Metabolic syndrome, lipoprotein(a) and subclinical atherosclerosis in Mexican population

Síndrome metabólico, lipoproteína(a) y aterosclerosis subclínica en población mexicana

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Abstract

Objective: To assess the relationship of metabolic syndrome (MetS) and Lp(a) with subclinical atherosclerosis (CAC) in Mexican adults. **Method:** Clinical, biochemical and tomographic data of visceral, subcutaneous, hepatic abdominal fat and CAC were evaluated in 953 women and men. Lp(a) was determined by nephelometry and MetS was diagnosed according to ATP III criteria. Multivariate logistic regression analysis was performed to determine the independent association of these variables with CAC. **Results:** Age, weight, body mass index, systolic and diastolic blood pressure, volumes of visceral, subcutaneous and hepatic abdominal fat, lipids, glucose, insulin and HOMA-RI were significantly higher in subjects with MetS. The median Lp(a) was lower in subjects with MetS compared to subjects without MetS (3.7 [IR: 2.3-9.2 vs. 5.9 [IR: 2.5-13.1) mg/dL; $p < 0.01$). The number of components and the MetS were inversely associated with the elevated Lp(a) (> 30 mg / dL). The presence of MetS was associated with a CAC risk > 0 (OR: 2.19, [95% CI (1.64-2.94)]; $p < 0.001$), independently of elevated Lp(a). The components of MetS that were independently associated with the presence of CAC > 0 UA were glycaemia > 100 mg/dL (OR 2.42, [95% CI (1.7-3.4)]; $p < 0.0001$) and high blood pressure (OR 2.14 [95% CI (1.5-3.1)]; $p < 0.0001$). **Conclusions:** In Mexican population there is an inverse association between Lp(a) levels and MetS. The MetS and its components were associated with subclinical atherosclerosis. The high prevalence of obesity, diabetes, high blood pressure high triglycerides and low HDL-C, characteristics of Mexican population could explain the differences with other populations.

Key words: Subclinical atherosclerosis. Lipoprotein (a). Metabolic syndrome.

Resumen

Objetivo: Investigar la asociación del síndrome metabólico y la lipoproteína(a) [Lp(a)] con el riesgo de aterosclerosis subclínica en adultos mexicanos. **Método:** En 953 mujeres y hombres se evaluaron datos clínicos, bioquímicos y tomográficos de grasa abdominal visceral, subcutánea, hepática y calcio arterial coronario. La Lp(a) se determinó mediante nefelometría y el síndrome metabólico se diagnosticó con los criterios del Adult Treatment Panel III. La asociación independiente de estas variables con el calcio arterial coronario se obtuvo con análisis de regresión logística multivariada. **Resultados:** La edad, el peso, el índice de masa corporal, la presión arterial sistólica y diastólica, los volúmenes de grasa abdominal, los lípidos, la

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glucosa, la insulina y el índice de resistencia a insulina fueron significativamente mayores en los sujetos con síndrome metabólico, mientras que la mediana de Lp(a) fue más baja en comparación con los sujetos sin el síndrome (3.7 [rango intercuartílico (RIC): 2.3-9.2 vs. 5.9 [RIC: 2.5-13.1) mg/dl; $p < 0.01$). El número de componentes y el síndrome metabólico se asociaron inversamente con la Lp(a) elevada (> 30 mg/dl). La presencia de síndrome metabólico se asoció con un riesgo de calcio arterial coronario > 0 (odds ratio [OR]: 2.19; intervalo de confianza del 95% [IC95%]: 1.64-2.94; $p < 0.001$), independientemente de la Lp(a) elevada. La glucemia > 100 mg/dl (OR: 2.42; IC95%: 1.7-3.4; $p < 0.0001$) y la presión arterial elevada (OR: 2.14; IC95%: 1.5-3.1; $p > 0.0001$) se asociaron con calcio arterial coronario > 0 . **Conclusiones:** En población mexicana existe una asociación inversa entre la concentración de Lp(a) y el síndrome metabólico. Este y sus componentes se asociaron positivamente con aterosclerosis subclínica. La elevada prevalencia de obesidad, diabetes, hipertensión arterial, triglicéridos elevados y concentración de colesterol unido a lipoproteínas de alta densidad que caracterizan a la población mexicana pudieran explicar las diferencias con otras poblaciones.

Palabras clave: Aterosclerosis subclínica. Lipoproteína (a). Síndrome metabólico.

Introduction

Metabolic syndrome (MetS) is characterized by insulin resistance, excess weight, glucose intolerance, atherogenic dyslipidemia (elevated triglycerides and low high-density lipoprotein cholesterol [HDL-C]), inflammation and pro-thrombotic state^{1,2}. Retrospective clinical trials and meta-analyses have shown that patients with MetS are at increased risk of coronary artery disease (CAD)^{3,4}. Lipoprotein(a) [Lp(a)] is a macromolecular complex formed by a low-density lipoprotein and Apo(a), a protein similar to plasminogen⁵ that binds to fibrin and thus blocks fibrinolysis and increases thrombogenesis^{6,7}. Several studies have shown that Lp(a) elevated concentration is an independent risk factor for CAD⁸⁻¹³. However, the association with calcium buildup on coronary arteries is controversial: some evidences are positive^{14,15} and others are negative^{16,17}. The inconsistency of results could be mainly due to: 1) the wide variation in Lp(a) concentration, which is genetically determined in ethnic groups; 2) the prevalence of LPA gene polymorphisms associated with Lp(a) elevated concentrations¹⁸⁻²⁰; and 3) differences in the prevalence of obesity, diabetes, hypertension and smoking in the studied groups. According to the 2018 National Survey on Health and Nutrition (<https://ensanut.insp.mx/encuestas/ensanut2018/informes.php>) in the Mexican adult population, the prevalence of MetS is 45%; that of excess weight (overweight and obesity), 75.2%; of diabetes mellitus, 10.3%; hypertension, 18.4%; and that of smoking is 7.1%. In a previous study in the Mexican population, the prevalence of elevated Lp(a) ≥ 30 mg/dL was 14%, and in 33% of patients with CAD, it was associated with acute myocardial infarction²¹. In a study in Mexican mestizos with no personal or family history of CAD, the prevalence of coronary

artery calcification (CAC) > 0 , which is an independent risk factor for CAD²², was 27%²³.

Considering that the prevalence of both MetS and L(a) ≥ 30 mg/dL is high in our population, and that the effect of the coexistence of both risk factors on subclinical atherosclerosis is unknown, the purpose of this study was to investigate, in subjects without personal or family history of CAD, the association of MetS and Lp(a) concentration with the presence of subclinical atherosclerosis as assessed by CAC.

Method

Study subjects

953 subjects participating in the Atherosclerotic Disease Genetics (GEA – *Genética de la Enfermedad Ateroesclosa*) project²⁴, designed at Ignacio Chávez National Institute of Cardiology, were included in order to investigate the association of genetic factors with traditional and emerging cardiovascular risk factors in an adult Mexican population of Mexico City with no history of premature CAD, with an age between 35 and 70 years, in subjects recruited among donors who attend the blood bank of said Institute or by invitation in health centers of the metropolitan area of Mexico City. None of the participants had liver, kidney, thyroid or oncological disease. The study protocol was approved by the Ethics Committee of the National Institute of Cardiology and designed according to the guidelines of the Declaration of Helsinki. All participants signed an informed consent document.

Validated questionnaires were applied to all subjects in order to obtain demographic information, personal and family history of risk factors for CAD, physical activity and medication use. The body mass index (BMI) was obtained with the following formula: weight (kg)/

height (m²). The waist circumference (cm) was measured with a fiberglass measuring tape, placed on the midpoint between the last rib and the iliac crest, with a 0.5-cm approximation.

Heart rate and systolic and diastolic blood pressure were measured three times with 1-minute intervals, after 10 minutes of rest in a sitting position. For statistical analyses, average of the second and third measurements was used. Hypertension was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure guidelines²⁵. Subjects who smoked at least one cigarette a day or seven per week within 6 months prior to the study were considered active smokers. Physical activity during work and free time was assessed using an internationally-validated questionnaire²⁶.

Participants' blood samples were obtained in the morning after a fast of at least 10 hours, without having practiced exercise before the venous puncture and after 20 minutes at rest in a sitting position. Glucose, total cholesterol (TC), triglycerides (TG), HDL-C, Apo A1 and B100 plasma values were determined with colorimetric enzymatic methods (Roche/Hitachi, Germany) on a Hitachi 902 automatic chemistry analyzer (Hitachi LTD, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated with the Friedewald formula modified by DeLong et al.²⁷, and non-HDL cholesterol was calculated with the difference between TC minus HDL-C (non-HDL cholesterol = TC – HDL-C).

Insulin concentration was determined by radioimmunoassay (Millipore, St. Charles, Missouri, USA) and insulin resistance was estimated with the HOMA-IR homeostatic model ($\text{HOMA-IR} = \text{insulin} [\mu\text{IU/mL}] \times \text{glucose} [\text{mmol/L}] / 22.5$)²⁸.

The presence of dyslipidemia was defined, according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria¹, as hypercholesterolemia ($\text{TC} \geq 200$ or $\text{LDL-C} \geq 160$ mg/dL), hypertriglyceridemia ($\text{TG} \geq 150$ mg/dL) and hypoalphalipoproteinemia ($\text{HDL-C} < 40$ mg/dL in men and < 50 mg/dL in women). Precision and accuracy in the lipid and lipoprotein measurements were periodically certified with the Lipid Standardization Program of the Center for Disease Control and Prevention (LSP-CDC, Atlanta, GA, USA). Intra- and inter-analysis coefficients of variation were $< 3\%$.

Lp(a) concentration was determined by kinetic immunonephelometry with the N Latex Lp(a) reagent (Siemens Healthcare Diagnostics Products GmbH,

Marburg, Germany)²⁹ on a BN ProSpec® automated nephelometer, with calibrators, controls and reagents of the same brand. Intra- and inter-analysis coefficients of variation were $< 6\%$.

MetS was defined according to the NCEP-ATP III guidelines¹ if the participant had at least three of the following five components: 1) waist circumference ≥ 90 cm in men or ≥ 80 cm in women; 2) $\text{TG} \geq 150$ mg/dL; 3) $\text{HDL-C} < 40$ mg/dL in men and < 50 mg/dL in women; 4) systolic blood pressure ≥ 130 mmHg and diastolic ≥ 85 mmHg, or antihypertensive pharmacological treatment; and 5) fasting plasma glucose ≥ 126 mg/dL, or previous diabetes mellitus diagnosis or treatment.

Tomographic determinations

Computed tomography is a validated method for the measurement of visceral adipose tissue and CAC³⁰. In this study, chest and abdomen tomography was performed using a 64-channel multi-detector helical system (Somatom Cardiac Sensation 64, Forchheim, Bavaria, Germany) and was interpreted by experienced radiologists. The tomographic images were evaluated to quantify total, abdominal subcutaneous and visceral adipose tissue^{31,32}. Coronary artery calcium buildup is expressed in Agatston units (AU)³³. All areas with > 130 -Hounsfield units attenuation were considered, and with the sum of the coronary arteries individual scores, total Agatston score was obtained. Intra-observer correlation coefficient was 0.99 ($p < 0.001$).

Statistical analysis

Data are expressed as the average and standard deviation or as the median with interquartile range (IQR) for variables with asymmetric distribution, while categorical variables are presented as percentages. Continuous variables were compared using Student's t-test or Mann-Whitney's U-test, depending on the type of distribution. Categorical variables were compared with the chi-square test.

Coronary artery calcium buildup was analyzed as a categorical variable (presence or absence of $\text{CAC} > 0$ AU). To investigate the independence of associations between $\text{Lp(a)} \geq 30$ mg/dL, MetS and presence of $\text{CAC} > 0$ AU, a multiple regression analysis was performed adjusting for gender and age, and then adjusting for BMI, TG, LDL-C, diabetes mellitus, hypertension and smoking. A p -value < 0.05 was considered to be

Table 1. Subjects' characteristics according to the presence or not of metabolic syndrome

	No MetS (n = 555)	MetS (n = 398)	p
Age, years*	52.7 ± 9.6	54.1 ± 8.8	0.006
Males (%)	52.1	47.9	< 0.001
BMI, kg/m ² *	27.3 ± 4.1	29.9 ± 4.1	< 0.001
Waist, cm*	90.7 ± 11.3	98.7 ± 10.4	< 0.001
AVF, mm ³ *	138.2 ± 60.8	182.3 ± 61.1	< 0.001
ASF, mm ³ *	112.3 ± 14.4	123.7 ± 19.0	< 0.001
SBP, mmHg*	112.3 ± 14.4	123.7 ± 19.0	< 0.001
DBP, mmHg*	69.8 ± 8.3	75.4 ± 9.8	< 0.001
TC, mg/dL*	188.8 ± 32.9	199.2 ± 40.0	< 0.001
LDL-C, mg/dL*	115.0 ± 28.3	123.7 ± 35.1	0.003
TG, mg/dL*	130.9 ± 58.8	236.2 ± 193.7	< 0.001
HDL-C, mg/dL*	51.5 ± 13.0	38.5 ± 9.6	< 0.001
Glucose, mg/dL [†]	88 (82-93)	96.5 (88-109.2)	< 0.001
Insulin, µIU/mL [†]	14.4 (10.6-19.9)	20.5 (15.6-27.1)	< 0.001
HOMA-IR [†]	3.1 (2.2-4.4)	5.3 (3.8-7.6)	< 0.001
Lp(a), mg/dL [†]	5.9 (2.5-13.1)	3.7 (2.3-9.2)	< 0.001
CAC, AU [†]	0.0 (0.0-0.0)	0.0 (0.0-11.3)	< 0.001
Lp(a) ≥ 30 mg/dL (%)	10.8	7.5	0.087
CAC > 0 AU (%)	23.6	39.9	< 0.001
ASCVD risk (% at 10 years) [†]	1.2 (0.8-2.0)	1.6 (1-3.2)	< 0.001

ASCVD: Atherosclerotic cardiovascular disease; CAC: coronary artery calcification; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; AVF: abdominal visceral fat; ASF: abdominal subcutaneous fat; HOMA-IR: insulin resistance; BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; MetS: metabolic syndrome; TG: triglycerides.

*Average ± standard deviation.

[†]Median (interquartile range).

statistically significant. All statistical analyses were performed with SPSS V.16.

Results

The characteristics of the 953 subjects without and with MetS are shown in [table 1](#). Three hundred and ninety-eight participants (41.7%) were diagnosed with MetS. In the subjects with MetS, average or median anthropometric variables, such as BMI, waist circumference, abdominal visceral and subcutaneous fat volume, and biochemical variables, such as lipid, lipoprotein, glucose and insulin concentrations, and insulin resistance index (HOMA-IR), were significantly higher than

in those without MetS, while HDL-C average was significantly lower ($p < 0.001$) ([Table 1](#)).

Median Lp(a) was significantly lower in subjects with MetS: 3.7 (IQR: 2.3-9.2) vs. 5.9 (IQR: 2.5-13.1); $p < 0.001$. Compared to subjects without MetS, the prevalence of Lp(a) ≥ 30 mg/dL was lower in subjects with MetS (7.5 vs. 10.8%; $p = 0.087$). However, the prevalence of subclinical atherosclerosis (CAC > 0 AU) in subjects without MetS was significantly lower than in subjects with MetS (23.6 vs. 39.9%; $p < 0.001$) ([Table 1](#)).

As shown in [figure 1](#), the prevalence of Lp(a) ≥ 30 mg/dL is inversely associated, and the prevalence of CAC is positively associated with the number of MetS components. The percentage of subjects with

Figure 1. Prevalence of lipoprotein(a) [Lp(a)] ≥ 30 mg/dL and coronary artery calcification (CAC) > 0 AU in a Mexican population according to the number of metabolic syndrome (MetS) components.

high Lp(a) decreased, and that of individuals with CAC > 0 AU did progressively increase with the presence of one to all five MetS components. These relationships were evaluated with logistic regression analysis to investigate the independence of the association between MetS components and a Lp(a) concentration ≥ 30 mg/dL and the presence of CAC > 0 AU. In subjects with MetS with blood glucose ≥ 100 mg/dL or blood pressure $\geq 130/85$ mmHg, the risk of CAC > 0 AU was twice higher than in subjects without MetS (odds ratio [OR]: 2.19, 95% confidence interval [CI]: 1.6-2.6, $p < 0.001$; OR: 2.4, 95% CI: 1.7-3.4, $p < 0.001$; and OR: 2.1, 95% CI: 1.6-3.1, $p < 0.001$; respectively). TG ≥ 150 mg/dL, HDL-C low concentration (< 50 mg/dL in women and < 40 mg/dL in men) and obesity (waist circumference) were not associated with higher risk of CAC > 0 AU (Fig. 2).

Discussion

Lp(a) is an independent risk factor for CAD³⁴; however, the degree of association with atherosclerosis broadly varies between different ethnic groups. In this cross-sectional study in 953 Mexicans with no personal or family history of premature CAD, Lp(a) ≥ 30 mg/dL median and prevalence were significantly lower in subjects with MetS, while the prevalence of CAC > 0 AU was significantly higher. The prevalence of CAC > 0 AU progressively increased, with the presence of one to five MetS components. However, the percentage of subjects with elevated Lp(a) decreased and was not associated with CAC. Body adiposity measurements, such as BMI and abdominal visceral and subcutaneous fat, and cardiometabolic markers such as plasma insulin and HOMA-IR, were significantly

Figure 2. Risk of subclinical atherosclerosis (coronary artery calcification > 0 AU) in subjects with metabolic syndrome and its components in a Mexican population. Multiple regression analysis adjusted for gender, age, low-density lipoprotein cholesterol, smoking and physical activity. HDL-C: high-density lipoprotein cholesterol; CI: confidence interval; OR: odds ratio; BP: blood pressure.

higher in subjects with MetS, but blood glucose > 100 mg/dL and hypertension $> 130/85$ mmHg were the only MetS components that were independently and significantly associated with the presence of subclinical atherosclerosis.

The 2014 ATP III consensus³⁵ suggests that the first therapeutic target for the treatment of atherosclerosis is LDL-C elevated concentration, and the next one should be MetS, because each one of its components is a risk factor for CAD. Lp(a) elevated concentration is an emerging risk factor for CAD^{13-36,37}. It has been suggested that the coexistence of elevated Lp(a) with MetS could potentiate the risk of premature atherosclerosis or accelerate the atherosclerotic process³⁸; however, studies where this association has been investigated are scarce and the results are controversial. In the vast majority of studies, each one of the MetS components and their association with Lp(a) concentration are analyzed separately. In patients with heart conditions with and without MetS, those who had MetS were found to have Lp(a) concentrations 1.8 times higher than those without MetS (median, 29.2 vs. 16.2 mg/dL; $p < 0.0001$) and a prevalence 2.3 times higher of Lp(a) ≥ 30 mg/dL (51.4 vs. 21.6%; $p < 0.001$)³⁹. In another study, Lp(a) mean concentrations (5-17 mg/dL) in women, in comparison with men with MetS, were found to be associated with atherosclerosis progression³⁸. However, Lp(a) concentrations have been reported to be significantly lower in patients with MetS in comparison with subjects without MetS, with Lp(a) showing to be a predictor of cardiovascular events in subjects without MetS⁴⁰; furthermore, in subjects with higher Lp(a) concentration,

the risk of MetS has been documented to be significantly lower⁴¹. These authors suggest that the inverse relationship between MetS and Lp(a) could be due to a survival bias in subjects with a history of CAD. The presence of Lp(a) ≥ 30 mg/dL and MetS at early ages might increase mortality in young subjects, which would explain the higher proportion of low Lp(a) among survivors of older age⁴¹.

Our data in subjects without CAD, grouped by age decades, showed that, from 20 to 70 years, the prevalence of elevated Lp(a) is higher in subjects without MetS, and, therefore, this does not support the hypothesis of a survival effect that tries to explain the inverse relationship between both these risk factors for CAD; in fact, the prevalence of Lp(a) ≥ 30 mg/dL is not associated with MetS or subclinical atherosclerosis at any age range. Similar results have been reported by other researchers⁴².

In other studies that included patients with CAD⁴³ or with dyslipidemias⁴⁴, an inverse association has been observed between Lp(a) concentrations and elevated TG and low HDL-C. The authors suggest that the association could be due to a shared metabolic mechanism between these three biochemical factors. In the present study, a negative and significant correlation between TG and Lp(a) was observed ($r = -0.073$; $p = 0.024$), which was lost when the sample was grouped in subjects with and without MetS. These results confirm the findings reported in another study⁴⁵ and support the results, in vitro, where Lp(a) is shown to be a ligand for the very-low density lipoprotein receptor in endothelial cell membranes, in macrophages, foamy cells and smooth muscle cells in atherosclerotic plaques. Lp(a) internalization into these cells could significantly contribute to Lp(a) catabolism and to the development of atherosclerotic plaques⁴⁶. It is well documented that Lp(a) decreases the effects of PAI-1 and plasmin formation, which generates a pro-thrombotic state. In subjects with MetS, there are hemostatic alterations that decrease fibrinolysis and favor coagulation⁴⁷. It has been suggested that PAI-1 increased concentration in subjects with MetS could decrease Lp(a) synthesis^{48,49}. The pathophysiological mechanism of the relationship between MetS, Lp(a) and atherosclerosis is unknown; however, a prospective study in subjects with MetS and elevated Lp(a) could generate information that allows knowing, at least in part, the relationship between these cardiovascular risk factors.

This study has as limitations that it is of the cross-sectional type, and thus only associations between variables can be established, and it is not

possible for causality to be established. The study included volunteers who were residents of Mexico City's metropolitan area and the sample is not representative of the Mexican population; however, the prevalence of the CAD risk factors that were observed in this study is similar to that found in the 2016 National Survey on Health and Nutrition (ENSANUT MC 2016), a nation-wide randomized and representative study⁵⁰. The strengths of the study include the sample size (larger than in other studies), the fact that the study subjects are of both genders, with ages ranging from 20 to 70 years and with no presence of personal or family history of atherosclerosis, which reduces bias in interpretation of results, and subclinical atherosclerosis (CAC) evaluation in the entire sample.

Conclusions

This study in an asymptomatic Mexican population without a history of coronary artery disease found: 1) an inverse association between Lp(a) concentration and MetS and its components; 2) an elevated Lp(a) concentration in subjects with MetS is not associated with subclinical atherosclerosis due to CAC; and 3) the high prevalence of overweight, obesity, diabetes mellitus, high blood pressure and atherogenic dyslipidemia (high TG and low HDL-C) that characterizes the Mexican population could explain the differences with other populations.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures that were followed

adhered to the ethical standards of the responsible committee for experimentation on human beings and were in agreement with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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