1$  mg/dl) as compared to those with TG levels of  $< 150$  mg/dl ( $25.2 \pm 15.6$  mg/dl). However, Lp(a) was higher ( $P < 0.0001$ ) in those with HDL-C levels of  $\leq 40$  mg/dl ( $43.6 \pm 24.9$  mg/dl) than those with levels  $> 40$

( $26.7 \pm 20.0$  mg/dl). Furthermore, Lp(a) levels were significantly lower ( $P < 0.0001$ ) among those whose TG levels were  $< 150$  mg/dl and HDL was  $> 40$  mg/dl ( $15.6 \pm 8.9$  mg/dl) as compared to others ( $43.3 \pm 24.6$  mg/dl) [Table 4].

CAD patients were classified according to their SYNTAX scores:  $< 20$ ,  $20-30$ , and  $> 30$ ; Lp(a) levels in these subgroups were analysed and found significantly different [Table 5]. According to the correlation coefficient, there was a positive association between Lp(a) levels and SYNTAX scores for the diseased vessel patient group ( $r = 0.70$ ,  $P < 0.0001$ ) [Figure 1].

## Discussion

In this study, Lp(a) level  $> 20$  mg/dl was not only associated with the presence of coronary disease but also with the severity of the coronary atherosclerosis. This finding is consistent with previous reports.<sup>13</sup> A study carried out in southern India reported the cut-off level of Lp(a) as being 25 mg/dl for determination of a patient's risk of coronary heart disease (CHD).<sup>14</sup> Higher mean levels of Lp(a) were observed in our cases as compared to the control group in studies reported in other parts of India, where levels ranged from 12 to 41 mg/dl in CAD patients, and 8 to 24 mg/dl in healthy controls.<sup>15-18</sup> Mean Lp(a) levels in patients in our study were also within the range of values reported in earlier Indian studies.<sup>19</sup> Upper limits of normal Lp(a) have not been defined in the Indian population.<sup>15</sup> In Caucasians, an Lp(a) of 30 mg/dl is considered the upper limit of normal. Erbagci *et al.* showed that the optimal cut-off values for Lp(a) levels were 22.6 and 9.8 mg/dl for men and women, respectively, in cases of CHD, with or without angiographically



**Figure 1:** Scatter diagram showing the correlation between lipoprotein (a) [Lp(a)] levels and synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) scores. *Pearson correlation coefficient (r = 0.70, P < 0.0001)*

demonstrable lesions.<sup>20</sup> Our results showed Lp(a) as 21.4 mg/dl in minimal angiographically-proven single vessel disease even when cardiovascular risk factors and specific treatments (statins and/or aspirin) were taken into account; therefore, a level >20 mg/dl should be considered the cut-off value in the northern Indian population [Table 2].

Contrary to the notion that these risk factors are highly prevalent in northern Indians, we found increased TG and very low HDL levels in diseased vessel patients as compared to those with normal

**Table 4:** Lipoprotein(a) levels as a subgroup of triglycerides and high-density lipoprotein cholesterol (HDL-C) parameters

Parameters	No.	Lp(a) mg/dl	P value
<b>TG</b>			
<150 mg/dl	102	25.2 ± 15.6	<0.001
>150 mg/dl	258	47.6 ± 25.1	
<b>HDL-C</b>			
<40 mg/dl	311	43.6 ± 24.9	<0.001
>40 mg/dl	49	26.7 ± 20.0	
<b>TG &lt;150 and HDL-C</b>			
>40 mg/dl	26	15.6 ± 8.9	<0.001
<b>TG &gt;150 and HDL-C</b>			
<40 mg/dl	334	43.3 ± 24.6	

TG = Triglycerides; HDL-C = high density lipoprotein cholesterol; Lp(a) = Lipoprotein (a).

coronary status. High TG levels in our patients appeared to contribute to CAD risk. TG levels >130 mg/dl are strongly associated with the extent of a patient's coronary atherosclerosis; therefore, the present coronary angiography proven study is in agreement with the documented epidemiologic observations reported by Austin, which was that hypertriglyceridemia commonly occurs in CAD patients [Table 3].<sup>21-23</sup>

A delayed clearance of VLDL and chylomicron, and/or increased hepatic production of large VLDL results in the increased production of precursors of small dense LDL particles, a phenotype of which was reported to be associated with increased production of potentially atherogenic remnant-like particles.<sup>24</sup> Enrichment of the TG of this product through the action of cholesteryl ester transfer protein, together with hydrolysis of TG by hepatic lipase leads to an increased production of small dense LDL. Increased

**Table 5:** Lipoprotein(a) level by synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score

SYNTAX Score	No. of Patients	Lipoprotein(a) mg/dl
<20	226	42 ± 18
20–30	21	75 ± 16
>30	23	88 ± 24

levels of small dense LDL have been identified as a risk factor for an increased incidence of CAD in several epidemiological studies.<sup>25</sup>

Furthermore, a subgroup analysis of TG and HDL-C cut-offs showed significant Lp(a) variation in our study. Significantly higher Lp(a) levels increased TG >150 mg/dl and it was also observed that Lp(a) levels markedly increased in subjects with low levels of HDL-C ( $P < .0001$ ). Lp(a) levels depend on lipid profiles and suggest that treatment of dyslipidemia may also affect Lp(a) concentrations. Future studies are needed to clarify common mechanisms, enzymes, and receptors involved in Lp(a) and HDL/TG metabolism with a focus on how these mechanisms are modified in the setting of hypertriglyceridemia.

A marked raise in Lp(a) levels was found in patients with a SYNTAX score >30 ( $88 \pm 24$  mg/dl). Subjects with an intermediate to high SYNTAX score (20–30) observed higher Lp(a) levels ( $75 \pm 16$  mg/dl,  $P = 0.0001$ ) as compared to subjects with low SYNTAX scores <20 ( $42 \pm 18$  mg/dl). These values show that Lp(a) is directly related to SYNTAX score grading of atherosclerotic lesions. Our findings show that Lp(a) levels correlate with CAD severity [Table 5] and with SYNTAX scores. Assuming that the SYNTAX score has the ability to describe anatomical and functional features of CAD, we suggest that Lp(a) levels can predict the extent of coronary artery impairment. The SYNTAX score predicts mortality and morbidity in patients irrespective of disease severity, at both short- and long-term follow-ups. The relationship between Lp(a) and the extent of CAD assessed by SYNTAX score had not been investigated in previous studies.

The mechanism implicated in the atherogenicity of Lp(a) includes proatherogenic Lp(a), via its apo(a) moiety, which is a proinflammatory molecule that directly interacts with the leukocyte  $\beta$ 2-integrin Mac-1, thereby facilitating the recruitment of inflammatory cells. TGF- $\beta$ 1 activation is another mechanism via which Lp(a) contributes to the development of atherosclerotic vasculopathies. TGF- $\beta$ 1 is subject to proteolytic activation by plasmin and its active form leads to an inhibition of the proliferation and migration of smooth muscle cells, which play a central role in the formation and progression of atherosclerotic vascular diseases. If TGF- $\beta$ 1 fails to be activated, for example due to Lp(a) accumulation in the vascular wall, it is

associated with an increased proliferation and migration of the smooth vascular muscle cells and the formation of atherosclerotic lesions.<sup>26</sup>

In assessing appropriate cardiovascular preventive measures, clinical investigations using niacin alone or in combination with other lipid-lowering agents such as statins have provided evidence for its dose-dependent cardiovascular benefit of up to 40%, and its amelioration of the global cardiovascular risk profile of patients.<sup>27,28</sup> Bruckert *et al.* published a meta-analysis of 11 randomised controlled trials, involving 2,682 patients in the active group and 3,934 in the control group, which examined the effects of niacin alone or in combination with other lipid-lowering drugs on cardiovascular events and atherosclerosis.<sup>29</sup> Recently, a report suggested that a 2-month treatment with a ginkgo biloba extract reduced Lp(a), with results attributed due to the anti-inflammatory effect of this natural extract.<sup>30</sup> Finally, there is reliable evidence to show that antiplatelet therapy with aspirin decreases platelet function, and may decrease plasma Lp(a) as well. The physiological basis of this pleiotropic effect of aspirin is still uncertain, although it may decrease the hepatic synthesis of apo(a) by inhibiting the transcriptional activity of the gene and suppressing messenger ribonucleic acid (RNA) expression.<sup>31</sup> Other studies investigated the effect of other compounds like carnitine and coenzyme Q10.<sup>32–37</sup>

A large number of apheresis techniques have been described based on plasma separation (lipid filtration, LDL-precipitation, and direct adsorption of lipoproteins). All methods have been primarily developed for treatment of high plasma LDL concentrations. However, because of the numerous structural similarities between LDL and Lp(a), the effect of these methods on both lipoproteins is very similar. Essentially, depending on the treated plasma or blood volume concentrations of Lp(a) and LDL, levels are lowered by 50–74 %, and >60 % at each therapy. Even other haemorrhological parameters such as fibrinogen and viscosity are positively influenced.<sup>38</sup>

This study confirms Lp(a) levels >20 mg/dl as a cut-off value to predict the severity of coronary atherosclerosis, suggesting that Lp(a) levels should be determined in patients with CAD, especially in normolipidemic individuals. Lp(a), considered an emerging risk factor by the National Cholesterol

Education Program's (NCEP) Adult Treatment Panel (ATP) III, has been implicated in the development of the premature atherosclerotic disease seen in South Asians.<sup>39</sup> Among patients with excessive Lp(a), CAD risk increases 3-fold in the absence of other risk factors. The risk increases 8-fold with low HDL-C, 12-fold with high LDL-C, 16-fold with diabetes, and 25-fold with a TC/HDL-C ratio. The higher the Lp(a) level the lower the age of first heart attack, and the most affected individuals develop myocardial infarction (MI) by the third to fifth decade of life. High levels of Lp(a) correlate with the prematurity, severity, extent, and progression of coronary atherosclerosis as well as the occurrence and recurrence of MI among Asian Indians.<sup>40</sup> Although all patients with hypertension and CAD require aggressive risk modification, the subgroup with high Lp(a) and TG levels may have multiple-vessel involvement and probably will need close clinical surveillance.

There are limitations to our study. The enrolled subjects might not be representative of the entire CAD population, as subjects recruited were referred to tertiary care for a coronary angioplasty restenosis trial (CART) and percutaneous transluminal coronary angioplasty (PTCA) and SYNTAX score grading considers over 50% coronary artery luminal reduction. The generally used estimation of luminal reduction is not exact and can be incorrect in spite of an investigator's experience.

## Conclusion

In conclusion, this cross-sectional analysis suggests that Lp(a) levels differ significantly among Indians. The association between Lp(a) and cardiovascular outcomes may differ by race/ethnicity as well. Further studies should strive to disaggregate racial/ethnic groups and stratify by gender when examining Lp(a) among Asians. If replicated, our study suggests that the determination of Lp(a) levels may be particularly important in Asian Indians for the prevention of cardiovascular disease.

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