

The Visceral-Fat-Area-to-Hip-Circumference Ratio as a Predictor for Insulin Resistance in a Chinese Population with Type 2 Diabetes

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Keywords

Hip circumference · Insulin resistance · Visceral-fat area

Abstract

Introduction: Adipose tissue deposited on the viscera is the main culprit in the development of insulin resistance (IR) and cardiometabolic diseases, whereas subcutaneous adipose tissue may have a protective role. This study aimed to propose a new predictive index – the visceral-fat area (VFA)-to-hip-circumference ratio (VHR) and explore its efficacy for prediction of IR in a Chinese population with type 2 diabetes mellitus. **Methods:** A total of 643 patients with newly diagnosed diabetes were enrolled in this study. Body composition, anthropometrical, and biochemical measurements were performed. IR was defined as homeostatic model assessment of IR (HOMA-IR) > 2.69. The association between VHR and IR was analyzed. **Results:** Regardless of gender, subjects in the IR group had higher VHR, body mass index (BMI), VFA, body fat percentage, systolic blood pressure, diastolic blood pressure (DBP), fasting blood glucose, fasting insulin, triglyceride (TG), uric acid (UA), homocysteine, and aminotransferases than those in the non-IR group. The other comorbid metabolic disorders were more common in the IR

group. Further analysis showed that with the increase of VHR, the levels of HOMA-IR, BMI, VFA, DBP, TG, UA and the prevalence of nonalcoholic fatty-liver disease, hypertension, and hyperuricemia increased continuously (p trend <0.01). The linear trend test showed that VHR and IR remained closely correlated after adjusting for possible confounders (p trend <0.05). The receiver operating characteristic curve analysis showed that the area under the curve was 0.69, and the optimal cutoff of VHR was 0.89 (sensitivity 79.3%, specificity 61.5%). **Conclusion:** VHR was positively associated with IR regardless of gender, and it might be a reliable predictor for IR.

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Introduction

Obesity and diabetes are worldwide epidemics. About 463 million people are diagnosed with diabetes globally, of whom more than 90% are diagnosed with type 2 diabetes mellitus (T2DM) [1]. According to the latest epidemiological investigation in China, the prevalence of diabetes has been skyrocketing to 12.8% due to westernized lifestyle and lack of physical activities [2]. Obesity and its

usually accompanied insulin resistance (IR) play important roles in the pathogenesis of T2DM. The euglycemic hyperinsulinemic clamp technique, which is considered as the gold standard method for measuring IR, lacks strong practicality in routine clinical practices and large-scale epidemiological studies, owing to its complex, invasive, and time-consuming procedures [3]. Homeostatic model assessment of IR (HOMA-IR) has been widely accepted as a reliable surrogate indicator for IR in the past few years [4]. However, the calculation of HOMA-IR requires fasting plasma insulin, the determination of which is not standardized yet, although insulin detection has been studied for over 50 years [5]. Therefore, the measured values of insulin may have huge discrepancies across different laboratories, which would bring some challenges to doctors' judgments of the outcome of HOMA-IR. Thus, many surrogate indexes for IR just using easily available anthropometric and biochemical variables have been in extensive focus in the past few decades. However, the application of these new surrogate predictors in different populations and different kinds of metabolic disorders may yield conflicting results [6].

As is well known, adipose tissue deposited on the viscera such as the liver and pancreas is the main culprit in the development of IR and metabolic diseases [7], whereas subcutaneous adipose tissue may have a protective role [8]. Based on the above considerations, this study aimed to propose a new predictive index – the visceral-fat area (VFA)-to-hip-circumference (HC) ratio (VHR) and explore its efficacy for prediction of IR in a Chinese population with T2DM.

Methods

Study Population

A total of 643 newly diagnosed diabetic patients hospitalized in the department of Endocrinology of Tianjin Union Medical Center from May 2017 to September 2020 were included in this study. The diagnosis of DM was established according to the 1999 World Health Organization (WHO) criteria [9]. The exclusion criteria were as follows: unstable angina; cardiac function was grade II or above according to New York Heart Association's cardiac function rating; unstable neurological or psychiatric disorders; and those who did not agree to sign the informed consent. The study protocol was approved by the Ethics Committee of the Tianjin Union Medical Center (No. 2021C06), and written informed consents were provided by all the participants.

Sociodemographic Characteristics Collection

Sociodemographic characteristics including age, gender, smoking, and drinking status were recorded in detail in all of the participants.

Anthropometrical Evaluation and Body Composition Measurement

After overnight fasting, all participants were instructed to perform anthropometrical evaluations including height, weight, waist circumference (WC), and HC. Height and weight were measured in light clothing without shoes. Body mass index (BMI) was calculated by weight in kilograms divided by the square of height in meters. The measurements of WC and HC were carried out according to the WHO recommended protocols which were at the midpoint between the iliac crest and the costal margin and at the level of trochanters, respectively [10]. Body composition was evaluated by the direct segmental multi-frequency bioelectrical impedance analysis method (Inbody 770, Bio-space Inc., South Korea), which is systematically improved currently and is a more reliable and popular tool for assessing both body fat mass and lean mass. All the subjects were instructed to stand upright with light clothes and barefoot and place their hands and feet on the 8-pole electrodes. We had to make sure that their palms, thumbs, heels, and soles were in full contact with the electrodes before the measurement began. Next, they were required to slightly abduct their arms and maintain the posture during the entire measurement. Then the measurement began and lasted for about 3–4 min. The data were automatically saved on the computer. Body fat percentage (BFP), VFA, and skeletal muscle mass (SMM) were obtained from body composition analysis. VHR was the ratio of VFA to HC.

Clinical and Biochemical Assessment

Information on other comorbidities such as nonalcoholic fatty-liver disease (NAFLD), hypertension, dyslipidemia, hyperuricemia, and medications was extracted from the medical records. According to abdominal ultrasonography, hepatic steatosis was established when two or more of the following requirements were met: diffuse enhanced echo of the liver with liver echogenicity greater than that of the kidney or spleen; deep attenuation of ultrasound signal; vascular blurring. NAFLD was diagnosed as hepatic steatosis related to overnutrition in the absence of excessive alcohol consumption [11]. Blood pressure was measured after a 10-min rest with a standard sphygmomanometer three times, and the mean value was used. Fasting blood samples were taken before hypoglycemic medications or insulin was given. Fasting blood glucose (FBG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid (UA), and homocysteine (Hcy) were determined by an automatic biochemical analyzer. Fasting insulin (FINS) was measured by chemiluminescent immunoassay.

Definition of IR

IR was assessed by HOMA-IR which was calculated as the following formula: $FINS (IU/L) \times FBG (mmol/L) / 22.5$. IR was defined as HOMA-IR > 2.69, based on an epidemiology survey in China [12].

Statistical Analysis

Statistical analysis was performed using SAS version 9.4 for Windows (SAS Institute., Cary, NC, USA). Continuous data were expressed as mean \pm standard deviation or median (interquartile range), depending on whether it was normally distributed or not. Categorical variables were presented as frequency and percentage.

Table 1. Characteristics of the subgroups according to gender and IR status

	Male (n = 367)		Female (n = 276)	
	IR (n = 261)	non-IR (n = 106)	IR (n = 200)	non-IR (n = 76)
Age, years	56.46±11.16	56.99±11.00	60.91±10.06	60.45±10.23
Current smoker, %	68.59	31.41	69.23	30.77
Current drinker, %	69.46	30.54	66.67	33.33
BMI, kg/m ²	27.17±3.56	25.35±3.25	26.54±4.09	24.49±3.75
WC, cm	98±12	92±10	93±11	87±10
HC, cm	100±6	98±5	97±6	93±6
BFP, %	27.82±5.87	24.59±6.69	35.18±6.46	33.34±6.31
VFA, cm ²	105.75±31.05	88.90±30.43	108.05±30.18	96.26±26.50
VHR, cm	1.04±0.26	0.90±0.28	1.11±0.25	1.02±0.23
SMM, kg	54.77±6.68	53.19±5.86	41.44±5.12	38.93±4.86
SBP, mm Hg	135±16	132±15	135±16	130±17
DBP, mm Hg	83±10	81±9	80±10	77±9
Comorbidities, %				
NAFLD	77.7	22.3	79.4	20.6
Hypertension	67.1	60.0	75.6	64.4
Dyslipidemia	64.7	54.0	54.1	43.8
Hyperuricemia	14.9	9.0	9.3	5.1
Medications, %				
Hypotensive agents	46.9	31.6	51.8	41.2
Statins	65.9	53.7	53.8	42.7
UA-lowering agents	5.0	4.2	6.5	4.4
FBG, mmol/L	8.89 (7.32 11.04)	7.34 (5.84 8.74)	8.87 (7.37 10.44)	7.27 (6.07 8.45)
FINS, U/L	13.03 (9.79 19.11)	6.04 (4.57 7.82)	13.91 (9.96 20.98)	5.98 (4.61 7.51)
TG, mmol/L	1.89 (1.30 2.80)	1.26 (0.98 2.06)	1.69 (1.27 2.44)	1.57 (1.11 2.12)
HDL-C, mmol/L	1.14±0.28	1.17±0.31	1.27±0.26	1.26±0.28
ALT, U/L	23.10 (17.00 36.60)	18.00 (13.00 25.20)	19.60 (13.60 31.50)	17.20 (13.95 23.20)
AST, U/L	17.10 (13.00 22.90)	14.85 (12.50 19.00)	16.00 (13.55 21.50)	15.95 (12.80 20.05)
UA, µmol/L	320±83	294±82	280±78	264±61
Hcy, µmol/L	11.39 (9.99 13.22)	10.61 (9.38 13.66)	9.45 (8.04 10.74)	9.55 (7.66 11.20)

Continuous data were presented as mean ± standard deviation or median (interquartile range). Categorical variables were expressed as frequency or percentage. BMI, body mass index; WC, waist circumference; HC, hip circumference; BFP, body fat percentage; VFA, visceral-fat area; VHR, visceral-fat-area-to-hip-circumference ratio; SMM, skeletal muscle mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; NAFLD, nonalcoholic fatty-liver disease; UA, uric acid; FBG, fasting blood glucose; FINS, fasting insulin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hcy, homocysteine.

Continuous data were analyzed using a one-way analysis of variance test and Mann-Whitney U test. The χ^2 test was adopted for analysis of categorical data. To explore the correlation between VHR and IR, logistic regression was performed to calculate the odds ratio (OR) and 95% confidence interval (CI) in multiple models. Model 1 was adjusted for age; model 2 was further adjusted for TG and HDL-C; model 3 was then adjusted for age, TG, HDL-C, systolic blood pressure (SBP), and ALT; model 4 was finally adjusted for age, TG, HDL-C, SBP, ALT, and NAFLD. The receiver operating characteristic (ROC) curve analysis was performed to further evaluate the ability of VHR to predict IR. All *p* values were two-sided, and *p* < 0.05 was considered statistically significant.

Results

Clinical Characteristics of the Subgroups Divided by Gender and IR Status

A total of 643 patients with T2DM were recruited for this study. All the subjects were divided into two groups based on gender, and each group was further divided into IR and non-IR. The characteristics of all the subgroups were presented in Table 1. Regardless of gender, subjects in the IR group had higher BMI, WC, HC, BFP, VFA, VHR, SMM, SBP, diastolic blood pressure (DBP), FBG, TG, ALT, AST, UA, and Hcy. Moreover, the percentage

Table 2. Characteristics of subjects according to VHR tertiles

	Tertiles of VHR			<i>p</i> trend
	T1	T2	T3	
Age, years	59.27±0.86	58.73±0.61	56.90±0.86	0.05
Current smoker, %	46.20	56.48	60.51	<0.05
Current drinker, %	58.86	69.75	71.97	<0.05
BMI, kg/m ²	22.89±0.21	26.05±0.15	30.49±0.21	<0.001
WC, cm	82.45±0.58	92.94±0.41	108.07±0.58	<0.001
HC, cm	93.23±0.41	97.55±0.29	103.93±0.41	<0.001
BFP, %	21.76±0.38	30.74±0.27	37.87±0.38	<0.001
VFA, cm ²	66.11±1.15	100.81±0.81	143.13±1.15	<0.001
SMM, kg	47.64±0.70	47.60±0.50	51.02±0.70	<0.001
SBP, mm Hg	132±1	135±1	135±1	0.09
DBP, mm Hg	79±1	81±1	84±1	<0.001
NAFLD, %	32.3	50.0	65.61	<0.001
Hypertension, %	55.2	71.1	75.4	<0.001
Dyslipidemia, %	54.7	54.2	59.8	0.272
Hyperuricemia, %	6.5	6.0	14.6	0.002
FBG, mmol/L	9.02 (8.60 9.45)	8.68 (8.38 8.98)	8.97 (8.54 9.40)	0.85
FINS, U/L	13.34 (11.20 15.48)	13.63 (12.11 15.14)	17.70 (15.55 19.84)	<0.05
HOMA-IR	4.54 (3.87 5.22)	5.09 (4.62 5.56)	6.54 (5.86 7.22)	<0.001
TG, mmol/L	1.73 (1.50 1.95)	2.16 (2.00 2.32)	2.31 (2.09 2.54)	<0.001
HDL-C, mmol/L	1.24±0.02	1.20±0.02	1.15±0.02	<0.05
ALT, U/L	23.49 (20.45 26.54)	26.02 (23.87 28.17)	32.19 (29.14 35.25)	<0.001
AST, U/L	18.34 (16.78 19.90)	18.33 (17.22 19.43)	21.36 (19.79 22.92)	<0.01
UA, μmol/L	273.28±6.34	298.28±4.48	316.64±6.36	<0.001
Hcy, μmol/L	11.25 (10.66 11.84)	10.94 (10.52 11.36)	11.51 (10.92 12.11)	0.54

Continuous data were presented as mean ± standard deviation or median (interquartile range). Categorical variables were expressed as frequency or percentage. VHR: $T^1 < 0.91$, $0.91 \leq T^2 < 1.00$, $T^3 \geq 1.00$. *p* for trend was calculated by analysis of variance and the Mann-Whitney U test for continuous data or the χ^2 test for categorical variables. A *p* trend less than 0.05 was considered statistically significant. BMI, body mass index; WC, waist circumference; HC, hip circumference; BFP, body fat percentage; VFA, visceral-fat area; VHR, visceral-fat-area-to-hip-circumference ratio; SMM, skeletal muscle mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; NAFLD, nonalcoholic fatty-liver disease; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UA, uric acid; Hcy, homocysteine.

of smoking and drinking in the IR group was much higher than that in the non-IR group. Subjects in the IR group were more likely to have other metabolic disorders.

Clinical Characteristics of the Subjects according to VHR Tertiles

All the participants were divided into three groups according to the tertiles of VHR. The characteristics of the three groups were shown in Table 2. We could see that with the increase of VHR, the level of HOMA-IR rose, and other indicators including BMI, WC, HC, BFP, VFA, DBP, TG, and UA, which predicted increased risks of metabolic and cardiovascular diseases were also on upward trends (*p* trend <0.001). As expected, HDL-C which

had cardiometabolic protective effects presented an opposite change trend (*p* trend <0.05), compared to the former metabolically unfavorable ones. The prevalence of NAFLD, hypertension, and hyperuricemia and the levels of aminotransferases went up as VHR increased (*p* trend <0.01).

Correlation between VHR and IR

To further explore the correlation between VHR and IR, a linear trend test was performed. Table 3 showed that VHR was positively correlated with IR both in male and female subjects. In model 1, taking T1 as reference, the adjusted ORs in T2 and T3 were 1.932 (95% CI: 1.159 3.229), 2.954 (1.521 5.987), respectively, for males and

Table 3. Adjusted OR with 95% CI for IR according to the VHR tertile

Tertiles	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Male				
Tertile 1	1	1	1	1
Tertile 2	1.932 (1.159 3.229)	1.707 (1.010 2.887)	1.656 (0.968 2.834)	1.655 (0.961 2.856)
Tertile 3	2.954 (1.521 5.987)	2.623 (1.329 5.387)	2.293 (1.139 4.787)	2.282 (1.118 4.822)
<i>p</i> trend	<0.01	<0.05	<0.05	0.05
Female				
Tertile 1	1	1	1	1
Tertile 2	1.178 (0.593 2.294)	1.159 (0.580 2.269)	1.048 (0.516 2.082)	0.980 (0.477 1.966)
Tertile 3	3.530 (1.501 8.653)	3.280 (1.384 8.090)	2.902 (1.199 7.295)	2.571 (1.043 6.557)
<i>p</i> trend	<0.01	<0.05	<0.05	<0.05

Model 1: adjusted for age; model 2: adjusted for age, TG, and HDL-C; model 3: adjusted for age, TG, HDL-C, SBP, and ALT; model 4: adjusted for age, TG, HDL-C, SBP, ALT, and NAFLD. IR, insulin resistance; VHR, visceral-fat-area-to-hip-circumference ratio; OR, odds ratio; CI, confidence interval.

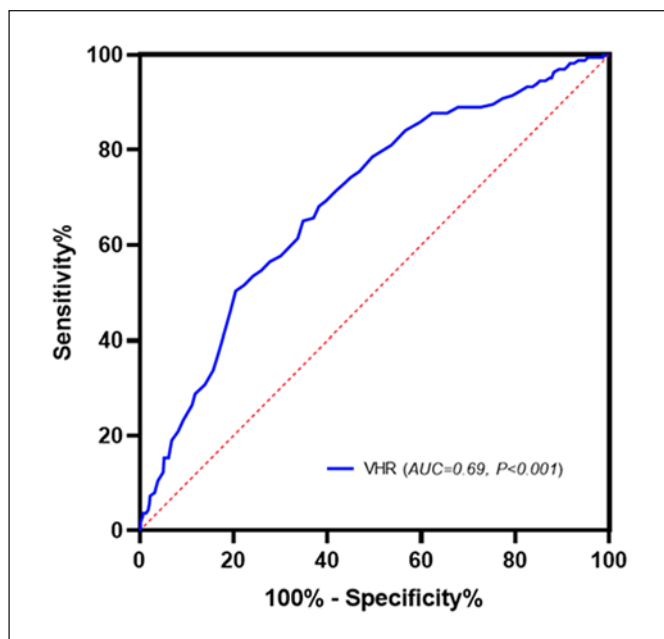


Fig. 1. ROC analysis of VHR for prediction of IR. The area under the curve was 0.69, the optimal cutoff of VHR for predicting IR was 0.89, the sensitivity was 79.3%, and the specificity was 61.5%. ROC, receiver operating characteristic; VHR, visceral-fat-area-to-hip-circumference ratio; IR, insulin resistance.

1.178 (0.593 2.294), 3.530 (1.501 8.653), respectively, for females (*p* trend <0.01). This association remained even after adjustment of other possible confounding variables in model 2 and model 3. However, in model 4 after additionally adjusting for NAFLD, an obvious linear trend

was observed in females (*p* trend <0.01) but not in males (*p* trend = 0.05).

ROC Curve of VHR for Prediction of IR

The ability of VHR to predict IR was evaluated by the ROC curve (Fig. 1). Results showed the area under the curve was 0.69, the optimal cutoff of VHR for prediction of IR was 0.89, the sensitivity was 79.3%, and the specificity was 61.5%.

Discussion

The rapid economic growth in China results in an alarming rise in obesity. The latest national epidemiological survey data show that more than half of Chinese adults are now living with overweight and obesity [13]. Obesity is closely associated with a wide range of diseases including T2DM, hyperuricemia/gout, NAFLD, hypertension, cardiovascular disease, and even cancers [14]. Numerous studies suggest that IR is the key pathophysiological process in the development of the abovementioned diseases [15, 16].

Although BMI is still the main basis for the diagnosis of obesity, mounting evidence has revealed that using BMI for assessment of obesity and cardiometabolic risk has some limitations. BMI cannot differentiate between an increased body fat content and an elevated lean mass, and moreover, it fails to reflect the distribution of body fat. According to the third National Health And Nutrition Examination Survey (NHANES), in the USA, about 10% of the population has a normal BMI but high body

fat content and a higher prevalence of cardiometabolic disorders [17]. Many studies have reported that visceral adipose tissue is the major contributor to IR and cardiometabolic risk; however, subcutaneous adipose tissue may have a protective effect [7, 18]. Taking these two factors into account, we proposed VHR as a new predictor for IR and explored the value of VHR for prediction of IR in this study.

Considering the difference in body fat distribution between males and females, first, we divided all the subjects into two groups by gender. We found that regardless of gender, subjects in the IR group had higher VHR than those in the non-IR group, which suggested that VHR was associated with IR. As predicted, indicators of cardiometabolic unfavorable outcomes and the prevalence of other metabolic disorders were higher in the IR group than in the non-IR group. These results could be explained by the fact that obesity, especially abdominal obesity, was much more common in the IR population, and visceral adipose deposition was strongly related to cardiometabolic disorders [19]. The underlying mechanism for the association between visceral adiposity and IR may be that the buffering capacity of adipose tissue to suppress the release of fatty acids into the circulation is impaired in obesity, and then lipids gradually accumulate in the form of triacylglycerol, leading to IR [20]. Moreover, the deposition of visceral fat increases the secretion of pro-inflammatory cytokines such as interleukin-6, interleukin-8, and monocyte chemoattractant protein-1, which results in a low-grade chronic inflammation state and further triggers the development of IR [21].

NAFLD is also a worldwide public health concern, the prevalence of which has mounted to 25.24% globally [22]. Sex chromosomes and sex hormones may lead to gender differences in some diseases [23]. Therefore, gender differences in NAFLD has become the research focus in recent years since NIH announced that the preclinical studies it funded should assess gender differences [24]. In this study, the prevalence rates of NAFLD in males and females were assessed separately. The results showed the prevalence in females were higher than that in males, which was inconsistent with most of the previously published studies which reported that NAFLD was more common in men than in women in general adult populations [25]. Growing evidence suggests that estrogen can protect women suffering from NAFLD [26]. Hence, the prevalence inconsistency between our study and the previous studies that did not consider menopause or gender difference might be due to the mean age of females included in this study, which was more than 55 years old.

Most women in this age-group were already in their postmenopausal stage and lost the protective effect of estrogen. Likewise, the prevalence of hypertension was also higher in women than in men in this study. Data from the NHANES in the USA investigating the gender- and age-related differences in hypertension prevalence had shown similar results, with elderly women having a higher prevalence of isolated systolic hypertension than men [27].

To further explore the association between VHR and IR, we then divided all subjects into three groups based on the tertiles of VHR. With the increase of VHR, the level of HOMA-IR rose, and other indicators that predicted increased risks of metabolic and cardiovascular diseases were also on upward trends. This proved that VHR was positively correlated to IR and cardiometabolic disorders. As far as we know, this is the first study that evaluates the relationship between VHR and IR as well as cardiometabolic risks. In the past few decades, overwhelming studies demonstrated that the waist-to-HC ratio could be used as a determinant of IR, and it was highly associated with cardiometabolic complications [28, 29]. The waist-to-HC ratio is a simple index of body fat distribution, but it is only a rough indicator of visceral fat content. However, VHR we used in this study was the ratio of VFA to HC, and naturally, it could accurately reflect the content of visceral fat. The prevalence of NAFLD, hypertension, and hyperuricemia and the levels of aminotransferases went up as VHR increased. As we all know, NAFLD is caused by excessive accumulation of fat on the liver [30]. Both visceral fat and liver fat were also independently associated with hyperuricemia, which had been demonstrated in a previous study conducted by Yamada et al. [31]. Therefore, the prevalence of NAFLD and hyperuricemia of the subjects in the T3 group was more than twice that in the T1 group. Elevated aminotransferases suggested that nonalcoholic steatohepatitis might be present, and of course, characteristic histological features such as the presence of hepatic inflammation and liver injury were necessary to confirm this diagnosis [32].

Considering some possible factors that might affect the association between VHR and IR, we gradually adjusted for these potential confounders. Results showed that VHR remained positively correlated with IR after adjusting for possible confounding variables. The only exception was that no significant linear trend was found in men after additionally adjusting for NAFLD, which might be a result of sample size not being large enough. Similarly, it was visceral adipose tissue, rather than subcutaneous adipose tissue, that was strongly associated with IR and cardiometabolic risk that had been demonstrated in

previous studies [33, 34]. A study by Noordam et al. [35] showed that there was an association between visceral adiposity and IR, and this association was mediated by low-grade systemic inflammation and adipokines. The results in this study also robustly suggested that VHR was directly associated with IR, and the potential mechanisms were needed to be elucidated by further studies. The subsequent ROC analysis further demonstrated that VHR could be used to predict IR.

In conclusion, we first put forward a new index – VHR, which precisely reflected the distribution and content of visceral fat – and explored the efficacy of VHR for predicting IR. Our results demonstrated that VHR was positively associated with IR regardless of gender, and it might be a reliable predictor for IR. This conclusion is needed to be further confirmed and replicated in later studies including larger sample sizes and other ethnic groups.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Tianjin Union Medical Center (approval number: 2021C06) and was conducted in accordance with the guidelines laid down in the Declaration of Helsinki. All subjects had given their written informed consent to participate in the study.

References

- 1 International Diabetes Federation. *IDF diabetes atlas*. 9th ed. Gent, Belgium: International Diabetes Federation; 2019.
- 2 Li Y, Teng D, Shi X, Qin G, Qin Y, Quan H, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. *BMJ*. 2020 Apr; 369:m997.
- 3 DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979 Sep;237(3):E214–23.
- 4 Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care*. 2000 Jan;23(1): 57–63.
- 5 Thomas A, Thevis M. Recent advances in the determination of insulins from biological fluids. *Adv Clin Chem*. 2019 Sep;93(11):115–67.
- 6 Fiorentino TV, Marini MA, Succurro E, Andreozzi F, Sesti G. Relationships of surrogate indexes of insulin resistance with insulin sensitivity assessed by euglycemic hyperinsulinemic clamp and subclinical vascular damage. *BMJ Open Diabetes Res Care*. 2019 Nov;7(1): e000911.
- 7 Neeland IJ, Ross R, Després JP, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol*. 2019 Sep;7(9):715–25.
- 8 Jakšić VP, Grizelj D. Under the surface of subcutaneous adipose tissue biology. *Acta Dermatovenerol Croat*. 2016 Dec;24(4):250–60.
- 9 Colman PG, Thomas DW, Zimmet PZ, Welborn TA, Garcia-Webb P, Moore MP. New classification and criteria for diagnosis of diabetes mellitus. The Australasian Working Party on diagnostic criteria for diabetes mellitus. *N Z Med J*. 1999 Apr;112(1086):139–41.
- 10 Molarius A, Seidell JC, Sans S, Tuomilehto J, Kuulasmaa K. Waist and hip circumferences, and waist-hip ratio in 19 populations of the WHO MONICA Project. *Int J Obes Relat Metab Disord*. 1999 Feb;23(2):116–25.
- 11 Wong VW, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, et al. Asia-Pacific Working Party on non-alcoholic fatty liver disease guidelines 2017-part 1: definition, risk factors and assessment. *J Gastroenterol Hepatol*. 2018 Jan;33(1):70–85.
- 12 Xing X, Yang W, Yang Z. The diagnostic significance of homeostasis model assessment of insulin resistance in metabolic syndrome among subjects with different glucose tolerance (Chinese). *Chin J Diabetes*. 2004 Jun; 12(3):182–6.
- 13 Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. *Lancet Diabetes Endocrinol*. 2021 Jun;9(6):373–92.
- 14 Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: pathophysiology and management. *J Am Coll Cardiol*. 2018 Jan; 71(1):69–84.
- 15 Barazzoni R, Gortan Cappellari GG, Ragni M, Nisoli E. Insulin resistance in obesity: an overview of fundamental alterations. *Eat Weight Disord*. 2018 Apr;23(2):149–57.
- 16 Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR, et al. Insulin resistance, cardiovascular stiffening and cardiovascular disease. *Metabolism*. 2021 Jun;119:154766.
- 17 Romero-Corral A, Somers VK, Sierra-Johnson J, Korenfeld Y, Boarin S, Korinek J, et al. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *Eur Heart J*. 2010 Mar;31(6):737–46.
- 18 Booth AD, Magnuson AM, Fouts J, Wei Y, Wang D, Pagliassotti MJ, et al. Subcutaneous adipose tissue accumulation protects systemic glucose tolerance and muscle metabolism. *Adipocyte*. 2018 Sep;7(4):261–72.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Shi Zhang analyzed and interpreted the patient data and was the major contributor in writing the manuscript. Ya-Ping Huang and Jing Li interpreted the analyzed data. Wen-Hong Wang, Min-Ying Zhang, and Xin-Cheng Wang assisted with data collection. Jing-Na Lin and Chun-Jun Li provided equal contribution to the present study as corresponding authors. All the authors read and approved the final paper.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

- 19 Després J-P, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol.* 2008 Jun;28(6):1039–49.
- 20 Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia.* 2002 Sep;45(9):1201–10.
- 21 Wu H, Ballantyne CM. Metabolic inflammation and insulin resistance in obesity. *Circ Res.* 2020 May;126(11):1549–64.
- 22 Araújo AR, Rosso N, Bedogni G, Tiribelli C, Bellentani S. Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: what we need in the future. *Liver Int.* 2018 Feb;38 Suppl 1(Suppl 1):47–51.
- 23 Zore T, Palafox M, Reue K. Sex differences in obesity, lipid metabolism, and inflammation: a role for the sex chromosomes? *Mol Metab.* 2018 Sep;15:35–44.
- 24 Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature.* 2014 May;509(7500):282–3.
- 25 Lonardo A, Nascimbeni F, Ballestri S, Fairweather D, Win S, Than TA, et al. Sex differences in nonalcoholic fatty liver disease: state of the art and identification of research gaps. *Hepatology.* 2019 Oct;70(4):1457–69.
- 26 Palmisano BT, Zhu L, Stafford JM. Role of estrogens in the regulation of liver lipid metabolism. *Adv Exp Med Biol.* 2017;1043:227–56.
- 27 Martins D, Nelson KDP, Pan N, Tareen K, Norris K. The effect of gender on age-related blood pressure changes and the prevalence of isolated systolic hypertension among older adults: data from NHANES III. *J Gend Specif Med.* 2001;4(3):10–3, 20.
- 28 Canoy D, Boekholdt SM, Wareham N, Luben R, Welch A, Bingham S, et al. Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation into cancer and nutrition in Norfolk cohort: a population-based prospective study. *Circulation.* 2007 Dec;116(25):2933–43.
- 29 Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH Jr, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke.* 2006 Oct;37(10):2493–8.
- 30 Mundi MS, Velapati S, Patel J, Kellogg TA, Abu Dayyeh BK, Hurt RT. Evolution of NAFLD and its management. *Nutr Clin Pract.* 2020 Feb;35(1):72–84.
- 31 Yamada A, Sato KK, Kinuhata S, Uehara S, Endo G, Hikita Y, et al. Association of visceral fat and liver fat with hyperuricemia. *Arthritis Care Res.* 2016 Apr;68(4):553–61.
- 32 Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA, Ikramuddin S. Nonalcoholic steatohepatitis: a review. *JAMA.* 2020 Mar;323(12):1175–83.
- 33 Machann J, Stefan N, Wagner R, Fritsche A, Bellizzi D, Wittchen B, et al. Normalized indices derived from visceral adipose mass assessed by magnetic resonance imaging and their correlation with markers for insulin resistance and prediabetes. *Nutrients.* 2020 Jul;12(7):2064.
- 34 Liu L, Feng J, Zhang G, Yuan X, Li L, Yang T, et al. Visceral adipose tissue is more strongly associated with insulin resistance than subcutaneous adipose tissue in Chinese subjects with pre-diabetes. *Curr Med Res Opin.* 2018 Jan;34(1):123–9.
- 35 Noordam R, Boersma V, Verkouter I, le Cessie S, Christen T, Lamb HJ, et al. The role of C-reactive protein, adiponectin and leptin in the association between abdominal adiposity and insulin resistance in middle-aged individuals. *Nutr Metab Cardiovasc Dis.* 2020 Jul;30(8):1306–14.