Triglycerides to High-density Lipoprotein Cholesterol Ratio is the Best Surrogate Marker for Insulin Resistance in Non-obese Middle-aged and Elderly Population: A Cross-sectional Study

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Research

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Abstract

Background

Insulin resistance is closely associated with metabolic profiles, including obesity and dyslipidemia. However, there are few studies to demonstrate a relationship between lipid profiles and insulin resistance, categorized by BMI, especially in Chinese. The aim of the present study was to examine how lipid profiles were associated with insulin resistance in non-obese middle-aged and elderly Chinese population.

Methods

This cross-sectional study included 1608 (596 men and 1012 women) subjects, without prior known diabetes mellitus and lipid regulating therapy history, older than 45 years. Insulin resistance was defined by homeostasis model assessment of insulin resistance (HOMA-IR) of at least 2.5. The areas under the curve of the receiver operating characteristic curves (AROC) were used to compare the power of these serum markers. SPSS 17.0 software was used for the statistical analysis.

Results

In non-obese subjects (BMI < 25 kg/m², n = 996), triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio (OR = 1.43, 95% CI 1.13-1.81, P = 0.003), and SBP (OR = 1.01, 95% CI 1.00-1.02, P = 0.03) were independently risk factors for the insulin resistance. The best marker for insulin resistance in non-obese subjects was triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio with the AROC of 0.73 (95% CI 0.68-0.77, P < 0.001), and the positive likelihood ratio was greatest for TG/HDL-C ratio in the metabolic profiles including BMI. The optimal cut-off point to identifying insulin resistance for TG/HDL-C ratio was ≥ 1.50 in the non-obese population. The BMI, TG, total cholesterol (TC)/HDL-C ratio and HDL-C also discriminated insulin resistance, as the values for AROC were 0.70 (95% CI 0.66-0.75, P < 0.001), 0.71 (95% CI 0.67-0.76, P < 0.001), 0.70 (95% CI 0.65-0.74, P < 0.001), 0.34 (95% CI 0.29-0.38, P < 0.001), respectively. In overweight subjects (BMI ≥ 25.0 kg/m², n = 612), BMI was still the best marker for insulin resistance with the AROC of 0.65 (95% CI 0.60-0.69, P < 0.001).

Conclusions

TG/HDL-C ratio may be the best reliable marker for insulin resistance in the non-obese population.

Background

Type 2 diabetes mellitus (T2DM) is a world-wide growing health problem. Insulin resistance (IR) and impaired β-cell function are considered as the primary defects in T2DM(1). Currently, the standard methods of measuring IR include the glucose clamp, the modified insulin suppression test, and the homeostasis model assessment of IR[HOMA-IR](2–4), but these tests are not routinely measured in most clinical practices owing to the time and cost involved. Thus, early identification of IR by using simple and inexpensive method is essential for preventing T2DM.
IR is characterized by a decrease in the ability of insulin to stimulate the use of glucose by muscles and adipose tissues and to suppress hepatic glucose production and output(5). It is worth noting that IR is often accompanied by dyslipidemia. LDL, HDL and cholesterol can regulate the function and survival of β-cells. HDL even improves insulin sensitivity of muscle and liver. Evidences suggested that dyslipidemias may not only be consequences but also contributors to the pathogenesis of T2DM(6).

McLaughlin et al first proposed that triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio could be used to identify overweight individuals who are insulin resistant in 2003(7). Thereafter, several studies have reported that TG/HDL-C ratio could be a simple marker of IR(3, 4, 8, 9). However, the relationship between TG/HDL-C ratio with IR differs by ethnicity(3, 10). The TG/HDL-C ratio may be a good marker to identify insulin-resistant individuals of Aboriginal, Chinese, and European, but not South Asian(3).

Previous studies in Chinese population have suggested that TG/HDL-C ratio could be a good predictor of IR(4, 8). But the relationship between TG/HDL-C ratio and IR in non-obese middle-aged and elderly people remains unknown. This study aims to develop a simple predictive marker as a clinical tool for the evaluation of IR in non-obese middle-aged and elderly Chinese population, and to further explore the optimal cut-offs.

**Methods**

**Study population**

This cross-sectional study included 1608 (596 men and 1012 women) subjects aged 63 ± 10 years, without prior known diabetes mellitus. Patients using any medication known to influence insulin resistance or lipid metabolism (such as corticosteroids and lipid-lowering drugs) were excluded.

**General clinical data collection**

The patients’ demographic data, including age and sex were obtained from the clinical documents. Anthropometric measures were collected by trained nurses. Body weight (kg) and height (m) were measured while the participants were wearing light clothing and no shoes. The body mass index (BMI; weight/height$^2$) was calculated by weight in kilograms divided by height in meters squared. Waist circumferences was measured to the nearest 0.1 cm with a tape at the high point of the iliac crest at minimal respiration. Systolic blood pressure (SBP) and diastolic blood pressure were measured by a nurse with a mercury sphygmomanometer adapted for arm size after 5 min of rest with the participants in the sitting position. Two blood pressure measurements were recorded at 5-min intervals, the means were used for the data analysis.

After overnight fasting for 10 h, a 75-g glucose tolerance test was carried out, and blood samples were collected both during fasting and 120 min after administration of the glucose load. Plasma glucose concentration was measured using an enzymatic reaction; a radioimmunoassay method was used to measure serum insulin levels. Standard enzymatic tests were used for fasting lipid profiles (total
cholesterol [TC], TG and HDL-C). LDL-C concentration was calculated as TC minus the cholesterol in the supernatant by the precipitation method using the Friedewald equation, non-HDL-C was calculated by subtracting HDL-C from TC, and the TC/HDL-C ratio, TG/HDL-C ratio and LDL-C/HDL-C ratio were separately calculated. HOMA-IR was calculated as FPG (mmol/L) × fasting insulin (mU/L)/22.5. Insulin resistance was defined by homeostasis model assessment of insulin resistance (HOMA-IR) of at least 2.5.

Statistical analysis

Data are presented as means ± standard deviation (SD) for normal variables or median + interquartile range for skewed variables. Non-normal values were log-transformed before analysis. Comparisons between groups were performed by Student's *t*-test for normal variables and by the χ²-test for categorical variables, respectively. Partial Spearman's correlation analysis was used to determine the correlation among the lipid profiles. We analyzed the association of the lipid profiles with IR by multivariate logistic regression in different models. The associations of the lipid profiles with IR were analyzed by using multivariate linear regression. Areas under the receiver operating characteristic (ROC) curves were used to examine the discriminatory power. AROC of 0.5 = no discrimination, 0.7 ≤ AROC < 0.8 = acceptable, 0.8 ≤ AROC < 0.9 = excellent, AROC ≥ 0.9 = outstanding. The analyses were carried out by SPSS software (version 17.0; SPSS, Chicago, IL, USA).

Results

The characteristics of the participants are presented in Table 1. According to the BMI levels, the subjects were divided into two groups: non-obese (BMI < 25 kg/m²) and obese (BMI ≥ 25 kg/m²). Obese people were slightly older than non-obese subjects. Obese individuals have larger waist circumference, higher systolic and diastolic blood pressure, and higher lipid profiles than non-obese individuals. Obese individuals have significantly higher TG, HDL-C, TC / HDL-C, and TG / HDL-C than non-obese individuals, while TC and LDL-C levels have no significant difference. In obese subjects, fasting blood glucose, 2 h postprandial blood glucose, INS and HOMA-IR were significantly higher. TC and LDL-C concentrations did not differ among the groups. Obviously, obese individuals tend to have higher serum lipid profiles.

The odds ratios (ORs) for IR of all subjects are shown in Table 2. Whether in obese or non-obese individuals, dyslipidemia is positively correlated with insulin resistance. After adjustments for sex and age, TC/HDL-C (OR = 1.976,95%CI 1.678–2.326, p < 0.001), LDL-C/HDL-C (OR = 1.940,95%CI 1.524–2.471, p < 0.001) and TG/HDL-C (OR = 1.894,95%CI 1.588–2.259, p < 0.001) had significant associations with IR in non-obese subjects. After multivariate adjustments for sex, age, BMI, SBP and DBP, TC/HDL-C (OR = 1.741,95%CI 1.434–2.114, p < 0.001), LDL-C/HDL-C (OR = 1.618,95%CI 1.258–2.081, p < 0.001) and TG/HDL-C (OR = 1.704,95%CI 1.420–2.047, p < 0.001) had significant associations with IR in non-obese subjects. After multivariate adjustments, the association between the TG/HDL-C ratio and IR was attenuated, but remained significant. Among the single lipid markers, the TG levels also showed strong associations with IR in non-obese subjects (OR = 1.917 in model 1 or OR = 1.754 in model 2).
To further investigate the potential independent risk factors for IR among the lipid profiles in non-obese subjects, a multivariate stepwise logistic regression was carried out (Table 3). SBP (OR = 1.012, 95%CI 1.001–1.023, p = 0.027), TC/HDL-C (OR = 1.482, 95%CI 1.150–1.909, p = 0.002) and TG/HDL-C (OR = 1.434, 95%CI 1.132–1.816, p = 0.003) were independently associated with IR in non-obese subjects. Namely, for a 1-unit increase in TG/HDL-C, the odds of being insulin resistant increased 1.434 times in non-obese individuals.

The area under the ROC curves for potential markers of insulin resistance are presented in Table 4 and Fig. 1. The best marker for insulin resistance in non-obese subjects was TG/HDL-C ratio with the AUC of 0.728. The AUC of TG/HDL-C ratio for predicting IR is 0.728 in non-obese vs. 0.624 in obese individuals, indicating that the association between TG/HDL-C ratio and IR may differ by BMI categories, and this association was stronger among people with a lower BMI. According to the maximum value of the Youden index, the optimal cut-off point to identifying insulin resistance for TG/HDL-C ratio was ≥ 1.50 in the non-obese population. The BMI, TG, TC/HDL-C ratio, HDL-C also discriminated insulin resistance, as the values for AUC were 0.705 (95% CI 0.66–0.75, p < 0.001), 0.712 (95% CI 0.67–0.76, p < 0.001), 0.696 (95% CI 0.65–0.74, p < 0.001), 0.336 (95% CI 0.29–0.38, p < 0.001), respectively. In obese subjects, BMI was still the best marker for insulin resistance with the AUC of 0.647 (95% CI 0.60–0.69, p < 0.001).

Discussion

The findings of our study indicate that the TG/HDL-C ratio is strongly associated with IR in non-obese middle-aged and elderly Chinese people. After adjusting for potential confounding variables (sex, age, BMI, SBP and DBP), TG/HDL-C ratio was still positively related to HOMA-IR.

There are conflicting data on the association of TG/HDL ratio with insulin resistance among different populations. Previous studies have reported different cut-off values of TG/HDL-C ratio to detect the presence of IR. McLaughlin et al first proposed TG/HDL-C to identify overweight individuals who are insulin resistant in 2003(7). This cross-sectional study included 258 nondiabetic overweight or obese individuals, of whom 87% were non-Hispanic whites. They reported that a cut-off value of TG/HDL-C ratio of 3.0 could reliably predict IR in overweight people. Furthermore, only 129 of the overweight or obese persons were identified as insulin resistant (positive predictive value, 50%), which means not all overweight or obese people are insulin resistant. In fact, resistance to insulin-mediated glucose disposal is distributed continuously throughout the general population(11). This conclusion emphasized the importance of early identification of high-risk individuals in non-obese population. One year later, a study demonstrated that the TG/HDL-C ratio only positively correlates with insulin resistance in severely obese nondiabetic individuals but not in patients with overt diabetes(12). Racial/ethnic differences in triglyceride concentrations and HDL-C values have been widely reported. A study found that non-Hispanic blacks had lower TG concentrations than non-Hispanic whites or Mexican Americans(13). They proposed race/ethnicity-specific TG/HDL-C cutoff points to predict IR. Cutoff points of 3.0 for non-Hispanic whites and Mexican Americans and 2.0 for non-Hispanic blacks. Moreover, the findings of their study suggested that the association of the TG/HDL-C ratio with hyperinsulinemia was stronger among people with a BMI
<25 kg/m² than those with a BMI ≥ 30 kg/m². As reported in a previous study, about 16% people with normal weight (BMI < 25 kg/m²) was identified to be insulin resistant(14). This result encourages us to establish a simple and useful method to detect IR individuals among non-obese people. However, a cross-sectional study in overweight African Americans have reported that the triglyceride or TG/HDL-C ratio was not significantly associated with IR. The AUC value of the TG/HDL-C ratio to predict IR was 0.56, which is not significant(15).

It is worth noting that TG/HDL-C has also been shown to predict cardiovascular events and nonalcoholic fatty liver disease (NAFLD) independently(16, 17). In addition to being associated with insulin resistance, the lipoprotein phenotype is also associated with increased cardiovascular disease. A study of McLaughlin’s group showed that TG/HDL ratio ≥ 3.5 mg/dl predicts the presence of the small dense LDL phenotype (LDL phenotype B) with high sensitivity and specificity. Those insulin-resistant, dyslipidemic patients are at increased risk of cardiovascular disease. A cross-sectional study reported that a cut-off value of TG/HDL-C ratio of 0.9 in women (sensitivity = 78.8%, specificity = 77.3%) and 1.4 in men (sensitivity = 70.7%, specificity = 73.5%) to predict NAFLD.

The mechanism of TG/HDL-C predicting IR is still unclear. When circulating TG persists at high levels, heparin activates lipoprotein lipase to increase intravascular lipolysis of TG, thus increasing the risk of tissue exposure to free fatty acids (FFAs). High FFAs may deteriorate insulin sensitivity via oxidative stress pathway(18, 19). Previous studies have indicated that the TG/HDL-C ratio as a marker of lipotoxicity in β-cells resulting in impaired insulin secretion(20) and increased β-cell apoptosis from high circulating TG levels(21). M Shimabukuro et al. demonstrated that β cell apoptosis is induced by increased FFA via de novo ceramide formation and increased NO production. Elevated levels of circulating FFA and lipoproteins transport to islets far more FFA than can be oxidized, leading to an increase in ceramide, iNOS expression, and NO production, which cause apoptosis(21).

There are several limitations in our study. First, the major limitation of this study was our failure to use a glucose clamp, an insulin suppression test, or the frequently sampled intravenous glucose tolerance test. However, we used fasting insulin concentration and HOMA-IR to demonstrate insulin resistance, which is practical in clinical settings. Second, because of the relatively small sample size, the results of our study might have limited statistical power. Third, this study was a cross-sectional design that made it difficult to establish the causal relationship between TG/HDL-C and IR. No comparisons between different races might be another limitation.

**Conclusion**

In conclusion, our findings demonstrated that the elevated TG/HDL-C ratio was significantly associated with IR and could be used as an indicator of IR among the non-obese middle-aged and elderly Chinese population. TG/HDL-C ratio could be recommended in clinical practices to early identify insulin resistant patients, and interventions such as lifestyle changes could be taken.
Abbreviations

BMI
body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol ratio; Non-HDL-C: Non-high-density lipoprotein cholesterol; FBG: fasting plasma glucose; 2hPG: 2 hours postprandial blood glucose; INS: serum insulin; HOMA-IR: homeostasis model assessment method of insulin resistance. OR: Odds ratio; CI: confidence interval. AROC: area under receiver operating characteristic curves.

Declarations

Ethics approval and consent to participate

All procedures were carried out in compliance with the Helsinki Declaration. The present study was approved by Zhong-Shan Hospital ethics committee, Fudan University, China. All participants were informed of the purposes and procedures of the study and provided written consent before participation.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Yumei Yang took part in study design and writing the manuscript. Baomin Wang and Haoyue Yuan collected the data. Xiaomu Li performed the statistical analyses. All authors also read and approved the final version of this manuscript.

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Tables
Due to technical limitations, table 1, 2, 3 and 4 is only available as a download in the Supplemental Files section.