Triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) index as a reference criterion of risk for metabolic syndrome (MetS) and low insulin sensitivity in apparently healthy subjects

Blanca Guadalupe Baez-Duarte[1], Irma Zamora-Gínez[1], Ramiro González-Duarte[2], Enrique Torres-Rasgado[1], Guadalupe Ruiz-Vivanco[1], Ricardo Pérez-Fuentes[1,3] and The Multidisciplinary Research Group Of Diabetes

[1]Faculty of Medicine, Benemérita Universidad Autónoma de Puebla (BUAP), Puebla, Pue.; [2]Faculty of Medicine, UNAM, Mexico City; [3]Centro de Investigación Biomédica de Oriente (CIBIOR), IMSS, Atlixco, Puebla, Pue. Mexico

Abstract

Aim: *To evaluate if the TG/HDL-C index can be considered as a reference criterion of MetS and low insulin sensitivity in apparently healthy subjects.* **Methods:** *The subjects were Mexican mestizos who resided in Puebla City, Mexico, who were anthropometrically, biochemically, and clinically characterized. The TG/HDL-C index was calculated by dividing triglyceride (TG) levels by HDL-C levels. MetS was diagnosed by the Third Report from the Adult Treatment Panel-National Cholesterol Education Program (ATP-III NCEP) criteria, while insulin sensitivity was evaluated by the Quantitative Insulin sensitivity Check Index (QUICKI).* **Results:** *The study included 813 subjects, with an average age of 38.6 ± 12.1 years, of which 564 were women and 249 men. An association was found between high TG/HDL-C index and low insulin sensitivity (Odds ratio [OR]: 4.09; p < 0.01) and with MetS (OR: 15.29; p < 0.01). A correlation was found between the TG/HDL-C index and QUICKI (rho: –0.4989; p < 0.01) and with MetS (rho: 0.6581; p < 0.01).* **Conclusion:** *The results indicate that the TG/HDL-C index is associated with low insulin sensitivity and MetS in apparently healthy subjects, suggesting this index as a reference criterion of risk for low insulin sensitivity and MetS.*

KEY WORDS: *Metabolic syndrome. QUICKI. Cardiovascular risk. Insulin sensitivity. TG/HDL-C index.*

Introduction

The MetS involves a cluster of metabolic abnormalities including centrally distributed obesity, decreased concentration of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides (TG), high blood pressure, and hyperglycemia[1]. MetS is also a risk factor for developing type 2 diabetes mellitus (DM2), ischemic heart disease, and arteriosclerosis-associated stroke, which are causes of mortality[1,2]. Given the previously mentioned information, MetS is considered a public health problem worldwide, especially in Westernized countries[1], presenting a prevalence of 39.7% in Mexico[3,4].

Recent studies have suggested that MetS might be the result of different, but interrelated, pathophysiological mechanisms such as endothelial dysfunction, low-intensity inflammatory process, visceral obesity, oxidative stress, genetic factors, and alterations in insulin sensitivity[2,5,6].

Insulin sensitivity can be defined as the responsiveness to the metabolic actions of insulin, as determined by both genetic and environmental factors, and plays an important pathophysiological role in diabetes[7].

When insulin sensitivity is impaired, compensatory hyperinsulinemia is produced, which generates, in the long term, a pancreas beta cell dysfunction, promoting

Correspondence:
Blanca Guadalupe Baez-Duarte
Av. 13 Sur, 2702
Col. Volcanes
C.P. 72410, Puebla, Pue., México
E-mail: blanquis121280@yahoo.com.mx

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the development of DM[28]. During this period, diverse metabolic changes increase the risk of cardiovascular disease[8].

Insulin sensitivity can be determined by various methods. One of these is the hyperinsulinemic-euglycemic (HIE) glucose clamp technique that is the "gold standard" for quantifying insulin sensitivity *in vivo,* but none of these have been easily implemented in large studies[7].

Instead of the HIE glucose clamp technique, a Quantitative Insulin sensitivity Check Index (QUICKI = 1/[log fasting insulin + log fasting glucose]) was defined, which has substantially good correlation with the HIE glucose clamp technique[7,9]. QUICKI is obtained from fasting blood samples and may be useful for clinical research because it can be used for easy and accurate estimation of insulin sensitivity in subjects at risk. QUICKI has been validated extensively against the reference standard glucose clamp method[7,10-12] and comprises a simple, robust, accurate, and reproducible method that appropriately predicts changes in insulin sensitivity[13].

In a previous study, we detected a decrease in insulin sensitivity (measured by QUICKI) in subjects with metabolic imbalance without MetS and a progressive deterioration of insulin sensitivity in subjects with MetS as the number of features of MetS increased[14]. We suggested that assessment of insulin sensitivity in subjects with a metabolic imbalance might detect early stages of metabolic abnormalities (the pre-metabolic syndrome phase) that characterize MetS, not only detecting it at an early stage, but also enabling prevention strategies[14].

As mentioned previously, MetS is a risk factor for cardiovascular diseases[1,2]. In this context, a new index has been proposed to estimate cardiovascular risk, which considers the TG/HDL-C ratio. This index has been utilized in different types of populations, such as in subjects at high risk for coronary disease[15], in subjects with DM2[16], and in patients with coronary artery disease[17]; in all of these studies, the TG/HDL-C index was an independent predictor of cardiovascular disease. In a study conducted in Mexican obese subjects, we found that the TG/HDL-C index was higher in overweight and obese subjects compared with healthy subjects[18].

Taking this information into account, we assessed whether the TG/HDL-C index may serve as a reference criterion of risk for low insulin sensitivity and MetS, managing to detect individuals at risk at an early stage, where one of the targets for clinical practice is to facilitate the application of criteria for early disease detection and to provide the cut-off point for their application in patients.

Materials and methods

Subjects and setting

A total of 875 Mexican subjects (Central Mexico) participated in the study. Subjects with an incomplete clinical history or who had ongoing chronic inflammatory (arthritis, rhinitis, and trauma), endocrine (hyperthyroidism and hypothyroidism), or any chronic disease (except hypertension and hyperlipidemia) were excluded from the study. Use of medications, alternative treatments, smoking, and alcoholism were also considered exclusion criteria, as well as subjects with a previous diagnosis of DM2. The 813 subjects who met the selection criteria had an average age of 38.6 ± 12.1 years; 564 were women (who were not pregnant or breastfeeding) and 249 men. The subjects of the present study were Mexican mestizos who resided in Puebla City, Mexico.

The study was approved by the Scientific Research and Ethics Committee of the Instituto Mexicano del Seguro Social (IMSS) and informed consent was obtained from all individual participants included in the study.

Clinical characterization

Anthropometric measurements such as height, weight, and percentage of body fat (%BF) were determined using an electronic digital scale (Tanita® Body Composition Analyzer, Model TBF-215; Tokyo, Japan); scale capacity, 200 kg. Waist circumference (WC) was measured at the midpoint between the highest point of the iliac crest and the lowest point of the costal margin at the mid-axillary line, employing a non-stretching anthropometric measuring tape. Body mass index (BMI) was calculated using the Quetelet BMI formula. Subjects without overweight or obesity were considered if BMI was < 25 kg/m^2 and with overweight or obesity if their BMI was ≥ 25 kg/m^2 [19]. Blood pressure was determined in a sitting position and after five minutes of rest according to the Mexican Official Standard[20] for the prevention, treatment, and control of hypertension, using a Baumanometer® (Microlife AG, Heerbrugg, Switzerland) and a stethoscope (3M Littmann® Classic II; Neuss, Germany).

Biochemical characterization

Following an overnight fast (10-12 hours) by the study participants, blood samples were obtained by venipuncture. Fasting glucose, fasting insulin, total cholesterol (TC), TG, HDL-C, and glucose levels of the oral

tolerance test (GlcOTT), determined two hours after a 75 g glucose load, were measured according to conventional laboratory protocols using the periodic endpoint method. Plasma glucose levels and lipid profile were determined using the Synchron CX5 Analyzer System (Beckman Coulter, Fullerton, CA, USA). Insulin concentration was determined by chemiluminescence in an immunoassay utilizing anti-insulin mouse monoclonal antibodies with alkaline phosphatase (Beckman Coulter Access System).

Insulin sensitivity was calculated according to the Quantitative Insulin sensitivity Check Index (QUICKI) with the following formula: QUICKI = 1/(log fasting insulin + log fasting glucose mg/dl)[7]; values < 0.357 are representative of low insulin sensitivity, based on a report by Hrebıcek, et al.[21].

According to the cut-off point established[22] for diagnosis of glucose intolerance and DM2, subjects were detected with new-onset DM2 or glucose intolerance.

Normal values of TC levels < 200 mg/dl, TG levels < 150 mg/dl, and HDL-C levels ≥ 40 mg/dl were considered according to the Third Report from the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) criteria[23]. Low-density lipoprotein cholesterol (LDL-C) was determined using the formula cited in Mexican Norm NOM-037-SSA2-2012 for the prevention, treatment, and control of dyslipidemia[24] in which very low-density lipoprotein cholesterol (VLDL-C) = TG/5 and LDL-C = TC – (VLDL-C + HDL-C).

The TG/HDL-C index was calculated by dividing the concentration of TG by HDL-C. The cut-off point for cardiovascular risk was TG/HDL-C > 3[16,25].

MetS was defined according to ATP III-NCEP criteria[23] with WC values adjusted to the Mexican population (NCEP-ATP IIIm)[14]. Diagnosis of MetS was established if three or more of the following risk factors were present: blood pressure ≥ 130/85 mmHg; fasting glucose ≥ 100 mg/dl; TG ≥ 150 mg/dl; HDL-C < 40 mg/dl in males and < 50 mg/dl in females; and WC ≥ 90 cm in males and ≥ 80 cm in females.

Statistical analysis

The Kurtosis Normality of Residuals test was employed to determine normality of data distribution. Continuous variables with normality and equal variances were analyzed utilizing the Student *t* test. When not normality, but equal variances were observed, a Kruskal-Wallis test was employed. Nonparametric continuous variables were analyzed using the Mann-Whitney *U* test and, to establish an association between the variables, we utilized multinomial logistic regression. Correlation analysis was carried out using the Spearman rank test. Data were analyzed with SPSS software (v. 21.0 for Windows; SPSS, Inc., Chicago, IL, USA). Differences between groups were considered significant at $p < 0.05$.

Results

In the study, 813 subjects participated who had an average age of 38.6 ± 12.1 years, among whom 564 were women and 249 men. Of all of the participating subjects, 69.86% were overweight or obese in accordance with the BMI determined; women had a higher percentage of body fat compared with men (Table 1). In all, 247 subjects had glucose intolerance and both males and females had, on average, low levels of HDL-C and high levels of TG (Table 1).

Diastolic and systolic blood pressure averages apparently fell within the normal range (110.2 ± 14.2 and 72.8 ± 9.8 mmHg, respectively); however, 145 subjects presented blood pressure above the range recommended by ATP-III NCEP (130/85 mmHg)[23].

We identified 518 subjects who had low insulin sensitivity. The group of subjects with low insulin sensitivity had a higher average WC as well as higher levels of glucose, insulin, and TG/HDL-C index compared with the group of subjects with normal insulin sensitivity; 68.4% of subjects with low insulin sensitivity had high cardiovascular risk (Table 2).

There were 362 subjects with a diagnosis of MetS and 451 without a diagnosis of MetS; however, of these 451 subjects, 358 had one or two diagnostic criteria for MetS. A total of 76.5% of subjects with MetS had a high TG/HDL-C index (Table 3).

We found in this study a statistical association between cardiovascular risk and insulin sensitivity (odds ratio [OR]: 4.09; $p < 0.01$; adjusted by age, gender, and WC) and with MetS (OR: 15.29; $p < 0.01$, adjusted by age, gender, and WC). We found a correlation between the TG/HDL-C index and QUICKI (rho: -0.4989; $p < 0.01$), and between the TG/HDL-C index and MetS (rho: 0.6581; $p < 0.01$).

Discussion

In this study, despite our study population being one of apparently healthy subjects, we found that they had metabolic disorders that condition the development of cardiovascular disease and DM2. Proof of this includes low insulin sensitivity and the high TG/HDL-C index

Table 1. Anthropometrical and biochemical variables of study subjects

	Study subjects (n = 813)
BMI (kg/m2)	27.8 ± 5.3
WC M (cm)	96.1 ± 13.2
WC W (cm)	91.5 ± 12.1
BF M (%)	25.3 ± 8.0
BF W (%)	34.8 ± 7.2*
Fasting glucose (mg/dl)	93.1 ± 11.2
GlcOTT (mg/dl)	114.1 ± 28.8
Fasting insulin (µU/ml)	10.2 ± 7.7
QUICKI	0.348 ± 0.034
TG (mg/dl)	163.1 ± 105.6
TC (mg/dl)	187.5 ± 43.1
HDL-C M (mg/dl)	36.8 ± 12.9
HDL-C W (mg/dl)	43.0 ± 15.1
LDL-C (mg/dl)	116.2 ± 34.9
VLDL-C (mg/dl)	30.1 ± 18.4
TG/HDL-C index	4.2 ± 3.7

Results were expressed as means ± standard deviation (SD). *P ≤ 0.05, two-tailed Student *t* test, statistically significant differences between men and women.
BMI: body mass index; WC: waist circumference; M: Men; W: women; BF: body fat; GlcOTT: glucose levels of the oral tolerance test; QUICKI: Quantitative Insulin sensitivity Check Index; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL-C: very low-density lipoprotein cholesterol.

found in the subjects. This is in agreement with our previous studies conducted in subjects with MetS[14,26] and in obese subjects[18], in which subjects with metabolic disorders had decreased insulin sensitivity and increased cardiovascular risk compared with healthy subjects. In all of these studies, the behavior of these two indices (QUICKI and TG/HDL-C index) was similar, which leads us to suggest that both of the indices independently may comprise reference criteria for the early metabolic alterations that are widely related with MetS. QUICKI was previously proposed as a risk marker for the development of MetS[14]. In the present study, we suggest the TG/HDL-C index as an additional and useful reference criterion of risk for MetS, providing the opportunity to have a criterion for indicating risk for developing both MetS and low insulin sensitivity. This is important, considering that this index requires simple calculation (its equation is a simple one) for application.

On the other hand, the cut-off point of the TG/HDL-C index of > 3 for cardiovascular risk strongly correlated with diagnosis of MetS and insulin sensitivity, and a strong association with these two variables is also demonstrated. This cut-off point has been employed in other studies[16,25].

The application of this TG/HDL-C index to detect subjects at risk for MetS is simple, and the obtaining of its components (TG and HDL-C) lies within routine testing at the majority of hospitals. The use of this index might avoid indiscriminate utilization of laboratory tests, as well as related expenditures[27].

Table 2. Anthropometrical and biochemical characteristics of the study subjects divided by insulin sensitivity

	Study groups	
	Normal insulin sensitivity (n = 295)	Low insulin sensitivity (n = 518)
Age (years)	36.8 ± 12.0	39.6 ± 11.9*
Gender (M/W)	84/211	165/353
BMI (kg/m2)	25.2 ± 3.9	29.3 ± 5.5*
WC (cm)	86.2 ± 9.9	96.8 ± 12.4*
Fasting glucose (mg/dl)	87.6 ± 9.0	96.2 ± 11.2*
GlcOTT (mg/dl)	101.3 ± 23.8	122.4 ± 28.8*
Fasting insulin (µU/ml)	5.0 ± 1.4	13.3 ± 8.2*
QUICKI	0.384 ± 0.025	0.328 ± 0.019*
TG/HDL-C index	2.5 ± 1.6	5.1 ± 4.3*
%S CVR	28.7	68.4

Results were expressed as means ± standard deviation (SD). *P ≤ 0.05 Mann-Whitney *U* test
M: men; W: women; BMI: body mass index; WC: waist circumference; GlcOTT; glucose levels of the oral tolerance test; QUICKI: Quantitative Insulin sensitivity Check Index; TG: triglycerides; HDL-C, high-density lipoprotein cholesterol; %S CVR: percentage of subjects with cardiovascular risk.

Table 3. Anthropometrical and biochemical characteristics of the study subjects divided by metabolic syndrome

	Study groups	
	Without MetS (n = 451)	**With MetS (n = 362)**
Age (years)	36.1 ± 12.1	41.6 ± 11.3*
Gender (M/W)	126/325	123/239
BMI (kg/m2)	25.9 ± 4.5	30.1 ± 5.3*
WC (cm)	87.9 ± 11.4	99.2 ± 11.2*
Fasting glucose (mg/dl)	88.7 ± 9.0	98.5 ± 11.4*
GlcOTT (mg/dl)	103.9 ± 23.9	126.7 ± 29.4*
Fasting insulin (μU/ml)	7.8 ± 5.0	13.2 ± 9.2*
QUICKI	0.363 ± 0.03	0.330 ± 0.03*
TG/HDL-C index	2.5 ± 1.4	6.4 ± 4.6*
%S CVR	26.8	76.5

Results were expressed as means ± standard deviation (SD). *P ≤ 0.05 Mann-Whitney *U* test.
MetS: metabolic syndrome; M: men; W: women; BMI: body mass index; WC: waist circumference; GlcOTT: glucose levels of the oral tolerance test; QUICKI: Quantitative Insulin sensitivity Check Index; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; %S CVR: percentage of subjects with cardiovascular risk.

The TG/HDL-C index has been advocated as a simple clinical indicator of cardiovascular disease, estimating atherogenic small dense LDL-C particles and predicting arterial stiffness and acute cardiovascular events in adults with DM2[16] and healthy subjects without diabetes[28], which has been demonstrated in different studies. Furthermore, the TG/HDL-C index has been described as an independent determinant of arterial stiffness in adolescents and young adults, especially in obese youths, suggesting that the use of the TG/HDL-C index may also be helpful in identifying young adults requiring aggressive intervention to prevent atherosclerotic cardiovascular disease[29].

Although there are diverse studies that support the TG/HDL-C index as reference criteria of cardiovascular risk, there are, to our knowledge, no studies that have reported the relationship with MetS or insulin sensitivity (measured by QUICKI).

Within this context, there are two studies conducted in Mexican population. One of these examined the clinical usefulness of the TG/HDL-C index and MetS in healthy college students (17-24 years of age) of Mexican mestizo ancestry to identify insulin resistance and increased cardiometabolic risk. These authors concluded that both a higher TG/HDL-C index and a diagnosis of MetS identified young insulin-resistant individuals with an increased cardiometabolic risk profile. It is noteworthy that the authors reported no association between the TG/HDL-C index and MetS[30].

The other study conducted in a Mexican population showed an elevated TG/HDL-C index detected in 61.3% of subjects with insulin resistance and an association between these two variables with an OR of 2.64[25].

We found a strong correlation between the TG/HDL-C index and insulin sensitivity (measured by QUICKI), and also with MetS, both reported, to our knowledge, for the first time. Together with this, we also found a strong association between these variables, respectively.

Detection of an elevated TG/HDL-C index will identify the onset of metabolic alterations related with MetS such as decreased insulin sensitivity and altered lipid profile. Thus, the initiation of appropriate treatment according to the therapeutic goals is recommended by different studies[23,31].

The results of this study indicate that the TG/HDL-C index is associated with insulin sensitivity (measured by QUICKI) and with MetS in the studied subjects, allowing to suggest this index as an adequate reference criterion of risk for low insulin sensitivity and MetS, which might facilitate the detection of metabolic changes in early stages and avoid further complications.

Declaration of interest

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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