

Evaluation of the predictive value of body mass index (BMI), waist circumference, and visceral fat to differentiate non-alcoholic fatty liver (NAFLD) in women with polycystic ovary syndrome

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Background: Our objective was to determine the overall prevalence of nonalcoholic fatty liver disease (NAFLD) in women with polycystic ovarian syndrome (PCOS) in our sample population. The second aim was to evaluate the predictive value of body mass index (BMI), waist circumference (WC), and visceral fat for the onset of NAFLD in these patients. **Materials and Methods:** This cross-sectional study was performed on 71 women with PCOS who were referred to Arash Women's Hospital in Tehran. Demographic and clinical information and anthropometric and biomedical indices were collected by a trained nurse. Liver ultrasonography was performed for all participants by a radiologist. **Results:** NAFLD was identified in 53.5% ($n = 38$) of subjects and the frequency of mild, moderate, and severe grades were 65.8%, 31.6%, and 2.6%, respectively. BMI and visceral fat of patients with NAFLD were significantly higher than non-NAFLD ($P < 0.001$). Receiving operating characteristic (ROC) curve analysis revealed that BMI was the best indicator of predicting NAFLD (cutoff = 25.5 kg/m², sensitivity 75%, and specificity 75%), whereas visceral fat (cutoff = 5.5%, sensitivity 79%, and specificity 67%) and WC (cutoff = 89.5 cm, sensitivity 73%, and specificity 64%) were inferior for predicting NAFLD in PCOS patients. **Conclusion:** The prevalence of NAFLD in the study population is high. Our findings supported the use of BMI as a simple and practical predictive factor for the NAFLD onset, with a cutoff level of 25.5. The use of this cutoff level will enable physicians to identify PCOS patients at risk for NAFLD.

Key words: Body mass index, nonalcoholic fatty liver disease, polycystic ovarian syndrome, predictive value of test, visceral fat, waist circumference

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a condition associated with chronic anovulation, insulin resistance, and androgen excess. It is considered to be one of the most common endocrinopathies among reproductive-age women and it affects approximately 7.1%–14.6% of reproductive-age women in Iran using

different criteria.^[1] Women with a diagnosis of PCOS have twice as many hospital admissions as women without PCOS and are at an increased risk of many other significant medical comorbidities such as adult-onset diabetes, obesity, and hypertensive disorder.^[2] A descriptive cross-sectional study in 3200 adolescents aged 14–18 years manifested the risk of metabolic disorders such as glucose metabolism and dyslipidemia

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in PCOS adolescents was more than non-PCOS and these comorbidities should be screened in patients with PCOS at any ages.^[3]

Nonalcoholic fatty liver disease (NAFLD) or hepatic steatosis is a common form of liver disease that is high in women with PCOS.^[4-7] NAFLD histologically consists of triglycerides (TG) accumulated in the cytoplasm of liver cells that may progress to liver fibrosis and steatohepatitis due to NAFLD that can cause cirrhosis.^[8] NAFLD and PCOS are both associated with metabolic syndrome (MBS). Common features such as central obesity, hypertension, type 2 diabetes mellitus, dyslipidemia, and a common pathophysiological mechanism, indicate insulin resistance in these two diseases.^[5-7,9,10] The prevalence of MBS in PCOS Iranian women was reported as 22.7% and the rate of central obesity was estimated at 31%.^[11]

Obesity, as one of the most common disorders associated with PCOS, is also one of the most important risk factors for fatty liver disease.^[12] However, several studies have suggested that central obesity (visceral fat accumulation) is more important than body mass index (BMI) which indicates total body fat mass (visceral fat and subcutaneous fat), in metabolic complications such as hepatic steatosis; and current guidelines on obesity and the identification of high-risk individuals recommend that waist circumference (WC) and waist to hip ratio (WHR) be calculated to determine central obesity in individuals.^[13-15] Evidence has shown that women and men with normal BMI who have abdominal obesity (based on a waist-to-hip ratio and waist-to-height ratio) have a higher risk of developing metabolic disorders and cardiovascular disease.^[16] Also in patients with type II diabetes, abdominal obesity may be a predictor of future fatty liver disease.^[17]

In women with PCOS, a review of the association between mesenteric fat thickness and other ultrasound indicators of central obesity with fatty liver disease has shown that visceral fat plays an important role in the pathogenesis of fatty liver in these individuals.^[4] On the other hand, a study found that women with PCOS with normal BMI (under 23) had higher rates of NAFLD compared to people without PCOS. Therefore, they had suggested a hypothesis that PCOs alone, independently of obesity, are a potential risk factor for NAFLD.^[18] This result manifested that high BMI may not be the only appropriate indicator for assessing the risk of NAFLD, and in women evaluating central obesity indices such as mesenteric fat measurement using imaging techniques (ultrasound and MRI), central fat accumulation analysis using body composition devices, and WHR measurement are required.

Therefore, it seems more evaluation of anthropometric variables such as BMI and visceral fat are necessary to find

a useful and practical variable for identifying PCOS patients who are at risk of NAFLD. Given the high prevalence of PCOs and its association with NAFLD and related complications such as liver failure and hepatocellular carcinoma,^[5,7] this study was designed to determine the prevalence of NAFLD in women with PCOS in our study population. The second aim was to evaluate the predictive value of BMI, WC, and visceral fat and finding the best cutoff value to differentiate NAFLD in this population.

MATERIALS AND METHODS

Study design and participants

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (no number 92-01-39-20141) and informed consent was obtained from all participants. This cross-sectional study was performed on women with polycystic ovary syndrome who were referred to Arash Women's Hospital in Tehran from September 2014 to December 2016. Diagnosis of PCOS was made according to the Rotterdam 2003 diagnostic criteria (clinical and/or biochemical symptoms of hyperandrogenism, reduced or no ovulation, and ultrasound diagnosis). Pregnant women, women with a history of abdominal surgery, autoimmune liver disease, viral liver disease, other causes of liver disease, and elevated liver enzyme, as well as those who consume more than 20 g/day of alcohol or who have taken hormone medication for the past 3 months, were excluded. Demographic and clinical information including age, blood pressure, history of internal diseases and surgery, and medications were collected by a trained nurse, and then anthropometric, biochemical, and ultrasound indices were assessed.

Anthropometrics measurement

The anthropometric measurement of each subject was performed by a trained nurse. Participants' weight was measured without shoes and with the least amount of clothing using the calibrated scales of the Omron BF 511 with an accuracy of 100 g and height using a wall gauge. BMI was calculated by dividing the weight in kilograms by the square of the height in meters. WC was measured with an irreversible tape meter between the lowest rib and the iliac crest while the person was at the end of the expiration.

Biochemical variables measurement

Blood samples were taken in the morning after fasting for 10–12 h. The biochemical variables measured in this study included fasting blood sugar (FBS), 2 h postprandial blood sugar, total cholesterol, high-density cholesterol, low-density cholesterol, TG, liver enzyme tests (alanine aminotransferase [ALT], aspartate aminotransferase, and alkaline phosphatase), follicle-stimulating hormone (FSH), and luteinizing hormone (LH).

Biochemical indices were measured using Bionic kits (Bionic Company, Tehran, Iran), a biochemical auto-analyzer (model BT 2000, Italy), and Pars Azmoon Kits (Pars Azmoon Kit, Pars Azmoon Inc., Tehran, Iran). Hormone indices were measured by Roche Cobas e411 automated analyzer. All laboratory tests were performed at the Arash hospital laboratory.

Measurement of visceral fat mass

Percentage total body fat (%) and visceral fat (%) were measured by bioelectrical impedance analysis using a body composition monitor (OMRON 511, OMRON healthcare Co., Ltd. Japan) in the fasting state. The participants stood with the knees and back straight and looked straight ahead. The arms were horizontally raised and extended at a 90° angle to the body and the elbows were extended straight. The participants stood with weight evenly distributed on the measurement platform. Considering the entered data (age, gender, and height) into the device, an accurate entire body measurement and classification of body fat percentage, visceral fat, skeletal muscle fat, BMI, and resting metabolic rates were recorded.

Ultrasound evaluation of hepatic steatosis

Liver ultrasonography was performed by a radiologist who was unaware of the results of liver enzyme tests for all participants. Fatty liver was diagnosed according to the criteria of Scatarige *et al.*^[19] These criteria included an increase in hepatic echogenicity, decreased penetration of the deep part of the liver, and decreased echogenicity of the diaphragm and intrahepatic portal vessels. The subjects were classified according to the absence or presence of fatty liver, as well as the severity of the fatty infiltration, into Grade 1 (mild infiltration), Grade 2 (moderate infiltration), and Grade 3 (severe infiltration).

Statistical analysis

The analyses were carried out using Stata version 16 (Stata Corp., College Station, TX, USA). Data normality was checked by normal probability plots, Kolmogorov–Smirnov test, and coefficients of skewness and kurtosis. Data were presented as mean \pm standard deviation and numbers with percentages. Data from PCOS subjects with NAFLD were compared to those without NAFLD. All variables were presented as continuous variables and a Student *t*-test was used to compare the differences between the two groups. BMI was presented as categorical (nonobese and obese) and the Chi-square test was used for comparison between groups. Finally, to find the cutoff points, a receiver operating characteristic (ROC) curve analysis was performed for each parameter (visceral fat, WC, and BMI). The area under the ROC curve was computed as an indicator of the diagnostic value associated with each variable. Sensitivity, specificity, positive predictive value (PPV), negative predictive

value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-) with 95% confidence intervals (CIs) were reported. Statistical significance was set at a two-sided $P < 0.05$.

RESULTS

Seventy-one patients completed all phases of biochemical and ultrasonographic evaluation. Therefore, the final analysis was performed on these patients. Table 1 shows the total characteristic of the study participants. NAFLD was identified in 53.5% ($n = 38$) of subjects (according to sonographic finding) and the frequency of mild, moderate, and severe grades were 65.8%, 31.6%, and 2.6%, respectively. Considering the diagnosis of NAFLD, the general, anthropometric, and biochemical characteristics were compared between the two groups [Table 2]. BMI and visceral fat of patients with NAFLD were significantly higher than the non-NAFLD ($P < 0.001$). Triglyceride, FBS, and ALT were significantly higher in NAFLD compared with a non-NAFLD group. There was no significant difference between the two groups in terms of FSH and LH level.

In all samples, 25 women had normal BMI (BMI < 25 kg/m²). NAFLD was diagnosed in six women (24%) of the normal BMI group and 32 women (69.6%) in the obese group. In women with normal BMI, there was not any significant difference between body fat, visceral fat, and skeletal muscle fat, and WC as well as other chemical variables between NAFLD and non-NAFLD (Data are not shown in the Table).

The sensitivity and specificity of visceral fat (cutoff level = 5.5%), WC (cutoff level = 89.5 cm), and BMI (cutoff level = 25.5 kg/m²) were 79%, 67%; 73%, 64%; and 75%, 75%, respectively. As shown in Table 3, in addition to sensitivity and specificity, BMI had the best PPV (0.67, 95% CI = 0.49–0.82) and NPV (0.85, 95% CI = 0.69–0.94). Figure 1 shows the ROC analysis for three predictive parameters.

DISCUSSION

The present study shows the prevalence of NAFLD was 53.5% in this sample size of women with PCOS, the majority of them belonged to the mild grade category (65.8%). Our findings revealed the prevalence of NAFLD in PCOS patients as high as NAFLD in type 2 diabetes mellitus (55.8%) in the Iranian population.^[20] Depending on the diagnostic index used for both NAFLD and PCOS in the world, the prevalence of NAFLD in the PCOS population has been estimated between 15% up to 71%,^[21] therefore, it seems the prevalence of NAFLD in Iranian women with PCOS is high. Therefore, PCOS patients should be screened for NAFLD and appropriate advice is essential

Table 1: Clinical and biochemical characteristics of the study subjects

	Total population (n=71)	NAFLD (n=38)	Non-NAFLD (n=33)	P
Age (years)	30.94±6.01	30.78±5.98	31.1±6.13	0.82
BMI (kg/m ²)	27.43±4.83	29.56±4.73	24.97±3.62	<0.001
BMI category				
Nonobese	25 (35.2)	6 (15.8)	19 (57.6)	<0.00
Obese	46 (64.8)	32 (84.2)	14 (42.4)	1
Body fat (%)	39.53±6.41	42.25±4.75	36.40±6.70	<0.001
Visceral fat (%)	6.04±2.17	6.81±2.25	5.15±1.69	<0.001
Skeletal muscle fat (%)	25.99±2.83	25.06±1.72	27.05±3.45	0.003
RMR	1314.33±371.88	1304.37±461.72	1325.77±236.14	0.16
WC (cm)	90.03±11.75	94.22±11.42	85.33±10.39	0.001
Systolic blood pressure	112.10±10.45	112.88±9.15	111.30±11.73	0.54
Diastolic blood pressure	76±8.72	76.97±7.60	75±9.75	0.36
FBS (mg/dl)	91.77±9.06	93.93±9.04	89.46±8.62	0.05
Total cholesterol (mg/dl)	165.85±38.94	168.96±40.71	162.53±37.35	0.52
LDL (mg/dl)	196±93.37	96.53±30.93	90.40±30.17	0.45
HDL (mg/dl)	42.55±8	42.14±9.18	42.93±6.86	0.71
TG (mg/dl)	107.37±55.85	127.53±65.75	85.86±31.82	0.003
ALT (U/L)	18.74±8.92	21.78±10.56	15.50±5.20	0.005
AST (U/L)	18.16±6.19	18.88±7.10	17.40±5.05	0.35
ALP (U/L)	168.74±47.48	166.34±48	171.23±47.63	0.69
FSH (mIU/mL)	6.49±6.32	5.71±2.15	7.29±8.75	0.35
LH (mIU/L)	8.29±5.09	8.48±4.31	8.08±5.85	0.77

Data are presented as mean±SD and number with percentages in parenthesis; Comparison was performed between two groups (NAFLD versus non-NAFLD) and P value refers to Student's t-test for all continuous variables; Chi-squared test was used for BMI category. NAFLD=Nonalcoholic fatty liver disease; BMI=Body mass index; RMR=Resting metabolic rates; FBS=Fasting blood sugar; HDL=High density cholesterol; LDL=Low density cholesterol; TG=Triglycerides; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; ALP=Alkaline phosphatase; FSH=Follicle stimulating hormone; LH=Luteinizing hormone; SD=Standard deviation; WC=Waist circumference

Table 2: Comparison of clinical and biochemical variables according to severity of nonalcoholic fatty liver disease

	Mild (Grade 1) (n=25)	Moderate and severe (Grade 2 and 3) (n=13)	P
Age (years)	29.92±5.92	32.46±5.98	0.22
BMI	28.21±4.44	32.16±4.40	0.01
Body fat (%)	40.86±4.65	44.93±3.83	0.01
Visceral fat (%)	6.16±1.18	8.08±3.20	0.06
Skeletal muscle fat (%)	25.43±1.72	24.37±1.59	0.07
RMR	1301±413.74	1310.85±561.15	0.95
WC (cm)	91.12±11.13	100.67±9.47	0.02
FBS (mg/dl)	93.48±10.60	94.82±5.27	0.70
Total cholesterol (mg/dl)	164.86±37.22	176.82±47.59	0.44
LDL (mg/dl)	89.44±28.72	109.30±32.12	0.11
HDL (mg/dl)	43±10.39	40.6±6.72	0.52
TG (mg/dl)	129.10±70.80	124.55±58	0.86
ALT (U/L)	20.14±8.72	24.91±13.32	0.23
AST (U/L)	18.24±6.10	20.09±8.90	0.49
ALP (U/L)	154.80±27.72	187.31±68.56	0.07
FSH (mIU/mL)	5.74±2.08	5.66±2.44	0.92
LH (mIU/L)	7.91±4.34	9.78±4.21	0.29

P-value refers to Student's t-test. BMI=Body mass index; RMR=Resting metabolic rates; FBS=Fasting blood sugar; HDL=High density cholesterol; LDL=Low density cholesterol; TG=Triglycerides; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; ALP=Alkaline phosphatase; FSH=Follicle stimulating hormone; LH=Luteinizing hormone; WC=Waist circumference

to prevent the progression of the disease to moderate and severe grades.

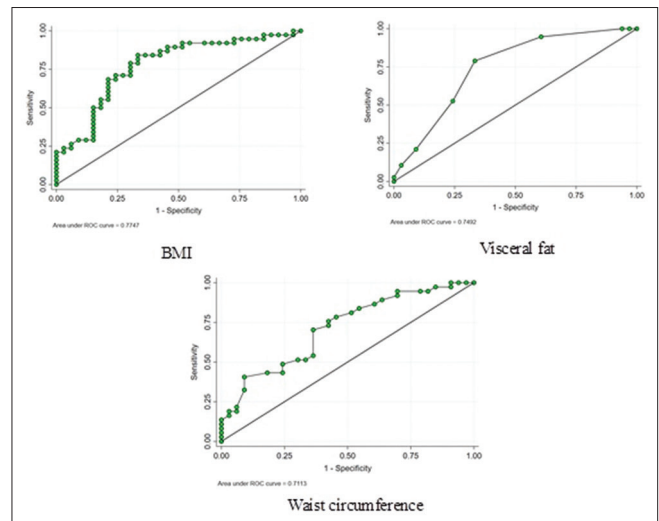


Figure 1: Receiver operating characteristic curves of three predictive variables with reference lines

As we expected, we found the BMI, WC, visceral fat, triglyceride, and FBS were higher in PCOS patients diagnosed with NAFLD than in the non-NAFLD group. These results were similar to several studies that have previously demonstrated PCOS subjects with fatty liver had higher BMI, WC, triglyceride, and FBS than PCOS without NAFLD.^[4,6,10] Furthermore, they reported other factors such as higher age, higher diastolic blood pressure,

Table 3: Diagnostic indices of three factors related to nonalcoholic fatty liver disease using receiver operating characteristic (receiving operating characteristic curve)

	Visceral fat (%)	WC (cm)	BMI (kg/m ²)
Cutoff level	5.5	89.5	25.5
AUC	0.75 (0.63-0.84)	0.71 (0.59-0.83)	0.78 (0.66-0.86)
Sensitivity	0.79 (0.54-0.87)	0.73 (0.49-0.82)	0.75 (0.60-0.92)
Specificity	0.67 (0.57-0.86)	0.64 (0.52-0.83)	0.75 (0.59-0.87)
PPV	0.67 (0.49-0.82)	0.64 (0.46-0.80)	0.67 (0.49-0.82)
NPV	0.79 (0.63-0.91)	0.71 (0.53-0.85)	0.85 (0.69-0.94)
LR +	2.73 (1.58-4.74)	2.08 (1.22-3.53)	3.07 (1.78-5.31)
LR -	0.37 (0.19-0.68)	0.50 (0.30-0.85)	0.29 (0.14-0.60)

Data are presented as value and 95% CI in parenthesis. AUC=Area under the receiver operating characteristic curve; PPV=Positive predictive value; NPV=Negative predictive value; LR=Likelihood ratio; CI=Confidence interval; WC=Waist circumference; BMI=Body mass index

and lower high-density lipoprotein cholesterol in PCOS patients with fatty liver^[4,10] those were in contrast with our findings. Despite these findings, one study did not find any statistically significant differences in clinical and biochemical variables in NAFLD with PCOS and without PCOS and they only reported the differences in WC ($P=0.07$) and TG ($P=0.09$) according to the ALT level.^[4] In the present study, the ALT level was higher in the NAFLD group compared with a non-NAFLD group [Table 1] and it was confirmed by other studies.^[10,18] However, despite Ma *et al.*'s study,^[10] ALT was not different between the two groups [Table 2] according to the grade of NAFLD.

The prevalence of NAFLD is increasing in parallel with the prevalence of obesity; both processes are closely linked to insulin resistance.^[8] Since we measured the FBS level in this study, we evaluated the correlation of FBS with BMI, WC, and visceral fat. We found strong positive correlation between FBS and WC ($r=0.40$, $P=0.001$). The correlation between FBS and BMI ($r=0.29$, $P=0.02$), and visceral fat ($r=0.25$, $P=0.05$) were lower than WC (data are not shown in the table).

A recent study has reported the rate of NAFLD in PCOS women with normal BMI (under 23) is higher than women without PCOS and their hypothesis explains that PCOS alone independently of obesity could be a potential risk factor for NAFLD.^[18] Kim *et al.* and colleagues also suggested that high BMI may not be the only appropriate indicator for assessing the risk of NAFLD.^[18] However, in the present study, we evaluated whether individuals with normal BMI may be prone to the fatty liver due to increased WC and visceral fat. There were not any significant differences in visceral fat and WC between NAFLD and non-NAFLD groups (Data are not shown in Table). Furthermore, the frequency of NAFLD in normal weight was not high and women with higher BMI were at increased risk of NAFLD and our study did not confirm the previous study hypothesis.

Another study believed, in PCOS patients with fatty liver disease, central obesity has an important role.^[4] On the other hand, evaluation of the severity of fatty liver by ultrasonography showed a significant relationship with the visceral fat accumulation and WC,^[22] which were consistent with our study [Table 2].

To the best of our knowledge, this investigation evaluates the prevalence of NAFLD in PCOS patients in Iran for the first time and it was our study advantage. On the other hand, we suggested the use of BMI as a simple and practical indicator for more attention to NAFLD in our PCOS patients.

This study had some limitations. First, because of the low budget, continuing our study was not possible for a longer period. Therefore, the sample size of our study was very low and we cannot generalize the results to Iranian women with PCOS. Meanwhile, conducting further analysis such as logistic regression was accompanied by inaccurate results with wide confidence intervals. Some studies have suggested that androgen excess levels such as free testosterone and free androgen index indicate the increased risk of NAFLD in PCOS women.^[18,23,24] In this study, we did not measure the androgen levels and we are unable to explain the effect of androgenicity on the risk of NAFLD and it was another limitation of the present study. The third limitation was, the data on hip circumference was not available, so, the waist/hip ratio did not calculate and maybe the sensitivity and specificity of the waist/hip ratio would be higher than BMI. Finally, some of the clinicians believe elastography is the best method for the diagnosis of NAFLD. Since many diagnostic studies of NAFLD are still based on ultrasound and this method is a simple, cheap, safe, and available method, we used this modality for the diagnosis of NAFLD.

CONCLUSION

The present study showed the high prevalence of NAFLD in PCOS patients in our sample population. Furthermore, diagnostic value evaluation for three parameters (visceral fat, WC, and BMI) at given cutoff points confirmed that BMI as a simple and practical indicator was useful for identifying NAFLD in PCOS patients who are at risk. Preventive interventions and metabolic complications screening should be considered in Iranian women with PCOS and clinicians should focus not only on PCOS signs and treatment but also on an increased risk of NAFLD. In order to find the best predictor of NFLAD in the high-risk population, the role of abdominal obesity and visceral fat in the pathogenesis of metabolic complications in PCOS patients, further investigation with more sample size is recommended.

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Conflicts of interest

There are no conflicts of interest.

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