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Should triglycerides and the triglycerides to high-density lipoprotein cholesterol ratio be used as surrogates for insulin resistance?

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Abstract

The aims of the present study were to examine whether triglycerides (TG) and the triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) could predict insulin resistance in healthy African Americans and whites. This cross-sectional study included 99 African American and 50 white men and women between 18 and 45 years of age with body mass indexes between 18.5 and 38.0 kg/m^2. Anthropometric measures were obtained; and overnight fasting blood was collected for TG, HDL-C, glucose, and insulin. *Insulin resistance* was defined by fasting insulin concentration of at least 13.13 μU/mL and homeostasis model assessment of insulin resistance (HOMA-IR) of at least 2.5. Receiver operating characteristic curves were used to analyze the data. African Americans and whites had comparable demographic and anthropometric measures. Fasting insulin was higher in African Americans (12.4 ± 7.8 μU/mL) than whites (10.2 ± 7.5 μU/mL), but HOMA-IR did not differ significantly (African Americans, 2.9 ± 2.0; whites, 2.4 ± 1.9). Triglycerides and TG/HDL-C were significantly lower in African Americans (TG, 68.2 ± 43.3 mg/dL; TG/HDL-C, 1.8 ± 2.1) compared with whites (TG, 105.4 ± 55.2 mg/dL; TG/HDL-C, 2.8 ± 1.8). Area under the receiver operating characteristic curves revealed that both TG and TG/HDL-C were acceptable markers of insulin resistance, as defined by fasting insulin concentration, in whites, 0.770 and 0.765, respectively, but poor predictors in African Americans, 0.633 and 0.651, respectively. Similarly, TG and TG/HDL-C were acceptable in predicting insulin resistance, as measured by HOMA-IR, in whites, 0.763 and 0.770, respectively, but poor in predicting HOMA-IR in African Americans, with areas of 0.625 and 0.639, respectively. In conclusion, the relationship between TG and TG/HDL-C with insulin resistance differs by ethnicity; and using TG and TG/HDL-C to predict insulin resistance in African Americans would not be appropriate.

1. Introduction

Insulin resistance, characterized by an inadequate physiologic response to insulin, is one of the major risk factors for type 2 diabetes mellitus [1,2]. When impaired glucose metabolism is actually detected by elevated fasting glucose concentrations or a glucose tolerance test, a significant proportion of β-cells may have already been destroyed or compromised [3]. There is no cure for diabetes; thus, prevention is the best intervention. However, if insulin resistance is detected early, while glucose responses are still intact, interventions using lifestyle modifications are more likely to be successful [4,5].

It is well established that insulin resistance is associated with cardiovascular disease (CVD) development and death [6-8]. Therefore, the aggregation of CVD risk factors, or

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Institutional approval: The authors and researchers involved in this study complied with ethical standards in the treatment of the human subjects in this study and are in compliance with regulations of the USUHS Institutional Review Board. All participants went through the informed consent procedure, knew risks and benefits associated with participation in the study, and provided written consent prior to participation. This study was approved and monitored by the USUHS Institutional Review Board.

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metabolic syndrome, has been developed to identify individuals at an increased risk for CVD, with insulin resistance as the common denominator that precedes other facets of the syndrome [8,9]. However, the use of insulin resistance as one of the criteria for metabolic syndrome was limited by the impracticality of quantifying insulin resistance in clinical settings. Thus, surrogates of insulin resistance, which would be more practical and reliable in clinical settings, were proposed.

Triglycerides (TG) and the triglyceride to high-density lipoprotein cholesterol concentration ratio (TG/HDL-C) have been reported to be closely related to insulin resistance, and use of TG and TG/HDL-C as surrogates for insulin resistance has been recommended [10-12]. On the other hand, some authors have emphasized interethnic differences in lipid profiles and insulin resistance, and cautioned the use of lipid surrogates for insulin resistance. In fact, recent literature shows that African Americans have more favorable lipid profiles than whites despite African Americans being more insulin resistant [13-15]. Therefore, the aim of our study was to examine how well insulin resistance could be predicted from TG and TG/HDL-C in a group of young, healthy African American and white participants.

2. Methods

2.1. Participants

African American and white men and women between the ages of 18 and 45 years were recruited from the surrounding Washington, DC, metropolitan area. Of the 160 volunteers, data for 99 African American (45 men, 54 women) and 50 white participants (26 men, 24 women) were available for analysis. Participants were free of other known major diseases, such as heart disease, diabetes, peripheral vascular disease, liver disease, thyroid, and other endocrine diseases, or medication for any of these conditions. Each volunteer underwent a thorough telephone health screening and an on-site medical examination to ensure that all inclusion/exclusion criteria were met. Participants' body mass index (BMI) values ranged between 18.5 and 38.0 kg/m^2; and because obesity and insulin resistance are comorbid conditions, participants were recruited by BMI category to achieve a comparable distribution among normal-weight, overweight, and obese participants.

All participants were informed of the purposes and procedures of the study and provided written consent before participation. This study was approved and monitored by the Uniformed Services University of the Health Sciences Institutional Review Board.

2.2. Procedures/measurements

Participants reported to the laboratory at the university between 7:00 and 8:00 AM after overnight fast. Participant assessments included anthropometric measures (weight, height, waist circumference, and percentage body fat) and blood draws for fasting blood glucose, insulin, and lipid profiles (total cholesterol, TG, HDL-C, and calculated low-density lipoprotein cholesterol [LDL-C]).

Body weight was measured with a calibrated balance beam metric scale to the nearest 0.1 kg and height was measured to the nearest 0.1 cm while the participant was wearing light clothing and no shoes. Body mass index was calculated by weight in kilograms divided by height in meters squared. Percentage body fat was estimated by bioelectric impedance with the portable RJL body composition analyzer (RJL Systems, 1992, Clinton Township, MI) by using the National Health and Nutrition Examination Survey formula [16]. Waist circumference was measured with an inelastic tape around the waist by standard techniques [17].

Blood was collected in fasting state by standardized venipuncture techniques between 8:00 and 9:00 AM. Samples were collected with anticoagulant for insulin and lipid profiles, and in sodium fluoride tubes for glucose. Plasma was extracted and stored in a −80°C freezer. Blood glucose concentration was measured with the YSI Biochemistry Analyzer Model 2700/115V (Yellow Springs Instrument, Yellow Springs, OH). Serum insulin was measured by standard radioimmunoassay (Diagnostic Systems Laboratory-1600, Webster, TX). Insulin samples were assayed in duplicate, and intra- and interassay coefficients of variation were less than 10%. All samples were within 0.2 μU/mL apart, or a third sample was measured; the closest 2 measurements were used. Lipid profiles were determined in the Clinical Laboratory at the National Institutes of Health Department of Laboratory Medicine using an LX-20 analyzer (Beckman, San Diego, CA). Low-density lipoprotein cholesterol was calculated by the Friedewald equation. Intra- and interassay coefficients of variation for lipid measures were less than 5%.

2.3. Definition of insulin resistance

Insulin resistance was defined using the 75th percentile cutoff values of the fasting insulin concentrations among nondiabetic adult participants in the National Health and Nutrition Examination Survey 1999-2002 data [10,18]. The 75th percentile cutoff was 13.13 μU/mL. Insulin resistance was also defined by using homeostasis model assessment method of insulin resistance (HOMA-IR) (glucose [in millimoles per liter] × insulin [in microunits per milliliter]/22.5) values of at least 2.5 [19-22].

2.4. Statistical analyses

Data are presented as mean ± standard deviation. χ^2 analyses and multivariate analyses of variance were used to compare baseline characteristics by ethnicity. For multivariate analysis of variance, parameters were transformed if they were not normally distributed; and analyses were only performed using transformed data. However, untransformed data are presented in the table. Areas under the receiver

operating characteristic (ROC) curves were used to examine the predictive value of TG and the TG/HDL-C for insulin resistance measures in whites and African Americans. The areas under the ROC curves are presented with standard errors: area under the ROC curve of 0.5 = no discrimination, 0.7 ≤ ROC< 0.8 = acceptable, 0.8 ≤ ROC < 0.9 = excellent, ROC ≥0.9 = outstanding [23]. The statistical significance level was set at < .05, and all data were analyzed using the SPSS statistical package (SPSS, version 16.0.1; SPSS, Chicago, IL).

3. Results

Demographic information of 99 African American and 50 white participants is presented in Table 1. African Americans were slightly older than whites; but African Americans and whites did not differ by percentage of women, education, income, or anthropometric measures. Fasting morning glucose, HOMA-IR, blood pressure, total cholesterol, and LDL-C did not differ by ethnicity; but fasting insulin concentrations and HDL-C were significantly higher and TG and TG/HDL-C were significantly lower in African Americans compared with whites. The range of fasting insulin concentrations was 4 to 38.2 μU/mL for whites and 4 to 50.5 μU/mL for African Americans.

Table 1
Participant characteristics by ethnicity

	Whites	African Americans
	Mean (±SD)	Mean (±SD)
	n = 50	n = 99
Demographics		
Age (y)*	28.2 (5.5)	30.8 (8.2)
Sex (female/male)	24/26	54/45
Income		
<25 000	7	26
25 000-50 000	17	42
50 000-80 000	12	20
>80 000	8	7
Missing or would not say	6	5
Education		
HS	0	6
Some college	19	47
>BA/BS	25	42
Missing or would not say	6	5
Anthropometrics		
Height (cm)	173.3 (10.4)	170.1 (10.2)
Weight (kg)	83.3 (19.4)	80.4 (16.8)
BMI (kg/m^2)	27.5 (5.2)	27.6 (4.5)
BMI groups (NW/OW/OB)	18/15/17	31/34/34
Waist circumference (cm)	88.1 (15.4)	87.7 (12.0)
Body fat %	30.5 (9.6)	31.9 (8.2)
Metabolic characteristics		
Fasting glucose (mmol/L)	5.3 (.7)	5.1 (.7)
Fasting insulin (μU/mL)*	10.2 (7.5)	12.4 (7.8)
HOMA-IR	2.4 (1.9)	2.9 (2.0)
Systolic BP (mm Hg)	123 (11.4)	124 (13.0)
Diastolic BP (mm Hg)	68 (8.6)	69 (9.1)
Total cholesterol	155.1 (34.0)	155.8 (24.8)
TG (mg/dL)†	105.4 (55.2)	68.2 (43.3)
HDL-C (mg/dL)*	42.5 (11.3)	46.9 (12.5)
LDL-C (mg/dL)	91.5 (30.9)	95.3 (23.0)
TG/HDL-C†	2.8 (1.8)	1.8 (2.1)

NW indicates normal weight, OW, overweight; OB, obese; BP, blood pressure.
Ethnic differences significant at *P < .05 and †P < .001.

When the fasting insulin concentration criterion was applied to the definition of insulin resistance, 13 (26%) of whites and 35 (35.4%) of African Americans were found to be insulin resistant. Using the HOMA-IR cutoff criterion, 17 (34%) whites and 45 (45.5%) African Americans were classified as insulin resistant. When the TG and the TG/HDL-C cutoffs recommended for predicting insulin resistance in a previous study were used (TG ≥130 and TG/HDL-C ≥3) [11], we found that 13 (26%) whites and 9 (9.1%) African Americans fell into the high-TG category and 17 (34%) whites and 12 (12.1%) African Americans were in the high–TG/HDL-C category. The proportion of whites and African Americans meeting TG and TG/HDL-C cutoffs differed significantly between the 2 ethnic groups, χ^2 (1, n = 149) = 7.55, P = .006 and χ^2 (1, n = 149) = 10.15, P < .001, respectively.

Fig. 1 presents the ROC curves predicting insulin resistance from TG and TG/HDL-C in whites and African Americans. The area under the ROC curves for potential markers of insulin resistance are presented in Table 2 by ethnicity. Fig. 1 (A and B) shows the ROC curve predicting HOMA-IR using TG and TG/HDL-C for whites and African Americans, respectively. Both TG and TG/HDL-C were acceptable markers for insulin resistance as estimated by HOMA-IR in whites: 0.763 ± 0.074 and 0.770 ± 0.084, respectively [23]. In contrast, both TG and TG/HDL-C were poor predictors for HOMA-IR in African Americans: 0.625 ± 0.056 and 0.639 ± 0.055, respectively. Similarly, areas under the ROC curve showed that TG and TG/HDL-C were acceptable in predicting insulin resistance as defined by fasting insulin concentration in whites, 0.770 ± 0.084 and 0.765 ± 0.083, respectively, whereas the predictability remained poor for African Americans, 0.633 ± 0.056 and 0.651 ± 0.055, respectively (Fig. 1C and D). None of the lipid surrogate markers for African Americans was in the acceptable range.

The best surrogate of both HOMA-IR and fasting insulin concentration in whites was waist circumference (Table 2). In African Americans, BMI was the best surrogate for HOMA-IR. For fasting insulin concentration, percentage body fat was the best marker in African Americans. However, none of the anthropometric surrogate markers for African Americans was excellent or outstanding.

4. Discussion

The current study examined the appropriateness of using TG and TG/HDL-C as surrogates of insulin resistance in

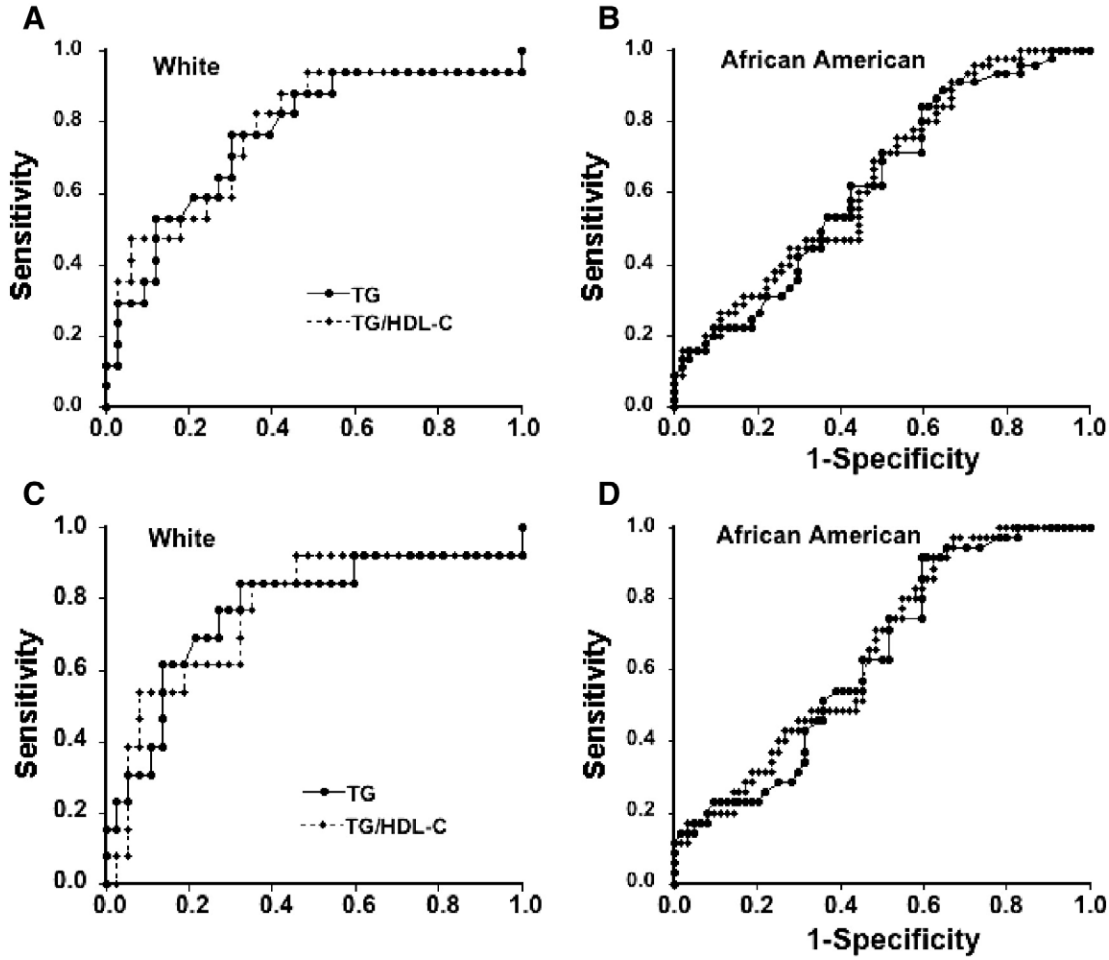

Fig. 1. Receiver operating characteristic curves of TG and TG/HDL-C predicting insulin resistance by ethnicity. Note: ROC curve of TG and TG/HDL-C for predicting HOMA-IR in white (A) and in African American (B) subjects. Receiver operating characteristic curve of TG and TG/HDL-C for predicting fasting insulin concentrations in white (C) and in African American (D) subjects.

whites and African Americans. Our findings showed that, although more African Americans were insulin resistant, a significantly lower percentage of African Americans met the proposed cutoffs for high TG and TG/HDL-C. Furthermore, the predictability of insulin resistance when using TG and TG/HDL-C was poor in African Americans. The low sensitivity noted in predicting insulin resistance in African Americans may reflect a nonrelationship between TG and TG/HDL-C with HOMA-IR or fasting insulin concentrations, as suggested by others [24]. However, the correlations between TG and TG/HDL-C with HOMA-IR and fasting insulin concentrations were similar for both whites and African Americans (r for TG and HOMA-IR: whites = 0.30 and African Americans = 0.30; TG and fasting insulin: whites = 0.28 and African Americans = 0.27; TG/HDL-C and HOMA-IR: whites = 0.34 and African Americans = 0.33; and TG/HDL-C and fasting insulin: whites = 0.32 and African Americans = 0.29; all associations, $P < .05$). Thus, the appropriateness of the cutoffs for TG and TG/HDL-C may be an issue, rather than the lack of correlation between these variables across ethnic groups. Another commonly used surrogate for insulin resistance is abdominal obesity [8,25,26]. In fact, the National Cholesterol Education program Adult Treatment Panel III diagnostic criteria for metabolic syndrome use waist circumference as a surrogate for insulin resistance. However, our study indicates that, although waist circumference was an outstanding predictor of insulin resistance in whites, it was not as predictive in African Americans. Thus, neither the lipid nor the waist circumference criteria appear adequate in predicting insulin resistance for African American men and women.

Defining insulin resistance is difficult because no clear guidelines or cutoffs exist for either HOMA-IR or fasting insulin concentrations [27]. One of the criterion standard methods for diagnosing insulin resistance is the glucose clamp method, which is invasive, time consuming, and not practical in a clinical setting. Thus, the use of other related markers, such as TG or TG/HDL-C, has been encouraged. However, considering the unacceptable predictive value of lipid markers and waist circumference in African Americans, other surrogates of insulin resistance, such as HOMA-IR or fasting insulin concentration, may be preferable in a clinical

Table 2
Area under ROC curves for potential markers of HOMA-IR and fasting insulin

Predicting variable	Whites		African Americans	
	Area under ROC curve Mean ± SE	95% Confidence interval	Area under ROC curve Mean ± SE	95% Confidence interval
HOMA-IR				
Total cholesterol	0.626 ± 0.082	0.466-0.785	0.554 ± 0.059	0.438-0.670
TG	0.763 ± 0.074[a]	0.618-0.907	0.625 ± 0.056[b]	0.516-0.735
HDL-C	0.309 ± 0.076	0.160-0.459	0.379 ± 0.058	0.266-0.492
LDL-C	0.576 ± 0.087	0.404-0.747	0.585 ± 0.058	0.471-0.699
TG/HDL-C	0.772 ± 0.073[a]	0.629-0.915	0.639 ± 0.055[b]	0.531-0.747
BMI	0.866 ± 0.053	0.762-0.970	0.696 ± 0.053	0.592-0.801
Waist	0.923 ± 0.039	0.847-1.00	0.671 ± 0.058	0.557-0.786
Body fat %	0.744 ± 0.077	0.592-0.896	0.649 ± 0.059	0.533-0.765
Fasting insulin				
Total cholesterol	0.660 ± 0.088	0.488-0.832	0.556 ± 0.064	0.430-0.681
TG	0.770 ± 0.084[c]	0.606-0.935	0.633 ± 0.056[d]	0.523-0.743
HDL-C	0.350 ± 0.084	0.185-0.515	0.371 ± 0.062	0.248-0.493
LDL-C	0.590 ± 0.100	0.395-0.786	0.579 ± 0.055	0.459-0.699
TG/HDL-C	0.765 ± 0.083[c]	0.603-0.928	0.651 ± 0.055[d]	0.543-0.759
BMI	0.906 ± 0.052	0.804-1.00	0.712 ± 0.055	0.605-0.819
Waist	0.910 ± 0.044	0.823-0.996	0.691 ± 0.057	0.579-0.803
Body fat %	0.840 ± 0.064	0.714-0.967	0.715 ± 0.058	0.601-0.828

[a] Corresponds to Fig. 1A.
[b] Corresponds to Fig. 1B.
[c] Corresponds to Fig. 1C.
[d] Corresponds to Fig. 1D.

setting. Some suggested that fasting insulin concentration is the best marker of insulin resistance [24,28], and others showed insulin resistance defined by HOMA-IR mirrors clamp method results [29]. Oterdoom and colleagues [21] proposed sex-specific cutoffs (the upper quartile) for fasting insulin and HOMA-IR, respectively, of 11.2 μU/mL and 2.3 for women and 12.8 μU/mL and 2.7 for men. Their sample of more than 800 men and women were from the Netherlands and likely primarily white. However, the HOMA-IR cutoff of 2.5 without regard to sex seems justified. Importantly, efforts should be undertaken to determine sex- and ethnic-appropriate cutoffs for fasting insulin concentration and/or HOMA-IR as markers of insulin resistance so that they can be included as criteria for metabolic syndrome. This may help identify African Americans with CVD predisposition and eliminate ethnic-specific differences in metabolic syndrome rates when using the current criteria.

The major limitation of this study was the relatively small sample size and the stringent inclusion and exclusion criteria. We included only healthy adults with BMI not exceeding 38 kg/m^2; thus, generalizability may be only limited to relatively healthy normal-weight to obese category I individuals. However, if the intent of these criteria/surrogates is early detection, then our findings can be generalized to a healthy population without any major illness. Future studies should include a larger number of participants with a wide range of BMI and diverse ethnic backgrounds. Another limitation of the study was our failure to use a glucose clamp, an insulin suppression test, or the frequently sampled intravenous glucose tolerance test. However, we used fasting insulin concentration and HOMA-IR to demonstrate the practical usage of insulin resistance in clinical settings. Fasting insulin and HOMA-IR are easy to use, take minimal time, are not invasive, and show excellent predictability for insulin resistance as defined by the criterion standard methods [24,29]. In addition, to establish more stable values of fasting insulin and lipids, future studies should use multiple measurement points for insulin and lipids.

In summary, it is important to note that, if TG and/or TG/HDL-C are to be used as surrogates for insulin resistance, they show moderate predictability in whites and poor predictability in African Americans. Our findings indicate that the relationship between TG and TG/HDL-C with insulin may differ by ethnicity: insulin resistance and/or metabolic syndrome will be underdiagnosed in seemingly healthy African Americans if TG and TG/HDL-C are used to predict insulin resistance. Studies of CVD risk factors should be stratified by ethnicity to make accurate predictions and implement effective interventions.

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