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ORIGINAL ARTICLE

Histopathological differences in patients with biopsy-proven non-alcoholic fatty liver disease with and without type 2 diabetes

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KEYWORDS
Liver fibrosis;
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Abstract
Background and aims: Prevalence of non-alcoholic fatty liver disease (NAFLD) in developed countries is 30% in the general population and 50% in patients with type 2 diabetes mellitus (T2DM). The aim of this study was to compare the severity of NAFLD, as assessed by liver biopsy and using the non-invasive index NAFLD Fibrosis Score (NFS), in subjects with and without T2DM.
Patients and methods: The study sample consisted of 217 patients with biopsy-proven NAFLD. Anthropometric assessments, laboratory tests, histological criteria established by the Non-alcoholic Steatohepatitis Clinical Research Network (NASH CRN), and the NFS were recorded.
Results: Patients with T2DM ($n = 36$; 16.5%) had higher HOMA-IR values (6.3 ± 3.6 vs. 3.3 ± 2.4; $p < 0.0001$), GGT levels (125.2 ± 102.3 vs. 82.5 ± 70.6 IU/l; $p < 005$), and NFS index (-0.6 ± 0.2 vs. -1.8 ± 0.1; $p < 0.001$) than subjects with no T2DM. Patients with T2DM were found higher rates of NASH (72.2% vs. 48.6%; $p < 0.05$), advanced steatosis (80.6% vs. 63%; $p < 0.05$), and liver fibrosis (75% vs. 43.1%, $p < 0.05$) than patients with no T2DM. Patients with T2DM also had higher

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HOMA-IR, homeostatic model assessment insulin resistance; GGT, Gamma glutamyl transpeptidase; HDL-C, high density lipoprotein cholesterol; INR, international normalized ratio; IR, insulin resistance; LDL-C, low density lipoprotein cholesterol; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NAS, score non alcoholic steatohepatitis score; NASH, non-alcoholic steatohepatitis; NFS, NAFLD Fibrosis Score; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus; WC, waist circumference.

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NFS values (-0.6 ± 1.2 vs. -1.8 ± 1.8: $p = 0.01$). A logistic regression analysis adjusting for age, gender and BMI showed a significant independent association between NASH and presence of T2DM (OR = 4.2: 95% CI: 1.4–12.1; $p = 0.007$). A second model adjusting for the same covariates showed T2DM to be an independent factor associated to advanced fibrosis (OR = 4.1; 95% CI: 1.7–9.7).

Conclusion: Patients with T2DM have more advanced degrees of NAFLD and advanced fibrosis as assessed by liver biopsy and the NFS index. Particular attention should be paid to the study and monitoring of NASH in patients with T2DM.

PALABRAS CLAVE
Fibrosis hepática;
Enfermedad hepática no alcohólica;
Histopatología;
Diabetes mellitus tipo 2

Diferencias histopatológicas en pacientes con diabetes mellitus tipo 2 y no diabéticos con enfermedad hepática grasa no alcohólica diagnosticada con biopsia

Resumen

Antecedentes y objetivos: La prevalencia de la enfermedad hepática grasa no alcohólica (NAFLD) en los países desarrollados es del 30% de la población general y del 50% de los pacientes con diabetes mellitus tipo 2 (DM2). El objetivo de este estudio fue comparar la gravedad de NAFLD evaluado por biopsia hepática y con un índice no invasivo NAFLD Fibrosis Score (NFS) en sujetos con DM2 frente a pacientes no diabéticos.

Pacientes y métodos: Este estudio se llevó a cabo entre 217 pacientes con diagnostico mediante biopsia de NAFLD. Se registraron la valoración antropométrica, pruebas de laboratorio, criterios histológicos establecidos por la Red de Investigación Clínica de Esteatohepatitis No Alcohólica (NASH) y NFS.

Resultados: Los pacientes con DM2 (n = 36; 16,5%) tuvieron más HOMA-IR ($6,3 \pm 3,6$ vs. $3,3 \pm 2,4$; $p < 0,0001$), GGT ($125,2 \pm 102,3$ vs. $82,5 \pm 70,6$ UI/L); $p < 0,05$) e índice NFS ($-0,6 \pm 0,2$ vs. $-1,8 \pm 0,1$; $p < 0,001$) que los sujetos sin DM2. Los pacientes con DM2 presentaron mayor porcentaje de EHNA (72,2 vs. 48,6%; $p < 0,05$), grado avanzado de esteatosis (80,6 vs. 63%; $p < 0,05$) y fibrosis hepática (75 vs. 43,1%; $p < 0,05$) que los pacientes sin DM2. Los pacientes con DM2 presentaron también valores más altos de NFS ($-0,6 \pm 1,2$ vs. $-1,8 \pm 1,8$; $p = 0,01$). El análisis de regresión logística ajustado por edad, sexo e IMC mostró asociación significativa independiente entre la esteatohepatitis y la presencia de DM2 (OR = 4,2; IC 95%: 1,4-12,1; $p = 0,007$). Un segundo modelo ajustado por las mismas covariables mostró que la DM2 fue un factor independiente asociado a la fibrosis avanzada (OR = 4,1; IC 95%: 1,7-9,7).

Conclusión: Los pacientes con DM2 tienen grados más avanzados de NAFLD y fibrosis avanzada evaluados mediante biopsia hepática y el índice NFS. Debe prestarse especial atención al estudio y seguimiento de la esteatohepatitis en pacientes con DM2.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome.[1] The spectrum of NAFLD severity is variable, ranging from mild symptoms to different degrees of inflammation, non alcoholic steatohepatitis (NASH), or a severe form of decompensated liver cirrhosis which occurs in a minority of patients.[2] The prevalence of the NAFLD in developed countries is up to 30% for the general population, 50% in patients with type 2 diabetes mellitus (T2DM), 76% in obese people and almost 100% in patients with morbid obesity[3] but prevalence is influenced by the diagnostic criteria used.[4]

The link between NAFLD and obesity, concurrent hypertension and dyslipidemia is not surprising and it has been well characterized in diabetic populations worldwide. The key pathogenesis of this association is related to insulin resistance.[5,6]

In addition to genetic predisposition, lifestyle changes and dietary habits increase the prevalence of obesity, diabetes mellitus, metabolic syndrome, cardiovascular disease and NAFLD. Insulin resistance plays a dominant role in the pathogenesis of NAFLD.[7] Data from the 698 patients, obtained within 6 months of liver biopsies, showed that patients with definite NASH were more likely to be female and diabetics and these patients had higher levels of AST, ALT, alkaline phosphatase, GGT and HOMA-IR.[8]

Mortality of NAFLD patients with T2DM is three times higher compared with nondiabetic NAFLD patients.[9] T2DM plays an important role in the pathogenesis and evolution of NAFLD, and it is included in the majority of non-invasive composite predictive scores for NASH and advanced