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ORIGINAL ARTICLE

Gender differences in liver fibrosis among patients younger than 50 years: A retrospective cohort study



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KEYWORDS

Non-alcoholic fatty liver disease (NAFLD);
Fibroscan;
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Metabolic disorder

Summary

Background & aims: Liver fibrosis is a metabolic disease associated with several factors, mainly age, gender, immune suppression, viral hepatitis, alcohol and metabolic diseases. Here, we are assessing the gender impact on liver status in NAFLD patients younger than 50 years.

Methods: All males younger than 50 years and premenopausal females diagnosed with NAFLD were included in this study. Fibroscan results, demographics and clinical data were collected and analyzed by SPSS software. Patients were stratified based on fibrosis scores as mild or no fibrosis for F0–F1–F2 and severe fibrosis for F3 and F4. Data was analyzed and compared based on gender.

Results: A total of 221 patients 134 males and 80 premenopausal females were included. Factors that affected liver fibrosis scores were different between males and females, where only body-mass index (BMI), white blood cells (WBC) count, and glucose level were associated with severe liver fibrosis in females. Also, liver fibrosis scores were associated with severe liver fibrosis in males only, no difference in these scores was observed in premenopausal females with severe or mild liver fibrosis.

Abbreviations: NAFLD, Non-Alcoholic Fatty Liver Disease; T2DM, Type II Diabetes Mellitus; LFTs, Liver Function Tests; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ALP, Alkaline Phosphatase; G-gt, Gamma-glutamyl transferase; PT-INR, Prothrombin Time-International Normalized Ratio; TG, Triglycerides; LDL, Low density Lipoproteins; HDL, High Density Lipoproteins; CAP, Fibroscan's Controlled Attenuation Parameter; LSM, Liver Stiffness Measure; BMI, Body Mass Index; AAR, Alanine Aminotransferase Ratio; APRI, Aspartate Aminotransferase to Platelet Ratio Index; BMI, Body Mass Index; BARD, AAR-Diabetes; FIB4, Fibrosis Index Based on the 4 Factor; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; DL, Dyslipidaemia.

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Conclusions: Gender differences are prominent in NAFLD and different factors are associated with liver status in males as compared to females. Besides, fibrosis score could predict liver status in males but not in females. Further larger-scale studies are necessary to verify gender impact on liver fibrosis development.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic hepatic metabolic syndrome and is becoming a worldwide public health problem [1,2]. It is the second etiology of liver diseases that necessitate liver transplantation and the third leading cause of hepatocellular cancer (HCC) in the United States (US) [2]. NAFLD rate is highest in the Middle East (31.8%), South America (30.5%), Asia (27.4%), US (24.1%), Europe (23.7%) and lowest in Africa (13.5%) [3,4]. It is defined by the presence of steatosis on imaging or histological modalities with the exclusion of secondary causes of hepatic fat accumulation [5]. Liver biopsy is the gold standard for the diagnosis of NAFLD; however, it is an invasive procedure often associated with complications such as bleeding, infections, bile leak, longer hospital stay and mortality rate 3/10,000 [6,7]. Several alternative methods including biochemical parameters, blood markers and fibrosis scores have been introduced. Of these parameters, serum aspartate aminotransferase and alanine aminotransferase ratio (AAR), aspartate amino-transferase to platelet ratio index (APRI) and Fibrosis index 4 (FIB-4) [5,8,9]. These scores are dependent on individual biomarkers and highly affected by age of patient [10,11]. APRI, ARR and FIB-4 are best used in combination to optimize positive predictive value and negative predictive value for the assessment of liver fibrosis [12]. Fibroscan is a non-invasive device that assesses the 'hardness' (or stiffness) of the liver via the technique of transient elastography, has been introduced as an imaging tool and validated by many medical centers to be used as a first step in the diagnosis of fatty liver diseases with varying sensitivities and specificities [13,14].

NAFLD is often associated with several metabolic disorders such as dyslipidaemia, insulin resistance and/or type-II diabetes mellitus, hypertension, high body mass index (BMI) and waist circumference [15]. It is reported to be more prevalent in males [16]; Xu et al. reported that severe hepatic injury observed in male patients with NAFLD may be attributed to the suppression of SIRT1 gene, which encodes Sirtuin 1 (NAD-dependent deacetylase sirtuin-1) signalling induced by hyperuricemia [17]. Several studies have highlighted gender differences in NAFLD, and that female and male livers are metabolically distinct with unique regulators modulating gender specific metabolic outcomes [18,19]. The gender based metabolic profile is also affected by other factors such as age and race, as NAFLD is more prevalent in Asians and black post-menopausal females [20]. It has been reported that liver fibrosis due to HCV infection increases following in post-menopausal women with rates that are

comparable to men [21,22]. Moreover, the rate of fibrosis progression and histological changes in postmenopausal women were much higher when compared to premenopausal women with HCV infection [23,24]. It was suggested that the gender related differences observed regarding the prevalence of NAFLD could be related to the protective effect of oestrogen that reduces the risk of developing this disease in the premenopausal period [25]. Studies that have been published regarding the gender effect on the pathophysiology of NAFLD have also shown that body fat distribution and lipid metabolism differs between males and females which would have an impact on fatty liver distribution [26,27]. However, the metabolic factors and blood parameters that would explain how gender may affect the development of NAFLD in patients based on gender are still not well identified. Menopause and hormonal changes have been reported to play a role in NAFLD development in females [18,19]. In addition, Tang et al. have reported differences in NAFLD based on age group younger and older than 50 [19]. We analysed gender disparity, clinical characteristics and blood parameters, and to determine the efficacy of fibrosis scores in determining liver fibrosis status among young males younger than 50 years and pre-menopausal females.

Methods

From January 2016 till August 2018, 637 patients underwent Fibroscan at the American University of Beirut Medical Center (AUBMC) Lebanon. This study was approved by the institutional review board (IRB) at the American University of Beirut.

Our inclusion criteria included pre-menopausal females and males younger than 50 years old. All charts for male patients and premenopausal females younger than 50 years were reviewed. All patients with positive blood antigens of hepatitis B or C viruses, alcohol intake or on medications that might affect the liver function (i.e. methotrexate) were excluded from the study. Data collected included demographic data, comorbidities, blood tests and liver markers obtained within one month of the Fibroscan examination, and liver fibrosis as determined by Fibroscan. The patients were attributed to four stages of fibrosis as defined by the Fibroscan manual according to the fibrosis score of NAFLD as F0/F1 (2 to 7), F2 (>7 to 10), F3 (>10 to 14) and F4 (14 or higher) [28,29]. Patients with F2 score and below were categorized as patients with mild or no fibrosis, and those with fibrosis score of F3 and F4 were categorized as patients with severe liver fibrosis.

Fibrosis scores APRI, FIB and AAR were calculated based on the score formula and cut off for defining liver fibrosis was 0.7 for APRI score, 2.67 for FIB-4 score and more than one for the AAR score [30–32]. Data were entered and analysed by Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 24.0 software. Percentages were used to report categorical variables, and mean \pm standard deviation (SD) to report continuous variables. Chi² test and One-way Anova were used to compare gender differences among categorical and continuous variables respectively. Statistical significance was accepted at $P < 0.05$ (two-tailed) and Confidence Intervals CI (95%).

Results

Of the 637 patients underwent Fibroscan at our institution, 221 patients were found to have NAFLD. There were 134 males and 80 premenopausal females less than 50 years included in this study, the mean age of males and females were 34.27 ± 8.73 and 36.65 ± 9.77 years, respectively, with a significant smoking prevalence among males 56(41.7%) and 18(22.5%) females ($P = 0.001$). Baselines characteristics of males and females were mainly comparable. However, females had higher platelets count, and lower SGPT and TG levels ($P = 0.001$, 0.001 and 0.003 respectively) (Table 1). In addition, females had significantly higher AAR scores (1.21 ± 0.33) and lower APRI scores (20.38 ± 8.33) compared to males who had mean AAP score (0.85 ± 0.32) and mean APRI score (29.23 ± 8.45) ($P = 0.001$ and 0.005, respectively).

Low white blood cells (WBC) and platelets counts, high levels of haemoglobin A1c (HbA1c), glucose, triglycerides (TG), serum glutamate-pyruvate transaminase (SGPT), alkaline phosphatase (ALP), and prothrombin time-international normalized ratio (PT-INR), and low levels of low density lipoproteins (LDL) were significantly associated with severe liver fibrosis in males (Table 2). In premenopausal females, significant high body mass index (BMI) was observed in patients with severe fibrosis (29.1 ± 6.6) compared to 19.8 ± 10.1 in patients with mild or no fibrosis ($P = 0.005$). Significantly higher glucose level was also observed in severe fibrosis premenopausal females ($P = 0.007$). In addition, females with severe fibrosis had higher WBC counts compared to mild or no fibrosis females (12.8 ± 13.7 vs 6.9 ± 2.9 ; $P = 0.020$) (Table 2).

As shown in Table 3, FIB-4, AAR and APRI scores were not different in females with fibrosis compared to females with mild or no fibrosis. However, the three scores were significantly different between males based on their fibrosis status, where higher scores were associated with severe liver fibrosis status ($P = 0.001$, 0.004 and 0.001 respectively). Moreover, Pearson correlation showed a significant positive correlation between FIB-4 ($r = 0.23$, $P = 0.02$), AAR ($r = 0.37$, $P = 0.00$), APRI ($r = 0.2$; $P = 0.01$) scores and liver stiffness in males but not in females.

Discussion

The development of NAFLD from steatosis to cirrhosis to the development of cancer is multifactorial. Multiple metabolic abnormalities such as obesity, genetic disposition, insulin resistance, hypertension and dyslipidaemia have been found

Table 1 Gender baseline characteristics.

Characteristics	Total (N=214)		P-value
	Males(N=134)	Females(N=80)	
Age ^a	34.3 \pm 8.7	36.3 \pm 9.7	0.124
BMI ^a	28.6 \pm 6.9	26.9 \pm 8.4	0.385
Alcohol intake	65(48.5%)	45(56.2%)	0.866
Smoking	56(41.7%)	18(22.5%)	0.001
HTN	14(10.4%)	15(18.7)	0.134
CAD	2(1.5%)	0(0%)	0.526
CHF	5(3.7%)	4(5%)	0.726
CKD	2(1.5%)	1(1.3%)	1.000
Diabetes	11(8.2%)	10(12.5%)	0.346
Dyslipidaemia	8(6.0%)	4(5.0%)	1.000
WBC $\times 10^3$ ^a	7.0 \pm 3.0	8.6 \pm 8.0	0.107
Platelets $\times 10^3$ ^a	214.3 \pm 75.4	280.6 \pm 179.5	0.001
BUN ^a	13.3 \pm 4.1	11.44 \pm 7.6	0.146
Creatinine ^a	0.8 \pm 0.2	0.8 \pm 0.6	0.167
albumin ^a	39.5 \pm 13.5	36.3 \pm 9.7	0.118
SGOT ^a	51.0 \pm 52.3	37.1 \pm 34.1	0.100
SGPT ^a	87.3 \pm 105.9	40.0 \pm 36.0	0.003
gGT ^a	118.0 \pm 211.0	70.0 \pm 103.9	0.175
ALP ^a	136.2 \pm 159.1	108.0 \pm 121.8	0.324
HbA1c ^a	5.6 \pm 0.9	5.6 \pm 1.2	0.824
Glucose level ^a	100.5 \pm 36.9	106.3 \pm 45.8	0.546
HDL ^a	41.3 \pm 11.5	44.4 \pm 20.6	0.393
LDL ^a	120.4 \pm 44.6	101.0 \pm 39.5	0.611
TG ^a	154.2 \pm 73.5	112.0 \pm 56.5	0.010
INR ^a	1.1 \pm 0.2	1.0 \pm 0.3	0.427
Fibrosis scores			
F0–F1	43(32.2%)	39(48.7%)	0.063
F2	69(51.4%)	22(27.5%)	0.015
F3	18(13.5%)	11(13.8%)	0.052
F4	4(2.9%)	8(10%)	0.312
AAR ^a	0.8 \pm 0.3	1.2 \pm 0.3	0.001
APRI ^a	29.2 \pm 8.4	20.4 \pm 8.3	0.005
FIB-4 ^a	1.0 \pm 0.6	0.9 \pm 0.4	0.452

BMI: body mass index; AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DL: dyslipidaemia; HTN: hypertension; HbA1: chemoglobin A1c; TG: triglycerides; HDL: high density lipoproteins; LDL: low density lipoproteins; BUN: blood urea nitrogen; WBC: white blood cell count; CRP: C-reactive protein; SGPT: serum glutamate-pyruvate transaminase; SGOT: serum glutamic-oxaloacetic transaminase; ALP: Alkaline Phosphatase; G-gt: gamma-glutamyl transferase; PT-INR: prothrombin time-international normalized ratio.

^a Reported as mean \pm SD, other variables as N(%) of yes.

to be part of the pathogenesis of NAFLD [33,34]. We identified several different factors between males and premenopausal females that can play a role in liver fibrosis. Those factors were more prominent in the males' population including TG, LDL, INR and SGPT levels and platelets count. This might be linked to physiological factors that are protective against NAFLD in females. For example, a high level of oestrogen in premenopausal women may prevent visceral fat deposition in the central area which is known as a risk factor for the development of NAFLD [35]. This might explain high triglycerides level present in males with

Table 2 Gender based differences between mild and severe fibrosis status.

Characteristic	Males (N = 134)			Females (N = 80)		
	Mild or No fibrosis (N = 112)	Severe fibrosis (N = 22)	P-value	Mild or No fibrosis (N = 61)	Severe fibrosis (N = 19)	P-value
Age ^a	34.1 ± 8.5	34.8 ± 9.7	0.748	36.8 ± 9.9	34.3 ± 9.4	0.337
BMI ^a	28.0 ± 5.5	31.2 ± 12.7	0.354	29.1 ± 6.6	19.8 ± 10.1	0.005
Alcohol intake	55(49.0%)	10(45.4%)	0.849	43(70.4%)	11(57.8%)	1.000
Smoking	48(42.8%)	8(36.3%)	0.786	16(26.2%)	2(10.5%)	0.203
Comorbidities						
HTN	13(11.6%)	1(4.5%)	0.678	12(19.6%)	3(15.7%)	0.728
CAD	1(0.89%)	1(4.5%)	0.288	0	0	—
					0 (0%)	0.558
CHF	3(2.6%)	2(9.1%)	0.183	4(6.5%)	0	—
CKD	2(1.7%)	0(0%)	—	1(1.6%)	0	—
Diabetes	9(8.1%)	2(9.1%)	0.992	7(11.4%)	3(15.7%)	0.694
Dyslipidaemia	7(5.7%)	1(4.5%)	0.971	3(4.9%)	1(5.2%)	1.000
Blood tests						
WBC × 10 ^{3a}	7.5 ± 427	4.8 ± 3.5	0.003	6.9 ± 2.9	12.8 ± 13.7	0.020
Platelets × 10 ^{3a}	222.7 ± 68.4	164.2 ± 95.0	0.002	267.6 ± 119.4	317.0 ± 292.0	0.057
BUN ^a	12.9 ± 3.1	14.6 ± 7.0	0.261	10.30 ± 3.57	14.40 ± 13.30	0.152
Creatinine ^a	0.9 ± 0.2	0.8 ± 0.2	0.615	0.79 ± 0.84	0.65 ± 0.50	0.546
Albumin ^a	40.2 ± 14.2	36.7 ± 9.6	0.524	36.59 ± 16.68	30.99 ± 13.45	0.299
SGOT ^a	48.5 ± 54.2	65.7 ± 36.8	0.293	34.11 ± 26.65	44.71 ± 48.39	0.330
SGPT ^a	74.2 ± 32.8	89.5 ± 40.6	0.034	38.61 ± 33.35	43.92 ± 43.88	0.653
gGT ^a	111.0 ± 218.8	158.0 ± 159.9	0.498	71.60 ± 119.41	66.61 ± 72.73	0.888
ALP ^a	121.6 ± 134.1	211.6 ± 247.1	0.026	86.80 ± 71.26	157.00 ± 189.55	0.083
HbA1c ^a	5.5 ± 0.6	6.5 ± 1.8	0.017	5.50 ± 0.90	5.80 ± 1.87	0.638
Glucose level ^a	94.3 ± 14.9	132.7 ± 82.7	0.006	92.95 ± 11.34	144.57 ± 79.93	0.007
HDL ^a	41.6 ± 11.7	38.4 ± 10.4	0.553	48.29 ± 19.16	31.50 ± 21.54	0.079
LDL ^a	124.6 ± 42.0	77.6 ± 52.8	0.023	106.20 ± 35.32	83.66 ± 50.87	0.227
TG ^a	176.9 ± 81.3	109.2 ± 69.4	0.013	118.14 ± 58.54	90.50 ± 47.97	0.300
INR ^a	0.8 ± 0.2	1.2 ± 0.1	0.032	1.01 ± 0.26	1.11 ± 0.38	0.410

^a Reported as mean ± SD, other variables as N(%) of yes.

Table 3 Fibrosis scores of patients based on gender.

Fibrosis scores	Males (N = 134)			Females (N = 80)		
	Mild or No fibrosis (N = 112)	Severe fibrosis (N = 22)	P-value	Mild or No fibrosis (N = 61)	Severe fibrosis (N = 19)	P-value
APRI	23.8 ± 6.7	40.1 ± 19.1	0.001	20.7 ± 7.3	19.3 ± 11.9	0.692
FIB-4	0.8 ± 0.3	2.3 ± 1.0	0.001	0.9 ± 0.5	0.8 ± 0.5	0.820
AAR	0.7 ± 0.3	1.1 ± 0.6	0.004	1.1 ± 0.4	1.2 ± 0.3	0.373

fibrosis in this cohort ($P=0.013$) but showed no difference in premenopausal females. In a previous study among diabetic patients, serum LDL was significantly associated with fibrosis status [14]; this is also evident here where only males had predominantly lower LDL levels associated with severe liver fibrosis. In several studies, diabetes and liver fibrosis are often associated in patients; however, no association was observed in both genders. This might be linked to the young age group analyzed in our cohort and diabetes would be a significant factor in older patients [19]. Hence, our

study showed no association between diabetes and NAFLD in pre-menopausal women in accordance to previous studies that suggested a link between diabetes and NAFLD in post-menopausal women [36]. This could be explained by the protective effect of estrogen against insulin resistance; however, high glucose in pre-menopausal females was associated with severe fibrosis in circulation which might be due to higher level of gluconeogenesis and reduction of insulin clearance, all of which predispose to high glucose concentrations in the plasma [37].

Another important finding is the effectiveness of liver fibrosis scores in determining liver status. Several studies have reported that simple non-invasive scoring systems can reliably determine fibrosis status in patients with NAFLD [10,11]; however, in our cohort, these scores were able to determine liver status in males but not in pre-menopausal females, this might be related to several physiological and metabolic factors that are different between males and females. Even though this is a retrospective study with limited patient number and follows up, this is the first study that reports gender differences and factors that affect liver status in adults less than 50 years. Further studies of larger cohort are needed to further identify the possible underlying mechanisms of fat deposition and enhancement of liver fibrosis in males and females.

Nevertheless, Fibroscan is not the best method to diagnose NAFLD as it has multiple limitations. First, it is difficult to obtain liver stiffness in obese patients and patients with diabetes. Second, the reliability of the liver stiffness is affected by inflammation and necrosis in the hepatic cells [38]. It was reported that the failure rate for obtaining accurate results in patients with a BMI ≥ 30 kg/m² is 3.1% (OR=7.5). In addition to false positive/negative predictive value related to operator inexperience which was defined as having performed less than 500 measurements (OR=2.5) [39]. Therefore, further prospective and case-control studies are required to assess gender impact on liver fibrosis; however, our study is one of the few studies that studies factors that impact gender role in liver fibrosis in young adults.

Contribution

AH has contributed to data collection, analysis and write-up.

MK, DM have contributed to write-up and revision.

MK, SH and AA have contributed to data collection and revision of paper.

RJ has participated in conception and design of the work, ensuring data integrity, statistical analysis, write-up, revision and final approval of manuscript.

WF has contributed in conception of the work, write-up, revision and final approval of manuscript.

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Disclosure of interest

The authors declare that they have no competing interest.

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