Factors Associated With Advanced Liver Fibrosis in a Population With Type 2 Diabetes: A Multicentric Study in Mexico City

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Background and objectives: **Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major cause of chronic liver disease, primarily due to insulin resistance and type 2 diabetes (T2D). Despite the strong link between T2D and MASLD, identifying and treating liver fibrosis in T2D patients is still poor. This study aimed to identify the factors related to advanced liver fibrosis in T2D patients.** ***Methods:*** **This retrospective observational study used medical records from four centers in Mexico City from 2018 to 2023. The study included 2000 patients with T2D. Liver fibrosis was evaluated using the Fibrosis-4 (FIB-4) index, and insulin resistance was assessed using the estimated glucose disposal rate (eGDR).** ***Results:*** **The mean age of the patients was 58.9 years, with 63.7% being women. The median duration of T2D was 7 years, and the mean HbA1c was 7.63%. Overall, 20.4% had advanced liver fibrosis. The multivariate logistic regression analysis showed that diabetes duration >10 years {odds ratio (OR) = 2.105 (95% confidence interval [CI] 1.321–3.355)}, fasting glucose >126 mg/dL (OR = 1.568 [95% CI 1.085–2.265]), and microalbuminuria >300 mg/24 h (OR = 2.007 [95% CI 1.134–3.552]) were associated with advanced liver fibrosis. Conversely, the eGDR (OR = 0.805 [95% CI 0.703–0.888]), statins (OR = 0.111 [95% CI 0.073–0.168]), and pioglitazone (OR = 0.082 [95% CI 0.010–0.672]) were inversely associated.** ***Conclusion:*** **Longer diabetes duration, insulin resistance, and microalbuminuria are independently linked to advanced liver fibrosis in T2D patients. Statins and pioglitazone may protect against liver fibrosis. Enhanced screening and management strategies targeting these factors could slow fibrosis progression and reduce the global burden of MASLD. (J Clin Exp Hepatol 2025;15:102536)**

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease.[1,2] The critical metabolic dysfunction underlying MASLD is insulin resistance and type 2 diabetes.[3] Although type 2 diabetes is commonly linked with cardiovascular disease, retinopathy, and chronic kidney disease, the unrecognized, growing prevalence of liver fibrosis due to MASLD presents a significant global burden for every healthcare system.[1–4]

Both diabetes and MASLD are independent risk factors for cardiovascular disease and all-cause mortality.[5] However, in the progression of type 2 diabetes, MASLD may remain silent and asymptomatic until the patient develops clinical manifestations of advanced liver fibrosis.[5,6] In this context, better efforts to recognize and screen for liver

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Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; DPP-4i: dipeptidyl peptidase 4 inhibitors; eGDR: estimated glucose disposal rate; FIB-4: Fibrosis-4; GGT: gamma-glutamyl transferase; GLP-1: glucagon-like peptide-1 agonists; HbA1c: hemoglobin A1c; HCC: hepatocellular carcinoma; HDL-C: high-density lipoprotein cholesterol; HT: hypertension; LDL-C: low-density lipoprotein cholesterol; MASLD: metabolic dysfunction-associated steatotic liver disease; OR: odds ratio; SGLT-2i: sodium-glucose cotransporter 2 inhibitors; WC: waist circumference
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disease in patients with type 2 diabetes, as routinely done for other microvascular and macrovascular complications, could reduce the global burden of chronic liver disease.[6]

Assessing liver fibrosis plays a pivotal role in determining the prognosis of chronic liver disease.[4] It stands as a distinct risk factor for the progression of liver cirrhosis and hepatocellular carcinoma (HCC), especially in patients with cardiometabolic diseases.[7,8] Hence, evaluating liver fibrosis is essential in managing chronic liver conditions.[1–3] The present study aimed to determine the factors associated with advanced liver fibrosis in patients with type 2 diabetes from Mexico City. The study assessed liver fibrosis using the Fibrosis-4 (FIB-4) index.[9] Since almost every patient included was already taking medications for diabetes, we incorporated the estimated glucose disposal rate (eGDR) as a surrogate for insulin resistance.[10,11] Additionally, we aimed to determine the differences in clinical and biochemical variables among the various liver fibrosis subgroups.

METHODS

Ethics Approval and Consent to Participate

The study was approved by the HGDMGG Research Committee and Research Ethics Committee (REF 14-68-2023) and conducted according to the 1975 Declaration of Helsinki. Upon medical admission, the patient or a family member signed an informed consent form permitting the use of their medical file information for didactic, research, and publication purposes.

Patients

This was a multicentric retrospective observational study performed at four centers in Mexico City: Hospital General Dr. Manuel Gea Gonzalez (HGDMGG); Hospital General de Mexico (HGM); Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran (INNSZ); and Centro Medico Nacional 20 de Noviembre (CMN20). The data were obtained using medical files from the (Internal Medicine, Gastroenterology, or Hepatology) outpatient clinics from January 2018 to December 2023. We report our findings to the STROBE guidelines for observational studies. The inclusion criteria were patients with type 2 diabetes diagnosed or referred at our outpatient clinic. The exclusion criteria included incomplete biochemical and clinical data, loss of variables of interest, patients with an average daily alcohol consumption of more than 30 g/day or a history of alcoholic hepatitis, patients with a history of hepatitis B or C, those undergoing antiretroviral therapy or treatment for tuberculosis, patients with a history of systemic lupus or rheumatoid arthritis, patients with a history of autoimmune-related liver diseases, and any nondiabetic glomerulopathy. The present study was approved by the HGDMGG Research Committee and Research Ethics Committee (REF 14-68-2023), and patient anonymity was guaranteed according to the 1975 Declaration of Helsinki. When the patient was admitted to the hospital, either the patient or a family member signed a form agreeing to let the hospital use their medical information for teaching, research, and publishing purposes. The FIB-4 index for liver fibrosis was calculated using the following formula: Age × AST (IU/l)/platelet count (× 109/l) × $\sqrt{\text{ALT}}$ (IU/l).[9] Afterward, the following cutoff points were considered for liver fibrosis: <1.299 indicated F0, 1.3 to 2.66 indicated F1–F2, and >2.67 indicated F3–F4. The eGDR was used as a surrogate for insulin resistance.[10,11] The formula was: eGDR = 21.158 − (0.09 × WC) − (3.407 × HT) − (0.551 × HbA1c); WC = waist circumference (cm), HT = hypertension (yes = 1/no = 0), and HbA1c = hemoglobin A1c (%).

Biochemical Analysis

The central laboratory of each center performed all the respective biochemical measurements. Blood samples from the patients were collected after at least 10 h of fasting. The measurements were carried out with commercially available standardized methods. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), fasting glucose, HbA1c, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured using DxC 700 AU Chemistry Analyzer (Beckman Coulter, Fullerton CA). The Sampson *et al.* formula calculated low-density lipoprotein cholesterol (LDL-C).[12]

Statistical Analysis

Statistical analysis was performed using SPSS 26 (SPSS Inc., Chicago, IL). Data were screened for outliers and normality assumptions. The normality of continuous variables was assessed with the Kolmogorov–Smirnov normality test and visually using histograms and Q–Q plots. Values are expressed as mean ± standard deviation, median (interquartile range), or frequencies (%). Means and medians were compared using student's *t test*, ANOVA, Mann–Whitney's U or Kruskal–Wallis' test when needed, and frequencies with the χ^2 test. Binary logistic regression models were used to determine the association between variables of interest or with biological plausibility and advanced liver fibrosis. Odds ratios (ORs) with 95% confidence intervals (95%CIs) were reported, and a statistical significance *P* an0.005.

RESULTS

A total of 2000 patients with type 2 diabetes, without any known liver disease, were included in the study (Figure 1). Clinical and biochemical data of the patients stratified by estimated fibrosis stage using the FIB-4 index is shown

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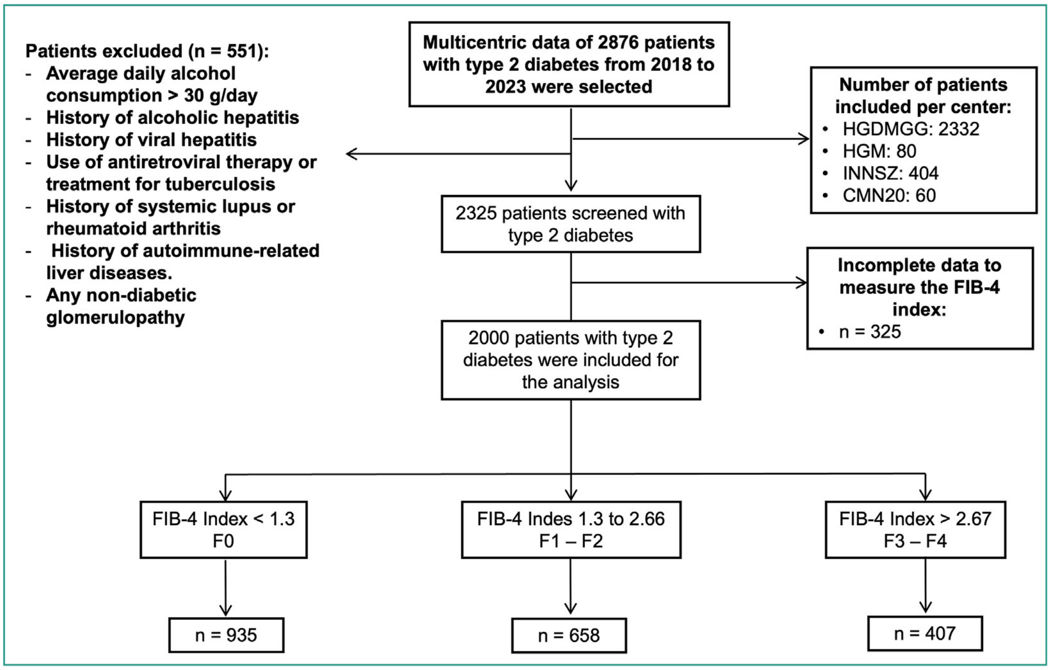

Figure 1 Patient selection flow diagram.

in Table 1. Compared with patients who had advanced liver fibrosis, those with F2 or less were younger, more likely to be women, had lower WC, had a shorter duration of type 2 diabetes, higher use of metformin, lower use of subcutaneous insulin, higher use of thiazolidinediones (pioglitazone), higher use of any fibrates and statins, lower fasting plasma glucose, higher serum sodium levels and INR, lower serum creatinine, lower microalbuminuria, higher total cholesterol, LDL-C, triglycerides, GGT, and serum albumin. Patients in the F1–F2 group had the highest frequency of hypertension and sulfonylurea use. As expected for the variables included in the FIB-4 index formula, platelet count, AST, and ALT were higher. Supplementary Table 1 shows clinical and biochemical data of the patients stratified for the duration of type 2 diabetes. Compared with patients with disease duration longer than 10 years, those with 9 years or less had lower BMI, lower prevalence of estimated F3–F4 by FIB-4 index, lower frequency of hypertension, higher use of metformin, lower use of subcutaneous insulin, DDP-4i, and sulfonylureas. Only those with diabetes duration <5 years had lower use of SGLT-2i. Biochemically, those with disease duration <10 years had lower fasting glucose, HbA1c, serum creatinine, microalbuminuria, and higher LDL-C, platelet count, ALT, and serum albumin.

wTo evaluate the variables independently associated with advanced liver fibrosis, those with statistical differences in the bivariate analysis and those with biological plausibility were included. The first model was adjusted by sex, BMI, duration of diabetes, hypertension, metformin, subcutaneous insulin, SGLT-2i, DPP-4i, GLP-1, pioglitazone, sulfonylureas, fibrates, statins, fasting glucose >126 mg/dL, HbA1c, microalbuminuria, total cholesterol categories, LDL-C categories, triglycerides >150 mg/dL, and the eGDR. After multiple logistic regression analyses, duration of diabetes >10 years, use of pioglitazone, hypertension, use of any statin, microalbuminuria between 30 and 300 mg/24 h, microalbuminuria >300 mg/24 h, LDL-C between 101 and 130 mg/dL, LDL-C > 130 mg/dL, triglycerides >150 mg/dL, and eGDR were significantly associated with advanced liver fibrosis (Figure 2). Furthermore, a second logistic regression model was used, excluding BMI and including WC. In this model, the WC (Wald = 16.535, OR: 1.024, 95% CI [1.012–1.036]), duration of diabetes >10 years (Wald = 15.044, OR: 2.392, 95% CI [1.540–3.717]), the use of pioglitazone (Wald = 6.334, OR: 0.064, 95% CI [0.007–0.544]), use of any statin (Wald = 102.763, OR: 0.119, 95% CI [0.079–0.179]), fasting glucose >1260 mg/dL (Wald = 5.741, OR: 1.568, 95% CI [1.085–2.265]), microalbuminuria between 30 and 300 mg/24 h dL (Wald = 4.985, OR: 1.657, 95% CI [1.064–2.581]), microalbuminuria >300 mg/24 h dL (Wald = 6.951, OR: 2.141, 95% CI [1.216–3.769]), LDL-C between 101 and 130 mg/dL (Wald = 16.254, OR: 0.349, 95% CI [0.209–0.582]), LDL-C > 130 mg/dL (Wald = 29.957, OR: 0.180, 95% CI [0.097–0.333]), and triglycerides >150 mg/dL (Wald = 8.816, OR: 0.567, 95% CI [0.390–0.824]), were associated with advanced liver fibrosis. Finally, a third logistic regression model was created, excluding the categorical variables and utilizing continuous variables instead.

Table 1 Clinical and Biochemical Variables of the Patients With Type 2 Diabetes Stratified by Approximate Fibrosis Stage Using the FIB-4 Index.

	FIB-4 stages				
	Total (n = 2000)	**F0 (n = 935)**	**F1–F2 (n = 658)**	**F3–F4 (n = 407)**	***P* value**
Age (years)	59.0 ± 14.0	52.4 ± 13.6	65.0 ± 11.4	64.4 ± 11.9	<0.001
Women (%)	63.7	68.4	62.0	55.8	<0.001
Body mass index (kg/m^2)	28.3 ± 6.3	28.5 ± 6.6	28.3 ± 6.2	28.1 ± 5.8	0.412
Waist circumference (cm)	90.9 ± 16.8	90.2 ± 17.7	90.1 ± 16.8	94.1 ± 14.4	0.005
Duration of type 2 diabetes (years)	7 (3–14)	5 (2–11)	8 (4–15)	10 (4–19)	<0.001
Duration of type 2 diabetes (%)					
0–4 years	37.2	46.3	29.9	28.5	<0.001
5–9 years	23.2	23.6	25.5	18.6	
>10 years	39.6	30.1	44.6	52.9	
Hypertension (%)	50.3	43.3	58.5	53.1	<0.001
Metformin (%)	70.2	70.6	72.9	64.9	0.018
Subcutaneous insulin (%)	40.5	39.9	37.3	46.7	0.010
SGLT-2i (%)	14.7	14.2	13.9	17.0	0.335
DPP-4i (%)	16.3	15.6	15.2	19.4	0.154
GLP-1 (%)	2.5	2.6	1.8	3.4	0.257
Pioglitazone (%)	3.2	4.3	2.9	1.0	0.006
Sulfonylureas (%)	9.3	6.9	11.7	10.8	0.002
Fibrates (%)	15.7	16.5	19.5	8.6	<0.001
Statins (%)	45.6	51.5	53.2	22.6	<0.001
Fasting glucose (mg/dL)	120 (98–162)	117 (95–158)	118 (99–156)	128 (104–176)	0.001
Fasting glucose >126 mg/dL (%)	46.6	54.0	54.7	49.0	0.296
Hemoglobin A1c (%)	7.63 ± 2.12	7.70 ± 2.20	7.54 ± 1.98	7.60 ± 2.18	0.331
HbA1c categories (%)					
HbA1c < 7%	48.4	48.3	48.2	48.7	0.092
HbA1c 7–7.9%	19.3	17.0	22.7	18.9	
HbA1c 8–8.9%	10.9	12.0	10.1	9.6	
HbA1c > 9%	21.5	22.7	19.0	22.8	
Serum sodium (meq/L)	133 ± 21	134 ± 20	133 ± 20	129 ± 26	0.001
International normalized ratio	1.10 ± 0.37	1.04 ± 0.14	1.06 ± 0.18	1.24 ± 0.65	<0.001
Serum creatinine (mg/dL)	0.86 (0.68–1.09)	0.82 (0.66–1.01)	0.89 (0.72–1.11)	0.89 (0.70–1.22)	<0.001
Microalbuminuria (mg/24 h)	11.4 (2.8–58.3)	10.8 (2.4–37.0)	10.1 (2.3–66.6)	21.1 (5.1–120.0)	<0.001
Microalbuminuria stages (%)					
<30 mg/24 h	67.5	71.7	67.9	55.5	<0.001
30–299 mg/24 h	22.3	19.6	22.1	30.1	
>300 mg/24 h	10.2	8.8	10.0	14.4	
Total cholesterol (mg/dL)	168 ± 53	175 ± 55	170 ± 47	149 ± 55	<0.001
HDL-C (mg/dL)	43 ± 15	43 ± 15	44 ± 14	42 ± 17	0.302
LDL-C (mg/dL)	90 ± 42	94 ± 43	90 ± 40	78 ± 40	<0.001
LDL-C categories (%)					

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Table 1 (*Continued*)

	FIB-4 stages				
	Total (n = 2000)	**F0 (n = 935)**	**F1–F2 (n = 658)**	**F3–F4 (n = 407)**	***P* value**
<70 mg/dL	34.3	29.3	33.4	48.6	<0.001
71–100 mg/dL	27.7	28.1	28.1	26.0	
101–130 mg/dL	21.3	22.4	23.1	15.5	
>130 mg/dL	16.7	20.2	15.4	9.9	
Triglycerides (mg/dL)	154 (104–216)	160 (111–229)	158 (114–218)	123 (81–191)	<0.001
Triglycerides >150 mg/dL (%)	52.4	44.5	45.0	58.9	<0.001
Platelet count (10^3/uL)	231 (175–287)	276 (234–335)	217 (184–250)	104 (57–163)	<0.001
Total bilirubin (mg/dL)	0.69 (0.47–0.95)	0.60 (0.42–0.83)	0.71 (0.52–0.92)	0.92 (0.63–1.42)	<0.001
AST (U/L)	24 (18–37)	20 (16–27)	27 (21–38)	42 (27–60)	<0.001
ALT (U/L)	23 (16–35)	22 (15–32)	23 (16–34)	29 (18–45)	<0.001
GGT (U/L)	35 (20–76)	31 (19–61)	34 (20–71)	71 (27–155)	<0.001
Albumin (g/dL)	3.80 (3.24–4.18)	3.90 (3.35–4.26)	3.88 (3.32–4.20)	3.45 (2.90–3.89)	<0.001
MELD 3.0	11.19 ± 4.66	10.44 ± 3.96	10.57 ± 4.14	13.92 ± 5.80	<0.001
Estimated glucose disposal rate	6.80 (5.25–9.09)	7.31 (5.53–9.60)	6.50 (5.17–8.61)	6.42 (4.71–8.58)	<0.001

SGLT-2i: sodium-glucose cotransporter 2 inhibitors; DPP-4i: dipeptidyl peptidase 4 inhibitors; GLP-1: glucagon-like peptide-1 agonists; LDL-C: low-density lipoprotein cholesterol; AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase; GGT: Gamma-Glutamyl Transferase.
Variables are mean ± standard deviation, median (interquartile range), or percentages. *P* value: ANOVA test or Kruskal–Walli's test, or χ^2.

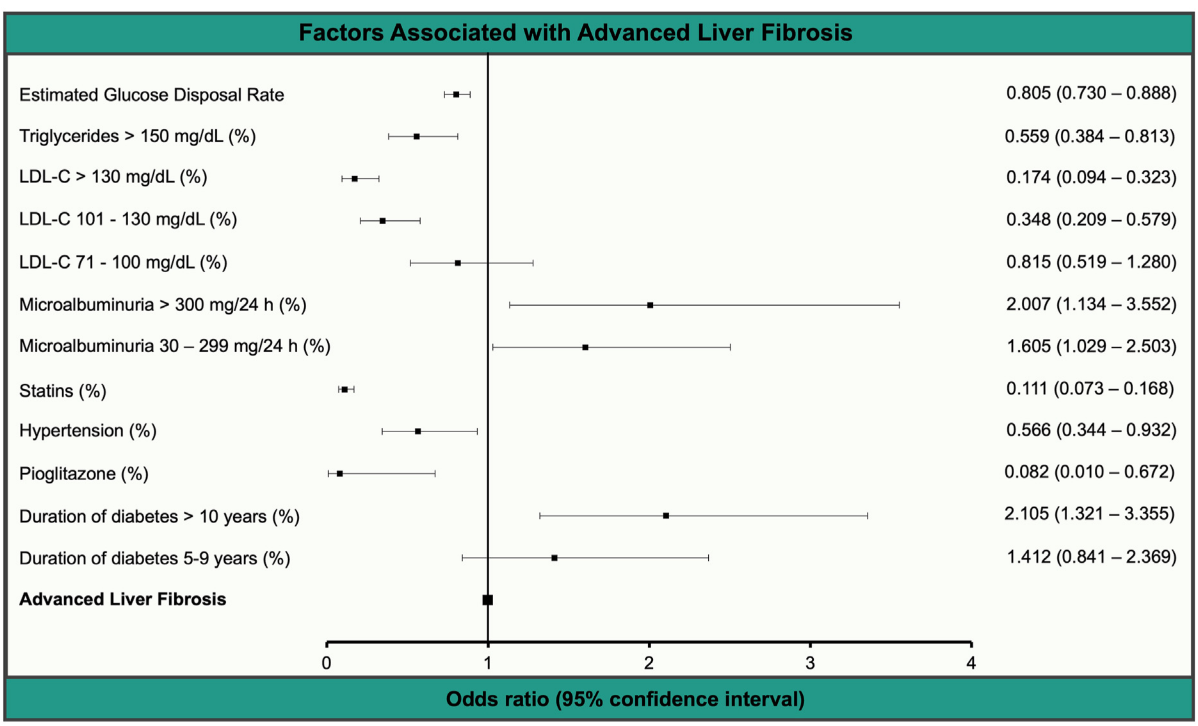

Figure 2 Factors associated with advanced liver fibrosis in patients with type 2 diabetes. Logistic regression analysis adjusted by sex, body mass index, duration of diabetes, metformin, subcutaneous insulin, sodium–glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 agonists, pioglitazone, sulfonylureas, fibrates, statins, fasting glucose >126 mg/dL, microalbuminuria, total cholesterol categories, low-density lipoprotein cholesterol categories, triglycerides >150 mg/dL, and the estimated glucose disposal rate.

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Categorical variables such as sex and medications remained in this analysis. In this model, for each year elapsed since the diagnosis of type 2 diabetes, the probability of having advanced liver fibrosis increased by 3.0% (95% CI 1.8–4.2%), for each centimeter of WC, the OR increased by 3.0% (95% CI 1.8–4.2%), and for each mg/dL of fasting glucose, the OR increased by 0.5% (95% CI 0.2–0.7%). On the other hand, for each mg/dL of LDL-C, the OR reduced by 1.4% (95% CI 0.9–1.9%), and for each mg/dL of triglycerides, the OR reduced by 0.4% (95% CI 0.2–0.6%). Additionally, statins reduced the association of advanced liver fibrosis by 87.7% (95% CI 81.4–91.9%).

DISCUSSION

Reports published over the past few decades have remarked the socioeconomic burden of chronic liver disease and liver fibrosis in almost every high-, middle-, and low-income country.[1,2] While the global incidence of viral and alcoholic liver diseases has decreased, the rates of MASLD-associated liver fibrosis have significantly increased worldwide as a consequence of the pandemic of diabetes and obesity.[1,2] Despite type 2 diabetes being a well-established etiological factor for MASLD, the recognition, screening, and management of liver disease in patients with diabetes remain suboptimal.[4,6,13] Until effective treatments are available, MASLD requires the combined focus of primary care physicians, specialists, and health policymakers.[5] This effort should begin with implementing preventive strategies to mitigate excessive weight gain and the progression of diabetes.[5]

Additionally, identifying the factors associated with the onset and advancement of liver fibrosis in patients with diabetes could significantly reduce the increasing burden of liver disease.[1,8] This study aimed to identify these factors in a large sample of patients with type 2 diabetes. The results highlighted that longer duration of diabetes, hypolipidemia, insulin resistance, and microalbuminuria were the main factors associated with advanced liver fibrosis in this population. It is important to highlight that this analysis included glucose-lowering drugs, statins, and fibrates. In the regression analysis, pioglitazone and statins showed lower odds of advanced liver fibrosis. Thus, these findings could partially suggest that using statins and improving insulin resistance and diabetic kidney disease might offer protective benefits against advanced liver fibrosis.[14,15]

Advanced age and the duration of type 2 diabetes have been identified as risk factors for advanced liver fibrosis, cirrhotic complications, and HCC.[16,17] In this study, a longer duration of diabetes (particularly >10 years) was associated with an increased risk of advanced liver fibrosis. For each year since the diagnosis of type 2 diabetes, the probability of having advanced liver fibrosis increased by 3.0% (95% CI 1.8–4.2%). Although it might be biologically plausible that longer disease duration could bring more risk to liver fibrosis, there is scarce data on diabetes duration and liver-related complications. As a matter of fact, Xinrong Zhang *et al.* aimed to determine the impact of age and the duration of diabetes on the development of liver-related events, including HCC and cirrhotic complications.[16] In contrast with our results, in their large cohort study, the duration of T2D (>10 years) did not significantly increase the risk of liver-related events as the incidence of these events increased linearly over time without a significant difference in the annual incidence rate between the first ten years and subsequent years (0.06% vs. 0.10%, $P = 0.136$). Moreover, Miele *et al.* explored the relationship among diabetes, its duration, and the risk of HCC.[17] They found that a diagnosis of diabetes was associated with HCC, with an OR of 2.25 (95% CI = 1.42–3.56), and duration of diabetes <10 years and >10 years was associated with nearly three-fold and five-fold higher odds for HCC.[17] Further studies are needed to clarify the association between diabetes duration and liver fibrosis.[8,16,17]

Insulin resistance plays a crucial role in the pathogenesis and progression of MASLD, chronic liver disease, and liver fibrosis.[18–21] Likewise, the eGDR has been proposed as a reliable non-insulin–based tool to evaluate insulin resistance.[10,11] A recent study by Song *et al.* assessed the relationship between eGDR and various outcomes in patients with MASLD.[11] The study found that lower eGDR levels, which indicate higher insulin resistance, were significantly associated with increased arterial stiffness and higher all-cause and cardiovascular mortality rates.[11] This relationship was stronger compared with other measures of insulin resistance, like the triglyceride-glucose index and the homeostasis model assessment of insulin resistance. The present study found that, independent of glycemic control and glucose-lowering treatment, having a low eGDR is associated with liver fibrosis. The two studies support the hypothesis that insulin resistance plays a significant role in developing MASLD and its progression to more severe steatosis and fibrosis. Insulin resistance promotes hepatic steatosis by increasing the influx of free fatty acids into the liver, enhancing *de novo* lipogenesis, and inhibiting fatty acid oxidation.[19] This fat accumulation in hepatocytes leads to lipotoxicity, triggering cellular stress responses, inflammation, and subsequent activation of hepatic stellate cells (HSCs). Activated HSCs are the primary effector cells in liver fibrogenesis, producing excessive extracellular matrix components that result in fibrosis.[19]

Lipoprotein abnormalities are common in chronic liver disease, and low cholesterol levels are often indicative of hepatic dysfunction rather than a protective effect. While the prognostic significance of lipoprotein deficiency in cirrhosis is well recognized, its clinical importance in earlier fibrosis stages is often overlooked.[22,23] Data from other causes of liver fibrosis have demonstrated that

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hypocholesterolemia is linked with poorer prognosis and increased morbidity and mortality, likely due to impaired hepatic lipoprotein synthesis.[22,24] In our study, lower LDL-C and triglyceride levels were associated with advanced liver fibrosis, even after adjusting for statin and fibrate use.[23] However, rather than suggesting a protective effect of higher LDL-C and triglycerides, this likely reflects a decline in hepatic lipoprotein production as liver disease progresses. The liver plays a central role in the synthesis of apolipoproteins such as apolipoprotein B100 and in the metabolism of most circulating lipids.[19,22,25] Thus, patients with more severe stages of liver fibrosis may exhibit a reduction in total cholesterol, LDL-C, and HDL-C levels due to hepatic dysfunction and decreased lipoprotein production.[19,22] This finding supports the notion that hypolipidemia in advanced fibrosis is a marker of disease severity rather than a protective metabolic adaptation.

The association among MASLD, liver fibrosis, and chronic kidney disease has been debatable.[26,27] Some reports have found a significantly increased risk of albuminuria in patients with MASLD.[27–30] In line with these reports, we observed that significant albuminuria was associated with liver fibrosis. Chronic inflammation is linked to advanced liver fibrosis, which involves the release of various proinflammatory cytokines and chemokines like TNF-α, IL-6, and TGF-β. These inflammatory mediators could partially lead to glomerular damage and increased permeability, causing what is known as fatty kidney disease.[19,28,29] However, most of these observations are made by observational studies, and causality cannot be inferred. In Mexico, the prevalence of type 2 diabetes has significantly increased over the last three decades, rising from 9.6% in 1990 to 14.3% in 2017, with notable heterogeneity across regions. This trend has been largely driven by delayed diagnosis and suboptimal management of diabetes, particularly in areas with limited healthcare access.[31] The prevalence of MASLD and liver fibrosis in this population is concerning, given the high rates of undiagnosed or poorly controlled diabetes, which often leads to chronic complications such as advanced liver disease and kidney damage.[31,19] Studies have demonstrated that insulin resistance, chronic hyperglycemia, and prolonged duration of diabetes exacerbate systemic inflammation and oxidative stress, which could further contribute to liver and renal dysfunction.[31,32,27]

A major strength of this study is its comprehensive analysis of the combined influence of demographic, clinical, and biochemical factors in patients with type 2 diabetes and advanced liver fibrosis. This includes using the eGDR as an indicator of insulin resistance and evaluating glucose-lowering treatments, which are areas with limited existing research. Recent studies, such as those analyzing dyslipidemia and its association with liver fibrosis progression in nonalcoholic steatohepatitis, underscore the metabolic interrelations and the impact of managing insulin resistance and related factors on disease outcomes.[33] Moreover, the multicentric design strengthens the generalizability of our findings by incorporating data from four medical centers. However, it is noteworthy that most of the patients were recruited from a single center, which could introduce a potential selection bias despite the broader scope of the study. Our study, conducted across three major institutions in Mexico City, identified a 20% prevalence of advanced fibrosis among patients with type 2 diabetes, with statins and pioglitazone use inversely associated with fibrosis. Compared with other populations, such as India, a study in a primary healthcare center in northern India found a lower prevalence of high-risk fibrosis (4.6%) using FIB-4.[34] Likewise, a study by Panikar *et al.* in Mumbai reported 28% fibrosis prevalence based on transient elastography, reinforcing the importance of waist circumference and BMI as risk factors.[35] Finally, Kumar *et al.* highlighted the role of visceral fat and diabetes in fibrosis progression among patients with MASLD, suggesting bioelectrical impedance analysis as a helpful noninvasive tool.[36] These studies emphasize the geographical and methodological variations in the prevalence of fibrosis, with our findings significantly contributing to understanding the risk factors associated with fibrosis in a Latin American population.

The most significant limitation is the reliance on the FIB-4 index instead of liver biopsies, imaging, or elastography to estimate liver fibrosis stages. While the FIB-4 index is a validated and widely used tool for assessing advanced liver fibrosis,[3,37] it may not capture the complete diagnostic accuracy of more advanced techniques. Additionally, the study's cross-sectional design prevents us from establishing causal relationships between the identified factors and advanced liver fibrosis. Future longitudinal studies are needed to confirm these associations and explore causality.

In summary, the present study found that a longer duration of diabetes, insulin resistance, and microalbuminuria were associated with advanced liver fibrosis in patients with type 2 diabetes. Conversely, the analysis showed that statins and hyperlipidemia had an inverse association with liver fibrosis. This study provides valuable insights into the factors associated with advanced liver fibrosis in diabetes patients, particularly in an underrepresented Latin American population. However, we acknowledge that the retrospective design and FIB-4 alone as a fibrosis assessment tool limit causal interpretation. Additionally, hypolipidemia in advanced fibrosis likely reflects impaired hepatic function rather than a protective effect. Future prospective studies incorporating transient elastography, liver biopsy validation, and longitudinal follow-up will be crucial in further elucidating these associations and improving fibrosis risk stratification in this population.

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CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

J.C.G., F.D.M.S., and N.M.S. conceived the project, researched, and analyzed data, contributed to the discussion, and wrote the manuscript. F.D.M.S. edited the final draft. M.J.C.N, S.M.F.A., V.M.P.Z., C.M.P., and A.D.J. researched data from the HGDMGG and contributed to the discussion. F.M.S., V.A.S.G., A.R.P., and I.G.J. researched data from the INNSZ and contributed to the discussion. M.B.G., J.M.R., F.H.T., and J.L.P.H. researched data from the HGM and contributed to the discussion. B.B.F. researched data from the CMN20 and contributed to the discussion. F.D.M.S., J.C.G., and N.M.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DECLARATION OF COMPETING INTEREST

All authors have no conflicts of interest to declare about this article.

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AVAILABILITY OF DATA AND MATERIALS

All data and materials from the corresponding author will be available upon reasonable request.

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SUPPLEMENTARY DATA

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