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The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio as a predictor of insulin resistance, β-cell function, and diabetes in Hispanics and African Americans

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ABSTRACT

Objective: The TG/HDL-C ratio is used as a marker of insulin resistance (IR) in Caucasians; however, there is limited data in other ethnic groups. We hypothesized that the TG/HDL-C ratio is associated with IR in Hispanics and African Americans (AA).

Research design and methods: Data from the Insulin Resistance Atherosclerosis Family Study was examined for associations between TG/HDL-C ratio and IR, β-cell function and incident diabetes in non-diabetic Hispanics ($n = 872$, 63% female) and AA ($n = 371$, 61% female). Insulin sensitivity index (S_I) and disposition index (DI) from frequently-sampled intravenous glucose tolerance tests were used as markers of IR and β-cell function respectively. Incident type 2 diabetes was determined by fasting glucose ≥ 126 mg/dl or initiation of anti-hyperglycemia agents over 5 year follow-up.

Results: Higher TG/HDL-C ratio was associated with IR in Hispanic and AA men and women ($P < 0.0002$), as well as β-cell function in Hispanic women and AA men and women ($P < 0.02$). TG/HDL-C predicted incident type 2 diabetes in women (area under the curves 0.703 and 0.795 for Hispanics and AA respectively).

Conclusions: Similar to Caucasians, the TG/HDL-C ratio can be used to identify IR in Hispanics and AA, and may predict type 2 diabetes in women.

1. Introduction

There is a striking ethnic disparity in the prevalence of type 2 diabetes among minority populations in the United States. Several studies have reported increased incidence of type 2 diabetes in African Americans and Latinos (17.7%) as compared to non-Hispanic whites (NHW) (6.0%).[1] Clinical trials have consistently demonstrated that targeted interventions can reduce the risk of developing type 2 diabetes in high-risk individuals[2]; identifying these individuals early could delay or prevent the onset of type 2 diabetes. Insulin resistance (IR) and β-cell dysfunction are characteristics of type 2 diabetes,[3–5] but are not feasible to measure clinically. Therefore, simple markers that correlate with IR or β-cell dysfunction may identify those at high risk for developing type 2 diabetes.

The triglyceride to high-density lipoprotein-C (TG/HDL-C) ratio has been shown to be associated with IR[6,7] in NHW. However, conflicting data has emerged in African Americans[8–12] and Hispanics,[9,13] and it is unclear if the TG/HDL-C predicts IR in this population. Most of the studies in African Americans and Hispanics are small and additionally, comparison of these studies is difficult because of the variability in methodology used to assess insulin resistance. Whereas some studies use the frequently sampled IV glucose tolerance test (FSIGT)[10,11] as a direct measure of IR, others use surrogate markers of IR such as HOMA IR or fasting insulin levels.[8,9,12]

The variability of previous results may also be affected by race- and gender-specific differences in β-cell function, insulin clearance, and lipid metabolism. Compared to NHW, Hispanics have higher TG, lower HDL-C, and increased insulin levels, while African Americans have lower TG,

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higher HDL-C, and increased insulin levels.[9,14] In this study we use measurements of insulin sensitivity and secretion calculated by FSIGT from a large group of African Americans and Hispanic subjects in the Insulin Resistance and Atherosclerosis (IRAS) Family Study to identify race and gender specific associations between the TG/HDL-C ratio and IR as well as β-cell function. Additionally, we are the first to investigate the TG/HDL-C ratio as a predictor of incident type 2 diabetes prospectively in a large cohort of African Americans and Hispanics followed for 5 years.

2. Research design and methods

The IRAS Family Study was designed to explore genetic and epidemiologic contributions to abdominal adiposity and glucose homeostasis traits among Hispanic and African Americans using a family-based design.[15] Family members of the original IRAS participants were recruited to participate in a baseline exam. Additional families were recruited from the general population to supplement the IRAS families. Ascertainment and recruitment of families were based upon family size, and not on phenotype. Hispanic families were recruited from San Antonio, TX, and the San Luis Valley, CO. African American families were recruited from Los Angeles, CA. A follow-up examination was conducted approximately five years after the baseline examination (mean follow-up: 5.34 years). The Institutional Review Boards at the respective institutions approved the protocol and informed consent was given by each subject. Identical protocols were followed for the baseline and follow-up visits.

Insulin sensitivity (S_I) was assessed by the frequently sampled intravenous glucose-tolerance test.[15,16] An injection of insulin was used to ensure adequate plasma insulin levels for the accurate computation of insulin resistance across a broad range of glucose tolerance using reduced sampling protocol for efficiency. Glucose in the form of a 50% solution (0.3 g/kg) and regular human insulin (0.03 U/kg) were injected through an intravenous line at 0 and 20 min, respectively. Blood was collected at −5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min for the determination of plasma glucose and insulin concentrations. Plasma glucose was measured using the glucose oxidase technique on an automated autoanalyzer (YSI, Yellow Springs, OH); and insulin was assessed by radioimmunoassay.[16–18] S_I was calculated by minimal model analysis.[15] Acute insulin response to glucose (AIRg) was the mean insulin increment in the plasma insulin concentration above the basal in the first 8 min after the administration of glucose. Disposition index (DI) was calculated as the product of S_I and AIRg which represents β-cell compensation for insulin resistance or β-cell function.

Type 2 diabetes was determined by a fasting glucose of ≥126 mg/dL, or if a subject was taking diabetes medications (insulin or pills). Those diagnosed with gestational diabetes during the follow up were not classified as having diabetes. Impaired fasting glucose (IFG) was defined as a fasting glucose ≥100 and <126 mg/dL.

Total cholesterol and triglyceride were measured using enzymatic methods. HDL-C was measured using the direct method. TG/HDL-C ratio was calculated.

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Data on smoking habits was gathered by standard questionnaire.[15] Physical activity was assessed by a 1-year recall using a modification of a validated instrument.[19] These activities were queried in groups according to home, work, or leisure time and according to intensity of activities (light, moderate, or vigorous) based on metabolic equivalent (MET) values. For each activity group, usual frequency and duration of participation were recorded, from which estimated energy expenditure (EEE) was determined. Total energy expended (in kcal/kg) per year was calculated by summing across all activity groups, plus the EEE from sleep (MET value of 1.0), plus the EEE from light activities (e.g., sitting MET value of 1.5).

3. Statistical methods

Individuals with type 2 diabetes at baseline were excluded from the analysis cohort. Due to gender differences in lipid metabolism, we tested for interactions with gender and TG/HDL-C ratio; significant interactions were present, and therefore analyses were performed separately in women and men in each racial/ethnic group. TG/HDL-C ratio was used as a continuous variable. Outcomes were positively skewed; S_I was log ($S_I + 1$) transformed, while AIRg and DI was signed square root transformed for normalization.

Variance component analysis implemented in SOLAR was used to examine associations between TG/HDL-C ratio and measures of insulin sensitivity and β-cell function while accounting for the correlations among family members in pedigrees of arbitrary size and complexity.[20] For S_I and DI, the models are adjusted for age, BMI, current smoking status, and physical activity (total EEE). For AIRg, the model is adjusted for age, BMI, current smoking status and S_I. The models in Hispanics were also adjusted for clinic site (San Antonio and San Luis Valley).

Analyses with the dichotomous outcomes were run in SAS 9.4 (Cary, NC). The diagnostic accuracy of the TG/HDL-C ratio in predicting incident type 2 diabetes was assessed using the area under the curve (AUC) from receiver-operating characteristic (ROC); for these analyses, an AUC >0.70 was considered predictive. The maximum value of the Youden index was used to determine the TG/HDL-C ratio cutoff for predicting type 2 diabetes.

Generalized estimating equations (GEE), adjusting for correlation within families assuming an exchangeable correlation matrix and sandwich estimator of the variance, were used to assess associations between TG/HDL-C ratio and the categorical outcomes of impaired fasting glucose at baseline, and incident diabetes at the follow-up. Odds ratios were determined per unit increase in the TG/HDL-C ratio. GEE models were adjusted for age and BMI at baseline. We first determined the association of TG/HDL-C ratio and the risk of incident type 2 diabetes. We then included S_I and DI individually as covariates to determine if the TG/HDL-C ratio-diabetes association was due to the association of TG/HDL-C with these measures.

4. Results

Characteristics of the participants at baseline and follow-up are shown in Table 1. At baseline, mean TG/HDL-C ratio was significantly higher in Hispanics than in African-Americans, and was significantly higher in males compared to females in both Hispanics and African Americans. In both Hispanics and African Americans, males had a higher mean TG level, whereas females had a higher mean HDL-C level. Mean S_I was higher in Hispanics, whereas mean DI was higher in African-Americans; however, there were no significant differences in S_I and DI by gender within each race/ethnic group. At follow-up, between 6.3% and 8.3% of individuals developed type 2 diabetes, with no significant differences by gender.

We found significant interactions between TG/HDL-C ratio and gender for S_I ($p_{interaction} = 0.0006$ for Hispanics and $p_{interaction} = 0.15$ for African-Americans) and DI ($p_{interaction} = 0.009$ in Hispanics and $p_{interaction} = 0.02$ in African-Americans). Therefore, all analyses were performed separately in women and men in each race/ethnic group, and are detailed in Table 2. At baseline, TG/HDL-C ratio was inversely associated with S_I in both Hispanics and African-Americans, after adjustment for age, BMI, current smoking status and physical activity. A higher TG/HDL-C ratio was also inversely associated with DI in Hispanics (only in women) and African-Americans. The association between TG/HDL-C ratio and AIRg was only significant in Hispanic women (Table 2).

We evaluated the TG/HDL-C ratio as a predictor of incident type 2 diabetes using baseline TG/HDL-C ratio as a single variable predictor. The TG/HDL-C ratio was predictive of incident type 2 diabetes using ROC curves in women both Hispanic and African-American (AUC = 0.703 and AUC = 0.795, respectively) (Fig. 1). However, the cut offs

Table 1
Descriptive characteristics of the Hispanic and African-American populations.

Characteristic[a] [mean ± SD (median)]	Hispanics $N = 875$		*p*-Value	African Americans $N = 371$		*p*-Value
	Female $N = 546$	Male $N = 326$		Female $N = 225$	Male $N = 157$	
Age	42.1 ± 13.3 (41.6)	39.9 ± 13.7 (37.3)	0.02	41.9 ± 12.9 (40.8)	43.6 ± 14.4 (42.1)	0.22
F/U time (yrs)	5.1 ± 0.6 (5.1)	5.1 ± 0.6 (5.1)	0.48	5.7 ± 0.8 (5.8)	5.8 ± 0.8 (5.9)	0.65
Current smoker (*n*, %)	109 (20.0%)	87 (26.7%)	0.02	52 (23.1%)	37 (23.6%)	0.92
Total EEE[b] (kcal/kg/yr)	15,427.6 ± 3007.1 (14,594.6)	18,181.1 ± 4909.5 (16,954.0)	<0.0001	14,893.8 ± 2836.1 (13,782.3)	15,921.1 ± 3740.3 (14,603.9)	0.003
BMI (kg/m^2)	28.8 ± 6.3 (27.7)	28.2 ± 5.13 (27.9)	0.11	29.8 ± 7.4 (28.3)	29.1 ± 8.1 (28.0)	0.39
TG (mg/dL)	110.28 ± 71.67 (91.00)	133.40 ± 94.31 (109.00)	<0.0001	67.85 ± 41.28 (57.00)	87.47 ± 64.69 (73.00)	0.0003
HDL-C (mg/dL)	46.02 ± 12.23 (45.00)	40.08 ± 12.80 (38.00)	<0.0001	51.23 ± 13.39 (49.00)	43.48 ± 10.37 (42.00)	<0.0001
TG/HDL-C ratio	2.75 ± 2.59 (1.97)	3.95 ± 3.80 (2.74)	<0.0001	1.48 ± 1.13 (1.15)	2.27 ± 2.28 (1.68)	<0.0001
S_I[c]	2.13 ± 1.87 (1.67)	2.06 ± 1.86 (1.61)	0.55	1.58 ± 1.21 (1.36)	1.56 ± 1.14 (1.31)	0.87
AIRg[c]	743.14 ± 643.42 (584.95)	809.20 ± 663.88 (622.46)	0.15	985.55 ± 787.87 (784.20)	997.90 ± 841.50 (689.60)	0.88
DI[c]	1269.03 ± 1183.30 (984.90)	1304.83 ± 1181.23 (1001.26)	0.69	1407.00 ± 1335.63 (1082.08)	1306.2 ± 1186.7 (1046.2)	0.45
Impaired fasting glucose (*n*, %)	100 (18.3%)	91 (27.9%)	0.0009	51 (22.7%)	56 (35.7%)	0.005
Incident diabetes at F/U (*n*, %)	39 (7.2%)	27 (8.3%)	0.52	15 (7.1%)	9 (6.3%)	0.77

[a] All variables listed are for the baseline visit unless otherwise noted.
[b] Total energy expenditure is missing for 1 Hispanic female and 3 African American males and 5 African American females.
[c] Untransformed mean presented for S_I, AIRg, and DI.

for prediction of incident diabetes were different. In Hispanic women, the maximum Youden index indicated a TG/HDL-C cutoff of 2.14 mg/dL, with a sensitivity of 80% and 58% specificity. In African-American women, the maximum Youden index indicated a TG/HDL-C cutoff of 1.67 mg/dL, with a sensitivity of 80% and a specificity of 75%.

In a multivariable model, TG/HDL-C ratio was significantly associated with incident type 2 diabetes in African-American women (adjusted OR: 1.68, 95% CI (1.24–2.29)), after adjusting for age and BMI (Table 3). We then included S_I and DI individually as covariates to determine if the TG/HDL-C ratio-type 2 diabetes association was independent of S_I and DI. After adjusting for S_I, the association between the TG/HDL-C ratio and incident type 2 diabetes was attenuated, but remained significant (adjusted OR: 1.47, 95% CI (1.06–2.02)). However, after adjustment for DI, the association between TG/HDL-C ratio and risk of type 2 diabetes was no longer significant (adjusted OR: 1.22, 95% CI (0.87–1.70)).

5. Conclusions

There are conflicting data on the association of TG/HDL ratio with insulin resistance in non-Caucasian populations.[8–13] Our study is unique in that we have a large sample size of African American and Hispanic non-diabetic subjects with a wide range of BMI and insulin sensitivity to investigate the association between TG/HDL-C ratio with insulin resistance and β-cell function in a cross sectional manner. Insulin sensitivity and β-cell function were measured using FSIGT, which is more accurate than other measures such as HOMA. We found that similar to Caucasians, the TG/HDL-C ratio is associated with insulin sensitivity in Hispanics and African Americans. A higher TG/HDL-C ratio was associated with decreased insulin sensitivity (lower S_I) regardless of gender and race. This is important especially in African Americans because metabolic syndrome is a poor predictor of IR in this population[21] due to their favorable lipid profile[22].

Different cut-off values for the TG/HDL-C ratio have been proposed to predict IR with varying success.[8–13] We did not stratify subjects as insulin resistant vs. insulin sensitive as no universal cutoff for insulin resistance has been established and depending on the method and population the cutoff for insulin resistance will be different. Instead, for the first time, we reported that the TG/HDL-C ratio cut off of 1.67 in African American women and 2.17 in Hispanic women had an 80% sensitivity in predicting type 2 diabetes. The cut off values for incident type 2 diabetes were different among ethnic groups which could be due to decreased TG and increased HDL levels in African Americans compared to other ethnic groups.[9,14] The TG/HDL-C ratio was not a predictor for diabetes in men, possibly due to a smaller number of incident diabetes in men or gender differences in lipid metabolism. Distinct differences in the mobilization, metabolism, and storage of fat between genders have been reported which could explain our findings.[23,24] It is also possible that since the TG/HDL-C ratio association with insulin sensitivity and β-cell function was in the same direction in men and women, but the association with type 2 diabetes was only seen in women, that the differences in HDL-C and TG noted between men and women in this population confer different risk for diabetes that the ratio obscures. Further investigations in a larger population with longer follow up are needed.

Both S_I[5] and DI[25] have been reported to be associated with incident type 2 diabetes in this cohort of Hispanics and African Americans. We

Table 2
Association of TG/HDL-C ratio with insulin sensitivity, and disposition index at baseline in Hispanics and African-Americans in the IRAS Family Study.

Outcome	TG/HDL-C ratio Coefficient ± SE (*p*-value)			
	Hispanics		African Americans	
	Female $N = 513$	Male $N = 312$	Female $N = 211$	Male $N = 149$
Insulin sensitivity (S_I)	-0.06 ± 0.007 ($p = 6 \times 10^{-6}$)	-0.02 ± 0.006 ($p = 0.001$)	-0.09 ± 0.02 ($p = 0.0002$)	-0.05 ± 0.01 ($p = 0.0002$)
Acute insulin response (AIRg)	0.52 ± 0.17 ($p = 0.003$)	0.06 ± 0.16 ($p = 0.70$)	-1.27 ± 0.73 ($p = 0.08$)	-0.52 ± 0.42 ($p = 0.22$)
Disposition index (DI)	-1.03 ± 0.24 ($p = 1 \times 10^{-5}$)	-0.35 ± 0.23 ($p = 0.13$)	-4.16 ± 1.02 ($p = 7 \times 10^{-5}$)	-1.31 ± 0.52 ($p = 0.01$)

For all models, Hispanics are adjusted for clinic site.
For DI and S_I, model is adjusted for age, BMI, current smoking status, and physical activity (total EEE).
For AIR, model is adjusted for age, BMI, current smoking status and S_I.
S_I was transformed using Log ($S_I + 1$); AIRg was transformed using the signed square root transformation; DI was transformed using the signed square root transformation.

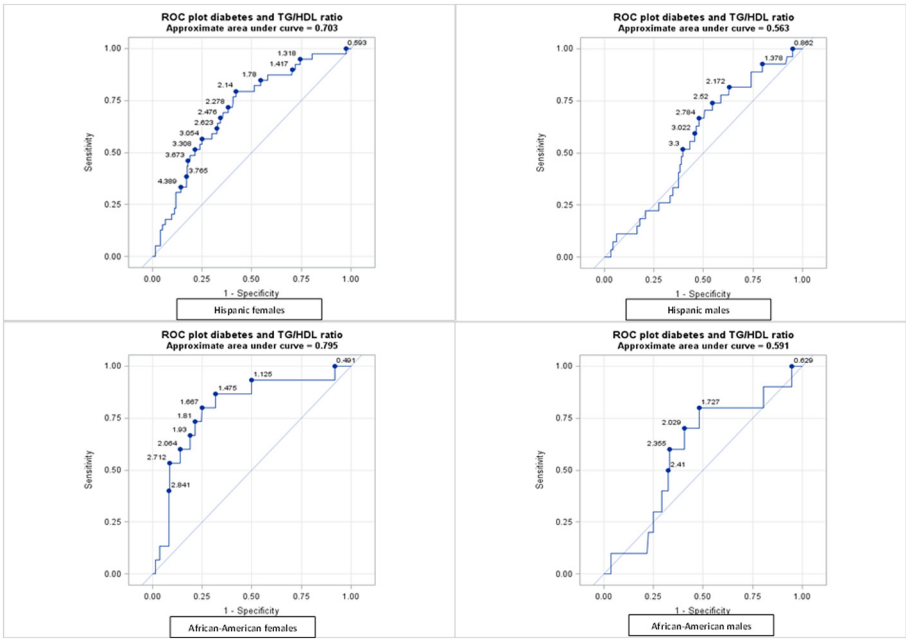

Fig. 1. Receiver operating characteristic curves for TG/HDL-C ratio as a single predictor of incident diabetes and/or incident impaired fasting glucose. Area under the curve (AUC) was 0.703 for Hispanic females and 0.563 for Hispanic males, and 0.795 for African-American females and 0.591 for African-American males.

therefore wanted to assess whether the association between the TG/HDL-C ratio and type 2 diabetes was independent of these direct measures of IR. This relationship was slightly attenuated but remained significant after additional adjustment for S_I, but was largely attenuated and became non-significant after adjustment for DI. This suggests that while insulin resistance is important in the relationship between the TG/HDL-C ratio and type 2 diabetes, the largest effect of the association between TG/HDL-C ratio and incident type 2 diabetes may be through β-cell dysfunction. Potential mechanisms indicate the TG/HDL-C ratio as a marker of lipotoxicity in β-cells resulting in decreased insulin secretion[26] and increased β-cell apoptosis from increased triglyceride concentrations[27].

A previous study indicated that among normoglycemic Caucasians and African Americans, increased HDL-C levels were inversely associated with conversion to prediabetes, whereas increased TG levels were positively associated with conversion to prediabetes[28]. Combined with our results, recognizing patients at risk for developing diabetes using data from fasting lipid profile is of great value because interventions such as lifestyle changes could delay the progression to diabetes and prevent subsequent complications[2]. Measures of insulin sensitivity and β-cell dysfunction (such as S_I and DI) are also predictive of incident diabetes but are not clinically applicable. TG/HDL-C with race-specific cutoffs could be used as a novel predictor of type 2 diabetes in certain populations.

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Table 3
Association of TG/HDL-C ratio at baseline in multivariable models of incident diabetes at follow-up in the IRAS Family Study.

Outcome Incident type 2 diabetes	TG/HDL-C ratio OR (95% CI) *p*-value			
	Hispanics		African Americans	
	Female $N = 544$	Male $N = 325$	Female $N = 210$	Male $N = 142$
Model 1	1.10 (0.98–1.23) $p = 0.10$	0.95 (0.82–1.10) $p = 0.52$	1.68 (1.24–2.29) $p = 0.0009$	1.05 (0.93–1.19) $p = 0.42$
Model 2: $+S_I$	1.06 (0.94–1.19) $p = 0.34$	0.92 (0.78–1.09) $p = 0.34$	1.47 (1.06–2.02) $p = 0.02$	0.98 (0.85–1.13) $p = 0.77$
Model 3: +DI	0.97 (0.88–1.08) $p = 0.63$	0.91 (0.77–1.07) $p = 0.27$	1.22 (0.87–1.70) $p = 0.25$	0.97 (0.83–1.12) $p = 0.66$

Odds ratio is calculated for a 1 unit increase in TG/HDL-C ratio.
Model 1 is adjusted for age and BMI at baseline. Models in the Hispanic population were also adjusted for clinic site.
Model 2 is adjusted for model 1 + S_I.
Model 3 is adjusted for model 1 + DI.

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