

Fatty Liver Increases the Association of Metabolic Syndrome With Diabetes and Atherosclerosis

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OBJECTIVE—To analyze the participation of fatty liver (FL) in the association of metabolic syndrome (MS) with type 2 diabetes and coronary artery calcification (CAC).

RESEARCH DESIGN AND METHODS—A total of 765 subjects (52% women) aged 30 to 75 years without clinical atherosclerosis were included in this study. MS was defined in accordance with the Adult Treatment Panel III (ATPIII) guidelines, while FL and CAC were identified by computed tomography.

RESULTS—There were increasing frequencies of type 2 diabetes and CAC in all three groups: control, MS without FL, and MS plus FL. Multivariable-adjusted logistic regression analyses showed that FL increased the association of MS with type 2 diabetes in both women [odds ratio 10.6 (95% CI 3.4–33.7)] and men [12.1 (4.1–36.1)]. In women, FL also increased the association of MS with CAC [2.34 (1.07–5.12)].

CONCLUSIONS—FL increases the association of MS with type 2 diabetes and subclinical atherosclerosis.

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Numerous studies have reported controversial associations of metabolic syndrome (MS) with type 2 diabetes and coronary artery disease (CAD) (1–4). Nonalcoholic fatty liver (FL) has been considered a hepatic expression of MS and has been suggested to be a key element in the development of type 2 diabetes and CAD (5). We studied the participation of FL in the association of MS with type 2 diabetes and subclinical CAD in subjects with no personal or family history of premature CAD.

RESEARCH DESIGN AND METHODS

Participants were from the Genetics of Atherosclerosis Disease Study [*Genética de la Enfermedad Aterosclerosa* (GEA)], which was designed to examine the genomic bases of coronary heart disease

in a Mexican Mestizo population. In this ongoing study, 1,500 control subjects aged 30–75 years are currently being recruited. From 918 control individuals enrolled in the GEA project by September 2011, 765 subjects for whom data were complete; who had no history of viral hepatitis, renal, malignant, or drug-induced liver disease; whose alcohol consumption was <20 g/day; and who had a BMI <40 kg/m² and triglycerides <6.78 mmol/L were selected.

Blood pressure and anthropometric and biochemical variables were measured. Central obesity was defined as waist circumference >90 cm in men and >80 cm in women. Metabolic syndrome was diagnosed on the basis of the presence of three or more of the following features: 1) central obesity, 2)

triglycerides ≥1.695 mmol/L, 3) HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women, 4) glucose ≥5.55 mmol/L, and 5) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg (6). Subjects were considered to have type 2 diabetes when they either self-reported use of medication or had a fasting plasma glucose level ≥7 mmol/L (7).

Multidetector computed tomography is a validated method for identifying the presence of FL (8) and coronary artery calcification (CAC) (9). In this study, FL was defined by a liver-to-spleen attenuation ratio <1.0 (10), and subclinical CAD was defined as positive CAC (score >0.0), using a 64-slice scanner (Somatom Cardiac Sensation; Medical Solutions, Forchheim, Germany).

Subjects were classified in three groups: individuals with neither MS nor FL (control group), participants with MS but no FL (MS group), and those with MS plus FL (MS + FL). The effect of FL on the association of MS with the presence of type 2 diabetes and CAC was assessed by multivariate logistic regression analysis. Statistical procedures were performed using SPSS 15 software (SPSS, Chicago, IL).

RESULTS—The general prevalence was as follows: MS 43.9%, FL 21.3%, type 2 diabetes 9.4%, and positive CAC 29.8%. As shown in Table 1, type 2 diabetes showed an ascending tendency from the control, the MS, and the MS + FL group without sex differences. Compared with women, men had a higher prevalence of positive CAC in each of the three groups ($P < 0.05$ in each case). Compared with the control group, men and women with MS had higher levels of adiposity, blood pressure, non-HDL cholesterol, triglycerides, glucose, insulin, and C-reactive protein. Also, the group with MS plus FL had higher concentrations of aspartate aminotransferase, alanine aminotransferase, and γ -glutamyl transferase, as well as lower values of HDL-C. The most prevalent MS component in the MS and MS + FL groups was central obesity, followed by

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high values of triglycerides, glucose, and systolic and diastolic blood pressure and low levels of HDL-C.

The logistic regression analysis, adjusted for age, smoking, BMI, total cholesterol and C-reactive protein, showed that MS was associated with type 2 diabetes [women odds ratio 8.0 (95% CI 2.6–24.7); men 8.3 (2.7–25.4)]. This association was significantly higher in subjects with MS + FL [women 10.6 (3.4–33.7); men 12.1 (4.1–36.1)]. In addition, and despite the fact that MS alone was not found to be associated with CAC in either sex, the women with MS + FL had a higher probability of presenting CAC [2.34 (1.07–5.12)].

CONCLUSIONS—MS groups include metabolic disorders associated with insulin resistance and based on the lipotoxic hypothesis, which posits that the flow of free fatty acids from adipose tissue toward ectopic fat deposits can alter the via of the intrahepatic signaling of insulin (5,11), it is possible that the combination of MS + FL favors the development of type 2 diabetes. In accordance with this, the data from the current study indicate—for the first time—that FL significantly increases the association of MS with type 2 diabetes in both sexes, even after adjusting for traditional risk factors. These findings are supported by previous epidemiological and animal studies, showing that hepatic steatosis may favor the development of type 2 diabetes (5,11).

Our study shows that isolated MS is not independently associated with the presence of CAD. Consistent with findings of other studies, the prevalence of positive CAC was higher in men than in women (12). However, we found that FL significantly favored the association of MS with CAC only in women. Although the association of FL with CAC may be mediated by factors closely linked to FL, earlier data suggest that this association remains significant even after those factors are controlled for (13,14). Therefore, these results support the hypothesis that FL may be not only a marker but even a direct mediator of atherosclerosis in women with MS (15).

The cross-sectional nature of the GEA study does not enable us to identify causality as it relates to the effect of FL on the association of MS with type 2 diabetes and CAD. In addition, the sample included only subjects who were free of personal or family antecedents of premature CAD; thus, our results may not be applicable to

Table 1—Study population: characteristics by metabolic status

	Female (n = 398)				Male (n = 367)			
	Control	MS	MS + FL	P*	Control	MS	MS + FL	P*
n	245	84	69		184	89	94	
Age (years)	53 ± 10	57 ± 8†	55 ± 8	0.002	54 ± 11	55 ± 10	54 ± 9	N.S.
Waist circumference (cm)	87 ± 11	94 ± 9†	97 ± 8†	<0.001	93 ± 9	102 ± 10†	102 ± 8†	<0.001
BMI (kg/m ²)	26 (24–29)	29 (26–32)†	30 (28–32)†	<0.001	26 (24–28)	29 (27–31)†	29 (27–32)†	<0.001
SBP (mmHg)	111 ± 17	125 ± 22†	123 ± 18†	<0.001	119 ± 16	132 ± 19†	126 ± 18‡	<0.001
DBP (mmHg)	68 ± 8	73 ± 9†	75 ± 8†	<0.001	74 ± 9	81 ± 10†	79 ± 10†	<0.001
HDL-C (mmol/L)	1.42 (1.24–1.71)	1.06 (0.93–1.34)†	1.03 (0.91–1.29)†	<0.001	1.19 (0.98–1.40)	0.91 (0.83–1.11)†	0.93 (0.80–1.11)†	<0.001
Triglycerides (mmol/L)	1.31 (1.00–1.57)	2.21 (1.87–2.71)†	2.14 (1.80–2.54)†	<0.001	1.40 (1.05–1.83)	2.24 (1.85–3.34)†	2.28 (1.93–2.96)†	<0.001
Glucose (mmol/L)	4.8 (4.5–5.1)	5.5 (4.9–6.3)†	5.9 (5.2–6.6)†	<0.001	4.9 (4.7–5.2)	5.4 (4.9–6.1)†	5.7 (5.2–6.1)†	<0.001
Insulin (pmol/L)	86 (64–110)	118 (81–160)†	148 (116–197)‡	<0.001	83 (63–107)	122 (100–159)†	138 (107–169)†	<0.001
HOMA-IR	3.0 (2.2–4.2)	4.9 (3.3–7.7)†	6.8 (5.2–8.7)‡	<0.001	3.0 (2.2–4.1)	5.4 (3.7–7.2)†	5.7 (4.7–8.2)†	<0.001
L:SAR	1.20 (1.11–1.27)	1.16 (1.07–1.23)†	0.78 (0.64–0.89)‡	<0.001	1.16 (1.10–1.23)	1.14 (1.05–1.21)	0.80 (0.69–0.91)‡	<0.001
Type 2 diabetes (%)	2.0	16.7†	18.8†	<0.001	2.7	16.9†	21.3†	<0.001
Positive CAC (%)	10.7	19.0†	23.2†	0.015	43.5	46.1	51.1	<0.001
CRP (mmol/L)	12.4 (5.7–23.8)	27.6 (12.4–44.7)†	32.4 (17.1–49.5)†	<0.001	9.5 (6.7–18.6)	15.2 (9.5–22.8)	17.1 (9.5–33.3) ‡	<0.001
AST (units/L)	23.9 ± 9.3	26.7 ± 13.8	31.8 ± 14.5‡	<0.001	25.8 ± 8.4	27.8 ± 10.5	33.7 ± 15.7	<0.001
ALT (units/L)	20.4 ± 12.0	23.5 ± 12.1	36.1 ± 23.4‡	<0.001	23.9 ± 11.1	26.4 ± 15.0	40.6 ± 23.0‡	<0.001
GGT (units/L)	26.0 ± 30.2	30.5 ± 21.8	35.1 ± 20.1†	0.038	34.2 ± 27.4	48.0 ± 45.1	53.8 ± 39.7‡	<0.001

Data are means ± SD, median (interquartile range), or percent. AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, γ-glutamyl transferase; HOMA-IR, homeostasis model assessment of insulin resistance; L:SAR, liver-to-spleen attenuation ratio; SBP, systolic blood pressure. *P for trend using ANOVA for mean, Kruskal-Wallis for median, or X² for percent. †P < 0.05 vs. control group. ‡P < 0.05 vs. control and MS groups.

the general population. Finally, though we have no histological confirmation, FL can be easily diagnosed by computed tomography scan (8).

This study suggests that FL increases the strength of the association of MS with type 2 diabetes. Moreover, the combination FL + MS is independently associated with subclinical atherosclerosis in women.

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J.G.J.-R. conceived the project, researched data, contributed to discussion, and wrote the manuscript. A.X.M.-U. researched data, provided critical review and revision, and contributed to discussion. E.J.-G., C.G.-S., E.K.-H., G.C.-S., R.P.-S., and R.M.-A. researched data and contributed to discussion. C.P.-R. conceived the project, contributed to discussion, and provided critical review and revision. J.G.J.-R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Eckel RH. Mechanisms of the components of the metabolic syndrome that predispose to diabetes and atherosclerotic CVD. *Proc Nutr Soc* 2007;66:82–95
2. Ginsberg HN, MacCallum PR. The obesity, metabolic syndrome, and type 2 diabetes mellitus pandemic: Part I. Increased cardiovascular disease risk and the importance of atherogenic dyslipidemia in persons with the metabolic syndrome and type 2 diabetes mellitus. *J Cardiometab Syndr* 2009;4:113–119
3. Stern MP, Williams K, González-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care* 2004;27:2676–2681
4. Sundström J, Vallhagen E, Risérus U, et al. Risk associated with the metabolic syndrome versus the sum of its individual components. *Diabetes Care* 2006;29:1673–1674
5. Lattuada G, Ragogna F, Perseghin G. Why does NAFLD predict type 2 diabetes? *Curr Diab Rep* 2011;11:167–172
6. Alberti KG, Eckel RH, Grundy SM, et al.; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640–1645
7. American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care* 2010;33(Suppl. 1):S11–S61
8. Pantongrag-Brown L. Imaging of non-alcoholic fatty liver disease. *Thai Journal of Gastroenterology* 2010;11:118–122
9. McCollough CH, Ulzheimer S, Halliburton SS, Shanneik K, White RD, Kalender WA. Coronary artery calcium: a multi-institutional, multimanager international standard for quantification at cardiac CT. *Radiology* 2007;243:527–538
10. McKimmie RL, Daniel KR, Carr JJ, et al. Hepatic steatosis and subclinical cardiovascular disease in a cohort enriched for type 2 diabetes: the Diabetes Heart Study. *Am J Gastroenterol* 2008;103:3029–3035
11. Shyangdan D, Clar C, Ghouri N, et al. Insulin sensitizers in the treatment of non-alcoholic fatty liver disease: a systematic review. *Health Technol Assess* 2011;15:1–110
12. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2005;111:1313–1320
13. Brea A, Mosquera D, Martín E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. *Arterioscler Thromb Vasc Biol* 2005;25:1045–1050
14. Assy N, Djibre A, Farah R, Grosovski M, Marmor A. Presence of coronary plaques in patients with nonalcoholic fatty liver disease. *Radiology* 2010;254:393–400
15. Targher G, Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. *Atherosclerosis* 2007;191:235–240