The Triglyceride Paradox in People of African Descent

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Abstract

Even though insulin resistance, cardiovascular disease (CVD), and type 2 diabetes (T2D) are associated with hypertriglyceridemia, blacks with these conditions usually have normal triglyceride (TG) levels. This is often called a lipid paradox. More precisely, it is a “TG paradox.” The pathways that lead to hypertriglyceridemia have been intensively explored. Yet, the pathways that allow TG levels to be normal in the presence of insulin resistance have received little attention and this is problematic. Tests designed for the early detection of insulin-resistant conditions often use elevated TG levels as a diagnostic criterion. However, insulin resistance, CVD, and T2D are not usually associated with hypertriglyceridemia in people of African descent; therefore, the widespread use of TG levels to predict these conditions needs re-evaluation. This review focuses on black–white differences in: (1) the lipid profile across North America, Europe, and Africa; (2) the efficacy of TG-based screening tests, specifically the metabolic syndrome and its two abbreviated versions, the hypertriglyceridemic waist and TG/high-density lipoprotein cholesterol (HDL-C) ratio; and (3) the mechanisms that allow TG to be normal even in the presence of insulin resistance. Overall, a broader understanding of how TG physiology varies by race could lead to better diagnostic tests and improved health outcomes.

Introduction

CONSENSUS IS NOW WORLDWIDE that an elevated triglyceride (TG) level is an important cardiovascular disease (CVD) risk factor.^{1,2} Furthermore, hypertriglyceridemia is a marker of insulin resistance, a major cause of type 2 diabetes (T2D). Therefore, screening programs for the early detection of CVD and T2D have incorporated elevated TG as a key diagnostic criterion.^{3–11} However, TG levels in people of African descent are usually normal even when insulin resistance, CVD, or T2D are present.^{12–14} Thus, the widespread use of TG levels in screening programs needs re-evaluation.^{15–18}

Much of what is known about the history and presentation of CVD and T2D comes from classic investigations such as the Framingham Heart Study, the Physicians Health Study, and the Nurses Health Study.^{11,19} However, greater than 90% of the participants in each of these studies are white. With CVD and T2D now reaching epidemic proportions on every continent, there is an increasing awareness that observations about CVD and T2D made in one population may not be universally applicable. Racial differences in TG levels highlight the importance of multiethnic investigations. In this review, North American, European, and African data revealing black–white differences in TG levels are des-

cribed. Next, racial differences in the ability of screening programs to detect risk for CVD and T2D are discussed. Finally, mechanisms that allow TG to be normal in the presence of insulin resistance are reviewed.

Lipid Profile

This section is divided into three parts. First, the relationship between TG and high density lipoprotein-cholesterol (HDL-C) is described. Second, the TG and HDL-C profiles in healthy black and white populations are discussed. Third, racial differences in the dyslipidemia of insulin resistance are presented.

TG and HDL-C

As HDL particles participate in the clearance of TG-rich lipid particles, TG and high HDL-C levels are usually evaluated together and typically are inversely correlated.^{12,20–22} For example, if TG levels are low, HDL-C levels are high. Conversely, if TG levels are high, HDL-C levels are low. This latter pattern, high TG and low HDL-C, is highly atherogenic and often called the “dyslipidemia of insulin resistance.”

By many different routes insulin resistance leads to CVD. One well-described pathway occurs when hepatic fat content

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is high. In that setting, insulin resistance promotes hepatic production and secretion of TG-rich very-low-density lipoproteins (VLDL) particles. After secretion, a bidirectional lipid exchange process is undertaken by cholesteryl ester transfer protein (CETP). CETP transfers TG from VLDL to HDL and low-density lipoprotein (LDL). Simultaneously, CETP transfers cholesterol from HDL and LDL back to VLDL.²³ The result of this exchange process is the formation of TG-enriched small dense LDL (sdLDL) particles, which are easily oxidized and accumulate in atherosclerotic plaques.^{24,25} As TG-enriched HDL particles are rapidly cleared by the liver, there is also a decline in HDL levels. Due to the many anti-atherogenic properties of HDL particles, low levels of HDL lead to CVD.

TG and HDL-C profile in population studies

In population-based studies such as the National Health and Nutrition Examination Survey (NHANES), blacks typically have lower TG and higher HDL levels than whites.^{18,26,27} This finding has been repeated in other comparisons of black and white Americans, as well as black and white Canadians and London-based African Caribbeans and whites.^{28–31} This racial difference is also true in children and is more prominent in men than women.^{28,30–32} As blacks have a higher prevalence of stroke and myocardial infarction than whites,³³ the favorable lipid profile of low TG and high HDL-C observed in blacks is considered to be both surprising and paradoxical.¹⁶

Racial differences in the dyslipidemia of insulin resistance

To better understand the lipid paradox, it is necessary to examine racial differences, specifically in the “dyslipidemia of insulin resistance.” In whites, the dyslipidemia of insulin resistance follows the classic pattern of elevated TG and low HDL-C. However in blacks, normal TG and low HDL-C is the characteristic lipid profile of insulin resistance.¹⁷ This pattern has been observed in insulin-resistant African Americans, West Africans, and black South Africans.^{13,18,34} Hence, the lipid paradox in insulin-resistant blacks is more accurately a “TG paradox.” It is a paradox because TG levels are expected to be elevated in the presence of insulin resistance, but this is not the case in blacks. It is important to recognize that even though TG levels are normal, isolated low HDL-C levels could be a major factor contributing to cardiometabolic disease in blacks.

Underestimating the significance of the “TG paradox” may have public health consequences. Many screening tests are based on the principle that TG levels will be elevated in the presence of insulin resistance.^{3–11} As discussed below, these programs may not be optimally effective in people of African descent.

Efficacy of Three Important TG-Based Screening Tests in Blacks: Metabolic Syndrome, Hypertriglyceridemic Waist, and the TG/HDL-C Ratio

Metabolic syndrome

Metabolic syndrome, initially called syndrome X, was presented in 1988 by Gerald M. Reaven in the Banting Lec-

ture of the American Diabetes Association.³⁵ In an effort to prevent cardiometabolic disease, the metabolic syndrome has received worldwide attention.³⁶ Overall, metabolic syndrome may carry two times the risk of CVD and five times the risk of T2D.³⁶ Yet there is no universal agreement on the value of the metabolic syndrome.³⁷ A major area of controversy has been the lack of agreement on a single definition. Therefore, in 2009, the International Diabetes Federation, the National Heart Lung and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity held a Consensus Conference.³ As a result of their deliberations, it was decided that metabolic syndrome would be diagnosed if any three of these five criteria were present: (1) hypertriglyceridemia (TG ≥ 150 mg/dL), (2) low HDL-C with sex-specific thresholds, (3) central obesity with population- and sex-specific waist circumference (WC) thresholds, (4) either diastolic or systolic hypertension, and (5) fasting hyperglycemia. The fundamental principle binding these five parameters together is that in the presence of insulin resistance, HDL-C will be low and the other features elevated. Therein lies the problem for metabolic syndrome in blacks; TG is usually normal even in the presence of insulin resistance.

Emerging evidence suggests that metabolic syndrome is underdiagnosed in people of African descent. As blacks have a higher prevalence of CVD and T2D than whites, it would be logical to assume that the prevalence of metabolic syndrome is higher in blacks than whites. However, NHANES data have revealed that the prevalence of metabolic syndrome is lower in blacks than whites.^{18,26,27} Additional evidence that the metabolic syndrome criteria are not effective in blacks comes from a study in which two groups of black men were compared: African immigrants to the United States and African Americans.³⁸ Metabolic syndrome prevalence was similar in the African and African-American men (10% vs. 13%, respectively, $P=0.74$). However, the African men had higher rates of hypertension, glucose intolerance, previously undiagnosed diabetes, and central obesity (Fig. 1). If the metabolic syndrome were able to effectively detect metabolic risk in blacks, the prevalence of metabolic syndrome would have been higher in the African men than the African-American men.

The most commonly cited reason for the underdiagnosis of metabolic syndrome in blacks is that hypertriglyceridemia, one of the five features of metabolic syndrome, is not applicable.^{15–17} In fact, only a fraction of blacks with metabolic syndrome ever meet the TG threshold.^{13,26,27} Furthermore, West Africans with metabolic syndrome are even less likely than African Americans to have hypertriglyceridemia (Fig. 2). It appears that when the metabolic syndrome criteria were formulated, the lack of association between insulin resistance and hypertriglyceridemia in blacks was not fully appreciated.

Hypertriglyceridemic waist

The hypertriglyceridemic waist (HTGW) has been proposed as a streamlined alternative to metabolic syndrome.^{6,9} The HTGW has only two features: elevated TG (TG ≥ 177 mg/dL in men and TG ≥ 133 mg/dL in women) and central obesity (WC ≥ 90 cm in men and WC ≥ 85 cm in women).³⁹ In whites, the HTGW predicts the presence of

FIG. 1. Comparison of metabolic variables in African men living in the United States and African-American men. (Black) Africans living in the United States; (gray) African Americans. (A) Systolic blood pressure (SBP); (B) diastolic blood pressure (DBP); (C) fasting glucose; (D) 2-h glucose after an oral glucose tolerance test (OGTT); (E) visceral adipose tissue (VAT) area; (F) metabolic syndrome prevalence. For parts A–E, data are presented as mean $\pm$ standard error (SE) with comparison by the Student's *t*-test. For panel F, data are presented as percent with comparison by chi-squared. (*) $P < 0.05$; (**) $P < 0.01$. Data were adapted from Ukegbu et al.³⁸

the metabolic triad.⁶ The metabolic triad consists of three universally established but expensive CVD risk factors: hyperinsulinemia, hyperapolipoprotein B, and small dense LDL. In contrast to the metabolic triad, the HTGW is easy to obtain and inexpensive. Cross-sectional and prospective studies in Canada and Europe have demonstrated that the HTGW is very effective in predicting the presence of the metabolic triad, as well as coronary artery disease (proven by catheterization) and future coronary events.^{6,39} However, the HTGW is not well known in the United States, and no validation studies of the HTGW in populations of African descent have been performed. Therefore, we identified 58

black men (17 Africans and 41 African Americans) with the metabolic triad and found that only 4 (7%) had HTGW (unpublished data) (Fig. 3). We are expanding our study, but on the basis of our preliminary data, we cannot recommend the use of HTGW to detect the metabolic triad or CVD risk in blacks.

TG/HDL-C ratio

Another abbreviated version of the metabolic syndrome is the TG/HDL-C ratio. The TG/HDL-C ratio was formulated as a proxy for insulin resistance. It is based on the principle

FIG. 2. Prevalence of diagnostic variables in West Africans and African Americans with metabolic syndrome. HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; WC, waist circumference; TG, triglycerides. (Reproduced with permission from Sumner-AE et al., *CVD Prevention* 2010;5:75–80.)

FIG. 3. Frequency distribution of triglyceride (TG) levels in men with the metabolic triad. (*Top*) Africans living in the United States; (*bottom*) African-American men. The dotted line represents the TG threshold for hypertriglyceridemic waist. Only 2 African men (*top*) and 2 African-American men (*bottom*) have both metabolic triad and hypertriglyceridemic waist (unpublished data).

that the “dyslipidemia of insulin resistance” is universally associated with high TG and low HDL-C levels. In a cross-sectional study of 258 individuals, McLaughlin et al. found that $TG/HDL-C \geq 3.0$ was sufficiently sensitive to predict insulin resistance.⁷ However, only 1% of the participants were African American. Our subsequent study of 90 African Americans found that TG levels were not elevated in insulin-resistant African Americans, and the ratio could not predict the presence or absence of insulin resistance in this group.⁴⁰ In an analysis of NHANES 1999–2002 data, Li et al. reported that the TG/HDL-C ratio could predict insulin resistance in African Americans and whites, but that the threshold had to be lower in African Americans because TG levels were lower.⁴¹ The race-specific thresholds reported by Li et al. were ≥ 3.0 in whites and ≥ 2.0 in African Americans. However, no analysis by sex was performed.

As TG levels are even lower in African-American women than men, differences in race-specific thresholds for TG/HDL-C ratio are magnified when stratified by sex. To examine the efficacy of the ratio to predict insulin resistance by sex, it was necessary to identify a cohort of African Ameri-

cans that was large enough for separate analyses of men and women. Modeled after the Framingham Heart Study, the Jackson Heart Study is a prospective investigation of CVD risk in African Americans.⁴² By studying the nearly 2000 nondiabetic African-American participants, the optimal TG/HDL-C threshold to predict insulin resistance in men was determined to be ≥ 2.5 .⁴³ However, for most women, TG levels were in the low normal range and the TG/HDL-C ratio was unable to predict insulin resistance.

The ability of the TG/HDL-C ratio to predict insulin resistance has also been tested in African women, specifically black South African women from a single tribal group (Xhosa) and West African women from four different tribal groups (Ibo, Yoruba, Akan, and Gaa). As was previously shown in the African-American women, the TG/HDL-C ratio did not predict the presence of insulin resistance in either the black South African or the West African women.⁴⁴ In summary, predicting insulin resistance, CVD or T2D risk based on a criteria set that requires TG to be elevated is problematic in blacks, especially black women.

Mechanisms Proposed to Explain Normal TG Levels in Insulin-Resistant Blacks

A few reasons for normal TG in the presence of insulin resistance have been identified. Activity of lipoprotein lipase (LPL), the enzyme that clears TG-rich lipid particles from the circulation, is higher in blacks than whites.³⁰ In addition, LPL activity is inhibited by apolipoprotein CIII (apoCIII), and apoCIII levels are lower in blacks than in whites.⁴⁵ LPL activity is also inhibited by insulin resistance in whites, but not in blacks.^{46,47} Thus, there is greater activity and less inhibition of LPL in blacks than whites. Consequently, there is greater clearance of TG-rich lipoproteins in blacks than whites.

High insulin concentrations could be another factor contributing to low normal TG levels in insulin-resistant blacks. To compensate for insulin resistance and maintain normoglycemia, hyperinsulinemia must occur. As blacks are more insulin-resistant than whites, insulin concentrations are higher in blacks than whites.^{29,48,49} We suggest that higher insulin concentrations in blacks may lead to greater inhibition of hormone sensitive lipase in adipose tissue and less release of free fatty acids (FFA) from peripheral adipose tissue.²⁹ In a direct comparison of African-American and white women matched for age and BMI, we have shown that African-American women have more peripheral fat (*i.e.*, higher thigh circumference), higher acute insulin response to an intravenous glucose challenge, and greater clearance of FFA from the circulation.²⁹ Lower circulating levels of FFA may lead to less accumulation of hepatic fat and less substrate for hepatic production of TG. Therefore, insufficient substrate for hepatic production of TG may account for the low normal TG levels observed in the “TG paradox.” In fact, we hypothesize that insulin resistance cannot promote hepatic production and secretion of TG-rich lipoproteins in the absence of hepatic fat. In support of this concept, the Dallas Heart Study has demonstrated in a large cohort that African Americans are more insulin-resistant than whites, but have substantially less hepatic fat.⁵⁰ Interestingly, thiazolidinediones decrease peripheral lipolysis, and this may account for how thiazolidinediones lower TG levels.⁵¹ In the future, we postulate that the investigation of TG metabolism in

blacks may need to transition from the effect of insulin resistance on the liver to the effect of hyperinsulinemia on peripheral fat.

Investigations into the genetic factors that influence TG levels are also essential, but they are beyond the scope of this review. However, because TG levels are low despite insulin resistance in Africans as well as African Americans, genetic factors that influence TG levels are likely to be important.

Conclusion

The absence of elevated TG in people of African descent does not mean the absence of risk for CVD and T2D. For prevention strategies to be introduced at a time when intervention could improve outcome, it is essential to identify risk factors that predict insulin resistance and the development of CVD and T2D in blacks.

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