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TG/HDL-C RATIO AS CARDIO-METABOLIC BIOMARKER EVEN IN NORMAL WEIGHT WOMEN

G. Borrayo[1], L. Basurto[2], E. González-Escudero[2,3], A. Diaz[2], A. Vázquez[2], L. Sánchez[3], G.O. Hernández-González[3], S. Barrera[4] , J.A. Degollado[5], N. Córdova[2], F. Avelar[5]

[1]Cardiology Hospital National Medical Center, [2]Endocrine Research Unit, National Medical Center, Instituto Mexicano del Seguro Social, [3]Universidad Veracruzana, School of Medicine, [4]School National of Medicine, Instituto Politécnico Nacional, [5]National Medical Center, Department of Radiology, Mexico City, México

Abstract

Context. Despite that the Triglycerides/High Density Lipoprotein Cholesterol (TG/HDL-C) ratio has been associated with insulin resistance and cardiovascular disease, some outcomes differ between populations.

Objective. The objective of this study was to evaluate the association between TG/HDL-C ratio and cardio-metabolic risk factors in both obese and normal weight women.

Design. Cross sectional, from January to December of 2015.

Subjects and Methods. Two hundred and fifty three women aged 40 to 60 years. Anthropometric and laboratory measurements were performed. Insulin resistance was measured by the homeostasis model assessment for insulin resistance (HOMA-IR). All participants underwent a Doppler ultrasound to measure intima-media thickness of carotid artery (cIMT).

Results. TG/HDL-C ratio correlated with body mass index (r=0.194, p=0.01), and visceral adipose tissue (r=0.193, p=0.002). Additionally, TG/HDL-C correlated with glucose (r=0.367, p=0.001), insulin (r=0.354, p=0.001) and HOMA-IR (r=0.396 p=0.001). TG/HDL-C was associated with prediabetes, Odds Ratio (OR) was 1.83 (95%CI 1.07-3.13) and insulin resistance 3.27 (95%CI 1.78-6.01), and this risk remains in normal weight women 4.7 (95%CI 1.2-17.81) for prediabetes and 4.38 (95%CI 1.42-13.84) for insulin resistance. No significant risk for cIMT.

Conclusion. A TG/HDL-C ratio ≥ 3.0 is a potential risk factor for prediabetes and insulin resistance in women 40-60 years, even in normal weight women.

Key words: TG/HDL-C, Insulin Resistance, Carotid Intima-Media Thickness, Prediabetes.

INTRODUCTION

It is well known that obesity correlates with the risk of developing diabetes or cardiovascular disease (1). The prevalence of overweight and obesity in Mexican women is 73% (2) and is estimated that every 15 minutes a woman dies secondary to a cardiovascular disease in the country (3). Despite this association, there are obese patients without metabolic abnormalities who are described as "metabolically healthy obese patients" (4). Also, there are normal weight subjects with metabolic abnormalities, "metabolically unhealthy normal weight" (5). Therefore, finding risk factors to target in order to prevent or reduce the risk of mortality has become necessary even in normal weight women. However, there are no universal criteria for distinguishing metabolically healthy from metabolically unhealthy (6).

Some identified factors associated with cardio-metabolic risk are hyperinsulinemia, insulin resistance (IR)(7) and carotid intima-media thickness (cIMT) (8). However, the accurate measurement of insulin or IR parameters is complicated in the clinical practice. Recently it has been observed that the Triglycerides/ High Density Lipoprotein Cholesterol (TG/HDL-C) ratio can identify IR, cardio-metabolic risk and cardiovascular disease (9, 10). Nevertheless, there are discrepancies in the discriminatory power and the cutoff points among populations (11-13). As such, it is expected that a commonly available and standardized measurement of TG/HDL-C ratio could help clinicians to identify patients who are not only IR but also display the characteristic of dyslipidemia (14). In some studies, TG/HDL-C ratio has demonstrated a similar or better sensibility than the metabolic syndrome criteria(13, 15), but with variations in the cutoff points within the population. Interestingly, some prospective studies have been developed in order to identify if TG/HDL-C ratio could predict a major cardiovascular outcome, or is just a useful parameter in hypertensive subjects (10).

*Correspondence to: María de Lourdes Basurto Acevedo MD, Instituto Mexicano del Seguro Social, Unidad de Investigación en Enfermedades Endocrinas, Av. Cuauhtémoc 330, Colonia Doctores, DF, Mexico, Ciudad de México, 06720, Mexico, E-mail: uiendocrinologia@gmail.com

To our knowledge, only a few studies have compared the TG/HDL-C ratio with IR, or independent markers of cardiovascular disease such as carotid intima-media thickness (cIMT) and prediabetes, even in normal weight women.

The present study was performed to address this issue by evaluating the efficacy of TG/HDL-C ratio as a simple way to identify cardiometabolic risks in both obese and normal weight women.

SUBJECTS AND METHODS

A cross-sectional comparative study was performed in 253 women aged 40 to 60 years who consecutively attended the Endocrine Medical Research Unit, of the National Medical Center, Mexican Social Security Institute (Unidad de Investigación Médica en Enfermedades Endocrinas, Centro Medico Nacional IMSS). The exclusion criteria included women with an established diagnosis of diabetes mellitus, renal or liver failure, chronic infections, endocrine or blood disorders, history of cardiovascular disease or thrombosis. Participants who were found to be under hormone treatment were also excluded. The protocol was approved by the Scientific Committee of the Instituto Mexicano del Seguro Social. Participants were informed about the study and provided their written informed consent.

Clinical assessment

The medical history of the participants was taken and their anthropometric parameters were also recorded. Heights and weights were measured without shoes and with light clothing using a Bame weight and height scale. With the participant standing, the waist circumference was measured at the midpoint of the distance between the iliac crest and the inferior border of the last rib. This measurement was performed at the end of expiration. Systolic and diastolic blood pressures were recorded using an aneroid sphygmomanometer. Body Mass Index (BMI) in kg/m^2 was calculated. For analysis, subjects were separated into two categories by BMI: BMI < 25 for normal weight women and ≥25 for overweight and/or obese.

We defined prediabetes as Impaired Fasting Glucose (IFG) 100-125mg/dL and/or HbA1c (5.7-6.4%) in accordance with ADA criteria(16).

Body composition analysis

Body composition was assessed with a 353 ioiJAWON Body Composition analyzer. Bioelectrical impedance was analyzed in the morning after a 12-hour fast and adequate hydration. Bioelectrical impedance was measured with the patient upright, wearing light clothing, and without shoes. The analyzer measured weight within an accuracy of 0.1kg, as well as body impedance (in ohms), with calculation of the Visceral Adipose Tissue (VAT) and the percentage of Total Body Fat.

Carotid intima-media thickness assessment

The cIMT was measured with the patient in supine position with neck slightly in extension, both common carotid arteries were assessed using a high resolution B-Mode ultrasonography device (Aloka-α7 lineal multifrequency transductor). The average IMT of the posterior wall of the right and left common carotid arteries and the presence of atheromatous plaque were evaluated according to the Mannheim Consensus (17). All measurements were taken by the same operator. At-risk group was defined for those women with cIMT >0.70 mm and/or the presence of atheromatous plaque (18).

Laboratory procedures

Venous blood samples were collected after an overnight fast of 10 hours between 7.30 am and 8 am. After centrifuging at 3500 rpm for 15 minutes to separate the serum, 500 µL-aliquots were prepared and stored at −70°C until assayed. Serum glucose, cholesterol, triglycerides and HDL-C were determined using enzymatic methods in the semiautomatic chemical Ekem Kontrol Lab Analyzer.

Insulin was measured by a solid-phase radioimmunoassay (Millipore, Billerica; Mississippi, USA); the sensitivity of this assay was 2 µU/ mL and the intra- and inter-assay coefficient of variation was 4.0% and 8.6%, respectively. IR was evaluated through homeostasis model assessment (HOMA) according to the method of Matthews *et al.* (19): HOMA-IR = insulin (mU/L) X fasting glucose (mmol/L) / 22.5. Using a cutoff of 3.0, the subjects were classified as IR if HOMA-IR ≥3.0 and non-IR if <3.0(20).

To identify the optimal cut-off for TG/HDL-C ratio, Receiving Operating Characteristics Curve (ROC) was performed to examine the discriminatory power of TG/HDL-C ratio for IR with an Area Under the Curve (AUC) of 0.716 (95%IC 0.649-0.783), using a 3.0 cut-point equal with the one used in a previous Mexican study (20). The sensitivity and specificity were 66 and 69% respectively for predicting IR. In this way we made two groups: low risk group <3.0 and high risk group ≥3.0.

Statistical analysis

Prediabetes, IR, and cIMT were considered as nominal variables. All the other variables were considered as quantitative.

In order to identify the distribution of the variables, skewness, kurtosis and Kolmogorov-Smirnov were conducted. These parametric variables are represented as mean and standard deviation (M+SD), while non-parametric variables are shown as median and interquartile ranges 25-75.

To determine differences between groups according to TG/HDL-C ratio, t-Student test for independent variables and Mann-Whitney U test were performed for parametric or non-parametric variables respectively. For nominal variables, Chi-Square test was performed. Therefore, to define correlations, we used the Spearman correlation coefficient and for associations, Odds Ratio (OR) and confidence interval (95%CI). A p value < 0.05 was considered statistically significant. Analysis was performed using the software program SPSS 21.

RESULTS

A total of 253 women were evaluated with a mean age of 52.3 ± 5.85 years. 76.3% were overweight or obese (mean BMI 28.84 Kg/m^2 ± 5.08). The median of IR was 3.57 assessed by HOMA, 62.7% had IR with a cut-off of 3.0 and 54.3% had high risk of cardiovascular disease assessed by cIMT. The median of TG/HDL-C ratio was 2.70 with an interquartile range (1.82 - 4.13). The other characteristics of the participants are as shown in Table 1.

There was no significant difference between groups by age, systolic and diastolic blood pressure, HDL-C, or LDL-C. In comparison to women with TG/HDL-C ratio <3.0, the group with TG/HDL-C ratio >3.0 had an increased BMI, IR, VAT (Table 2).

Table 1. Characteristics of study participants

Variable	n	
Age (years)	253	52.3 ± 5.8
Weight (Kg)	253	68.8 ± 12.5
Body Mass Index (Kg/m^2)	253	28.8 ± 5
Normal	60	23.7 %
Overweight	99	39.1 %
Obese	94	37.2 %
Waist (cm)	253	105.5 ± 10.4
Visceral Adipose Tissue (cm^2)	253	138.4 ± 57.8
Total Fat (%)	253	37.7 ± 4.9
Systolic Blood Pressure (mmHg)	253	111 ± 14
Diastolic Blood Pressure (mmHg)	253	74 ± 9
Glucose (mg/dL)	253	86.7 ± 19.6
Normal	221	87.4%
Impaired Fasting Glucose	32	12.6%
HbA1C (%)	247	5.54 ± 0.5
Normal	158	64%
Prediabetes	89	36%
Insulin (mU/L)*	253	17.0 (13.0 - 24.8)
HOMA-IR *	253	3.57 (2.60 - 5.32)
Normal	94	37.2%
Insulin Resistance	159	62.8%
Triglycerides (mg/dL)*	253	140.0 (110.0 - 193.0)
Total-Cholesterol (mg/dL)	253	233.70 ± 47.9
HDL-C (mg/dL)	253	55.0 ± 15.0
LDL-C (mg/dL)	253	145.6 ± 42.9
cIMT (mm)	188	0.69 ± 0 .11
Normal Risk	86	45.7 %
High Risk	102	54.3 %
TG/HDL-C ratio*	253	2.7 (1.8 - 4.1)
Low Risk	159	62.8%
High Risk	94	37.2%

Parametric variables are represented as mean + standard deviation, HOMA-IR, homeostasis model assessment of insulin resistance, TG/HDL-C ratio Low Risk: <3.0, High Risk: >3.0

* Non parametric variables are represented as median and interquartile ranges.

Table 2. Characteristics of participants according to TG/HDL-C ratio > 3.0 cut-off point

	TG/HDL-C ratio		*p*-Value
	<3.0 (62.8%)	≥3.0 (37.2%)	
Age (years)	52.4 ± 5.9	52.2 ± 5.6	NS
Weight (kg)	67.6 ± 12	70.9 ± 13	0.045
Body Mass Index (Kg/m^2)	28.2 ± 4.9	29.9 ± 5.1	
Normal	26.4%	19.1%	0.009
Overweight	43.4%	32.0%	0.012
Obesity	30.2%	48.9%	
Waist (cm)	90.4 ± 11.5	95 ± 12.1	0.003
Visceral Adipose Tissue (cm^2)	132.7 ± 59.2	148.1 ± 54.2	0.041
Total Fat (%)	37.5 ± 4.8	38 ± 5.1	NS
Systolic Blood Pressure (mmHg)	111.1 ± 13.4	112.8 ± 15.1	NS
Diastolic Blood Pressure (mmHg)	74.8 ± 9.2	75.2 ± 9.3	NS
Glucose (mg/dL)	83.3 ± 18.6	92.6 ± 20	<0.001
Normal Glucose	93.7%	76.6%	<0.001
Impaired Fasting Glucose	6.3%	23.4.%	
HbA1c (%)	5.4 ± 0.4	5.6 ± 0.3	0.044
<5.7	67.1%	58.7%	0.184
(5.7-6.4)	32.9%	41.3%	
Insulin (mU/L)*	15.9 (12.1 - 22.5)	19.9 (15.4 - 29.6)	<0.001
HOMA-IR*	3.2 (2.3 - 4.7)	4.4 (3.1 - 6.8)	<0.001
Normal	46.5%	20.9%	<0.001
Insulin Resistance	53.5%	79.1%	
Triglycerides (mg/dL)*	118 (94 - 142)	209 (177 - 257.5)	<0.001
Total Cholesterol (mg/dL)	233.3 ± 47.2	234.3 ± 49.1	NS
HDL–C (mg/dL)	61.3 ± 13.2	44.4 ± 11.5	<0.001
LDL–C (mg/dL)	147 ± 43.6	143.3 ± 41.6	NS
cIMT (mm)	0.69 ± 0.10	0.7 ± 0.11	NS
Normal Risk	51.9%	36.8%	0.81
High Risk	48.1%	63.2%	

HOMA-IR, homeostasis model assessment of insulin resistance; cIMT, Carotid intima-media thickness. Parametric variables are represented as mean and standard deviation.
*Non-parametric variables are represented as median and interquartile range.

Table 3. Correlations between TG/HDL-C ratio and metabolic variables

Variable	r	*p -Value*
Glucose (mg/dL)	0.367	<0.001
HbA1c (%)	0.167	0.009
Insulin (mU/dL)	0.354	<0.001
HOMA-IR	0.396	<0.001
Total Fat (%)	0.183	0.004
Visceral Adipose Tissue (cm^2)	0.193	0.002
Total Cholesterol (mg/dL)	0.38	NS
LDL-C (mg/dL)	-0.010	NS
cIMT (mm)	0.002	NS

HOMA-IR: Homeostasis model assessment of insulin resistance, cIMT: Carotid intima-media thickness.

A positive correlation was found of TG/HDL-C ratio with BMI (r= 0.194, p= 0.01), waist circumference (r=0.203, p=0.001), VAT (r= 0.193, p=0.002), Total Fat (r= 0.183, p=0.004), also with glucose, HbA1c, insulin and HOMA-IR, but not with cIMT (Table 3).

Women with a TG/HDL-C ratio of ≥3.0 had a statistically significantly increased risk of prediabetes (OR 1.83, 95%CI 1.07-3.13) and IR (OR 3.27, 95%CI 1.78-6.01). However, no statistical significance was found for cIMT. Meanwhile, overweight and/or obese women had a higher OR of prediabetes 3.52 (95%CI 1-67-6.7) and IR 4.09 (95%CI 2.27-7.58), however, cIMT remained with no statistical significance. Moreover, a subgroup of women with normal weight and TG/HDL-C ratio ≥3.0 has 4.7 (95%CI 1.2-17.81) risk of prediabetes and 4.38 (95%CI 1.48-13.84) risk of IR. Nonetheless, there was no significance with cIMT (Fig. 1).

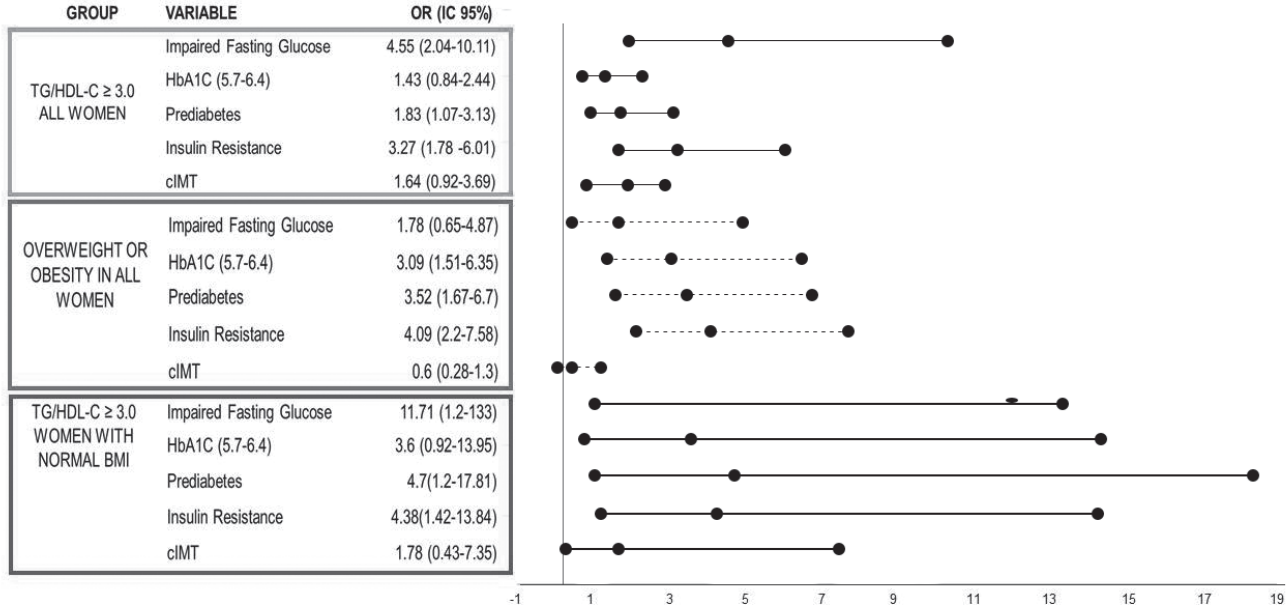

Figure 1. Forest Plot using association by Odds Ratio (OR) of cardiometabolic risk factors among three groups 1) All women with TG/HDL ratio ≥ 3.0, 2) Women with overweight and obesity and 3) Women with normal BMI and TG/HDL-C ratio ≥ 3.0.
cIMT: Carotid intima-media thickness.

DISCUSSION

This study demonstrated that TG/HDL-C ratio is a predictor of insulin resistance and prediabetes in women aged 40-60 years, even in normal weight women. Previous studies have shown that TG/HDL-C ratio is able to identify IR and increased cardiometabolic risk, including the development of type 2 diabetes mellitus in populations of different ages (21, 22). However, studies in women aged 40 to 60 years are limited.

In a study conducted by Salazar *et al.*, which included both women and men aged 17 to 80 years, TG/HDL-C ratio had the ability to identify IR and cardiometabolic risk comparable with that achieved using the harmonized version of the metabolic syndrome(15),(23). Another study by González-Chavez *et al.* conducted in a 177 apparently healthy Mexican subjects, confirmed that TG/HDL-C ratio >3.0 was associated with presence of IR (OR of 2.64, 95%CI 1.12-6.29)(20). In a younger Mexican population it was found that TG/HDL-C ratio identified a greater number of IR subjects than the metabolic syndrome criteria, suggesting that TG/HDL-C ratio >2.5 for women is clinically useful in detecting IR in apparently healthy young individuals (24). In the present study, the cut-off point was identified by ROC curve. This cut-off was similar to that reported by Gonzalez-Chavez *et al.* (20), in the same way as the BMI. By contrast, in the study by Murguía *et al.* (24), the population was younger and had a lower BMI.

Different from other studies that include men and women (10, 15, 20, 22, 24), the present study focused on women, not only because there are important differences in the distribution of risk factors between the genders, but also because women at this age increases their cardiometabolic risk.

TG/HDL-C ratio has been proposed as atherogenic marker (25, 26). This marker correlates with LDL phenotype and small HDL particles (27, 28). TG/HDL-C ratio strongly predicts risk of myocardial infarction (26, 29). Moreover, among women with suspected ischemia, the TG/HDL-C ratio is a powerful independent predictor of all cause of mortality and cardiovascular events (26). Recently, in other large population survey, with participants of 20 to 90 years old, TG/HLD-C ratio was associated with cardiovascular disease and all cause of mortality, included coronary heart disease (30).

Carotid IMT is considered a surrogate marker for atherosclerotic cardiovascular disease (31). In the present study carotid IMT was measured for identifying women at future risk for cardiovascular disease, nonetheless, TG/HDL-C ratio was not associated with IMT. By contrast, in a clinical trial conducted

by Maki *et al.* (32), TG/HDL-C ratio was predictor of IMT progression, however, this study enrolled patients at moderate cardiovascular risk, higher carotid IMT and did not report gender-specific risk ratios. Further studies are required to clarify the relationships between cIMT and TG/HDL ratio.

One limitation of this study is the lack of glucose tolerance curve to identify prediabetes. Nonetheless, in the present study prediabetes criteria were defined using but the impaired fasting glucose and HbA1c levels (16), which may have a close correlation to identify prediabetes (33). The main strength of this study is that it was conducted in women among 40 to 60 years old. Study of women is important because during this stage, some risk factors, such as insulin resistance and abdominal fat increase, which, together with other changes, such as those occurring in lipid profile, increase cardio-vascular risk (34). Although in this study the participants were not grouped as premenopausal and postmenopausal women. In a previous study it was found that TG/HDL-C ratio was different between premenopausal and postmenopausal women (35). The authors suggested that the difference could be attributed to age and abdominal visceral fat modification (35). These variables were analyzed in the present study. However, it is necessary to design studies to evaluate whether the menopausal state affects the efficacy of TG/HDL-C ratio to identify cardio-metabolic risk.

In conclusion, TG/HDL-C ratio was associated with cardio-metabolic risk factors, even in normal weight women who are insulin resistant and who go on to develop diabetes. This is important, since this marker has the ability to identify equally lean and obese women before development of manifest disease.

Conflict of interest

Authors declare no conflict of interest.

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