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High prevalence of undiagnosed liver cirrhosis and advanced fibrosis in type 2 diabetic patients

Juan P. Arab,* Francisco Barrera,* Consuelo Gallego,† Juan P. Valderas,† Sergio Uribe,‡ Cristian Tejos,‖ Cristóbal Serrano,‡ Álvaro Huete,‡ Jessica Liberona,† Pilar Labbé,* Teresa Quiroga,§ Carlos Benítez,* Pablo Irarrázaval,‖ Arnoldo Riquelme,* Marco Arrese*

Departamento de * Gastroenterología, † Nutrición, ‡ Radiología, § Laboratorio Clínico, ‖ Escuela de Medicina and Departamento de Ingeniería Eléctrica, Escuela de Ingeniería, Pontificia Universidad Católica de Chile, Santiago, Chile.

ABSTRACT

Background. Patients with type 2 diabetes mellitus (T2DM) are at risk for developing end-stage liver disease due to nonalcoholic steatohepatitis (NASH), the aggressive form of non-alcoholic fatty liver disease (NAFLD). Data on prevalence of advanced fibrosis among T2DM patients is scarce. **Aim.** To evaluate prevalence of steatosis, advanced fibrosis and cirrhosis using non-invasive methods in T2DM patients. **Material and methods.** 145 consecutive T2DM patients (> 55 years-old) were prospectively recruited. Presence of cirrhosis and advanced fibrosis was evaluated by magnetic resonance imaging (MRI) and NAFLD fibrosis score (NFS) respectively. Exclusion criteria included significant alcohol consumption, markers of viral hepatitis infection or other liver diseases. Results are expressed in percentage or median (interquartile range). **Results.** 52.6% of patients were women, the median age was 60 years old (57-64), mean BMI was 29.6 ± 4.7 kg/m^2 and diabetes duration was 7.6 ± 6.9 years. A high prevalence of liver steatosis (63.9%), advanced fibrosis assessed by NFS (12.8%) and evidence of liver cirrhosis in MRI (6.0%) was observed. In a multivariate analysis GGT > 82 IU/L (P = 0.004) and no alcohol intake (P = 0.032) were independently associated to advanced fibrosis. **Conclusion.** A high frequency of undiagnosed advanced fibrosis and cirrhosis was observed in non-selected T2DM patients. Screening of these conditions may be warranted in this patient population.

Key words. NAFLD. NASH. Fibrosis. Diabetes. Insulin resistance. Obesity. Metabolic Syndrome. Mortality.

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic diseases, with an estimated prevalence of 8.3% of the world's adult population and currently represent the 7th leading cause of death in the United States,[1] which represent a significant health burden due to diabetes-associated complications. Liver disease is a relevant cause of morbidity and mortality in type 2 diabetes mellitus (T2DM).[2] Diabetic patients are at higher risk of developing cirrhosis and liver failure.[3] However liver disease remains a neglected end organ complication of diabetes.

Chronic liver disease in T2DM patients is mostly attributable to Non-Alcoholic Fatty Liver Disease (NAFLD).[4] NAFLD refers to a clinicopathological entity that comprehends a liver disease spectrum spanning from bland hepatic steatosis to non-alcoholic steatohepatitis (NASH) with the latter being a more aggressive form of the disease which ultimately leads to fibrosis, cirrhosis and hepatocellular carcinoma (HCC).[5] The estimated prevalence of NAFLD in T2DM patients ranges between 42-70% in ultrasound-based large scale population studies[6] which doubles the NAFLD prevalence figures found in the general population.[5] Moreover, T2DM is a strong predictor of the presence of NASH and liver fibrosis in NAFLD patients.[7] Even diabetic subjects with normal aminotransferases exhibit a high prevalence NAFLD and NASH (76% and 56% respectively) as recently shown by Portillo-Sánchez, *et al*.[8] Thus, T2DM patients seem to have higher prevalence and severity of NAFLD.[9]

In the NAFLD field, the identification of patients with advanced fibrosis or cirrhosis has been focus of intense research. Although liver biopsy is still the gold standard for NASH and liver fibrosis diagnosis, the associated costs and

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potential adverse events precludes its use as a surveillance method to detect NAFLD in general population.[10] A wide number of non-invasive biomarkers have been validated for assessing the severity of liver fibrosis in NAFLD.[11] One of the most extensively validated scores is the NAFLD fibrosis score (NFS), which accurately predicts NAFLD patients with advanced fibrosis[12,13] and is recommended for non-invasive assessment in current AASLD and EASL guidelines.[11,14] A metanalysis of thirteen studies (n = 3064) estimated the AUROC, sensitivity and specificity of NFS on predicting advanced fibrosis was 0.85 (0.80-0.93), 0.90 (0.82-0.99) and 0.97 (0.94-0.99).[15] NFS has also been validated in Latin-American population.[16]

The diagnosis of advanced liver fibrosis and cirrhosis in T2DM patients has important implications, since it enables high-risk patients to undergo esophageal varices and HCC surveillance. However, data on the prevalence of advanced liver disease in T2DM is still scarce. Therefore, the aim of this study was to assess the frequency of advanced liver disease among T2DM patients using non-invasive surveillance approach. For this purpose we evaluated the prevalence of steatosis, advanced fibrosis and cirrhosis in an otherwise unselected > 55 years-old T2DM patients population using the NFS and magnetic resonance imaging (MRI).

MATERIAL AND METHODS

Patient population

We asked for diabetologists and family physicians to invite their diabetic patients older than 55 years old for liver disease surveillance assessment. After referral, patients were evaluated by our team and enrolled if they met the following inclusion criteria:

- Presence of type 2 diabetes mellitus.
- Being > 55 years-old.
- No history of liver disease.
- Alcohol consumption < 20 g/day in women and < 30 g/day in men.
- No use of hepatotoxic drugs (over 4 g/day of acetaminophen, methotrexate, nitrofurantoin, and rifampicin).
- Agree and sign the informed consent form in agreement with the ethical guidelines of the 1975 Declaration of Helsinki.

The study was approved by the Pontificia Universidad Católica de Chile Human Research Committee.

Clinical examination and liver assessment

For all patients, clinical and biochemical parameters were determined at baseline. Clinical parameters included height and weight measurements, body mass index (BMI), blood pressure, hypertension and dyslipidemia history, alcohol use (g/day), duration of diabetes, relatives with diabetes, microvascular complications (retinopathy, nephropathy and neuropathy), and macrovascular complications (myocardial infarction, stroke or revascularization). Alcohol consumption was estimated by an experienced interviewer (Physician, MSc Clinical nutrition), who estimated it based on alcohol degrees (percentage of alcohol per total volume) and amount of alcohol consumed. Subjects that consumed one drink per month or less were considered as no alcohol drinkers.

Biochemical parameters measured included the following: liver chemistry (including serum levels of aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, gamma-glutamyl transpeptidase [GGT] and total bilirubin), fasting glucose, fasting serum insulin, glycated hemoglobin A1c (HbA1c), lipid profile and complete blood count. On insulin requiring patients, fasting serum insulin was not measured. Homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated according to the standard formula.[8]

NFS was calculated as described in Angulo, *et al.*[12] Anthropometry was assessment was also included (height, weight and waist circumference). Metabolic syndrome was diagnosed based on ATP III criteria.[17] All patients had no markers of infection by hepatitis B or C viruses.

Magnetic resonance imaging were performed using a Philips Intera® 1.5T system (Achieva, Philips, Best, The Netherlands). The MR protocol included the following sequences: T2 with fat saturation, T1 gradient echo, half-Fourier single-shot turbo spin echo, in-phase and out-of phase sequences. Liver steatosis was graduated in MRI using a gradient echo sequence employing the IDEAL method[18] and categorized as it follows: 1: mild, 2: moderate and 3: severe.

The presence of liver cirrhosis in MRI was assessed using conventional morphological criteria such as enlarged caudate lobe and left lobe lateral segment (segments II and III) with concomitant atrophy of the posterior segments (VI and VII) of the right lobe, enlargement of hiliar portal space, nodular surface of the liver and increased spleen diameter.[19-21] Liver biopsy was offered to selected patients based on current recommendations.[22,23]

Based on the available data patients were classified in one of the following categories:

- No evidence of liver disease.
- As having steatosis if steatosis was present on imaging studies .

- As having advanced liver fibrosis if the NFS value was over 0,675.
- As having cirrhosis based on the liver morphology on MRI.

Data analysis

Clinical and biochemical variables are presented as mean ± standard deviation (SD) for continuous data with normal distribution. Median (Q1-Q3) for those variables without normal distribution and as percentage for categorical data. Clinical data were analyzed employing χ^2 test for categorical variables and Student *t*-test for continuous variables following a normal distribution. Variables without normal distribution were analyzed by using Mann-Whitney *U* test. Receiver-operating characteristic (ROC) curves were used to obtain a cut-off value when the area under the curve was larger than 60%. Based on ROC curve cut-off values, continuous variables were transformed into discrete ones. Univariate and multivariate analyses were performed. Potential clinical and biochemical variables associated with advanced liver fibrosis were examined by comparing the means and proportions of variables among people with or without advanced liver fibrosis. To study these relationships further, univariate analysis was performed using χ^2 test for categorical variables and Student *t*-test for continuous variables. In order to identify independent variables associated with advanced liver fibrosis, a stepwise procedure for a multivariate logistic regression analysis was conducted, which included variables that appeared significant in univariate analysis. Log transformation was performed for variables not normally distributed. Variables involved in the estimation of NFS were excluded to avoid multicollinearity. The χ trend test was performed to evaluate possible statistical tendencies for the additive value of variables found to be significant in multivariate analysis. Analyses were performed using IBM SPSS Statistics 20 version software (Chicago, IL). Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Differences were considered significant when P-values < 0.05.

RESULTS

General features of patients

A total of 145 patients were enrolled between March 2011 and April 2014. One hundred thirty-six patients agreed to undergo an abdomen MRI and were evaluated for anthropometry, clinical and laboratory measurements. Three patients did not attend to MRI evaluation; hence 133 patients underwent MRI assessment. The general features of enrolled patients are shown in table 1. 52.6% were women, the median age was 60 years old (57-64), the mean BMI was 29.6 ± 4.7 kg/m^2, the mean diabetes duration since diagnosis was 7.6 ± 6.9 years and the median HbA1c levels was 6.9% (6.3-7.9) [52 mmol/mol (45-63)]. Of note, 66.7% of patients met the criteria for metabolic syndrome, 10.5% had history of macrovascular complications, and the median HOMA-IR was 3.9 (2.7-6.2).

Table 1. General features of enrolled patients.

	n = 133
Age, years	60 (57- 64)
Male, n (%)	63 (47.4)
Dyslipidemia, n (%)	67 (50.4)
Waist circumference (cm)	
Male	99.2 ± 10
Female	98.5 ± 11
Metabolic syndrome, n (%)	89 (66.7)
Number first relative with diabetes, n (%)	
0	37 (27.8)
1	57 (42.9)
> 2	39 (29.3)
Years of diabetes diagnosis	7.6 ± 6.9
Daily alcohol, g/day	
Male	5 (0- 14)
Female	0 (0- 2.5)
Retinopathy history, n (%)	18 (13.5)
Nephropathy history, n (%)	8 (6.0)
Neuropathy history, n (%)	17 (12.8)
Macrovascular complications, n (%)	14 (10.5)
AST (IU/L)	21 (17- 27.5)
ALT (IU/L)	25 (19- 39)
GGT (IU/L)	27 (19- 47.5)
Total bilirubin (mg/dL)	0.52 (0.43- 0.69)
Alkaline Phosphatase (IU/L)	84 (69- 103)
A lbumin (g/dL)	4.5 (4.3- 4.7)
LDL cholesterol (mg/dL)	90.8 (67- 110.5)
HDL cholesterol (mg/dL)	46.5 (40- 54.8)
Triglycerides (mg/dL)	141 (105- 204.8)
Glycated hemoglobin A1c, % [mmol/mol]	6.9 (6.3- 7.9) [52 (45-63)]
Platelet count, x 10^9/L	227 (187- 267)
Hematocrit (%)	41.3 ± 3.6
White blood cell count (/mm^3)	6,857 ± 1,421
Creatinine (mg/dL)	0.8 (0.68- 0.97)
Urine albumin/creatinine ratio (µg/mg)	7.3 (3.8- 17.8)
HOMA-IR	3.9 (2.7- 6.2)
Body mass index (BMI), (kg/m^2)	29.6 ± 4.7
NAFLD fibrosis score (NFS) > 0.675(F3-4), n (%)	17 (12.8)

AST: aspartate aminotransferase. ALT: alanine aminotransferase. GGT: gamma-glutamyl transferase. LDL: low-density lipoprotein. HDL: high-density lipoprotein. HOMA-IR: Homeostasis Model Assessment of Insulin Resistance. Results are expressed in median (interquartile range) for variables with abnormal distribution and average ± standard deviation for variables with normal distribution.

Prevalence of liver disease

Of the 133 patients studied 43 (32.3%) showed no evidence of liver disease. Ninety-three patients had abnormal findings including 85 (63.9%) with radiological steatosis and 8 (6.0%) with evidence of cirrhosis in the abdominal MRI. Seventeen patients (12.8%) of the group had a NFS > 0.675 suggesting the presence of advanced liver fibrosis. Only one subject agreed to have liver biopsy because of persistently elevated liver tests. She was classified as liver steatosis without cirrhosis on MRI analysis and advanced fibrosis by NFS on non-invasive assessment. Liver biopsy demonstrated NASH with stage 3 fibrosis .

Variables associated to advanced liver fibrosis

Variables associated to advanced liver fibrosis or cirrhosis in a univariate analysis are shown in table 2. Daily alcohol consumption, serum levels of GGT, platelet count and albumin were associated with the presence of advanced liver disease. Notably, when a cut off on GGT level was established we were able to improve its discriminative power (AUC 0.728, 95% CI 0.604-0.852, p = 0.002, sensibility 35%, specificity 93%) (Table 2). A multivariate analysis showed that a GGT > 82 IU/L and no alcohol consumption were independently related to advanced fibrosis, as is shown in table 3.

DISCUSSION

The issue of detecting liver disease in diabetics is relevant since cirrhosis is a significant cause of morbidity and mortality in this patient population[3] and this end-organ damage is frequently overlooked in the primary care setting.[24] In the present study we used a non-invasive surveillance approach for detecting liver disease in unselected diabetic patients older than 55 years-old. Considering our inclusion criteria, liver alterations found in our assessment are more likely to be related to NAFLD.[25]

Table 2. Variables associated to advanced liver fibrosis. Univariate analysis.

	Advanced fibrosis (n = 17)	Absence of advanced fibrosis (n = 116)	p
Age	62 (58 - 68.5)	60 (57- 64)	0.103[a]
Male, n (%)	6 (35.3)	57 (49.1)	0.286[b]
Hypertension, n (%)	13 (76.5)	67 (57.8)	0.141[b]
Dyslipidemia, n (%)	8 (47.1)	59 (50.9)	0.770[b]
Waist circumference	103.6 ± 8.1	98.1 ± 10.6	0.076[c]
Metabolic syndrome, n (%)	12 (70.5)	77 (66.3)	0.835[b]
Number first relative with diabetes	1 (1- 3)	1 (0 - 2)	0.267[a]
Years of diabetes diagnosis	9 (4- 16.5)	5 (2 - 10)	0.1[a]
Daily alcohol (g/day)	0 (0- 0)	1.5 (0 - 10)	**0.011[a]**
No alcohol consumption, n (%)	14 (82.4)	57 (49.1)	**0.01[b]**
Retinopathy history, n (%)	1 (6.2)	17 (14.7)	0.358[b]
Nephropathy history, n (%)	1 (6.2)	7 (6.0)	0.973[b]
Neuropathy history, n (%)	3 (17.6)	14 (12.1)	0.455[b]
Macrovascular complications, n (%)	2 (11.7)	12 (10.3)	0.793[b]
GGT (IU/L)	37 (31- 135)	26 (18 - 45.8)	**0.003[a]**
GGT > 82 IU/L, n (%)	6 (35.3)	8 (6.9)	**0.0004[a]**
Total bilirubin (mg/dL)	0.53 (0.43 - 0.62)	0.51 (0.43 - 0.70)	0.584[a]
Alkaline phosphatase (IU/L)	91 (76.5 - 107.5)	83.5 (68.3 - 101.8)	0.262[a]
LDL cholesterol (mg/dL)	96 (79.5 - 108.5)	87 (66 - 113)	0.622[a]
HDL cholesterol (mg/dL)	47 (42.5 - 56.5)	45 (39 - 54)	0.471[a]
Triglycerides (mg/dL)	144 (136.5 - 207.5)	136 (103 - 205)	0.407[a]
Glycated hemoglobin A1c (%)	6.3 (6.1 - 7.1)	7 (6.3- 8)	0.072[a]
Hematocrit (%)	41.2 ± 4.7	41.5 ± 3.5	0.754[c]
White blood cell count (/mm^3)	6,611 ± 1,287	6,829 ± 1,374	0.538[c]
Platelet count, x 10^9/L	192 (143.5 - 211.5)	234.5 (191.3 - 269.8)	**0.001[a]**
Albumin (g/dL)	4.4 (4.2 - 4.4)	4.5 (4.4 - 4.7)	**0.001[a]**
Creatinine (mg/dL)	0.72 (0.62 - 0.91)	0.81 (0.68 - 0.97)	0.142[a]
Urine albumin/creatinine ratio (µg/mg)	8.8 (4.2 - 21.6)	6.9 (3.7 - 17.6)	0.458[a]
$HOMA_{IR}$	5.6 (3.1 - 7.1)	3.8 (2.6 - 5.9)	0.283[a]
% fat hepatic content	40.7 (33.2 - 45.7)	36.4 (30.1 - 41.9)	0.209[a]

GGT: gamma-glutamyl transferase. LDL: low-density lipoprotein. HDL: high-density lipoprotein. HOMA-IR: Homeostasis Model Assessment of Insulin Resistance. p-value obtained by: [a] Mann-Whitney U test; [b] χ^2; [c] t-Student.

Table 3. Variables associated to advanced liver fibrosis. Multivariate analysis.

	OR	95% Confidence interval	p
GGT > 82 IU/L	6.4	1.8-22.9	**0.004**
No alcohol consumption	4.3	1.1-16.3	**0.032**

GGT: gamma-glutamyl transferase.

The frequency of steatosis (63.9%) see in our T2DM patients is similar to figures found in two recent reports conducted in primary care setting that used magnetic resonance spectroscopy and MRI assessment respectively.[8,26] Previous data on NAFLD prevalence in diabetic patients is mostly ultrasound-based and included patients of different ages.[27] In our study we selected T2DM patients with > 55 years old, and used an MRI based diagnosis of steatosis which is a more sensitive diagnostic test. Hence, the prevalence of NAFLD was within the higher end of previous reports and in agreement with the recent report by Doycheva, *et al.*[26] (65%) that used MRI for steatosis assessment. A more recent report that screened diabetic patients using a novel ultrasound-based technique (controlled attenuation parameter) to detect NAFLD found that 72.8% of subjects had evidence of steatosis, which is also consistent with our findings.[28] Noteworthy, we found a significant proportion of diabetic patients with evidence of advanced liver disease including those with significant liver fibrosis (12.8%) and undiagnosed liver cirrhosis (6.0%). These figures are also in agreement with the recent report by Doycheva, *et al.* that enrolled 100 consecutive patients with T2DM (mean age 59.7 and BMI 30.8 kg/m^2 without liver disease) and found that advanced liver fibrosis (as assessed by MRI elastography) in 7.1% of their patients[26] and with the report by Kwok, *et al.* that, using liver stiffness measurements, found that 17.7% of diabetics had significant liver fibrosis.[28] When compared with the general population, the frequency of advanced liver fibrosis (significant fibrosis and cirrhosis) in T2DM patients seems to be significantly higher although the information on prevalence of, and variables associated with, liver fibrosis in general population is scarce. Some authors have roughly estimated the prevalence of liver cirrhosis in 1% of the general population using transient elastography based diagnosis,[29] but data is limited. The recent study of Koehler, *et al.,*[30] a population-based study among subjects > 45 years, found a 5.6% of the individuals with clinically relevant liver fibrosis assessed by liver stiffness measurement. Interestingly, in this study diabetes was strongly associated with liver fibrosis confirming that this subgroup of individuals is at risk of liver disease. Collectively, the available data including that of the present study, give support to the concept that advanced liver disease, likely secondary to progressive NAFLD, is an important and under-recognized condition in T2DM patients and that awareness about this issue among health care providers of diabetic patients should be improved in order to increase the detection of patients at risk of developing or having liver fibrosis/cirrhosis and prevent their complications.

In our study, the multivariate analysis showed that serum levels of GGT and absence of alcohol consumption were independently associated with advanced fibrosis assessed by NFS. The association between liver fibrosis and elevated GGT is in line with prior studies.[31-33] Hence, serum levels of GGT may have value in detecting significant fibrosis in diabetic subjects. As for the potential protective role of moderate alcohol intake in NAFLD, this has been previously reported in non-diabetic subjects.[34-38] The mechanisms that explain this protective effect of alcohol consumption on NAFLD are unknown; however, it can be related to the anti-oxidant effects of some alcoholic beverages, such as red wine, that can reduce reactive oxygen species and reduce cell damage in the setting of NASH. Patients who consume alcohol have increased circulating adiponectin, which has a protective role in NAFLD mediated through adenosine monophosphate-activated protein kinase and peroxisome proliferator-activated receptor a enhanced by activation of adiponectin receptor 2 in hepatocytes.[39] Importantly, we do not recommend to promote drinking habits in NAFLD patients (evidence 1B, AASLD guidelines), however there is no evidence to completely stop alcohol in NAFLD patients with non-significant drinking habits as our data support a potential protective effect.

As in previous reports, the main limitation of the present study is the absence of liver histology assessment. Since many patients and physicians are reluctant to perform or undergo liver biopsy due to associated health costs and potential adverse events, this study was designed to use a non-invasive approach to determine the prevalence of liver disease and cirrhosis in unselected diabetic patients older than 55 years-old taken into account the fact that liver fibrosis increases with age in NAFLD, which has been recently shown also in diabetics.[26] Regarding liver fibrosis, we used the most exten-

sively validated score (NFS), recommended in most of current guidelines NAFLD for non-invasive liver fibrosis assessment.[10,40] However data on validation of these scores in diabetic population is scarce and there is no consensus in cut-off values. In addition, 75 subjects presented indeterminate NFS, many of them might present advanced fibrosis if they undergo histology assessment. Based on these facts, we believe our surveillance approach is likely to underestimate the prevalence of advanced liver fibrosis. Regarding liver cirrhosis diagnosis, we selected the morphological features that have been described to have a high sensitivity (87-93%) and specificity (92%) for cirrhosis diagnosis.[20,21] Another limitation of our study is the possibility of selection bias on the referral; however patients were consecutively invited directly on diabetes and family medicine clinics and referred to our team. In spite of the limitations of our non-invasive diagnosis, we observed that our estimate of advanced liver disease (12.8% of significant fibrosis plus 6% cirrhosis) is in agreement with findings using other techniques such as MRI elastography[26] and vibration controlled transient elastography.[28]

Current diabetes society guidelines[41] do not provide specific recommendations for liver assessment in diabetic patients. We believe that our data and that of other recent studies[26,28] strongly suggest that patients with T2DM may benefit from screening of liver fibrosis.[24] The early diagnosis of significant fibrosis would give the opportunity for lifestyle and pharmacologic intervention to prevent further progression of liver disease which would be meaningful in the context of emerging therapies for NAFLD.[42] However, even more important is the early diagnosis of liver cirrhosis, since patients with this condition would benefit of esophageal varices and HCC surveillance. Timely diagnosis will enable the implementation of primary prophylaxis for variceal bleeding and/or curative treatment for early HCC if detected. The best strategy to screen T2DM for liver fibrosis remains to be established but current non-invasive tests for evaluation of liver disease severity and prognosis guidelines suggest that NFS and transient elastography are good options.[11] Further research is needed to confirm the cost-effectiveness of this approach and to better define both the natural history of NAFLD in T2DM and the effect of novel treatments on it.

CONCLUSION

The present study shows that T2DM patients have significant rates of NAFLD, advanced liver fibrosis and cirrhosis. Screening of these conditions using non-invasive tests may be warranted after validation in larger prospective studies.

ABBREVIATIONS

- **ALT:** alanine aminotransferase.
- **AST:** aspartate aminotransferase.
- **BMI:** body mass index.
- **GGT:** gamma-glutamyl transpeptidase.
- **HCC:** hepatocellular carcinoma.
- **MRI:** magnetic resonance imaging.
- **NAFLD:** Non-Alcoholic Fatty Liver Disease.
- **NASH:** Non-Alcoholic Steatohepatitis.
- **NFS:** NAFLD fibrosis score.
- **ROC:** receiver-operating characteristic.
- **T2DM:** type 2 diabetes mellitus.

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CONFLICT OF INTERESTS

Authors have no relevant conflict of interest to disclose.

REFERENCES

1. Ng CS, Lee JY, Toh MP, Ko Y. Cost-of-illness studies of diabetes mellitus: a systematic review. *Diabetes Res Clin Pract* 2014; 105: 151-63.
2. Bhatt HB, Smith RJ. Fatty liver disease in diabetes mellitus. *Hepatobiliary Surg Nutr* 2015; 4: 101-8.
3. Porepa L, Ray JG, Sanchez-Romeu P, Booth GL. Newly diagnosed diabetes mellitus as a risk factor for serious liver disease. *CMAJ* 2010; 182: E526-E531.
4. Smith BW, Adams LA. Nonalcoholic fatty liver disease and diabetes mellitus: pathogenesis and treatment. *Nat Rev Endocrinol* 2011; 7: 456-65.
5. Satapathy SK, Sanyal AJ. Epidemiology and Natural History of Nonalcoholic Fatty Liver Disease. *Semin Liver Dis* 2015; 35: 221-35.
6. Williamson RM, Price JF, Glancy S, Perry E, Nee LD, Hayes PC, Frier BM, et al. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes Care* 2011; 34: 1139-44.
7. Doycheva I, Patel N, Peterson M, Loomba R. Prognostic implication of liver histology in patients with nonalcoholic fatty liver disease in diabetes. *J Diabetes Complications* 2013; 27: 293-300.
8. Portillo Sanchez P, Bril F, Maximos M, Lomonaco R, Biernacki D, Orsak B, Subbarayan S, et al. High prevalence of

nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. *J Clin Endocrinol Metab* 2015; 100: 2231-8.
9. Marra F, Lotersztajn S. Pathophysiology of NASH: perspectives for a targeted treatment. *Curr Pharm Des* 2013; 19: 5250-69.
10. Nascimbeni F, Pais R, Bellentani S, Day CP, Ratziu V, Loria P, Lonardo A. From NAFLD in clinical practice to answers from guidelines. *J Hepatol* 2013; 59: 859-71.
11. European Association for Study of the Liver, Asociación Latinoamericana para el Estudio del Hígado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015; 63: 237-64.
12. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007; 45: 846-54.
13. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015; 149: 389-397 e310.
14. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; 55: 2005-23.
15. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med* 2011; 43: 617-49.
16. Pérez-Gutiérrez OZ, Hernández-Rocha C, Candia-Balboa RA, Arrese MA, Benítez C, Brizuela-Alcántara DC, Méndez-Sánchez N, et al. Validation study of systems for noninvasive diagnosis of fibrosis in nonalcoholic fatty liver disease in Latin population. *Ann Hepatol* 2013; 12: 416-24.
17. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C, American Heart A, National Heart L, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109: 433-8.
18. Reeder SB, McKenzie CA, Pineda AR, Yu H, Shimakawa A, Brau AC, Hargreaves BA, et al. Water-fat separation with IDEAL gradient-echo imaging. *J Magn Reson Imaging* 2007; 25: 644-52.
19. Yeom SK, Lee CH, Cha SH, Park CM. Prediction of liver cirrhosis, using diagnostic imaging tools. *World J Hepatol* 2015; 7: 2069-79.
20. Ito K, Mitchell DG, Gabata T. Enlargement of hilar periportal space: a sign of early cirrhosis at MR imaging. *J Magn Reson Imaging* 2000; 11: 136-40.
21. Numminen K, Tervahartiala P, Halavaara J, Isoniemi H, Hockerstedt K. Non-invasive diagnosis of liver cirrhosis: magnetic resonance imaging presents special features. *Scand J Gastroenterol* 2005; 40: 76-82.
22. Spengler EK, Loomba R. Recommendations for diagnosis, referral for liver biopsy, and treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Mayo Clin Proc* 2015; 90: 1233-46.
23. Stinton LM, Loomba R. Recommendations for liver biopsy evaluation in non-alcoholic fatty liver disease. *Minerva Gastroenterol Dietol* 2014; 60: 5-13.
24. Arrese M, Arab JP, Arancibia JP, Candia R, Riquelme A, Barrera F. Liver disease: A neglected complication of diabetes mellitus. In: Bagchi D, Sreejayan N (Eds.). Nutritional and therapeutic interventions for diabetes and metabolic syndrome. New York: Academic Press; 2012, p. 289-94.
25. Yri-Järvinen H. Diagnosis of non-alcoholic fatty liver disease (NAFLD). *Diabetologia* 2016, 59:1104-11.
26. Doycheva I, Cui J, Nguyen P, Costa EA, Hooker J, Hofflich H, Bettencourt R, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. *Aliment Pharmacol Ther* 2016; 43: 83-95.
27. Arrese M. Nonalcoholic fatty liver disease: liver disease: an overlooked complication of diabetes mellitus. *Nat Rev Endocrinol* 2010; 6: 660-1.
28. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, Shu SS, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. *Gut* 2015.
29. Castera L. Screening the general population for cirrhosis using transient elastography: finding a needle in a haystack? *Gut* 2011; 60: 883-4.
30. Koehler EM, Plompen EP, Schouten JN, Hansen BE, Darwish Murad S, Taimr P, Leebeek FW, et al. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: The Rotterdam study. *Hepatology* 2015.
31. Leite NC, Villela-Nogueira CA, Pannain VL, Bottino AC, Rezende GF, Cardoso CR, Salles GF. Histopathological stages of nonalcoholic fatty liver disease in type 2 diabetes: prevalences and correlated factors. *Liver Int* 2011; 31: 700-6.
32. Tahan V, Canbakan B, Balci H, Dane F, Akin H, Can G, Hatemi I, et al. Serum gamma-glutamyltranspeptidase distinguishes non-alcoholic fatty liver disease at high risk. *Hepatogastroenterology* 2008; 55: 1433-8.
33. Junior WS, Nonino-Borges CB. Clinical predictors of different grades of nonalcoholic fatty liver disease. *Obes Surg* 2012; 22: 248-52.
34. Hashimoto Y, Hamaguchi M, Kojima T, Ohshima Y, Ohbora A, Kato T, Nakamura N, et al. The modest alcohol consumption reduces the incidence of fatty liver in men; a population based large scale cohort study. *J Gastroenterol Hepatol* 2014.
35. Moriya A, Iwasaki Y, Ohguchi S, Kayashima E, Mitsumune T, Taniguchi H, Ikeda F, et al. Alcohol consumption appears to protect against non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2011; 33: 378-88.
36. Dunn W, Sanyal AJ, Brunt EM, Unalp-Arida A, Donohue M, McCullough AJ, Schwimmer JB. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). *J Hepatol* 2012; 57: 384-91.
37. Moriya A, Iwasaki Y, Ohguchi S, Kayashima E, Mitsumune T, Taniguchi H, Ando M, et al. Roles of alcohol consumption in fatty liver: a longitudinal study. *J Hepatol* 2014.
38. Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. *Hepatology* 2008; 47: 1947-54.
39. You M, Considine RV, Leone TC, Kelly DP, Crabb DW. Role of adiponectin in the protective action of dietary saturated fat against alcoholic fatty liver in mice. *Hepatology* 2005; 42: 568-77.
40. Arab JP, Candia R, Zapata R, Munoz C, Arancibia JP, Poniachik J, Soza A, et al. Management of nonalcoholic fatty liver disease: an evidence-based clinical practice review. *World J Gastroenterol* 2014; 20: 12182-201.
41. American Diabetes A. Standards of medical care in diabetes–2014. *Diab Care* 2014; 37(Suppl. 1): S14-S80.
42. Gawrieh S, Chalasani N. Pharmacotherapy for Nonalcoholic Fatty Liver Disease. *Semin Liver Dis* 2015; 35: 338-48.

Correspondence and reprint request:

Marco Arrese, M.D.
Departamento de Gastroenterología, Facultad de Medicina,
Pontificia Universidad Católica de Chile
Marcoleta, No. 367. 833-0024, Santiago, Chile
Tel. and Fax: 56-2-26397780
E-mail: marrese@med.puc.cl