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Association of fatty liver with cardiovascular risk factors and subclinical atherosclerosis in a Mexican population

María del Rocío Martínez-Alvarado,* Juan Gabriel Juárez-Rojas,* Aída Xóchitl Medina-Urrutia,* Guillermo Celestino Cardoso-Saldaña,* María del Carmen González-Salazar,* Rosalinda Posadas-Sánchez,* Esteban Jorge-Galarza,* Enrique Mendoza-Pérez,* Gilberto Vargas-Alarcón,** Carlos Posadas-Romero*

* Departamento de Endocrinología, ** Departamento de Genética.
Instituto Nacional de Cardiología Ignacio Chávez.

ABSTRACT

Introduction. Individuals with fatty liver (FL) have an increased risk of coronary artery disease (CAD) probably due to its association with cardiometabolic risk factors (CMRF). **Objective.** To know the prevalence of FL and analyze its association with CMRF and subclinical atherosclerosis, in a sample of Mexican Mestizo population. **Material and methods.** This study included 846 subjects from the Genetic of Atherosclerosis Disease (GEA) study (53 ± 9 years, 50.7% women) without diabetes and no personal or family history of premature CAD. Blood samples were taken for measurements of lipids profile, uric acid, and insulin. The presence of FL was identified by computed tomography. Carotid intima media thickness (CIMT) was measured by B mode ultrasound, using the > 75 percentile as cutoff value to define subclinical atherosclerosis. **Results.** The general prevalence of FL was 32.4%. In men, FL was associated with hyperuricemia, whereas in women, hyperuricemia, low level of high density lipoprotein cholesterol, and metabolic syndrome were the factors associated with this hepatic alteration. In women, FL was associated with a 66% higher probability of having high CIMT, independently of age, hypertension, dyslipidemia, and waist circumference, but not of HOMA-IR. **Conclusions.** In women, FL was associated with the presence of subclinical atherosclerosis independently of traditional CMRF. Our study suggests that, in women, insulin resistance could be a mediator of metabolic abnormalities and of subclinical atherosclerosis.

Key words. Fatty liver. Subclinical atherosclerosis. Insulin resistance.

Asociación de esteatosis hepática con factores de riesgo cardiovascular y aterosclerosis subclínica en población mexicana

RESUMEN

Introducción. *Los sujetos con esteatosis hepática (EH) tienen riesgo incrementado de enfermedad arterial coronaria (EAC), probablemente debido a su asociación con factores de riesgo cardiometabólico (FRC).* ***Objetivo.*** *En una muestra de población mestiza mexicana, conocer la prevalencia de EH y analizar su asociación con FRC y con aterosclerosis subclínica.* ***Material y métodos.*** *Se incluyeron 846 sujetos participantes del estudio Genética de la Enfermedad Aterosclerosa (53 ± 9 años, 50.7% mujeres), sin diabetes y sin antecedentes personales ni familiares de EAC prematura. En sangre se midieron perfil de lípidos, ácido úrico e insulina. Por tomografía axial computarizada (TAC) se identificó la presencia de EH. El grosor de íntima media (GIM) carotídeo se midió por ultrasonido, utilizando la percentila 75 como punto de corte para definir aterosclerosis subclínica.* ***Resultados.*** *La prevalencia general de EH fue de 32.4%. En los hombres la EH se asoció con hiperuricemia; mientras que en las mujeres, la hiperuricemia, los valores bajos de colesterol de lipoproteínas de alta densidad y el síndrome metabólico fueron los factores asociados a esta alteración hepática. En el sexo femenino la EH se asoció con una probabilidad 66% mayor de tener GIM elevado, independientemente de la edad, hipertensión, dislipidemia y circunferencia de cintura, pero no del HOMA-RI.* ***Conclusiones.*** *En las mujeres la EH se asoció con la presencia de aterosclerosis subclínica, independientemente de los FRC tradicionales. Nuestro estudio sugiere que en mujeres, la resistencia a la insulina pudiera ser mediadora de las anormalidades metabólicas y de la aterosclerosis subclínica.*

Palabras clave. *Esteatosis hepática. Aterosclerosis subclínica. Resistencia a la insulina.*

INTRODUCTION

Overweight is a growing health problem that increases the risk of developing multiple comorbidities, such as fatty liver (FL).[1] FL is a condition characterized by increased accumulation of fat in the liver (over 5%), in the absence of excessive alcohol consumption and of other hepatic diseases.[2] Approximately 3.5% of FL patients evolve to steatohepatitis and 15% of them develop cirrhosis.[3] In western countries, general prevalence of FL has been reported to be 30%[4] being lower than that reported (46%) among Hispanics living in the USA.[5] FL prevalence between 7.1 and 32.1% has been reported in México.[6-9] However, the limited amount of studies, differences in sample size, and characteristics of the included subjects, as well as the diversity of methods used to identify FL, do not allow defining the prevalence of this abnormality in our population or to compare it with other ethnic groups.

Subjects with FL have a high risk of developing coronary artery disease (CAD),[10,11] probably because of its association with multiple cardiometabolic risk factors (CMRF), particularly central obesity, insulin resistance,[12] besides dyslipidemia, arterial hypertension, and elevated uric acid,[13] all of them components of the metabolic syndrome (MS).[14]

Some studies have shown the association of FL with an increase in carotid intima media thickness (CIMT),[15,16] independently of traditional CMRF, metabolic syndrome, and insulin resistance.[17] These findings suggest a role for FL not only as early marker, but also as a direct mediator of atherosclerosis. Considering the high FL prevalence in Mexican-Americans,[5] and that in México no previous studies have analyzed the association of FL with early atherosclerosis markers, the objectives of this study were:

- To know the FL prevalence in a Mexican Mestizo population, and
- To analyze the association of FL with the presence of CMRF and with subclinical atherosclerosis, defined as high CIMT.

MATERIAL AND METHODS

The Genetics of Atherosclerotic Disease (GEA) study was designed at the Instituto Nacional de Cardiología Ignacio Chávez (INCICh) (National Institute of Cardiology) to examine the genomic bases of CAD and to assess its relationship with traditional and emerging risk factors in the adult Mexican population. The study included 1,000 CAD patients and a control group of 1,500 individuals without family or personal history of premature CAD, aged 30 to 75 years old, residents of Mexico City. Subjects of control group were volunteers attending the blood bank for donation, or invited through written media posted in social service centers. The GEA study was approved by the institutional Research and Ethics Committee. Subjects that accepted to participate signed the informed consent format.

Clinical methods

Standardized questionnaires were applied to all participants to obtain demographic data, personal antecedents of cardiovascular risk, eating habits, physical activity, alcohol consumption, and use of medication. In the present work we included 846 subjects of the GEA study control group of either gender, with complete measurements of all variables and without clinical history or evidence of hepatic or renal disease, acute or chronic inflammatory processes, diabetes mellitus (DM), and alcohol consumption below 20 g/day. Weight and height were measured and body mass index (BMI) was calculated as weight (kg)/height (m^2). Waist circumference was measured at the midpoint of the distance between the lower part of the last rib and the iliac crest, with a 0.5 cm approximation. Blood pressure was measured three times with a digital sphygmomanometer Wellch Allyn, after at least 5 min of rest, in sitting position. The average of the last two measurements was used for the analysis.

Laboratory analyses

After 10 h fasting and 20 min in sitting position, venous blood was collected in assay tubes without anticoagulant and in tubes with K_2 EDTA (1.8 mg/mL). Glucose, total cholesterol (TC), triglycerides (TG), and high density lipoprotein cholesterol (HDL-C) concentrations were measured in plasma. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and uric acid were measured in serum. These measurements were performed during the first 3 days after obtaining the sample. Measurements were performed in a Hitachi 902 (Hitachi LTD, Tokyo Japan) autoanalyzer, using enzymatic-colorimetric reagents (Roche/Hitachi, Germany). Reproducibility and accuracy of lipid and lipoprotein determinations were periodically evaluated by the Lipids Standardization Program of The Centers for Disease Control and Prevention

(LSP-CDC, Atlanta, GA. USA). Intra- and inter-assay variation coefficients were lower than 3% in all measurements. Serum insulin was determined by radioimmunoanalysis (Millipore RIA Kit, St. Charles, MI, USA), with intra- and inter-assay variation coefficient of 2.1 and 6.8%, respectively. Insulin resistance (IR) was estimated with the homeostasis model:[18]

$$\left(\frac{\text{insulin [UI/mL]} * \text{glucose [mmol]}}{22.5}\right)\left(\text{HOMA-IR}\right)$$

Computed tomography study

A 64-channel multidetector tomograph (Somaton Sensation, 64, Forcheim, Germany) was used. Liver and spleen attenuation was measured with a single 3-mm tomographic section at the level of T11-T12 or T12-L1.[19] During images analysis, three 1-cm^2 regions were marked on both hepatic lobes and in the spleen parenchyma. Diagnosis of FL was defined as a liver/spleen attenuation ratio (L/S AR) below 1.0.[20]

To assess CIMT, we used high resolution ultrasound equipment in B mode (Sonosite MicroMaxx), with a 13-6-MHz transducer. The study was performed in supine position, with extended neck. All measurements of the intima media of the common carotid artery were performed in the longitudinal plane in the distal wall of the carotid artery at 2 cm from the carotid bulb bifurcation. Thickness of the intima media was quantified by the distance between the arterial intima-lumen interface and the media-adventitia interface of the distal wall. Five measurements were performed in the right and left carotid artery. The CIMT was defined as the average of all measurements. A high CIMT was defined according to the 75% percentile specific for age group and gender.[21] Procedures were performed by one single previously trained observer. Reproducibility of measurements was obtained with 5% of the cohort, obtaining an intra-observer correlation coefficient of 0.96.

Definition of cardiovascular risk factors

Dyslipidemia was defined according to the following cut-off values:

- Hypercholesterolemia = LDL-C ≥ 130 mg/dL.
- Hypertriglyceridemia = TG ≥ 150 mg/dL.
- Hypoalphalipoproteinemia = HDL-C < 40 mg/dL in men and < 50 mg/dL in women.
- And/or use of lipid regulating drugs.

Hypertension was defined when systolic and/or diastolic blood pressure values were ≥ 140/90 mmHg or when subjects were using antihypertensive drugs. Overweight was considered when BMI was between 25 and 29.9 kg/m^2 and obesity when it was ≥ 30 kg/m^2. Abdominal obesity was defined when waist circumference was ≥ 80 cm in women and ≥ 90 cm in men.[22] Fasting plasma glucose from 100 to 125 mg/dL was considered as altered fasting glycemia, whereas glucose values of ≥ 126 mg/dL or treatment with hypoglycemic drugs was used to define the presence of DM. Metabolic syndrome (MS) was defined based on NCEP-ATP III criteria.[23] Insulin resistance was considered when HOMA-IR was ≥ p75 (3.58 in women, 3.12 in men). These cut-off values were obtained from 101 men and 180 women in the GEA study, without obesity and normal lipid, glucose, and blood pressure values.

Statistical analysis

General characteristics of the population stratified per gender and presence or absence of FL are shown as mean ± standard error. Comparison between groups was performed with age-adjusted ANCOVA test. Association of FL with CMRF and with CIMT was evaluated by means of logistic regression analysis, adjusting for confounding variables indicated in each model. Values of $p < 0.05$ were considered significant. Analyses were performed with SPSS v15.0 software (SPSS, Chicago, II).

RESULTS

The study included 846 subjects (50.7% women). General prevalence of FL was 32.4% (36.5 % in men and 28.4% in women [p = 0.01]) that gradually increased with weight, being similar between men and women of normal weight (8.1 *vs.* 10.9%) or overweight (35.0 *vs.* 27.5%), but significantly higher in obese men (58.4 *vs.* 40.5%; p = 0.003). Despite that FL subjects were younger ($p < 0.05$), they were characterized for having a more adverse cardiometabolic risk profile in relation to subjects without FL (Table 1).

The analysis of association between FL and CMRF, adjusted by age and waist circumference (Model 1), revealed that in men, altered fasting

plasma glucose, hyperuricemia, and HOMA-IR >p75, were significantly associated with the presence of FL (Table 2). When HOMA-IR values were included in the adjustment (Model 2), only hyperuricemia was independently associated with FL (Table 2). On the other hand, high TG and low HDL-C values, altered fasting plasma glucose, hyperuricemia, and HOMA-IR > p75 were associated with the presence of FL in women in Model 1. In Model 2, only low HDL-C values and hyperuricemia were associated with FL (Table 2). Besides, in women, the metabolic syndrome was associated with the presence of FL, even after adjusting by HOMA-IR.

When analyzing the association of FL with subclinical atherosclerosis, we found that the prevalence of elevated CIMT was significantly higher in women with FL as compared with women without FL (32.8 *vs.* 22.8%, $p < 0.05$). Figure 1 shows that, in women, FL was associated with a 66% higher probability of having a high CIMT, independent of age, hypertension, hypercholesterolemia, hypertriglyceridemia, low HDL-C (Model 1) and waist circumference (Model 2). Association of FL with high CIMT was lost when HOMA-IR was included in the model. In men, prevalence of high CIMT was similar in those with and without FL (21.7 and 21.5%, respectively); no association was found between FL and elevated CIMT.

DISCUSSION

Prevalence of FL was 32.4% in the studied sample of Mexican Mestizo population without diabetes or cardiovascular disease. The CMRF independently associated with FL were hyperuricemia in men, whereas, in women, these were hyperuricemia, low HDL-C values and MS. Our work shows, for the first time, that FL is independently associated with subclinical atherosclerosis in Mexican women. This study expands the available information on the association of HOMA-IR with cardiovascular disease. Results of this study and other reports[24] suggest that, in women with FL, insulin resistance is an important mediator in metabolic abnormalities associated to cardiovascular disease.

It has been suggested that in comparison with Caucasian population, Mexican-Americans have a greater susceptibility to accumulate liver fat (33 *vs.* 46%).[5] Studies performed in Mexican adults without DM, reported prevalences of FL between 15%[6-8] to 32.1%.[9] Considering, that higher frequency of obesity has been associated to higher prevalence of FL,[25] and that our data show that FL is more common in overweight and obese subjects than in normal weight individuals, it is reasonable to suggest that the discrepancies among Mexican studies, could be explained by the differences in overweight prevalence. The first studies[6-8] were performed in groups

Table 1. Clinical and biochemical characteristics of the studied population.

Variable	Men			Women		
	Without FL (n = 265)	With FL (n = 152)	p*	Without FL (n = 307)	With FL (n = 122)	P*
Age (years)	53.5 ±9.9	51.4 ± 8.3	< 0.05	54.1 ± 8.7	52.1 ±8.8	< 0.05
SBP (mmHg)	116.7 ±0.9	121.1 ± 1.2	< 0.01	111.3 ± 0.9	114.5 ±1.4	< 0.05
DBP (mmHg)	72.4 ±0.6	75.1 ± 0.8	< 0.01	68.8 ± 0.5	70.3 ±0.7	0.1
Waist circumference (cm)	95.9 ±0.6	103.5 ± 0.8	< 0.0001	89.8 ± 0.6	97.5 ±1.0	< 0.0001
BMI (kg/m^2)	27.2 ±0.2	30.2 ± 0.3	< 0.0001	27.9 ± 0.3	30.7 ±0.4	< 0.0001
T. cholesterol (mg/dL)	189.8 ±36	193.6 ± 37.7	0.29	197.8 ± 36.3	190.9 ±40	0.08
LDL-C (mg/dL)	117.8 ±2.0	118.8 ± 2.7	0.77	119.1 ± 1.8	116.6 ±2.8	0.407
HDL-C (mg/dL)	42.4 ±0.7	40.4 ± 0.9	< 0.05	52.9 ± 0.8	45.6 ±1.2	< 0.0001
Triglycerides (mg/dL)	176.9 ±6.1	196.7 ± 8.1	< 0.01	146.4 ± 4.1	175.1 ±6.5	< 0.01
Glucose (mg/dL)	90.4 ±0.6	93.2 ± 0.7	< 0.01	87.3 ± 0.5	94.7 ±0.8	< 0.001
Insulin (μU/mL)	16.3 ±0.7	24.0 ± 0.9	< 0.0001	16.6 ± 0.5	25.1 ±0.8	< 0.001
HOMA-IR	3.7 ±0.2	5.5 ± 0.2	< 0.0001	3.6 ± 0.1	5.9 ±0.2	< 0.001
Uric acid (mg/dL)	6.1 ±0.1	7.1 ± 0.1	0.0001	4.7 ± 0.1	5.5 ±0.1	< 0.0001
AST (UI/L)	26.5 ±0.02	32.1 ± 0.8	< 0.0001	24.2 ± 0.6	31.6 ±0.9	< 0.0001
ALT (UI/L)	27.2 ±1.0	41.8 ± 1.3	< 0.0001	22.8 ± 0.9	31.9 ±1.1	< 0.0001

Mean values ± SD. * ANCOVA adjusted for age. FL: fatty liver. SBP: systolic blood pressure. DBP: diastolic blood pressure. BMI: body mass index. T. cholesterol: total cholesterol. HOMA-IR: homeostasis model to assess insulin resistance. LDL-C: low density lipoprotein cholesterol. HDL-C: high density lipoprotein cholesterol. AST: aspartate aminotransferase. ALT: alanine aminotransferase.

Table 2. Logistic regression analysis to assess FL association with cardiometabolic risk factors.

	FL (Model 1) OR (95% CI)	FL (Model 2) OR (95% CI)
Men		
Hypertension	1.10 (0.67-1.80)	0.92 (0.49-1.72)
Hypertriglyceridemia	1.28 (0.82-1.98)	0.97 (0.56-1.68)
Low HDL-C	0.93 (0.60-1.43)	0.99 (0.58-1.69)
Glucose > 100 mg/dL	1.84 (1.07-3.17)*	1.48 (0.73-3.02)
Hyperuricemia	3.28 (2.02-5.32)***	3.43 (1.87-6.29)***
Metabolic syndrome	1.27 (0.81-1.98)	0.95 (0.54-1.69)
HOMA-IR > p75	4.60 (2.40-8.82)***	-
Women		
Hypertension	1.41 (0.84-2.36)	0.96 (0.50-1.83)
Hypertriglyceridemia	2.01 (1.31-3.10)**	1.67 (0.97-2.88)
Low HDL-C	2.61 (1.66-4.10)***	2.34 (1.32-4.15)**
Glucosa > 100 mg/dL	4.56 (2.55-8.14)***	2.05 (0.98-4.31)
Hyperuricemia	3.51 (2.17-5.68)***	2.02 (1.11-3.69)*
Metabolic syndrome	2.51 (1.57-4.02) ***	2.07 (1.19-3.60)*
HOMA-IR > p75	7.29 (3.76-14.13)***	-

FL: fatty liver. OR: odds ratio. CI: confidence interval. HDL-C: high density lipoprotein cholesterol. HOMA-IR: homeostasis model to assess insulin resistance. Hypertension: blood pressure ≥ 140/90 mmHg or antihypertensive treatment. Hypertriglyceridemia: TG > 150 mg/dL. Low HDL-C: < 40 mg/dL in men and < 50 mg/dL in women. Hyperuricemia: uric acid > 7 mg/dL in men and > 6 mg/dL in women; HOMA-IR > p75: > 3.12 in men and > 3.19 in women. * P < 0.05. ** P < 0.001. *** P < 0.0001. Model 1: adjusted for age and waist circumference. Model 2: adjusted for age, waist circumference and HOMA-IR.

with less than 45% excess body weight, whereas our study and that of Lizardi-Cervera, *et al.*,[9] which showed similar FL prevalences (32.4 and 32.1%, respectively), included individuals in which the excess body weight was approximately 80%.

It has been previously observed that around 90% of people with FL present more than one MS component, and approximately 33% have three or more components.[26] The present results indicate that almost half of the subjects with FL have MS (men, 55.3%; women, 48.4%); which is significantly higher than in subjects without FL (men, 38.1%; women, 23.1%). Our results also show that, independently from obesity, FL was associated to high plasma glucose, uric acid, and HOMA-IR values in men and women, and with hypertriglyceridemia and low HDL-C values in women. Although MS was more prevalent in subjects with FL, the odds ratio for this condition was not higher than that observed for individual components (Table 2). After adjusting for HOMA-IR, most associations were lost. These findings support the hypothesis that FL is a manifestation of MS, with IR as the main pathogenic mechanism.[27] On physiological conditions, insulin decreases fatty acids release by adipose tissue. However, in an insulin resistance state, the hormone

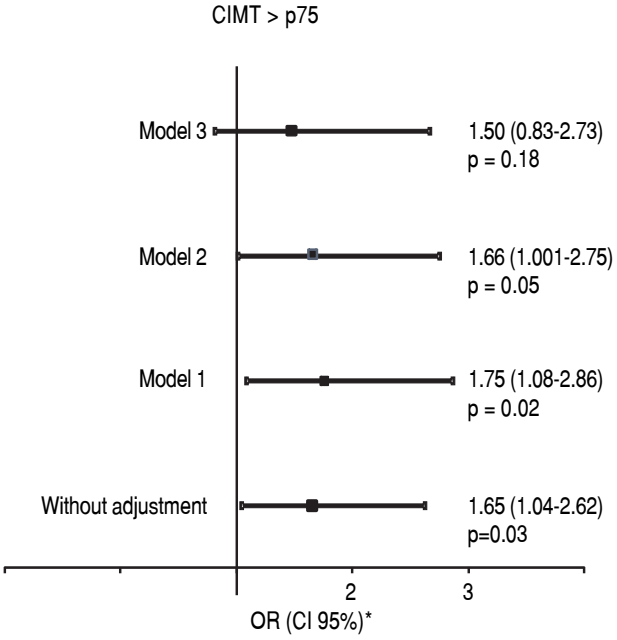

Figure 1. Association of hepatic steatosis with elevated carotid intima media thickness (CIMT) in women. CIMT > p75: carotid intima media thickness greater than 75 percentile, specific for age and gender (see Methods). Model 1, adjusted for age, arterial hypertension, hypercholesterolemia, hypertriglyceridemia, and low HDL-C. Model 2, adjusted for model 1 + waist circumference. Model 3, adjusted for model 2 + HOMA-IR.

sensitive lipase is not adequately regulated, resulting in excessive release of free fatty acids by adipocytes.[28] The increased flow of these fatty acids to the liver, favours hepatic synthesis and secretion of TG-rich lipoproteins, and reduction in HDL-C levels; this would explain the atherogenic dyslipidemia characteristic of subjects with FL.[29] On the other hand, although increases the synthesis and reduces renal excretion of uric acid, it has also been suggested that hyperuricemia could be a compensatory mechanism that regulates the excess production of reactive oxygen species (ROS), resulting from the increased circulating fatty acids during IR.[30]

IR is a key abnormality of FL that affects pancreas, liver, muscle and adipose tissue.[31] This insulin resistance state is linked to systemic inflammation and higher levels of pro-inflammatory molecules such as tumor necrosis factor-α, Interleukin1β, Interleukin 6, resistin and free fatty acids. These molecules reduce the release of nitric oxide and lead to endothelial dysfunction, which is one of the most important early steps in the atherogenic process. The cluster of these disorders enhance the risk of cardiovascular disease and death.[32]

Recent studies have shown a close relation between the presence of FL and subclinical atherosclerosis.[33-34] In 633 non-diabetic subjects, Kang, *et al.*,[17] found that subjects with FL had 23% more risk to present elevated CIMT, even in the absence of MS. Targher, *et al.*,[35] reported that the CIMT is high in non-obese volunteer subjects with FL. Our present results show that, in women, FL was associated with a 66% higher probability of having elevated CIMT, regardless of age, hypertension, dyslipidemia, and waist circumference. The fact that this association was attenuated after adjusting for HOMA-IR, suggests that cardiovascular risk associated to FL could be explained, at least in part, by etiopathogenic mechanisms associated to IR. In men, no association was observed between FL and elevated CIMT. This difference between genders might be explained, by our results showing that FL in women was associated with a higher number of cardiovascular risk factors (Table 2). Similar results have been previously reported, suggesting that the deleterious effects of obesity and cardiovascular risk associated to MS, are more evident in women.[36,37]

It is important to consider that due to the cross-sectional characteristics of the GEA study, the present results do not allow identifying causality between FL and cardiovascular risk factors. Another characteristic of the GEA study is that sample selection only included people without personal or family history of premature CAD, hence the results may not be applied to the general population.

FL can be identified by several noninvasive methods. Magnetic resonance spectroscopy is considered the best diagnostic tool, because it can detect as little as 5% liver fat accumulation. However, it is relative expensive and not widely available. Ultrasonography is an easy method, of low cost, and commonly used, but it is operator dependent and provides only a qualitative assessment of the fatty liver. Similar to ultrasonography, computed tomography (CT) identifies a fatty liver only in those subjects with liver fat accumulation higher than 30%.[19] However, compared with ultrasound, CT has a greater reproducibility and specificity, and a significant correlation has been demonstrated between the liver attenuation images on CT and the histologic grade of the steatosis.

CONCLUSIONS

Our results showed that FL is present in 32.4% of the Mexican Mestizo population studied. FL was independently associated with high uric acid levels in both genders and also with low HDL-C concentrations and the MS in women. Additionally, only in women, FL showed independent association with subclinical atherosclerosis after adjustment for traditional CMRF. These findings suggest that in Mexican women with FL, IR could be an important mediator in both metabolic abnormalities and in subclinical atherosclerosis.

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Reimpresos:

Dr. Carlos Posadas Romero
Departamento de Endocrinología, Edificio B
Instituto Nacional de Cardiología Ignacio Chávez
Juan Badiano, Núm. 1
Col. Sección XVI
14080, México, D.F.
Tel.: 5573-2911, Ext. 1272
Fax: 5573-4687
Correo electrónico: cposadasr@yahoo.com

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