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The Triglyceride/High-Density Lipoprotein Cholesterol Ratio Fails to Predict Insulin Resistance in African-American Women: An Analysis of Jackson Heart Study

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Abstract

Background: Compared to whites, insulin-resistant African Americans have worse outcomes. Screening programs that could identify insulin resistance early enough for intervention to affect outcome often rely on triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) levels. Racial differences in TG and HDL-C may compromise the efficacy of these programs in African Americans. A recommendation currently exists to use the TG/HDL-C ratio $\geq$2.0 to predict insulin resistance in African Americans. The validity of this recommendation needs examination. Therefore, our aim was to determine the ability of TG/HDL-C ratio to predict insulin resistance in African Americans.

Methods: In 1,903 African Americans [895 men, 1,008 women, age 55 ± 12 years, mean $\pm$ standard deviation (SD), range 35–80 years, body mass index (BMI) $31.0 \pm 6.4\,kg/m^2$, range $18.5–55\,kg/m^2$] participating in the Jackson Heart Study, a population-based study of African Americans, Jackson, Mississippi tricounty region, insulin resistance was defined by the upper quartile ($\geq$4.43) of homeostasis model assessment of insulin resistance (HOMA-IR). An area under the receiver operating characteristic curve (AUC-ROC) of $>$0.70 was required for prediction of insulin resistance by TG/HDL-C. The optimal test cutoff was determined by the Youden index.

Results: HOMA-IR was similar in men and women (3.40 ± 2.03 vs. 3.80 ± 2.46, $P = 0.60$). Women had lower TG (94 ± 49 vs. 109 ± 65 mg/dL $P < 0.001$) and TG/HDL-C (1.9 ± 1.4 vs. 2.7 ± 2.1, $P < 0.001$). For men, AUC-ROC for prediction of insulin resistance by TG/HDL-C was: 0.77 ± 0.01, mean $\pm$ standard error (SE), with an optimal cutoff of $\geq$2.5. For women, the AUC-ROC was 0.66 ± 0.01, rendering an optimal cutoff indefinable. When women were divided in two groups according to age, 35–50 years and 51–80 years, the results did not change.

Conclusions: In African-American men, the recommended TG/HDL-C threshold of 2.0 should be adjusted upward to 2.5. In African-American women, TG/HDL-C cannot identify insulin resistance. The Jackson Heart Study can help determine the efficacy of screening programs in African Americans.

Introduction

African Americans have disproportionately high rates of diseases related to insulin resistance, specifically type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[1,2] This disparity is independent of health insurance and socioeconomic status.[3,4] Although there are many theories for why this disparity exists, there has been little inquiry into the effectiveness of screening programs for early diagnosis of insulin resistance, T2DM, and CVD in African Americans.[3,4]

The lipid levels measured by most screening programs designed to achieve early diagnosis of insulin resistance, T2DM, and CVD are triglyceride (TG) alone or TG with

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high-density lipoprotein cholesterol (HDL-C). A few examples are metabolic syndrome, hypertriglyceridemic waist syndrome, Framingham Offspring Study Score, and TG/HDL-C ratio.[5–8] Each has a unique system for incorporating TG values into the syndrome or scoring definition, but little consideration is given to either ethnic or sex differences in TG levels. Population studies have consistently shown that African Americans have lower TG levels than whites or Hispanics.[9] In addition, African-American women have lower TG levels than men.[9] As a consequence, the TG values used by these scoring systems may be inappropriate for African Americans.[10]

To explore this issue, we examined the ability of the TG/HDL-C ratio to predict insulin resistance in African Americans. The decision to focus on the TG/HDL-C ratio was made because the TG/HDL-C ratio as a predictor of insulin resistance relies only on lipid levels.[6,11] In addition, the TG/HDL-C ratio was originally developed in cross-sectional studies and could be tested in African Americans using cross-sectional data from the Jackson Heart Study, a population-based study of African Americans living in the Jackson, Mississippi, tricounty region. The prevalence of T2DM in the Jackson Heart Study cohort is 19%. Because insulin resistance is a key risk factor for the development of T2DM, the nondiabetic African-American participants in the Jackson Heart cohort would be expected to have a high prevalence of insulin resistance.

The initial recommendation to use the TG/HDL-C ratio as a predictor of insulin resistance comes from a cross-sectional study of 258 individuals that reported that a TG/HDL-C ratio $\geq$3.0 reliably predicted insulin resistance in overweight people; however, only 3 of the participants in this study were African Americans.[6] Subsequently, the TG/HDL-C ratio was tested in a cross-sectional cohort of 90 overweight African Americans.[12] In that investigation, the area under the receiver operating characteristic (AUC-ROC) curve for the ability of the TG/HDL-C ratio to predict insulin resistance was 0.56, meaning that the rate of true positivity was nearly equal to the rate of false positivity. Consequently, that study did not support the use of the TG/HDL-C as a predictor of insulin resistance in African Americans.

More recently, the ratio was tested in National Health and Nutrition Examination Study (NHANES) 1999–2002 data.[11] In that study, Li et al. reported that the TG/HDL-C predicted insulin resistance, but ethnic differences in the TG/HDL-C threshold were identified. In whites and Hispanics, the TG/HDL-C ratio $\geq$3.0 predicted insulin resistance. In African Americans, the threshold for the prediction of insulin resistance was TG/HDL-C $\geq$2.0. However, in the NHANES sample, there were only 479 African Americans, and sex differences in the ability of the TG/HDL-C ratio to predict insulin resistance were not examined. Our goal was to determine the ability of the TG/HDL-C ratio to predict insulin resistance in African Americans participating in the Jackson Heart Study.

Methods

The Jackson Heart Study is a population-based cohort designed to prospectively evaluate CVD risk in African Americans.[13] Between 2000 and 2004, participants were recruited from the Atherosclerosis Risk in the Community (ARIC) study site in Jackson, Mississippi, supplemented by random and constrained volunteer samples from defined demographic cells within the tricounty region of Hinds, Madison, and Rankin counties, thereby ensuring that the cohort reflected the regional African-American population. The study was approved by Institutional Review Boards of University of Mississippi, Jackson State University, and Tougaloo College. Participants gave informed consent.

There were 2,270 unrelated, nondiabetic Jackson Heart Study participants between ages 35 and 80 years with a body mass index (BMI) of 18.5–55 kg/m^2. Medications that led to exclusion were hypolipidemics, thyroid hormone, oral contraceptives, and postmenopausal estrogen replacement. Data entry error led to the exclusion of 1 participant. There were no persons with missing values for TG, HDL-C, fasting glucose, or insulin. Fasting glucose and insulin were used to calculate homeostasis model assessment of insulin resistance (HOMA-IR).[14] To avoid the impact of outliers, inclusion required TG $\leq$500 mg/dL and HDL-C $\leq$100 mg/dL. In the final analyses, there were 1,903 participants (895 men, 1,008 women) divided into quartiles of HOMA-IR, with insulin resistance defined by the upper quartile ($\geq$4.43).

AUC-ROC was used to determine the ability of TG, HDL, and the TG/HDL-C ratio to predict insulin resistance.[6,11,12] A ROC curve is a plot of sensitivity (true positive) versus 1-specificity (false positive). When the AUC-ROC equals 0.5, then the rate of true positivity is equal to that of false positivity, an indication that the test (i.e., TG/HDL-C ratio) does not predict the disorder (i.e., insulin resistance). However, if the AUC-ROC is $\geq$0.7, the test is an acceptable predictor of insulin resistance.[11] The Youden index can then be used to determine the TG/HDL-C threshold with the optimal combination of sensitivity and specificity for the prediction of insulin resistance.[11] The Youden index is defined as the maximum value of sensitivity + specificity -1.[15]

Analyses were performed with SAS 9.2 (Cary, NC). $P < 0.05$ defined significance.

Results

Participant characteristics are provided by gender in Table 1. Women were more obese than men, and before adjustment for BMI, women appeared to be more insulin resistant than men. After adjusting for BMI, there was no difference between the sexes in HOMA-IR.

The TG/HDL-C ratio was a better predictor of insulin resistance (higher AUC-ROC) than either TG or HDL-C (Table 2). For men and women combined, AUC-ROC for the prediction of insulin resistance by TG/HDL-C was 0.70 ± 0.01(mean $\pm$ SE). When men were examined separately, the AUC-ROC curve was higher, 0.77 ± 0.01, and the Youden Index defined the optimal TG/HDL-C cutoff as $\geq$2.5. In contrast, for women, the AUC-ROC was only 0.66 ± 0.01. Results were similar when women were subdivided into two groups according to age, 35–50 years and 51–80 years (Table 2). Therefore, in women, TG/HDL-C did not predict insulin resistance, and the Youden index was indefinable.

Discussion

This investigation in African Americans reports for the first time that the ability of TG/HDL-C ratio to predict insulin resistance is sex specific. The TG/HDL-C ratio at a threshold of 2.5 can be used to screen for insulin resistance in African-American men. However, the TG/HDL-C ratio as a marker of insulin resistance is not effective in African-American women. Our results suggest that the recommendation by Li et al. to use the TG/HDL-C ratio at a

Table 1. Participant Characteristics

Parameter	*Men*[a] *n = 895*	*Women*[a] *n = 1008*	*P value*[b]	*P value*[c]
Age (years)	55 ± 11	55 ± 12	0.14	
Weight (kg)	92.8 ± 19.2	87.2 ± 19.1	<0.001	
Height (cm)	177.3 ± 7.1	164.0 ± 6.5	<0.001	
BMI (kg/m^2)	29.4 ± 5.5	32.4 ± 6.8	<0.001	
HOMA-IR	3.40 ± 2.03	3.80 ± 2.46	<0.001	0.60
TG (mg/dL)	109 ± 65	94 ± 49	<0.001	<0.001
HDL-C (mg/dL)	45 ± 12	54 ± 13	<0.001	<0.001
TG/HDL-C ratio	2.7 ± 2.1	1.9 ± 1.4	<0.001	<0.001

[a]Data presented as mean ± standard deviation (SD).
[b]Comparisons by unpaired *t*-test.
[c]Comparisons adjusted for body mass index.
BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; TG, trigycerides; HDL-C, high-density lipoprotein cholesterol.

cutoff of 2.0 in all African Americans was not optimal.[11] Because they combined men and women into one group, the lack of efficacy of the ratio in African-American women was masked.

Using TG/HDL-C at a cutoff of 2.0 in African-American men will lead to over diagnosis of insulin resistance and the lost opportunity to focus resources on those with the greatest need for intervention. In African-American women, there is no TG/HDL-C ratio that should lead to the presumption of good health or the absence of insulin resistance.

In African-American women, the failure of the TG/HDL-C ratio to predict insulin resistance probably occurred due to normal TG levels rather than high HDL-C levels. This view is based on the observation that the African-American women with the metabolic syndrome are more likely to have low HDL-C levels than elevated TG levels.[16]

Table 2. Area Under the Receiver Operating Characteristic Curves for the Ability of Triglyceride, High-Density Lipoprotein Cholesterol, and Triglyceride/High-Density Lipoprotein Cholesterol Ratio to Predict Insulin Resistance

Variable	*Mean ± SE*	*95% Confidence Interval*
Men and women ($n = 1{,}903$)		
TG	0.68 ± 0.01	0.65–0.71
HDL	0.64 ± 0.01	0.62–0.67
TG/HDL-C ratio	0.70 ± 0.01	0.67–0.73
Men ($n = 895$)		
TG	0.75 ± 0.01	0.71–0.78
HDL	0.69 ± 0.01	0.65–0.73
TG/HDL-C ratio	0.77 ± 0.01	0.73–0.80
Women ($n = 1{,}008$; ages 35–80 years)		
TG	0.63 ± 0.01	0.59–0.67
HDL	0.64 ± 0.01	0.60–0.68
TG/HDL-C ratio	0.66 ± 0.01	0.62–0.69
Women ($n = 410$; ages 35–50 years)		
TG	0.65 ± 0.03	0.58–0.72
HDL	0.66 ± 0.03	0.60–0.72
TG/HDL-C ratio	0.68 ± 0.03	0.61–0.74
Women ($n = 598$, ages 51–80 years)		
TG	0.60 ± 0.03	0.55–0.65
HDL	0.64 ± 0.03	0.59–0.69
TG/HDL-C ratio	0.64 ± 0.03	0.59–0.68

SE, standard error; TG, triglyceride; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol.

Li et al. reported from a NHANES 1999–2002 data sample that TG/HDL-C >2.0 predicted insulin resistance in African Americans, and this study was modeled after their investigation.[11] However, Li et al. defined insulin resistance as the upper quartile of fasting insulin. We chose to use the upper quartile of HOMA-IR. HOMA-IR is superior to fasting insulin, because fasting insulin cannot identify insulin resistance in the presence of β-cell failure.[14] Nevertheless, to test the robustness of our results, we repeated the analyses using the upper quartile and tertile of fasting insulin as well as the upper tertile of HOMA-IR (data not shown). In each analyses, the TG/HDL-C ratio predicted insulin resistance in men with the optimal cutoff of 2.5. In contrast, for women, all analyses, including TG alone, HDL-C alone, and the TG/HDL-C ratio, had AUC-ROC <0.70. Therefore, none predicted insulin resistance in women.

A challenge associated with this type of investigation is how best to measure insulin resistance. Glucose clamps and the minimal model determination of the insulin sensitivity index from frequently sampled intravenous glucose tolerance tests would yield more precise results, but they are expensive and often infeasible for large cohorts. Fasting insulin and HOMA-IR are less sensitive measures of insulin resistance, but this weakness can be minimized by having a large sample size.

Using the TG/HDL-C ratio as a paradigm for screening programs designed to detect insulin resistance, we demonstrated with the use of a population-based study of African Americans—the Jackson Heart Study—that this ratio is not effective in African-American women. We recommend a search for other easy-to-obtain measurements such as waist circumference that could identify insulin resistance in African-American women. For African-American men, we found that the TG/HDL-C ratio did identify insulin resistance, but the threshold of 2.0 should be adjusted upward to 2.5.

With the TG/HDL-C ratio as an example, our study demonstrates the need for more extensive testing of screening programs in African-American men and women. Health disparities research should examine the possibility that screening programs currently in use for conditions related to insulin resistance may not be optimal in African Americans. The consequence of inadequate screening programs could be late diagnosis and poor outcomes.

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Author Disclosure Statement

The authors have no conflict of interest to disclose.

References

1. Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, Saydah SH, Williams DE, Geiss LS, Gregg EW. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999–2002. *Diabetes Care* 2006;29:1263–1268.
2. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:e21–e181.
3. Groman R, Ginsburg J. Racial and ethnic disparities in health care: A position paper of the American College of Physicians. *Ann Intern Med* 2004;141:226–232.
4. Spertus JA, Jones PG, Masoudi FA, Rumsfeld JS, Krumholz HM. Factors associated with racial differences in myocardial infarction outcomes. *Ann Intern Med* 2009;150:314–324.
5. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640–1645.
6. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med* 2003;139:802–809.
7. St-Pierre J, Lemieux I, Perron P, Brisson D, Santuré M, Vohl MC, Després JP, Gaudet D. Relation of the "hypertriglyceridemic waist" phenotype to earlier manifestations of coronary artery disease in patients with glucose intolerance and type 2 diabetes mellitus. *Am J Cardiol* 2007;99:369–373.
8. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB, Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med* 2007;167:1068–1074.
9. Sumner AE, Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. *Atherosclerosis* 2008;196:696–703.
10. Sumner AE. Ethnic differences in triglyceride levels and high-density lipoprotein lead to underdiagnosis of the metabolic syndrome in black children and adults. *J Pediatr* 2009;155:S7 e-
11. Li C, Ford ES, Meng YX, Mokdad AH, Reaven GM. Does the association of the triglyceride to high-density lipoprotein cholesterol ratio with fasting serum insulin differ by race/ethnicity? *Cardiovasc Diabetol* 2008;7:4.
12. Sumner AE, Finley KB, Genovese DJ, Criqui MH, Boston RC. Fasting triglyceride and the triglyceride-HDL cholesterol ratio are not markers of insulin resistance in African Americans. *Arch Intern Med* 2005;165:1395–1400.
13. Fuqua SR, Wyatt SB, Andrew ME, Sarpong DF, Henderson FR, Cunningham MF, Taylor HA Jr. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. *Ethn Dis* 2005;15:S6-18-29.
14. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004;27:1487–1495.
15. Perkins NJ, Schisterman EF. The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. *Am J Epidemiol* 2006;163:670–675.
16. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006. *Natl Health Stat Report* 2009:1–7.

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