

# Risk Factors for Liver Fibrosis in Diabetic Patients with End-stage Renal Disease

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## Abstract

**Introduction:** Liver cirrhosis is the fourth cause of death in the world. Fatty liver disease is the most common cause of chronic liver disease (CKD) in most countries. Identifying risk factors for liver fibrosis in a population with end-stage renal disease (ESRD) may facilitate early diagnosis of this complication and allow the activation of follow-up protocols to reduce morbidity and mortality in these patients. **Materials and methods:** A cross-sectional and analytical study was carried out. Patients on hemodialysis, older than 18 years with a diagnosis of diabetes *mellitus* and ESRD were included. The hypotheses were contrasted through the chi-square test and Student's T-test, as appropriate. Statistical significance was established at a  $p$ -value = 0.05. **Results:** A prevalence of significant liver fibrosis and cirrhosis of 17% was found. Factors associated with liver fibrosis were a history of cerebrovascular disease, peripheral vascular disease, body mass index (BMI), total cholesterol, glycosylated hemoglobin, sodium, and aspartate aminotransferase (AST). No relationship was observed between the NAFLD (non-alcoholic fatty liver disease) score, the APRI index (AST to Platelet Ratio Index), and fibrosis. **Conclusion:** The prevalence of significant liver fibrosis in patients with diabetes and ESRD is similar to that reported in other populations of patients with diabetes. However, some factors, such as BMI, could behave differently and favor the appearance of liver injury with lower degrees of obesity than previously reported in the literature.

## Keywords

Liver cirrhosis, chronic renal failure, dialysis, diabetes *mellitus*, elasticity imaging.

## INTRODUCTION

Liver cirrhosis is the fourth cause of death worldwide. Patients with decompensated cirrhosis have a ten-fold increased risk of death compared to the general population<sup>(1)</sup>. Currently, fatty liver disease (FLD) is the most common cause of chronic liver disease in most Western countries<sup>(1-3)</sup>.

Type 2 diabetes *mellitus* (T2DM), obesity, hyperlipidemia, and high blood pressure (HBP) are considered risk factors for the development of FLD, and this subgroup of patients is considered to be the one with the highest risk

of advanced liver fibrosis, hepatocellular carcinoma, and cirrhosis<sup>(2,3)</sup>. At the same time, FLD is an independent risk factor for cardiovascular events<sup>(4)</sup>.

It has been described that end-stage renal disease (ESRD) and FLD have common pathophysiology pathways, and the diagnosis of metabolic syndrome has been associated with the progression of both pathologies<sup>(3)</sup>. Some studies have pointed out an increase in the prevalence (odds ratio [OR]: 2.1; 95% confidence interval [CI]: 1.69-2.66) and incidence of ESRD (1.79; 95% CI: 1.65-1.95) in patients with FLD<sup>(3,5)</sup>. A recent study that included 1,992 patients with diabetes found a bidirectional relationship between

the appearance of FLD and chronic kidney disease and even pointed out some pathways through which these two entities can mutually influence their risk of manifestation<sup>(6)</sup>.

In patients with cirrhosis, chronic kidney disease (CKD) is associated with a higher risk of adverse renal and hospital outcomes and decreased survival<sup>(7)</sup>. On the other hand, patients with cirrhosis due to FLD on the transplant list face unique challenges and require simultaneous liver and kidney transplantation in more significant numbers compared to other etiologies<sup>(8-10)</sup>.

Transient elastography (Fibroscan) is a non-invasive technique used to estimate liver fibrosis<sup>(11)</sup>, assessing the hardness of the organ by measuring the speed at which a vibrating wave passes through the liver parenchyma. In addition to avoiding all the risks inherent in performing the biopsy, the procedure incorporates some quality criteria<sup>(12,13)</sup> that allow the soundness of results to be determined at the bedside. Elastography has proven to be a valid tool for estimating the degree of liver fibrosis in FLD and other pathologies<sup>(14)</sup>.

Although the risk factors for liver fibrosis and cirrhosis have been well characterized in patients with FLD<sup>(15,16)</sup>, the studies carried out paradoxically exclude patients on dialysis in whom many of these factors frequently coexist and in whom the diagnosis of chronic liver disease may have important prognostic implications<sup>(17)</sup>.

The identification of risk factors for liver fibrosis in a population with ESRD can facilitate the early diagnosis of this complication and allow the activation of monitoring protocols that have been shown to reduce the morbidity and mortality associated with chronic liver disease<sup>(18,19)</sup>.

This study aims to describe the factors associated with advanced liver fibrosis in diabetic patients with ESRD on hemodialysis.

## MATERIALS AND METHODS

### Study design and population

A cross-sectional study was conducted, identifying diabetic patients on hemodialysis from the database of a hemodialysis unit in Cartagena until November 12, 2019. These patients attend three hemodialysis sessions weekly and are evaluated through a monitoring protocol that includes evaluation by a nephrologist and the performance of a set of laboratory tests. Medical history, sociodemographic, anthropometric, and analytical data were obtained from the medical records of each patient. We included patients on hemodialysis, over 18 years of age, with a diagnosis of diabetes *mellitus* and ESRD defined as GFR by Cockcroft-Gault formula  $<15 \text{ mL/min/1.73 m}^2$ .

Transient elastography and steatosis estimation were performed, taking advantage of the patients' attendance at their hemodialysis sessions, and information from the medical records was collected simultaneously on the same day of the procedure. We used results from medical records to calculate the NAFLD score (for FLD) and the APRI score (AST to platelet ratio index); none were older than one month at the time of calculation.

### Transient elastography and controlled attenuation parameter

The Fibroscan Touch Compact 530 was employed. All patients had fasted at least six hours before the study. The M or XL probes were used as appropriate. The result was the median value of ten valid kilopascal (kPa) measurements. The manufacturer's quality criteria were considered to validate the robustness of results (interquartile range [IQR]  $\leq 30\%$  and success rate  $\geq 60\%$ ). A cohort point of 8.2 kPa and 13.6 kPa were used to diagnose significant liver fibrosis and cirrhosis, respectively<sup>(13)</sup>. A controlled attenuation parameter (CAP) value  $\geq 302 \text{ dB/m}$  was the cohort point for the diagnosis of hepatic steatosis<sup>(13)</sup>.

Technical failure was deemed to occur when no valid measurement could be obtained. Only results that met the manufacturer's quality criteria were included for analysis<sup>(12-14)</sup>.

### NAFLD Score

The NAFLD score was calculated with the following formula:

$$\begin{aligned} & -1.675 + (0.037 * \text{age [years]}) + (0.094 * \text{BMI [kg/m}^2\text{]}) \\ & + (1.13 * \text{carbohydrate intolerance/diabetes [yes = 1, no} \\ & = 0]) + (0.99 * \text{AST/ALT ratio}) - (0.013 * \text{platelet count} \\ & [\times 10^9/\text{L}]) - (0.66 * \text{albumin [g/dL]}). \end{aligned}$$

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index.

Three categories were identified according to a range of values as follows:

- 1.455- > low risk of liver fibrosis (sensitivity: 77%, specificity: 71%; positive predictive value [PPV]: 52%, negative predictive value [NPV]: 88%)
- $\geq -1.455$  to 0.676: undetermined risk.
- > 0.676: high risk of liver fibrosis (sensitivity: 43%, specificity: 96%, PPV: 82%, NPV: 80%, LR +: 11)<sup>(20)</sup>.

### Aspartate aminotransferase to platelet ratio index

The APRI score was calculated with the following formula:

$(\text{AST in IU/L}) / (\text{AST upper limit of normal in IU/L}) /$   
 $(\text{platelets in } 10^9/\text{L})$

A cut-off point of 0.7 was used to discriminate fibrosis (sensitivity of 65% and specificity of 72%)<sup>(21)</sup>.

## Bioimpedanciometry

Bioimpedanciometry is a non-invasive technique used to accurately estimate total body water (TBW). With assumptions based on tissue hydration constants, we obtain fat-free mass (FFM) and fat mass (FM). These data help adjust renal replacement therapy<sup>(22)</sup>.

## Statistical analysis

The mean (SD) and percentages described quantitative and categorical variables. The hypotheses were contrasted through the chi-squared test and the Student's T-test, as appropriate. OR (95% CI) and mean differences were used to estimate the magnitude of associations. Statistical significance was established with a  $p$ -value = 0.05. The data were analyzed with Statistical Package for the Social Sciences (SPSS) version 15.

## RESULTS

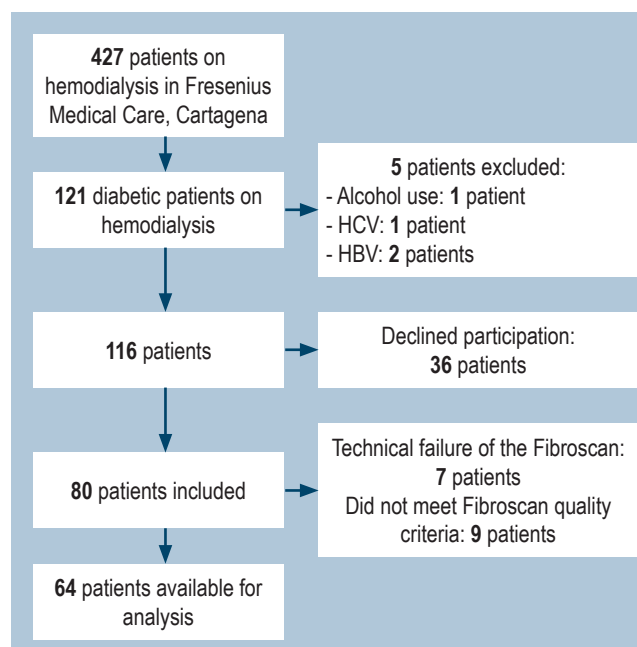
### Clinical and sociodemographic description of the study population

Eighty patients were included in the study, of which 16 were excluded due to failure to obtain a reliable elastographic measurement (seven did not meet the quality criteria and nine due to technical failure) (**Figure 1**). Of the 64 patients included, 56% were obese or overweight. The baseline characteristics of the population are shown in **Table 1**.

The population's average age was 63.5 years; a similar proportion was observed between both sexes, and 77% belonged to SELs 1 and 2. Metabolic syndrome was found in 33 patients (52%). Sixty-two patients (96.9%) were hypertensive, 33 patients were dyslipidemic (50%), and 41 patients had an abdominal circumference above that recommended for their sex (64%).

Depending on the BMI values, 3% are underweight, 43% are normal weight, 34% are overweight, and 18% are obese. The average fatty tissue index was 17.7 kg/m<sup>2</sup>, and the lean tissue index was 12.1 kg/m<sup>2</sup>. According to CAP measurements, hepatic steatosis was found in 13.8% of patients.

Despite being a cohort of diabetic patients with ESRD, 100% had a triglyceride value, and 77% had a glycosylated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) value within the established goals;



**Figure 1.** Study flow chart. A total of 57 patients were excluded. Image owned by the authors.

however, only 17% had adequate control of LDL levels, and 63% of blood pressure levels.

The most frequent secondary chronic complications of diabetes, apart from chronic renal failure, were heart failure (20%), retinopathy (11%), peripheral vascular disease (11%), acute myocardial infarction (6%), and cerebrovascular disease (5%).

The leading cause of CKD is the combination of diabetic and hypertensive nephropathy (72%), followed by diabetes (14%) or high blood pressure (11%) independently. The cohort of patients studied had a mean time on dialysis of 5 years; of these, 67% received some antihypertensive treatment. The most frequently used were calcium antagonists, clonidine, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARBs).

84% of the patients received treatment with erythropoietin analogs and 60% with parenteral iron. Only 18 patients have hemoglobin levels below the expected values. Alterations in mineral and bone metabolism are also present in the studied patients, of which 43% received treatment with calcium carbonate and 34% with calcitriol. For the treatment of hyperparathyroidism, 11 patients received sevelamer (Renvela-Renagel) and six cinacalcet (Mimpara-Sensipar).

Regarding indirect markers of liver injury, aminotransferases and albumin were within typical values in 89% and

**Table 1.** Baseline characteristics of study patients\*

Variable	(n,%)	Variable	(n,%)
Age (years)	63.5 (9.2)	- Platelets x 10 <sup>9</sup> /L	213 196 (83 915)
Male sex	34 (53)	- LDL (mg/dL)	88.1 (33)
High blood pressure	62 (96.9)	- Total cholesterol (mg/dL)	155.6 (41.1)
HBP > 10 years	62 (96.9)	- HDL (mg/dL)	32.6 (9.1)
DM > 10 years	63 (98.4)	- Triglycerides (mg/dL)	174.3 (91.7)
- Cerebrovascular disease	3 (4.7)	- Glycosylated hemoglobin (%)	6.5 (2)
- Myocardial infarction	4 (6.3)	- Creatinine (mg/dL)	9.1 (3)
- Peripheral vascular disease	7 (10.9)	- Urea nitrogen (mg/dL)	48 (15.1)
- Heart failure	13 (20.3)	- Potassium (mEq/L)	5 (0.8)
- Atrial fibrillation	1 (1.6)	- Sodium (mEq/L)	139.2 (2.4)
- Retinopathy	7 (10.9)	- Phosphorus (mEq/L)	4.1 (1.3)
Causes CKD		- Parathyroid hormone (pg/mL)	372 (372)
- Hypertension and diabetes	46 (71.9)	- Calcium (mEq/L)	8.5 (0.6)
- Hypertension	7 (10.9)	- AST (UI/L)	14.7 (6.7)
- Diabetes	9 (14.1)	- ALT (UI/L)	14 (10.6)
- Other	2 (3.1)	- Albumin (g/dL)	4 (0.4)
Time on dialysis (years)	5 (3.3)	- Alkaline phosphatase (IU/L)	137.3 (95)
Weight (kg)	66.6 (13)	Fibroscan (kPa)	7.2 (5.6)
Height (m)	1.61 (0.07)	IQR (kPa)	0.15 (0.05)
BMI (kg/m <sup>2</sup> )	25.57 (5)	CAP (dBm)	244.1 (54.6)
Classification according to BMI		APRI score (> 0.7)	17 (26.6)
- Normal	28 (43.8)	NAFLD Score	
- Overweight	22 (34.4)	- Low risk	3 (47)
- Obesity	12 (18.8)	- Indeterminate	46 (71.9)
- Underweight	2 (3.1)	- High risk	15 (23.4)
Waist circumference (cm)	94.2 (10.7)	Hepatic steatosis	7 (10.9)
Metabolic syndrome	33 (51.6)	Liver fibrosis	11 (17.2)
- Hemoglobin (g/dL)	10.6 (1.5)	Hepatic cirrhosis	7 (10.9)

\*Quantitative variables are expressed as mean and standard deviation (SD), and categorical variables are expressed as absolute frequencies and percentages (%). APRI: AST to platelet ratio index; ARA: angiotensin receptor antagonists; CAP: controlled attenuation parameter; DM: diabetes mellitus; CKD: chronic kidney disease; HDL: high-density lipoproteins; HBP: high blood pressure; ACEI: angiotensin-converting enzyme inhibitor; LDL: low-density lipoproteins; NAFLD score: nonalcoholic fatty liver disease score; IQR: interquartile range. Table prepared by the authors.

84% of patients, respectively. The risk assessment scales for liver fibrosis indicated that ten (19%) were at high risk for liver fibrosis according to the NAFLD score and twelve (23%) according to the APRI score.

### Descriptive analysis of the population with significant liver fibrosis

There were eleven (17%) patients with significant liver fibrosis, among which seven (63%) had elastographic

values compatible with established liver cirrhosis at the time of their evaluation, and none of whom had a previous diagnosis of chronic liver disease.

All patients had more than ten years of evolution for HBP and DM. The most common complications of diabetes were heart failure (36.4%), peripheral vascular disease (27.3%), cerebrovascular events (18%), retinopathy (18%), and myocardial infarction (9%). Besides, 54% of the patients were of normal weight, 36% were overweight, and 9% were underweight (**Table 2**).

**Table 2.** Characteristics of patients with fibrosis\*

Variable	Fibrosis n (%)	Variable	Fibrosis n (%)
Male sex	8 (72.7)	- Underweight	1 (9.1)
Age	67.9 (8)	Metabolic syndrome	4 (36.4)
Health system		Treatment	
- Subsidized	5 (45.5)	- ACEI or ARA	3 (27.3)
- Contributory	5 (45.5)	- $\beta$ blockers	4 (36.4)
- Special	1 (9.1)	- Clonidine	6 (54.5)
HBP	11 (100)	- Calcium antagonist	10 (90.9)
HBP > 10 years	11 (100)	- Minoxidil	2 (18.2)
DM > 10 years	11 (100)	- Erythropoietin	8 (72.7)
Cerebrovascular disease	2 (18.2)	- Parenteral iron	5 (45.5)
Myocardial infarction	1 (9.1)	- Calcitriol	3 (27.3)
Peripheral vascular disease	3 (27.3)	- Calcium carbonate	4 (36.4)
Heart failure	4 (36.4)	- Aluminum hydroxide	1 (9.1)
Atrial fibrillation	0 (0)	- Paricalcitol	1 (9.1)
Retinopathy	2 (18.2)	- Cinacalcet	1 (9.1)
Causes CKD		- Sevelamer	2 (18.2)
- Hypertension and diabetes	5 (45.5)	NAFLD score	
- Hypertension	3 (27.3)	- Low risk	1 (9)
- Diabetes	3 (27.3)	- Indeterminate	5 (45.5)
BMI classification		- High risk	5 (45.5)
- Normal	6 (54.5)	APRI	
- Overweight	4 (36.4)	- Low risk	6 (55)
- Obesity	0 (0)	- High risk	5 (45)

\*Quantitative variables are expressed as mean, SD, and categorical variables as absolute frequencies and percentages (%). APRI: AST to platelet ratio index; ARA: angiotensin receptor antagonists; CAP: controlled attenuation parameter; DM: diabetes mellitus; CKD: chronic kidney disease; HDL: high-density lipoproteins; HBP: high blood pressure; ACEI: angiotensin-converting enzyme inhibitor; LDL: low-density lipoproteins; NAFLD score: nonalcohol fatty liver disease score; IQR: interquartile range. Table prepared by the authors.



The NAFLD score identified only 45% of patients with fibrosis within the high-risk group; one of the eleven patients was classified within the low-risk group, and the remaining five were within the indeterminate risk group. The APRI score correctly classified 45% within the high-risk group (**Table 3**).

**Table 3.** Classification of patients according to NAFLD and APRI scores in patients with and without fibrosis

Variable	No fibrosis n (%)	Fibrosis n (%)	p
NAFLD			0.1
- Low risk	2 (4)	1 (9)	
- Indeterminate	41 (77)	5 (45.5)	
- High risk	10 (19)	5 (45.5)	
APRI			0.1
- Low risk	41 (77)	6 (55)	
- High risk	12 (23)	5 (45)	

APRI: AST to platelet ratio index; NAFLD score: nonalcoholic fatty liver disease score. Table prepared by the authors.

### Factors associated with significant liver fibrosis

The factors associated with liver fibrosis were a history of cerebrovascular disease ( $p = 0.02$ ), peripheral vascular disease ( $p = 0.05$ ), BMI ( $p = 0.05$ ), total cholesterol ( $p = 0.05$ ), HbA<sub>1c</sub> ( $p = 0.01$ ), sodium ( $p = 0.001$ ), and AST ( $p = 0.02$ ) (**Tables 4 and 5**).

No relationship was found between NAFLD and APRI scores and the presence of fibrosis ( $p = 0.1$ ). Among patients without fibrosis, 19% were in the high-risk group and 77% within the indeterminate group when the NAFLD score was used; for the APRI score, 77% of the group without fibrosis was in the low-risk group (**Table 3**).

### DISCUSSION

This study noticed a prevalence of significant liver fibrosis and cirrhosis of 17%, of which more than 50% had liver cirrhosis, which may have important prognostic implications in the evolution of the natural history of these two pathologies. These results are similar to those previously reported in which a prevalence of significant fibrosis between 13% and 21% has been found in diabetic patient populations<sup>(17,23-25)</sup>.

The relationship between the duration of diabetes and glycemic control with the risk of target organ damage has

been fully established in other clinical scenarios<sup>(15,26-28)</sup>. The fact that 100% of patients with fibrosis had a diabetes history of more than ten years and worse glycemic control (HbA<sub>1c</sub> 7.6% vs. 5.6%) could partly explain the high prevalence of liver cirrhosis within this group of diabetic patients<sup>(29,30)</sup>.

Patients in this cohort have a high prevalence of cardiovascular risk factors such as age, male sex, lower glomerular filtration rate (GFR), dyslipidemia, and HBP, which are known synergistic risk factors for the development of liver fibrosis<sup>(15,16)</sup>.

However, despite T2DM and cardiovascular risk factors in this group, the presence of hepatic steatosis due to CAP was low, approximately 14%. This contradictory finding could be explained by the low prevalence of obesity in this sample (18%). The intense multidisciplinary interventions aimed at reducing cardiovascular risk factors that these patients undergo when included in a dialysis program may have positively affected weight and steatosis control at the time of evaluation. Some studies also indicate that patients with cirrhosis due to FLD in advanced stages may not have histological findings of steatosis despite multiple risk factors for metabolic syndrome<sup>(31)</sup>. Although the pathways by which this phenomenon occurs have not been elucidated, there has been speculation about the effect of changes in hepatic blood flow, exposure to insulin, and the release of glucose and lipoproteins from the hepatocyte on the reduction of fat in cirrhotic livers due to FLD<sup>(31)</sup>.

In several studies, a BMI > 30 kg/m<sup>2</sup> is associated with fibrosis in diabetic patients<sup>(15,18)</sup>. Paradoxically, none of our patients with fibrosis exceeded this cut-off point. However, BMI was associated with liver injury, suggesting the possibility that liver damage in patients with ESRD begins at lower weight levels than those observed in other populations. It is also possible that the interventions that patients undergo in a structured dialysis program have improved weight control and that the highest degrees of obesity have occurred before their admission to renal replacement therapy, which confounds the observed relationship between overweight and fibrosis and that the latter was already present at the time the patients joined the program<sup>(19,32)</sup>.

A recent study in a cohort of diabetic patients whose objective was to identify common risk factors for FLD and CKD, as well as possible pathways through which these two pathologies could be interrelated, found that BMI and uric acid seem to act as mediators of the increased risk of CKD in diabetic patients with FLD, which again points out the role of overweight as a risk factor for the progression of both diseases<sup>(6)</sup>.

Established cardiovascular disease and, among these, cerebrovascular disease and peripheral vascular disease were significantly associated with advanced liver fibro-

**Table 4.** Bivariate analysis of continuous variables and comparison of means between patients with and without fibrosis\*

Variable	Fibrosis (mean, SD)	No fibrosis (mean, SD)	Mean difference	95% CI	p
Age (years)	67.9 (8)	63.4 (9.2)	4.4	(-10.4)-3	0.14
Time on dialysis (years)	6.4 (2.4)	4.6 (3.3)	1.6	(-3.9)-0.6	0.15
Weight (kg)	61.9 (13.4)	67.8 (12.8)	6	(-2.3)-14.4	0.15
Height (m)	1.6 (0.03)	1.6 (0.08)	0.02	(-0.05)-0.007	0.13
BMI (m/m <sup>2</sup> )	23.3 (4.5)	26.3 (5)	3.2	(-0.01)-1.6	0.05
Waist circumference (cm)	91.9 (12.8)	96.1 (10.5)	5	(-2.1)-12.2	0.16
Systolic blood pressure (mm Hg)	151.6 (32.8)	151.9 (27.8)	1.2	(-19)-9.3	0.89
Diastolic blood pressure (mm Hg)	64.1 (10.9)	75.6 (13.2)	8.9	0.3-17.5	0.42
Lean tissue index (kg/m <sup>2</sup> )	14.9 (8.8)	11.3 (5.7)	4	(-10)-2.7	0.17
Fat tissue index (kg/m <sup>2</sup> )	21.6 (16.5)	16.9 (8.9)	5.5	(-16)-5	0.29
Hydration status (L)	30 (6)	29 (7.2)	0.8	(-5.4)-2.3	0.73
Hemoglobin (g/dL)	10.9 (2.3)	10.3 (1.7)	0.1	(-1.3)-0.5	0.72
Platelets x 10 <sup>9</sup> /L	197(106)	222 (83)	24626	(-31858)-81110	0.38
Ferritin (ng/mL)	964 (649)	666 (472)	155.7	(-492)-180.8	0.35
Transferrin saturation index (%)	37 (24.6)	27.3 (14.6)	6.4	(-22.6)-9.7	0.4
LDL (mg/dL)	66.5 (19.7)	88.5 (35.9)	20.6	(-2.1)-11.4	0.75
Total cholesterol (mg/dL)	124.2 (26.6)	156.2 (50)	31.5	0.0004-63	0.05
HDL (mg/dL)	29.3 (11.1)	32.7 (10.8)	3.7	(-3.3)-10.8	0.29
Triglycerides (mg/dL)	141.7 (75.5)	175 (99)	35.9	(-27.2)-99.1	0.26
HbA1c (%)	7.2 (1.1)	5.6 (2.8)	1.4	(-0.2)-(-2.5)	0.01
Creatinine (mg/dL)	8.8 (3)	8.5 (3.1)	0.06	(-2.1)-2	0.95
Urea nitrogen (mg/dL)	45.4 (15.1)	47.1 (14.9)	3.2	(-7.1)-13.5	0.5
Potassium (mEq/L)	5.1 (1.1)	4.9 (0.7)	0.1	(-0.6)-0.3	0.5
Sodium (mEq/L)	136.9 (2.1)	139.3 (2.4)	2.7	1.1-4.4	0.001
Phosphorus (mEq/L)	3.6 (1.5)	4.2 (1.2)	0.39	(-0.4)-1.2	0.37
Parathyroid hormone (pg/mL)	140 (88.1)	381 (366)	153	(-85)-391	0.2
Calcium (mEq/L)	8.6 (0.4)	8.6 (0.6)	0.06	(-0.4)-0.3	0.7
AST (UI/L)	21.3 (10.8)	13 (5.7)	8.5	(-15.7)-(-1.3)	0.02
ALT (UI/L)	22.3 (14)	11.9 (9)	8.3	(-17.6)-0.9	0.07
Albumin (g/dL)	3.8 (0.7)	3.9 (0.4)	0.1	(-0.1)-0.4	0.3
Alkaline phosphatase (IU/L)	119 (26.7)	146 (119.7)	11	(-16)-(-7)	0

\*Quantitative variables are expressed as mean and standard deviation (SD). Table prepared by the authors.

**Table 5.** Bivariate analysis of the sociodemographic characteristics and background of the population and the presence or absence of liver fibrosis\*

Variable	Fibrosis n (%)	No fibrosis n (%)	OR	95% CI	p
Female sex	3 (27)	27 (51)	2.8	0.6-11.5	0.15
Urban residence	9 (82)	49 (92)	2.7	0.4-17.1	0.27
Socioeconomic levels 1 and 2	11 (100)	53 (82)	0.28	0.03-2.3	0.21
Subsidized system	5 (45)	29 (54)	1.4	0.3-5.3	0.57
Mixed race	8 (72)	47 (89)	2.9	0.6-14.1	0.16
High blood pressure	11 (100)	51 (96)	1.2	1-1.3	0.51
HBP > 10 years	11 (100)	51 (96)	1.2	1-1.3	0.51
DM > 10 years	11 (100)	52 (98)	1.2	1-1.3	0.64
Cerebrovascular disease	2 (18)	1 (1.9)	11.5	0.9-141	0.02
Myocardial infarction	1 (9)	3 (6)	1.6	0.1-17.7	0.66
Peripheral vascular disease	3 (27)	4 (7)	4.5	0.8-24	0.05
Heart failure	4 (36)	9 (17)	2.7	0.6-11.5	0.14
Atrial fibrillation	0 (0)	1 (2)	0.8	0.7-0.9	0.64
Retinopathy	2 (18)	5 (9)	2.1	0.3-0.1	0.39
Overweight and obesity	5 (45)	31 (58)	0.5	0.1-2.1	0.42
Metabolic syndrome	4 (36)	23 (36)	0.4	0.1-1.7	0.24

DM: diabetes mellitus; HBP: high blood pressure. Table prepared by the authors

sis<sup>(19,33)</sup>. However, their presence has not been described in other studies. Still, it is plausible to speculate that this association reflects a more severe metabolic disease with a greater probability of target organ damage and a higher risk of liver disease progression.

In our study, AST levels were associated with liver fibrosis and higher levels of AST were found compared to patients without fibrosis, with a mean difference of 8.5 IU/L. AST has been recurrently associated with fibrosis in this type of patient and is part of most non-invasive predictive models of fibrosis, such as NAFLD, APRI, Fibrometer, Lok index, and BARD scores<sup>(20,21,34-36)</sup>. Still, despite finding an association between fibrosis and AST in our patients, neither the NAFLD nor APRI scores adequately classified the subjects based on fibrosis. A possible explanation may be that ESRD has a modifying effect on the factors that have traditionally been associated with chronic liver injury in this population<sup>(37-40)</sup>.

The dilutional hyponatremia characteristic of patients with cirrhosis has been described as a predictor of morta-

lity in patients with decompensated disease<sup>(27,33)</sup>. However, although patients with fibrosis did not present with hyponatremia, they had lower sodium levels when compared to their counterparts (136 mEq/L vs. 139 mEq/L;  $p = 0.001$ ), suggesting an early marker of more advanced liver disease in this group of patients.

The elastographic values used to determine liver fibrosis and cirrhosis were 8.2 kPa (sensitivity: 71%, specificity: 70%) and 13.6 kPa (sensitivity: 85%, specificity: 79%), respectively, were validated in a multicenter study that included 383 patients with suspected FLD in the United Kingdom<sup>(11)</sup>. However, in our study, 10 of the 11 patients with fibrosis had elastographic values  $\geq 10.3$  kPa; the American FLD guideline indicates that values  $\geq 9.9$  kPa have a sensitivity of 95% and a specificity of 77%<sup>(3)</sup>, which, added to the quality criteria established by the manufacturer and normal transaminase levels in the vast majority of patients, reduces the risk of false positives occurring in our study.

Technical failure was observed in 14% ( $n = 7$ ) of the patients, and the manufacturer's quality criteria were not



met in 10.9% (n = 9) of the cases, which is very similar to what is described in the literature reporting approximately 15% of patients for whom adequate measurements are not achieved<sup>(12-14)</sup>. Technical failure is similar to other studies in which its frequency ranges between 1% and 41.7%<sup>(14)</sup>. The most important factors associated with technical failure are a BMI >30 kg/m<sup>2</sup>, operator experience of fewer than 500 examinations, Hispanic race, age over 52 years, hip diameter, and T2DM<sup>(41-43)</sup>. It is possible that including only diabetic patients, among whom more than 50% were overweight or obese, with 96% of patients having a hip diameter above the permitted values, has influenced these differences.

ESRD is a microvascular complication of DM. In our study, 72% of patients with liver fibrosis have kidney damage due to diabetes, which supports the opinion that there is a synergistic relationship between these two diseases<sup>(44,45)</sup>. Furthermore, an epidemiological fact that supports the relationship between trinomial diabetes, chronic liver disease, and ESRD is that patients with FLD, which is considered the initial stage of liver disease due to diabetes, have a higher incidence of ESRD<sup>(46,47)</sup>.

Patients with liver cirrhosis have a higher risk of acute kidney injury and progression of kidney disease, so its timely diagnosis can have important prognostic implications<sup>(48,49)</sup>. In our study, 63% of the patients with liver fibrosis were in the cirrhotic stage, and in no case had this disease been previously identified. The lack of familiarity of dialysis units with the liver complications of diabetes may be causing an underdiagnosis of the disease; an active search is required in these patients to try to reduce the morbidity and mortality associated with the synergy of these two complications.

Chronic liver disease could increase the need for combined kidney and liver transplantation, and this procedure currently represents 10% of all transplants performed in the United States<sup>(50)</sup>.

The use of non-invasive markers in recent years has displaced the use of liver biopsy to determine advanced fibrosis. Positive predictive values (PPV) have been reported for the NAFLD score of 90% to detect cases of advanced fibrosis<sup>(20,51,52)</sup>. However, in this study, the positive and negative predictive value of the NAFLD score was 33% and 66%, respectively, which could suggest that these patients may possess unique characteristics that require validation of the scores in this subgroup before recommending its widespread use in this population. Besides, the APRI score in this study showed a PPV of 41% and NPV of 87% and misclassified more than 50% of patients.

To our knowledge, this is the first study that estimates liver fibrosis in diabetic patients with ESRD on dialysis. Liver fibrosis is an independent predictor of mortality, so its determination in this group of patients is essential<sup>(18)</sup>; its active search in this population could result in strategies that slow the progression of both diseases and improve the quality of life of patients, reduce the number of complications and increase their survival. However, prospective studies are needed to understand better the natural history of patients with ESRD and advanced liver fibrosis.

## CONCLUSION

The prevalence of significant liver fibrosis in patients with diabetes and ESRD is similar to that reported in other populations of patients with diabetes. However, some factors, such as being overweight, could behave differently, which favors the appearance of liver injury with lower degrees of obesity than those previously reported in the literature.

## Conflicts of interest

None.

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