# The Epidemic of Diabetes Mellitus and the Metabolic Syndrome in African Americans

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*The metabolic syndrome and type 2 diabetes mellitus are increasingly associated with cardiovascular disease morbidity and mortality in African Americans. African Americans are specifically prone to the negative effects of hypertension and risk factor clustering associated with the metabolic syndrome and diabetes. Data demonstrate a decrease in cardiovascular events in diabetic patients with secondary prevention and, most recently, primary prevention with lipid-lowering therapy. African Americans should benefit from intense risk factor control, including antihypertensive therapy and lipid lowering, to prevent cardiovascular disease. Appropriate lifestyle modification programs, glucose control, and cardiovascular risk reduction therapy will reduce the excessive morbidity and mortality in this population.*
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The recently defined metabolic syndrome (also known as insulin-resistance syndrome, metabolic syndrome X, and dysmetabolic syndrome), along with type 2 diabetes mellitus, are increasingly associated with cardiovascular disease morbidity and mortality in African Americans. African Americans have one of the highest cardiovascular disease rates in the world.[1] Hypertension develops earlier in life in this population than in the general population. Furthermore, the rates of target organ damage are much higher than in Whites,

Table 1
Clinical Identification of the Metabolic Syndrome: 3 or More Criteria

| Risk Factor | Defining Level |
|---|---|
| Abdominal obesity (waist circumference) | |
| Men | > 102 cm (40.2 in) |
| Women | > 88 cm (34.6 in) |
| Triglyceride level | ≥ 150 mg/dL |
| High-density lipoprotein cholesterol level | |
| Men | < 40 mg/dL |
| Women | < 50 mg/dL |
| Blood pressure | ≥ 130/≥ 85 mm Hg |
| Fasting glucose level | ≥ 110 mg/dL |

including more severe hypertension, left ventricular hypertrophy, heart failure, end-stage renal disease, and fatal and nonfatal stroke.[1] Although the reasons for the excess mortality among African Americans have not been fully elucidated, a high prevalence of certain coronary risk factors, delays in the treatment of high-risk persons, and limited access to cardiovascular care all play a role.

Blood pressure lowering with a wide range of agents, specifically diuretics and calcium channel blockers (CCBs), has been shown to be effective in decreasing cardiovascular disease in all patients, including African Americans with diabetes.[2] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) also are effective in decreasing cardiovascular and renal disease rates in controlled trials, but they have been less definitively proved as protective in African Americans with diabetes. The African American Study of Kidney Disease and Hypertension (AASK) trial showed a reduction in renal outcomes with ramipril treatment among a nondiabetic population with hypertension and nephrosclerosis.[1]

Type 2 diabetes is more prevalent in African Americans than in Whites, and obesity, a major risk factor for this condition, is disproportionately common in African American women.[3] Long-term trends suggest that in the United States there will be an alarming increase in diabetes in the future. The combination of multiple risk factors that are the hallmarks of the metabolic syndrome and type 2 diabetes profoundly impacts the African American population. Data now demonstrate clear protection from cardiovascular events in diabetic patients with secondary prevention of coronary heart disease (CHD) and, more recently, primary prevention with lipid-lowering therapy.

## Definition and Diagnosis

As specifically defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, the metabolic syndrome is a constellation of any 3 out of 5 abnormalities.[4] These conditions, when clustered, not only indicate a diagnosis but also help identify patients at risk for accelerated cardiovascular disease and offer an opportunity for early and intensive intervention. The metabolic syndrome abnormalities are: waist circumference greater than 102 cm (40.2 in) in men or greater than 88 cm (34.6 in) in women; serum triglyceride level at or above 150 mg/dL; HDL cholesterol level less than 40 mg/dL in men or less than 50 mg/dL in women; blood pressure at or above 130/85 mm Hg; and fasting serum glucose level at or above 110 mg/dL (Table 1).[4]

According to the recent analysis from the Third National Health and Nutrition Examination Study (NHANES III), approximately 47 million Americans, or 23.7% of the population, have the metabolic syndrome. Further analysis suggests that of this population, as many as 10 to 15 million persons have type 2 diabetes.[5] The prevalence of type 2 diabetes is increased in the African American population. Furthermore, the prevalence of diabetes in African American women is approximately 57% higher than in African American men.[1] As the population ages and becomes increasingly obese, cardiovascular disease related to diabetes and metabolic syndrome will become more apparent.

Prevalence of the metabolic syndrome among American adults appears to be highest in Mexican American women (35.6%), based on the NHANES III, but increased in African American women (25.7%) versus white women (22.8%). Paradoxically, among African American men there is an unexpected, lower rate of metabolic syndrome (16.4%) versus Mexican American men (28.3%) and white men (24.8%).[3] This is perhaps related to an underestimation of the presence of metabolic syndrome due to relatively higher HDL cholesterol levels and lower triglyceride levels. The presence of these apparently favorable levels does not appear, however, to be protective against the negative effects of CHD.

Perhaps the most profound component of the metabolic syndrome in African Americans, and a common

comorbid condition of diabetes, is elevated blood pressure. In African Americans, hypertension is 50% more frequent, often seen earlier, and often associated with an increased prevalence of target organ damage (including fatal and nonfatal stroke, left ventricular hypertrophy, heart failure, and end-stage renal disease) and CHD-related mortality.[1] Type 2 diabetes, as defined recently as a fasting glucose level of 126 mg/dL or above or a 2-hour plasma glucose level of 200 mg/dL or above, is considerably more frequent in African Americans. In the NHANES III report, there were 1.9-fold higher rates of type 2 diabetes in non-Hispanic blacks compared with non-Hispanic Whites. In the Atherosclerosis Risk in Communities (ARIC) study, the incidence of diabetes was 2.4-fold greater among African American women and 1.5-fold greater among African American men than among their white counterparts.[6] Obesity and adiposity apparently account for almost half of the increased risk of type 2 diabetes, especially in African American women.

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Regardless of the specific causes, including obesity and inactivity, the combination of type 2 diabetes and hypertension remains a hallmark for an increased risk of cardiovascular disease. Hypertension with diabetes is seen in 75.4% of non-Hispanic blacks with diabetes, with dismal rates of control of blood pressure to lower than 130/80 mm Hg.[1] Early diagnosis of type 2 diabetes and identification of the metabolic syndrome provide an opportunity to identify patients at risk before disabling metabolic and cardiovascular events occur (including stroke, acute coronary syndrome and myocardial infarction, and renal insufficiency leading to end-stage renal disease).

In the Coronary Artery Risk Development in Young Adults (CARDIA) Study, the prevalence of elevated low-density lipoprotein (LDL) cholesterol level was lower in African Americans than in Whites. Moreover, African Americans had slightly higher levels of high-density lipoprotein (HDL) cholesterol. Nevertheless, neither the slightly lower LDL cholesterol levels nor the slightly higher HDL cholesterol levels are cardioprotective. In fact, CHD-related death rates within this population remain among the highest in the world.[6,7]

Many factors place the African American population at increased risk for metabolic syndrome and diabetes: elevated blood pressure (perhaps related to increased renal sodium absorption), insulin resistance, microalbuminuria, increased prevalence of overweight/obesity status (especially in African American women), dyslipidemia (although in some surveys HDL cholesterol levels have not been excessively low in African Americans and triglyceride levels appear similar to those of the general population), and perhaps an increase in an inflammatory/prothrombotic state (including an increase in plasminogen activator inhibitor-1 and high-sensitivity C-reactive protein levels and decreased fibrinolysis).[7] African Americans are more prone to hypertension, glucose intolerance, and obesity. It is not unexpected that they have the highest CHD mortality rate, highest out-of-hospital coronary death rate, and highest rate of complications of hypertension, including heart failure and end-stage renal disease, of any ethnic group in the United States.

## Hypertension Treatment and the Metabolic Syndrome and Diabetes Mellitus

Racial and ethnic differences in CHD rates, risk factor clustering with the metabolic syndrome, and the prevalence of type 2 diabetes suggests a need for more intensive intervention in the African American population. Increase in outcomes related to the metabolic syndrome, type 2 diabetes, and concomitant dyslipidemia and hypertension are probably related to under-treatment and less intense treatment in African Americans. This treatment includes not only the control of hyperglycemia but, perhaps more important, the control of hypertension, dyslipidemia, and thrombotic factors via use of antihypertensive agents, lipid-lowering medication, aspirin therapy, and lifestyle modification.

Hypertension should be treated with a combination of therapies, including lifestyle modification and, in most patients, the use of a thiazide-type diuretic, unless contraindicated.[8] Diuretic therapy in African Americans appears to be successful in blood pressure lowering and decreases cardiovascular events, as noted in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[2] While the Joint National Committee 7 of the National High Blood Pressure Education Program has noted benefits of diuretic-based therapies, hypertensive patients receiving these agents, in whom new-onset diabetes with impaired fasting glucose subsequently develops, may potentially have

an increase in cardiovascular risk.[8] New-onset diabetes, based on increased plasma glucose level, is usually not seen with the use of ARBs, CCBs, or ACE inhibitors.

In ALLHAT, mean fasting glucose levels in patients with previous normal levels at baseline increased with chlorthalidone versus amlodipine or lisinopril ($P < .05$ vs chlorthalidone).[2] The fasting glucose levels across the treatment groups are shown in Table 2. The 2-year incidence of diabetes was almost 2-fold higher in the chlorthalidone group than in the lisinopril group, and although the difference was smaller at 4 years, it was still marked.

In ALLHAT, chlorthalidone was effective in preventing cardiovascular disease in patients with or without diabetes. Nevertheless, among the patients classified as nondiabetic at baseline, with fasting glucose levels < 126 mg/dL, the incidence of diabetes at 4 years was 11.6% for the diuretic cohort versus 9.8% for the amlodipine group and 8.1% for the lisinopril group.[2] There was no definite relationship between serum potassium level and the risk of diabetes; however, in patients who had low potassium levels and required potassium supplementation, there was an increased risk of diabetes.

The use of ß-blockers (atenolol as a second-step agent) in ALLHAT also may have had an effect on the rates of diabetes.[2] Most ß-blockers are known to decrease insulin sensitivity and may also increase the risk of diabetes. Since the use of ß-blockers was similar in all treatment arms, diabetes cannot be associated specifically with this particular class of medication and no specific protective or deleterious effects regarding diabetes can be identified. The ALLHAT investigators specifically noted that this metabolic derangement did not translate into significant outcomes during the length of the trial.[2] At the end of the analysis of ALLHAT and in the primary paper, there was no significant association with the higher baseline fasting glucose levels or changes in fasting glucose levels in any of the cardiovascular end points of ALLHAT, including CHD, all-cause mortality, and combined cardiovascular disease (composite of cardiovascular disease, stroke, heart failure, and end-stage renal disease).[2] Nevertheless, there are data on populations that do not include African Americans indicating that the adjusted risk of cardiovascular events is increased to 2.92 in patients with new diabetes related to hypertensive treatment, suggesting an increased risk with new-onset glucose intolerance.[9]

Table 2
Glucose Levels in ALLHAT

| | Fasting glucose level (mg/dL) | | |
|---|---|---|---|
| | Chlorthalidone (n = 4255) | Amlodipine (n = 2501) | Lisinopril (n = 2501) |
| Baseline | 91.2 | 91.1 | 91.3 |
| 2 Years | 99.3 | 96.3* | 95.1* |
| 4 Years | 102.2 | 99.5* | 98.4* |

*$P < 0.05$ vs chlorthalidone.

There are new data to suggest that ACE inhibitors and ARBs prevent diabetes. Such results have been seen with ramipril in the HOPE trial, captopril in the CAPPP trial, enalapril in the SOLVD trial, losartan in the LIFE trial, and candesartan in the CHARM trial.[8,10]

Multiple-drug therapy will generally be required to control blood pressure in patients with hypertension and diabetes. Initial drug therapy should include agents that have been shown to decrease cardiovascular disease in diabetic patients—ACE inhibitors, ARBs, ß-blockers, diuretics, and CCBs. While guidelines are not conclusive, patients with diabetes and hypertension should include in their regimen an ACE inhibitor or an ARB.

While there are no head-to-head comparisons with ACE inhibitors and ARBs in clinical trials, there is general agreement that in patients with type 2 diabetes and hypertension with microalbuminuria, ACE inhibitors and ARBs may delay progression to macroalbuminuria. In patients with type 2 diabetes and hypertension with macroalbuminuria along with renal insufficiency, ACE inhibitors or ARBs may delay progression to nephropathy.[8] ACE inhibitors are also beneficial for the reduction of cardiovascular events in diabetic persons.[10] African American patients will usually need, in addition to an ACE inhibitor and an ARB, thiazide diuretics and/or CCBs, including dihydropyridine CCBs, to lower blood pressure to goal levels.[8]

When added to ACE inhibitors and ARBs, amlodipine has been shown to decrease urinary albuminuria and help preserve renal function in a blood-dependent manner. In patients with clinical nephropathy, blood pressure lowering is important, and the addition of a dihydropyridine CCB to therapy with an ACE inhibitor or ARB does not detract from the renal protective benefit.[8]

In the lisinopril cohort of ALLHAT, there was a 4 mm higher systolic blood pressure difference in African Americans than with chlorthalidone.[2] Many African American patients will not get appropriate blood pressure lowering without the use of additional agents, including thiazide diuretics and CCBs.

## Dyslipidemia Treatment and the Metabolic Syndrome and Diabetes

The control of dyslipidemia will be an important component in the treatment of patients with diabetes and metabolic syndrome. Most patients, including those with relatively low baseline LDL cholesterol levels (< 115 mg/dL and possibly even < 100 mg/dL), benefit from statin therapy. A recent meta-analysis of 6 primary prevention studies of diabetes demonstrated that lipid-lowering medications reduce the risk of cardiovascular outcomes.[11] This analysis showed that 1 major cardiovascular event could be prevented by treating 34 to 35 patients.[11] Similarly, a meta-analysis of studies of secondary prevention showed a similar risk reduction but more than twice the absolute risk reduction; the number needed to treat for benefit was only 13 to 14.[11]

The role of lipid-lowering therapy for secondary prevention of CHD in diabetes, particularly with statins, is clear. In a secondary analysis of 202 patients with diabetes, the Scandinavian Simvastatin Survival Study (4S) showed that simvastatin had significant benefits relative to cardiovascular events: relative risk, 0.5 (CI, 0.33 to 0.76).[11] More data are needed to confirm the benefits of primary prevention of CHD and stroke, especially in patients with diabetes and average LDL levels.

The Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), in which patients were randomized to receive lovastatin, 20 mg, or placebo, showed a statistically significant reduction in risk for CHD among diabetic patients.[11] However, in other primary prevention trials, the benefits were not statistically significant because of small sample sizes. The Heart Protection Study (HPS) demonstrated benefit of both primary and secondary prevention in patients with diabetes.[12] In 3982 patients with diabetes, simvastatin resulted in a reduction in CHD events.[12] The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) randomly assigned patients without CHD, but with hypertension and 3 other risk factors, to receive atorvastatin, 10 mg, or placebo. Of the 2532 patients with diabetes, hypertension, and 2 other risk factors, there was a surprisingly low rate of events: 3.6% in the control group, and 3.0% in the intervention group.[13] Lipid-lowering treatment with atorvastatin did not lead to statistically significant improvements in outcomes in the diabetic subgroup, but this may have been a result of small sample size and relatively low risk.

The recent Collaborative Atorvastatin Diabetes Study (CARDS) studied 2838 patients in the United Kingdom and Ireland with type 2 diabetes and no history of coronary, cerebrovascular, or severe peripheral vascular disease. Patients were required to have at least 1 of the following risk factors: hypertension, retinopathy, microalbuminuria or macroalbuminuria, or current smoking. Atorvastatin, 10 mg, was safe and highly efficacious in reducing the risk of major cardiovascular disease, including stroke, in patients with average or lower LDL levels.[14] The study population was 94% white, however.

## Summary

Metabolic syndrome and diabetes are common conditions reaching near-epidemic levels in the United States. African Americans are specifically prone to the negative effects of the combination of risk factors associated with the metabolic syndrome and diabetes. Most adverse outcomes in diabetes are specifically related to cardiovascular disease, either at the macrovascular level (coronary artery disease, cerebrovascular disease, or peripheral vascular disease) or at the microvascular level (retinopathy, nephropathy, and neuropathy).

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Eighty percent of diabetic persons die of a major cardiovascular event. Optimal therapy for these patients includes control of the major risk factors of hypertension and dyslipidemia with lipid-lowering agents, specifically the 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins). Other components of intensive therapy include smoking cessation and aspirin therapy. Intensive blood pressure lowering has been shown to be beneficial in this population. However, in most of the lipid trials, African Americans are underrepresented or not present at all. Nevertheless, until more data have been con-

firmed, African Americans should benefit from intense control of risk factors, including not only antihypertensive therapy but also lipid lowering to prevent cardiovascular disease, especially in the presence of diabetes and the metabolic syndrome.

The goal of cardiovascular protection is the equal application of appropriate lifestyle changes and hypertensive and lipid-lowering therapy for all patients, regardless of ethnicity and income level. Appropriate programs of weight reduction and increased physical activity, combined with glucose control and therapy for hypertension and high cholesterol, will go far in reducing the excessive morbidity and mortality in this population. ■

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## Main Points

- African Americans have one of the highest cardiovascular disease rates in the world: hypertension develops earlier in life, rates of target organ damage and type 2 diabetes mellitus are much higher than in Whites, and obesity is disproportionately common in African American women. Appropriate lifestyle modification, glucose control, and cardiovascular risk reduction therapy are needed to reduce the excessive morbidity and mortality in this population.
- The factors that place African Americans at increased risk for metabolic syndrome and diabetes include: elevated blood pressure, insulin resistance, microalbuminuria, increased prevalence of overweight/obesity status, dyslipidemia, and perhaps an increase in an inflammatory/prothrombotic state.
- Hypertension should be treated with a combination of factors, including lifestyle modification; patients with diabetes and hypertension should include in their regimen an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). Many African American patients will not get appropriate blood pressure lowering without the use of additional agents, including thiazide diuretics and calcium channel blockers.
- When added to ACE inhibitors and ARBs, amlodipine has been shown to decrease urinary albuminuria and help preserve renal function in a blood-dependent manner.
- There are new data to suggest that ACE inhibitors and ARBs prevent diabetes; the addition of amlodipine to a regimen has been shown to decrease urinary albuminuria and help preserve renal function.
- The control of dyslipidemia with statin therapy is key to reducing coronary heart disease in diabetic patients, especially in high-risk populations.