# Increased Serum Levels of Lipoprotein(a) Correlated with the Severity of Coronary Artery Disease in Patients Submitted to Angiography

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## Objective

To determine serum levels of lipoprotein(a) and lipid profile of a group of individuals submitted to coronary angiography, with the aim of establishing the possible correlation between these parameters and the severity of coronary artery disease.

## Methods

Serum levels of total cholesterol, HDLC, LDLC, triglycerides, lipoprotein(a), apolipoproteins A-I and B were measured in blood samples of 17 subjects with absence of atheromatosis in the coronary arteries (control), 12 subjects presenting mild/moderate atheromatosis and 28 subjects presenting severe atheromatosis.

## Results

No significant statistical differences were found between the means of the three groups for the parameters assessed, except for lipoprotein(a) serum levels which presented significant differences between the means of the control, mild/moderate atheromatosis and severe atheromatosis groups ($p<0.001$).

## Conclusion

The means obtained in the three groups for Lp(a) indicate a progressive increase in the serum levels of this parameter according to the severity of coronary atheromatosis. These findings suggest the need of additional studies in order to obtain enough evidence to support the introduction of routine assessment of Lp(a) levels in clinical laboratories in the monitoring of patients at risk for coronary artery disease (CAD).

## Key words

Coronary artery disease, coronary angiography, lipoprotein(a).

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Coronary artery disease (CAD) has a multifactorial origin, including hereditary and acquired risk factors which may be the direct cause of the disease or merely associated with it[1,2]. Changes in lipid metabolism play a relevant role in the progression of atherosclerosis[3] and the laboratory assessment of lipoproteins is of fundamental importance to diagnose and treat this condition[4].

Lipoprotein(a) was described by Berg in 1963[5] as a genetic variation of LDL. Lp(a) presents a lipid composition which is similar to the composition of LDL, but with a different protein content, since it presents the apolipoprotein(a) or apo(a) linked to apolipoprotein B by disulfide bridges[6-9]. The serum levels of Lp(a) and the molecular mass of apo(a) vary greatly between people and are genetically determined[10]. Lp(a) has no function in the transport of lipids and therefore its absence in the serum does not cause metabolic disruptions.

Apo(a) is highly homologous to plasminogen, the inactive precursor of plasmin - the protein that breaks up the fibrin produced during the coagulation process - due to the varied number of repetitions of aminoacid sequences which are homologous to the kringle 4 region of plasminogen. This structure allows the binding of Lp(a) to fibrin and to the proteins of the cell surface of endotelial cells and monocytes, as well as the competitive inhibition of tissue plasminogen activator (t-PA), reducing the generation of plasmin and fibrinolysis[11]. These characteristics provide Lp(a) with pro-atherogenic[12-14] properties, in that high levels of this lipoprotein are associated with early CAD risk, cerebrovascular disease and restenosis of coronary lesions. Some authors consider Lp(a) an independent risk factor for coronary and brain[10,14-16] artery atherosclerosis in Caucasian, Chinese, African and Indian individuals[9].

The apo(a) gene presents polymorphism as regards size, with more than 30 alleles varying from 300 to 800 KDa, and it has been suggested that such polymorphism may contribute to the increase of Lp(a) in patients with CAD[9,13]. The actual risk factor seems to be associated with the sub-population of Lp(a), in that isoforms which are smaller and have higher fibrin affinity are the ones more highly associated with CAD[11,13].

A large number of patients who develop CAD have normal or moderately increased[17] lipid levels which demonstrates that, despite the great contribution of dyslipidemias to the development of CAD, other factors also play a role in the progression of atherosclerosis. Lp(a) is involved in the pathogenesis and progression of atherosclerosis through different mechanisms. Prospective epidemiological and meta-analysis studies[10,14,16,18] have shown the positive correlation between Lp(a) and CAD. Frohlich et al[14] suggested that the determination of Lp(a) is an important tool to assess patients with CAD, and is especially useful in the prediction of risk in women. However, the development and size of lesions from CAD established on angiography and the correlations with serum lipids and Lp(a) are controversial.

It is believed that further understanding about lipid changes in the different stages of CAD may be a potential tool to help clinical practitioners follow up patients with atherosclerosis, providing information on the early detection of the severity of the lesion.

In view of the above, this study aimed at investigating the existence of changes in serum levels of Lp(a) and parameters of the lipid profile in patients diagnosed with CAD established on angiography, comparing them to individuals with normal angiographies to try to correlate possible changes with the severity of the lesion.

## Methods

Fifty-seven subjects were assessed throughout a three-month period, ranging from 46 to 68 years of age, of both genders, selected in the Department of Hemodynamics of the Socor Hospital of Belo Horizonte, after undergoing coronary angiography. The participants of this study were selected according to a criterium of homogeneity as regards the following variables: gender, age, social and economic level, and Body Mass Index (BMI). Based on the results of the coronary angiography, the components of this study were distributed in three groups: control (n=17), mild/moderate atheromatosis (n=12) and severe atheromatosis (n=28). Table 1 presents the characterization of the groups as regards gender, age and BMI. The study protocol was approved from the ethical and formal standpoints by the Research Ethics Committee of the Socor Hospital and by the Research Ethics Committee of the Federal University of Minas Gerais.

The individuals selected were informed on the objectives of the study and those who agreed to participate signed the Term of Free and Informed Consent (TCLE). A clinical record of each individual including personal data, demographic data, family history and result of the coronary angiography was filled out by the cardiologists of the Department of Hemodynamics.

Individuals with a prior history (up to three months) of acute coronary syndrome (ACS); those using oral anticoagulants, hypolipidemic agents or estrogens; individuals suffering from intercurrent diseases such as coagulation disorders, renal, hepatic and auto-immune diseases, diabetes mellitus and cancer; individuals presenting triglyceride levels above 400mg/dL were excluded from the study.

The characterization of the groups as regards risk factors associated with CAD and the presence of ACS more than three months prior to the interview is presented in table 1, as the number of individuals and the percentage of presence of a certain variable. The presence of the following variables: smoking, sedentary lifestyle and family history for CAD was verified with base on the recommendations of the 3rd Brazilian Guidelines on Dyslipidemias and Atherosclerosis Prevention[4]. Those participants who had a prior diagnosis of arterial hypertension and made regular use of hypotensive

**Table 1 – Characterization of the groups of the study**

| | Control | Mild/moderate Atheromatosis | Severe Atheromatosis |
|---|---|---|---|
| n (M/F) | 17 (8/9) | 12 (8/4) | 28 (16/12) |
| Age (years) | 58.9 ± 7.7 | 61.0 ± 11.6 | 60.9 ± 9.6 |
| BMI (Kg/m2) | 24.9 ± 4.6 | 26.1 ± 4.9 | 24.3 ± 3.2 |
| Smoking | 3 (17.6%) | 3 (25.0%) | 9 (32.1%) |
| Arterial hypertension | 14 (82.4%) | 9 (75.0%) | 24 (85.7%) |
| Sedentary lifestyle | 16 (94.1%) | 9 (75.0%) | 21 (75.0%) |
| Family history | 7 (41.2%) | 5 (41.7%) | 12 (42.9%) |
| ACS prior to 3 months | 2 (11.8%) | 4 (33.3%) | 16 (57.1%)a |

*Characterization as n (size), M (male) and F (female), age and BMI (body mass index), expressed as mean and standard deviation, percentage presence of the risk factor and acute coronary syndrome (ACS) in the groups studied. It was observed a significant difference only between the presence of ACS, represented by 'a' as compared with smooth coronaries (p<0.01).*

medication were considered hypertensive. There was no statistically significant difference for the following variables: smoking, arterial hypertension, sedentary lifestyle and family history between the three groups. The participants did not present overweight or obesity, which suggests the absence of the metabolic component in these individuals. For the ACS variable, it was considered the individuals who presented acute myocardial infarction or unstable angina. There was a statistically significant difference between the control group and the severe atheromatosis group (p<0.01).

The samples of venous blood were obtained from the patients after a 12-hour fast. They were told not to engage in vigorous physical activity and to avoid drinking ethanol within 24 and 72 hours respectively prior to the collection of the sample, in an attempt to obtain biological samples from patients in a balanced metabolic state. The collection of blood was effected using Vacuette® system (Geiner Bio-One) tubes, and the samples were centrifuged at 2,500 rpm for 15 minutes to separate the serum, which was in turn divided into aliquots and stored at -70ºC for three months.

Total cholesterol and triglycerides were determined using colorimetric enzymatic methods - *Randox Cholesterol CHOD-PAP* and *Randox Triglycerides GPO-PAP*, respectively. $HDL_c$ and $LDL_c$ were determined using the enzymatic method of elimination of *Randox HDL Cholesterol Direct* and *Randox LDL Cholesterol Direct*, respectively. The concentrations of apo B and apo A-I were established using the turbidimetry methods of Biotécnica, Apolipoproteína B and Apolipoproteína A-I, respectively. Lp(a) serum levels were measured using the turbidimetry method, with the diagnostic set lipoprotein(a) *In Vitro*. All the concentrations above were determined in a *Cobas Mira Plus* device, using control-serums to verify assay performance. The equation of Friedewald[19] was employed with the aim of investigating the performance of two different $LDL_C$ quantification processes.

Coronary angiography was performed using the Judkins technique. The films were examined by three experienced cardiologists and the reports were produced according to criteria defined for the stenosis of artery lumen: stenosis of up to 30% was classified as mild atheromatosis; stenosis from 30 to 70% was classified as moderate atheromatosis and stenosis above 70% was classified as severe atheromatosis, in one or more arteries affected.

In the statistical analysis, the test of analysis of variance (ANOVA) was used for the following parameters: total cholesterol, apo B, $HDL_C$, $LDL_C$-direct and $LDL_C$-Friedewald, all of which presented normal distribution and homocedasticity. The Kruskal-Wallis analysis of variance test was used for the apo A-I and triglycerides parameters which did not present normal distribution and/or homocedasticity. The level of significance adopted was 0.05. Especially for the parameter Lp(a), the analysis of variance was carried out using the Student-Newman-Keuls method, after the logarithmic transformation of the data. The Sigma Stat version 1.0 and the Prism version 3.0 programs were employed to perform the analyses and plot the graph respectively.

## Results

The results of the biochemical parameters are presented in table 2 as means and the respective standard deviations. There were no statistically significant differences for the following parameters: total cholesterol, $HDL_C$, $LDL_C$, triglycerides, apo A-I and apo B. For Lp(a) serum levels, a significant difference was observed between the control group and the mild/moderate atheromatosis group (p<0.0001), between the control group and the severe atheromatosis group (p<0.0001) and between the mild/moderate and severe atheromatosis groups (p<0.001). Figure 1 presents the distribution of lipoprotein(a) values in the groups studied.

The prevalence of Lp(a) levels greater than 30mg/dL was 0%, 50% and 67.9%, respectively for the control, mild/moderate atheromatosis and severe atheromatosis groups. There was a significant difference between the

control group and the mild/moderate atheromatosis group ($p<0.001$) and between the control group and the severe atheromatosis group ($p<0.0001$).

## Discussion

The development of laboratory tests able to identify patients at higher risk of developing CAD is of concern to many researchers and the object of many studies. With base on this type of study it is possible to judge the usefulness of determining a certain parameter in the laboratory to prevent the disease, establish its extent or monitor the efficacy of the treatment adopted.

This cohort cross-sectional study assessed a population of intermediate to high risk, since all individuals had been referred for coronary angiography to assess thoracic pain and epidemiologic profile and risk factors for CAD are shown in table 1. The three groups assessed were homogenous as regards age, gender and BMI. No significant differences were observed between the clinical variables – smoking, arterial hypertension, family history and sedentary lifestyle (tab. 1). However, it was observed that in the severe atheromatosis group there was a higher incidence of smoking and hypertensive subjects as compared to the other groups. Among the 22 subjects with a history of ACS prior to three months, 16 (57.1%) had severe atheromatosis, presenting a significant difference as regards the control group (tab. 1).

Upon assessing the lipid profile, the means of the three groups did not present statistically significant differences ($p<0.05$) for the following parameters: total cholesterol, $HDL_C$, $LDL_C$ (direct and estimated through the Friedewald formula), triglycerides, as well as for the concentrations of apo A-I and apo B. The values of the means obtained for total cholesterol, $HDL_C$, triglycerides, apo A-I and apo B are practically within the range of adequate and borderline values[4], demonstrating that the individuals selected did not present significant changes in these parameters (tab. 2). A similar result was obtained in a study with the Indian population, in subjects with CAD established by angiography[20].

As regards $LDL_C$, the means obtained in this study for the mild/moderate atheromatosis and severe atheromatosis groups are above the levels recommended for individuals with CAD[4], demonstrating the presence of a major and independent causal factor for atherosclerosis and CAD in these patients.

With the objective of assessing the performance of two different methods in the determination of $LDL_C$ values, we used the Friedewald equation, widely used in laboratories to estimate $LDL_C$ values, in that it was observed a positive correlation of 96% with the direct $LDL_C$ ($r=0.96$; $p<0.0001$).

For the Lp(a) parameter, the difference between the means was statistically significant ($p<0.0001$) between the control group and the severe atheromatosis group, and between the control group and the mild/moderate atheromatosis group ($p<0.0001$) and between the mild/moderate atheromatosis and the severe atheromatosis group ($p<0.001$) (tab. 2), confirming the idea of the American, European and Brazilian consensus about classifying it as a marker of emerging and independent risk for CAD[1,2,4]. Based on the data presented in table 2 it was verified that the mean obtained for the mild/moderate atheromatosis group was almost three times higher than the mean obtained for the control group, and that the mean obtained for the severe atheromatosis group was approximately five times higher than the mean of the control group and approximately one and a half times higher than the mean observed for the mild/moderate atheromatosis group, indicating a progressive increase in Lp(a) serum levels according to the severity of coronary atherosclerosis. The analysis of Lp(a) results showed also that in the control group all of the 17 subjects presented Lp(a) levels within the reference range of the method (fig.1). In this figure, we observed that in the mild/moderate atheromatosis group ($n=12$) only one subject presented a significant increase, with a far higher level than the mean of the severe atheromatosis group, whereas five other subjects presented moderate increases,

**Table 2 – Biochemical parameters in patients with coronary arteries without atheromatosis and groups with coronary artery disease (CAD)**

| | Control | Mild/moderate Atheromatosis | Severe Atheromatosis |
|---|---|---|---|
| TC (mg/dL) | 209.1 ± 53.5 | 212.4 ± 56.3 | 203.1 ± 42.7 |
| HDLc (mg/dL) | 50.0 ± 9.2 | 48.2 ± 7.6 | 48.1 ± 7.8 |
| LDLc f (mg/dL) | 130.8 ± 43.9 | 131.6 ± 48.8 | 124.7 ± 38.3 |
| LDLc d (mg/dL) | 139.4 ± 45.7 | 143.3 ± 50.8 | 135.8 ± 37.0 |
| TG (mg/dL) | 140.4 ± 62.6 | 162.9 ± 69.4 | 155.6 ± 68.5 |
| Apo A-I (mg/dL) | 125.1 ± 6.7 | 124.2 ± 5.9 | 125.9 ± 7.4 |
| Apo B (mg/dL) | 76.9 ± 16.5 | 81.3 ± 17.4 | 79.4 ± 16.4 |
| Lp (a) (mg/dL) | 11.0 ± 7.3 | 29.4 ± 25.6[a] | 51.7 ± 39.7 [a, b] |

*Means and standard deviations of TC (total cholesterol) values, HDLc (HDL cholesterol), LDLc f (LDL cholesterol estimated by the Friedewald formula), LDLc d (direct LDL cholesterol), TG (triglycerides), Apo A-I (apolipoprotein A-I), Apo B (apolipoprotein B) and Lp(a) [lipoprotein (a)]. It was observed significant difference between the groups relative to the Lp(a) parameter represented by 'a' as compared to the control group ($p<0.0001$) and 'b' as compared to the mild/moderate atheromatosis ($p<0.001$).*

however lower than this mean. It was observed that the mean of the mild/moderate atheromatosis group was in the high borderline of the reference range, thus indicating a rising trend for Lp(a) in this group.

The positive correlation between Lp(a) and CAD established on angiography was demonstrated by Gupta et al[20] in the Indian population and also by Labeur et al[8] in the Belgian population. They observed an increase in Lp(a) levels with the increase in the severity of CAD, in the most severe cases with major stenosis in more than two coronary arteries. In the Brazilian population, Maranhão et al[21] demonstrated the association between elevated serum levels of Lp(a) and the extent of CAD in Brazilian Caucasians submitted to cinecoronariography.

No correlations were observed between Lp(a) and other variables of the lipid profile in the subjects studied, in that a similar result was described by Genest et al[10]. However, Labeur et al[8] described significant correlations between Lp(a) and $LDL_c$, calculated by Friedewald formula, in addition to an inverse correlation between Lp(a) and triglycerides.

There were significant differences regarding the prevalence of increased levels of Lp(a) between the control group and the mild/moderate atheromatosis group ($p<0.001$) and between the control and severe atheromatosis groups ($p<0.0001$). The increase in Lp(a) in the severe atheromatosis group was highly prevalent (67.9%). The assessment of the prevalence of increased Lp(a) levels irrespective of the degree of stenosis (mild/moderate and severe atheromatosis, n=40), showed a high percentage (62.5%). A significant difference was observed between this group as compared with the control group ($p<0.01$).

The analysis of table 1 and figure 1 allows us to infer the existence of a nonlinear relation between Lp(a) and the risk of developing CAD in the population assessed, supported by the absence of significance regarding the risk factors for the three groups studied. Therefore Lp(a) did not behave in the study as a risk factor but rather as a marker or determinant of cardiovascular risk, since it was not possible to establish a relationship of cause and effect.

Some studies demonstrate that the predictive value of Lp(a) for the severity and extent of CAD would be higher in women[14,21]; however, this study did not evidence a significant difference between the prevalence of high levels of Lp(a) between men and women in the population studied. On the other hand, some studies did not demonstrate a correlation between Lp(a) serum levels and CAD[22] and others assign a real predictive value to the sub-population of Lp(a) with high fibrin affinity[11]. According to this concept, some phenotypes of Lp(a) would not be associated with atherothrombosis and not all individuals with increased Lp(a) would present increased risk of CAD.

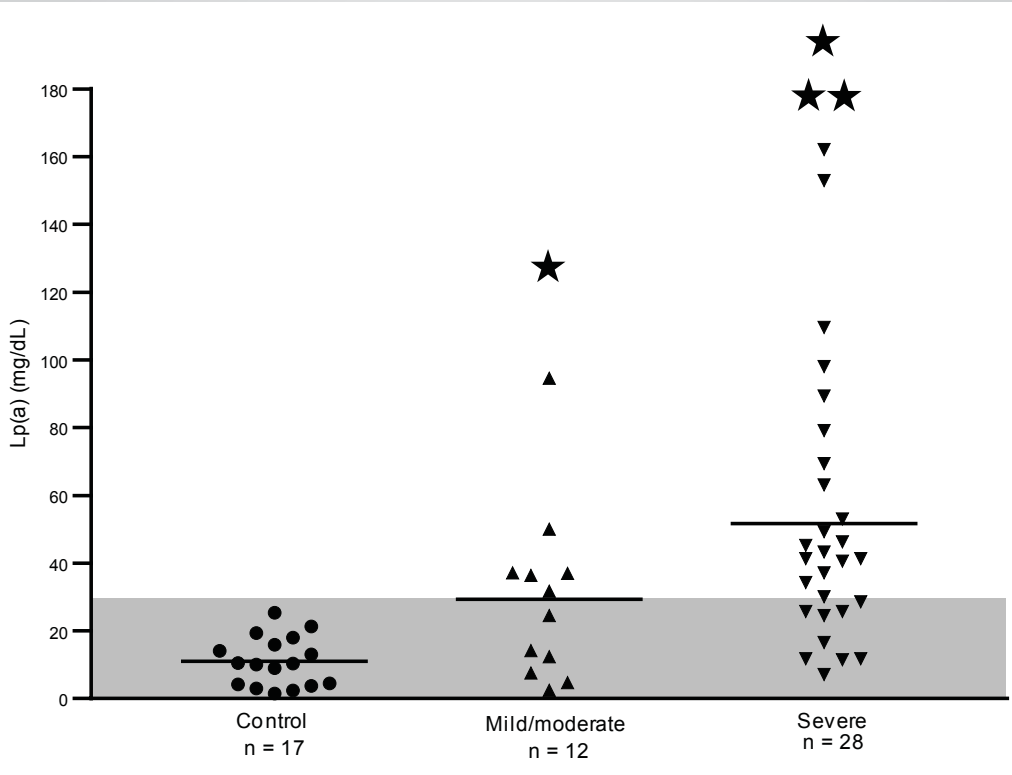


***Fig. 1** – Distribution of lipoprotein(a) [Lp(a)] values. Values expressed in mg/dL for the control, mild/moderate and severe atheromatosis groups. The shaded area corresponds to the reference range (up to 30mg/dL), the horizontal lines represent the group means, (★) indicates significant difference relative to the control group ($p<0.0001$) and (★ ★) indicates significant difference relative to the mild/moderate atheromatosis group ($p<0.001$).*

In the Brazilian population, which is ethnically diverse, this type of study is scarce. The group studied in this paper (n=57) consisted of 28.1% caucasians, 22.8% nigros and 49.1% subjects of mixed race (mulatto or other), with no statistically significant differences between the three groups for different ethnic groups. Maranhão et al[21] demonstrated significantly higher values in Afro-Brazilian subjects as compared to caucasians. However, higher values in Afro-Brazilian subjects were not associated with the presence or extent of CAD in the population assessed. The multivariate analysis of this study demonstrated that the presence of increased levels of Lp(a) contributed to the development of CAD in Brazilian caucasians.

In conclusion, the data of this study confirm the usefulness of Lp(a) to predict the severity of coronary atherosclerosis, suggesting that Lp(a) levels should be determined in patients with CAD, especially in normolipidemic individuals, since Lp(a) behaved as a predictive severity marker for coronary atherosclerosis, independent from smoking, arterial hypertension, sedentary lifestyle, family history and lipid profile. In the light of what is presently known about this matter and in view of remarkable controversies, and with base on the data presented here, we hope that this study may encourage the development of other studies involving the Lp(a) measure in normal individuals and with increased degrees of coronary obstruction, angiographically confirmed, in our population. Although it is known that there are several Lp(a)[12] isoforms which may hamper the performance of the fibrinolytic system, inhibiting it to a greater or lesser degree, it is a very relevant fact that all the subjects of the severe atheromatosis group presented very high serum levels of Lp(a) when compared with the levels presented by normal subjects, all angiographically proved. Even though the several Lp(a) variants may affect with different intensities the efficiency of the fibrinolytic system, the relation between Lp(a) and coronary disease should be a constant concern and object of investigation especially in normocholesterolemic individuals. An analysis of the data found allows us to infer the usefulness of introducing the determination of Lp(a) in the assessment of individuals with increased risk for CAD, but not in the stratification of risk for the population in general. The statement above is also supported by the continuous and growing association between increased levels of Lp(a) and risk for cardiovascular[6,14-16,23-25] disease, and also by the possibility of adopting therapeutic and control measures[26,27].

Although Lp(a) values are not yet used to determine the severity of CAD, they may play a relevant and additional role in the assessment of the development and especially in the progression of CAD. This line of research is a challenge for many areas of study on the involvement of Lp(a) and other factors in the pathogenesis and progression of atherosclerosis.

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### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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