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Detection of Metabolic Dysfunction-Associated Steatotic Liver Disease with FIB4 in End-Stage Renal Disease

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Abstract

Introduction and aim: Liver disease is associated with obesity, diabetes, and steatotic liver, aside from viral causes and alcohol consumption. Likewise, chronic kidney disease shares metabolic risk factors and a viral etiology with liver disease, contributing to its development and accelerated progression. The clinical data for both pathologies is very similar, which makes early identification of liver damage difficult when they overlap. The aim of this study was to identify metabolic dysfunction-associated steatotic liver disease using the fibrosis-4 index (FIB4) since the associated hepatic events impair the quality of life in end-stage renal disease, also describing cardiovascular-kidney metabolic factors that affect both diseases. **Patients and Methods:** The study was realized at a secondary-level referral hospital for hemodialysis of the Mexican Social Security Institute in Northeast Mexico. **Results:** All patients with end-stage renal disease undergoing hemodialysis between 2017 and 2019 were included. Of the 362 patients evaluated, 56.6% were men with an average age of 58 years. The main etiology attributable to chronic kidney disease was hypertension in 92.8%, followed by type 2 diabetes in 71.8%, primary glomerulopathies in 6.9%, and hepatitis C and human immunodeficiency viruses in 0.3% each. The time in hemodialysis was 19 months. Anemia was identified in 93%. The risk of liver fibrosis was identified at 29.5%, and of these, 8% had a FIB4 > 2.67, indicating advanced liver fibrosis. **Conclusions:** The FIB4 is an accessible and useful method for identifying the risk of liver fibrosis in metabolic dysfunction-associated steatotic liver disease in end-stage renal disease undergoing hemodialysis and can be used as an initial tool for assessing liver disease.

Keywords: cirrhosis; liver enzymes; metabolic risk; chronic kidney disease

1. Introduction

Liver disease (LD) has been linked in the last decade to the triad of obesity, diabetes, and steatotic liver [1,2], preceded only by alcohol consumption and viral causes, with hepatitis C (HCV) and B (HBV) viruses standing out and having a significant impact on liver-related morbidity and mortality in the global population [3,4]. This metabolic triad develops due to excessive calorie intake and lack of physical activity, particularly in developing regions such as Latin America [5]. Metabolic dysfunction, including increased insulin, hyperglycemia, dyslipidemia, and systemic inflammatory response, is recognized as the featured event in the development of obesity, diabetes, and steatotic

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liver [6]. Related to this pathophysiological implication, the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, the Latin American Association for the Study of the Liver, and other societies and patient organizations reclassified fatty liver, creating the new terminology of LD, the metabolic dysfunction-associated steatotic liver disease (MASLD) with at least one of the five cardiometabolic risk factors, highlighting the latter due to its progression to cirrhosis [7]. MASLD is a multifaceted disorder with a broad range of clinical phenotypes [8]. The high prevalence of MASLD and chronic kidney disease in patients with diabetes is also noteworthy [9]. It is important to spy on the land MASLD in ERSD, since it could behave as a new phenotype with implications for the response to treatment. ESRD is considered a catastrophic illness due to its impact on quality of life and added cost to healthcare systems, as it entails increased healthcare resources that most hospitals cannot cover. Steatotic liver, superimposed on chronic kidney disease, complicates and accelerates the decline of health and quality of life [10,11]. Liver events related to LD, such as encephalopathy, ascites, anasarca, coagulopathy with thrombosis, and hemorrhagic diathesis, which occur in ESRD undergoing Hemodialysis (HD), are difficult to associate in this context as secondary to liver damage, since they can be attributed to uremia and mask the LD, preventing its timely detection [12]. LD is staged for study and treatment based on inflammation and fibrosis liver, evaluated with needle biopsy; however, non-invasive indirect indices are increasingly used, notably the fibrosis index-4 (FIB4), which is also a simple and safe method that uses four parameters accessible in most hospitals: aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets, and age [13]. The usefulness of FIB4, since its development for evaluating liver fibrosis in hepatitis C and coinfection with the human immunodeficiency virus (HIV) [14], has been demonstrated in the community studies in open population and in specific pathologies such as hepatitis B, C, obesity, and diabetes [15,16]. The relationship between hepatic fibrosis, MASLD and end-stage renal disease (ESRD) undergoing HD has been scarcely explored, with increasing evidence of bidirectional factors affecting the development and progression of both pathologies, making it important to identify liver disease. [17,18]. The aim of this study was to identify undetected MASLD in ESRD undergoing HD using FIB4.

2. Patients and Methods

2.1. Study Design and Ethics Approval

A cross-sectional study was designed to identify hidden MASLD using FIB4, describing cardiovascular kidney metabolic risk factor and biochemical variables in the population with ESRD undergoing HD. The study was approved by the institutional ethics and research committee.

2.2. Patients and Setting

The hospital where the study was conducted is a secondary-level unit of the Mexican Social Security Institute, which attends more than 450,000 beneficiaries in northeastern Mexico, including southern Tamaulipas, northern Veracruz, Hidalgo, San Luis Potosí, and Querétaro. It has 12 hemodialysis machines, performing 76 procedures on a typical day. All patients with ESRD undergoing HD from January 1, 2017, to December 31, 2019, were included.

2.3. Data Collection, Outcomes and Assessments

Electronic medical records and laboratory data were reviewed. FIB4 was calculated using the formula: Age (years) × AST (U/L) / platelets (10^9/L) / ALT (U/L). The variables analyzed were: age, sex, alcohol consumption (considering intake <280g/week in men and <170g/week in women as not significant), etiology of kidney damage, presence or absence of T2D, hypertension, primary glomerulopathies, polycystic kidney disease, ALT, AST, glucose, urea, creatinine, hemoglobin, and platelets, and presence or absence of infection with HCV (Architect HCV core Ag assay® Abbott Diagnostics), HBV (HBsAg Qual II® Abbott Diagnostics), and HIV (HIV Ag/Ab Combo assay®

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Abbott Diagnostics). The degree of anemia was staged using the World Health Organization criteria [18], considering grade 1 anemia with hemoglobin <13 g/dL and >10 g/dL; grade 2: <10 and >8 g/dL; grade 3: <8 and >6 g/dL, and grade 4: <6 g/dL. Glucose was assessed according to the international diabetes management guidelines [19], considering the following in diabetic patients: control; fasting glucose (mg/dL) >70 and <180, uncontrolled >180, and hypoglycemia <70. Transaminases are considered elevated when the ALT or AST value exceeds the upper limit of normal. The cardiovascular metabolic risk factor: sex, age, presence of hypertension, diabetes, and glucose levels were included in the analysis of this study. The risk of hepatic fibrosis, assessed by FIB4, adhered to the parameters previously established for non-alcoholic fatty liver disease: no risk or grade 1 (F0-1) <1.3; advanced fibrosis/cirrhosis (F3-4) >2.67; and for hepatitis C with or without HIV: fibrosis F0-F1 (FIB4 <1.45), F3-F4 (FIB4 >3.25).

2.4. Statistical Analysis

Continuous variables expressed as means (standard deviation). Categorical variables, such as number and percentage, were included. Data normality was assessed using the Shapiro-Wilk test, and the Kruskal-Wallis test was used for comparisons when normality was not found. A p-value <0.05 was considered significant. Statistical analysis performed using SPSS v. 25.

3. Results

The characteristics of the study population from admission to the hemodialysis program, as well as from laboratory results, are presented (Table 1).

Table 1. Study group characteristics.

Variables	**Total (n=362)**
Demographic	
Male	205 (56.6)
Age, years	58.58 ± 13.5
Time on HD, months	19.04 ± 12.86
Etiology of ESRD	336 (92.8)
Hypertension	260 (71.8)
T2D	25 (6.9)
Primary glomerulopathies	9 (2.5)
Polycystic kidney disease	0
HBV	1 (0.3)
HCV	1 (0.3)
HIV	131.02 ± 79.33
Laboratory	117.70 ± 77.23
Glucose (mg/dL)	6.66 ± 4.72
Urea (mg/dL)	6.46 ± 1.45
Creatinine (mg/dL)	0.67 ± 0.86
Total protein (g/dL)	23.22 ± 42.56
Total bilirubin (mg/dL)	25.09 ± 38.08
AST (U/L)	9.11 ± 2.26
ALT (U/L)	228 ± 98.82
Hemoglobin (g/L)	255 (70.4)
Platelets (10^9/L)	78 (21.5)

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FIB4	29 (8)
<1.3	
≥ 1.3 – 2.66	
≥ 2.67	

Abbreviations: HD: Hemodialysis, ESRD: End stage renal disease, T2D: Type 2 diabetes, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, AST: Aspartate amino transferase, ALT: Alanine aminotransferase, FIB4: Fibrosis -4 index.

The majority were male (56.6%), with a mean age of 58. No patient has consumed alcohol above the limit considered harmful by the World Health Organization. The cause of ESRD was hypertension in 92.8%, followed by T2D in 71.8%. The mean time undergoing hemodialysis was 19 ± 12.8 months. All patients underwent serological testing upon admission to the hemodialysis program to assess the presence or absence of hepatitis C, hepatitis B, and HIV. One patient with positive HCV serology and origin of end-stage renal disease was detected, and a real-time viral load test (Abbott Real Time HCV Genotype II®) was performed with a positive result. This patient received treatment with glecaprevir 100 mg and pibrentasvir 40 mg in a fixed-dose combination, three tablets daily for 12 weeks, as indicated by hepatitis C and ESRD management guidelines [20]. The patient was uncomplicated and had a sustained viral response 12 weeks after completing treatment. Additionally, one patient with HIV-associated ESRD, receiving highly active antiretroviral therapy with bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg in a fixed-dose combination, one tablet daily, as indicated in the HIV and ESRD management guidelines[21]. No cases of hepatitis B were detected. Anemia was reported in 93%. The mean hemoglobin level was 9 g/dL. Ninety-one (25%) patients had grade 1 anemia, 128 (35%) grade 2, 98 (27%) grade 3, and 21 (6%) grade 4. All patients received at least one red blood cell transfusion. Regarding blood glucose levels, 260 (71.8%) patients had diabetes, of whom 119 (45.7%) were uncontrolled, 38 (14.6%) had hypoglycemia, and 103 (39.6%) had controlled glucose levels. Table 2 shows the variables associated with the risk of liver fibrosis. No patient had a prior diagnosis of liver disease. Transaminase levels below the lower limit of normal were identified in 89 (24.5%) patients. Regarding the estimation of liver fibrosis risk, 255 (70.4%) had a FIB4 index <1.3, 107 (29.5%) had a FIB4 >1.3, and of these, 29 (8%) had a FIB4 >2.67, indicative of advanced liver disease (F3-4). The patient with hepatitis C presented with advanced fibrosis with a FIB4 >3.25, and the patient with HIV presented moderate fibrosis. In the independent analysis advanced age and prolonged time on hemodialysis increase the risk of liver fibrosis, as did elevated liver enzymes and decreased platelets.

Table 2. Comparation of variables between fibrosis 4 index groups.

Variables	FIB4 <1.3	FIB4 ≥ 1.3- 2.66	FIB4 ≥ 2.67	*p*
Female	109 (42.7)	31 (39.7)	17 (58.6)	0.201
Men	146 (57.3)	47 (60.3)	12 (41.4)	**<0.001**
Age, years	57 (48-66)	63 (58-70)	61 (51.5-72)	**0.029**
Time on HD, months	13 (5-32)	21 (8.7-36)	25 (12-30.5)	0.951
Etiology of ESRD	236 (92.5)	73 (93.6)	27 (93.1)	0.227
Hypertension	189 (74.1)	50 (64.1)	21 (72.4)	0.629
T2D	18 (7.1)	4 (5.1)	3 (10.3)	0.245
Primary glomerulopathies	6 (2.4)	1 (1.3)	2 (6.9)	**0.003**
Polycystic kidney disease	0	0	0	0.161
HBV	0	0	1 (3.4)	0.367
HCV	0	1(1.3)	0	0.062
HIV	104 (82-141)	104 (88.5-154.7)	101 (75-162.5)	0.697

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Laboratory	96 (52-158)	112 (87-159)	108 (85.5-202)	0.121
Glucose (mg/dL)	5.9 (2.4-9.6)	6.9 (2.4-9.6)	6.7 (3.6-9.65)	**0.015**
Urea (mg/dL)	6.34 (5.6-7.3)	6.6 (5.8-7.3)	5.9 (5.2-6.9)	**<0.001**
Creatinine (mg/dL)	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.6 (0.47-1.05)	**<0.001**
Total protein (g/dL)	13 (10-18)	22.5 (16-35.2)	44 (26.5-64.5)	0.613
Total bilirubin (mg/dL)	16 (10-23)	19.5 (15-39.2)	23 (17.5-37)	**<0.001**
AST (U/L)	8.8 (7.8-10.5)	9 (7.8-10.45)	8.1 (7.2-11.15)	
ALT (U/L)	229 (189-295.5)	181 (150-210)	139 (99-163)	
Hemoglobin (g/L)				
Platelets (10^9/L)				

Abbreviations: HD: Hemodialysis, ESRD: End stage renal disease, T2D: Type 2 diabetes, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, AST: Aspartate amino transferase, ALT: Alanine aminotransferase, FIB4: Fibrosis -4 index.

4. Discussion

In this study of 362 Mexican patients with ESRD undergoing HD, 21.5% were detected MASLD by FIB4 > 1.3 and 8% with cirrhosis by FIB4 > 2.67. Cardiovascular-kidney metabolic (CVKM) risk factors predominate, which are also implicated in the development of MASLD. One of the major CVKM risk factors, hypertension, was found to be the main etiology of ESRD, as already reported in previous studies [23]. One underexplored factor is the relationship between hypertension and the development of MASLD; however, published studies have implicated high salt intake and large vessel stiffness, which are related to both hypertension and the development of MASLD [24,25]. Therefore, further studies are needed on how hypertension can affect inflammation and liver damage in populations with cardiovascular-kidney metabolic syndrome. The second most common etiological factor was T2DM, highlighting metabolic uncontrolled in half of the patients (48%), which has been identified as an independent risk factor for the progression of liver and kidney injury [26,27]. Diabetic nephropathy with albuminuria with insulin deficiency leading to hyperglycemia and glycosylation of proteins affecting the renal filtration membrane is a recognized entity; however, diabetic nephropathy without albuminuria has been identified as well as without diabetes as obese nephropathy, where other factors, such as adipose tissue, contribute to kidney injury, releasing proinflammatory cytokines and growth factors, leading to podocyte and mesangial cell injury and glomerulosclerosis, it could also associated with other phenotypes of MASLD [28,29]. This is not yet clearly defined, and prospective studies are needed that may explore pathways of fibrosis that decrease functional reserve in both organs. Furthermore, the presence of steatotic liver in patients with diabetes alters the response to treatment, so the presence or absence of MASLD should be integrated into therapeutic algorithms for diabetes management [30]. The prevalence of HCV infection was 0.3%, like that reported in the 2018 Mexican National Health and Nutrition Survey [31], which, compared to previous reports, has decreased considerably, with prevalences >2% and the highest rates identified in people with chronic liver disease, ranging from 6.7% to 77% [32]. All patients have received at least one unit of red blood cells, which continues to be a risk for the transmission of HCV, HBV, and HIV. Although no cases of HBV were found in this study, one case of HCV and HIV was found, in addition to 47 patients (13%) with elevated liver enzymes. Genomic testing was only performed in two patients, guided by positive serology for HCV and HIV. However, it is necessary to emphasize that, especially in risk groups and with a marker of liver damage such as elevated liver enzymes, molecular determination for the main hepatotropic viruses (HBV, HCV) should not be omitted, since a clinical variant in this group is occult hepatitis with negative antibodies [33]. Carry out genomic testing, timely diagnosis, and treatment in the hepatitis C population, where universal access to direct-acting antivirals can improve liver function and prevent advanced damage,

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and where timely initiation of highly active antiviral therapy for HIV can improve liver and kidney function, as has already been demonstrated [34,35].

The main limitation of the study is its retrospective nature, which means that information about physical activity, diet, hip circumference, and specific lipid profiles such as HDL, LDL, cholesterol, and triglycerides could not be included for analysis and weighting on the overall population risk associated with MASLD. Therefore, prospective studies focused on identifying cardiovascular and metabolic risk factors in this population, which is known to have one of the highest cardiovascular risks considered a leading cause of death, are necessary. The prevalence of liver fibrosis identified in this study by FIB4 >1.3 was 29.5%, above the reported global prevalence of 25% [36] but lower than reported in the Mexican population at 45% [37] It is possible that the transaminase washout is related to HD in this group, but this has been reported by few researchers with contradictory results, primarily in liver damage secondary to hepatitis C and ESRD undergoing HD so more studies are needed to clarify it [38,39]. Highlight that in this study, etiologies of renal damage are recognized also for the development of liver disease, such as diabetes, which stood out in this study. Therefore, it is necessary to perform timely detection of LD in populations with cardiovascular- kidney metabolic risk, since the main factors, such as diabetes and dyslipidemia, are modifiable [40]. We need studies about the effect that regression of hepatic fibrosis would have on renal function, since the evidence so far is scarce [41]. In this study, we found 8% with advanced fibrosis, which increases the incidence of liver events, raising mortality. The predominant cardiovascular risk phenotype was hypertension; we can also mention that being a woman aged 61 years and having been on hemodialysis for ESRD for at least 25 months is associated with advanced hepatic fibrosis (FIB4 > 2.67). The use of FIB4, as recommended by the European Association for the Study of Liver Disease in its guideline for the management of steatotic liver disease, is a simple and safe tool for implementing active screening [42], detecting and addressing high-impact comorbidities for its development, and controlling obesity, diabetes, hypertension, and viral liver diseases [43].

5. Conclusions

The FIB4 is a handy and safe tool for the initial screening of LD in ESRD undergoing HD, to achieve timely diagnosis and address modifiable risk factors to prevent the development of liver cirrhosis in this population. However, even more valuable is its systematic approach to the early identification of steatotic liver disease in the initial stages of obesity, diabetes, hypertension, vascular disease, and coronary artery disease, since the effect that metabolic dysfunction associated with steatotic liver disease may have on the progression and development of catastrophic events such as end-stage renal disease, cirrhosis, stroke, and heart attack is still unclear.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Health Research committee 2801 of Hospital General Regional 6, register COFEPRIS 20 CI 28 009 001.

Informed Consent Statement: The study was conducted using only electronic medical record and laboratory data.

Data Availability Statement: Where no new data was created.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ESRD	End stage renal disease
FIB4	Index of fibrosis – 4
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Hemodialysis
HIV	Human Immunodeficiency virus
LD	Liver Disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
T2D	Type 2 diabetes

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