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Sex hormone binding globulin (SHBG) as a predictor of liver fibrosis in subjects with nonalcoholic fatty liver disease (NAFLD)

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Abstract

Background Nonalcoholic fatty liver disease (NAFLD) is the fastest growing cause of chronic liver disease worldwide. The prevalence of NAFLD increases in parallel with the increasing prevalence in obesity, metabolic syndrome and type 2 diabetes (T2DM). Recently, more evidence indicates the important role of sex hormone binding globulin (SHBG) on metabolic health.

Methods A controlled cross-sectional cohort study was conducted upon 60 patients (NAFLD and control group). Patients were categorized according to the NAFLD fibrosis score. All patients subjected to routine labs and SHBG measurement.

Results BMI was 35.80 ± 6.56 SD and 23.23 ± 2.5 SD in the NAFLD group and control group respectively. The NAFLD fibrosis score was 2.12 ± 1.47 SD. Fifty patients were categorized as advanced liver fibrosis: F3–F4 (> 0.675). No patients scored to exclude advanced liver fibrosis: F0–F2 (< -1.455). The remaining 10 patients were categorized as indeterminate (in-between). There was a significant correlation between age, mid-arm circumference, waist circumference, BMI, serum albumin level, lipid profile components, as well as the NAFLD fibrosis score and SHBG levels using univariable regression analysis. There was also a significant correlation between mid-arm circumference, waist circumference, lipid profile components as well as SHBG levels and the NAFLD fibrosis score using univariable regression analysis. SHBG can predict severe liver fibrosis (F3–F4) in our NAFLD female cohort at a cut-off level of > 10 ng/mL, with 34% sensitivity and 90% specificity, area under the ROC curve (AUC) $= 0.548$, with 95% Confidence interval 0.414 to 0.677.

Conclusion SHBG is positively correlated to severe fibrosis in female NAFLD patients. It is an efficient positive predictor of severe fibrosis in female NAFLD patients at a cut-off level > 10 ng/ml, with a high specificity and modest sensitivity.

Keywords Nonalcoholic fatty liver disease, Sex hormone binding globulin, Metabolic health, Liver fibrosis

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is now considered to be the fastest growing cause of chronic liver disease worldwide. Recent estimates suggest that 25% of the world population have got NAFLD. In fact, NAFLD is now one of the leading causes of cirrhosis and indications for liver transplantation in the USA [1]. NAFLD is characterized by increased liver fat content, with a threshold of $> 5\%$, in the absence of significant alcohol consumption (characterized as 30 g/day for men and 20 g/day for

women) or other secondary cause of steatosis [2]. It can be subcategorized as nonalcoholic fatty liver (NAFL), when there is only evidence of hepatic steatosis on liver histology, and nonalcoholic steatohepatitis (NASH), when there are steatosis, lobular inflammation and hepatocyte ballooning with or without perisinusoidal fibrosis [3]. NAFLD may progress to cirrhosis and hepatocellular carcinoma, but its cardio metabolic counterparts are the main cause of morbidity and mortality in those patients [4]. Worldwide prevalence of obesity among NAFLD and NASH patients were 51 and 81%, respectively [5].

Metabolic syndrome is characterized as a cluster of metabolic disorders such as abdominal obesity, hypertension, dyslipidemia and impaired glycemia. Metabolic syndrome was defined according to ATP III criteria: any 3 out of the following 5: IFG, fasting glucose ≥ 100; DM, standard ADA criteria; TG ≥ 150; HDL < 50 (female cohort); Hypertension: BP > 130/85 and waist circumference ≥ 88 (female cohort) [6].

Sex hormone binding globulin (SHBG) a glycoprotein produced by the liver that transports the hormones testosterone, dihydrotestosterone, and estradiol in the blood as biologically inactive forms. Changes in SHBG levels can affect the amount of hormone that is available to be used by the body tissues [7]. Studies have shown that low SHBG levels are predictive of higher risk for developing hypertension, T2DM, and metabolic syndrome in the general population. Moreover, lower serum SHBG is also associated with elevated serum liver enzymes in men with hepatic steatosis [8].

The relationship between SHBG and metabolic disorders might be explained by androgen. Lower SHBG usually leads to free and biologically active androgens in the circulation and might disrupt insulin secretion and pancreatic β-cell function and aggravate the metabolic syndrome and insulin resistance. Moreover, lower expression of SHBG in NAFLD may occur secondary to inflammation. An increase in TNFα in response to activation of JNK and NF-κB, reduces SHBG production in HepG2 cells [9]. The relationship between low SHBG levels and development of various metabolic derangements including components of the metabolic syndrome and NAFLD is well established in the literature. However, little is known about the relationships between SHBG and liver fibrosis in NAFLD.

Materials and methods

This work was a controlled cross-sectional cohort study. The present study included 60 Egyptian patients recruited from Kasr Al Ainy Hospital in the period from March 2019 to July 2022. Patients were consecutively recruited from the ultrasonography unit in the Department of Internal Medicine.

Patients (NAFLD group) were included according to inclusion criteria: 18–60 years old adult female patients and fulfillment of ultrasound criteria of NAFLD. Exclusion criteria included clinical, biochemical, or histological evidence of cirrhosis; exclusion of other causes of liver disease; current or past excessive alcohol drinking was defined by an average daily consumption of more than 20 g alcohol; pregnancy, hormonal contraception (oral or parenteral), hormone replacement. To exclude other causes of liver disease, all subjects were screened for viral hepatitis (hepatitis B and C viral markers) and autoimmune hepatitis. Patients known to have primary biliary cirrhosis, celiac disease or Wilson disease were excluded. Control subjects included 30 age matched healthy female volunteers (control group).

A written informed consent was obtained from each participant or her legal guardian. The study was approved by the ethical committee of internal Medicine in Cairo University (MS-224–2019).

The patients were subjected to review of medical history. Vital signs and full general and local examination was done to all study patients. Anthropometric measurements were done in the form of body weight and height were measured in light clothing and without shoes to the nearest 0.5 kg, using calibrated scales. BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured in cm, midway between the lower costal margin and the iliac crest, with subjects standing with their heels together, during normal expiration with a non-stretchable measuring tape. Mid-arm circumference was measured by a flexible non-stretchable tape on the front of the left upper arm at a distance halfway between inferior aspect of the acromion and the olecranon.

Ultrasound diagnosis of fatty liver was done using the following 4 parameters by experienced operators: (1) diffuse hyperechoic echotexture ("bright liver"); (2) increased liver echotexture compared with the kidneys; (3) vascular blurring; (4) deep attenuation.

Laboratory investigations were done to all patients and control including: complete blood picture, coagulation profile (PT, PC, INR), ALT, AST, albumin, bilirubin total and direct, ALP, GGT, lipid profile, FBG, and SHBG. Known concentrations of Human SHBG Standard and its corresponding reading OD is plotted on the log scale (*x*-axis) and the log scale (*y*-axis) respectively. The concentration of Human SHBG in sample is determined by plotting the sample's O.D. on the *Y*-axis. The original concentration is calculated by multiplying the dilution factor. Assay range: 0.3 ng/mL–20 ng/mL. NAFLD fibrosis score was calculated using the equation by excel sheet [10] :

" $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m2) $+ 1.13 \times$ IFG/diabetes (yes $= 1$, no $= 0$) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet ($\times 10^9$/l) $- 0.66 \times$ albumin (g/dl)"

Patients were categorized according to the NAFLD fibrosis score:

- NAFLD Score $< -1.455 =$ F0–F2.
- NAFLD Score -1.455–$0.675 =$ indeterminate score.
- NAFLD Score $> 0.675 =$ F3–F4.

Statistical methods

All data was entered into a Microsoft Excel sheet. Statistical analysis was done using MedCalc software. Continuous data was tested for normal distribution using the D'Agostino-Pearson test. Data with normal distribution were presented as mean and standard deviation, and subsequently analyzed using parametric tests as *T* test for unpaired comparison. While data that was not normally distributed was presented as maximum, minimum, median and 25th–75th percentiles, and subsequently analyzed using non-parametric tests as the Mann–Whitney test for unpaired comparison. Regression analysis was done to calculate correlation coefficients with greater accuracy and probable causal relationships. Receiver operating characteristic (ROC) curve analysis was done to test SHBG as a marker of liver fibrosis and to assess its sensitivity and specificity. *P* values were considered significant if < 0.05.

Results

Age and anthropometric measurements

The age ranged between 18 years as the minimum and 60 years as the maximum. The median was 40 years and 25th to 75th percentiles were 31 to 50 years. There was no significant difference between the two study groups regarding age of the subjects.

The mean $\pm$ SD of BMI was 35.80 ± 6.56 and 23.23 ± 2.5 in the NAFLD group and control group respectively. BMI was significantly higher in the NAFLD group.

The mean $\pm$ SD of the mid-arm circumference in the NAFLD group was 37.41 ± 3.35. The mean $\pm$ SD of the waist circumference in the NAFLD group was 89.97 ± 8.83.

Frequency of the metabolic syndrome and its components among NAFLD patients

Of the 60 NAFLD patients, 39 (65%) had a waist circumference ≥ 88 cm; 8 (13%) had hypertension; 45 (75%) had TG ≥ 150 mg/dl; 31 (52%) had HDL mg/dl < 50; 17 (28%) had IFG/DM and finally 28 patients (47%) fit the ATP III definition for metabolic syndrome as shown in Fig. 1.

Comparison between the NAFLD group and control group regarding laboratory variables

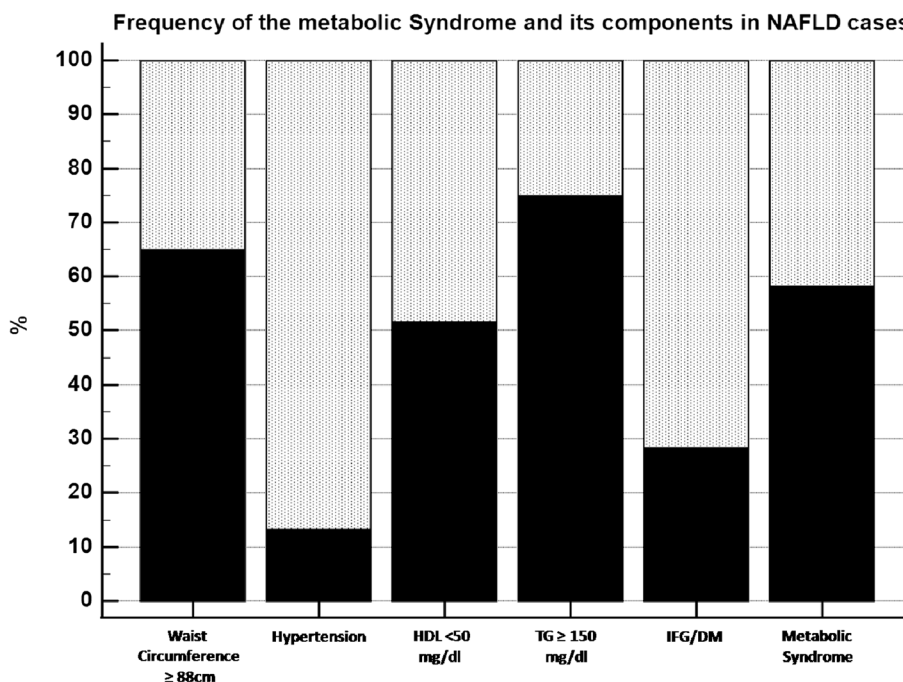Hemoglobin, serum albumin, and HDL were significantly lower in the NAFLD group than the control

Fig. 1 Frequency of the metabolic syndrome and its components in NAFLD cases

group. On the other hand, ALT, AST, ALP, INR, TG, and LDL were significantly higher. There was NO difference in SHBG levels between the 2 groups. *P* values were illustrated in Table 1.

Table 1 Comparison between the NAFLD group and control group regarding laboratory variables

	Control group *n* = 30		NAFLD group *n* = 60		*P* [a]
	Median	Average rank	Median	Average rank	
TLC	7.70	49.25	6.80	43.63	0.3354
HB	12.00	55.92	11.00	40.29	0.0073
PLT	220.50	49.60	212.50	43.45	0.2922
T.BIL	0.69	44.78	0.70	45.86	0.8538
T.PTN	8.00	41.73	8.00	47.38	0.3147
Albumin	4.00	55.28	3.95	40.61	0.0106
ALT	17.50	19.38	44.00	58.56	< 0.0001
AST	13.50	22.82	34.00	56.84	< 0.0001
ALP	114.50	36.65	138.50	49.93	0.0230
GGT	98.50	52.58	78.00	41.96	0.0688
INR	0.99	37.60	1.00	48.76	0.0464
TG	118.50	24.22	186.50	56.14	< 0.0001
LDL	67.50	26.70	98.00	54.90	< 0.0001
HDL	73.00	64.55	47.50	35.98	< 0.0001
Cholesterol	163.50	42.37	163.50	47.07	0.4209
SHBG_ng\ml_	9.50	43.55	9.50	46.48	0.6102

[a] Mann-Whitney test

NAFLD fibrosis score and severity of fibrosis in NAFLD patients

The mean ± SD of the NAFLD fibrosis score was 2.12 ± 1.47. According to the NAFLD fibrosis score, 50 patients were categorized as advanced liver fibrosis: F3-F4 (> 0.675). No patients scored to exclude advanced liver fibrosis: F0-F2 (< -1.455). The remaining 10 patients were categorized as indeterminate (in-between) (Fig. 2).

Regression analysis of various variables and SHBG levels

There was a significant correlation between age, mid-arm circumference, waist circumference, BMI, serum albumin level, lipid profile components as well as the NAFLD fibrosis score (all as continuous variables) and SHBG levels using univariable regression analysis as shown in Fig. 3. Likewise, a significant correlation between diabetes mellitus, hypertension and the metabolic syndrome (all as categorical variables) and SHBG levels using univariable regression analysis. All correlation coefficients were positive, as demonstrated in Table 2.

Regression analysis of various variables and NAFLD fibrosis score

There was a significant correlation between mid-arm circumference, waist circumference, lipid profile components as well as SHBG levels (all as continuous variables) and the NAFLD fibrosis score using univariable regression analysis. Likewise, a significant correlation between
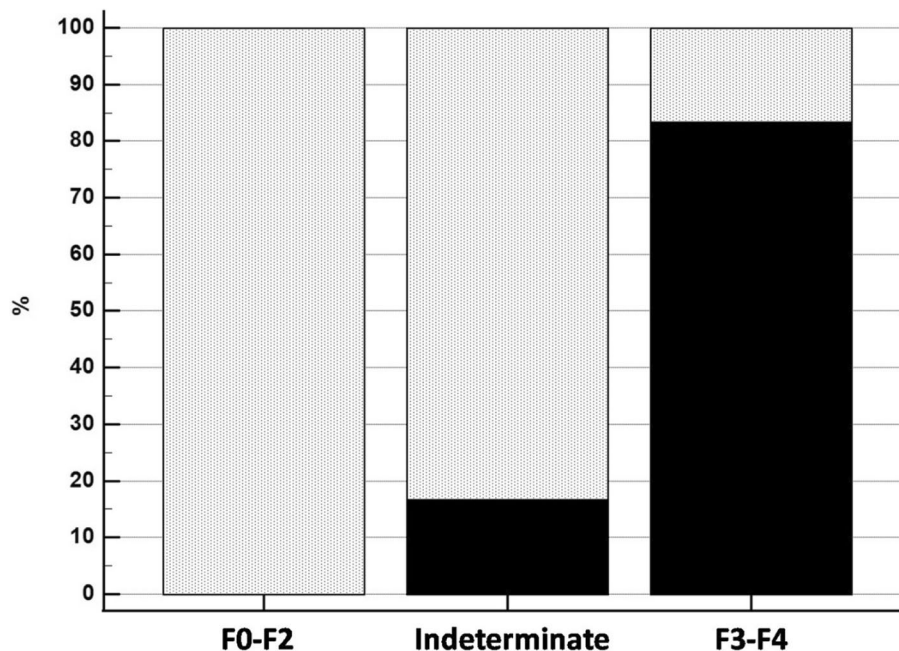

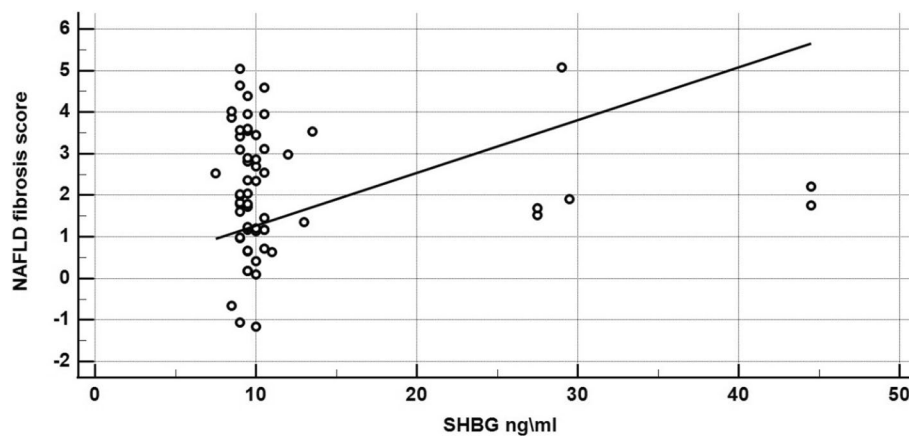**Fig. 2** The frequency of different degrees of fibrosis in NAFLD patients

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Fig. 3 Scatter diagram showing the relation between NAFLD fibrosis score and SHBG levels

Table 2 Regression analysis of various variables versus SHBG levels

	Correlation coefficient	95% confidence interval	*P* value
Age	0.2800	0.2372 to 0.3229	< 0.0001
Midarm circumference/cm	0.3226	0.2693 to 0.3759	< 0.0001
Waist circumference/cm	0.1328	0.1102 to 0.1555	< 0.0001
BMI	0.3638	0.3099 to 0.4176	< 0.0001
DM	12.1176	5.8450 to 18.3903	0.0003
Serum albumin	3.0556	2.6274 to 3.4837	< 0.0001
LDL	0.1074	0.08916 to 0.1256	< 0.0001
HDL	0.2065	0.1755 to 0.2375	< 0.0001
TG	0.06600	0.05494 to 0.07706	< 0.0001
HTN	12.1875	2.4558 to 21.9192	0.0150
Metabolic syndrome	10.1964	5.1565 to 15.2364	0.0001
NAFLD fibrosis score	3.9446	2.9189 to 4.9703	< 0.0001

hypertension and the metabolic syndrome (as categorical variables) and NAFLD fibrosis score using univariable regression analysis. All correlation coefficients were positive, as demonstrated in Table 3.

Receiver operating characteristic curve analysis (ROC) for testing the performance of SHBG in detection of severe liver fibrosis (F3–F4)

SHBG can predict severe liver fibrosis (F3–F4) in our NAFLD female cohort at a cut-off level of > 10 ng/mL, with 34% sensitivity and 90% specificity, area under the ROC curve (AUC) = 0.548, with 95% confidence interval 0.414 to 0.677 (Fig. 4).

Discussion

As aforementioned, only few studies addressed the relationship of SHBG to liver fibrosis. In contrast to previous findings showing low SHBG concentrations in NAFLD, a recent study involving 363 Japanese men provided evidence that high SHBG was associated with liver fibrosis [11]. No similar studies were done to study female patients with NAFLD. The aim of this study was to study the association of SHBG to liver fibrosis in female NAFLD patients.

In our study, BMI was significantly higher in the NAFLD group. This expectedly agrees with many previous studies like the study of Chang et al. which included 77,425 men and women free of NAFLD and metabolic abnormalities at the baseline. They found that increasing baseline BMI showed a strong and approximately linear relationship with the incidence of NAFLD. This association was present in both men and women, although it was stronger in women ($P < 0.001$), and it was evident in all clinically relevant subgroups evaluated, including participants with low inflammation status [12].

Moreover, among the 60 NAFLD patients, 28 patients (47%) fit the ATP III definition for metabolic syndrome.

Table 3 Regression analysis of various variables versus NAFLD fibrosis score

	Correlation coefficient	95% confidence interval	*P* value
Midarm circumference/cm	0.05784	0.04826 to 0.06742	< 0.0001
Waist circumference/cm	0.02403	0.02005 to 0.02801	< 0.0001
LDL	0.01799	0.01484 to 0.02114	< 0.0001
HDL	0.04142	0.03342 to 0.04941	< 0.0001
TG	0.01073	0.008711 to 0.01275	< 0.0001
HTN	2.5465	0.8338 to 4.2592	0.0042
Metabolic syndrome	2.9690	2.3643 to 3.5737	< 0.0001
SHBG	0.1270	0.09397 to 0.1600	< 0.0001
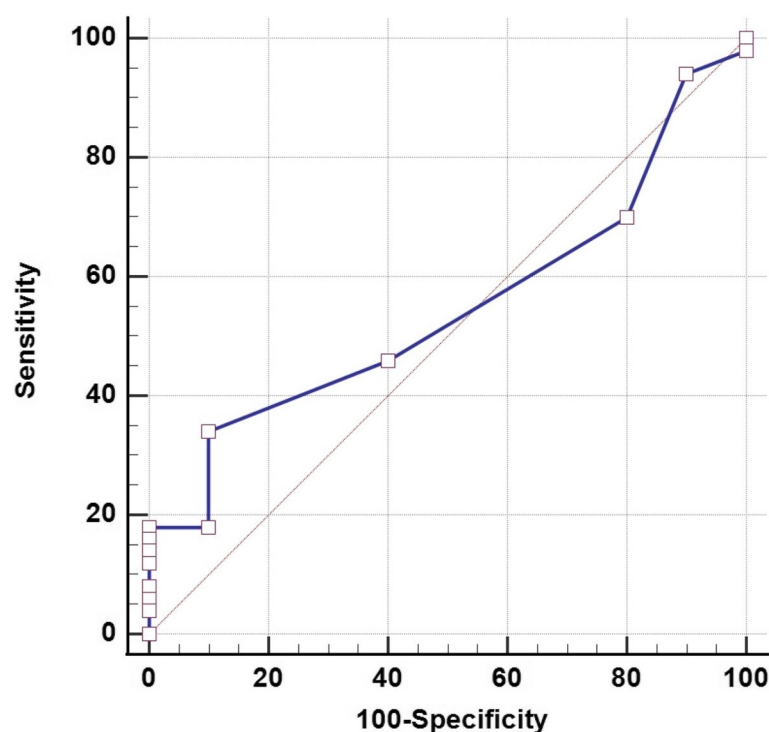
Fig. 4 Roc curve for SHBG ng/ml in prediction of advanced liver fibrosis in NAFLD patients

This also agrees with many previous studies. An American study by Marchesini G et al. assessed the prevalence of the metabolic syndrome in 304 consecutive NAFLD patients without overt diabetes, on the basis of 3 or more criteria out of 5 defined by the U.S. National Institutes of Health (waist circumference, glucose, HDL-cholesterol, triglycerides, and arterial pressure). The prevalence of the metabolic syndrome increased with increasing body mass index, from 18% in normal-weight subjects to 67% in obesity. Insulin resistance (Homeostasis Model Assessment method) was significantly associated with the metabolic syndrome. Liver biopsy was available in 163 cases (54%). A total of 120 patients (73.6%) were classified as having nonalcoholic steatohepatitis (NASH); 88% of them had the metabolic syndrome [13].

Fattahi MR et al. also found that NAFLD was associated with the metabolic syndrome in a study conducted on 2980 peoples aged ≥ 18 years. Metabolic syndrome was detected in 65.9%of men and 64.6% of women with NAFLD, based on NCEP/ATP-III criteria [14].

Other significant p-values were found comparing the liver function tests including AST, ALT, ALP, and INR. Elevated transaminases and impairment of liver functions is an expected finding in patients with NAFLD. This agrees with the study of NoeLopez-Amador that

showed among 40 hospital patients with NAFLD, the most frequent disorder was elevation of ALT levels (72.5%), and also AST (25%) and ALP (45%) to a lesser extent [15].

Also, a study by Debmalya Sanyal et al. showed that mild elevations of liver enzymes in the upper normal range are associated with features of metabolic syndrome and NAFLD in a cross-sectional study including 152 patients with impaired glucose tolerance and 158 recently detected T2DM subjects aged between 30 and 69 years [16]. Another study by Chen Z et al. found a strong relationship between ALT levels and metabolic syndrome in NAFLD and revealed that the cluster of metabolic syndrome components might be the predictor for ALT ($P < 0.001$) [17].

Although liver enzymes are raised in most cases, both fatty liver and NASH with histologically significant disease may exist without elevation of ALT in a significant proportion of patients as highlighted before in several studies [18, 19].

This study shows a significant correlation between SHBG and age. Previous studies show significant variability of SHBG levels with age changes. A cohort study by Maggio M et al. performed on 616 Italian women, found that serum SHBG levels showed a U-shaped trajectory with age, declining from the 2nd to the 6th decade of life and increasing after the 6th decade ($p < 0.0001$) [20].

This study also demonstrates a positive correlation between SHBG and the anthropometric measures in the form of BMI, mid-arm circumference and waist circumference (p value < 0.0001 for each). In contrary, Luboslav et al. had recently showed that obese and overweight patients had significantly lower total SHBG than lean control subjects [21].

Similarly, and controversial to previous literature, SHBG showed no significant difference between NAFLD patients and controls. Previous literature has repeatedly proven lower SHBG levels with NAFLD female patients in particular [22–27].

Most important to the target of this study, a significant positive correlation between SHBG and NAFLD fibrosis score was highlighted. So, higher SHBG levels were associated with more severe liver fibrosis. This was the opposite relationship to that observed between NAFLD and lower SHBG levels, as discussed above. The precise mechanisms for the positive relationship between SHBG and NAFLD fibrosis score are unclear, but theoretical presumptions are possible.

High SHBG concentration may reflect less fat deposition in the liver. Importantly, Miyaaki et al. reported that the amount of liver fat may decrease with the progression of fibrosis in patients with hepatic steatosis [28]. Furthermore, Stefan et al. reported that serum SHBG increases as liver fat mass decreases and SHBG has been shown to increase in parallel with a decrease in intrahepatic fat mass, assessed using ultrasound [29], computed tomography, or magnetic resonance imaging. Interestingly, these clinical observations may be explained by the finding that SHBG has anti-inflammatory and lipolytic effects on cultured adipocytes and macrophages. Thus, the increase in SHBG alongside that of NAFLD fibrosis score may reflect a compensatory increase, which may lead to a reduction in intrahepatic fat mass and retard the progression of inflammation and liver fibrosis. This data suggests that there may be a specific pathologic association between liver fibrosis and SHBG in NAFLD [30].

Worthy of note, this presumed fluctuation in SHBG, that increases with the development of NAFLD with subsequent decrement with advancing fibrosis is the likely reason that explains the absence of any significant difference in SHBG level between the NAFLD cohort as a whole when compared to healthy controls.

An essential observation in this study cohort is that despite consecutive enrolment of patients, all turned out to fall in the F3–F4 or indeterminate categories. None had mild or no fibrosis. This explains the higher SHBG levels in our cohort, which gives us a probably false positive correlation with multiple variables, including the metabolic syndrome and its components. Past studies included the full spectrum of asymptomatic NAFLD patients and a negative correlation of SHBG levels with the metabolic syndrome and its components as well as NAFLD was established. This is opposed to our cohort that was recruited from the internal medicine ultrasonography department which mainly comprises ward inpatients. Therefore, this study represents a specific subcategory of NAFLD patients with severe disease. Higher SHBG in contrast to previous literature is due to advancing fibrosis.

ROC curve analysis showed that SHBG can predict severe liver fibrosis (F3–F4) in our NAFLD female cohort at a cut-off level of > 10 ng/ml (equivalent to 0.105 nmol/L), with 34% sensitivity and 90% specificity, Area under the ROC curve (AUC) = 0.548. A similar study involving 363 Japanese men with NAFLD also showed that high SHBG was associated with liver fibrosis. Their cut-off for SHBG was > 49.8 nmol/L as a predictor of FIB-4 index ≥ 1.3, AUC = 0.649. Sensitivity and specificity were not stated though [11].

The sensitivity in our female NAFLD cohort was modest which makes it a poor negative test, while its high specificity renders the suggested cut-off > 10 ng/ml an excellent positive test for predicting severe fibrosis, without the need to perform further testing as a fibroscan and/or a core biopsy.

Another earlier study with a similar result, but also involving male patients with NAFLD, was done in 2016. It was a retrospective cross-sectional study of 534 participants. SHBG was positively correlated with the NAFLD fibrosis score [31].

This study was the first to be performed on female patients with NAFLD. This study has some limitations. The authors view the study as a preliminary one that requires further validation in a larger cohort. Also, despite consecutive enrolment; no patients were in the F0–F1 category. This category still needs to be tested.

Conclusion

SHBG is positively correlated to severe fibrosis in female NAFLD patients. It is an efficient positive predictor of severe fibrosis in female NAFLD patients at a cut-off level > 10 ng/ml, with a high specificity and modest sensitivity. The authors conclude that SHBG is a potential non-invasive marker of liver fibrosis in female patients with NAFLD. Authors recommend further validation of the above results to consider SHBG as a potential non-invasive, cost effective marker of liver fibrosis in NAFLD patients.

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
T2DM	Type 2 diabetes
SHBG	Sex hormone binding globulin
AUC	Area under the ROC curve
NAFL	Nonalcoholic fatty liver
NASH	Nonalcoholic steatohepatitis

Declarations

Ethics approval and consent to participate
The study was approved by the institutional ethics committee and form review board (MS-224–2019). Oral and written informed consent was obtained from all subjects or from their eligible relatives.
The medical record profession has its own code of ethics that applies to all medical record practitioners. Confidentiality of data, safe data storage, and privacy rights are respected by all who handle patient information. Data were coded and patient names or identity did not appear on any of the data collection forms or during statistical analysis.

Consent for publication
Oral and written informed consents were obtained from the patients or from their eligible relatives.

Competing interests
The authors declare that they have no competing interests.

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