Use of the triglyceride/high-density lipoprotein cholesterol ratio to identify cardiometabolic risk: impact of obesity?

M R Salazar,[1,2] H A Carbajal,[2] W G Espeche,[1,2] M Aizpurúa,[3] A G Marillet,[4] C E Leiva Sisnieguez,[1,2] B C Leiva Sisnieguez,[1,2] R N Stavile,[1,2] C E March,[1,2] G M Reaven[5]

[1]Hospital Universitario General San Martín, La Plata, Argentina
[2]Facultad de Ciencias Médicas, UNLP, La Plata, Argentina
[3]Hospital Municipal de Rauch, Buenos Aires, Argentina
[4]Hospital Municipal de San Andrés de Giles, Buenos Aires, Argentina
[5]Stanford University School of Medicine, Stanford, California, USA

Correspondence to
Dr MR Salazar, Hospital Universitario General San Martín, 14 n 320, La Plata, Buenos Aires 1900, Argentina;
salazarlandea@gmail.com

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ABSTRACT

There is evidence that the plasma concentration ratio of triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) identifies insulin resistance and increased cardiometabolic risk and outcome in apparently healthy individuals. Since use of the TG/HDL-C ratio to accomplish this task in persons over a wide range of adiposity has not been studied, the ability of previously defined sex-specific TG/HDL-C cut-points to identify increased cardiometabolic risk was evaluated in apparently healthy normal weight, overweight, and obese individuals. Data were analyzed from a population-based study of apparently healthy men (n=416) and women (n=893), subdivided into categories by body mass index (BMI, kg/m^2): normal weight (BMI 20.0–24.9), overweight (BMI 25.0–29.9) and obese (BMI 30.0–34.9). The adiposity groups were further stratified on the basis of their TG/HDL-C ratio into groups defined as being either at 'high risk' versus 'low risk' of cardiometabolic disease. Multiple cardiometabolic risk factors were compared between these subgroups, as was their degree of insulin resistance assessed by fasting plasma insulin concentration and homeostasis model assessment of insulin resistance. The proportion of high-risk individuals varied with BMI category, ranging from 14% (normal weight) to 36% (obese). However, within each BMI category high-risk individuals had a significantly more adverse cardiometabolic risk profile. Finally, the adjusted OR of being insulin resistant was significantly greater in those with a high TG/HDL-C ratio in the normal (3.02), overweight (2.86), and obese (2.51) groups. Thus, irrespective of differences in BMI, the TG/HDL-C ratio identified apparently healthy persons with a more adverse cardiometabolic risk profile associated with an increased prevalence of insulin resistance.

Significance of this study

What is already known about this subject?

- Insulin resistance exists in a significant number of apparently healthy individuals.
- The plasma triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) concentration ratio can help identify insulin resistance and predict adverse cardiometabolic risk and clinical outcomes in apparently healthy individuals.
- There is a direct relationship between body mass index (BMI) and magnitude of insulin resistance in apparently healthy individuals.

What are the new findings?

- Prevalence of 'high-risk' TG/HDL-C ratio was greater as BMI increased from normal (14%) to overweight to obese (36%).
- Irrespective of BMI category, persons at 'high risk' on the basis of their TG/HDL-C ratio were significantly more insulin resistant, associated with a more adverse cardiometabolic risk profile.
- The adjusted OR of being insulin resistant was significantly greater in those with a 'high' TG/HDL-C ratio in the normal (3.02), overweight (2.86), and obese (2.51) groups.

How might these results change the focus of research or clinical practice?

- The results presented showed that wide differences in obesity did not decrease the ability of the TG/HDL-C ratio to identify insulin resistance and enhanced cardiometabolic risk in a homogeneous ethnic/racial population using sex-specific cut-points. Thus, the TG/HDL-C ratio appears to offer a relatively simple way to identify the subset of apparently healthy persons who are insulin resistant, and at significantly greater cardiometabolic risk. From a research stand-point, a good deal needs to be learnt about how best to implement the clinical use of the TG/HDL-C ratio, for example, what are the 'best' cut-points, how effective will it be in different racial groups, does its effectiveness vary with clinical end point, etc. However, at a clinical level, this supports the initiation of appropriate interventions within the racial/ethnic group studied aimed at improving insulin sensitivity and thereby decreasing the risk of the multiple abnormalities and clinical syndromes associated with insulin resistance before they occur.

INTRODUCTION

Given the importance of insulin resistance in the pathogenesis of several clinical syndromes[1 2] identification of this metabolic defect in apparently healthy individuals would seem to be of significant clinical benefit. Since methods to specifically quantify insulin-mediated glucose disposal are not practical for use in a clinical

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setting, plasma glucose and/or insulin concentrations have been used to create a number of surrogate estimates.[3–5] Although many of these approaches are significantly correlated with direct measures of insulin sensitivity, they all suffer from the lack of a standardized insulin assay.[6] Thus, a specific value of any of the surrogate estimates used to identify insulin resistance based on measurement of plasma insulin concentration could not be universally applied.

In contrast to measurements of plasma insulin concentration, efforts of the Centers for Disease Control and Prevention's Lipid Standardization Program and Cholesterol Reference Method Laboratory Network have led to significant standardization of lipid and lipoprotein measurements. Since increases in plasma triglyceride (TG) and decreases in high-density lipoprotein cholesterol (HDL-C) are independently associated with insulin resistance,[7] efforts were initiated to see if these measurements might provide clinically useful surrogate estimates of insulin resistance.[8 9] The results indicated that both TG and HDL-C concentrations were significantly related to direct measures of insulin-mediated glucose disposal and associated cardiometabolic risk, and that the correlation was of somewhat greater magnitude using the plasma concentration ratio TG/HDL-C.

Subsequent studies have shown that in addition to identifying apparently healthy persons at increased cardiometabolic risk,[10–12] an elevated TG/HDL-C ratio also predicts incident cardiovascular disease (CVD) and type 2 diabetes.[11 12] However, it is now clear that absolute values of the TG/HDL-C ratio used to identify insulin resistance and increased cardiometabolic risk will vary as a function of sex and ethnic/racial background,[10 13] and must be taken into consideration when evaluating the predictive ability of the TG/HDL-C ratio. On the other hand, although differences in degree of adiposity profoundly affect insulin resistance and associated cardiometabolic risk factors,[14] we are unaware of any information concerning how differences in degree of adiposity might affect the clinical utility of the TG/HDL-C ratio to identify apparently healthy, insulin-resistant persons at increased cardiometabolic risk. The current analysis will address this issue by using previously established sex-specific values[10] of the TG/HDL-C ratio that identified increased cardiometabolic risk in apparently healthy individuals of European ancestry to evaluate their clinical utility when applied to individuals varying significantly in degree of adiposity.

MATERIALS AND METHODS

The experimental population consisted of apparently healthy individuals who had participated in either the Rauch project (Rauch, Buenos Aires, Argentina) or the PROCER project (San Andrés de Giles, Buenos Aires, Argentina). Both projects were community-based surveys of cardiometabolic risk performed on random samples.[15 16] Those with known CVD, heart disease, or taking pharmacological agents to treat diabetes were excluded from this analysis. Ethical Committee permission for these studies was provided by the relevant health authorities in the two communities.

San Andrés de Giles and Rauch are small rural towns located in the Pampean region of Argentina, near Buenos Aires city. This region had a major influx of immigrants throughout the 19th and 20th centuries, the vast majority of whom were from Italy or Spain. Individuals of African and Asian ethnicity are a small minority of the population in this area, but there is undoubtedly some genetic admixture between subjects of European ancestry and Amerindian. There are no quantitative data concerning the genetic admixture in Rauch or San Andrés de Giles, but it seems reasonable to assume it would be comparable to the results of the 2006 study performed in Buenos Aires which demonstrated a genetic admixture of ~80% European, 16% Amerindian, and 4% African.[17]

The method of sampling, the socioeconomic features, and the prevalence of cardiovascular risk factors of the two populations have been published previously.[15 16] In brief, the surveys were performed on simple random samples of subjects aged 15–80 years who lived in the chosen blocks (Rauch n=1307, PROCER n=1591). Blood pressure (BP) was measured in sitting position, after a minimum rest period of 5 min, using a mercury sphygmomanometer. Phase I and V Korotkoff sounds were used to identify systolic BP and diastolic BP, respectively, and values were averages of three different measurements separated by 2 min from one another. Weight was determined with subjects wearing light clothing and no shoes. Height was also measured without shoes, using a metallic metric tape. Body mass index (BMI) was calculated, and concentrations of plasma glucose, total cholesterol, TG, HDL-C, and fasting plasma insulin (FPI) were determined after an overnight (12-hour) fast. Low-density lipoprotein cholesterol (LDL-C) levels were estimated by the Friedewald formula.[18] Plasma for the insulin measurements was extracted by centrifugation (15 min at 3000 rpm) and frozen at −20°C until assayed. FPI concentrations in the Rauch population were determined using an immunoradiometric assay, with two monoclonal antibodies against two different epitopes of the insulin molecule. The interassay and intra-assay coefficients of variation were 8.0% and 3.8%, respectively, with the lowest detectable level of 1.4 pmol/L. FPI concentrations in the San Andrés de Giles population were determined using a solid phase chemiluminescent assay, using commercially available kits (Immunolite Diagnostic Products, Los Angeles, California, USA), with an analytic sensitivity of 1.4 pmol/L, interassay and intra-assay coefficients of variation <8%, and proinsulin cross-reactivity <8.5. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula (insulin (μU/mL)×glucose (mmol/L)/22.5).[19]

In order to avoid the potential confounding impact of extreme outliers, subjects with TG concentrations >500 mg/dL and/or HDL-C concentrations >100 mg/dL and/or BMI<20 or >35 were excluded from the analysis. Participants with positive histories of diabetes or fasting glucose concentrations >126 mg/dL were also excluded. The present analysis was performed with the remaining 893 women (mean age 46±18 years) and 416 men (mean age 47±17 years).

The experimental population was stratified according to their BMI into three categories: (1) normal weight 20–24.9 kg/m^2, (2) overweight 25.0–29.9 kg/m^2, and (3) mild obesity 30.0–34.9 kg/m^2. Individuals within each BMI categories were further subdivided into two groups, defined as having either a high or a low TG/HDL-C ratio based on

previously described sex-specific cut-points, >2.5 and >3.5 for women and men, respectively.[10] Values for age, systolic BP, diastolic BP, BMI, total cholesterol, HDL-C and LDL-C, glucose, TG, and TG/HDL-C ratio, FPI, and HOMA-IR were compared within each BMI category between subjects with a high versus low TG/HDL-C ratio using independent samples 't-test'. Experimental variables between BMI categories were compared using analysis of variance with post hoc analyze using Tukey's test and χ^2 for continuous variables and categorical variables, respectively.

HOMA-IR was used as the primary surrogate estimate of insulin resistance.[19] FPI concentration, shown to correlate significantly with specific measures of insulin-mediated glucose disposal, as well as with HOMA-IR,[20 21] was also used to compare experimental groups. Twenty-five percent of the population with the highest HOMA-IR values was classified as being insulin resistant. This cut-point was based on a prospective study in which 647 apparently healthy factory workers were followed for 12–15 years, showing that a significant increase in coronary heart disease (CHD), glucose intolerance, and hypertension developed in the 25% with the highest postglucose challenge insulin concentrations at baseline, compared with the other 75% of the population.[22]

Since there were two different populations, and two different insulin assay methods, each population was divided into quartiles on the basis of their HOMA-IR values and the respective quartiles from each population combined for analysis. HOMA-IR quartiles were calculated separately for each sex and for each sample, and subjects were assigned to a given HOMA-IR quartile according to their relative positions in the HOMA-IR distribution curve (men and women, Rauch and San Andrés de Giles separately), and not according their absolute HOMA-IR values. Remarkably, the cut-points used to define insulin resistance in Rauch and San Andrés de Giles were reasonably comparable (2.1 vs 2.5 in women and 2.0 vs 2.5 in men). In addition, the models used in order to estimate risk were adjusted for origin of the sample.

Prevalence of insulin resistance was compared using χ^2. Also, in each BMI category, OR of individuals with high TG/HDL-C ratio (compared with those with low TG/HDL ratio) being insulin resistant were estimated using three models of binary logistic regression, (1) unadjusted; (2) sex and age adjusted; and (3) sex, age and origin of the sample.

All significant tests were two-tailed, and p values <0.05 were considered statistically significant and statistical analyses were performed using SPSS (SPSS, Chicago, Illinois, USA).

RESULTS

Demographic and cardiometabolic risk factors of the three BMI groups are compared in table 1. These data show that every individual cardiometabolic risk factor was more adverse in the overweight and obese populations when compared with normal weight subjects. The differences between overweight and obese persons was less generalized, and basically limited to variables related to glucose and insulin metabolism, with higher values for plasma glucose, FPI, HOMA-IR, and percent classified as being insulin resistant in the obese subgroup.

Table 2 compares the cardiometabolic risk factors in those with a low TG/HDL-C ratio versus a high ratio within each weight category. Only 14% of the normal weight group had a high TG/HDL-C ratio, but these individuals had a significantly worse cardiometabolic risk profile than the remaining normal weight subjects; the only exception being comparable fasting plasma glucose concentrations. The prevalence of a high TG/HDL-C ratio increased to 32% in the overweight population, and every cardiometabolic risk factor was significantly more adverse than in those with a low TG/HDL-C ratio. The prevalence of a high TG/HDL-C ratio was greatest (36%) in the obese

Table 1 Cardiometabolic risk profile according to BMI categories (normal weight, overweight, obese)

	Normal BMI 20–24.9 N=514	Overweight BMI 25.0–29.9 N=541	Obese BMI 30.0–34.9 N=254	p*		
	Mean±SD	Mean±SD	Mean±SD	Normal vs overweight	Normal vs obese	Overweight vs obese
Age (years)	41±18	49±16	50±16	<0.001	<0.001	0.515
Women (%)	74	63	67	<0.001	0.032	<0.001
Systolic BP (mm Hg)	121±17	130±19	132±19	<0.001	<0.001	0.702
Diastolic BP (mm Hg)	73±12	79±13	80±13	<0.001	<0.001	0.959
BMI (kg/m^2)	22.7±1.4	27.2±1.4	32.1±1.4	<0.001	<0.001	<0.001
Cholesterol (mg/dL)	200±46	217±47	219±45	<0.001	<0.001	0.871
HDL-C (mg/dL)	62±14	60±14	58±13	0.011	0.001	0.334
LDL-C (mg/dL)	116±42	129±42	131±40	<0.001	<0.001	0.792
Triglycerides (mg/dL)	106±50	141±68	147±65	<0.001	<0.001	0.393
Glucose (mg/dL)	90±10	94±11	97±11	<0.001	<0.001	<0.001
FPI (μU/mL)	6.1±3.7	7.8±5.4	10,6±6.8	<0.001	<0.001	<0.001
HOMA-IR	1.4±0.9	1.8±1.3	2.5±1.7	<0.001	<0.001	<0.001
Insulin resistance (%)	13	24	42	<0.001	<0.001	<0.001

*ANOVA with post hoc analysis using Tukey's test for continuous variables and χ^2 for categorical variables.
ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; FPI, fasting plasma insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance. LDL-C, low-density lipoprotein cholesterol.

Table 2 Comparison of cardiometabolic risk profile between individual with 'low' vs. 'high' TG/H-C ratio stratified in normal weight, overweight and obese individuals

	Normal weight			Overweight			Obese		
	Low TG/HDL-C n=444 (86%)	High TG/HDL-C n=70 (14%)		Low TG/HDL-C n=370 (68%)	High TG/HDL-C n=171 (32%)		Low TG/HDL-C n=163 (64%)	High TG/HDL-C n=91 (36%)	
	Mean±SD	Mean±SD	p*	Mean±SD	Mean±SD	p*	Mean±SD	Mean±SD	p*
Age (years)	40±18	49±17	<0.001	47±17	52±14	0.006	51±17	49±15	0.451
Women (%)	73	80	0.242	64	61	0.594	66	68	0.761
Systolic BP (mm Hg)	120±17	128±20	<0.001	129±19	134±19	0.003	132±18	131±20	0.814
Diastolic BP (mm Hg)	73±12	77±13	0.009	78±13	82±12	0.003	79±12	81±14	0.356
BMI (kg/m^2)	22.6±1.4	23.1±1.2	0.007	27.1±1.4	27.5±1.4	0.006	32.1±1.4	32.3±1.5	0.319
Cholesterol (mg/dL)	196±44	224±50	<0.001	208±42	235±51	<0.001	215±41	225±52	0.090
HDL-C (mg/dL)	64±13	50±11	<0.001	65±13	49±11	<0.001	63±12	50±12	<0.001
LDL-C (mg/dL)	113±41	136±43	<0.001	122±38	144±46	<0.001	129±38	135±44	0.250
TG (mg/dL)	93±28	192±70	<0.001	108±32	212±71	<0.001	116±35	203±69	<0.001
Glucose (mg/dL)	90±10	91±13	0.554	93±11	95±12	0.039	97±11	97±12	0.662
FPI (μU/mL)	5.8±3.6	7.7±4.0	<0.001	7.0±5.1	9.5±5.4	<0.001	9.2±5.8	13.1±7.7	<0.001
HOMA-IR	1.3±0.9	1.7±0.9	<0.001	1.6±1.2	2.3±1.3	<0.001	2.2±1.4	3.1±1.9	<0.001
Insulin resistance (%)	11	24	0.003	18	39	<0.001	34	56	0.001

*Independent samples 't-test' for continuous variables and χ^2 for categorical variables.
BMI, body mass index; BP, blood pressure; FPI, fasting plasma insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; TG, triglycerides.

subgroup, and these individuals were significantly more insulin resistant than persons with a low HDL-C ratio, associated with higher TG and lower HDL-C concentrations.

The adjusted relative risk for insulin resistance increased through BMI categories (normal weight OR=1, overweight OR=2.35, obese OR=5.55, p for trends <0.001). The results in table 3 present the relative risk of individuals being insulin resistant if they have a high TG/HDL-C ratio, unadjusted and adjusted for sex, age, and study site. These data show that there is a significant increase in the likelihood of being insulin resistant, defined by being in the highest quartile of HOMA-IR values, in those with a high TG/HDL-C ratio, irrespective of BMI category. Furthermore, the ORs in the three BMI categories were relatively comparable. It should also be noted that the findings were comparable if the highest quartile of FPI concentrations was used instead of HOMA-IR values to define insulin resistance (data not shown).

DISCUSSION

This analysis was undertaken to see if the use of previously described sex-specific TG/HDL-C ratio cut-points[10 11] were able to identify increased cardiometabolic risk and estimated insulin resistance in apparently healthy individuals varying widely in degree of adiposity. In the most general sense, the results in table 2 strongly support the notion that the TG/HDL-C ratio provides a simple means to identify enhanced cardiometabolic risk, irrespective of the degree of obesity. On the other hand, this does not imply that excess adiposity is without an adverse effect on cardiometabolic risk as is apparent from table 1, in which the greater the BMI category, the worse the cardiometabolic risk. This same pattern is obvious from the results in table 2, with the prevalence of those with a high TG/HDL-C ratio increasing from 14% in participants with a normal BMI to 36% in obese persons. However, despite the impact of differences in BMI on the prevalence of those with the elevated TG/HDL-C, within each category these high-risk persons have adverse cardiometabolic profiles.

Regarding insulin resistance, the most direct evidence of the association between an elevated TG/HDL-C ratio and insulin resistance is seen in table 3 which demonstrates a significant increase in the OR of being insulin resistant when the TG/HDL-C ratio is high, with reasonably comparable values for irrespective of three BMI

Table 3 OR of normal weight, overweight and obese individuals with high TG/HDL-C ratio (compared with those with 'low' TG/HDL-C ratio) to being insulin resistant defined by the upper quartile of HOMA-IR

	Model 1 Unadjusted			Model 2 Adjusted for sex and age			Model 3 Adjusted for sex, age, and origin		
BMI (kg/m^2)	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
20.0–24.9	2.84	1.52 to 5.32	0.001	3.08	1.61 to 5.88	0.001	3.02	1.58 to 5.78	0.001
25–29.9	2.89	1.93 to 4.35	<0.001	2.90	1.92 to 4.37	<0.001	2.86	1.90 to 4.37	<0.001
30–34.9	2.59	1.53 to 4.39	<0.001	2.61	1.54 to 4.42	<0.001	2.51	1.48 to 4.28	0.001

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides.

category. It can also be seen in table 2 that all estimates of insulin resistance are significantly higher when subgroups within each of the three BMI categories with a high TG/HDL-C ratio are compared with the subgroups with a low ratio.

Although the results are relatively straightforward, there are certain draw-backs to our findings that must be addressed. To begin with, this was a cross-sectional analysis of data obtained as part of a larger epidemiological study.[15 16] Furthermore, our findings are based on a relatively few individuals, essentially all of whom were of European ancestry. First, insulin resistance was defined on the basis of HOMA-IR values, a surrogate estimate, not a direct measure of insulin resistance. However, this estimate has been widely used, and shown to be highly correlated with direct measures of insulin-mediated glucose disposal.[20 21] Second, we used the HOMA-IR value that separated the 25% of the population with the highest value from the remainder to define the prevalence of insulin resistance. This decision was based on results of a prospective study in which a similar separation was evaluated and in which the magnitude of the plasma insulin response to an oral glucose challenge was used as the estimate of insulin resistance.[22] The estimate used in that study is more closely related to a direct measure of insulin-mediated glucose disposal than HOMA-IR,[23] and the results demonstrated that incident glucose intolerance, hypertension, and CHD were significantly greater in the 25% of the population classified as in being insulin resistant. Finally, our findings do not necessarily apply to individuals with BMI values <20.0 or ≥ 35.0 kg/m^2.

In conclusion, the plasma concentration ratios of TG/HDL-C used in this study have previously been shown to identify insulin resistance and incident CVD in apparently healthy individuals.[11] The current results provide further evidence that this simple measurement can be of clinical utility by showing that reasonably wide variations in adiposity do not impede the ability of the ratio to identify insulin resistance and increased cardiometabolic risk in apparently healthy individuals.

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Contributors HAC and MRS performed the design of both projects, RAUCH and PROCER. GMR, MRS and HAC performed the study design. MA was involved in epidemiological survey in Rauch. AGM was involved in epidemiological survey in San Andrés de Giles. CEM, RNS and WGE were involved in Rauch's data collection and analysis. CELS and BCLS were involved in San Andrés de Giles's data collection and analysis. CELS, BCLS, RNS and CEM were involved in initial manuscript written. GMR, HAC, WGE and MRS were involved in final version and manuscript revision. All the authors approved the final version.

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