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 amino transferases than those in the non-IR group. The other concomitant 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.

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.

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) × 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 ± standard deviation or median (interquartile range), depending on whether it was normally distributed or not. Categorical variables were presented as frequency and percentage.
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, DBP, FBG, FINS, TG, HDL-C, ALT, AST, UA, and Hcy. Moreover, the 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/m²              | 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, cm²                | 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          |

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.
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).

### Table 2. Characteristics of subjects according to VHR tertiles

| Tertiles of VHR | T1 | T2 | T3 | p trend |
|----------------|----|----|----|---------|
| 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/m²     | 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, cm²       | 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 |
| HDL-C, mmol/L  | 32.3 | 50.0 | 65.61 | <0.001 |
| DBP, mm Hg     | 132±1 | 135±1 | 135±1 | 0.09 |
| 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<sup>1</sup> < 0.91, 0.91 ≤ T<sup>2</sup> < 1.00, T<sup>3</sup> ≥ 1.00. p for trend was calculated by analysis of variance and the Mann-Whitney U test for continuous data or the χ² 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.
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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 predicting 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 have 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 was 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.

Conflicts 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.

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