THE METABOLIC SYNDROME IN AFRICAN AMERICANS: A REVIEW

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The Metabolic Syndrome represents a specific clustering of cardiovascular risk factors. One of several recently proposed definitions encompasses 3 or more of the following 5 abnormalities: waist circumference >102 cm in men or >88 cm in women, serum triglyceride level ≥150 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men or <50 mg/dL in women, blood pressure (BP) ≥130/≥85 mm Hg, and serum glucose ≥110 mg/dL. The diagnosis of Metabolic Syndrome allows early recognition of an increased risk of cardiovascular disease.

African Americans have the highest coronary heart disease mortality of any ethnic group in the United States. African-American women and Hispanic men and women have the highest prevalence of the Metabolic Syndrome. This phenomenon is attributable mainly to the disproportionate occurrence of elevated BP, obesity, and diabetes in African Americans, and the high prevalence of obesity and diabetes in Hispanics.

Management of the Metabolic Syndrome consists primarily of modification or reversal of the root causes and direct therapy of the risk factors. The first strategy involves weight reduction and increased physical activity, both of which can improve *all* components of the syndrome. The second strategy often involves drug treatment of the individual risk factors to further improve BP, lipids, and glucose thereby decreasing the risk of cardiovascular disease.

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DEFINITION

Metabolic Syndrome X was described by Reaven in 1988.[1] A syndrome, by definition, is an aggregation of clinical and/or laboratory findings that has not yet reached designation as a disease. In the case of the Metabolic Syndrome, the aggregation is represented by a clustering of cardiovascular risk factors. Definition of the specific risk factors, and therefore the definition of the Metabolic Syndrome, differs considerably among a variety of expert panels.[2–5] The definition recommended by the Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP III)[4] and used by Ford et al[5] in an analysis of the Third National Health and Nutrition Examination Survey (NHANES III) is 3 or more of the following 5 abnormalities:

- Waist circumference >102 cm (40.2 in) in men or >88 cm (34.6 in) in women
- Serum triglyceride level ≥150 mg/dL (1.69 mmol/L)
- High-density lipoprotein (HDL) cholesterol level <40 mg/dL (1.04 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women
- Blood pressure (BP) ≥130/≥ 85 mm Hg
- Serum glucose ≥110 mg/dL (6.1 mmol/L)

In African Americans, abnormalities associated with the Metabolic Syndrome are summarized in Table 1. The syndrome has been linked with increased plasma insulin levels associated with insulin resistance[6–20] and is sometimes referred to as the Insulin Resistance Syndrome. Although not fully elucidated, the Metabolic Syndrome appears to have 2 root causes: acquired (overweight/obesity, physical inactivity, and high-carbohydrate intake) and genetic origin. An often-quoted article has referred to the syndrome as the "deadly quartet" of central obesity, glucose intolerance, hypertriglyceridemia, and elevated BP.[21] Aggressive management of patients with the Metabolic Syndrome is important because of the associated increased risk of morbidity and mortality from coronary and cardiovascular disease (CVD).[22–25]

This review considers the Metabolic Syndrome (ICD-9-CM code 277.7) as the cluster of cardiovascular risk factors that includes central obesity, elevated BP, glucose intolerance, hypertriglyceridemia, and low HDL cholesterol. The main purpose of this review is to introduce emerging concepts of the Metabolic Syndrome, especially as they apply to African Americans, who have the highest coronary heart disease (CHD) mortality of any ethnic group in the United States.[4,26] The syndrome should not be confused with microvascular an-

Table 1. Abnormalities associated with the Metabolic Syndrome in African Americans

Elevated blood pressure
↑ Renal sodium absorption
Insulin resistance
Microalbuminuria
Overweight/Obesity
Insulin resistance
Type 2 diabetes mellitus
Insulin resistance
Microalbuminuria
Dyslipidemia
↑ Triglyceride levels
↓ HDL cholesterol levels
↑ Hepatic lipase activity
Endothelial dysfunction
↓ Vasodilation
↑ Asymmetric dimethylarginine (ADMA)
Prothrombotic state
↑ Plasminogen activator inhibitor-1 (PAI-1)
↓ Fibrinolysis
Hyperuricemia
Polycystic ovary syndrome (PCOS)

gina that has sometimes also been referred to as Syndrome X.[27]

PREVALENCE

Susceptibility to the specific risk factors of the Metabolic Syndrome is variable in African-American and other ethnic groups. Whites of European origin appear to have a greater predisposition to atherogenic dyslipidemia, whereas Blacks of African origin are more prone to HBP, type 2 diabetes and obesity.[11] Native Americans and Hispanics are less likely to develop HBP than Blacks, but appear particularly susceptible to type 2 diabetes. Of particular note is the considerable genetic admixture among Native Americans and Mexican Americans.[28]

African Americans have the highest overall CHD mortality and the highest out-of-hospital coronary death rates of any ethnic group in the United States.[4,26] Recent data from the 1988–1994 NHANES III survey indicated that the age-adjusted prevalence of the Metabolic Syndrome was higher in African-American women (25.7%) vs White women (22.8%), but lower in African-American men (16.4%) vs White men (24.8 %)[5] (Table 2). The highest prevalence of the Metabolic Syndrome occurred in Mexican-American men (28.3%) and women (35.6%). Native Americans and South Asians are also prone to insulin resistance with more type 2 diabetes and premature CHD. Most of the subsequent discussion and recommendations for African Americans probably also apply to these populations, although the data are considerably more sparse.[29]

Table 2. Prevalence of the Metabolic Syndrome in U.S. adults (Third National Health and Examination Survey, NHANES III, 1988–1994)

	N	Prevalence
White women	3,599	22.8%
African-American women	2,412	25.7%
Mexican-American women	2,449	35.6%
White men	1,712	24.8%
African-American men	1,116	16.4%
Mexican-American men	1,277	28.3%

JAMA. 2002;287:356–359.[5]

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COMPONENTS AND PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME

Obesity in Adults

The most recent NHANES data (1999–2000) show that obesity (ie, BMI≥30 kg/m²) is more than 50% more prevalent in non-Hispanic African-American women (49.7%) than non-Hispanic White women (30.1%)[30] (Table 3). Obesity is not more prevalent, however, in non-Hispanic African-American men (28.1%) than non-Hispanic White men (27.3%). Because obesity is a major component of the Metabolic Syndrome and such a strong correlate of insulin resistance, it is no surprise that African-American women (49.7% obese) and Mexican-American women (39.7% obese) have such a high prevalence of the Metabolic Syndrome.

In the interval between NHANES II

Table 3. Age-adjusted prevalence of obesity (BMI≥30 kg/m²) in US adults aged 20–74 years (National Health and Nutrition Examination Survey, 1999–2000)

	Prevalence
White non-Hispanic women	30.1%
Black non-Hispanic women	49.7%
Mexican-American women	39.7%
White non-Hispanic men	27.3%
Black non-Hispanic men	28.1%
Mexican-American men	28.9%

JAMA. 2002;228:1723–1727.[30]

(1976–1980), NHANES III (1988–1994), and NHANES (1999–2000), the age-adjusted prevalence of obesity (BMI≥30 kg/m^2) increased relentlessly from 15.0% to 22.9% to 30.5%.[30,31] The increase was similar in men and women, and occurred in all ethnic groups studied. One obvious explanation could be a decrease in physical activity since one in 4 adults (more women than men and more so in ethnic minorities) has a sedentary lifestyle with *no* leisure time activity.[32–34]

Obesity in Children

The epidemic of obesity in adults has been accompanied by an increase (in all sex and age groups) in the proportion of children who are at risk of becoming overweight, or actually overweight, based on a BMI indexed to the 85th or 95th percentiles for age, respectively.[35–38] In both children and adults, there is indirect evidence for both an increase in energy (calorie) intake and a decrease in physical activity.[39,40] Among 8- to 16-year-old children, vigorous physical activity is lower among ethnic minority children than non-Hispanic White children.[41] Watching television occupies the greatest amount of non-sleeping leisure time in childhood; overweight is most frequent in children watching television for 4 or more hours daily, and least frequent in those watching one hour or less daily.[42] Overweight children (≥age 3) are at increased risk to become obese adults.[43–45] In a 12-year follow-up of 745 children aged 8 to 17 years, the presence of a high BMI in childhood predicted their subsequent risk of developing the Metabolic Syndrome as a young adult.[46] In addition, obese adults are more likely to raise overweight children.[43] If one parent has the Metabolic Syndrome, there is an 8-fold increase in the chance for the same cluster to exist in their 5- to 17-year-old children.[47] The increasing prevalence of overweight in school-aged and adolescent children has been associated with a marked increase in the incidence of insulin resistance and type 2 diabetes in children.[48–50]

Distribution of Body Fat

A predominantly upper body or abdominal (central) distribution of body fat, reflected by the waist circumference and the waist-to-hip circumference ratio (WHR), is a stronger CVD risk factor than is obesity *per se*.[51] Early studies documented excess CVD risk with a WHR of >0.95 in men or >0.80 in women.[52] Subsequent studies, however, have shown that a waist circumference >102 cm (40 in) in men or >88 cm (35 in) in women is a better predictor than BMI or WHR for the risks of hypertension, type 2 diabetes, or CVD.[53,54]

Abdominal fat includes 3 compartments: retroperitoneal, subcutaneous, and visceral. Estimating abdominal fat can be conducted by utilizing computerized tomography (CT), magnetic resonance imaging (MRI), or dual-energy x-ray absorptiometry (DEXA). Abdominal fat may be more metabolically active than femoral or gluteal fat, and lipolysis of abdominal fat releases free fatty acids as substrate for the liver synthesis and secretion of very low-density lipoproteins (VLDL), triglycerides, and atherogenic remnant lipoprotein particles.[55] Waist circumference correlates with both visceral and subcutaneous abdominal fat.[2] Some studies show that the best correlation of insulin resistance is with the more abundant subcutaneous compartment.[56,57] In a 4-month pilot study of 14 overweight women, large-volume liposuction of subcutaneous abdominal fat was associated with a decrease in total body fat (35.7 to 30.1 kg), fasting plasma insulin levels (14.9 to 7.2 mIu/mL), and systolic BP (132.1 to 120.5 mm Hg).[58] Total cholesterol, HDL cholesterol and triglyceride levels, however, did not change significantly.

Visceral fat is generally the compartment most strongly related to lipid abnormalities, including higher levels of total plasma cholesterol, LDL cholesterol, triglyceride, and plasminogen activator inhibitor 1 (PAI-1); and lower levels of HDL cholesterol.[51,59–64] Atherogenic small, dense LDL particles are disproportionately present in the Metabolic Syndrome.[15,65,66] Haffner and associates[67] reported ethnic differences in average LDL particle size (angstrom units): African Americans, 262.1; Whites, 259.2, and Hispanics, 257.6, P=.001. In all three ethnic groups, male sex was associated with smaller LDL size. Low-density lipoprotein (LDL) size correlated with higher levels of triglyceride or lower levels of HDL cholesterol, but was independent of obesity or insulin resistance. Visceral adiposity has been linked to endothelial dysfunction via increased oxidative stress.[68–71]

One would logically expect obese African-American women to have an excess of abdominal visceral fat relative to obese White women. The reverse is true. For example, in NHANES III, waist circumferences of overweight (ie, BMI 25–29.9 kg/m^2) or obese (ie, BMI ≥30 kg/m^2) individuals were *lower* in Black women than in White women.[72] Moreover, when similarly obese African-American and White women are compared, visceral fat is consistently higher in the White women[73–76] (Table 4). These data suggest that obesity (or more specifically, visceral fat mass) *per se* is not the sole explanation for the higher prevalence of the Metabolic Syndrome in African-American women compared to White women. African-American men are not more obese than non-Hispanic White men, and they have *less* visceral fat than White men, even after adjusting for total body fatness.[77]

Leptin is a peptide hormone released from adipocytes; it suppresses appetite. Levels correlate directly with body fat mass (especially subcutaneous abdominal fat)[78,79] and are high in obese patients, indicating that most obesity is reflective of a leptin-resistant state. Elevated leptin levels may activate the sympathetic nervous system and contribute to the HBP of obesity.[80,81] Furthermore,

Table 4. Visceral fat in similarly obese African-American (AA) versus White (W) women

Ref	*N*	Method	Group	BMI (kg/m²)	Visceral Fat Area (cm²)	*P**
73	18	CT	AA	40.0	105 ± 25†	.05
			W	38.2	160 ± 11†	
74	59	CT	AA	31.3	98.0 ± 8.5‡	.03
			W	29.6	117.3 ± 12.4‡	
75	50	MRI	AA	36.0	120 ± 11‡	<.05
			W	36.0	138 ± 11‡	
76	66	MRI	AA	35.1	81.5 ± 34.5†	<.001
			W	34.9	128.2 ± 53†	

Note: CT = computerized tomography; MRI = magnetic resonance imaging.
Source: *Am J Clin Nutr*. 1995;61:765–771[73]; *Metabolism*. 1996;45:1119–1124[74]; *Diabetes*. 1997; 46:456–462[75]; *J Appl Physiol*. 2000;89:636–643.[76]
* *P* value for ethnic differences in visceral fat area.
† Standard deviation.
‡ Standard error.

leptin also increases oxidative stress.[82] However, only minimal differences between the leptin levels of hypertensive vs normotensive individuals, or between type 2 diabetic patients and controls are evident.[80] Leptin correlates closely with body fat of African-American and White women; the levels do not differ between the 2 ethnic groups.[83]

A newly discovered adipocyte hormone, resistin, is concentrated in visceral fat and is associated with both obesity and insulin resistance.[84,85] Studies of variations in the resistin gene have thus far been conducted mainly among White subjects with diabetes.[86,87]

Insulin Resistance

Data from the Coronary Artery Risk Development in Young Adults (CARDIA) study established that plasma insulin levels were increased in hypertensive patients.[88] Insulin levels correlated positively with BP and low-density lipoprotein (LDL) cholesterol, and negatively with HDL cholesterol. The correlations were lower after adjusting for body mass index (BMI), but remained highly significant. Elevated insulin levels are probably a response to insulin resistance.[89–91] Insulin resistance also correlates strongly with obesity,[92,93] but is present more often than hyperinsulinemia in non-obese patients with hypertension (HBP).[90] Insulin resistance is recognized as a precursor of the majority of cases of type 2 diabetes mellitus in both White and African-American men and women.[94–96]

The pathogenesis of the insulin resistance of hypertensive, obese, or type 2 diabetic individuals is unknown and the subject of considerable metabolic and genetic research.[97–100] This abnormality occurs in selected tissues, primarily skeletal muscle and visceral adipocytes.[90,101,102] The higher insulin levels induce a short-term increase in catecholamines and renal sodium reabsorption, and stimulate growth of vascular smooth muscle and endothelial cells.[21,103,104] Insulin resistance (as well as obesity) has been linked to increased oxidative stress and elevated homocysteine levels.[105] Furthermore, insulin resistance has recently been associated with an endogenous nitric oxide inhibitor, asymmetric dimethylarginine (ADMA), that has in turn, been linked to an increased risk of cardiovascular disease.[68] In humans, oxidative stress has been associated with endothelial dysfunction.[69]

Hypertension

Hypertension (HBP) is about 50% more frequent in African Americans. For example, in NHANES III, the age-adjusted prevalence of HBP in US adults was 32.4%, 23.3%, and 22.6%, respectively, in non-Hispanic Blacks, non-Hispanic Whites, and Mexican Americans.[106] The prevalence was slightly higher in Black men (34.0%) vs Black women (31.0%). In all 3 ethnic groups combined, only 24% had control of BP to <140 mm Hg systolic and <90 mm Hg diastolic; only 45% of those receiving antihypertensive therapy were controlled.

The greater prevalence of HBP in African Americans contributes largely to their higher risks of stroke, left ventricular hypertrophy, heart failure, end-stage renal disease, and CHD.[107] Of particular interest is the much higher prevalence of HBP in African Americans than Mexican Americans, who also have a high frequency of obesity and diabetes, and are similarly disadvantaged with regard to measures of education and income.

Type 2 Diabetes

The recent obesity epidemic has been accompanied by an approximately 33% increase in the prevalence of diabetes in adults between 1990 and 1998.[108] Since 1998, the American Diabetes Association has defined "impaired fasting glucose" as levels 110 to 125 mg/dL and "diabetes" as levels ≥126 mg/dL or a 2 hour plasma glucose ≥200 mg/dL.[109] Type 2 diabetes is considerably more common in African Americans.[110] For example, the prevalence of diabetes in NHANES III was 1.9-fold higher in non-Hispanic Blacks compared to non-Hispanic Whites.[111] In the Atherosclerosis Risk in Communities (ARIC) study, the incidence of diabetes was 2.4-fold greater in African-American women and 1.5-fold greater in African-American men than in their White counterparts.[112] Adiposity accounted for almost half of the excess risk in African-American women, but little of the excess risk in African-American men. In NHANES III, African-American ethnicity was associated with an age-adjusted odds ratio (OR) for diabetes of

Table 5. Mean triglyceride levels in US adults aged 45–64 years (Atherosclerosis Risk in Communities Study, ARIC)

	N	Triglyceride Level (mg/dL)
White women	6,049	129 ± 85.5*
Black women	2,634	110 ± 70.3*
White men	5,340	148 ± 99.7*
Black men	1,630	120 ± 93.5*

Source: *Angiology*. 1997;48:279–290.[117]
* Standard deviation.

1.76 in women and 1.43 in men.[113] In women, the OR was reduced from 1.76 to 1.42 after controlling for income, but this had little effect in men. Hypertension was present in 70.7% of non-Hispanic Whites with diabetes, 75.4% of non-Hispanic Blacks with diabetes, and 64.5% of Mexican-Americans with diabetes.[114] Control of BP to <140/90 or <130/85 mm Hg was very low in all 3 ethnic groups of diabetics (ie, 39% to 44% and 9% to 14%, respectively).

The most frequent lipid abnormalities in patients with type 2 diabetes are high triglyceride and low HDL cholesterol levels. Isomaa and associates[115] reported that type 2 diabetics with the Metabolic Syndrome had a 3-fold higher prevalence of CHD and proteinuria (macro- or micro-) than did type 2 diabetics (matched for age, sex, duration of diabetes, and glycemic control) without the Metabolic Syndrome. Levels of serum creatinine in each group, however, were not specified.

Hypertriglyceridemia and Low HDL Cholesterol

Hypertriglyceridemia (≥150 mg/dL) is an independent risk factor for CHD.[116] This condition is associated with low HDL cholesterol, small LDL particles, procoagulant effects, HBP, and insulin resistance. Triglyceride levels in African-American men and women are lower than in White men and women, both with and without CHD[26,117–119] (Table 5).

A low level of HDL cholesterol (<40 mg/dL) is also an independent risk factor for CHD, whereas a high HDL cholesterol level (≥60 mg/dL) is protective. Increased levels of hepatic lipase with decreased synthesis of apolipoprotein A-1 may account partly for the low HDL cholesterol level in the Metabolic Syndrome.[120] Hepatic lipase activity is lower in African-American men than in White American men.[121]

HDL cholesterol levels are usually reported to be higher in African Americans than Whites[26,117,122,123] (Table 6). The higher level of HDL cholesterol in African Americans is not explained by body mass index or ethnic differences in life-style factors such as alcohol intake, smoking, or physical activity.[123] In contrast to Whites, however, higher levels of education or socioeconomic status are usually associated with *lower* levels of HDL cholesterol in African Americans.[122,124] The 40% higher incidence of CHD in 435 African-American physician graduates of Meharry Medical College (1957–1965) compared to 580 White physician graduates of Johns Hopkins University (1958–1965) after 23–35 years of follow-up may reflect this observation.[125]

The high prevalence of obesity, HBP, and type 2 diabetes accounts primarily for the disproportionate occurrence of the Metabolic Syndrome in African-American women. High triglyceride or low HDL cholesterol levels are less prevalent, but still contribute significantly to the increased risk of CHD. The lower prevalences of elevated triglyceride and low HDL cholesterol levels in African Americans suggest that the threshold at which these metabolic markers contribute risk could be lower for African Americans than for other groups. Obesity, insulin resistance, and type 2 diabetes are the major determinants of the Metabolic Syndrome in Mexican Americans.

Miscellaneous Associations

The dyslipidemia and hyperinsulinemia of the Metabolic Syndrome represent a prothrombotic state associated with increased levels of fibrinogen and PAI-1.[12,15,98] This is associated with impaired fibrinolytic activity, impaired endothelial function, and a propensity for acute arterial thrombosis.[98,126–130]

Table 6. Mean HDL cholesterol levels in US adults aged 35–75 years (Minnesota Heart Survey)

	N	HDL Cholesterol Level (mg/dL)
White women	786	54.0 ± 0.5*
Black women	572	56.1 ± 0.6*
White men	741	40.8 ± 0.5*
Black men	453	48.6 ± 0.7*

Source: *Epidemiology*. 1992;3:156–163.[123]
* Standard error.

Microalbuminuria is associated with insulin resistance and central obesity[131,132]; it is an independent risk factor for CHD.[133–135] Some experts include microalbuminuria as an integral component of the Metabolic Syndrome.[19,25,135]

Sleep-disordered breathing is associated with obesity, HBP, diabetes,[136] and African-American[137] or Hispanic[138] ethnicity. Some have considered it as a component of the Metabolic Syndrome.[139,140]

The polycystic ovary syndrome (PCOS, previously called the Stein-Leventhal syndrome) is one of the most common endocrinopathies in women of reproductive age.[141] This syndrome is often associated with obesity, insulin resistance, type 2 diabetes, dyslipidemia, and increased levels of PAI-1. Women with PCOS thus have a high prevalence of the Metabolic Syndrome and its associated cardiovascular risks.

In one relatively small study of young men in Finland, smokers had a 6-fold higher prevalence of the Metabolic Syndrome compared with nonsmokers.[142] The Metabolic Syndrome also is often associated with hyperuricemia.[15,143,144]

Table 7. Therapeutic options for management of the Metabolic Syndrome to improve coronary heart disease risk factors

Component	Therapy	Goal
Overweight/obesity	Weight reduction (low-calorie diet, 800–1,500 kcal/day) and	1–2 lb/week first 6 months, then change priority to maintenance of the effect
	Increased physical activity	*At least* 30–45 min, 3–5 days/week
Elevated blood pressure	Weight reduction (if overweight)	SBP <140 mm Hg and DBP <90 mm Hg
	Antihypertensive drugs	SBP <130 mm Hg and DBP <80 mm Hg (if diabetic)
Diabetes mellitus/insulin resistance	Weight reduction (if overweight)	HbA_{1c} <7%
	Insulin or oral agent (eg, sulfonylureas, metformin)	Fasting glucose <120 mg/dL
	Insulin sensitizers (eg, rosiglitazone or pioglitazone)	Postprandial glucose <150 mg/dL
Hypertriglyceridemia and low HDL cholesterol	Increased physical activity	See above (Overweight)
	Nicotinic acid	Non-HDL cholesterol <130 mg/dL (high-risk for CHD)
	Fibrates (eg, gemfibrozil or micronized fenofibrate)	or <160 mg/dL (≥2 CHD risk factors)
LDL cholesterol	Therapeutic lifestyle changes diet (see text)	<100 mg/dL (CHD or CHD equivalents)
	Lipid-lowering therapy (as needed to reach goal)	<130 mg/dL (≥2 CHD risk factors)
Prothrombotic state	Aspirin (81 to 160 mg/day) if at intermediate risk for CHD or stroke	Prevention of CHD or stroke

TREATMENT

Management of the Metabolic Syndrome consists primarily of 2 strategies: modification or reversal of the root causes and direct therapy of the risk factors (dyslipidemia, elevated BP, insulin resistance, and the prothrombotic state). The first strategy involves weight reduction and increased physical activity, both of which can decrease the underlying insulin resistance and indirectly modify the metabolic risk factors. The second strategy may involve drug treatment of the individual risk factors associated with the syndrome. Improvement in several of these individual risk factors has been shown to decrease the risk of CHD.

The recent ATP III guidelines emphasize that the *primary* target for risk-reduction therapy is reduction of LDL cholesterol to ≤100 mg/dL in patients with CHD or CHD equivalents (eg, diabetes) and <130 mg/dL in persons with 2 or more risk factors.[4] The report specifically addresses the Metabolic Syndrome as a secondary target of therapy to attain benefit beyond LDL-lowering. Table 7 provides a summary of the therapeutic options for management of the Metabolic Syndrome to improve CHD risk factors.

Weight Reduction

ATP III recommends a Therapeutic Lifestyle Changes (TLC) diet for reduction of LDL cholesterol in patients at risk for CHD.[4] The nutrient composition of this diet features reduction in the intake of total fat (25% to 35% of calories), saturated fat (<7% of calories), trans fatty acids, and cholesterol (<200 mg/d). Total calorie intake is modified to maintain desirable body weight. The Dietary Approaches to Stop Hypertension (DASH) diet, plus reduced sodium to about 2,300 mg daily, is very effective in many hypertensive patients, including African-American men and women.[145] The DASH diet is also low in total fat (26% of calories), saturated fat (6% of calories) and cholesterol (151 mg/d) with a carbohydrate composition of about 55%.

A low-fat diet is usually associated with only minimal weight loss unless it also is calorie restricted. Many patients with the Metabolic Syndrome are overweight hypertensive and/or diabetic individuals who need a weight reduction diet because weight reduction improves *all* components of the syndrome, including BP, insulin resistance, glucose, and triglyceride levels.[53] For this reason, a specific weight reduction program is vital in overweight and obese patients with the Metabolic Syndrome.

The initial target of weight loss therapy should be about a 10% decrease in body weight. A low-calorie diet (LCD, 800 to 1,500 kcal/d) is recommended and can decrease body weight by an average of 8% over 3 to 12 months.[53] A very low-calorie diet (VLCD, 250 to 800 kcal/d) is not recommended because, although the initial weight loss is greater, the diet requires supplementation with vitamins and minerals and produces no greater long-term (>one year) results than the LCD. For the first 6 months of a LCD, expect a weight loss of about 1 to 2 lb/week, after which the weight loss begins to plateau, in part because of decreased energy expenditure associated with the lower body weight. After 6 months, the LCD is continued but the priority should change to long-term efforts to maintain the lower weight and prevent weight gain.

Because a relatively high-carbohydrate intake can increase glucose, insulin, and triglyceride levels, some caution is indicated with use of a low-fat diet in patients with the Metabolic Syndrome.[146,147] For example, in one study, a low-fat (25% of calories) diet containing 60% of calories as carbohydrate re-

sulted in higher fasting triglyceride and insulin levels than a high-fat diet with 40% of total calories as carbohydrate.[148] The composition of the low-fat ATP III TLC diet is 50% to 60% carbohydrate.[4] Replacing saturated fat with unsaturated fat or low-fat foods (eg, fish rather than red meat) can help reduce triglyceride and raise HDL cholesterol levels in patients with the Metabolic Syndrome.[4,101,147]

The type of dietary carbohydrate can modify the effect on weight control, as previously suggested.[149] The glycemic index (GI) is a measure of the magnitude of postprandial hyperglycemia (and resultant hyperinsulinemia) induced per gram of carbohydrate intake. Diets with a high GI (eg, starchy foods) can promote hyperglycemia with oxidation of carbohydrates at the expense of oxidation of fats, thereby limiting the amount of weight loss.[150,151] In relatively short-term studies, replacing high GI carbohydrates with low GI carbohydrates (eg, whole grains, cereal fiber) can improve glycemic control, insulin resistance, lipids, weight loss, and the risk of developing diabetes.[152–154] Clinical recommendations, however, await the results of long-term studies on the risk of cardiovascular outcomes.

A lower correlation exists between BMI and all-cause or CHD mortality in African Americans vs Whites.[155,156] In addition, African Americans participating in weight reduction programs show a lesser degree of weight loss.[157–161] The reasons for this may be metabolic or behavioral and include the possibility that a different approach to nutrition counseling might be needed for optimal efficacy in African-American adults.[162–164] Nonetheless, weight reduction is clearly beneficial and can be accomplished in overweight African Americans. The Diabetes Prevention Program, which included 3,234 nondiabetic individuals (45% minority) with impaired glucose tolerance, documented a 58% reduction (relative to placebo) in the 3-year incidence of diabetes mellitus following a lifestyle-modification program that included weight reduction (≥7%) and increased physical activity (≥150 minutes per week).[165]

Increased Physical Activity

Physical inactivity is a risk factor for CHD.[4] Increased physical activity is a major component for the accomplishment of weight loss therapy.[53] An increase in aerobic physical activity should accompany all dietary programs because it can decrease triglyceride and VLDL cholesterol levels[4,53] while inducing small, but favorable increases in HDL cholesterol[166,167]; lower BP[168]; and decrease insulin resistance.[4,53] An excellent recent publication documented that regular exercise with only minimal weight change had broad and beneficial effects on lipoproteins as measured by nuclear magnetic resonance imaging rather than the traditional lipid profile.[169] The amount of exercise made a greater difference than the intensity of exercise. Even the group assigned to the lower amount of exercise (ie, the equivalent of walking 12 miles per week), however, had better responses than the control group.

Low cardiovascular fitness has been associated with the Metabolic Syndrome.[170] Increased physical activity can increase cardiorespiratory fitness independent of weight loss.[53] A special impact of physical activity in African Americans has yet to be evaluated rigorously.

Encourage moderate levels of physical activity for *at least* 30 to 45 minutes, 3 to 5 days a week with a long-term goal to accumulate at least 30 minutes of physical activity on most days of the week.[53] Walking is usually an accessible and relatively safe form of physical activity. Reducing sedentary time is another approach. Although studies in African Americans are limited, useful guidelines are now available for counseling by healthcare providers to promote physical activity in African Americans.[171]

Preventive measures must focus on children as well as adults. Measures to decrease sedentary lifestyle (eg, less television hours, etc) are apparent, but community and public health strategies are also needed. Increasing the number and safety of walking areas, eliminating high-calorie fast-food specials, providing simple nutrition information on food labels, and encouraging appropriate school-based programs that promote physical activity are examples of proactive strategies to address the growing problem.

Drug Therapy

General

Treatment of several of the individual risk factors associated with the Metabolic Syndrome has been shown to decrease CHD risk. The benefits of treating atherogenic dyslipidemia and lowering BP are well established. In addition, the most current guidelines for CHD risk reduction also recommend once daily aspirin (81 to 160 mg) for treatment of the prothrombotic state in adults at intermediate risk for CHD or stroke.[172] Although the benefit of treatment of hyperglycemia to reduce CHD risk is not yet established, tight control of fasting and postprandial glucose levels and HbA_{1c} are currently recommended.[109] Drug therapies that reduce insulin resistance are available, but there is as yet no evidence that they reduce the risk of CHD in persons with the Metabolic Syndrome.

Hypertension

The abnormalities associated with the Metabolic Syndrome should not be a primary consideration for selection of antihypertensive therapy. Thiazide diuretics, spironolactone, and most beta-blockers impair insulin sensitivity, whereas angiotensin converting enzyme (ACE) inhibitors, alpha blockers, and dihydropyridine calcium channel blockers improve insulin sensitivity.[173,174] The effects of the other calcium channel blockers and furosemide are neutral.

Some evidence exists that angiotensin receptor blockers, like ACE inhibitors, also improve insulin sensitivity.[175,176] Thiazide diuretics are associated with a short-term increase in total cholesterol and triglyceride levels.[177] Beta-blocker therapy (especially nonselective beta-blockers in high doses) can increase glucose and triglyceride levels, and lower HDL cholesterol levels.[6,177,178] However, both of these classes (ie, diuretics and beta-blockers) have been shown to reduce CVD in hypertensive African Americans. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), with more than 42,000 participants (including more than 15,000 Blacks and more than 15,000 diabetics), a drug (the alpha-blocker, doxazosin) known to reduce insulin resistance and have favorable effects on blood lipids, showed no significant benefit on atherosclerotic events vs the thiazide-type diuretic, chlorthalidone.[179,180] Indeed, the doxazosin arm of the study was discontinued because of worse cardiovascular outcomes, especially heart failure and stroke.[180] The final ALLHAT results, comparing outcomes with therapy based on a calcium antagonist or ACE-inhibitor vs a diuretic, showed equivalent changes in CHD death or nonfatal myocardial infarction (the combined primary study endpoint).[181] Diuretic-based therapy appeared to be superior to calcium antagonist-based therapy in preventing heart failure, and superior to ACE-inhibitor-based therapy in preventing stroke, combined CVD, and possibly heart failure. This advantage was also seen in the diabetic subgroup. Reduction in BP, however, was not equal across treatment groups; for example, participants randomized to the diuretic group achieved lower systolic BP than those randomized to the calcium antagonist (by 0.8 mm Hg) and ACE-inhibitor group (by 2 mm Hg). For only Black participants, the final systolic BP was 4 mm Hg lower in the diuretic vs the ACE-inhibitor group. Subsequent commentaries further discuss interpretation of the ALLHAT results.[182–184] In ALLHAT, as in other hypertensive clinical outcome trials, the vast majority of participants required more than one drug to control BP to $<$140/90 mm Hg.

Long-term beta-blocker therapy is clearly indicated after recent myocardial infarction,[185] and beta-blockers continue to be indicated but under-prescribed in African Americans with recent myocardial infarction.[186]

In 2003, the Joint National Committee (JNC-7) updated the guidelines for the treatment of hypertension 7 years ago.[187] Consensus guidelines for the treatment of hypertension in African Americans were also published this year by an expert working group of the International Society on Hypertension in Blacks (ISHIB).[188]

Dyslipidemia

As mentioned earlier, the primary treatment for patients with the Metabolic Syndrome is weight reduction and increased physical activity. Drug therapy is indicated in some high-risk patients or in those who have not reached goal after therapeutic lifestyle changes. Statin-therapy is associated with modest improvements in triglyceride and HDL cholesterol levels. In ALLHAT, 10,355 moderately hypercholesterolemic (average 224 mg/dL; 5.8 mmol/L), hypertensive patients were also randomized to pravastatin (40 mg daily) vs usual care.[189] Due to the large number of usual care participants who received lipid-lowering therapy, the difference in total cholesterol between groups was less than expected (ie, 7.6% reduction in the usual care group vs 17.2% in the pravastatin group) and no significant reduction in the primary outcome, all-cause mortality, was achieved after 6 years. When the ALLHAT Lipid Trial results are compared with other lipid-lowering trials, the outcome results are consistent with the results predicted by the difference in achieved cholesterol levels in the 2 groups. Black participants assigned to pravastatin did have a significantly (27%) lower risk of fatal CHD and myocardial infarction than the control group, but a 12% higher risk of stroke. ALLHAT was the first lipid-lowering outcome trial in Black patients.

Bile acid sequestrants can cause slight improvement in HDL cholesterol, but generally increase triglycerides and are contraindicated with triglyceride levels $>$200 mg/dL. Ezetimibe is a new selective inhibitor of cholesterol absorption and, when combined with a statin, induces complementary decreases in the level of total and LDL cholesterol with no increase in the level of triglycerides.[190,191]

ATP III recommends that "non-HDL cholesterol" should be a secondary target for patients with "high" triglyceride levels (ie, 200 to 499 mg/dL). Non-HDL cholesterol represents the sum of LDL cholesterol plus VLDL cholesterol and the other atherogenic proteins (ie, intermediate density lipoproteins, Lp(a), remnant particles). This figure can be calculated by subtracting the HDL cholesterol level from the total cholesterol level.[4] For example, a person with a total cholesterol of 210 mg/dL and an HDL cholesterol of 50 mg/dL would have a non-HDL cholesterol of 160 mg/dL. The goal for non-HDL cholesterol is $<$130 mg/dL for those at high-risk for CHD and $<$160 mg/dL for those with 2 or more risk factors. Patients with "very high" triglyceride levels (ie, $\geq$500 mg/dL) should receive a very low-fat diet ($\leq$15% of calories), weight reduction, increased physical activity, and a triglyceride-lowering drug to prevent acute pancreatitis. An exception to drug use in this setting might be the marked hypertriglyceridemia that can accompany extreme hyperglycemia, where a decrease in the glucose level can markedly improve the hypertriglyceridemia.

The drugs that primarily decrease triglycerides and increase HDL cholesterol are nicotinic acid and fibrates such

as gemfibrozil (600 mg twice daily, taken 30 min before meals) and micronized fenofibrate (160 mg daily, taken with food).[192] Nicotinic acid must be used with caution in diabetic individuals because high doses can worsen glycemic control. Low doses (eg, 1,000 to 1,500 mg/day of ER niacin), however, are a treatment option for the dyslipidemia of patients with type 2 diabetes.[193] Nicotinic acid is contraindicated in patients with chronic liver disease because of the risk of hepatotoxicity. Gemfibrozil significantly reduces the risk of major cardiovascular events (ie, nonfatal myocardial infarction or coronary death) in men with CHD and a HDL cholesterol of ≤40 mg/dL.[194] Fibrates and statins are often used together, but each or the combination has been associated with myopathy, and periodic monitoring of the complete blood count, liver function tests, and creatine phosphokinase (CPK) is prudent.

Diabetes Mellitus

Examples of oral anti-hyperglycemic agents used to treat diabetes include the sulfonylureas such as glyburide or glipazide and the alpha-glucosidase inhibitors such as acarbose.[195] The sulfonylureas increase endogenous insulin secretion. The glucosidase inhibitors delay the postprandial absorption of carbohydrates. Both have neutral or only slightly beneficial effects on plasma lipid levels. Metformin (initial oral dose of 500 mg/d, taken with food) is a biguanide that decreases glucose and insulin levels, and has modestly favorable effects on lipids, especially triglyceride levels.[196–198] Metformin is the only oral agent that, used as monotherapy, has been shown to reduce macrovascular complications of type 2 diabetes.[199] Thiazolidinediones such as rosiglitazone or pioglitazone are insulin-sensitizing drugs that are approved for the treatment of diabetes, but not for the treatment of insulin resistance *per se*.[20,200,201] Some of their actions are mediated through binding and activation of the peroxisome proliferator-activated receptor-γ (PPAR-γ), a receptor that regulates adipocytes.[201] The glitazones lower both plasma glucose and insulin, directly improving insulin resistance. Although there may be favorable effects on triglyceride and HDL cholesterol levels, there is a tendency for LDL cholesterol levels to increase.[202] The glitazones can cause fluid retention as well as weight gain and are not recommended in patients with New York Heart Association (NYHA) Class 3 or 4 cardiac status. Their long-term safety, efficacy, and cardiovascular effects are currently under evaluation.

A diagnosis of the Metabolic Syndrome provides early identification of accelerated cardiovascular risk, and therefore an earlier opportunity to intervene on all cardiovascular risk factors.

SUMMARY

Recent NHANES III data indicate that the Metabolic Syndrome (ie, hypertension, obesity, type 2 diabetes, hypertriglyceridemia, and low HDL cholesterol) is relatively prevalent in African Americans. The clustering of risk factors is associated with an increased morbidity and mortality from CHD and CVD. African Americans have the highest overall CHD mortality and the highest out-of-hospital coronary death rate of any ethnic group in the United States. Current research is attempting to unravel the specific metabolic or genetic mechanisms for the clustering of risk factors.

A diagnosis of the Metabolic Syndrome provides early identification of accelerated cardiovascular risk, and therefore an earlier opportunity to intervene on all cardiovascular risk factors. Early intervention also provides a critically important opportunity to evaluate the children of these patients because they have an increased risk of these same abnormalities.

Weight reduction and increased physical activity can improve *all* of the components of the Metabolic Syndrome. Special attention is needed to avoid a diet that is too high in carbohydrates, which can aggravate hyperglycemia, hyperinsulinemia, and hypertriglyceridemia. In patients with incomplete responses to therapeutic lifestyle changes, drug therapy to specifically reduce selected cardiovascular risk factors must be considered for prevention of CHD.

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The African-American Lipid and Cardiovascular Council (AALCC) was founded in 1991. As a nonprofit health professional advisory group, the council has as one of its goals the enhancement of professional and public awareness of the importance of coronary disease and coronary risk factors in African Americans and other minorities. Educational activities have included several symposia, 2 annotated bibliographies on Lipids in Blacks (1936–1994; 1993–2001), and a recent review article on Coronary Heart Disease in African Americans (reference 26). Most of these materials are available on the web site at http://www.aalcc.com. The council is sponsored by an unrestricted educational grant from Bristol-Myers Squibb Company.

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Appendix 1. Highlights of emerging concepts related to the metabolic syndrome

Concept	References
Asymmetric dimethylarginine	68
Cardiovascular mortality	22–25
DASH diet	145
Diabetes, type 2	49,50,108–115,165,173,195–201
Diagnostic criteria	2–5,11,14,15,20
Endothelial dysfunction	69–71
Fibrinogen	12,15,98
Glycemia index	149–154
Hepatic lipase	120,121
Hispanics	5,28–31,138
Homocysteine	105
Hypertension	26,104,106,107,114,168,177–184,187,188
Hyperuricemia	15,143,144
Insulin resistance	6–26,78,79,85–98,100,142,174–176
LDL particle size	65–67,169
Leptin	78–83
Liposuction	58
Microalbuminuria	19,25,131–135
Native Americans	11,28
Non-HDL cholesterol	4
Nuclear magnetic resonance imaging (lipids)	169
Overweight/obesity (adults)	2,11,16,30,31,40,53,59,72,92,160
Overweight/obesity (children)	35–48
Oxidative stress	69,82,105
Peroxisome proliferator-activated receptor-γ	201
Physical activity/exercise	32–34,40,53,165–172
Plasminogen activator inhibitor 1 (PAI-1)	63,64,126–130
Polycystic ovary syndrome (PCOS)	141
Resistin	84–87
Sleep-disordered breathing	136–140
Smoking	142
South Asians	11
Therapeutic Lifestyle Changes (TLC) diet	4
Visceral fat	51,54–57,59–64,73–77,102