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“Half the Dyslipidemia of Insulin Resistance” Is the Dyslipidemia of Insulin-Resistant Blacks

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Even though the dyslipidemia of insulin resistance is characterized by increased triglyceride (TG) and low high density lipoprotein-cholesterol (HDL-C) levels, insulin-resistant Blacks usually have normal TG levels.^{1,2} Therefore, the universality of the concept of the dyslipidemia of insulin resistance needs re-examination. Overall, a lack of appreciation of the absence of hypertriglyceridemia in insulin-resistant Blacks has led to the development of health screening programs that are not optimally effective in Blacks. For example, paradigms used to identify individuals at risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) often require that TG be elevated.³ Therefore, these programs often lead to the under-diagnosis of risk of T2DM and CVD in Blacks.⁴ As the dyslipidemia of insulin resistance, particularly elevated TG, is part of many screening programs,^{3,5–13} we need to critically review the effectiveness of these programs in Blacks.

The observation that Blacks often have only “half the dyslipidemia of insulin resistance” (ie, normal TG and low HDL-C levels) challenges established dogma that in the presence of insulin resistance, increased TG and low HDL-C are a couplet.¹⁴ To understand the physiology of insulin resistance, pathways that allow “half the dyslipidemia of insulin resistance” to occur in Blacks must be explored.

In this commentary, syndromes that emphasize elevated TG to predict risk for T2DM and CVD are identified and their effectiveness in Black populations examined. Then pathways that could account for the finding of “half the dyslipidemia of insulin resistance” in Blacks are described.

Syndromes

Syndromes that were designed to predict the presence of insulin resistance, pre-diabetes, T2DM or CVD include: Metabolic Syndrome (MetSyn), the simple clinical model of the Framingham Offspring Study, the enhanced diabetes prediction model of the Atherosclerosis Risk in the Community (ARIC) study and the Overweight-Lipid Syndrome.^{3,6,9,13} All of these syndromes incorporate both TG and HDL-C into their scoring system (Table 1, Panel A). Syndromes that use TG but not HDL-C include: the Hypertriglyceridemic Waist Syndrome, the Enlarged Waist Elevated TG Syndrome, the Rancho Bernardo Study, the

Abbreviated Metabolic Syndrome and the Lipid Accumulation Product.^{5,7,8,10-12} (Table 1, Panel B)

Among the syndromes that incorporate both TG and HDL-C levels into their scoring systems, the MetSyn is the most well-known. However there is a “Metabolic Syndrome Paradox”; meaning the prevalence of the MetSyn is lower in Blacks than Whites even though the prevalence of T2DM and CVD is higher in Blacks.^{1,4,15-17} It has been postulated that the relative under-diagnosis of MetSyn in Blacks is explained by the observation that Blacks are significantly more likely than other ethnic groups to have normal TG levels despite insulin resistance.¹ In fact, the majority of Blacks with MetSyn have normal TG levels and low HDL levels.¹⁷ In contrast, Whites with Met-Syn frequently have elevated TG and low HDL levels.¹⁷

As 99% of the participants in the Framingham cohort are White, the Simple Clinical Model of the Framingham Offspring Study was field-tested only in Whites.¹³ This model uses the same TG threshold as MetSyn (ie, TG 150 mg/dL). Therefore, as the MetSyn does not perform well in Blacks, it is possible that the Simple Clinical Model of the Framingham Offspring Study will not be effective in Blacks. In contrast, Blacks were included in the development and validation phases of the Enhanced Diabetes Prediction Model of ARIC.⁶ This model's scoring system gives additional points for Black race. These added points for Black race could be an effective way to offset the low frequency of elevated TG in Blacks. Further, unlike other scoring systems, the ARIC Enhanced Diabetes Prediction Model has sex-specific TG thresholds. As Black women have lower TG levels than Black men, consideration of sex differences in TG levels may enhance early identification of cardiometabolic and diabetic risk in Black women.

The Overweight-Lipid Syndrome was designed to predict insulin resistance.⁹ This syndrome incorporates both TG and HDL-C levels but, in contrast to MetSyn, HDL-C level is not scored as an independent variable. HDL-C is considered only within the context of the TG/HDL-C ratio. For diagnosis, the Overweight-Lipid Syndrome requires that either TG 130 mg/dL or that the TG/HDL-C ratio 3. As this syndrome was developed in a cohort in whom less than 2% of the participants were Black, we tested the Overweight-Lipid Syndrome in Blacks. In our study neither TG nor TG/HDL-C ratio predicted insulin resistance in overweight Blacks.²

Without consideration of HDL-C levels, the Hypertriglyceridemic Waist Syndrome, the Enlarged Waist Elevated TG Syndrome, the Rancho Bernardo Study, the Abbreviated Metabolic Syndrome and the Lipid Accumulation Product all use TG levels.^{5,7,8,10-12} (Table 1) Of all these syndromes, the Hypertriglyceridemic Waist Syndrome is the most well-known.^{8,11} In Whites, the Hypertriglyceridemic Waist Syndrome predicts the presence of the Metabolic Triad. The three characteristics of the Metabolic Triad are hyperinsulinemia, hyperapoprotein B and small, dense low-density lipoprotein particles. While the Metabolic Triad is highly predictive of premature CVD, the assays required to diagnose the Metabolic Triad are expensive and not widely available. Therefore Despres and colleagues^{8,11} undertook careful testing of a largely White population and found that the Metabolic Triad was highly associated with hypertriglyceridemia and central obesity. Based on this observation, Despres and colleagues^{8,11} coined the term Hypertriglyceridemic Waist Syndrome and defined it as TG 177 mg/dL and central obesity (men: waist circumference [WC] 90 cm, women: WC 85 cm).^{8,11} However, this high threshold for TG might preclude in Blacks the effectiveness of the Hypertriglyceridemic Waist Syndrome to serve as proxy for the Metabolic Triad. Testing the Hypertriglyceridemic Waist Syndrome in overweight, glucose-intolerant Blacks, we found that the prevalence of the Metabolic Triad was approximately 50% but the prevalence of Hypertriglyceridemic Waist Syndrome was less

than 10% (unpublished data). We speculate that this failure of the Hypertriglyceridemic Waist Syndrome to predict the Metabolic Triad may prove to be emblematic of the failure, in Blacks, of syndromes that require TG to be elevated.

Etiology of “Half the Dyslipidemia of Insulin Resistance”

Part A: Normal TG Levels in the Presence of Insulin Resistance

Even though TG levels are lower in Blacks than Whites, the reasons for this difference have not been extensively investigated. Factors that influence TG levels include body size (ie, obesity), diet, exercise and genetics. Based on the high prevalence of obesity, a high fat intake and a low rate of exercise, Blacks should have higher TG than Whites. However, the reverse is true. TG levels are higher in Whites than Blacks. Clearly, there will not be a simple explanation for this conundrum. From a metabolic perspective, we believe that normal TG levels in insulin-resistant Blacks are a function of both decreased production and increased clearance. The factors responsible for decreased production of TG are low visceral adipose tissue (VAT) mass and low intrahepatic TG content. High lipoprotein lipase (LPL) activity and low apolipoprotein CIII (apoCIII) levels account for increased clearance.

The Relationship of VAT and Intrahepatic Fat to TG Production—Visceral adipose tissue (VAT) is located within the peritoneal cavity and is measured, albeit imprecisely, by waist circumference (WC). Metabolically, VAT functions in an insulin-resistant manner; meaning in VAT, insulin is less effective in suppressing lipolysis and epinephrine has a greater lipolytic effect. As a result, VAT is a source, but not the only source of free fatty acids (FFA), used in the liver for synthesis of TG. For reasons that await elucidation, higher VAT volumes are associated with more FFA reaching the liver.^{14,18} With increased exposure to FFA, hepatic fat content increases. Consequently, hepatic production and secretion of very low density lipoprotein (VLDL) particles increases.^{14,18} Fasting TG levels are a measure of TG in VLDL particles.

This association between VAT, intrahepatic fat and increased production of the TG rich particles (ie, VLDL) occurs in Blacks and Whites. The difference is that Blacks have less VAT and consequently less intrahepatic fat than Whites.¹⁹ This is true even when Blacks and Whites are matched by BMI or WC.¹⁹ As Blacks have less VAT and less intrahepatic fat than Whites, it is logical that blacks would have lower TG levels as well. It is unknown why ethnic differences in VAT and intrahepatic fat occur.

The Relationship of LPL Activity and Intrahepatic Fat to TG Clearance—From the perspective of TG clearance, there are at least three reasons why TG levels are lower in Blacks than Whites. First, LPL activity is higher in Blacks than Whites.²⁰ LPL is the major enzyme responsible for clearing TG-containing lipoproteins from the circulation. As LPL activity levels are higher in Blacks than Whites, clearance of TG-containing lipoprotein particles is greater in Blacks than Whites. Second, apoCIII levels are lower in Blacks than Whites.²¹ ApoCIII, an apolipoprotein found on the surface of TG containing lipid particles, inhibits LPL activity. Lower apoCIII levels in Blacks than Whites allow for greater LPL activity in Blacks. Third, insulin resistance in Whites is highly associated with impaired LPL activity.²² However, in Blacks insulin resistance does not appear to interfere with LPL activity.²³ Therefore, in Blacks, even in the presence of insulin resistance, LPL is able to function effectively and clear TG containing lipoprotein particles from the circulation. Ethnic differences in apoCIII levels and LPL activity merit investigation.

Part B: Low HDL in the Presence of Insulin Resistance

For both Blacks and Whites insulin resistance is associated with low HDL-C levels.¹⁴ Hepatic lipase is the enzyme responsible for clearing HDL particles from the circulation. However, in the presence of insulin resistance, hepatic lipase activity increases and HDL-C levels decline.¹⁴ Blacks and Whites share this manifestation of the dyslipidemia of insulin resistance. This means that insulin-resistant Whites have low HDL-C levels and increased TG, while insulin-resistant Blacks usually have low HDL-C levels with normal TG levels.

Conclusion

The phrase “half the dyslipidemia of insulin resistance” describes the observation that insulin-resistant Blacks typically have normal TG and low HDL-C. Even as the etiology of normal TG levels in the presence of insulin-resistance in Blacks awaits elucidation, from a public health screening point of view, lower TG levels in Blacks than Whites must be recognized. If TG thresholds are set too high to identify health risk in Blacks, Blacks will not have the opportunity to maximally benefit from interventions designed to prevent or mitigate T2DM and CVD.

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Table 1

Syndromes which predict insulin resistance, pre-diabetes, T2DM or CVD

| Panel A: Syndromes that Require Measurement of both TG and HDL-C | |
|---|---|
| Syndrome | Other Parameters Measured |
| Metabolic Syndrome ³ | Waist circumference, blood pressure, fasting glucose |
| Simple Clinical Model Framingham Offspring Study ¹³ | Waist circumference, blood pressure, fasting glucose, age, family history of type 2 diabetes |
| Enhanced DM Prediction Model ARIC Study ⁶ | Waist circumference, blood pressure, fasting glucose, age, family history of type 2 diabetes, race, height, uric acid |
| Overweight-Lipid Syndrome ⁹ | Body mass index |
| Panel B: Syndromes that Require Measurement of TG without HDL-C | |
| Syndrome | Other Parameters Measured |
| Hypertriglyceridemic Waist Syndrome ^{9,11} | Waist circumference |
| Enlarged Waist Elevated TG Syndrome ¹² | Waist circumference |
| Rancho Bernardo Study ⁷ | Fasting glucose, age, sex |
| Abbreviated Metabolic Syndrome ¹⁰ | Waist circumference, fasting glucose |
| Lipid Accumulation Product ⁵ | Body mass index |