

METABOLIC SYNDROME: IMPLICATIONS OF RACE AND ETHNICITY

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INTRODUCTION

Ethnicity, a term that sociologically means “cultural characteristics that connect a group of people together,” may be considered a risk factor for cardiovascular disease. The metabolic syndrome, a constellation of characteristics that, when found together, portend a high risk for cardiovascular disease, is very common among certain ethnic groups. The National Cholesterol Education Program (NCEP) and the Adult Treatment Panel (ATP) III¹ has defined the metabolic syndrome as any 3 of the following:

- Blood pressure (BP) = 130/85 mm Hg
- Presence of abdominal obesity defined as a waist circumference >40 in (102 cm) in men and >35 in (88 cm) in women
- Fasting glucose = 110 mg/dL
- Triglycerides (TG) = 150 mg/dL
- High density lipoprotein (HDL) <40 mg/dL in men and <50 mg/dL in women

The World Health Organization (WHO) has set forth a definition² to aid research rather than to act as a strict definition of the metabolic syndrome. Several studies from Europe and Canada have used this definition in their studies. Their definition is as follows:

- One of either: 1) insulin resistance in the top 25% of the population as measured by the hyperinsulinemic-euglycemic clamp OR 2) the presence of impaired glucose tolerance or type 2 diabetes mellitus (DM)

AND at least two of the following:

- Abdominal obesity (waist-hip ratio of >0.90 or body mass index = 30 kg/m²)
- Dyslipidemia (serum triglycerides

=1.70 mmol/liter or high density lipoprotein cholesterol HDL <0.9 mmol/liter)

- Hypertension (HTN) (160/90 mm Hg)
- Microalbuminuria

The WHO definition has been criticized for including microalbuminuria and for using waist-hip ratio, as the waist circumference has been shown to better correlate with visceral fat deposits. The European Group for Insulin Resistance (EGIR) has proposed several modifications.³ These include: waist circumference as ≥ 94 cm; use of fasting insulin to estimate insulin resistance; and lower blood pressure cut-off ($\geq 140/90$ mm Hg). An epidemiological study from Finland found that including insulin sensitivity via clamps resulted in a more sensitive, but less specific, test for detecting type 2 diabetes.⁴

Individuals with the metabolic syndrome are at high risk for progressing to type 2 diabetes mellitus.

THE TWIN PANDEMICS OF DIABETES AND THE METABOLIC SYNDROME

Worldwide rates of type 2 diabetes and the metabolic syndrome have increased dramatically over the last few years. The projected growth rates for diabetes mellitus are highest for Southeast Asia with prevalence estimates of 80 million by the year 2025, up from 30 million in 2000. The Americas, Western Pacific, Europe, and East Mediterranean have estimates between 40 and 60 million by the year 2025. The data from Africa seems to lag behind the rest of the world with prevalence estimates of <10 million by the year 2025.⁵ In the United States, more than 30% of the population older than 60 years of age

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will have either impaired fasting glucose, undiagnosed type 2 diabetes, or overt type 2 diabetes mellitus.⁶ Several ethnic groups within the United States have been studied for prevalence of type 2 diabetes. Pima Indians have the highest prevalence (50%) of type 2 diabetes. European Americans have the lowest prevalence; only 11% of the population has diabetes.⁷

The NCEP/ATP III defined the metabolic syndrome in its 2001 report, leading to greater recognition of the metabolic syndrome among patients. Ford et al used pre-existing NHANES III data to estimate the prevalence of the metabolic syndrome among US adults.⁸ In that analysis, the age-adjusted prevalence of the metabolic syndrome was 23.7%. Data was also analyzed according to race or ethnicity; White, African Americans, Mexican Americans, and other were the categories used. Mexican Americans had the highest prevalence rates of metabolic syndrome (31.9%). White Americans had a slightly higher prevalence (23.8%) than African Americans (21.6%). There were striking racial differences in the specific components of the metabolic syndrome. Not surprisingly, there was a disproportionately higher prevalence of HTN among African Americans (46%). Mexican Americans had the highest prevalence of low HDL cholesterol, high TG, fasting glucose, medication use and abdominal obesity.

More recent data from the NHANES 1999–2000⁹ show that the racial differences persisted into 2000. Mexican-American women had the highest prevalence of the metabolic syndrome at 35.6%, followed by Mexican-American men (28.3%). Non-Hispanic White women and men had similar rates, 22.8% and 24.8% respectively.

Each of the individual parameters in the definition of the metabolic syndrome seems to be predominantly clustered in a particular racial group. Hypertension (HTN) is more prevalent in African Americans; visceral adiposity,

low HDL and high TG are more common in Mexican Americans. Mexican Americans have the highest rates of fasting hyperglycemia and type 2 DM. The overall effect of the metabolic syndrome in a particular ethnic group would need to be adjusted for that particular entity, eg, hypertension in African Americans.

ETHNICITY AND OBESITY

Obesity, defined in adults as a body mass index (BMI) greater than 30 kg/m² has significantly affected the rise in metabolic syndrome, with the escalation in metabolic syndrome being parallel to the rise in obesity. In addition, there are racial differences in the prevalence of obesity, as well as in the health complications associated with obesity. Between the NHANES III (1988–1994) and the NHANES 1999–2000, the prevalence of obesity increased in both men and women and in each racial group.¹⁰ The rise in obesity has been greatest in African-American women, followed by Hispanic, then Caucasian women. In men, the inter-racial trends have been similar to those in women. The age-adjusted prevalence of obesity increased from 22.7% to 30.5% by 2000 and that of overweight increased from 55.9% to 64.5%. The majority (greater than 80%) of non-Hispanic Black women older than 40 years of age are overweight.

Visceral Adiposity

Excess abdominal adiposity is a hallmark of the metabolic syndrome (Table 1). Racial differences have been reported in the proportion that visceral fat contributes to total body fat. White persons are more prone to develop visceral adipose tissue (AT) than Blacks with equal amounts of total body fat.¹¹ The main difference is higher visceral adiposity in White men than Black despite similar BMI and body fat mass values. Though African American women have increased total body fat mass than White

women, both groups have similar visceral AT, which suggests a higher proportion of body fat in White women is visceral. Higher visceral AT has been shown to be related to lower HDL cholesterol levels among Whites.

Lipid Profiles

According to Despres et al,¹¹ the relatively favorable lipid profile in Blacks (compared to Whites) could be explained at least in part by the racial differences in visceral adiposity. In their study, White subjects had higher fasting triglycerides and apoB levels than did Black subjects.

INSULIN RESISTANCE, IMPAIRED GLUCOSE TOLERANCE, AND DIABETES IN VARIOUS ETHNIC GROUPS

Insulin resistance has both acquired and inherited influences. The inherited influences include rare mutations of the insulin receptor, glucose transporter, or signaling proteins. Other unidentified mutations may also contribute. Growing evidence suggests that chromosome 1q harbors at least one loci related to the metabolic derangements in diabetes.¹² Acquired influences include overeating, overweight, inactivity, aging, medications and illness. Elevated free fatty acids and glucose toxicity have also been implicated.

The World Health Organization (WHO) definition of the metabolic syndrome includes an assessment of an individual's insulin sensitivity using a hyperinsulinemic-euglycemic clamp. Though not all persons with the metabolic syndrome have insulin resistance, it is thought to be an important underlying feature.

Adipokines, Insulin Resistance, and Inflammation

Visceral adiposity is more closely associated with cardiovascular disease than

Table 1. Cardiovascular risk factors associated with visceral obesity

Insulin resistance/hyperinsulinemia
Low serum high density lipoprotein cholesterol (HDL)
High serum triglyceride concentrations
Increased apolipoprotein B serum concentrations
Small, dense low density lipoprotein (LDL) particles
Increased serum fibrinogen concentrations
Increased production of plasminogen activator inhibitor-1 (PAT-1)
Increased serum levels of C-reactive protein (CRP)
Increased production of tumor necrosis factor α (TNF- α)
Increased production of interleukin 6 (IL-6)
Microalbuminuria
Increased blood viscosity
Increased systolic and pulse pressure
Left ventricular hypertrophy
Premature atherosclerosis

subcutaneous adiposity. Visceral adiposity tends to consist of large insulin resistant adipocytes that have several metabolic abnormalities including deficiency in adiponectin. Insulin-mediated anti-lipolysis is decreased and catecholamine-induced lipolysis increases. Numerous adipocyte derived cytokines (adipokines) produced by these viscera-ly located adipocytes mediate inflammation and insulin resistance. These cytokines include increased TNF- α , PAI-1, IL-6, and leptin.

Free Fatty Acids

Free fatty acids have been shown to contribute to the pathogenesis of type 2 DM. Increased lipolysis results in FFA mobilization with increased oxidation in the muscle and liver. In the muscle, this results in decreased glucose utilization and hyperglycemia and, in the liver, there is increased gluconeogenesis resulting in hyperglycemia.

Racial Differences in Insulin Sensitivity

Evidence supports racial differences in insulin resistance even in the absence of obesity. A study by Dickinson et al compared postprandial blood glucose after 75 g glucose challenge and insulin sensitivity in lean young adult Asian and Caucasian subjects.¹³ Despite similar fasting blood glucose readings, there was significantly higher postprandial glycemia in the Asian group; up to 100%

higher incremental area under curve (AUC) than Caucasians. In the same study, there was >2 fold higher incremental insulin AUC in the Asian subjects. Homeostasis Model Assessment modeling based on these values showed European subjects to be almost 2-fold more sensitive than the Asians.

In another study, healthy young adults of various ethnicities were evaluated prospectively for insulin resistance and dietary habits.¹⁴ Black subjects formed a significant proportion of the group under 24 years of age. The results suggest that racial differences may underlie the occurrence of fasting hyperglycemia and impaired glucose metabolism in the metabolic syndrome. With perhaps a genetic predisposition, external factors such as obesity, inactivity, and overeating may result in the higher prevalence of the metabolic syndrome in certain ethnic groups.

CARDIOVASCULAR IMPLICATIONS

Cardiovascular complications are the most dreaded outcomes of the metabolic syndrome. The risks are, in part, mediated by impaired endothelial function. Inflammation also plays a key role in the pathogenesis of cardiovascular complications of the metabolic syndrome. Factors contributing to endothelial dysfunction in the metabolic syndrome

include: small dense low density lipoprotein (LDL) particles; abnormal coagulation and fibrinolytic profiles; and RAS- (Renin angiotensin system) mediated reactive oxygen species (ROS) inflammation resulting in increased cardiovascular oxidative stress. Though not technically in the definition, elevated C-reactive protein (CRP) levels and microalbuminuria are key players.

C-reactive protein (CRP) and insulin-like growth factor (IGF) systems were studied by Heald et al in relation to risk of cardiovascular disease in different ethnic groups in the United Kingdom.¹⁵ African-Caribbean men and women had the lowest CRP compared to Pakistani and Caucasian patients. A high CRP, low IGF-1 and IGFBP-1 were independently associated with the risk of having the WHO-defined metabolic syndrome. Higher CRP, higher IGF, and metabolic syndrome are in keeping with epidemiologically higher rates of premature cardiovascular disease (CVD) in the Pakistani population.

Coronary artery disease (CAD) and stroke, the major contributors to CV mortality, also have racial trends. Stroke mortality is higher in Blacks than either Caucasians or Hispanics. There has been an overall decline in coronary heart disease (CHD) mortality, although the decline is less in Blacks, especially among Black women, who have had higher rates than Whites since the mid-1980s.¹⁶

Predicting Cardiovascular Mortality

Lakka et al studied 1209 Finnish men, aged 42–60 years, at baseline and without CVD, diabetes, or cancer for approximately 11.4 years.¹⁷ Cardiovascular disease (CVD) and all cause mortality were evaluated in relation to WHO and NCEP definitions and modifications of the metabolic syndrome. These outcomes were increased in patients with the metabolic syndrome even in the absence of CVD and diabetes at baseline. The major contributor to

Table 2. Cardiovascular risk factors that cluster with microalbuminuria

Central obesity
Insulin resistance
Low high density lipoprotein (HDL) cholesterol levels
High triglyceride levels
Systolic hypertension
Absent nocturnal drop in blood pressure
Salt sensitivity
Increased cardiovascular oxidative stress
Impaired endothelial function
Abnormal coagulation/fibrinolytic profiles
Increased inflammation

CVD death was CHD. This study used factor analysis to reduce variables. Other previous studies did not exclude persons with diabetes who might confound the findings of excess mortality and morbidity with the metabolic syndrome. However, the subjects were predominantly Caucasian. No prospective data are available to evaluate these trends by ethnicity.

Risk Factors for Excess Cardiovascular Mortality and Morbidity

Compared with patients without the metabolic syndrome, persons with the metabolic syndrome have increased atherosclerosis (maximum intimal medial thickness) and elevated PAI-1.¹⁸ For the same amount of atherosclerosis, individuals with the metabolic syndrome had a greater prevalence of CVD. This difference was attenuated after adjusting for levels of PAI-1, suggesting that fibrinolytic dysfunction mediates this increased risk. When adjusted for race, there was no difference.

Table 3. Multivariate odds ratio for chronic kidney disease or microalbuminuria based on the presence of components of the metabolic syndrome

Components	CKD OR	Microalbuminuria OR
0-1	1.0	1.0
2	2.21	1.22
3	3.38	1.62
4	4.23	2.45
5	5.85	3.19

Impaired Endothelial Dependent Vasodilation

Subjects without diabetes but with impaired glucose tolerance or first degree relatives with diabetes have been shown to have impaired endothelial dependent vasodilation. Caballero et al studied endothelial dependent and endothelial independent vasodilation and showed that subjects with first degree relatives with diabetes, impaired glucose tolerance and persons with diabetes had reduced responsiveness when expressed as a percent over baseline.¹⁹

MICROALBUMINURIA, CHRONIC KIDNEY DISEASE, AND METABOLIC SYNDROME

Microalbuminuria is strongly linked to CVD risk. Other risk factors that

cluster with microalbuminuria in the metabolic syndrome are shown in Table 2.

There exists a significant overlap between these cardiovascular risk factors and components of the metabolic syndrome. A finding of microalbuminuria may be an indication to evaluate a patient for the metabolic syndrome and cardiovascular risk factors. The converse is more likely since microalbuminuria is found in the general non-diabetic, non-hypertensive population. The risk of chronic kidney disease in the metabolic syndrome was evaluated by Chen et al²⁰ in a cross sectional study using NHANES data. The multivariate adjusted odd ratio (for age, race, gender, NSAID use, education, activity, and smoking) for chronic kidney disease and microalbuminuria in patients with and without the metabolic syndrome was 2.60 and 1.89, respectively. Chronic kidney disease was defined as a GFR of less than 60 ml/min/1.73 m². In that same study they found a relationship between the number of metabolic syndrome factors and odds ratio for microalbuminuria and chronic kidney disease (CKD). Using 0-1 components as the standard, the odds ratios for 2, 3, 4, 5 components were evaluated.

Though these data are striking, it is important to note that the differences in BP and fasting blood glucose in the 2

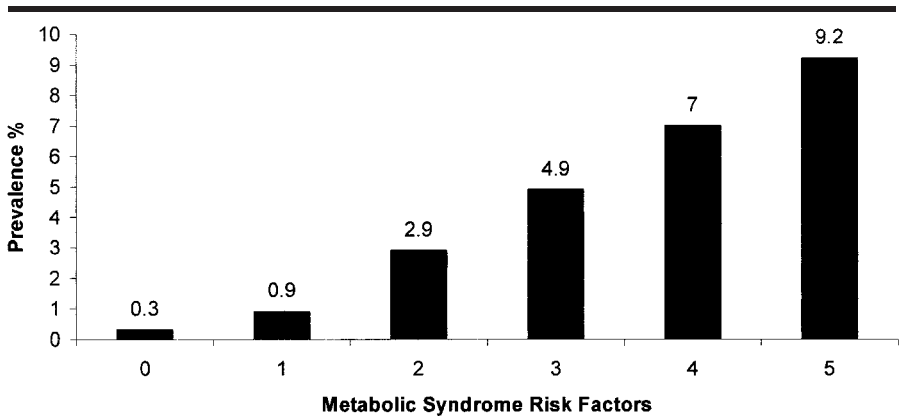


Fig 1. Increased prevalence of chronic kidney disease with number of metabolic syndrome components (adapted from Chen et al. *Ann Intern Med.* 2004; 140:167-174)

groups were statistically significant and the authors admit that these results cannot be entirely separated from the effects of BP and blood glucose differences.

A prospective study from Denmark found that proteinuria is an independent risk factor for all cause mortality in type 2 diabetes.²¹ Though a predominantly White group of subjects, subsequent studies have shown similar findings in studies incorporating other ethnic groups.

PROGRESSION TO DIABETES

Hypertension, a component of the metabolic syndrome and major CV risk factor, has been associated with increased propensity to insulin resistance. The mechanisms linked to insulin resistance in HTN are related to decreased non-oxidative glucose metabolism by skeletal muscle. The underlying mechanisms for this include post-receptor defects, altered skeletal muscle fiber type, and decreased delivery of insulin and glucose to skeletal muscle. Several studies designed to evaluate HTN medications have shown reduced development or progression to diabetes (HOPE/ALLHAT).^{22,23} In the ALLHAT trial, both amlodipine and lisinopril showed a 4 year progression to DM of 9.8% and 8.1%, respectively and was statistically significant ($P < .05$) when compared with chlorthalidone 11.6%. Ramipril has also been shown to reduce the occurrence of diabetes when compared with placebo in the HOPE-TOO trial which conducted evaluations over a 7-year period. Newer studies are directly evaluating the effect of medications traditionally used as anti-hypertensives on slowing the progression of or preventing diabetes altogether (DREAM/NAVIGATOR).

The VALUE trial²⁴ was a prospective comparison of amlodipine and valsartan designed to test the hypothesis that for

the same BP control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in patients at high risk. The main outcome of CVD did not differ between the 2 treatment groups. Of note, however, the incidence of new-onset diabetes was significantly lower in the valsartan (13.1%) arm as compared to the amlodipine (16.4%) arm. The risk reduction of 23% was statistically significant ($P < .0001$). These findings are similar to those in ALLHAT with amlodipine vs lisinopril and suggest a role of biological angiotensin II blockade. In this study, the majority of patients were White (~89%), with very little representation of other ethnic groups. It therefore cannot be determined what the effect of ethnicity would be on these results.

SUMMARY

Many of the studies evaluating implications of the metabolic syndrome have not looked specifically at varied ethnic groups to compare and contrast the effects of ethnicity on the metabolic syndrome. Most of the data regarding ethnicity comes from cross sectional studies of national data bases such as NHANES. Other studies seem to have lower numbers of ethnic groups other than Caucasians. For clinical practice, most of the data may be extrapolated until data from randomized prospective trials are available. Certainly it would appear that many of the cardiovascular implications persist when adjusted for race. Lifestyle changes such as diet and physical activity may be universally recommended for all persons at risk, regardless of ethnicity and, where necessary, pharmacological interventions may be used.

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