Original article

Prevalence of liver fibrosis in an unselected general population with high prevalence of obesity and diabetes mellitus. Time for screening?

Diego García-Compeán [a,*], Jesús Zacarías Villarreal-Pérez [b],
Manuel Enrique de la O. Cavazos [c,e], Fernando Javier Lavalle-Gonzalez [b],
Omar David Borjas-Almaguer [a], Angel Noé Del Cueto-Aguilera [a],
José Alberto González-González [a], Consuelo Treviño-Garza [c,e], Lourdes Huerta-Pérez [d,e],
Héctor Jesús Maldonado-Garza [a]

[a] Gastroenterology Service, Internal Medicine Department, University Hospital and Faculty of Medicine, Autonomous University of Nuevo León, Monterrey, N.L., Mexico
[b] Endocrinology Service, Internal Medicine Department, University Hospital and Faculty of Medicine, Autonomous University of Nuevo León, Monterrey, N.L., Mexico
[c] Department of Pediatric, University Hospital and Faculty of Medicine, Autonomous University of Nuevo León, Monterrey, N.L., Mexico
[d] Faculty of Public Health and Nutrition, Autonomous University of Nuevo León, Monterrey, N.L., Mexico
[e] Ministry of Health of the Government of the State of Nuevo León, Monterrey, N.L., Mexico

ARTICLE INFO

ABSTRACT

Introduction: Cirrhosis and liver cancer are currently common causes of death worldwide. The global epidemic of obesity has increased the incidence of nonalcoholic fatty liver disease (NAFLD) and cirrhosis in recent years. Advanced fibrosis increases the morbimortality rate in NAFLD. The Mexican population has one of the highest prevalence of obesity and diabetes mellitus (DM) worldwide.
Aim: To determine the prevalence of advanced liver fibrosis in Mexican general population.
Methods: Adult individuals, without a history of liver disease nor heavy alcohol consumption were randomly sampled from 20,919 participants of a health and nutrition survey applied to the general population. Clinical and laboratory evaluations were performed to calculate the NAFLD fibrosis score (NFS) (an extensively validated non-invasive method). Two cut-off points were used. Advanced fibrosis was defined as a result >0.676.
Results: In total 695 individuals were included. The mean age was 47.8 ± 16.4. The majority were between 20 and 50 years (59%), 70.2% were female, 35.5% showed obesity and 15.8% DM. The 93% had normal serum ALT. Based on the NFS results, 56 individuals (8.1%) had a high probability of fibrosis. Most patients from this subgroup showed normal serum ALT (92.9%), 89.3% were >45 yr. old, 52% were obese and 27% suffered from DM.
Conclusions: Based on these results, 8.1% of Mexican general population without a history of liver disease is at high risk of having advanced liver fibrosis and complications and death derived from cardiovascular disease and cirrhosis. Most of them showed normal ALT serum levels.

© 2020 Published by Elsevier España, S.L.U. on behalf of Fundación Clínica Médica Sur, A.C. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Cirrhosis and liver cancer are currently the 11th and the 16th most common cause of death globally. In Latin America, cirrhosis is the 9th cause of death, representing 2.7% of the total deaths. Cirrhosis has an incidence of 15.6 per 100,000 inhabitants. It is within the top 20 causes of disability-adjusted life years and years of life lost, accounting for 1.6% and 2.1% of the worldwide burden. Excessive alcohol consumption is the most frequent cause of cirrhosis in the world; other causes are viruses, medication intake, and autoimmunity. Recently, the global epidemic of obesity and diabetes mellitus which affects 2 billion and 400 million subjects worldwide respectively, have significantly increased the incidence of non-alcoholic fatty liver disease (NAFLD) and related liver disease (cirrhosis and hepatocellular carcinoma) [1].

NAFLD is a metabolic disorder characterized by macro vesicular steatosis in more than 5% of hepatocytes in individuals without significant alcohol consumption, drug intake, or other known causes of steatosis [2]. It is closely associated with the metabolic syndrome (MS) which is a constellation of abnormalities, such as visceral obesity, insulin resistance, diabetes mellitus (DM), hypertriglyceridemia, and arterial hypertension. It is the hepatic manifestation of a disequilibrium in the metabolic status (MS, intestinal dysbiosis, adipokine changes, vitamin D deficiency, hypercortisolism) in which the central factor is insulin resistance [3]

NAFLD affects a third of the world's population and its incidence continues to increase. The risk of progression to cirrhosis in NAFLD seems to be low, with an incidence of 3.1% over a mean 7.6-year follow-up [4]. However, these figures can be underestimated, since in about 25–30% of patients, NAFLD is diagnosed in the inflammatory phase called non-alcoholic steatohepatitis (NASH), characterized by hepatocellular damage. Currently 30–40% of patients with NASH-cirrhosis succumb to a liver related death within 10 years and hospitalizations have increased 97% between 2000 and 2012 which have significantly increased the burden of this condition [5].

Advanced age, diabetes mellitus, and visceral obesity are the most important factors involved in the development of liver fibrosis in NAFLD. The stages of liver fibrosis are classified as F0 (without fibrosis), F4 (cirrhosis) and >F2 advanced or significant fibrosis [6]. Advanced fibrosis, (and not inflammation) is independently associated with a significant increase in the mortality rate from cardiovascular disease (CVD) and liver disease [7–9]. The progression rate from NASH to cirrhosis and hepatocellular carcinoma is from 5 to 18% when fibrosis is absent and of 40% when is present [10–12]. For this reason, the detection of advanced fibrosis is crucial for therapeutic decisions [13]. Previously, liver biopsy was the only available method to evaluate liver fibrosis. However, it is an invasive and expensive procedure, subjected to sampling errors and to severe complications. In recent years, several non-invasive methods, based on serological biomarkers and radiological methods have been developed [14].

The improvement of socioeconomic conditions, the migration to urban areas and the changes in habits and diet of the Mexican population in recent decades have resulted in a significant increase in the prevalence of obesity, CVD and DM [15,16]. According to the Ministry of Health of Mexico, the number one leading cause of mortality in 2008 was DM (14%), followed by CVD (11%) and stroke (5.6%) [17]. The International Diabetes Federation estimates that Mexico has the highest prevalence of DM of adults in OECD countries (15%) [18]. All the above discussed led us to speculate that screening for liver fibrosis in the general population of Mexico might detect naïf individuals affected by chronic liver disease in whom the application of therapeutic measures might reduce mortality, as well as the financial burden derived from cirrhosis and hepatocellular carcinoma.

2. Aims

In a first step, we determined the prevalence of advanced liver fibrosis in Mexican general population; in subjects without excessive alcohol consumption or a history of known liver disease using an inexpensive, readily available and extensively validated non-invasive method.

3. Patients and methods

3.1. Design and patients

The subjects included in this research were randomly selected from a big sample of 20,919 individuals (of all ages and both sexes) of the general population who previously participated in the Health and Nutrition Survey applied by the Ministry of Health of the Government of the State of Nuevo León, in 2015. The survey was applied to gather information on the socio-demographic profile, health, and dietary and nutritional status of the population.

In an observational cross sectional and prospective survey, clinical and laboratory data were collected to select individuals. Laboratory evaluation included routine liver tests (AST and ALT, total bilirubin, total proteins, albumin, alkaline phosphatase, and γ-glutamyl transpeptidase (GGT)), and complete blood count, fasting serum glucose, total cholesterol, HDL cholesterol, and serum triglyceride levels. Additionally, (systolic and diastolic) blood pressure, body weight, height and waist circumference were measured. The socioeconomic level of individuals was also classified according to socioeconomic parameters established by the Instituto Nacional de Estadistica y Geografia (INEGI), an institution in charge of performing national population and economic censuses. These parameters were: housing characteristics, family and individual economic income, level of schooling, working conditions, etc.

The body mass index (BMI) was calculated using the formula: body weight (in kg)/height (in m^2). Waist circumference was measured in the midway between the lowest rib edge and the iliac crest. Visceral obesity was defined as a waist circumference >102 cm in men and >88 cm in women. The presence of DM was established by fasting serum glucose >126 mg/dL or treatment with antidiabetic drugs. Overweight and obesity were defined by BMI values from 25 to 29.9 kg/m^2 and >30 kg/m^2 respectively.

For the final analysis, the subjects under 20 years old, those with a history of known liver disease and those who recorded alcohol consumption greater than 30 g/day in men and 20 g/day in women for a period of more than 5 years were excluded.

The NAFLD fibrosis score (NFS) was calculated based on the previously published formula that can be found on http://nafldscore.com/ $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ impaired fasting glycemia or diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet ($\times 109$/L) $- 0.66 \times$ albumin g/dL [19].

Two cut-off points were used to categorize the subjects into three groups:

(a) Low probability of advanced fibrosis: value <-1.455
(b) High probability of advanced fibrosis: value >0.676
(c) Indeterminate probability: value from -1.455 to 0.676

The Ethics Committee of the Faculty of Medicine of the Autonomous University of Nuevo León approved this study, and all individuals gave their consent for participation into the study.

3.2. Statistical analysis

Categorical variables were expressed as medians and ranges and were statistically analyzed using Chi^2 tests. Continuous variables were expressed as means and standard deviations and were analyzed by Student's t-test, Mann–Whitney U-test, ANOVA, and Kruskal–Wallis test. Two-sided values of alpha <0.05 were considered statistically significant. Statistical software (Version 25.0, SPSS, and Chicago, IL) was used for the statistical analysis.

4. Results

4.1. Patient characteristics

From 1544 subjects evaluated, 695 were finally included. The causes of elimination were age <20 years: 588; incomplete data or history of liver disease: 202; and excessive alcohol consumption: 59 (Fig. 1).

The demographic, clinical and laboratory characteristics of the total number of subjects are shown in Table 1. The average age of the population was 47.8 ± 16.4 years. The majority of subjects were between 20 and 50 years old (59%). Likewise, 38% of the subjects were aged between 20 and 40 years. The majority were female (70.2%); 35.5% had obesity; 70.2% of the cases showed overweight or obesity and the average waist circumference was 97 ± 13.5 cm. Similarly, 71.2% of the subjects belonged to the medium socioeconomic strata. Finally, 15.8% of the subjects had DM and 93.2% showed normal ALT blood levels.

Fig. 1. Recruitment algorithm of the study.

4.2. NFS results

Based on the results of the NFS, 353 subjects (50.8%) had a low probability of fibrosis (NFS < −1.544); 56 (8.1%) had a high probability of fibrosis (NFS > 0.676), and 286 (41.2%) showed an indeterminate probability of fibrosis (NFS from −1.544 to 0.676) (Fig. 2).

Table 1
Demographic, clinical and biochemical characteristics of 695 individuals included into the study and comparison intergroup according the NAFLD fibrosis score results.

Characteristic	Total group N = 695	Low probablity N = 353	Indeterminate n = 286	High probability n = 56	p
Age, yr.	47.8 ± 16.4	39.3 ± 12.5	55.3 ± 14.7	63.7 ± 15.9	<0.001
≥45 yr. n (%)	372 (53.5)	111 (31.4)	211 (73.8)	50 (89.3)	<0.001
Female, n (%)	488 (70.2)	258 (73.1)	190 (66.4)	40 (71.4)	0.183
Body weight, kg	73.4 ± 17.3	70.8 ± 15.2	74.7 ± 16.6	83.1 ± 26.9	0.001
Height, m	1.59 ± 0.9	1.60 ± 0.9	1.59 ± 0.9	1.59 ± 0.8	0.039
Body mass index	28.6 ± 6.1	27.4 ± 4.9	29.2 ± 6.0	33.5 ± 10.0	<0.001
Overweight	241 (34.7)	124 (35.1)	101 (35.3)	16 (28.6)	0.33
Obesity	247 (35.5)	106 (30)	112 (39.1)	29 (52)	0.001
Overweight + Obesity	488 (70.2)	230 (65.1)	213 (74.4)	45 (80.3)	0.008
Waist, cm	96.9 ± 13.5	93.4 ± 12.0	99.2 ± 13.3	106.3 ± 16.6	<0.001
Systole, mmHg	117.1 ± 16.2	113.0 ± 14.3	121.6 ± 16.3	120.5 ± 19.9	<0.001
Diastole, mmHg	75.6 ± 12.1	74.1 ± 10.9	77.5 ± 12.3	75.5 ± 16.1	0.005
Economic level, n(%)					0.034
Low	179 (25.8)	109 (30.9)	58 (20.3)	12 (21.4)	0.15
Medium	495 (71.2)	233 (66)	219 (76.6)	43 (76.7)	0.10
High	21 (3)	11 (3.1)	9 (3.1)	1 (1.8)	0.56
Type 2 Diabetes Mellitus, >126 mg/dL	110 (15.8)	28 (7.9)	67 (23.4)	15 (26.8)	<0.001
Biochemistry, mean ± SD					
Hemoglobin, g/dL,	14.0 ± 4	13.8 ± 1.5	14.3 ± 5.9	13.8 ± 1.2	0.773
MCV, fL	87.5 ± 6.0	86.5 ± 6.5	88.3 ± 5.3	89.6 ± 4.0	<0.001
MCH, pg	30.3 ± 2.2	30.1 ± 2.38	30.5 ± 2.1	30.9 ± 1.8	0.021
Platelet count, K/uL	236.7 ± 67.0	267.2 ± 68.0	212.1 ± 46.1	170.3 ± 50.1	<0.001
MPV, fL	11.2 ± 1.1	11.01 ± 1.1	11.4 ± 1.1	11.8 ± 1.1	0.106
Serum glucose, mg/dL	113.8 ± 48.5	104.6 ± 44.1	122.8 ± 51.0	125.7 ± 51.3	<0.001
Total cholesterol, mg/dL	185.2 ± 37.8	184.1 ± 36.9	185.0 ± 38.1	193.2 ± 41.3	0.398
HDL, mg/dL mean ± SD	46.9 ± 13.7	46.9 ± 13.9	46.5 ± 12.9	48.9 ± 15.8	0.719
Triglycerides, mg/dL	165.9 ± 102.3	162.9 ± 104.8	166.6 ± 98.8	181.0 ± 104.6	0.001
Albumin, g/dL	4.46 ± 0.4	2.8 ± 0.4	2.8 ± 9.4	2.6 ± 0.5	<0.001
AST, UI/L	21.6 ± 12.0	21.2 ± 19.9	21.4 ± 10.8	25.6 ± 17.3	0.019
ALT, UI/L	23.1 ± 21.7	20.2 ± 16.1	21.0 ± 16.5	25.2 ± 25.7	0.043
ALP, UI/L	102.6 ± 50.6	95.5 ± 43.8	107.0 ± 51.6	124.4 ± 73.3	<0.001
ALT < 50 UI/L, n (%)	648 (93.2)	324 (91.8)	272 (95.1)	52 (92.9)	0.250

SD: standard deviation; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MPV: mean platelet volume; HDL: high-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase.
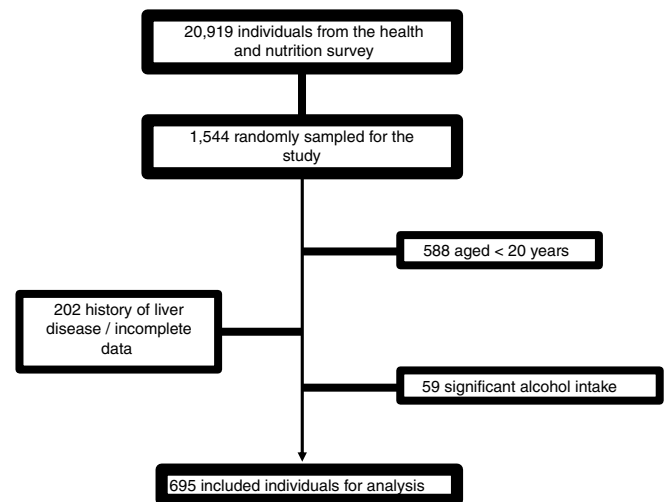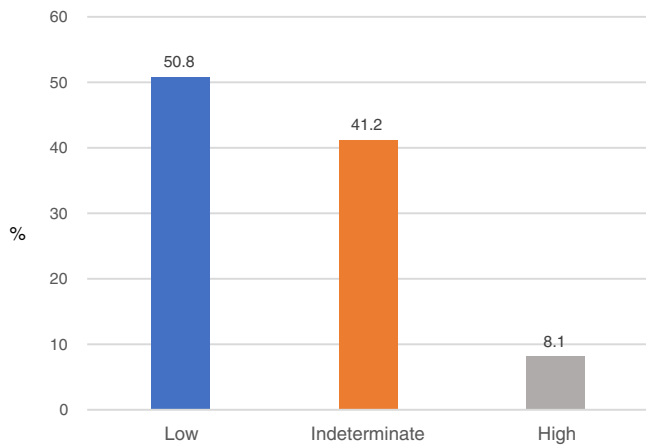
Fig. 2. Probability of advanced liver fibrosis of 695 patients of the general population according to the NAFLD fibrosis score results.

4.3. Differences among groups

Demographic, clinical and laboratory characteristics of the groups showing low, high and indeterminate probability of fibrosis are shown in Table 1. The subjects in the high-risk group were significantly older than those of the other groups. In this high-risk group, 89.3% were aged >45 years, 52% had any grade of obesity, and 80.3% were overweighed or obese and showed the highest values of waist circumference and blood pressure. The medium socioeconomic level was predominantly in the high-risk group. The prevalence of DM in the high-risk group was the highest compared to that observed in the indeterminate and low-risk groups: 27%, 23%, and 8% respectively.

Finally, high-risk subjects showed significantly lower values in blood platelet count, albumin levels, and higher values in total triglyceride, AST, ALT, and alkaline phosphatase blood levels as compared to subjects from the other groups. 92.9% of the patients from the high-risk group showed normal ALT serum levels.

5. Discussion

Although liver cirrhosis is a major health problem worldwide because of its high mortality and heavy financial burden, it has not received the required attention by policy-makers, public opinion, nor physicians.

Until now, most published screening studies for liver fibrosis have been performed in targeted population based on the presence of risk factors of NASH (DM, metabolic syndrome, visceral obesity). Only few screening studies in unselected population have been published worldwide [20–23] (Table 2). Fibro Test (FT) and transition elastography (TE) were used as screening tests. FT is a biomarker that includes α2 macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, and GGT [24]. TE involves measuring liver stiffness as a reflection of fibrosis [25]. Both methods have been extensively validated with histological confirmation of fibrosis of any etiology [26–28]. The prevalence of liver fibrosis obtained in unselected population ranged from 0.9 to 6.9% [20–23]. The studies showing a higher prevalence of fibrosis included individuals with a higher prevalence of DM, visceral obesity, metabolic syndrome or used lower cut-off points of the screening method. In the study with the lowest prevalence (0.9%), a high cut-off point of FT was used (>0.59) [22].

In other three studies that stratified members of the general population according to an age cutoff >40 and 45 years [29–31], the overall prevalence of fibrosis ranged from 2.6 to 7.5% (Table 2).

Table 2
Published studies screening for significant/advanced liver fibrosis (F>2) in general population.

Author (year)	Location	Sample size, n	Population selection. Age	Risk factor prevalence (%)	Method (cut-off points)	Fibrosis prevalence %	Normal ALT prevalence, %§
Wong VW[20] (2012)	Hong Kong	759	Unselected. Invited at random. >18 yr.	BMI > 25 (23) DM (5.2)	TE (>9.6 kPa)	2.0	54.2
Fabrellas N[21] (2013)	Spain	495	Unselected. Invited at random. >18 yr.	NS	TE (>6.8 kPa)	5.7	NS
Zelber-Sagi S[22] (2012)	Israel	338	Unselected. Sample from health and nutrition survey. >25 yr.	DM (6.8) BMI > 25 (33.7)	FT (>0.59)	0.9‡	NS
You SC[21] (2015)	South Korea	164	Unselected. Primary care. >18 yr.	BMI > 25(41.5) DM (11.9)	TE (>7.0 kPa)	6.9	91
Poynard T[27] (2010)	France	7463	Primary care. >40 yr.	BMI > 27 (32.5) DM (15.3)	FT (>0.48)	2.6	75
Roulot D[30] (2011)	France	1190	Primary care. >45 yr.	BMI >25(62) MS (20.3)	TE (>8 kPa)	7.5	43
Koehler EM[31] (2016)	Netherlands	3041	Invited at random >45 yr.	BMI > 25 (71.5) DM (11.1)	TE (>8 kPa)	5.6	NS
Koehler EM[31] (2016)	Netherlands	832	Sub analysis of the main study. >45 yr.	NAFLD (100) Age > 45 (100)	TE (>8 kPa)	8.4†	NS
Current study (2019)	México	695	Unselected. Sample from health and nutrition survey. >20 yr.	BMI > 25(70.2) DM (15.8)	NAFLD fibrosis score (>0.676)	8.1	93
Current study (2019)	México	372	Sub analysis of the main study. >45 yr.	BMI >25 (70.4) DM (21.5)	NAFLD fibrosis score (>0.676)	13.4†	92

BMI: body mass index, DM: diabetes mellitus, TE: transient elastography, FT: fibro test, NS: non-specified.

† Sub analysis of the main study.
‡ Without borderlines.
§ Prevalence in fibrosis-patients group.

Table 3
Results of studies of the NAFLD fibrosis score for diagnosis of advanced liver fibrosis (F > 2) determined by biopsy in patients with NAFLD.

Study (year, Country)	N	Design	AUROC	NPV (low cut-off)	PPV (high cut-off)	Accuracy
Angulo P (2007, International)[19]	480	P, MC	0.88	0.93	0.90	0.90
Ruffillo G (2011, Argentina)[34]	138	R, SC	0.70	0.81	1.00	0.82
Demir M (2013, Germany)[35]	120	R, SC	0.96	0.96	1.00	0.84
Pérez-Gutiérrez OZ (2013, México, Chile)[36]	228	R, TC	0.72	0.95	0.26	0.84
Cales P (2009, France)[38]	235	P, TC	0.88	0.86	0.86	0.86
Mc Pherson S (2010, United Kingdom)[39]	145	P, MC	0.81	0.92	0.79	0.88
Wong VW (2010, France, China)[40]	274	P, TC	0.75	0.89	0.61	–
Petta S (2015, Italy)[41]	321	P, TC	0.80	0.90	0.85	0.77
Boursier J (2016, France)[42]	588	R, TC	0.71†	0.80	0.54	0.66
Petta S (2017, Italy, France, China)[43]	761	P, MC	0.77	0.87	0.73	0.72

† Cut off point: −1.036; P: prospective; MC: multicenter; TC: two centers; R: retrospective; SC: single center; NPV: negative predictive value; PPV: positive predictive value.

Table 4
Results of studies of NAFLD fibrosis score for prediction of morbidity and mortality rates among patients with NAFLD.

Author (year)	N	Design	Follow-up, yr.	Primary outcomes	Results
Angulo P (2013)[47]	320	R, M	8.6	Liver related complications, death, or transplantation	The HRs for liver-related complications, deaths or transplantation in the indeterminate and high-risk groups, were significantly higher compared with the low-risk group. NFS was superior to APRI, BARD and Fib-4.
Treeprasertsuk S (2013)[50]	302	R, SC	12	All cause, CVD and liver related death	A higher NFS at baseline and a new onset of CVD were significantly predictive of death. All-cause mortality: 6.6% (low NFS), 19.4% (indeterminate NFS) and 46.2% (high NFS).
Kim WR (2013)[37]	4083†	P	14.5	All-cause mortality	High risk group showed 69% increased CVD mortality compared with low risk group for NFS, APRI and Fib-4.
Xun YH (2014)[51]	180	R, SC	6.6	All-cause mortality	NFS was the only predictor of death (HR 2.74, 95% CI 1.67–4.5). NFS was superior to FIB-4, APRI and BARD.
Sebastiani G (2015)[52]	148	R, SC	5	All-cause mortality	HR for all-cause mortality in the high-risk group (NFS > 0.676) was: 11.9 (95% CI: 3.7–37.3).

P: prospective; R: retrospective; SC: single center; HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease.

† This analysis utilized the National Health and Nutrition Examination Survey conducted in 1988–1994.

The lowest estimate used a two-step approach with only half of the patients re-attending for the second test [29].

Finally, in a sub-analysis of one of these studies involving 832 patients with NAFLD (after excluding excessive alcohol consumption, viral infection and drug toxicity) the prevalence of fibrosis was higher than that observed in the total group (8.4 vs. 5.6%) (Table 2).

Our study is the first screening study to detect liver fibrosis in an unselected general population in Latin America. The epidemiological characteristics (high prevalence of obesity and DM) of the Mexican population made us to carry out this research. Besides, Mexican population have higher genetic susceptibility, than other ethnic groups, to develop NAFLD, since the PNPLA3 gene (which is closely related to the development of steatosis, NASH, and liver cirrhosis), has been found in 70% in Mexican population [32,33].

The prevalence of fibrosis obtained in our study (8.1%) was higher than that observed in other unselected population studies [20–23] probably due to the higher prevalence of DM and obesity of our population. This prevalence was also higher than that observed in the studies stratified according to an age >40 and 45 years [29,30] and similar to that observed in the sub-analysis of NAFLD individuals stratified by age >45 years [31]. Notwithstanding, our work included subjects aged between 20 and 75 years. In a sub-analysis of our study, with 372 individuals aged >45 years, the prevalence of fibrosis increased to 13.4% that was higher compared to all the above-reviewed screening studies (Table 2).

The FT (Fibro Test®) is a patented method and the TE (Fibroscan®) is a radiological procedure requiring specialized equipment and trained personnel, so they are expensive and do not have wide availability in many centers. Due to this, their use as screening tools for large populations may not be cost-effective.

In our study, we decided to use NAFLD fibrosis score due to its following characteristics:

a. It uses an algorithm that includes clinical and biochemical parameters that can be easily obtained in the doctors' office at a very low cost. In Mexico, the approximate calculated cost per test of NFS is $ 34 dollars. In contrast, the costs of Fibrotest® and Fibroscan® are $ 260 and $ 215 dollars respectively.
b. It was designed for subjects with NAFLD [19].
c. It has been extensively validated with liver biopsy showing AUROC values from 0.70 to 0.96, negative predictive values (NPV) from 81 to 96%, positive predictive values (PPV) of 90% and an accuracy from 66 to 90%. Therefore, it is considered as an excellent method to rule out fibrosis [19,34–43], so that the American Association for the Study of Liver Diseases (AASLD) recommends it as a useful tool for screening fibrosis in patients with NASH [44] (Table 3).
d. It has a diagnostic performance mildly lower than the TE, which is currently the best noninvasive method for the diagnosis of fibrosis [45]. Besides, most published studies have reported that NFS has higher performance than other non-invasive biomarkers, such as APRI, FIB-4, BARD, AST/ALT ratio [46–49].
e. It has outcome-predictive capacity in NAFLD patients. In studies with a follow-up from 5 to 14.5 years, patients with a high and indeterminate probability of fibrosis had significantly higher rate

of death from any cause, due to CVD and liver disease compared to patients at low risk [37,47,50–52] (Table 4).

The individuals detected here as having high probability of fibrosis, represent a relevant proportion of the general population which may be at risk of suffering a chronic liver disease, and with a well-documented probability of having complications and death from CVD, cirrhosis and hepatocellular carcinoma. It is important to highlight that 93% of these individuals had normal ALT blood levels. A similar prevalence of normal liver enzymes in high-risk subjects (43 to 91%) has been reported in other screening studies [20,23,29,30]. Considering that Mexico's population is 120 million inhabitants, of which 63.6% are over 20 years old (76, 320,000 inhabitants) [53], extrapolating the results of this study, it can be estimated that around 6,181,920 subjects (8.1%) may be at risk.

Our study has some limitations: (a) No reinvestigations in order to confirm advanced fibrosis were performed; (b) No follow-up to determine morbidity and mortality rates, in high-risk subjects was done; and (c) We did not take into account subjects with an indeterminate probability of fibrosis. The proportion of fibrosis in this group is highly variable (from 35 to 60%) [19,34–36]. However, these limitations were the result of the nature of our research conducted in the open population.

The results of this and other similar studies may support the need to perform screening for liver fibrosis in general populations as part of public health policies [54,55], particularly in those communities with a high risk of liver disease. Screening should be done ideally with a non-invasive and low-cost test, with adequate reliability for fibrosis detection, easy to apply and widely available. Whether or not one of the currently available tests may be able to gather these properties is unknown.

The justification for screening for liver fibrosis in general populations is because subjects with early stages of fibrosis are completely asymptomatic, most of them have normal transaminase blood levels and the fibrosis progression is quietly slow (7.7 years for each stage of fibrosis in NASH) [56]. In most cases, liver fibrosis manifests clinically in advanced stage, as decompensated cirrhosis, particularly in diseases in which serological markers for early detection are lacking (such as NAFLD). The detection of patients in the pre-cirrhotic phase of the process, would allow the application of preventive or corrective measures to reduce the progression of the disease and consequently, the mortality rate and the financial burden derived from the care of complications. Although the FDA has not approved any drug for the treatment of NASH, the substantial loss of body weight by bariatric surgery or lifestyle changes, reduces liver fibrosis and inflammation in patients with NASH and possibly improves the prognosis [57–59]. Besides, new drugs that promise to have important therapeutic effects (Obeticholic acid, selonsertif, elafibranor, cenicriviroc) are under intensive evaluation currently [60,61].

6. Conclusions

According to the results of our study in the adult Mexican general population, the prevalence of advanced liver fibrosis is 8.1%. In the future, studies that confirm or rule out fibrosis through complementary studies, and that include long-term follow up with the application of preventive and corrective measures and the analysis of the cost-benefit relationship will be decisive to determine the validity of systematic screening for liver fibrosis in general populations.

Ethics

The study was approved by the Ethics Committee of the Faculty of Medicine of the Autonomous University of Nuevo León. Informed consent and assent were obtained from participants in the survey.

Funding

Conflict of interest

The authors have no conflicts of interest to declare.

References

[1] Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70:151–71, http://dx.doi.org/10.1016/j.jhep.2018.09.014.

[2] Puri P, Sanyal AJ. Nonalcoholic fatty liver disease: definitions, risk factors, and workup. Clin Liver Dis 2012;1:99–103, http://dx.doi.org/10.1002/cld.81.

[3] Abenavoli L, Milic N, Di Renzo L, Preveden T, Medić-Stojanoska M, De Lorenzo A. Metabolic aspects of adult patients with nonalcoholic fatty liver disease. World J Gastroenterol 2016;22:7006–16, http://dx.doi.org/10.3748/wjg.v22.i31.7006.

[4] Dam-Larsen S, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. Scand J Gastroenterol 2009;44:1236–43, http://dx.doi.org/10.1080/00365520903171284.

[5] Vreman RA, Goodell AJ, Rodriguez LA, Porco TC, Lustig RH, Kahn JG. Health and economic benefits of reducing sugar intake in the USA, including effects via non-alcoholic fatty liver disease: a microsimulation model. BMJ Open 2017;7:e013543, http://dx.doi.org/10.1136/bmjopen-2016-013543.

[6] Schuppan D, Afdhal NH. Liver cirrhosis. Lancet 2008;371:838–51, http://dx.doi.org/10.1016/s0140-6736(08)60383-9.

[7] Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011;53:1874–82, http://dx.doi.org/10.1002/hep.24268.

[8] Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389–97, http://dx.doi.org/10.1053/j.gastro.2015.04.043.

[9] Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547–54, http://dx.doi.org/10.1002/hep.27368.

[10] Wong VW, Wong GL, Choi PC, Chan AW, Li MK, Chan HY, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut 2010;59:969–74, http://dx.doi.org/10.1136/gut.2009.205088.

[11] Pais R, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol 2013;59:550–6, http://dx.doi.org/10.1016/j.jhep.2013.04.027.

[12] McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015;62:1148–55, http://dx.doi.org/10.1016/j.jhep.2014.11.034.

[13] Torres DM, Harrison SA. Nonalcoholic fatty liver disease: fibrosis portends a worse prognosis. Hepatology 2015;61:1462–4, http://dx.doi.org/10.1002/hep.27680.

[14] Smith JO, Sterling RK. Systematic review: non-invasive methods of fibrosis analysis in chronic hepatitis C. Aliment Pharmacol Ther 2009;30:557–76, http://dx.doi.org/10.1111/j.1365-2036.2009.04062.x.

[15] Rtveladze K, Marsh T, Barquera S, Sanchez Romero LM, Levy D, Melendez G, et al. Obesity prevalence in Mexico: impact on health and economic burden. Public Health Nutr 2014;17:233–9, http://dx.doi.org/10.1017/s1368980013000086.

[16] Barquera S, Campos Nonato I, Hernandez Barrera L, Flores M, Durazo Arvizu R, Kanter R, et al. Obesity and central adiposity in Mexican adults: results from the Mexican National Health and Nutrition Survey 2006. Salud Publica Mex 2009;51:595–603.

[17] Sanchez Castillo CP, Velasquez Monroy O, Lara Esqueda A, Berber A, Sepulveda J, Tapia Conyer R, et al. Diabetes and hypertension increases in a society with abdominal obesity: results of the Mexican National Health Survey 2000. Public Health Nutr 2005;8:53–60.

[18] OECD. Health at a glance 2017; 2017.

[19] Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in

patients with NAFLD. Hepatology 2007;45:846–54, http://dx.doi.org/10.1002/hep.21496.

[20] Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, Ong A, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012;61:409–15, http://dx.doi.org/10.1136/gutjnl-2011-300342.

[21] Fabrellas N, Alemany M, Urquizu M, Bartres C, Pera G, Juve E, et al. Using transient elastography to detect chronic liver diseases in a primary care nurse consultancy. Nurs Res 2013;62:450–4, http://dx.doi.org/10.1097/nnr.0000000000000001.

[22] Zelber-Sagi S, Ratziu V, Zvibel I, Goldiner I, Blendis L, Morali G, et al. The association between adipocytokines and biomarkers for nonalcoholic fatty liver disease-induced liver injury: a study in the general population. Eur J Gastroenterol Hepatol 2012;24:262–9, http://dx.doi.org/10.1097/MEG.0b013e32834f15dd.

[23] You SC, Kim KJ, Kim SU, Kim BK, Park JY, Kim DY, et al. Factors associated with significant liver fibrosis assessed using transient elastography in general population. World J Gastroenterol 2015;21:1158–66, http://dx.doi.org/10.3748/wjg.v21.i4.1158.

[24] Halfon P, Munteanu M, Poynard T. FibroTest-ActiTest as a non-invasive marker of liver fibrosis. Gastroenterol Clin Biol 2008;32:22–39, http://dx.doi.org/10.1016/s0399-8320(08)73991-5.

[25] Srinivasa Babu A, Wells ML, Teytelboym OM, Mackey JE, Miller FH, Yeh BM, et al. Elastography in chronic liver disease: modalities, techniques limitations, and future directions. Radiographics 2016;36:1987–2006, http://dx.doi.org/10.1148/rg.2016160042.

[26] Poynard T, Ingiliz P, Elkrief L, Munteanu M, Lebray P, Morra R, et al. Concordance in a world without a gold standard: a new non-invasive methodology for improving accuracy of fibrosis markers. PLoS ONE 2008;3:3857, http://dx.doi.org/10.1371/journal.pone.0003857.

[27] Ratziu V, Giral P, Munteanu M, Messous D, Mercadier A, Bernard M, et al. Screening for liver disease using non-invasive biomarkers (FibroTest SteatoTest and NashTest) in patients with hyperlipidaemia. Aliment Pharmacol Ther 2007;25:207–18, http://dx.doi.org/10.1111/j.1365-2036.2006.03182.x.

[28] Jacqueminet S, Lebray P, Morra R, Munteanu M, Devers L, Messous D, et al. Screening for liver fibrosis by using a noninvasive biomarker in patients with diabetes. Clin Gastroenterol Hepatol 2008;6:828–31, http://dx.doi.org/10.1016/j.cgh.2008.03.005.

[29] Poynard T, Lebray P, Ingiliz P, Varaut A, Varsat B, Ngo Y, et al. Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest). BMC Gastroenterology 2010;10:40, http://dx.doi.org/10.1186/1471-230X-10-40.

[30] Roulot D, Costes JL, Buyck JF, Warzocha U, Gambier N, Czernichow S, et al. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. Gut 2011;60:977–84, http://dx.doi.org/10.1136/gut.2010.221382.

[31] Koehler EM, Plompen EP, Schouten JN, Hansen BE, Darwish Murad S, Taimr P, et al. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: the Rotterdam study. Hepatology 2016;63:138–47, http://dx.doi.org/10.1002/hep.27981.

[32] Chinchilla Lopez P, Ramirez Perez O, Cruz Ramon V, Canizales Quinteros S, Dominguez Lopez A, Ponciano Rodriguez G, et al. More evidence for the genetic susceptibility of Mexican population to nonalcoholic fatty liver disease through PNPLA3. Ann Hepatol 2018;17:250–5, http://dx.doi.org/10.5604/01.3001.0010.8644.

[33] Lopez Velazquez JA, Silva Vidal KV, Ponciano Rodriguez G, Chavez Tapia NC, Arrese M, Uribe M, et al. The prevalence of nonalcoholic fatty liver disease in the Americas. Ann Hepatol 2014;13:166–78.

[34] Ruffillo G, Fassio E, Alvarez E, Landeira G, Longo C, Dominguez N, et al. Comparison of NAFLD fibrosis score and BARD score in predicting fibrosis in nonalcoholic fatty liver disease. J Hepatol 2011;54:160–3, http://dx.doi.org/10.1016/j.jhep.2010.06.028.

[35] Demir M, Lang S, Nierhoff D, Drebber U, Hardt A, Wedemeyer I, et al. Stepwise combination of simple noninvasive fibrosis scoring systems increases diagnostic accuracy in nonalcoholic fatty liver disease. J Clin Gastroenterol 2013;47:719–26, http://dx.doi.org/10.1097/MCG.0b013e3182819a89.

[36] Perez Gutierrez OZ, Hernandez Rocha C, Candia Balboa RA, Arrese MA, Benitez C, Brizuela Alcantara DC, 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.

[37] Kim D, Kim WR, Talwalkar JA, Kim HJ, Ehman RL. Advanced fibrosis in nonalcoholic fatty liver disease: noninvasive assessment with MR elastography. Radiology 2013;268:411–9, http://dx.doi.org/10.1148/radiol.13121193.

[38] Cales P, Laine F, Boursier J, Deugnier Y, Moal V, Oberti F, et al. Comparison of blood tests for liver fibrosis specific or not to NAFLD. J Hepatol 2009;50:165–73, http://dx.doi.org/10.1016/j.jhep.2008.07.035.

[39] McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut 2010;59:1265–9, http://dx.doi.org/10.1136/gut.2010.216077.

[40] Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454–62, http://dx.doi.org/10.1002/hep.23312.

[41] Petta S, Vanni E, Bugianesi E, Di Marco V, Camma C, Cabibi D, et al. The combination of liver stiffness measurement and NAFLD fibrosis score improves the noninvasive diagnostic accuracy for severe liver fibrosis in patients with non-alcoholic fatty liver disease. Liver Int 2015;35:1566–73, http://dx.doi.org/10.1111/liv.12584.

[42] Boursier J, Vergniol J, Guillet A, Hiriart JB, Lannes A, Le Bail B, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol 2016;65:570–8, http://dx.doi.org/10.1016/j.jhep.2016.04.023.

[43] Petta S, Wong VW, Camma C, Hiriart JB, Wong GL, Marra F, et al. Improved noninvasive prediction of liver fibrosis by liver stiffness measurement in patients with nonalcoholic fatty liver disease accounting for controlled attenuation parameter values. Hepatology 2017;65:1145–55, http://dx.doi.org/10.1002/hep.28843.

[44] Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, 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, http://dx.doi.org/10.1002/hep.25762.

[45] Tovo CV, Villela-Nogueira CA, Leite NC, Panke CL, Port GZ, Fernandes S, et al. Transient hepatic elastography has the best performance to evaluate liver fibrosis in non-alcoholic fatty liver disease (NAFLD). Ann Hepatol 2019;18:445–9, http://dx.doi.org/10.1016/j.aohep.2018.09.003.

[46] Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. Hepatology 2017;66:1486–501, http://dx.doi.org/10.1002/hep.29302.

[47] Angulo P, Bugianesi E, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Barrera F, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2013;145:782–9, http://dx.doi.org/10.1053/j.gastro.2013.06.057.

[48] Petta S, Wong VW, Camma C, Hiriart JB, Wong GL, Vergniol J, et al. Serial combination of non-invasive tools improves the diagnostic accuracy of severe liver fibrosis in patients with NAFLD. Aliment Pharmacol Ther 2017;46:617–27, http://dx.doi.org/10.1111/apt.14219.

[49] de Carli MA, de Carli LA, Correa MB, Junqueira Jr G, Tovo CV, Coral GP. Performance of noninvasive scores for the diagnosis of advanced liver fibrosis in morbidly obese with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2019, http://dx.doi.org/10.1097/MEG.0000000000001519.

[50] Treeprasertsuk S, Bjornsson E, Enders F, Suwanwalaikorn S, Lindor KD. NAFLD fibrosis score: a prognostic predictor for mortality and liver complications among NAFLD patients. World J Gastroenterol 2013;19:1219–29, http://dx.doi.org/10.3748/wjg.v19.i8.1219.

[51] Xun YH, Guo JC, Lou GQ, Jiang YM, Zhuang ZJ, Zhu MF, et al. Non-alcoholic fatty liver disease (NAFLD) fibrosis score predicts 6.6-year overall mortality of Chinese patients with NAFLD. Clin Exp Pharmacol Physiol 2014;41:643–9, http://dx.doi.org/10.1111/1440-1681.12260.

[52] Sebastiani G, Alshaalan R, Wong P, Rubino M, Salman A, Metrakos P, et al. Prognostic value of non-invasive fibrosis and steatosis tools hepatic venous pressure gradient (HVPG) and histology in nonalcoholic steatohepatitis. PLOS ONE 2015;10:e0128774, http://dx.doi.org/10.1371/journal.pone.0128774.

[53] Instituto Nacional de Estadística y Geografía. Encuesta Intercensal 2015: marco conceptual; 2015. Available from: https://www.inegi.org.mx/programas/intercensal/2015/.

[54] Gines P, Graupera I, Lammert F, Angeli P, Caballeria L, Krag A, et al. Screening for liver fibrosis in the general population: a call for action. Lancet Gastroenterol Hepatol 2016;1:256–60, http://dx.doi.org/10.1016/s2468-1253(16)30081-4.

[55] Harris R, Harman DJ, Card TR, Aithal GP, Guha IN. Prevalence of clinically significant liver disease within the general population, as defined by non-invasive markers of liver fibrosis: a systematic review. Lancet Gastroenterol Hepatol 2017;2:288–97, http://dx.doi.org/10.1016/s2468-1253(16)30205-9.

[56] Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13:643–54, http://dx.doi.org/10.1016/j.cgh.2014.04.014.

[57] Vilar Gomez E, Martinez Perez Y, Calzadilla Bertot L, Torres Gonzalez A, Gra Oramas B, Gonzalez Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367–78, http://dx.doi.org/10.1053/j.gastro.2015.04.005.

[58] Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology 2015;149:379–88, http://dx.doi.org/10.1053/j.gastro.2015.04.014.

[59] Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-alpha and -delta, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150:1147–59, http://dx.doi.org/10.1053/j.gastro.2016.01.038.

[60] Francque S, Vonghia L. Pharmacological treatment for non-alcoholic fatty liver disease. Adv Ther 2019;36:1052–74, http://dx.doi.org/10.1007/s12325-019-00898-6.

[61] Alkhouri N, Scott A. An update on the pharmacological treatment of non-alcoholic fatty liver disease: beyond lifestyle modifications. Clin Liver Dis 2018;11:82–6, http://dx.doi.org/10.1002/cld.708.