METABOLIC SYNDROME IN BLACK PEOPLE OF THE AFRICAN DIASPORA: THE PARADOX OF CURRENT CLASSIFICATION, DEFINITION AND CRITERIA

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According to the third National Health and Nutrition Examination Survey, African Americans have a lower prevalence of metabolic syndrome than do Whites. Recent reports in Blacks in other regions have confirmed these observations, but the rates vary. This lower rate of metabolic syndrome in Blacks can be partly ascribed to the lower prevalent rates of some major components of metabolic syndrome, namely serum triglyceride and high-density lipoprotein cholesterol levels in Blacks. This is in contrast with the higher prevalence of obesity (waist circumference) and blood pressure that meet National Cholesterol Education Program criteria in Blacks. Despite these seemingly favorable lipids and lipoprotein profiles, Blacks continue to have higher cardiovascular disease (CVD) mortality and morbidity, even in the absence of diabetes, than do Whites.

Insulin resistance is more prevalent in Blacks than in Whites. However, the relationships among insulin resistance and CVD risk factors such as hypertension, high-density lipoprotein cholesterol, and triglycerides are weak in contrast with Whites. The paradox of more favorable lipid profile and conversely the higher rates of unfavorable blood pressure in Blacks calls into question the validity of the current criteria for metabolic syndrome in Blacks. Thus, it can be argued that each of the components of the metabolic syndrome carry different CVD risk factors in Blacks.

The greater CVD mortality and morbidity in Blacks appear to be multifactorial. With the emerging epidemic of noncommunicable diseases, chronic kidney diseases due to both diabetes and hypertension have emerged as major CVD risks that are associated with increasing mortality and morbidity in Blacks. We need to emphasize specific components of metabolic syndrome, specifically blood pressure and chronic kidney disease, that carry higher CVD risk with associated greater morbidity and mortality for primary prevention of CVD and type 2 diabetes in Blacks. To this end, we believe the higher prevalence of hypertension and chronic kidney diseases in Blacks suggests that the current classification, definition, and criteria for metabolic syndrome in Blacks should be reconsidered. (*Ethn Dis*. 2009;19(Supp 2):S2-1–S2-7)

Key Words: Metabolic Syndrome, HDL Cholesterol, Triglycerides, Insulin Resistance, African Diaspora

INTRODUCTION

Noncommunicable diseases that affect Blacks tend to have strong concordance in Blacks of diverse origin. Indeed, there is increasing evidence that the rates of hypertension and type 2 diabetes in people of comparable age, weight, and lifestyles are similar among people of African ancestry.[1,2] Although the reasons are uncertain and appear to be multifactorial, Blacks have higher serum insulin and insulin resistance than do Whites.[3–5] Surprisingly, however, Blacks with insulin resistance have higher high-density lipoprotein cholesterol (HDL-C) levels and lower triglyceride levels than do their White counterparts.[6–8] Indeed, the lack of association between insulin resistance and serum HDL-C-to-triglyceride ratio[6–8] and blood pressure[4,9,10] is paradoxical and cannot explain the excess cardiovascular disease (CVD) deaths in Blacks.[5,11] Furthermore, these metabolic findings raise concerns as to whether the current metabolic thresholds or criteria defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III for metabolic syndrome are valid. Finally, these concerns question whether the components of metabolic syndrome carry similar CVD risk in Blacks and Whites. These issues could explain partly the differences in health disparities, morbidity, and mortality among different ethnic populations.

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CONSIDERATION OF COMPONENTS OF METABOLIC SYNDROME AS RISK FACTORS FOR CVD AND TYPE 2 DIABETES

Metabolic syndrome has been associated with increasing risk for developing CVD and type 2 diabetes.[11–13] The metabolic syndrome is defined by the NCEP-ATP III criteria as a constellation of fasting lipids and lipoproteins, waist circumference, glucose level, and blood pressure alterations.[14] The ATP III criteria for metabolic syndrome (Table 1) require 3 or more of 5 parameters: 1) blood pressure >130/85 mm Hg, 2) serum glucose >100 mg/dL, 3) HDL-C <40 mg/dL for men and <50 mg/dL for women, 4) triglycerides >150 mg/dL, and 5) waist circumference >102 cm (40 inches) for men and 88 cm (35 inches) for women.

According to ATP III criteria and the 2000 US Census data, ≈47 million US adults have metabolic syndrome. When comparing the first and second National Health and Nutrition Examination Surveys (1974–1978 vs 1978–1984 data), the prevalence of metabolic syndrome increased from 23% to 26%.[12,13] NHANES III also revealed racial/ethnic differences in the prevalence and incidence of metabolic syndrome in the United States.[12,13] According to NHANES III, the prevalence of metabolic syndrome was 13.9% for African American men and 20.9% for African American women during 1988–1994.[13] The corresponding rates of metabolic syndrome were 25% in White men and 23% in White women for the same time period. There is

Table 1. National Cholesterol Education Program. Report of the Adult Treatment Panel III (revised)

Risk Factors	Defining Measures
Abdominal obesity	Waist circumference
Men	>40 in (>102 cm)
Women	>35 in (>88 cm)
Triglycerides	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/85 mm Hg
Fasting glucose	≥100 mg/dL

>3 risk factors comprise metabolic syndrome
Adapted from: Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. *JAMA.* 2001;285:2486-2497

Table 2. International Diabetes Federation definition

Risk Factors	Defining Measures
Abdominal obesity	Waist circumference *
Men	>38 in (>94 cm)
Women	>30 in (>80 cm)
Plus 2 or more of the following	
Triglycerides	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/85 mm Hg or treatment for hypertension
Fasting plasma glucose	≥100 mg/dL or IGT, IFG or type 2 diabetes

Adapted from Alberti et al, *Diabetic Medicine*. 2006;23:469–480
* ethnic difference for waist circumference exist for South Asians, Chinese and Japanese.
IGT-impaired glucose tolerance
IFG-impaired fasting glucose
IDF has different WC cut off points for Asian males and females; Japanese Diabetes Association has different WC cut off points

evidence of increasing prevalence and incidence of metabolic syndrome in Blacks residing in sub-Saharan Africa, but data are scarce.[1,15–18] Nevertheless, a recent study[19] found a much higher prevalence of metabolic syndrome in Blacks residing in Jackson, Mississippi, than in NHANES III overall. These differences could be partly explained by differences in the prevalence of obesity and physical activity level and selection bias.

Different international bodies use different criteria for the definition of metabolic syndrome.[16] Several studies have reported differences in the prevalence and incidence of metabolic syndrome based on the 3 commonly used criteria. While ATP III required 3 or more of 5 of the components, the International Diabetes Federation (IDF) (Table 2) emphasizes waist circumference as a prerequisite in addition to ≥2 of the other components to define metabolic syndrome. In contrast, the World Health Organization (WHO) (Table 3) recommends insulin resistance or its surrogates (impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes) as the prerequisite in addition to ≥2 components for the definition of metabolic syndrome. Based on the higher CVD outcomes in Blacks despite the lower rates of metabolic syndrome, we surmised that there are racial/ethnic differences in the impact of the 5 components of metabolic syndrome for future CVD and type 2 diabetes.[15–19] These observations challenge us to reinvestigate the ATP III/IDF/WHO criteria and provide the impetus for redefinition of the components of metabolic syndrome among different ethnic and racial populations, especially in Blacks.

There is currently limited data from sub-Saharan Africa, therefore it has been difficult to make a definite recommendation on components of metabolic syndrome generalizable in Blacks. Pre-

Table 3. WHO metabolic syndrome definition 1999: based on clinical criteria

Risk Factors	Defining Measures
Insulin Resistance (type 2 diabetes, IGT, IFG)	
Plus 2 or more of the following	
Abdominal Obesity	Waist circumference
Men	>40 in (>102 cm)
Women	>35 in (>88 cm)
Triglycerides	≥150 mg/dL
HDL-C	
Men	<35 mg/dL
Women	<39 mg/dL
Blood pressure	≥140/90 mm Hg or drug use
Microalbuminuria	Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g
Body composition measures	
WHR	
Men	>0.90
Women	>0.85
BMI	>30 kg/m^2

Adapted from Alberti et al, *Diabetic Medicine*. 2006;23:469–480
IGT-impaired glucose tolerance
IFG-impaired fasting glucose
WHR-waist to hip ratio
BMI-body mass index

liminary studies[9,20] showed that Ghanaians and South African Blacks are more insulin resistant than are Whites. Frezeu et al[21] have reported lower prevalence rate of metabolic syndrome in Cameroonians, who live in rural vs urban areas. Second, the metabolic components of metabolic syndrome in Ghanaians, such as blood pressure and lipids and lipoprotein, were comparable to those of African Americans, South Africans, and Afro-Caribbeans.[22] These studies taken together confirm that the metabolic components and characteristics of people of the African Diaspora are similar, regardless of the country of origin, when obesity and physical activity are accounted for.

Paradox of Insulin Resistance and Metabolic Syndrome and Its Components

The major premise underpinning metabolic syndrome is insulin resistance in several populations. Although the etiology of insulin resistance remains uncertain in most populations, the relationships between several components of metabolic syndrome and insulin resistance are well established in Whites but remain controversial in Blacks.[4,6–13,15–22] The reasons are unclear. In this regard, Blacks are more insulin resistant and are more hyperinsulinemic than are their White counterparts. Furthermore, hyperinsulinemia is due to decreased hepatic insulin extraction in Blacks.[23] Unlike in Whites, the relationship between insulin resistance and blood pressure remains weak in Blacks.[4,6,9,10,19,20] We have referred to this relationship as the blood pressure and insulin resistance paradox in Blacks.[24] This weak relationship also extends to lipids and lipoproteins in Blacks.[6–8,25] In this regard, insulin-resistant Blacks show a weak association with serum triglyceride and HDL-C levels. These studies show that the association of components of metabolic syndrome and insulin resistance remains paradoxical, and indeed controversial, in Blacks. These metabolic differences could account in part for the racial disparities in CVD outcomes among Blacks and Whites.

Paradox of Insulin Resistance, Body Composition, and Metabolic Syndrome

Obesity and type 2 diabetes have become epidemic in Blacks in the Western world. Both diseases are undoubtedly increasing in sub-Saharan African developing countries.[1,26,27] Both contribute to cardiovascular diseases in Blacks and Whites.[5,11–13] In particular, Black women, have greater rates of CVD morbidity and mortality than do White women, probably because of higher rates of obesity, type 2 diabetes, hypertension, strokes, and congestive heart failure.[5,11–13,19] Paradoxically, coronary artery disease is less severe in African Americans and Afro-Caribbeans with angiographically documented diseases than in Whites, despite the higher CVD mortality and morbidity in Blacks. The reasons are unclear.

A major determinant of metabolic syndrome is waist circumference. This has been confirmed in recent studies[19] and NHANES III.[12,13] Apart from waist circumference, another determinant of insulin resistance is intraabdominal visceral adiposity. This concept is more applicable and relevant in several non-Black populations but remains controversial in Blacks. Indeed, at identical body mass index, Blacks residing in diverse geographic locations have lower visceral adiposity despite increased insulin resistance when compared with their White counterparts.[28] These have been confirmed in urban South African Blacks when compared to White South Africans.[26,27] The reasons are uncertain but paradoxical. Thus, there is a dissociation between insulin resistance and body fat distribution and composition in Blacks consistent with the metabolic and obesity paradox in Blacks.

Relevance of HDL-C Levels and CVD in Blacks

Serum HDL-C levels are a major independent predictor of CAD. Previous studies have confirmed the higher HDL-C levels in Blacks when compared with Whites residing in varying geographic locations.[6–8] A recent study[19] found the prevalence of metabolic syndrome was higher in African Americans in the Jackson Heart Study than the national averages reported by NHANES III. The Jackson Heart Study found that low serum HDL-C according to ATP III criteria was a major determinant of metabolic syndrome, while serum triglycerides were least predictive in African Americans. However, the average levels of HDL-C meeting ATP III criteria for metabolic syndrome in the Blacks remained much higher than those reported in Whites of similar obesity and insulin resistance. Based on our previous study and those in the literature, it is tempting to conclude that to achieve the presumed anti-atherogenic effects of HDL-C, Blacks may require levels far in excess of the 50 mg/dL recommended for Blacks in the ATP III. We should note that Haffner et al[25] found a higher HDL-C levels in African Americans than White Americans similar to the studies by Cowie et al[29] and Ford et al.[12] However, since the HDL-C isoforms or subspecies were not often studied in most previous studies, it is unknown whether the measured serum HDL-C levels are truly cardioprotective. If HDL-C levels are not cardoprotective, other factors may mitigate against the potential CVD beneficial effects of HDL-C in Blacks. This issue remains to be investigated in Blacks.

POTENTIAL MECHANISMS FOR THE HDL-C CARDIOVASCULAR DISEASE PARADOX IN BLACKS

Serum HDL-C is an independent risk factor for CVD. Indeed, several prospective studies have revealed that 1% reduction in HDL-C is associated with a 3% and 2% increase in CHD events in women and men, respectively.[30] Most of these studies were in White populations. Previous studies have attributed the antiatherogenic properties of HDL-C to the potent reverse cholesterol transport mechanism. However, recent studies have suggested that oxidative modification of plasma low-density lipoprotein cholesterol (LDL-C) by HDL-C plays a major role in the pathogenesis of atherosclerosis and that HDL-C protects LDL-C from oxidation.[30–33] Although the mechanism is not clear, increasing attention has focused on the potential antioxidant activity of serum enzymes associated with HDL-C. One of these enzymes, paraoxonase (PON1), which is co-associated with HDL-C and apoliporpotein A–1 (Apo-A1) in the circulation has been postulated to play a critical role in protecting LDL-C oxidation, thus preventing vascular injury and atherosclerosis.[31–33] Indeed, people with higher HDL-C have higher PON1 activity. Previous studies have shown an inverse relationship between coronary artery disease and PON1.[31] PON1 activity is increased by statins and aspirin and could play a role in the CVD protection associated with these drugs.[31] Thus, factors that could increase PON1 enzyme activity can prevent atherosclerosis and lower CVD morbidity and mortality. Indeed, studies on HDL-C functionality in Blacks could also address this HDL-C –CVD paradox. We believe the higher CVD in Blacks in the presence of higher HDL-C is paradoxical and suggests that: 1) the HDL appears to be dysfunctional in Blacks; 2) Blacks are resistant to the HDL-C cardioprotective effects, ie HDL-resistance; and 3) HDL-mediated anti-inflammatory and antioxidant properties are impaired in Blacks. We believe a better understanding of HDL function, the associated correlates such as proinflammatory, antiinflammatory and antioxidant properties, as well as, modalities to increase its function are warranted in Blacks. Thus, a better understanding of the functionality of HDL (as well as PON1 activity) in Blacks could provide additional mechanisms that might explain the increased CVD in Black populations when compared with Whites.

PARADOX OF SERUM TRIGLYCERIDES IN CVD IN BLACKS

Generally, high serum triglycerides are common in insulin resistant, obese humans with and without type 2 diabetes than in nondiabetic, insulin-sensitive subjects. It is well-known that pharmacological intervention studies targeting reduction of serum triglycerides (with concomitant rise in HDL-C) are very beneficial to CVD outcomes. (including morbidity and mortality) in Whites. However, such systematic CVD outcome studies have not been performed in people of the African Diaspora. Research has shown that people of the African Diaspora manifest greater insulin resistance and hyperinsulinemia when compared to Whites.[3,4,6–8,19–27] Despite the greater insulin resistance, people of the African Diaspora also paradoxically have relatively lower serum triglyceride levels (perhaps due to low hepatic lipase activity) when compared to their White counterparts.[6–8] Recently, Haffner et al[25] showed that, in addition to relatively lower serum triglycerides, Africans Americans have larger LDL-particle sizes, which are more buoyant and less atherogenic when compared to Whites. Whether high serum triglycerides is atherogenic *per se* remains controversial.

Despite, these favorable anti-atherogenic lipid and lipoprotein profiles, Blacks continue to suffer disproportionately from CVD mortality and morbidity.[5–11] The reasons are unclear. Consistent with our recent observation and NHANES III, the Jackson Heart Study found serum triglycerides as the least parameter to meet the ATPIII criteria and the least determinant of metabolic syndrome in African Americans.[12,13,19] Most importantly, this is consistent with several observations in Blacks residing in diverse geographic locations.[10,16–27]

METABOLIC SYNDROME AND PROINFLAMMATORY FACTORS AND OXIDATIVE STRESS BURDEN IN BLACKS

The weak association between conventional risk factors and CVD in Blacks suggests other possible non-conventional mechanism(s) for CVD in this population. In this regard, proinflammatory cytokines have received increasing attention. These peptides are generally and predominantly derived from adipose tissues and adipocytes. Most importantly, it is believed that these adipocyte-derived cytokines and peptides could be the link between obesity, insulin resistance, metabolic syndrome, type 2 diabetes and cardiovascular diseases. These fat derived-peptides include adiponectin, tumor necrosis factor-alpha (TNF-a), resistin, leptin, interlukin-6 (IL-6), c-reactive protein (hCRP), tp name a few.[27,34,35] In particular, serum adiponectin has received great interest since it has been associated with improved insulin sensitivity and predicts metabolic syndrome.[34,36] Adiponectin could potentially prevent type 2 diabetes and atherosclerosis. Paradoxically, serum adiponectin levels are decreased in obese individuals with insulin resis-

tance in Blacks, Whites and other populations.[34] In contrast to adiponectin, TNF-a and IL-6 levels are increased in obese subjects. Both TNF-a and IL-6 have been associated with increased incidence and prevalence of type 2 diabetes. These proinflammatory cytokines are intimately involved in insulin resistance and cardiovascular diseases.

African Americans have greater oxidative stress burden when compared to Whites. Of major concern is that Blacks appear to have greater oxidative stress burden as assessed by F2 isoprostane levels than their White counterparts.[30–33] Thus, either the generation of free oxygen radicals are higher, their clearance is impaired, or both, in Blacks compared to Whites.[30–33] These perturbations in oxidative stress could play a role in the accelerated atherosclerosis in Blacks.

Recent studies have shown that people of the African Diaspora residing in diverse geographical locations manifest lower total serum adiponectin levels.[35] Duncan et al[37] and Hulver et al[38] found lower serum total adiponectin levels in African American males and females when compared to White counterparts. Similarly, Ferris et al[35] have also shown that serum total adiponectin levels are lower in South African Blacks when compared to South African Whites. In this regard, recent studies in West Indies showed that adiponectin has strong genetic inheritance among multiple generations of these populations. In a recent study, we have demonstrated that serum adiponectin levels are lower in insulin resistant diabetic and non-diabetic subjects when compared with insulin-sensitive subjects. Thus, similar to the ARIC study by Duncan et al,[37] and consistent with those of other studies in different populations, the lower adiponectin levels in Blacks antecede the development of type 2 diabetes and was surprisingly independent of obesity.

THE RATIONALE FOR NEW CLASSIFICATION OF THE METABOLIC SYNDROME IN PEOPLE OF THE AFRICAN DIASPORA

We have attempted to address the ethnic and racial inconsistencies and disparities in each of the 5 components of the ATP III criteria for metabolic syndrome in Blacks of the African Diaspora, Whites and other ethnic populations. This issue is very important since the current NCEP-ATP III criteria assume that all the 5 ATP III parameters are equally weighted with respect to their ability to identify cardiovascular risk factors or predict CVD outcomes. This is in contrast with the IDF and WHO criteria in which some components are prerequisites, eg waist circumference and insulin resistance and its surrogates. In a recent report, Gaillard et al[24] reported that BP was an independent predictor of prevalence of metabolic syndrome in African American women, similar to the NHANES III[12,13] and Jackson Heart Study.[19] Further, Lea et al[39] reported that chronic kidney disease (CKD) is associated with higher prevalence rates of metabolic syndrome in African Americans with chronic hypertension.

In view of these concerns, we offer the following framework for consideration of the reclassification of metabolic syndrome in people of the African Diaspora. First, we propose the use of blood pressure and/or microalbuminuria (CKD surrogate) based on the well–established, conventional evidence that hypertension is more common and devastating in Blacks than Whites. Second, we argue that some of these components in ATP III should be ''weighted'' differently in terms of the greater risk to predict CVD and its outcomes in all racial and ethnic populations. Third, given the favorable lipoprotein metabolic profiles of Blacks in the African Diaspora, we suggest that the thresholds of metabolic factors that may be associated with CVD are different in Blacks when compared with current NCEP-ATP III criteria. These hypotheses need, however, to be reinvestigated in a prospective CVD outcome study of people of the African Diaspora.

In summary, the dissociation of CVD risk factors and insulin resistance and the conventional metabolic parameters (and the associated mortality and morbidity) in people of the African Diaspora have raised several concerns regarding the definition of metabolic syndrome. We have suggested that the prevalence and perhaps the CVD impact of the various components of metabolic syndrome and metabolic syndrome *per se* may not be uniform and indeed affects racial/ethnic groups differently. Indeed, the components of metabolic syndrome, such as hypertension and chronic kidney disease - with ultimate end-stage renal failure, appear to carry much greater CVD morbidity and mortality for people of the African Diaspora.[39] These issues are very important when viewed in the context of the higher HDL-C levels and lower triglyceride levels, which do not appear to have cardioprotective effects among people of the African Diaspora when compared to Whites. However, more prospective studies are needed for people of the African Diaspora, especially those living in sub-Saharan Africa to affirm our hypothesis.

WHY SHOULD CKD BE INCLUDED IN DEFINITION OF CARDIORENAL METABOLIC SYNDROME FOR PEOPLE OF THE AFRICAN DIASPORA?

High blood pressure or its surrogate, eg, CKD and microalbuminuria, is more prevalent in Blacks of the African Diaspora than Whites.[39] The prevalence of hypertension is 33%–40% in people of the African Diaspora compared to

Table 4. Proposed new classification and definition of metabolic syndrome in Black people of the African Diaspora

Risk Factors	Defining Measures
Blood pressure	>130/85 mm Hg
Microalbuminuria	>20µg/min
Albuminuria/creatinine	30mg/g
Plus 2 or more of the following	
Abdominal obesity	Waist circumference
Men	>40in (>102cm)
Women	>35in (>88cm)
Triglycerides	>150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Fasting glucose	>100 mg/dL

18%–22% in Whites. Both hypertension and CKD seem to carry remarkably, and significantly negative impact on CVD outcomes in Blacks of the African Diaspora. Thus, in the context of the African Diaspora, it is important to reconsider the current classification of metabolic syndrome by NCEP, WHO and IDF. As shown in Table 4, we propose that blood pressure or CKD surrogates (microalbuminuria, GFR etc) should be considered as a prerequisite in the definition of metabolic syndrome in people of the African Diaspora. We believe this modification of metabolic syndrome criteria (Table 4) could create more awareness of high blood pressure and/or CKD as a primary prerequisite component of metabolic syndrome and future CVD in people of the African Diaspora. With that proposal in mind and the evidence that reduction in blood pressure significantly reduces the rates of strokes and congestive heart failure, we are convinced that the new criteria could have significant impact on CVD morbidity and mortality in people of the African Diaspora. Consistent with the practical and clinical goals of identifying metabolic syndrome within a patient, we believe highlighting blood pressure or CKD could lead to early intervention and primary prevention of CVD in people of the African Diaspora. Nevertheless, we also believe long-term prospective studies will be necessary to investigate CVD outcomes using this proposed modified criteria vs established criteria for metabolic syndrome in people of the African Diaspora residing in diverse geographic locations including sub-Saharan Africa.

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