Elevated triglycerides/HDL-cholesterol ratio associated with insulin resistance

Antonio González-Chávez,* Luis Ernesto Simental-Mendía,** and Sandra Elizondo-Argueta***

Abstract

Background: Cardiovascular disease is the main cause of death worldwide and insulin resistance (IR) plays an important role for its development. In addition, IR has been associated with hypertension and metabolic syndrome according to the triglyceride/HDL-cholesterol (TG/HDL) ratio. We undertook this study to determine whether the TG/HDL ratio is associated with IR in apparently healthy subjects.

Methods: A cross-sectional study including healthy men and nonpregnant women was performed. Individuals with IR were compared against subjects without IR. Variables studied were age, gender, body mass index, and waist circumference. Exclusion criteria were chronic diseases such as renal disease, hepatic disease, malignancy, and diabetes.

Results: A total of 177 subjects were enrolled, 117 females (66.1%) and 60 males (33.9%). Of these, 145 (93 females and 52 males) with IR were compared against 32 subjects (24 females and 8 males) without IR. Elevated ratio TG/HDL was detected in 89 (61.4%) and 12 (38.6%) subjects with and without IR, respectively. The elevated TG/HDL ratio was significantly associated with IR (OR 2.64, 95% CI = 1.12–6.29).

Conclusions: In apparently healthy subjects, elevated TG/HDL ratio was significantly associated with the presence of IR.

Key words: insulin, triglycerides, HDL-cholesterol, metabolic syndrome.

Introduction

For more than five decades and until now, the leading cause of death worldwide is cardiovascular disease (CVD), an entity that has directed research efforts in medicine to try to determine the risk factors and progress in understanding the physiopathology and treatment of this disease as well as its relationship with other nontransmitted chronic diseases such as diabetes, systemic arterial hypertension (SAH), dyslipidemia and obesity.1-3 There are several criteria for cardiovascular risk stratification of patients according to the changes it presents such as background, anthropometry, laboratory tests and imaging studies. One of the objectives for clinical practice is to facilitate the application of these criteria for early detection of the disease, which is why predictive and prognostic indices of CVD have been established such as the triglyceride/HDL-cholesterol (TG/HDL-c) ratio used as a marker of atherogenicity. Furthermore, although evidence obtained regarding this relationship in terms of disease prognosis are still rare, it has demonstrated that its predictive value for heart disease is high. Moreover, it has established its direct relationship with entities such as SAH and metabolic syndrome (MetS) as demonstrated in the MESYAS (Metabolic Syndrome in Active Subject in Spain) study.4-8 The presence of IR allows for the identifying of a subject at risk for developing an assortment of metabolic disorders, which can trigger diseases such as diabetes, SAH and/or heart disease. Thus, considering that the current objective of the physician is to apply a preventive approach, it requires accessible means to identify these patients. Diagnosis of IR may sometimes make it difficult because it initially manifests subclinically, and because the type of laboratory studies required to IR are expensive and unavailable in most laboratories in cities of underdeveloped countries. Because IR plays an important role in the development of CVD and the TG/HDL ratio was significantly associated with these conditions, the
objective of this study was to determine whether the TG/HDL ratio is associated with IR.9-13

Materials and Methods

With the approval of the Ethics Committee of the General Hospital of Mexico and after obtaining informed consent from the participants, we conducted a cross-sectional comparative study in apparently healthy males and nonpregnant women <18 years of age and who were residents of Mexico City. The subjects were allocated into groups with and without IR, and matched by age, gender, body mass index (BMI) and waist circumference (WC). The presence of chronic diseases such as kidney disease, liver disease, neoplasms and diabetes were exclusion criteria.

Definitions

IR was determined by means of homeostasis model assessment index (Homeostasis Model Assessment—Insulin Resistance, HOMA—IR) using the formula:

\[
\text{HOMA—IR} = \frac{\text{fasting insulin (µU/mL)} \times \text{fasting glucose (mmol/L)}}{22.5}
\]

IR was considered an index of HOMA-IR >2.5.13

The TG/HDL ratio was calculated in the following manner: TGs of fasting (mg/dL)/HDL-cholesterol (mg/dL). The cut-off used was 3.0.14 Diabetes diagnosis was based on the presence of 2 h post-load plasma glucose ≥200 mg/dL.15

Measurements

Weight and height were measured with the subjects standing, without shoes and with light clothing. BMI was calculated as weight (kg) divided by height (m) squared. WC was measured at the level of the umbilicus with a tape measure with centimeter scale. The technique for measuring arterial blood pressure was as recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.16

Blood Analysis

A blood sample was obtained from the antecubital vein under conditions of 12 h of fasting and 2 h post-load. TG and cholesterol levels were measured by enzymatic techniques using spectrophotometric methods (Synthrom CX9 PRO analyzer, Beckman Coulter, Brea, CA). HDL-cholesterol fraction was obtained after precipitation by phosphotungstic reagent. Coefficients of intra- and interassay variation were 1.7% and 3.1% for TG and 1.3% and 2.6% for HDL-c, respectively.

Serum glucose was measured using the glucose oxidase method (YSI, Yellow Spring, OH). The intra- and interassay coefficients of variation for glucose measurements were 1.1% and 1.5%, respectively. Determination of the concentration of insulin was performed by RIA (Abbott Axsym System, Chicago IL), with intra- and interassay coefficients of variation of 4.5% and 6.9%, respectively.17-19

Statistical Analysis

Variables were expressed using measures of central tendency and dispersion. Between-group differences were determined using the Student t test (Mann Whitney U test) for numerical variables and \( \chi^2 \) test (Fisher exact test) for differences between proportions. The association between the TG/HDL ratio and insulin resistance was evaluated in a logistic regression analysis model. Statistical value was established with a 95% confidence interval or \( p <0.05 \). Data were analyzed using the SPSS v.15.0 statistical package (SPSS Inc., Chicago IL).

Results

Screening was performed in 189 subjects. Twelve subjects (6.3%) were excluded from the analysis because they did not meet the inclusion criteria or because exclusion criteria were found. A total of 177 apparently healthy subjects with a mean age of 38.6 ± 13.2 years were included in the study. There were 117 (66.1%) females and 60 (33.9%) males. Of these subjects, 145 (93 females and 52 males) were included in the IR group, and 32 subjects (24 females and 8 males) were included in the group without IR. Clinical and biochemical characteristics of the participants are presented in Table 1. Subjects with IR presented higher systolic and diastolic arterial pressure compared to the individuals without IR. Similarly, these subjects had higher levels of fasting serum glucose and post-load, total cholesterol, HDL-cholesterol, TGs, fasting insulin, HOMA-IR and a higher TG/HDL ratio.

Of the total population, a nonsignificant correlation was found (\( r = 0.138, p = 0.066 \)) and concordance (\( \kappa = 0.19 \)) between the HOMA-IR index and the TG/HDL ratio. IR was detected in 145 (81.9%) subjects. A high TG/HDL ratio was detected in 89 (61.3%) and 12 (37.5%) subjects in the groups with and without IR, respectively (Figure 1).
Triglycerides/HDL-cholesterol ratio and insulin resistance

The evidence suggests that IR probably precedes the onset of CVD, conditions in which there are metabolic, inflammation and thrombosis disorders. Many factors increase the risk for a subject to develop IR including genetic predisposition, sedentary lifestyle, and medications, in addition to other chronic diseases associated with this condition such as obesity, diabetes, SAH, and atherosclerosis. Considering that prevention is the top priority, we must find and identify the patient who acquires or is at risk of developing IR prior to the onset of the disease in order to delay or prevent its onset.5-6,20,21

One of the most widely used validation measures for IR is the HOMA-IR index, which uses the determination of fasting insulin and glucose; however, this is mainly used for clinical research purposes. For daily clinical practice, it is necessary to use other easily applied measurements in the general population. An alternative has recently been proposed for the identification of IR and uses the determination of TGL and fasting glucose (TyG index).23

Due to the association that exists between dyslipidemia and IR, one of the indexes that has been used to evaluate the ratio is the atherogenic index for TGL/HDL because it has been shown that obese individuals frequently present IR and alterations in lipid metabolism such as elevated concentrations of TG-rich lipoproteins and other chole-

### Table 1. Clinical and biochemical characteristics of the study participants

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>With IR</th>
<th>Without IR</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>38.6 ± 13.2</td>
<td>38.5 ± 13.2</td>
<td>40.4 ± 14.3</td>
</tr>
<tr>
<td>Females (n, %)</td>
<td></td>
<td>124 (65.6%)</td>
<td>93 (64.1%)</td>
<td>24 (75.0%)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>29.1 ± 5.4</td>
<td>29.4 ± 5.4</td>
<td>27.9 ± 5.7</td>
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<tr>
<td>WC (cm)</td>
<td></td>
<td>91.0 ± 15.6</td>
<td>92.0 ± 16.2</td>
<td>87.7 ± 13.6</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td></td>
<td>118.0 ± 15.7</td>
<td>119.2 ± 16.4</td>
<td>112.2 ± 11.0</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td></td>
<td>77.9 ± 11.7</td>
<td>78.7 ± 12.3</td>
<td>74.3 ± 7.0</td>
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<tr>
<td>Fasting glucose (mg/dL)</td>
<td></td>
<td>101.9 ± 45.0</td>
<td>94.1 ± 12.3</td>
<td>83.3 ± 6.4</td>
</tr>
<tr>
<td>Glucose post-load (mg/dL)</td>
<td></td>
<td>107.5 ± 71.2</td>
<td>93.5 ± 17.2</td>
<td>77.3 ± 11.4</td>
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<tr>
<td>TC (mg/dL)</td>
<td></td>
<td>202.9 ± 62.2</td>
<td>205.1 ± 67.2</td>
<td>184.7 ± 37.2</td>
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<tr>
<td>HDL-c (mg/dL)</td>
<td></td>
<td>42.3 ± 12.6</td>
<td>41.8 ± 12.0</td>
<td>45.3 ± 15.8</td>
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<tr>
<td>TG (mg/dL)</td>
<td></td>
<td>185.9 ± 201.6</td>
<td>183.2 ± 103.3</td>
<td>117.5 ± 70.5</td>
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<tr>
<td>Fasting insulin (µU/mL)</td>
<td></td>
<td>20.4 ± 12.2</td>
<td>22.4 ± 12.4</td>
<td>9.9 ± 2.2</td>
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<td>HOMA-IR index</td>
<td></td>
<td>5.3 ± 4.1</td>
<td>5.2 ± 3.2</td>
<td>2.0 ± 0.5</td>
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<tr>
<td>TG/HDL-c ratio</td>
<td></td>
<td>5.2 ± 6.5</td>
<td>5.2 ± 4.6</td>
<td>3.1 ± 2.7</td>
</tr>
</tbody>
</table>

* p < 0.05.

IR, insulin resistance; BMI, body mass index; WC, waist circumference; SAP, systemic arterial pressure; DAP, diastolic arterial pressure; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol.

Figure 1. Relation between triglycerides/HDL-elevated cholesterol in study groups.

The TG/HDL ratio was significantly associated with IR (OR 2.64, 95% CI = 1.12—6.29).

**Discussion**

Currently, one of the priorities in medicine is prevention and considering the health problems with which we live, the prevention of CVD and of the associated factors peak in the health system.
In addition, TG content in liver and muscle tissues is a determining factor for the development of IR. These findings support the important role played by TGs in IR. Hence, the results of this study showed a significant association, which translates into the possibility that the ratio between elevated TG/HDL suggests the presence of IR. It should be noted that between the HOMA-IR index and TG/HDL ratio, correlation was not significant and concordance was low. This may be due to the size of the study sample. The MESYAS study conducted by Cordero et al. in Spain revealed the presence of the TG/HDL ratio as part of the MetS and provides cut-off points of >2.75 in males and >1.65 in females to be able to establish their relationship. Other studies conclude that this atherogenic index is a predictor of CVD and first CV event. However, there are conflicting results such as that reported by Sumner et al. showing that the TG/HDL ratio is not a good marker of IR in African-American subjects, with one of the explanations being racial differences and the lipoprotein kinase activity responsible for the metabolism of TG. The results of our study establish the association of elevated TG/HDL ratio with IR, similar to the study of Kannel et al.

Currently, when discussing a patient with IR, we think immediately of the presence of the MetS entity, and we know that our duty is to identify it. We must begin the preventive process for the risk of developing chronic degenerative diseases, especially CVD, the leading cause of morbimortality. It becomes imperative to establish criteria for early identification of risk factors associated with not only the MetS but also one of its main components, IR, because early identification will prevent the development of any chronic diseases with which it interacts. According to the results obtained in this study, to determine an elevated TG/HDL ratio allows the assessment of the onset of treatment to reduce IR as well as to initiate prevention and appropriate treatment of dyslipidemia according to the therapeutic goals proposed by the ATP III. In turn, reduction of TG levels is a consideration. This latter aspect is based on the results obtained in this study, to determine an elevated TG/HDL ratio as part of the MetS and provides cut-off points of >2.75 in males and >1.65 in females to be able to establish their relationship. Other studies conclude that this atherogenic index is a predictor of CVD and first CV event. However, there are conflicting results such as that reported by Sumner et al. showing that the TG/HDL ratio is not a good marker of IR in African-American subjects, with one of the explanations being racial differences and the lipoprotein kinase activity responsible for the metabolism of TG. The results of our study establish the association of elevated TG/HDL ratio with IR, similar to the study of Kannel et al.

Our study has several limitations that should be considered. First, the causal and temporality between the TG/HDL ratio and IR cannot be established with certainty due to the study design. Therefore, there is no assurance that elevated TG/HDL ratio is a risk factor for the development of IR or simply an associated epiphenomenon. Second, the low conformation of the group without IR may be related to the size of our sample, even though this is how our population behaved.

The main strength of this study was the inclusion of incident cases with IR but without diabetes. In addition, groups were matched by age, gender and obesity markers, which minimize the bias analysis.

In conclusion, the results of this study showed that elevated TG/HDL ratio is associated with the presence of IR in apparently healthy individuals. Further studies are needed that demonstrate consistency in the association between TG/HDL ratio, IR and various metabolic disorders that comprise the MetS and CVD. In addition, future studies can determine the use of this ratio as a marker of IR, which requires an appropriate study design and adequate sample size to validate.

References

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