







Evaluation of neck circumference as an easy and reliable predictor for non-alcoholic fatty liver disease

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ABSTRACT

Background/Aims: The aim of the present study was to investigate the relationship between non-alcoholic fatty liver disease (NAFLD) and neck circumference (NC) and to compare the NC predictive value with other anthropometric indices in the prediction of NAFLD and metabolic syndrome (MetS) as well as to find the NC cut-off point for the prediction of NAFLD and MetS in an Iranian population.

Materials and Methods: A total of 590 individuals who fulfilled our criteria were enrolled in the study. Anthropometric measurements, physical examinations, and abdominal ultrasonography were performed by trained staff. Blood samples for biochemical tests were also obtained after fasting for 12 h.

Results: Neck circumference was associated with NAFLD and MetS in both genders ($p < 0.0001$) and remained significant even after adjustment for possible confounding factors. It was also significantly associated with other anthropometric indices, such as fatty liver severity, aspartate aminotransferase, alanine aminotransferase, fasting blood sugar, triglycerides, low-density lipoprotein, systolic and diastolic blood pressure, and family history of diabetes in both sexes ($p < 0.05$). There was a significant negative correlation between high-density lipoprotein levels and NC in both sexes ($p < 0.001$).

Conclusion: Neck circumference was significantly correlated with NAFLD and MetS. In addition, it had the highest predictive value for NAFLD and MetS among other common anthropometric indices. Therefore, it can be used as a simple and feasible tool for screening NAFLD in a large population.

Keywords: Non-alcoholic fatty liver disease, neck circumference, metabolic syndrome

INTRODUCTION

A marked increase in the prevalence of fatty liver and need for good control of the virus related to liver disease has generated a lot of concern and attention regarding fatty liver diseases among hepatologists. Fatty liver is one of the most common causes of chronic liver disease (1). It is also the third leading cause of liver transplantation in the USA and is predicted to be the major cause of liver transplantation by 2025 (2).

On the other hand, non-alcoholic fatty liver disease (NAFLD) as a subclass of fatty liver disease has become one of the major public health problems as it increases the risk of liver cirrhosis, liver cancer, and metabolic disorders and is regarded as a metabolic syndrome (MetS) exhibited by the liver (1). Therefore, early diagnosis and efficacious management in its primary stage will enhance prognosis and prevent secondary complications.

Liver biopsy is the gold standard for fatty liver diagnosis. Since it is invasive, it cannot be used widely in the general

population and is reserved for complicated forms of fatty liver. Blood serum transaminase sensitivity is very low and will fail to detect many cases since it is normal in most fatty liver disease cases. Although radiologic instruments, such as ultrasonography and magnetic resonance spectroscopy, have high sensitivity (3) and are widely used, they are not cost effective as primary screening tests in the general population.

Recently, anthropometric indices have been widely used as simple and feasible tools for screening the general population for metabolic disorders. Traditional indices, such as body mass index (BMI), are not accurate anymore because it only reflects the total body obesity, not the fat distribution, which is assumed to be much more imperative in metabolic diseases. Waist circumference (WC) and waist to height and waist to hip ratio as a surrogate to central obesity are strongly associated with visceral adipose tissue (VAT) (4). Recent studies have also demonstrated that upper body subcutaneous adipose tissue has a stronger relationship with metabolic disorders than VAT (5).

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In addition, neck circumference (NC) as a surrogate for measuring upper body subcutaneous fat has received attention from researchers. Several studies have shown the relationship between NC and MetS (6). However, to the best of our knowledge there are few studies that have demonstrated the relationship between NC and NAFLD as well as compared its prediction value with other anthropometrics.

The aim of the present study was to assess the relationship between NC and NAFLD as well as to investigate its prediction value among other anthropometric indices. We also wanted to set the NC cut-off point for predicting NAFLD in the population under study, which could be extended to the Iranian population.

MATERIALS AND METHODS

This was a cross-sectional study conducted in our outpatient clinic (Imam Reza Hospital) between October 2016 and February 2017. Patients who were scheduled for abdominal sonography were enrolled as potential candidates for the study. Patients were subjected to appropriate physical examination and history taking. Patients <18 years old; who had a history of current/previous alcohol consumption >20 g/day for men and 10 g/day for women; with chronic liver disease related to viral hepatitis, known cases of Wilson disease, hemochromatosis, and Cushing syndrome; with recent effort at losing weight (during the last 6 months); with prolong use of estrogen or regular consumption of drug associated with fatty liver disease, such as corticosteroid, methotrexate, tamoxifen, and amiodarone; and with thyroid disease, such as goiter or uncontrolled hypothyroidism or hyperthyroidism that may interfere with NC measurement, were excluded from the study. A total of 590 patients were included in our study. Informed consent was obtained from all patients before enrollment in the study. The ethics committee of Artesh University of Medical Sciences approved the study.

Data collection and biochemistry evaluation

Physical examination, history taking, and anthropometric measurements were performed by a single trained health care provider who was blinded to the ultrasonography report and blood biochemistry results of the patients. Patients were asked about their family history of diabetes and hypertension as well as their drug history and smoking status. Anthropometrics were measured in upright standing position while patients removed their excess clothes, such as jacket and shoe, and faced forward with shoulders relaxed. Height was measured using a height gauge with an

accuracy of 1 cm. Weight was measured using a standard digital scale with an accuracy of 0.1 kg. NC was measured using a plastic tape with an accuracy of 1 mm at the lower margin of the laryngeal prominence perpendicular to the axial axis with erect neck and eyes facing forward. WC was measured using a plastic tape with an accuracy of 1 mm on the midaxillary line at the midpoint between the lowest rib and the iliac crest. Hip circumference (HC) was measured at the widest point between the waist and the knee using a plastic tape with an accuracy of within 1 mm. BMI was computed as weight in kg divided by square of height in meter (kg/m^2). Waist to hip ratio (WHR) and neck to height ratio (NHtR) were simply measured by dividing the nominator with the denominator (both in cm).

Blood pressure was assessed, after 15 min of rest, in a sitting position on the upper left hand, and the systolic (SBP) and diastolic blood pressure (DBP) were recorded.

Blood samples were collected after fasting overnight for 8 h and were evaluated for fasting blood glucose (FBS); lipid profile, such as low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG); and liver function test, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). All biochemical parameters were determined by Roche Diagnostics enzymatic kits using a Beckman Coulter AU680 autoanalyzer.

MetS was defined according to the guidelines of the National Heart, Lung, and Blood Institute and the American Heart Association (7).

Abdominal ultrasonography was performed by expert radiologists, and fatty liver disease was reported based on its severity in a semi-quantitated manner according to Graif's criteria (8): (1) diffusion enhancement of the near field echo in the hepatic region (stronger than the kidney and spleen regions) and gradual attenuation of the far field echo, (2) unclear display of intrahepatic lacuna structures, (3) mild to moderate hepatomegaly with a round and blunt border, (4) color Doppler ultrasonography showing a reduction of blood flow signal in the liver or a difficult-to-display signal with a normal distribution of blood flow, and (5) unclear or non-intact display of the envelope of the right liver lobe and diaphragm.

Mild fatty liver was defined based on the first criterion and any one of item 2-4. Moderate fatty liver was defined based on the first criterion and any two of subsequent items (2-4). Finally, severe fatty liver was defined based on items 1 and 5 and any two of items 2-4.

Statistical analysis

All statistical analyses were performed using SPSS software, version 22 (IBM Corp.; Armonk, NY, USA). Normality for each variable was checked using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean \pm SD, whereas non-normally distributed variables were expressed as median and interquartile range. In some cases, non-normally distributed data were normalized by logarithmical transformation before analysis. Categorical data were expressed by frequency percentage. The chi-square test was used for categorical variables. For comparison of the two groups, we used the Student's t-test and analysis of variance for

normally distributed variable, and the Mann-Whitney U and Kruskal-Wallis tests for non-normally distributed data. Pearson's or Spearman's correlation coefficient was performed to analyze potential correlations between normally and non-normally distributed variables, respectively. In the present study, subgroup analyses were performed, participants were divided into subgroups based on NC quartile (Q1-Q4), and multivariate logistic regression analysis was used to compute odds ratios (ORs) with 95% confidence intervals for NAFLD according to the NC quartiles, with Q1 as the reference. The differentiation capability of anthropometrics in predicting NAFLD and MetS was evaluated by the receiver operating char-

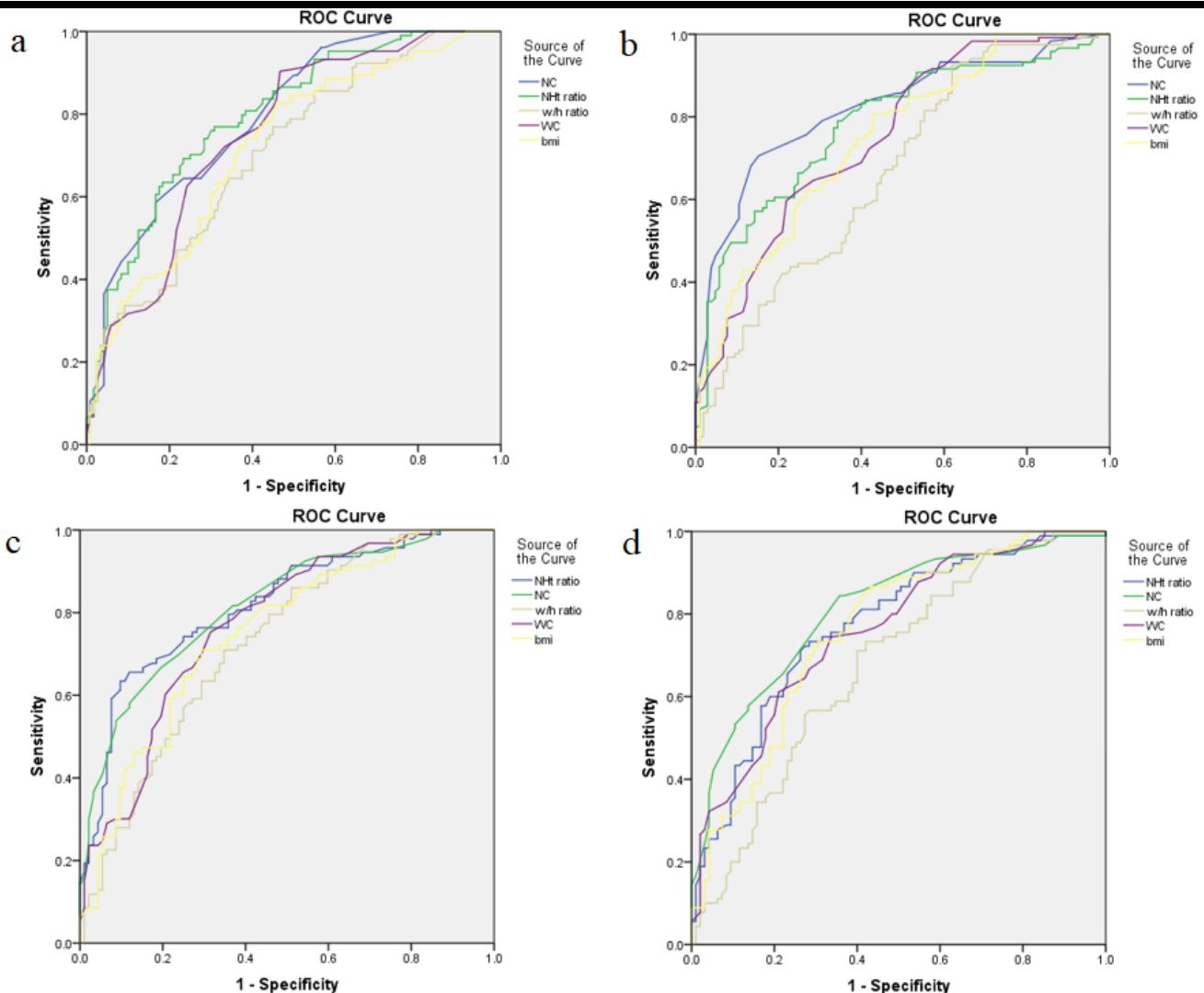


Figure 1. ROC curve analyses. Male \times NHt ratio, NC, WHR ratio, WC, and BMI predictive value for metabolic syndrome (a); Male \times NHt ratio, NC, WHR ratio, WC, and BMI predictive value for non-alcoholic fatty liver disease (b); Female NHt ratio, NC, WHR ratio, WC, and BMI predictive value for metabolic syndrome (c); Female \times NHt ratio, NC, WHR ratio, WC, and BMI predictive value for non-alcoholic fatty liver disease (d)

acteristic technique, and the optimal cut-off point was also determined by Youden's J index defined as $J = (\text{sensitivity} + \text{specificity}) - 1$ (Figure 1). All tests were two-sided. A $p < 0.05$ was accepted as statistically significant.

RESULTS

Our study was composed of a total of 590 individuals. The mean age of the patients was 44.8 ± 12.26 . Table 1 shows the basic characteristics of the participants according to their sex and fatty liver disease status. The total prevalence of MetS and NAFLD was 48% and 51%, respectively (46.4% in men vs 50.2% in women for MetS and 53.1% in men vs 48.6% in women for NAFLD).

The prevalence of fatty liver correlated significantly with an increase in age in women, but this relationship was not observed in men ($p = 0.88$ in men vs 0.009 in women). As shown in Table 1, participants with NAFLD had higher

NC value along with other anthropometric indices. They also had higher values of SBP, DBP, FBS, total cholesterol, TG, LDL, AST, and ALT, regardless of sex ($p < 0.05$). The mean HDL was lower in the NAFLD group in both sexes ($p < 0.05$).

Furthermore, the presence of MetS and family history of diabetes was higher in the NAFLD group in both sexes ($p < 0.05$).

NC correlated significantly with NAFLD, NAFLD severity, MetS status, WC, WHR, BMI, FBS, TG, LDL, DBP, SBP, AST, and ALT in both sexes (Table 2). The relationship between NC and NAFLD and NC and MetS remained significant even after adjustment for probable confounding factors, such as age, BMI, WC, WHR, diabetes mellitus (DM) family history ($p = 0.032$ in women and $p < 0.001$ in men for NAFLD and $p < 0.001$ in both sexes for MetS).

Table 1. Demographic characteristics of the patients with and without *Helicobacter pylori* infection

Row	Variable	Men (n=322)			Women (n=268)		
		NAFLD (n=171)	Non-FLD (n=151)	p	NAFLD (n=130)	Non-FLD (n=138)	p
1	Age (years)	43.64±13.41	44.32±17.52	0.880	48.21±11.27	43.71±15.24	0.009
2	Height (cm)	175.42±7.26	172.75±7.62	0.002	160.66±5.47	160.38±6.79	0.207
3	Weight (kg)	84.25±14.84	72.05±15.58	0.000	75.14±10.29	64.98±9.83	0.000
4	Neck circumference (cm)	41.90±3.19	38.19±2.47	0.000	36.66±3.15	33.81±2.42	0.000
5	Waist circumference (cm)	101.89±10.59	90.93±13.12	0.000	101.09±10.79	89.46±11.97	0.000
6	Hip circumference (cm)	104.76±7.35	97.78±7.26	0.000	107.54±9.24	100.30±8.96	0.000
7	BMI (kg/m ²)	27.29±3.87	24.08±4.67	0.000	29.13±3.90	25.33±3.98	0.000
8	Neck to height ratio	0.23±0.018	0.22±0.014	0.000	0.22±0.021	0.21±0.017	0.000
9	Waist to hip ratio	0.97±0.052	0.92±0.099	0.000	0.94±0.059	0.89±0.086	0.000
10	SBP (mm Hg)	129.98±14.35	126.45±16.50	0.045	124.73±15.74	132.94±18.01	0.000
11	DBP (mm Hg)	83.28±13.53	78.92±13.02	0.002	83.63±13.34	76.84±13.63	0.000
12	FBS (mg/dL)	96.96±17.14	91.74±10.72	0.028	101.43±29.72	90.50±15.82	0.000
13	Triglycerides	154.27±59.59	130.08±57.56	0.000	165.23±71.01	114.01±46.38	0.000
14	Total cholesterol	208.07±38.79	193.7±37.43	0.001	201.84±37.71	183.20±34.71	0.001
15	LDL cholesterol	130.93±32.91	114.73±31.94	0.001	120.96±33.76	109.85±26.94	0.023
16	HDL cholesterol	41.33±9.14	44.87±8.54	0.011	45.87±10.57	51.17±11.43	0.002
17	AST	33.23±38.74	21.59±8.26	0.000	24.81±17.95	16.80±6.96	0.000
18	ALT	44.98±51.17	27.98±20.21	0.000	33.42±39.19	19.37±7.06	0.002
19	Smoking status (%)	34%	18%	0.033	7%	5%	0.526
20	Family history of diabetes (%)	42%	19%	0.004	46%	17%	0.000
21	Presence of metabolic syndrome (%)	64%	26%	0.000	74%	23%	0.000

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood glucose; AST: aspartate aminotransferase; ALT: alanine aminotransferase; FLD: fatty liver disease; NAFLD: non-alcoholic fatty liver disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein

Table 2. Correlation between neck circumference and other parameters by sex

Variable	Men		Women	
	r	p	r	p
Weight	0.743	0.000	0.684	0.000
Waist circumference (cm)	0.765		0.749	
Hip circumference (cm)	0.738		0.691	
Waist to hip ratio	0.533		0.438	
BMI (kg/m ²)	0.725		0.683	
SBP (mm Hg)	0.296		0.376	
DBP (mm Hg)	0.318		0.289	
FBS	0.263		0.353	
Triglycerides	0.388		0.484	
NAFLD	0.556		0.533	
NAFLD severity	0.619		0.556	
Metabolic syndrome	0.511		0.547	
Family history of diabetes	0.307		0.271	
Total cholesterol	0.079	0.029	0.169	0.021
LDL cholesterol	0.002	0.039	0.148	0.044
HDL cholesterol	-0.165	0.013	-0.250	0.001
AST	0.163	0.014	0.321	0.000
ALT	0.298	0.000	0.178	0.015

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood glucose; AST: aspartate aminotransferase; ALT: alanine aminotransferase; NAFLD: non-alcoholic fatty liver disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein

Table 3. Odds ratio of NAFLD by quartile of neck circumference

Groups	Variable	NAFLD (%)	Model	
			Model 1	Model 2
Men	Q1 (32-37)	15	1.00	1.00
	Q2 (37.1-39.7)	46	3.53 (2.33-4.66)	1.38 (1.02-2.12)
	Q3 (39.7-42.4)	60	11.34 (8.43-15.63)	1.66 (1.21-2.36)
	Q4 (42.5-50)	91	40.12 (27.74-52.82)	3.23 (1.65-4.52)
Women	Q1 (26.5-33.8)	16	1.00	1.00
	Q2 (33.9-35.1)	41	3.15 (1.96-4.72)	1.24 (0.97-2.03)
	Q3 (35.2-37.4)	56	10.83 (8.15-14.69)	1.83 (1.54-2.63)
	Q4 (37.5-42)	87	37.77 (23.48-50.17)	2.89 (1.22-4.36)

Model 1: Age adjusted

Model 2: Age, BMI, WC, and WHR ratio adjusted

NAFLD: non-alcoholic fatty liver disease; BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio

HDL-C had a significant negative correlation with NC in both sexes ($p < 0.05$).

Table 3 shows the OR of NAFLD according to the participants' NC quartile. The correlation remained significant even after adjustment for age, BMI, WC, and WHR ratio.

The area under the curve (AUC) was performed to evaluate the prediction value of anthropometric indices for both MetS and NAFLD (Table 4).

As shown in Table 4, NC had the greatest AUC for NAFLD in both men and women (0.821 (0.766-0.876) and 0.807 (0.745-0.870), respectively), whereas MetS was second after NHR with a little difference in both sexes (0.795 (0.745-0.870) and 0.818 (0.755-0.875) in men and women, respectively).

The best NC cut-off point for NAFLD was 39.25 cm (sensitivity 79% and specificity 69%) in men and 34.85 cm (sensitivity 84% and specificity 64%) in women.

The best NC cut-off point for MetS was 36.7 cm (sensitivity 77% and specificity 60%) in men and 32.9 cm (sensitivity 80% and specificity 61%) in women.

DISCUSSION

In this cross-sectional study, the prevalence of NAFLD and MetS was 51% and 48%, respectively. This shows an increase in the prevalence of NAFLD and related diseases in comparison to previous studies conducted in Iran. The prevalence of NAFLD in previous studies was 21.5% in 2010 and approximately 44% in recent years (9). This difference could be attributed to the different study population and severe diet changes as well as substitution of Western diet and increase in the prevalence of obesity among the Iranian population. Recent studies in Iran showed that 3 out of 4 people are obese or overweight with an increasing trend in recent years (10). Therefore, the higher prevalence of obesity-related diseases, such as NAFLD and MetS, was expected in our study in comparison to previous studies.

MetS was more prevalent among women, whereas NAFLD prevalence was higher among men. On the other hand, the prevalence of NAFLD increased significantly with an increase in age in women alone. These results could be attributed to the protection provided by female hormones against NAFLD. As these female hormones diminish during aging and after menopause, the prevalence of NAFLD increases significantly in elderly women.

Table 4. Area under the ROC by different anthropometric indices as predictor of NAFLD and metabolic syndrome

Groups	Variable		NC		WC		NHtR		WHR		BMI
	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p	AUC (95% CI)	p	p
Male (n=322)	0.821 (0.766-0.876)	0.000	0.750 (0.687-0.813)	0.000	0.783 (0.722-0.843)	0.000	0.667 (0.596-0.738)	0.000	0.745 (0.682-0.808)	0.000	0.000
	0.795 (0.738-0.852)	0.000	0.754 (0.692-0.817)	0.000	0.797 (0.740-0.854)	0.000	0.709 (0.643-0.776)	0.000	0.721 (0.655-0.787)	0.000	0.000
Female (n=268)	0.807 (0.745-0.870)	0.000	0.761 (0.693-0.829)	0.000	0.770 (0.703-0.838)	0.000	0.678 (0.601-0.755)	0.000	0.759 (0.690-0.828)	0.000	0.000
	0.815 (0.755-0.875)	0.000	0.774 (0.707-0.840)	0.000	0.818 (0.758-0.879)	0.000	0.730 (0.658-0.802)	0.000	0.750 (0.680-0.820)	0.000	0.000

ROC: receiver operating characteristic; CI: confidence interval; AUC: area under the curve; NC: neck circumference; WC: waist circumference; NHtR: neck to height ratio; BMI: body mass index; WHR: waist to hip ratio; NAFLD: non-alcoholic fatty liver disease; MetS: metabolic syndrome

However, owing to the absence of protective hormones in men and the consumption of a high-fat diet by young men, younger men will present symptoms of NAFLD at the same level as older men.

In the present study, we demonstrated that TG, LDL, cholesterol, FBS, AST, ALT, SBP, DBP, BMI, NC, WC, and HC were all significantly higher in the NAFLD group, which was in accordance with previous studies (11,12). Furthermore, we showed that NAFLD was higher among patients with positive DM family history even after adjustment for their own DM status. This result could be attributed to the role of intrahepatic fat in the development of insulin resistance and metabolic disorders; NAFLD could be interpreted as the very first symptom of developing DM in the future. Fabrin et al. (13) demonstrated that intrahepatic fat and not VAT determines insulin sensitivity and other metabolic disorders. It was also demonstrated that patients with NAFLD even with normal weight and blood glucose level will show a higher incidence of hyperglycemia and cardiovascular disease than the normal population (14). Another prospective study showed that NAFLD can be a predictor of type 2 DM that is independent of obesity (15). Thus, it could be concluded that NAFLD could be an alarming sign or accurate predictor of the development of DM. Therefore, a detailed and watchful follow-up must be given to patients with NAFLD for screening and prevention of DM.

Our results showed that smoking could be a risk factor for developing NAFLD in men alone, which was in accordance with the previous study conducted by Yinglilu et al. (16). Low smoking level among women in our study may be one of the reasons for the absence of such relationship in women. It was demonstrated that smoking could induce oxidative stress as well as activation of sterol regulatory element-binding protein 1, which are contributory factors to fat accumulation in the liver (17).

In our study, we discovered that NC was significantly associated with other anthropometric indices and contributed significantly to the occurrence of NAFLD compared with other anthropometric indices. In addition to its higher predictive value, NC was more feasible, accessible, and had lower limitations. For example, BMI cannot account for fat distribution, and WC can be affected by external factors, such as clothing or abdominal bloating, whereas NC has excellent repeatability and minimal variance during the day (18). NC was also significantly associated with MetS and its components as reported in previous studies (18-20). The NC predictive value for MetS was

second after NHtR, but their difference was so negligible that the NC ease of use increased its preference. The potential mechanism for the association of NC with NAFLD and MetS could be related to upper body subcutaneous fat tissue, for which NC is a good surrogate for its measurement (20-22). Upper body subcutaneous fat can lead to an increase in circulation of free fatty acid (FFA) (21,22), followed by conversion of FFA to TG by the liver, and then the accumulation of TG in the liver may contribute to the "first hit" that will induce NAFLD and insulin resistance, which will be followed by other metabolic disorders (21-23). Donnelly et al. also reported that most hepatic triacylglycerol is raised from the circulation of non-esterified fatty acid with lesser portion arising from diet and liver de novo lipogenesis (24). Therefore, these evidences could support the relationship between NC and NAFLD or NC and MetS. Our results showed that the risk of having NAFLD increased dramatically with an increase in NC in such a way that the adjusted OR for having NAFLD at the highest (vs lowest) quartile was 3.26 and 2.89 in men and women, respectively. NC also correlated significantly with AST and ALT and the severity of the disease. Qin Huang et al. reported that an increase in NC is a predictor of inflammatory status and elevated ALT in NAFLD (25). Several studies showed that an increase in NC is associated with inflammatory response in many ways (26,27). It was demonstrated that NC significantly correlates with plasminogen activator inhibitor 1 level, which contributed to the creation of inflammatory status and cardiovascular disease (27). Thus, it can be concluded that an increase in NC leads to inflammatory response in the whole body as well as the liver, and it is more severe in fatty liver disease with higher liver enzymes, such as ALT and AST.

We demonstrated that NC had the biggest predictive value for predicting NAFLD in both sexes. Qin Huang et al. showed that WC has the highest predictive value for NAFLD in male, whereas NC has the highest predictive value in women (25). In our study, NC had the highest predictive value for MetS in both sexes. This result was in accordance with some studies (6,28,29), whereas others showed that the NC predictive value for MetS is proceeded by WC or has the same capability as WC (30,31).

In our study, the optimal NC cut-off point for predicting NAFLD was 39.25 cm and 34.85 cm in men and women, respectively. The NC cut-off point was slightly smaller for MetS (36.7 cm and 32.9 cm for men and women, respectively). Since fatty liver and MetS have many common symptoms, it was expected that their NC cut-off point would be close to each other. The NC cut-off point ob-

tained in previous studies was ≥ 34 cm in women and ≥ 38 cm in men for NAFLD and ≥ 33 cm in women and ≥ 37 cm in men for MetS in a Chinese population (11,19). The different cut-off points between our study and previous studies could be due to the difference in race and body in different population.

Our study had several limitations. First, our subjects were recruited from among patients who were referred to our center for routine check-up. This could lead to some bias in calculating the prevalence of NAFLD and MetS in comparison to cluster sampling. Second, this was a cross-sectional study, which has its own limitation, such as lack of study of the causality between factors. Finally, it was better to evaluate NAFLD by liver biopsy as its gold standard or magnetic resonance imaging as high sensitive modality rather than ultrasonography. However, these techniques are either invasive or costly, and as such, we could not use them because of ethical issues.

Ethics Committee Approval: Ethics Committee Approval has received for this study from the Artesh University of Medical Sciences Ethics Committee.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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