



Relationship between lipoprotein (a) and micro/macro complications in type 2 diabetes mellitus: a forgotten target

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Abstract

Objectives Increased lipoprotein (a) serum concentration seems to be a cardiovascular risk factor; this has not been confirmed in extracoronary atherosclerosis complications. We therefore wished to gain a deeper insight into relationship between the plasma concentrations of lipoprotein (a) and the micro- and macro-vascular complications of type 2 diabetes mellitus and to identify possible differences in this association. **Methods** This is a descriptive observational cross-sectional study. Two-hundred and seventeen elderly patients with type 2 diabetes mellitus were included from the internal medicine outclinic. Anthropometric data, analytical data (insulin reserve, basal and postprandial peptide C, glycosylated hemoglobin, renal parameters, lipid profile and clinical data as hypertension, obesity, micro- and macrovascular complications were collected. **Results** Patients were grouped according to the type 2 diabetes mellitus time of evolution. The mean plasma concentration of lipoprotein (a) was 22.2 ± 17.3 mg/dL (22.1 ± 15.9 mg/dL for males, and 22.1 ± 18.4 mg/dL for females). Patients with hypertension, coronary heart disease, cerebrovascular accident, microalbuminuria and proteinuria presented a statistically significant increased level of lipoprotein (a). Similarly, the patients with hyperlipoprotein (a) (≥ 30 mg/dL) presented significantly increased levels of urea and total cholesterol. In the multivariate regression model, the level of lipoprotein (a) is positively correlated with coronary heart disease and diabetic nephropathy ($P < 0.01$ and $P < 0.005$, respectively). **Conclusions** The elevation of plasma levels of lipoprotein (a) are associated with the development of coronary heart disease and diabetic nephropathy. Therefore, we consider that the determination of lipoprotein (a) may be a prognostic marker of vascular complications in patients with type 2 diabetes mellitus.

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1 Introduction

Lipoprotein (a) [Lp(a)] is resulted from the binding of a molecule of low density lipoproteins cholesterol (c-LDL), with a glycoprotein known as apoprotein (a) [apo(a)], via a disulfide bridge. The plasma concentration of Lp(a) is kept almost constant in each individual over the course of their life, since it is determined genetically. There are different plasma isoforms of apo(a), and the concentration of Lp(a) is inversely proportional to the size of these.

Type 2 diabetes mellitus (T2DM) chronic vascular complications are microvascular nephropathy and retinopathy, and macrovascular coronary heart disease (CHD); cerebral vascular disease (CVD) and peripheral vasculopathy (PV): intermittent claudication and/or atherosclerosis lesions of lower-limb arteries diseases, these latter being associated with the presence of atherosclerosis. It has been demonstrated that increased serum levels of Lp(a) represent a risk factor for CHD; in particular, two variants of Lp(a) have been identified that are strongly associated with an increase of the serum levels of Lp(a) and with the risk of CHD.^[1]

In this context, several epidemiological studies have demonstrated that an increase of the serum concentrations of Lp(a) is strongly associated with CHD, as determined by angiographic methods. Presumably, Lp(a) binds to the complex atheromatous plaque, since it has been detected in ath-

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atherosclerotic plaques of native arteries, and in those used in cardiac surgery for revascularization. This relationship between Lp(a) and the complications of atherosclerosis explains the growing interest, including the ongoing discovery of diverse isoforms related to its plasma concentrations, in the diabetic population, and in the atherosclerotic acceleration model. Given that currently there are few published results in relation to this association, and those results that are available differ widely, we consider it very important to carry out studies with a view to clarifying this matter.^[2,3]

The objective of this study is assess the possible relationship between the plasma concentrations of Lp(a) and the micro- and macro-vascular complications in a cohort of elderly with T2DM. All the previously mentioned variables in the extra-coronary complications will be analyzed, to identify possible differences in this association.

2 Methods

This is a descriptive observational cross-sectional study, conducted over two years, in a representative sample of patients diagnosed with T2DM and seen in outpatient consultations. Patients were grouped according to the time of evolution of the disease as follows: less than 10 years (49.5%), between 10 and 20 years (36.6%), more than 20 years (13.9%).

2.1 Data collection

(1) Anthropometric data: weight, body mass index (BMI) and waist hip ratio (WHR). (2) Analytical data: a sample of venous blood was taken from all the patients after nocturnal fasting (10–12 h) before the administration of the treatment. In all samples, the following were determined: fasting plasma glucose; insulin reserve, basal and postprandial peptide C (PCB and PCP respectively), glycosilated hemoglobin (HbA1c) expressed as percentage, and renal parameters (urea, creatinine, 24 h proteinuria); lipids profile, including total cholesterol (TC), triglycerides (TG), high density lipoproteins cholesterol (c-HDL), very low density cholesterol (c-VLDL) and c-LDL, apoprotein A1 (apoA1) and B (apoB), and Lp(a). The peptide C index (PCI) was defined as the difference between the concentrations of PCP and PCB. (3) Clinical data recorded were CHD, PV defined as intermittent claudication and/or atherosclerosis lesions of lower-limb arteries, CVD, diabetic retinopathy (DR). Diabetic nephropathy (DN) considered as microalbuminuria (> 30 mg/24 h and ≤ 300 mg/24 h), or proteinuria (> 300 mg/24 h), hypertension (HTN: systolic > 140 mmHg and/or diastolic > 90 mmHg), obesity (BMI > 30 kg/m², or WHR ≥ 0.80 in women, or ≥ 0.95 in men).

2.2 Statistical analysis

The epidemiological analysis program of the Centers for Disease Control and WHO was used for preliminary statistical treatment of the results. We used the *t* test of Student-Fisher to compare means of unpaired data with normal distribution, and the Mann-Whitney test for variables that did not show a Gaussian distribution. Analysis of variance (ANOVA) was used to identify differences between groups for quantitative variables with normal distribution. For nonparametric data, the Kruskal-Wallis test was used for analysis of variance. Categorical variables were compared using the Pearson test, with Yule's Q for determining the degree of association and its meaning. We used the linear trend test for comparison of proportions representing an increasing or decreasing prevalence. Multiple linear regression analysis was used to investigate the influence of different concentrations of Lp(a). We constructed a multivariate regression model to analyse the independent predictors of Lp(a).

3 Results

Two hundred and seventeen elderly patients were recruited (127 men and 90 women), with a mean age of 73.1 ± 11.2 years. Table 1 presents the anthropometric variables, time of evolution, and the clinical characteristics. It is notable that a high percentage of our patients (49%) presented a time of evolution of the disease of less than 10 years, and only 13.9% exceeded 20 years. The presence of vascular risk factors was also high in our population: hyperlipidemia (77%), HTN (66.4%) and obesity (43.8%). Smokers

Table 1. Anthropometric and clinical characteristics of T2DM.

Age, yrs	73.1 ± 11.2
BMI	29.3 ± 31.2
WHR	0.88 ± 0.06
Time of evolution, yrs	
< 10 yrs	49.5%
10–20 yrs	36.6%
> 20 yrs	13.9%
Smoker	18.9%
Obesity	43.8%
Hypertension	66.4%
Dyslipidemia	77.0%
CHD	26.7%
PV	20.8%
CVD	21.3%
Retinopathy	33.7%
Cataracts	31.3%
Microalbuminuria	42.5%
Proteinuria	12.3%

Data are presented as mean ± SD or percent. BMI: body mass index; CHD: coronary heart disease; CVD: cerebral vascular disease; PV: peripheral vasculopathy; WHR: waist hip ratio.

accounted for 18.9%. None of the patients were receiving pharmacological agents of known effect on the levels of Lp(a).

Table 2 presented the mean plasma concentrations of the glycemic control parameters, reserve of pancreatic insulin and total renal function in the total group of patients studied, stratified according to gender. The levels of PCB, PCP and PCI were similar in both groups, with a mean HbA1c of 7.9% (7.7% and 8% in men and women, respectively). Table 2 also gives the mean concentrations of the lipids profile in the total group of patients studied. The statistically significant increase of c-HDL and apo A1 in the females is similar to that described in non-diabetic populations. The mean plasma concentration of Lp(a) was 22.2 ± 17.3 mg/dL (22.1 ± 15.9 mg/dL for males, and 22.1 ± 18.4 mg/dL for females). Additionally, the correlations between the serum levels of Lp(a) and the anthropometric, lipids and glycemic

control parameters are shown. The simple linear correlation study evince that the serum concentrations of Lp(a) are directly correlated with the WHR ($P < 0.05$), urea ($P < 0.001$), TC ($P < 0.05$) and creatinine ($P < 0.05$). We do not find a significant correlation between the levels of Lp(a) and HbA1c, PCB, PCP, PCI, HTN, age and the rest of the anthropometric and lipids parameters analysed.

Plasma levels of Lp(a) lower and higher than 30 mg/dL, labelled as HyperLp(a), were presented by 28.6% and 32.7% of the patients, respectively. The mean plasma levels of Lp(a) were independent of gender and smoking habit. However, the patients with HTN, CHD, CVD, microalbuminuria and proteinuria presented a statistically significant increased level of plasma concentrations of Lp(a), in comparison with patients in whom these vascular risk factors were not present (Table 3). In the patients with macrovas-

Table 2. Glycemic control parameters, renal function and lipid profile according to sex in our population.

	Male	Female	Total	r
Lp(a), mg/dL	22.1 ± 15.9	22.1 ± 18.4	22.2 ± 17.3	–
Glycemia	182.1 ± 63.5	199.3 ± 64.9	191.6 ± 64.7	–0.04
PCB, ng/mL	2.58 ± 1.54	2.72 ± 1.61	2.66 ± 1.58	–0.07
PCP, ng/mL	4.59 ± 2.82	5.08 ± 3.59	4.86 ± 3.27	–0.02
PCI, ng/mL	$1.60 (1.20–3.20)$	$1.80 (1.10–3.10)$	$1.70 (1.10–3.20)$	0.03
HbA1c, %	7.78 ± 1.68	8.05 ± 2.02	7.93 ± 1.88	–0.05
Urea, mg/dL	44.2 ± 17.5	40.8 ± 11.5	42.4 ± 14.6	0.34**
Creatinine, mg/dL	0.75 ± 0.22	$0.60 \pm 0.18^{**}$	0.67 ± 0.21	0.12*
Cholesterol, mg/dL	208.0 ± 35.6	213.3 ± 38.8	210.4 ± 42.3	0.16*
Tryglicerides, mg/dL	$127.0 (92.0–184.0)$	$126.5 (96.5–169.5)$	$127.0 (94.0–176.0)$	0.11
c-HDL, mg/dL	40.8 ± 10.1	$47.3 \pm 11.0^{**}$	44.0 ± 9.7	–0.03
c-LDL, mg/dL	134.0 ± 34.5	129.7 ± 34.9	131.6 ± 34.7	0.05
Apo A1, mg/dL	124.4 ± 23.5	$140.2 \pm 25.7^{**}$	133.3 ± 25.9	–0.01
ApoB, mg/dL	108.4 ± 23.6	106.9 ± 18.5	107.6 ± 20.9	0.11

Data are presented as mean \pm SD. Glycemic control parameters, renal function and lipid profile male vs. female; the last column shows the simple linear correlation of different variables with serum concentrations of lipoprotein (a); * $P < 0.05$; ** $P < 0.01$. Apo A1: Apoprotein A1; Apo B: Apoprotein B; c-HDL: high density lipoprotein cholesterol; c-LDL: low density lipoprotein cholesterol; CHD: coronary heart disease; PCB: peptide basal C; PCI: peptide C index; PCP: peptide C postprandial; HbA1c: glycated haemoglobin.

Table 3. Mean concentrations of lipoprotein (a) in the chronic complications and atherogenic risk factors of type 2 diabetes mellitus.

	(+)	(–)	Lp(a) > 30 mg/dL (%)	Lp(a) < 30 mg/dL (%)
Smoker	20.2 ± 15.6	22.6 ± 17.7	25.0	15.7
Obesity	20.3 ± 17.3	23.6 ± 17.3	33.8	47.1
Hypertension	$24.2 \pm 18.5^*$	18.3 ± 14.2	72.1	62.9
Dyslipidemia	23.6 ± 17.9	17.6 ± 14.9	82.4	75.0
CHD	$30.3 \pm 18.9^{**}$	19.1 ± 15.7	41.2 ^{###}	20.0
PV	26.4 ± 19.5	21.0 ± 16.6	26.9	17.1
CVD	$30.7 \pm 20.5^{**}$	19.5 ± 15.4	34.3 ^{###}	16.4
Retinopathy	24.9 ± 19.0	20.3 ± 16.3	38.1	32.4
Cataracts	24.3 ± 18.4	21.1 ± 16.8	27.3	32.4
Microalbuminuria	$25.5 \pm 18.7^*$	19.8 ± 16.2	59.1 ^{###}	32.6
Proteinuria	$33.7 \pm 23.1^{**}$	20.7 ± 16.0	21.2 ^{###}	6.5

Data are presented as mean \pm SD or percent. * $P < 0.05$; ** $P < 0.01$ for comparisons of Lp(a) serum levels in patients with/without (+/–) chronic complications and atherogenic risk factors. [#] $P < 0.05$, ^{###} $P < 0.01$ for comparisons of the prevalence of Lp(a) higher or lower than 30 mg/dL. CHD: coronary heart disease; CVD: cerebrovascular disease; Lp(a): lipoprotein (a); PV: peripheral vasculopathy.

cular complications, the mean plasma concentration of Lp(a) was higher than that presented in the patients without these vascular complications (27.0 ± 18.3 mg/dL and 17.6 ± 15.3 mg/dL, respectively; $P < 0.001$).

The frequency of serum levels of Lp(a) above 30 mg/dL, i.e., HyperLp(a), was higher in those patients who smoked, and reached statistical significance in those with micro- and macro-vascular complications, particularly CHD, CVD and DN ($P < 0.01$). In our population, those who showed vascular complications and/or vascular risk factors, they also presented microalbuminuria and proteinuria 42% and 12.3%, respectively. Interestingly, Lp(a) levels were raised in those patients with DN so, the mean Lp(a) serum concentration were 25.5 mg/dL and 33.7 mg/dL with microalbuminuria or proteinuria severally (Table 1 and 3).

It should be noted that the value of Yule's Q is a quantitative indicator of the degree of association between the cited vascular complications and HyperLp(a). When this association is positive, it indicates that the diabetics patients with these concentrations of Lp(a), present these vascular complications more frequently than the patients with serum levels of Lp(a) lower than 30 mg/dL (Table 3).

Similarly, the patients with HyperLp(a) presented significantly increased levels of urea and TC. The rest of the variables evaluated for glycemic and lipids control did not present significant differences (Table 4).

Table 4. Concentrations of analytical parameters evaluated based on the presence of hyperLp(a).

	Lp(a) serum concentration > 30 mg/dL	Lp(a) serum concentration < 30 mg/dL
Glycemia	181.1 ± 60.9	194.4 ± 66.5
PCB ng/mL	2.44 ± 1.31	2.75 ± 1.70
PCP, ng/mL	4.92 ± 3.42	4.80 ± 3.21
PCI, ng/mL	1.60 (1.10–3.30)	1.70 (0.90–3.10)
HbA1c, %	7.6 ± 1.8	8.0 ± 1.9
Urea, mg/dL	47.5 ± 17.3**	39.5 ± 11.1
Creatinine, mg/dL	0.71 ± 0.21	0.65 ± 0.21
Cholesterol, mg/dL	218.4 ± 31.6*	207.4 ± 39.6
Tryglicerides, mg/dL	127.5 (92.0–190.5)	124.5 (93.0–164.0)
c-HDL, mg/dL	44.3 ± 10.9	44.7 ± 11.4
c-LDL, mg/dL	136.6 ± 29.5	130.3 ± 36.0
Apo A1, mg/dL	133.7 ± 26.1	134.0 ± 26.2
ApoB, mg/dL	111.5 ± 20.8	106.0 ± 20.8

* $P < 0.05$, ** $P < 0.01$ for comparison of Lp(a) higher or lower than 30 mg/dL. Apo A1: Apoprotein A1; Apo B: Apoprotein B; c-HDL: high density lipoprotein cholesterol; c-LDL: low density lipoprotein cholesterol; HbA1c: glycated haemoglobin; Lp(a): lipoprotein (a); PCB: peptide basal C; PCI: peptide C index; PCP: peptide C postprandial.

When the patients are assigned to three groups according to the time of evolution of the disease, it can be observed that the group with more than 20 years evolution presents higher levels of Lp(a) and greater prevalence of HyperLp(a), although the differences observed were not significant (1st group: 22.2 ± 16.3 mg/dL; 2nd group: 24.0 ± 20.4 mg/dL and 3rd group: 28.2 ± 18.7 mg/dL, $P = NS$).

We observed that the patients treated with insulin presented significantly higher values of Lp(a) than those receiving dietary treatment or with oral agents ($P < 0.01$).

The degree of association between the biochemical variables determined, vascular risk factors, vascular complications and the serum concentrations of Lp(a), are evaluated in the multiparameter regression analysis (Table 5). In the multivariate regression model, the level of Lp(a) is positively correlated, independently and directly, with CHD and DN (proteinuria) ($P < 0.01$ and $P < 0.005$, respectively).

4 Discussion

The results of this cross-sectional study demonstrate that the levels of Lp(a) are not influenced by sex, age, time since onset of the disease, insulin reserve and glycemic control. However, certain vascular risk factors such as HTN and the presence of macro- and micro-vascular complications of atherosclerosis such as CHD, PAD, CVD, DR and DN are associated with increased concentrations of Lp(a). This suggests that, regardless of the low-lipid therapy recommended by the different scientific societies to archive the objectives in serum concentrations of lipids, in diabetic patients a “residual risk” remains very high, where the Lp(a) plays a decisive role.

The relationship between atherosclerosis and high concentrations of Lp(a) has not been firmly established. It is possible that it could be related to the homology of Lp(a) with plasminogen. It has been suggested that Lp(a) inhibits the binding of plasminogen and stimulates the gene expression of the plasminogen activator inhibitor “*in vitro*”; in several studies this inhibitor has been considered as a modulating factor of the vascular complications in T2DM. It has also been suggested that the interaction of Lp(a) with residues of glucosaminoglycans and proteoglycans from the arterial wall, and/or with macrophage recipients or scavengers, could play an important role in this association.^[4] Similarly, it appears that, on the arterial wall or tunica intima, Lp(a) binds to fibrin forming a rigid complex that is firmly attached. Another pro-atherogenic mechanism could be associated with the inverse relationship between levels of Lp(a) and vascular reactivity. Increasing its serum concentration induces endothelial dysfunction.^[5]

Table 5. Correlations of lipoprotein A with different parameters studied in patients with type 2 diabetes.

Quantitative variables	B	EE(β)	B/EE (β)	Test-F	P
PCB	-1.863	0.9581	1.94	3.7807	NS/P = 0.05
PCP	-0.027	0.5067	0.053	0.0029	NS
Total Cholesterol	0.0638	0.0573	1.113	1.2420	NS
c-LDL	-0.0518	0.0628	0.825	0.679	NS
Apoprotein B	0.0242	0.0747	0.324	0.1052	NS
Urea	0.1340	0.0704	1.90	3.6205	NS
Smoker	0.1952	3.1477	0.062	0.0038	NS
Hypertension	2.4388	2.5480	0.960	0.9161	NS
CHD	8.4219	2.8256	2.98	8.9028	P < 0.01
PV	3.1005	3.375	0.919	0.8440	NS
CVD	2.041	3.114	0.656	0.4298	NS
Retinopathy	-0.8838	2.6850	0.329	0.1084	NS
Microalbuminuria	0.4571	2.6964	0.169	0.0287	NS
Proteinuria	12.905	4.1180	3.13	9.821	P < 0.005

B: regression coefficient β ; B/EE(β): standardized regression coefficient; CHD: coronary heart disease; c-LDL: low density lipoprotein cholesterol; CVD: cerebral vascular disease; EE(β): standard error of the regression coefficient β ; PCB: Peptide basal C; PCP: peptide C postprandial; NS: non significance; PV: peripheral vasculopathy.

The mean concentration of Lp(a) in the population studied was 22.2 ± 17.3 mg/dL, similar to that reported by other authors.^[6] The relationship between the concentration of Lp(a) and the different isoforms of apo(a) would largely explain the variable distribution of Lp(a) concentrations in different ethnic groups. In the Caucasian population, it has been observed that the levels of Lp(a) are relatively low, because the S4 isoform that determines low serum concentrations of Lp(a) is frequent in that group. Similarly, it has also been observed that the concentrations of Lp(a) are higher in ethnically black individuals than white individuals, both in the general population and in diabetics individuals. This difference is confirmed by the determination of the different isoforms of apo(a) and the study of the different phenotypes.^[7]

Many studies have demonstrated the existence of a strong association between the complications of atherosclerosis and high concentrations of Lp(a) both in the general population and in T2DM individuals.^[8,9] Thus, serum concentrations higher than 30 mg/dL could increase the risk of suffering the cited vascular complications. In our study, a high percentage (32.7%) of patients studied presented Lp(a) levels higher than 30 mg/dL. This prevalence is much higher than that described in patients diagnosed with type 1 diabetes mellitus (T1DM)^[10] and higher than the 18.7% described by other authors in patients with T2DM with characteristics similar to those of our population.^[7,11] Neverthe-

less, there are studies that refer to a prevalence of HyperLp(a) similar to the 33.2% found in our study.^[11]

As has been stated, genetic factors are the principal determinants of the concentrations of Lp(a), but they can be modulated by environmental and metabolic factors.^[12] No association was found between gender or time since onset of diabetes and the serum concentrations of Lp(a); this coincides with the results of other authors.^[13] However, it can be observed that the group with more than 20 years of evolution presents higher levels of Lp(a) and greater prevalence of HyperLp(a), but not significantly. Neither has a correlation been found between fasting glucose and the levels of Lp(a), a result consistent with most of the reviewed literature. In lipid parameters analysed, only TC and apo B concentrations are correlated with Lp(a) levels.^[14] This finding has been reported previously included with the concentration of c-LDL. Moreover, the co-existence of high values of TC, c-LDL, apo B and Lp(a) increases the risk of atherosclerotic vascular complications.^[15]

The concentrations of Lp(a) showed no differences between the patients with good or poor glycemic control, and the group of patients with HyperLp(a) did not present higher levels of HbA1c nor of fasting glucose. The results obtained in our study could be extrapolated to conclude that the optimization of glycemic control is not accompanied by a decrease of Lp(a) levels. However, some authors believe that these discrepancies can be explained by a number of possi-

ble confounding biases. Thus, the inclusion or exclusion of patients with renal disease, especially those with chronic renal disease, alterations of the lipid metabolism (primary hyperlipidemias) or the presence of CVD, also affects the assessment of the metabolic control of the blood glucose levels on Lp(a) in T2DM. Chronic renal disease is associated with higher Lp(a) levels both in the non-diabetic population and in patients with T1DM and T2DM.

DN, even in the subclinical stage of its natural history, is the principal marker for CVD, and an increase of the concentrations of Lp(a) in the presence of DN has been demonstrated. It is possible that the existence of this association modulates the high prevalence of CVD in diabetic patients with nephropathy.^[16] Our results, in patients with type 2 diabetes, show that the presence of microalbuminuria (nephropathy in subclinical phase) or proteinuria (nephropathy in established phase) are associated with increased levels of Lp(a) and with a greater prevalence of HyperLp(a).^[17]

The microalbuminuria is an easily measurable parameter assumed to reflect systemic endothelial leakiness; it is used as a predictor of cardiovascular end organ damage especially diabetic nephropathy.^[18] In diabetes, the endothelium is stressed by high glycosylation products, thus becoming more permeable for albumin. Also, disturbed proteoglycan synthesis causes the glomerular membrane to lose its sensitivity and integrity.^[19]

It is known that treatment with insulin in T2DM induces significant modifications in lipoprotein metabolism, and in particular a decrease in c-VLDL and an increase in c-LDL/apoB atherogenic particles.^[20] Logically, these changes in the lipoprotein profile constitute a factor of atherogenic risk. When we evaluated the possible relationship between the type of treatment administered to our patients and the concentrations of Lp(a), we found that the patients in treatment with insulin present higher levels of Lp(a).^[21-24]

Although the design of this study is cross-sectional and does not allow drawing a causal relationship, our results suggest that elevated plasma levels of Lp(a) influence the development of CHD and DN.

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