



Research Paper

The value of neck circumference (NC) as a predictor of non-alcoholic fatty liver disease (NAFLD)[☆]

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ABSTRACT

Aims: To analyze the correlation between neck circumference (NC) and non-alcoholic fatty liver disease (NAFLD) and compare the predictive value of NC for NAFLD with that of other simple anthropometric measures and other biochemical profiles.

Methods: 2761 subjects, undergoing a medical check-up at the Changhai Hospital between October 01, 2012 and November 30, 2012, were recruited to the study. NC, other simple anthropometric measures, and biochemical profiles were analyzed.

Results: NC in NAFLD subjects with or without elevated ALT were 38.94 ± 2.62 cm and 37.21 ± 3.06 cm respectively, which was significantly higher than that in subjects with other metabolic disorders (NC: 35.33 ± 3.03 cm) and in normal controls (NC: 32.60 ± 2.37) (both $P < 0.001$). NC in women with NAFLD increased by 1 cm and fasting insulin (FINS) and homeostasis model assessment-insulin resistance (HOMA-IR) increased by 1.87 mIU/L and 1.43, respectively. Compared with other anthropometric measures, neck circumference-height ratio (NHtR) had a significant impact both on the incidence of NAFLD. After adjustment for sex, abdominal obesity and other influencing factors, the incidence of NAFLD still tended to positively correlate with NC. Optimal cut-off points of NC and NHtR for predicting NAFLD in males were 37.25 cm and 0.224, respectively, and such points in females were 32.90 cm and 0.208, respectively.

Conclusion: NC was wider in NAFLD patients than in healthy subjects and other metabolic disorder sufferers. NC and NHtR could be used as simple predictive tools for NAFLD.

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Abbreviations: NC, Neck circumference; NAFLD, Nonalcoholic fatty liver disease; NHtR, Neck circumference-height ratio; T2DM, Type 2 diabetes mellitus; IR, Insulin resistance; MS, Metabolic syndrome; CVD, Cardiovascular diseases; TG, Triglyceride; HOMA-IR, Homeostasis model assessment-insulin resistance; VAT, Visceral adipose tissue; BMI, Body mass index; NWtR, Neck circumference-weight ratio; WC, Waist circumference; HC, Hip circumference; HUA, Hyperuricemia; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; FBG, Fasting blood glucose; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; γ -GT, gamma-glutamyltransferase; SUA, Serum uric acid; BUN, Blood urea nitrogen; Scr, Serum creatinine; HbA1c, Hemoglobin A1c; FINS, Fasting insulin; FT₃, Free triiodothyronine 3; FT₄, Free thyroxine; TSH, Thyroid stimulating hormone; QUICKI, Quantitative insulin-sensitivity check index; AUC, Area under the curve; OR, Odd ratio.

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Introduction

Similar to type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) is becoming a worldwide epidemic and one of the most important global public health issues [1,2]. It is a challenge for both eastern and western countries in the 21st century. NAFLD is a kind of metabolic hepatic injury that is closely related to insulin resistance (IR) and hereditary susceptibility. It had been recognized as both a liver manifestation and a major component of metabolic syndrome (MS); however, an increasing number of prospective studies indicate that NAFLD could be a predictor of T2DM, independent of obesity [3]. It is also an independent predictor of cardiovascular diseases (CVD) [4,5].

Although the exact pathogenesis of NAFLD and its causality with IR and MS have not been elucidated, it is indicated by both *in vivo* and *in vitro* studies that excess fat accumulation mainly in the form of triglyceride (TG) is the prerequisite for NAFLD, and could therefore be the root of MS. At present, the diagnosis of NAFLD is made by liver biopsy, known as “the golden standard,” or by MRI/CT scan. These methods are either invasive or costly, and therefore are not suitable for routine clinical practice. Furthermore, most early-stage NAFLD patients are virtually asymptomatic. They are diagnosed during medical checkups or ultrasound and CT tests due to other reasons. Most of NAFLD subjects are often complicated with other metabolic disturbances, including dysglycemia at diagnosis. Therefore, if simple and convenient methods like anthropometric measures could be established, early stage NAFLD could be detected and treated effectively, which ultimately could prevent or delay the onset and development of T2DM.

Neck circumference (NC) is the girth of the neck measured at a point just below the laryngeal prominence. It is easy to measure with excellent repeatability and minimal variance. NC is an important index reflecting the deposition of subcutaneous fat in the neck or fat surrounding the respiratory tract, and can help determine the degree of obesity, particularly upper body adiposity [6,7]. Recently, more and more studies indicate that NC is closely correlated with glucolipid dysregulation, hyperinsulinemia, homeostasis model assessment of insulin resistance (HOMA-IR) and other CVD risk factors [8,9]. Stronger correlations of NC with such risk factors were found more among women than men [9]. NC, visceral adipose tissue (VAT) and body mass index (BMI) are all independent risk factors for CVD [10].

In recent years, various studies have suggested that NC could be used as a screening tool for overweight and obesity. However, at present, more attention has been given to the correlation of NC with obesity and MS, while the connection between NC and NAFLD has rarely been investigated. Hence, our study aimed to analyze the data from subjects who had medical checkups in the medical checkup center at the Changhai Hospital. The viability and value of NC, neck circumference–height ratio (NHtR) and neck circumference–weight ratio (NWtR) in predicting NAFLD were examined and discussed in this study in order to provide clinicians and community health care givers with a potential simple, effective and convenient index for monitoring and prediction NAFLD.

Materials and methods

Study population and basic information

This study involved a total of 2939 people who had a medical examination at the Changhai Hospital from the beginning of October 2012 to the end of November 2012. For all participants a detailed medical history was taken and a physical examination, including height, body weight, NC, waist circumference (WC) and hip

circumference (HC), was performed. Fasting blood samples were collected and assayed for a series of metabolic parameters including hepatic and renal function, blood lipids, insulin, C-peptide, thyroid function, etc. Abdominal ultrasounds were also performed. 2761 subjects with complete medical data were recruited after excluding those who had excessive drinking problems, goiter, abnormal thyroid function, hepatic and renal insufficiency, or past history of stroke and/or heart conditions. There were 967 subjects with NAFLD (Group B, 694 men/273 women) and 1171 subjects with other metabolic disturbances (Group C, 703 males/468 females) including hypertension, diabetes or impaired glucose regulation, dyslipidemia, abdominal obesity, overweight and obesity, hyperuricemia (HUA) and gout. There were 623 healthy subjects (Group A, 183 men/440 women) without one of the aforementioned metabolic disorders. All participants signed an informed consent form and the study protocol was approved by the ethics committee at the Changhai Hospital.

Measurements

NC, WC and other anthropometric indexes, as well as blood pressure, were measured by a designated person according to uniform methods. Subjects were required to fast, empty their bladder, stand erect without shoes, breath normally and look straight ahead with both arms hanging naturally. They were also asked to relax their neck when NC was measured, and to stand with their feet shoulder distance apart when WC and HC were taken. WC and HC were taken to the nearest 1 mm, using a plastic tape measure at midpoint between the lower costal margin and the iliac crest, and at the point yielding the maximum circumference over the gluteus maximus, respectively. NC measurement was performed as previously described [11]. NC was taken to the nearest 1 mm, measuring the girth passing the superior margin of the seventh cervical vertebrae and the inferior margin of the laryngeal prominence, which is at the narrowest neck level. Height and body weight were measured using an electronic scale (Kaiyuan electronic HW-600, Zhengzhou, China) to the nearest 0.1 cm and 0.1 kg respectively.

Total cholesterol (TC) and TG were assayed enzymatically by a Roche MODULAR DPP automatic biochemistry analyzer. High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were assayed by immunoturbidimetry and ELISA, respectively, using an autoanalyzer (Advia1650, Bayer Co., Germany). Fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (γ -GT), serum uric acid (SUA), blood urea nitrogen (BUN), and serum creatinine (Scr) were measured by standard bioassay methods using an automatic biochemistry analyzer. Hemoglobin A1c (HbA1c) was measured by high performance liquid chromatography. The levels of fasting insulin (FINS) and C-peptide were determined by radioimmunoassay (Jiuding Biological Engineering Co., Tianjing, China). Free triiodothyronine 3 (FT₃), free thyroxine (FT₄) and thyroid stimulating hormone (TSH) were measured by electrochemiluminescence immunoassay. HOMA-IR = [FINS \times FBG/22.5] was employed. The quantitative insulin-sensitivity check index (QUICKI) = [1/(log FBG \times log FINS)] was performed as described earlier [12]. Liver ultrasounds were performed by the same doctor using a 3.5-MHz transabdominal probe and the GE LOGIQ E9 Agile color Doppler ultrasound system made in the USA.

Definition of cardio-metabolic risk factors

The diagnosis of NAFLD was based on the 2010-revised edition of the Guidelines for the diagnosis and management of non-alcoholic liver diseases by the Chinese National Consensus Workshop on NAFLD [13]. Diagnosis of the condition was made when imaging findings of liver coincided with the diagnostic criteria of

diffuse fatty liver change and was unexplainable by other causes including excessive drinking, various types of viral hepatitis, etc. NAFLD could be diagnosed when findings of liver ultrasonography met certain criteria, including diffuse of liver tissue in the near field as compared to echogenicity of kidney and spleen, gradual attenuation of liver echogenicity in the far field and obscure display of intrahepatic vessels. NAFLD patients with elevated level of serum ALT spanning more than half a year were further divided as NAFLD with elevated ALT. Hypertension was diagnosed according to 2010 Chinese guidelines for the management of hypertension [14]. T2DM and impaired glucose regulation were defined according to the WHO consultation in 1998 [15]. Dyslipidemia was diagnosed according to Guidelines for management of adult dyslipidemia in China [16]. Overweight and obesity were defined in accordance with The Guidelines for Prevention and Control of Overweight and Obesity in Chinese adults [17]. Abdominal obesity was diagnosed if WC was no less than 90 cm and 85 cm for men and women, respectively. Participants without history of gout attack whose fasting SUA exceeded 420 $\mu\text{mol/L}$ and 357 $\mu\text{mol/L}$ for men and women respectively were diagnosed as HUA [18].

Statistical analysis

All data were input using Excel software and analyzed using SPSS17.0 statistical software (SPSS Inc., Chicago, IL, USA). Means between two groups were compared using Student's *t*-test. Data with skewed distribution including FINS, FCP and HOMA-IR were converted to normal distribution after logarithmic transform prior to correlation analysis. Sample rates were compared using χ^2 test. Ranked data were analyzed by nonparametric test. Partial correlation analysis was used and the correlation coefficient was expressed as *r* after adjusting confounding factors. The one-sided 1- α reference value range formula was $<X + u_{\alpha}S$ or $>X - u_{\alpha}S$. A *P* value <0.05 was considered statistically significant.

Results

General characteristics and comparisons among metabolic profiles

According to the presence of NAFLD and other metabolic disturbances, 2761 participants were divided into 3 groups (Table 1). The prevalence of NAFLD without elevated ALT (Group B1) in men and women was 29.30% and 19.81%, respectively and the prevalence of NAFLD with elevated ALT (Group B2) was 14.62% and 3.30% in men and women, respectively. The difference between the incidence of both conditions was of statistical significance (Group B1: $\chi^2 = 32.252$, $P < 0.001$; Group B2: $\chi^2 = 98.123$, $P < 0.001$). Mean values of NWtR among groups were in ascending order of group B2, B1, C and A ($P < 0.05$). Mean values of NC, NHtR, WC, body weight, WHR and BMI among groups were in ascending order of group A, C, B1 and B2 in both sex ($P < 0.001$). The mean value of NWtR was in descending order of group A, C and B ($P < 0.001$) (Table 1).

Correlation analysis between anthropometric indices and IR in NAFLD subjects

FINS and HOMA-IR were log10 transformed prior to the following analysis. After adjusting for age, we found that NC, WC, BMI, NHtR, NWtR, WHR and weight were correlated with FINS and HOMA-IR in the NAFLD population, although the strength of correlation differed in terms of sex. Furthermore, we found that WC in men and NC in women had the strongest association with FINS and HOMA-IR, respectively (Table 2). Two regression models ($Y = 0.023x + 0.6028$ and $Y = 0.0267x + 0.1296$) were generated based on the analysis of associations of NC with FINS and HOMA-IR in women, respectively. Namely, an increment in NC of 1 cm was associated with an increase of 1.87 $\mu\text{IU/ml}$ and 1.43 in FINS and HOMA, respectively.

Table 1
Comparison of clinical features and biochemical criterion between each group

Clinical indexes	Group A	Group B1	Group B2	Group C	<i>P</i> -value
Case (n) (proportion)	623 (22.56%)	697 (25.24%)	270 (9.78%)	1171 (42.41%)	
M:F	183:440	463:234	231:39	703:468	<0.001
Age (year) ^a	36.70 \pm 11.82	48.97 \pm 12.09	42.07 \pm 12.01	45.29 \pm 14.75	<0.001
Weight (kg) ^a	56.21 \pm 7.31	72.73 \pm 10.50	79.56 \pm 11.71	65.44 \pm 10.16	<0.001
M ^a	62.49 \pm 7.06	76.89 \pm 8.96	81.20 \pm 11.09	70.11 \pm 8.74	<0.001
F ^a	53.59 \pm 5.62	64.43 \pm 8.17	69.91 \pm 10.65	58.40 \pm 7.84	<0.001
BMI (kg/m ²) ^a	20.92 \pm 1.84	26.29 \pm 2.83	27.70 \pm 3.27	23.77 \pm 2.65	<0.001
NC (cm) ^a	32.60 \pm 2.37	37.21 \pm 3.06	38.94 \pm 2.62	35.33 \pm 3.03	<0.001
M ^a	35.34 \pm 1.90	38.75 \pm 2.17	39.46 \pm 2.20	37.11 \pm 2.09	<0.001
F ^a	31.46 \pm 1.42	34.17 \pm 2.15	35.86 \pm 2.78	32.65 \pm 2.12	<0.001
NHtR ^a	0.20 \pm 0.01	0.22 \pm 0.02	0.23 \pm 0.01	0.21 \pm 0.02	<0.001
M ^a	0.21 \pm 0.01	0.23 \pm 0.01	0.23 \pm 0.01	0.22 \pm 0.01	<0.001
F ^a	0.19 \pm 0.01	0.22 \pm 0.01	0.23 \pm 0.02	0.21 \pm 0.01	<0.001
NWtR ^b	0.59 \pm 0.05	0.52 \pm 0.05	0.50 \pm 0.06	0.54 \pm 0.06	<0.001
M	0.57 \pm 0.05	0.51 \pm 0.05	0.49 \pm 0.05	0.54 \pm 0.05	<0.001
F	0.59 \pm 0.05	0.54 \pm 0.05	0.53 \pm 0.05	0.57 \pm 0.06	<0.001
WC (cm) M ^a	77.78 \pm 6.63	93.44 \pm 7.50	96.34 \pm 7.51	85.74 \pm 7.59	<0.001
F ^a	71.40 \pm 5.52	85.47 \pm 7.74	90.14 \pm 9.47	78.38 \pm 7.74	<0.001
WHR ^a	0.79 \pm 0.06	0.92 \pm 0.07	0.94 \pm 0.06	0.86 \pm 0.07	<0.001
M ^a	0.83 \pm 0.06	0.93 \pm 0.06	0.95 \pm 0.05	0.88 \pm 0.06	<0.001
F ^a	0.77 \pm 0.05	0.88 \pm 0.06	0.91 \pm 0.06	0.83 \pm 0.06	<0.001
ALT (U/L) ^a	15.65 \pm 10.77	24.22 \pm 7.95	66.26 \pm 30.16	21.38 \pm 12.19	<0.001
HbA1c (%) ^b	5.23 \pm 0.53	5.58 \pm 1.08	6.18 \pm 1.36	5.44 \pm 0.76	<0.001
FINS ($\mu\text{IU/ml}$) ^a	18.68 \pm 8.43	26.51 \pm 13.59	33.7 \pm 19.17	20.92 \pm 9.31	<0.001
FCP (ng/ml) ^a	2.55 \pm 0.93	3.79 \pm 1.43	4.51 \pm 1.62	3.01 \pm 1.25	<0.001
HOMA-IR ^a	1.18 \pm 1.99	6.85 \pm 5.12	9.17 \pm 7.50	5.05 \pm 3.07	<0.001
QUICKI	1.15 \pm 0.13	0.98 \pm 0.14	0.91 \pm 0.15	1.08 \pm 0.14	<0.001

Group A, healthy subjects; Group B, NAFLD subjects; Group B1, subjects without elevated ALT; Group B2, subjects with elevated ALT; Group C, subjects with other metabolic disturbances.

^a Differences are statistically significant between each group in four groups ($P < 0.05$).

^b Differences are no statistically significant between group B1 and B2 ($P > 0.05$).

Table 2
Correlational analysis between body measurements and FINS, HOMA-IR

Variables	Lg (FINS)				Lg (HOMA-IR)			
	Male		Female		Male		Female	
	r-value	P-value	r-value	P-value	r-value	P-value	r-value	P-value
NC (cm)	0.250	<0.001	0.345	<0.001	0.250	<0.001	0.339	<0.001
WC (cm)	0.351	<0.001	0.282	<0.001	0.325	<0.001	0.314	<0.001
BMI (kg/m ²)	0.303	<0.001	0.318	<0.001	0.270	<0.001	0.298	<0.001
NHtR	0.166	<0.001	0.322	<0.001	0.165	<0.001	0.294	<0.001
NWtR	-0.282	<0.001	-0.121	0.073	-0.243	<0.001	-0.147	0.029
WHR	0.262	<0.001	0.207	0.002	0.260	<0.001	0.291	<0.001
Wt (kg)	0.338	<0.001	0.266	<0.001	0.307	<0.001	0.281	<0.001

Comparisons of the impact of anthropometric measures on NAFLD

After adjusting for age, gender, hypertension, T2DM, hypercholesterolemia, hypertriglyceridemia, low HDL-C levels, high LDL-C levels, hyperuricemia, overweight, obesity, abdominal obesity and so on, we used standardized NC, WC, BMI, NHtR, NWtR and WHR as independent variables, and NAFLD as dependent variables respectively to perform a Logistic regression analysis. Independent variables finally entering the model were NC, NHtR, NWtR and WHR. After analyzing *P* value, we found that NHtR, NWtR and WHR are the influencing factors of NAFLD. Comparing the odd ratio (OR) presented in Table 3, NHtR was both the maximum risk factor for the incidence of NAFLD and NAFLD without elevated ALT, while both NHtR and WHR were risk factors for the incidence of NAFLD with elevated ALT. In addition, both NC and NWtR were protective factors for NAFLD, and NWtR was a protective factor for NAFLD with or without elevated ALT.

Correlation analysis between NC and the incidence of NAFLD

Subjects were divided into 4 groups according to their gender-specific NC quartiles (NC quartiles in men: <36 cm, 36–38 cm, 38–39 cm, ≥39 cm; NC quartiles in women: <31 cm, 31–32.5 cm, 32.5–34 cm, ≥34 cm). Those participants were further dichotomized by the presence of abdominal obesity. Chi-square trend analysis showed that the incidence of NAFLD was positively related to NC whether they had abdominal obesity or not (*P* < 0.001) (Table 4).

Analysis of the incidence of NAFLD in different groups

Normal reference ranges of NC, NHtR and NWtR in healthy controls were <38.51 cm, <0.23 and >0.49 in men and <33.80 cm, <0.22 and >0.51 in women, respectively. Based on the established

Table 3
Risk factors of NAFLD by logistic regression analysis

Risk factors	<i>B</i>	Wald	<i>P</i> -value	OR-value	95% CI of OR	
					Upper limit	Lower limit
NAFLD						
NC	-0.369	3.748	0.053	0.691	0.476	1.005
NHtR	1.124	54.903	<0.001	3.078	2.286	4.144
NWtR	-0.942	101.916	<0.001	0.390	0.325	0.468
WHR	0.647	52.313	<0.001	1.910	1.603	2.276
NAFLD without elevated ALT						
NHtR	0.490	45.717	<0.001	1.632	1.416	1.882
NWtR	-0.479	44.977	<0.001	0.619	0.538	0.712
WHR	0.315	13.526	<0.001	1.371	1.159	1.621
NAFLD with elevated ALT						
NHtR	0.543	24.273	<0.001	1.721	1.387	2.136
NWtR	-0.499	16.361	<0.001	0.607	0.477	0.773
WHR	0.549	15.993	<0.001	1.731	1.323	2.265

gender-specific ranges, we divided the NAFLD subjects into two groups, NC normal and abnormal. In both sexes, Chi-square trend analysis showed that the incidence of NAFLD was positively related to NC and NHtR, but inversely related to NWtR whether they had abdominal obesity or not (*P* < 0.05) Table 5.

Determination of the diagnostic validity of NC and NHtR in NAFLD by receiver operating characteristic (ROC) analysis

In males, the area under the curve (AUC) values for NC and NHtR were 0.768 and 0.758, respectively. The best cut-off points for NC and NHtR in men were 37.25 cm and 0.224, respectively (Youden indices = 0.386 and 0.377 for NC and NHtR). For males, the diagnostic value of NC in NAFLD was better than that of NHtR (Figure 1). As for women, AUC values for NC and NHtR were 0.798 and 0.806, respectively. The best cut-off points for NC and NHtR in women were 32.90 cm and 0.208, respectively (Youden indices = 0.460 and 0.478 for NC and NHtR). For females, the diagnostic value of NHtR in NAFLD was better than that of NC (Figure 1).

Discussion

NAFLD is a set of metabolic hepatic injuries caused by excess fat deposition in the liver and its related conditions of hepatic cirrhosis and liver cancer. It is closely related to metabolic abnormalities, as well as obesity and T2DM, and has become the primary etiology of the chronic liver disease. Our study demonstrated that NC in NAFLD patients was significantly wider than in patients with other metabolic conditions or healthy controls. We also found that NAFLD patients with elevated ALT had the largest NC among the NAFLD population, which indicates that increased NC is a predictor of inflammatory status in NAFLD sufferers and a risk factor for NAFLD with elevated ALT.

The occurrence and development of NAFLD mainly comprises resistance of insulin and leptin, overproduction of free radicals, excessive accumulation of VAT and inflammation of adipose and liver tissue. Studies in obese adult populations have shown that NC significantly correlated with levels of plasminogen activator inhibitor 1 (PAI-1), suggesting that NC could be a predictor of enhanced inflammatory status and CVD risk in obese adults [19].

Table 4
Comparison of NAFLD prevalence in different NC groups

NC	Non-abdominal obesity		Abdominal obesity	
	Cases (<i>n</i>)	Prevalence (%)	Cases (<i>n</i>)	Prevalence (%)
<P25	70	9.41 (70/744)	18	51.43 (18/35)
P25–P50	122	19.03 (122/641)	110	58.20 (110/189)
P50–P75	96	29.81 (96/322)	137	62.56 (137/219)
>75	52	37.41 (52/139)	362	76.69 (362/472)
Total	340	18.42 (340/1846)	627	68.52 (627/915)

P, percentage.

Table 5
Analytical between NAFLD prevalence and body measurements

Body measurements	Non-abdominal obesity		Abdominal obesity	
	Cases (n)	Prevalence (%)	Cases (n)	Prevalence (%)
NC (cm)				
Male				
<38.51	166	20.62 (166/805)	143	62.72 (143/228)
≥38.51	55	45.45 (55/121)**	330	77.46 (330/426)**
Female				
<33.80	67	8.69 (67/771)	42	48.28 (42/87)
≥33.80	52	34.90 (52/149)**	112	64.37 (112/174)*
NHtR				
Male				
<0.23	163	20.3 (163/803)	215	63.8 (215/337)
≥0.23	57	47.5 (57/120)**	256	81.3 (256/315)**
Female				
<0.22	90	10.5 (90/858)	76	53.5 (76/142)
≥0.22	28	49.1 (28/57)**	77	67.0 (77/115)*
NWtR				
Male				
>0.49	189	22.9 (189/829)	225	69.2 (225/325)
≤0.49	31	32.0 (31/97)*	246	75.2 (246/327)
Female				
>0.51	100	11.9 (100/843)	84	53.8 (84/156)
≤0.51	18	25.0 (18/72)**	69	68.3 (69/101)*

vs normal values of same sex.

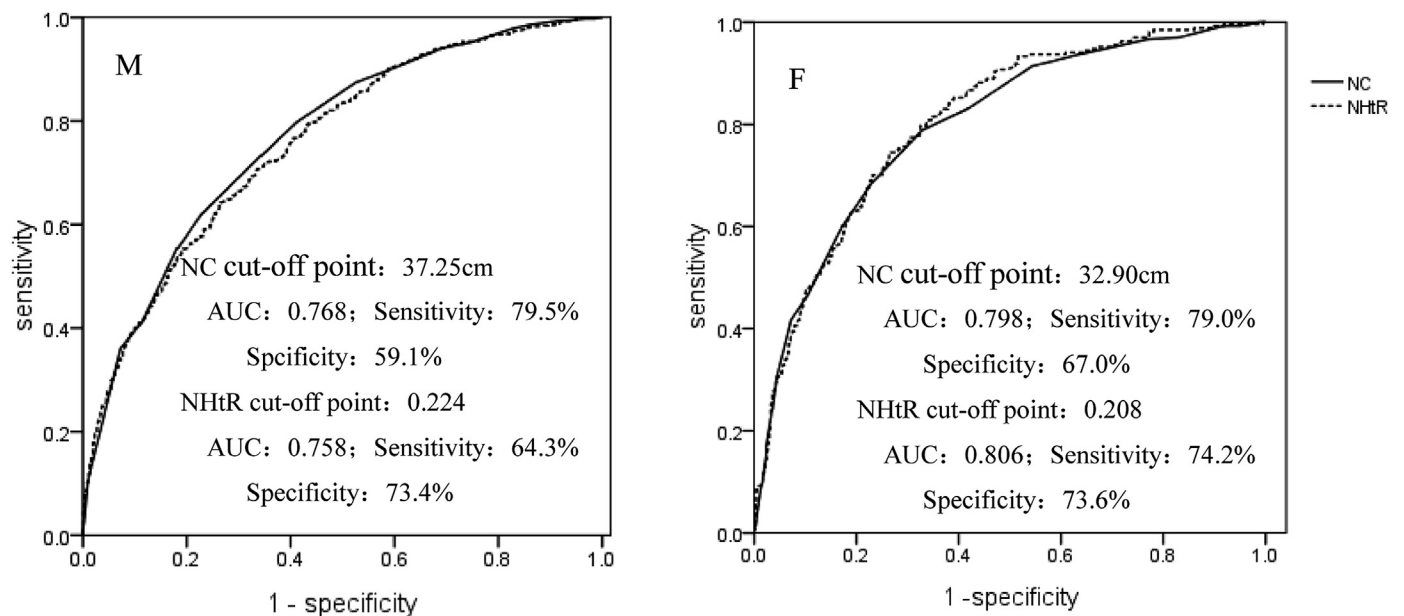
* $P < 0.05$, ** $P < 0.001$.

McPherson et al. [20] observed 285 patients (110 simple steatosis and 175 non-alcoholic steatohepatitis) which had serum immunoglobulins measured within 6 months of liver biopsy. They found the serum IgA level was frequently elevated in patients with NAFLD and was an independent predictor of advanced fibrosis. As indicated by previous studies, NAFLD is closely related to IR and is intertwined with the pathogenesis of MS and T2DM. Clustering of multiple metabolic disorders is commonly seen in NAFLD patients [21–23], which was also observed in our study. NAFLD patients had significantly higher levels of TG, TC and LDL-C than those with other metabolic disorders and healthy controls. Furthermore, the levels of

TG, TC and LDL-C were positively correlated with the severity of NAFLD in such patients (data unshown). It was indicated in recent studies that NAFLD could occur in individuals with normal weight, blood glucose and lipids. By following up those people, it was revealed that they would suffer a markedly high incidence of dysglycemia, dyslipidemia and coronary artery disease [24]. Recently, Hallsworth et al. [25] reported significant changes in cardiac structure and function are evident in adults with NAFLD in the apparent absence of metabolic changes or overt cardiac disease. Therefore, NAFLD could be a more accurate predictor for the odds of developing DM and atherosclerosis than BMI and WC.

Currently, the predictive value of BMI, WC and WHR in determining the odds of developing DM, hypertension and dyslipidemia and other metabolic disorders has been confirmed [26]. However, there are certain limitations in present simple anthropometric measurements. For example, BMI is unable to reflect the content of abdominal VAT precisely, and therefore it lacks accuracy in diagnosing abdominal obesity [27]. There are ethnic and sex variations in WC and WHR. Indices like WC and body weight are easily affected by external factors such as diet and exercise. Regardless of gender, our study found that NC, NHtR, WC, body weight and BMI in NAFLD patients were all significantly higher than those without it. Furthermore, these indices were positively correlated with the severity of the NAFLD (all $P < 0.001$). WHR was significantly higher in males with NAFLD than in NAFLD-free subjects ($P < 0.001$), while NWtR was significantly lower in females with NAFLD than in NAFLD-free subjects ($P < 0.001$). However, no statistically significant differences of WHR and NWtR were found between patients with or without elevated ALT regardless of sex.

The liver is the main target site of insulin besides skeletal muscle and adipose tissue. The inhibition of insulin during liver gluconeogenesis is enough to maintain normal levels of fasting plasma glucose. As shown in a hyperinsulinemic-euglycemic clamp procedure in conjunction with stable isotopically labeled glucose infusions, the ability of insulin to inhibit hepatic glucose production is impaired when excessive liver fat deposition or NAFLD occurs [28,29]. Insulin resistance in the liver could lead to mild elevations of plasma blood glucose thus stimulating insulin release. Our study



M:male;F:female;NC: neck circumference;NHtR: neck circumference-height ratio

Figure 1. Receiver Operating Characteristic (ROC) curve of NC and NHtR in distinguishing NAFLD or Non-NAFLD in different sex.

indicated that FINS in NAFLD patients was significantly higher than that in subjects with other metabolic disorders. Levels of FINS and HOMA-IR positively correlated with the severity of NAFLD. After adjusting for age, correlation analysis showed that among NAFLD patients, WC had the greatest correlation with FINS and QUICKI among men while NC had a similar correlation among women. So, it could be inferred that the ability of NC, WC and other anthropometric indices to reflect abdominal obesity and insulin sensitivity differs between sexes. In women, NC is a better index than WC, WHR and BMI to predict NAFLD and to evaluate insulin levels and its sensitivity in female NAFLD sufferers. We further analyzed the association of NC with Log (FINS) and Log (HOMA-IR) in women, and obtained two regression equations. According to the equations, FINS and HOMA-IR increase by 1.87 μ U/ml and 1.43, respectively with an increment of NC of 1 cm. It is corroborated in other studies that NC has correlations with FBG, FINS and IR-related markers including HOMA-IR [30,31], but to our knowledge, none of the reports covered numerical relationships between NC and FINS and HOMA-IR.

Adipose tissue is an important component of the human body. It comprises subcutaneous adipose tissue (SAT) and VAT [32,33]. If the body fat is predominately SAT, the fat is mainly accumulated below the waist. On the contrary, if the adipose tissue is mainly located in the abdominal cavity or upper body, it is mainly VAT, which is also known as visceral obesity. It is documented that great damage will arise if adipose tissue infiltrates or covers visceral organs. Hence, excessive VAT or abdominal obesity causes more impact on liver fat content compared with overall fat depot, and also positively correlates with the chance of developing NAFLD and MS. The present study showed that regardless of gender and abdominal obesity, the odds of having NAFLD positively related with NC and NHtR, but negatively related to NWtR, after we grouped the NAFLD subjects by NC quartiles (all $P < 0.05$). So, it could be inferred that NC has a predictive value in determining the chances of developing NAFLD. It was revealed by Logistic regression analysis that among the anthropometric indices in question, NC, NHtR, NWtR, and WHR correlated with NAFLD. Furthermore, NHtR had the greatest positive relationship with the odds of developing NAFLD without elevated ALT, while NWtR were protective factors for NAFLD with or without elevated ALT. In our study, the diagnostic validity of NC and NHtR for NAFLD was examined using ROC analysis. It was shown that NC and NHtR could be used as effective predictors for the risk of NAFLD. For the prediction of NAFLD, NHtR had better specificity and sensitivity in women than in men and NC also showed better specificity in women than in men. Our study also inferred that fat deposits in the cervical region among women were an overall better predictor than abdominal obesity.

In present study, objects were from physical examination center, so they were only performed regular test excluded liver biopsy. Although base on history and exits items, NAFLD can be diagnosed [13], it would be better to evaluate the correlation between NC and NAFLD process if liver biopsy or MRI could be performed. Liver biopsy is the gold standard for diagnosis of NAFLD, but it is an invasive examination, in the actual operation and ethical aspects, usually can't be used as the early detection and diagnosis of NAFLD and non-alcoholic steatohepatitis on the basic of choice. Recently, Angulo et al. [34] established a simple noninvasive scoring systems which can help identify patients with NAFLD who are at increased risk for liver-related complications or death. Currently we are also investigating the relationship of NC to NAFLD. Among them the important point is to identify liver fat deposit with magnetic resonance spectroscopy, try to estimate a non-invasion test for evaluating NAFLD.

Our study demonstrated that NC measurements could effectively predict the risk of NAFLD, especially among women. It has been proven that early detection and treatment of NAFLD and amelioration of concomitant IR are conducive to the prevention and

management of a series of metabolic diseases. Based on the current findings, measurement of WC should be highlighted among men while NC should be used among women in health care practices of prevention and management of NAFLD. Women with an NC ≥ 34 cm should be recommended to have liver ultrasonography every six months to ascertain the presence of liver steatosis. But the results of this study require further validation.

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