

The Triglyceride-to-HDL Cholesterol Ratio

Association with insulin resistance in obese youths of different ethnic backgrounds

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OBJECTIVE—We evaluated whether the triglyceride-to-HDL cholesterol (TG/HDL-C) ratio is associated with insulin resistance (IR) in a large multiethnic cohort of obese youths.

RESEARCH DESIGN AND METHODS—Obese youths (1,452) had an oral glucose tolerance test and a fasting lipid profile. Insulin sensitivity was estimated using the whole body insulin sensitivity index (WBISI) and homeostasis model assessment (HOMA)-IR and evaluated, in a subgroup of 146 obese youths, by the hyperinsulinemic-euglycemic clamp. The cohort was divided by ethnicity (612 whites, 357 Hispanics, and 483 African Americans) and then stratified into ethnicity-specific tertiles of TG/HDL-C ratio. Differences across tertiles were evaluated, and the association between the TG/HDL-C ratio and insulin sensitivity (WBISI) was defined by a multiple stepwise linear regression analysis. The area under the receiver operating characteristic (ROC) curve (AUC) was determined to calculate the TG/HDL-C ratio cutoff to identify insulin-resistant subjects by ethnicity.

RESULTS—In each ethnic group and across rising tertiles of TG/HDL-C ratio, insulin sensitivity (WBISI) progressively decreased, whereas 2-h glucose and the AUC-glucose progressively increased. The cutoff for TG/HDL-C ratio was 2.27, and the odds of presenting with IR, in youths with TG/HDL-C ratio higher than the cutoff, was 6.023 (95% CI 2.798–12.964; $P < 0.001$) in white girls and boys, whereas for both Hispanics and African Americans the AUC-ROCs were not significant, thus not allowing the calculation of an optimal cutoff TG/HDL-C value.

CONCLUSIONS—The TG/HDL-C ratio is associated with IR mainly in white obese boys and girls and thus may be used with other risk factors to identify subjects at increased risk of IR-driven morbidity.

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Insulin resistance (IR), the most common feature of childhood obesity, is a key risk factor for development of type 2 diabetes and the metabolic syndrome (MS) in obese youths (1,2). Even in pre-diabetic states of dysglycemia, there is clear evidence of IR in both adults and children (2,3). Therefore, its detection in obese youths is needed for identification of those who would benefit most from early interventions (4). Nevertheless, the gold

standard methods designed to measure insulin sensitivity, the hyperinsulinemic-euglycemic clamp and the frequently sampled intravenous glucose tolerance test (FSIGT), are impractical in the clinical setting and can only be performed in specialized centers (1). Even simpler methods, such as the whole body insulin sensitivity index (WBISI), the homeostasis model assessment of IR (HOMA-IR) and several other indexes proposed to date, present

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important limitations, related to their poor reproducibility and reliability (5). In addition, no clear guidelines and no universally accepted cutoffs are available for most of the main surrogate markers used (1). Therefore, there is an urgent need for the development of a measure of IR that is easy to implement clinically and that is suitable for large epidemiological studies.

The triglyceride-to-HDL cholesterol (TG/HDL-C) ratio has been reported to be closely related to IR in adults (6,7). However, although the association is widely described in white individuals, contrasting results have been reported in black adults and adolescents (6,8). Therefore, it is possible that given the racial/ethnic variations in both TG and HDL-C levels, the association of the TG/HDL-C with IR may be ethnicity dependent. Thus our goal was to determine the associations between TG/HDL-C and IR as assessed using the WBISI in a large multiethnic cohort of obese youths. Furthermore, in a subgroup of each of the three racial/ethnic groups, these associations were validated using the hyperinsulinemic-euglycemic clamp.

RESEARCH DESIGN AND METHODS

The cohort

We studied a multiethnic cohort of 1,452 obese children and adolescents (589 boys and 863 girls; mean age 13.1 ± 2.9 years; mean BMI z score [BMI-Z] 2.33 ± 0.5) referred to the Yale Pediatric Obesity Clinic. The study population was further divided by ethnicity and sex into three groups (Table 1). Subjects provided information regarding their ethnic group. The study was approved by the Yale University Human Investigation Committee. Parental informed consent and child assent were obtained from all participants.

Metabolic studies

On two separate days, oral glucose tolerance test (OGTT) and hyperinsulinemic-euglycemic clamp were performed, as previously described (see Supplementary Data) (9).

Table 1—Anthropometric and metabolic parameters of the three ethnic groups divided according to sex

	Whites			Hispanics			African Americans		
	Male	Female	P†	Male	Female	P†	Male	Female	P†
n*	243	369		171	186		175	308	
Age (years)	13.6 ± 3	13.4 ± 3	0.867	12.6 ± 2.7	12.6 ± 2.9	0.901	13.3 ± 2.6	13.07 ± 2.8	0.789
BMI (kg/m ²)	34 ± 8	34 ± 7	0.756	34 ± 7	33 ± 7	0.108	36 ± 7	36 ± 8	0.644
BMI-Z	2.37 ± 0.49	2.24 ± 0.51	0.083	2.39 ± 0.57	2.20 ± 0.65	0.018	2.46 ± 0.51	2.38 ± 0.46	0.829
WC (cm)	107 ± 17	102 ± 16	0.001	106 ± 17	96 ± 14	0.001	109 ± 17	106 ± 17	0.058
Body fat	41 ± 11	44 ± 6	0.000	44 ± 11	44 ± 6	0.473	45 ± 11	46 ± 6	0.078
LBM	55 ± 17	46 ± 8	0.000	51 ± 20	42 ± 9	0.002	54 ± 15	49 ± 11	0.054
FM	39 ± 18	39 ± 16	0.530	38 ± 19	34 ± 13	0.548	44 ± 24	44 ± 16	0.321
Lipid markers									
TG (mg/dL)	129 ± 71	120 ± 69	0.093	123 ± 86	115 ± 70	0.635	84 ± 49	81 ± 42	0.957
HDL (mg/dL)	40 ± 10	41 ± 8	0.149	40 ± 9	42 ± 8	0.090	45 ± 10	44 ± 9	0.606
TG/HDL-C	3.48 ± 2.46	3.16 ± 2.26	0.105	3.41 ± 3.09	3.00 ± 2.29	0.280	2.02 ± 1.39	1.98 ± 1.34	0.830

Data are expressed as means ± SD or number of participants. FM, fat mass; WC, waist circumference. *Number of participants; †independent-samples *t* test.

The hyperinsulinemic-euglycemic clamp was performed in a subgroup of 146 obese youths (50 whites, 21 boys and 29 girls, mean age 14.0 ± 2 years; 49 Hispanics, 22 boys and 27 girls, mean age 13.3 ± 2 years; and 47 African Americans, 20 boys and 27 girls, mean age 13.8 ± 2 years) who voluntarily agreed to participate in the clamp study. This subgroup had similar clinical and anthropometric characteristics of the main cohort.

Biochemical analyses

Plasma glucose was determined using the YSI 2700 Analyzer and fasting lipid levels using an auto-analyzer (model 747–200; Roche–Hitachi, Indianapolis, IN). TG and HDL-C values were used for determining the TG/HDL-C ratio. Plasma insulin was measured by the Linco RIA, which has less than 1% cross-reactivity with C-peptide and proinsulin.

OGTT-derived parameters

The HOMA-IR was calculated as the product of the fasting insulin level (in microunits per milliliter) and the fasting glucose level (in millimoles per liter) divided by 22.5. Using the 2-h OGTT data (0, 30, 60, 90, and 120 min), the WBISI was defined as: $10,000/\sqrt{[(\text{fasting glucose}\{\text{mg/dL}\}) \times (\text{fasting insulin}\{\mu\text{U/mL}\}) \times (\text{mean OGTT glucose}\{\text{mg/dL}\}) \times (\text{mean OGTT insulin}\{\mu\text{U/mL}\})]}$ (9). This index has been validated for the use in obese youths (10). Areas under the curve (AUCs) of glucose during the OGTT were calculated by the trapezoid rule.

Statistical analyses

The distribution of continuous variables was examined for skewness and kurtosis,

and parameters were logarithmically transformed, when appropriate. To investigate sex- as well as ethnicity-related differences on lipids as well as on TG/HDL-C ratio, the study population was divided into six groups: male and female, respectively, in whites, Hispanics, and African Americans. Differences in sex were assessed by χ^2 test, whereas independent-samples *t* test was used for testing in each ethnicity differences between the sexes. In addition, white as well as Hispanic and African American youths were divided into tertiles of TG/HDL-C according to the ethnicity-derived cutoff. In each ethnic group, differences across the tertiles were analyzed by one-way ANOVA test and post hoc pairwise comparisons were made, adjusting the level of significance for multiple comparisons with the post hoc Bonferroni correction. To evaluate whether the used surrogate markers (WBISI, HOMA-IR, and TG/HDL-C ratio) were related to the gold standard measure of insulin sensitivity, a Pearson correlation was performed between M-to-lean body mass (M/LBM) and TG/HDL-C ratio, WBISI, and HOMA-IR. In addition, a multiple stepwise linear regression in each of the three ethnic groups was performed using the WBISI values. In this model the WBISI was considered as the dependent variable, whereas the TG/HDL-C ratio as well as age, sex, glucose 120, and BMI-Z were considered independent variables.

Receiver operating characteristic (ROC) curve analysis was performed for TG/HDL-C ratio to discriminate those subjects who were insulin resistant from those who were insulin sensitive, in each ethnic group and also by sex. IR was

defined according to WBISI levels: in particular the percentiles for WBISI were calculated in each ethnic group. Subjects showing a WBISI lower than the 10th percentile were considered as insulin resistant (the 10th percentile for WBISI was 0.799 in whites, 0.734 in Hispanics, and 0.720 in African Americans). Using the WBISI, an optimal cutoff point for TG/HDL-C ratio was obtained using the Youden index (maximum [sensitivity + specificity – 1]) (11,12). Then, to assess the odds of subjects with high TG/HDL-C ratio for showing IR, a logistic regression analysis was run and sex, age, and BMI-Z were used as covariates. Values are expressed as odds ratios (ORs) with 95% CI.

In a subgroup of each ethnic group, insulin sensitivity was also determined by performing a hyperinsulinemic-euglycemic clamp. The definition of IR was done using the median value of the distribution of insulin-stimulated glucose metabolism (mg/LBM·min) obtained in more than 200 obese youths during a 80 mU per kg per minute insulin clamp. Therefore, the clamp derived insulin sensitivity data were used for determining the predictive value of the TG/HDL-C ratio by calculating the area under the ROC curve by race/ethnicity separately. Values for the area under the ROC curve of 0.5, ≥ 0.7 but < 0.8 , ≥ 0.8 but < 0.9 , and ≥ 0.9 have been suggested as reflecting the following levels of discrimination: none, acceptable, excellent, and outstanding (13).

Statistical analyses were performed with SPSS (16.0 for Windows; SPSS, Chicago, IL). All data were expressed as means ± SD. For all analyses, a *P* value < 0.05 was considered statistically significant.

Table 2—Anthropometric and metabolic parameters of the three ethnic groups divided according to TG/HDL-C tertiles

	Whites			Hispanics			African Americans		
	First	Second	Third	First	Second	Third	First	Second	Third
<i>n</i> *	204	204	204	119	119	119	161	161	161
Age (years)	13.3 ± 3.3	13.4 ± 2.9	13.9 ± 2.8	12.6 ± 3.1	12.5 ± 2.6	12.7 ± 2.7	13.4 ± 2.8	13.0 ± 2.7	12.9 ± 2.8
Sex (male/female)#	71/133	79/125	93/111	52/67	60/59	59/60	60/101	51/110	64/97
BMI (kg/m ²)	33.3 ± 8.8	36.09 ± 7.9	34.8 ± 6.1	31.5 ± 7.2	35.1 ± 7.1	34.3 ± 7.1	35.5 ± 8.0	37.9 ± 8.4	36.7 ± 7.6
BMI-Z	2.14 ± 0.67	2.41 ± 0.36	2.33 ± 0.38	2.09 ± 0.87	2.41 ± 0.39	2.37 ± 0.42	2.28 ± 0.65	2.48 ± 0.44	2.47 ± 0.35
WC (cm)	99 ± 18	106 ± 15	107 ± 15	95 ± 16	105 ± 16	104 ± 15	102 ± 18	110 ± 16	108 ± 17
Body fat	42.2 ± 10	44.6 ± 8.2	43.3 ± 8.5	42.5 ± 10	45.6 ± 8.9	44.6 ± 8.5	44.7 ± 9.6	46.8 ± 7.2	46.7 ± 7.7
LBM	47.9 ± 11	52.7 ± 14	52.3 ± 14	45.7 ± 17	47.8 ± 16	45.6 ± 11	50.2 ± 11	52.6 ± 11	51.8 ± 16
FM	36.2 ± 18	41.4 ± 16	41.7 ± 16	33.6 ± 16	40.4 ± 19	35.6 ± 12	40.2 ± 17	48.6 ± 20	46.8 ± 19
Glucose metabolism									
Glucose 0 (mg/dL)	91 ± 8	92 ± 9	92 ± 10	93 ± 9	94 ± 7	95 ± 9	92 ± 8	93 ± 11	93 ± 9
Glucose 120 (mg/dL)	117 ± 23	123 ± 24	127 ± 27	116 ± 21	119 ± 20	131 ± 25	115 ± 22	122 ± 33	129 ± 35
Insulin 0 (μU/mL)	25.4 ± 14	33.4 ± 16.4	40.2 ± 36	27.2 ± 16	35.9 ± 20	41 ± 22.2	27.4 ± 15	36.5 ± 18	42.5 ± 25
AUC-glucose 120	125 ± 20	131 ± 21	133 ± 22	125 ± 20	126 ± 19	137 ± 22	118 ± 18	125 ± 27	131 ± 28
Insulin sensitivity index									
HOMA-IR	5.75 ± 3.3	7.74 ± 4.2	9.75 ± 14	6.38 ± 4	8.55 ± 5	9.65 ± 5.2	6.35 ± 3.7	8.51 ± 4.7	9.97 ± 6.5
Lipid markers									
TG (mg/dL)	67 ± 18	107 ± 23	231 ± 173	62 ± 17	99 ± 20	194 ± 92	45 ± 11	72 ± 15	129 ± 45
HDL (mg/dL)	49 ± 10	40 ± 6	35 ± 6	48 ± 8	40 ± 7	35 ± 6	53 ± 12	45 ± 8	38 ± 7
TG/HDL-C	1.39 ± 0.38	2.69 ± 0.45	6.94 ± 6.6	1.32 ± 0.38	2.48 ± 0.38	5.76 ± 3.3	0.877 ± 0.21	1.62 ± 0.28	3.45 ± 1.3

Data are expressed as means ± SD or number of participants. FM, fat mass; WC, waist circumference; #χ² test; *Number of participants; #χ² test; †one-way ANOVA test.

RESULTS

Anthropometric and main biochemical parameters in each ethnic group according to sex and tertiles of TG/HDL-C

As shown in Table 1, although there were significant sex differences in body composition in each ethnic group, there were none for lipid levels. Therefore, the TG/HDL-C ratio was similar in both boys and girls in all ethnic groups.

Given the significant ethnic differences in both fasting TGs and HDL levels among the three groups, we stratified each ethnic group into tertiles of TG/HDL-C ratio (Table 2). The age and sex distribution across the tertiles were similar in all three ethnic groups. Although a significant increase in BMI, BMI-Z, and waist circumference across the tertiles of TG/HDL-C was seen in all three ethnic groups, no differences were documented for body composition.

As shown in Table 2, both 2-h glucose and AUC-glucose and fasting insulin levels rose across TG/HDL-C tertiles. In each ethnic group and across rising tertiles of TG/HDL-C, the WBISI progressively decreased (Fig. 1) and the HOMA-IR significantly increased, indicating a worsening of IR (Table 2).

Correlations and predictive value of the TG/HDL-C ratio

Modest correlations were found between the TG/HDL-C ratio and the M/LBM ($r = -0.388$, $P < 0.0001$), whereas a stronger one was found with WBISI ($r = 0.620$, $P < 0.0001$). Of note, however, the relationship between the TG/HDL-C ratio and the M/LBM is stronger ($r = -0.388$) than that between the M/LBM and the HOMA-IR ($r = -0.219$, $P = 0.001$). In addition, as shown in the Supplementary Data (see Supplementary Table 1), using the multiple stepwise linear regression analysis, a significant and strong negative association between the TG/HDL-C ratio and the WBISI value was documented in all three ethnic groups, even after adjusting for age, sex, 2-h glucose, and the degree of obesity (BMI-Z).

To finally test the ability of the ratio to predict IR, a ROC curve was calculated using data from both the OGTT and from the clamp. Regardless of sex or ethnicity, the AUC ROC for the ability of TG/HDL-C to predict IR was significant using both WBISI (0.712 ± 0.01 ; $P > 0.001$) and HOMA-IR (0.706 ± 0.01 ; $P > 0.001$) in the whole population. Similar results

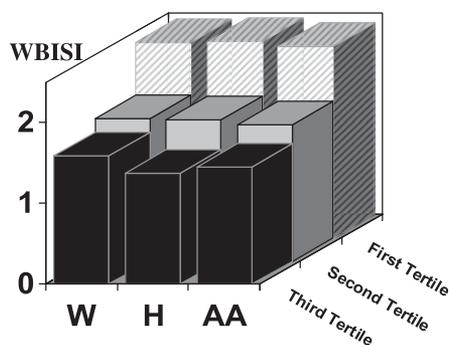


Figure 1—WBISI [(dL · mL⁻¹)/(mg · μIU⁻¹)] distribution across the three tertiles in white (W; P < 0.001), Hispanic (H; P < 0.001), and African American (AA; P < 0.001) children and adolescents.

were obtained after dividing the population into the three ethnic groups, regardless of sex (all AUC values of ≥0.70 with a P ≤ 0.001; Table 3). However, of note, when we divided the population according to sex and ethnicity, a significant AUC value of ≥0.70 was achieved for both sexes in whites and in Hispanics and only for African American girls. When we used the clamp data as the gold standard of insulin sensitivity, because of the much lower number of subjects, the evaluation of TG/HDL-C met our stringent criteria and was significant for only the whole cohort (0.752 ± 0.042; P < 0.001, regardless of ethnicity and sex; Table 3). Of note, however, after dividing the three ethnic groups into boys and girls, the TG/HDL-C ratio was only significant for both sexes in whites and in Hispanic girls, yet did not reach statistical significance in Hispanic males and in both sexes in African Americans (Table 3).

Given that the AUC-ROC values from the clamp was significant only in the whites, we calculated the TG/HDL-C cutoff value only for this ethnic group. In particular, using the WBISI, we found a cutoff of 2.27 (89% sensitivity and 45% specificity) and the odds of showing IR for white subjects with TG/HDL-C ratio higher than the cutoff was 6.023 (95% CI 2.798–12.964; P < 0.001).

CONCLUSIONS—In this study, using a large multiethnic cohort of obese youths, we found that the TG/HDL-C ratio was significantly associated with IR particularly in whites and that the TG/HDL-C varied by ethnicity, indicating the need for a race/ethnicity cutoff point of this index. We found a clear association between the TG/HDL-C ratio and both the 2-h glucose and the AUC-glucose as well as WBISI and HOMA-IR in the three ethnic groups. Across the tertile groups, WBISI significantly decreased and HOMA-IR significantly increased. These relationships remained even after adjusting for age, sex, 2-h glucose, BMI-Z, and waist circumference (1). In addition, by adopting a cutoff value of 2.27, an OR of 6.023 of presenting with severe IR was found in the whites. Because the AUC for the ROC from the clamp data did not reach statistical significance in the Hispanics and African Americans, we were not able to calculate the cutoffs for the TG/HDL-C ratio in these two ethnic groups. Thus, it is possible that using the TG/HDL-C ratio, at least in whites, could help clinicians identify young obese subjects who are not only IR but also display the early dysglycemia commonly associated to IR (6,14).

Elevated TG and low HDL cholesterol levels are known to be associated with IR and type 2 diabetes (15). Data from the Third National Health and Nutrition Examination Survey (NHANES III) indicated that the most frequently encountered components of the MS among adolescents are high TG (25–30% of adolescents) and low HDL cholesterol levels (40–50% of adolescents) (16). Steinberger et al. (17) originally reported that the degree of IR, as measured by the hyperinsulinemic-euglycemic clamp, explained a significant portion of the variance in the levels of TG, LDL cholesterol, and HDL cholesterol in obese adolescents. In addition, some studies indicated a greater predictive power of detecting the risk for cardiovascular disease by combining high TG and low HDL cholesterol in a single marker (18).

Given the interethnic differences in lipid profiles and IR, contrasting results have been reported in different ethnic groups in adulthood, cautioning the use of lipid surrogates for IR (7,8,19). In particular, the relationship between the TG/HDL-C ratio and a direct measure of IR was first reported among 258 overweight or obese adults, of whom 87% were non-Hispanic whites (6). This association has been replicated in a larger clinically based sample that represented the adult general population (14). In addition, in adult African Americans, the ability of the TG/HDL in defining IR has been found to differ by sex (20). In a study in an East African population, the TG/HDL-C ratio was found to be significantly associated with IR as measured by HOMA-IR (21). In contrast, further studies have reported no association between the TG or TG/HDL-C ratio and IR in black

Table 3—AUC ROC ± SE for the ability of TG/HDL-C to predict insulin resistance

	Boys and girls	P	Boys only	P	Girls only	P
IR determined from clamp (M/LBM)						
Number (whites/Hispanics/African Americans)	50/49/47		21/22/20		29/27/27	
Whites	0.860 ± 0.05	<0.001	0.975 ± 0.03	<0.001	0.778 ± 0.10	0.01
Hispanics	0.713 ± 0.07	0.01	0.675 ± 0.12	0.166	0.753 ± 0.09	0.031
African Americans	0.723 ± 0.08	0.01	0.716 ± 0.12	0.117	0.700 ± 0.11	0.122
IR determined from WBISI						
Number (whites/Hispanics/African Americans)	612/357/483		243/171/175		369/186/308	
Whites	0.707 ± 0.02	<0.001	0.743 ± 0.04	<0.001	0.700 ± 0.03	<0.001
Hispanics	0.701 ± 0.04	<0.001	0.700 ± 0.05	0.003	0.702 ± 0.05	0.003
African Americans	0.738 ± 0.03	<0.001	0.648 ± 0.08	0.101	0.782 ± 0.03	<0.001
IR determined from HOMA-IR						
Whites	0.720 ± 0.03	<0.001	0.777 ± 0.04	<0.001	0.701 ± 0.04	<0.001
Hispanics	0.716 ± 0.04	<0.001	0.706 ± 0.06	0.006	0.724 ± 0.05	0.002
African Americans	0.716 ± 0.03	<0.001	0.606 ± 0.08	0.238	0.764 ± 0.03	<0.001

adults (8,22) and adolescents (23). In our study, we were able to document a clear association between the TG/HDL-C ratio and insulin sensitivity in the three different ethnic groups and when combining the sexes together. However, when analyzing the ROC curves in boys and girls, separately, the significance remained only for both sexes in whites and in Hispanic girls, whereas no statistical significance was seen by sex in African Americans and in Hispanic boys. Thus the association in African Americans in particular seems to be affected by sex, as described by Sumner et al. (20).

Definition of IR in our study was based on estimates from the OGTT and direct measures from the clamp technique in a subgroup of obese youths that had very similar demographic characteristics to the entire cohort. This represents an important point since no universally accepted cutoff values for IR are available, especially in childhood (1). In addition, in our population we documented that the TG/HDL-C ratio correlation with the gold standard parameter of IR was stronger ($r = 0.388$) than HOMA-IR ($r = 0.219$). These results are important because the TG/HDL-C ratio determination requires only fasting TG and HDL and does not necessitate analysis of insulin or the performance of more elaborative studies (such as the WBISI, which requires an OGTT). Nevertheless, the OGTT allows determination not only of insulin sensitivity but also of glucose tolerance status adding relevant clinical information to the characterization of high-risk subjects. In our previous analysis (24), we documented that the metabolic syndrome, mainly driven by IR, is common among obese adolescents yet its prevalence seems lower in African American youths, mainly because of their seemingly favorable lipid profile. The ratio of TG to HDL-C seems to better reflect the effect of IR on lipid metabolism and overcomes the limitations of using TGs and HDL-C individually as indicators of risk.

IR may be the primary step in the development of adipose and lipid dysregulation. We provide evidence that the TG/HDL-C ratio is associated with both indirect and direct measures of insulin sensitivity in obese boys and girls together (Table 3) and in all three ethnic groups. Although this relationship remains strong in white boys and girls, it failed to reach significance in African American boys and girls and in Hispanic boys. The reason for why sex affects this relationship

in specific ethnic groups remains to be determined.

The strength of the current study is a result of the large sample size and the availability of both indirect and direct measures of insulin sensitivity. Limitations are mainly related to the fact that we used a clinic-based sample of obese youths, which may not be a true representative of the general population. Another potential weakness of this study could be the use of the Youden index to calculate the specific cut points. The accuracy of Youden index, in fact, can be questioned given that it is a single statistic deriving from the sum of sensitivity and specificity minus 1 ($J = \text{sensitivity} + \text{specificity} - 1$). In other words, a high J does not discriminate between sensitivity and specificity deriving from the sum of both.

In conclusion, the TG/HDL-C ratio is associated with IR, particularly in white obese boys and girls, and thus may be used with other risk factors to identify subjects at increased risk of the development of IR-driven morbidity.

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C.G. analyzed the data and wrote the manuscript. N.S. researched data. S.C. wrote the manuscript and reviewed and edited the manuscript. G.K., D.L., M.S., and B.P. researched data. R.W. wrote the manuscript and reviewed and edited the manuscript.

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