CARDIORENAL METABOLIC SYNDROME IN THE AFRICAN DIASPORA: RATIONALE FOR INCLUDING CHRONIC KIDNEY DISEASE IN THE METABOLIC SYNDROME DEFINITION

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Chronic kidney disease (CKD) is more likely to progress to end-stage renal disease (ESRD) in African Americans while the reasons for this are unclear. The metabolic syndrome is a risk factor for the development of diabetes, cardiovascular disease, and has been recently linked to incident CKD. Historically, fewer African Americans meet criteria for the definition of metabolic syndrome, despite having higher rates of cardiovascular mortality than Caucasians. The presence of microalbuminuria portends increased cardiovascular risks and has been shown to cluster with the metabolic syndrome. We recently reported that proteinuria is a predictor of CKD progression in African American hypertensives with metabolic syndrome. In this review we explore the potential value of including CKD markers—microalbuminuria/proteinuria or low glomerular filtration rate (GFR)—in refining the cluster of factors defined as metabolic syndrome, ie, ''cardiorenal metabolic syndrome.'' (*Ethn Dis.*2009;19[Suppl 2]:S2-11–S2-14)

Key Words: Metabolic Syndrome, Cardiovascular Disease, Chronic Kidney Disease, Ethnic

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INTRODUCTION

The tendency for cardiovascular disease (CVD) risk factors to occur in clusters has led to the description of metabolic syndrome, which has been associated with an increased risk of diabetes, CVD, and premature death. More recent data suggest that metabolic syndrome may be a risk factor for chronic kidney disease (CKD). CVD is highly prevalent among patients with CKD and especially in those patients with end-stage renal disease (ESRD), where available data indicates that they have CVD-related death rates some 10–30 times higher than the age-matched population.[1] Moreover, patients with CKD are more likely to develop CVD and die before reaching ESRD.

African Americans have a higher prevalence of hypertension, diabetes, CVD, and kidney disease, in the absence of dyslipidemia, which suggests a distinct constellation of factors contributes to their increased risk of CVD and premature death. Our objective is to review the available data on metabolic syndrome and focus on the contribution of independent risk factors for CKD and death and to explore the potential value of including CKD markers—microalbuminuria/proteinuria or low glomerular filtration rate (GFR)—in refining the cluster of factors driving premature CVD death, especially for African Americans. We believe that metabolic syndrome is more appropriately labeled the ''cardiorenal metabolic syndrome.''

METABOLIC SYNDROME OVERVIEW

The World Health Organization (WHO) criteria for metabolic syndrome include a fasting plasma glucose ≥110 mg/dL and at least 2 of the following: abdominal obesity, defined as body mass index (BMI) ≥30 kg/m^2, triglyceride level ≥150 mg/dL or high-density lipoprotein (HDL) cholesterol level <35 mg/dL, blood pressure >140/90 mm Hg, and microalbuminuria.[2] While WHO recognized renal markers (microalbuminuria) as part of metabolic syndrome, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) defines metabolic syndrome clinically as any 3 of the following traits (which do not include renal markers): abdominal obesity (waist girth >102 cm [men] or >88 cm [women]), serum triglyceride level >150 mg/dL, low HDL cholesterol level (<50 mg/dL [women] or <40 mg/dL [men]), blood pressure >130/85 mm Hg (or taking antihypertensive medication), and fasting blood sugar level >110 mg/dL (insulin resistance).[2,3] The third National Heath and Nutrition Survey (NHANES III) indicates that ≈25% of the US adult population aged ≥20 years and up to 45% of the population aged >50 years meets the NCEP/ATP III diagnostic criteria for metabolic syndrome. However, despite having increased rates of premature CVD death, African Americans have lower rates of metabolic syndrome, which are driven by lower rates of dyslipidemia.[4] These observations suggest that our current definition of metabolic syndrome should be reassessed from a clinical/public health perspective to ensure the right message for screening is reaching healthcare providers.

CHRONIC KIDNEY DISEASE DEFINITION AND EPIDEMIOLOGY

CKD, defined as reduced GFR or presence of albuminuria, is a major risk

factor for ESRD, as well as for CVD and death.[5,6] CKD has reached epidemic proportions in the United States; an estimated 26 million people are affected. Moreover, minorities are disproportionately affected by ESRD; rates for African Americans are ≈4.5-fold as high as corresponding rates in White Americans.[1]

INSULIN RESISTANCE, MICROALBUMINURIA, AND CHRONIC KIDNEY DISEASE

Insulin resistance has been associated with microalbuminuria in NHANES III, and accumulating data indicate that microalbuminuria is strongly associated with metabolic syndrome as a whole and with its components individually.[7] A positive relationship has been shown between insulin resistance and microalbuminuria in both diabetic and nondiabetic patients.[8] The close association between metabolic syndrome (defined by the NCEP/ATP III guidelines) and CKD (estimated GFR <60 mL/min/1.73 m^2) has been shown in >10,000 nondiabetic adults in the Atherosclerosis Risk in Communities Study.[9] The adjusted odds ratio (OR) for incident CKD among participants with metabolic syndrome, including the subsequent development of diabetes and hypertension during the 9 years of follow-up, was 1.24 (95% confidence interval [CI] 1.01–1.51), with a graded relationship between the number of metabolic syndrome traits and the incidence of CKD. These findings were supported in a study that found that metabolic syndrome was an independent risk factor for both CKD (defined as estimated GFR <60 mL/min/1.73 m^2) and macroalbuminuria among adult participants in NHANES III.[10] They also demonstrated a graded relationship between the number of individual components and the risk for CKD and macroalbuminuria. This evidence strongly links CKD with metabolic syndrome and supports the designation of a cardiorenal metabolic syndrome.

METABOLIC SYNDROME IN AFRICAN AMERICANS

Among 8608 NHANES III participants aged >20 years, the age-adjusted prevalence of metabolic syndrome was 23.9% according to the NCEP/ATP III definition and 25.1% according to the WHO criteria. However, results differed in some subgroups, including African American men, for whom the WHO estimate was 24.9%, compared with the NCEP/ATP III estimate of 16.5%.[11] The lower prevalence of dyslipidemia among African Americans, which accounts for 2 of the 5 potential metabolic syndrome components, places African Americans at increased risk for underdiagnosis and suboptimal treatment for linked metabolic factors. If renal factors were included in the diagnostic criteria (cardiorenal metabolic syndrome), more patients who are at risk for premature CVD death could be identified.

Insulin resistance is a more subtle marker of metabolic aberrations and diabetes risk and is more common among African Americans than among Whites at a similar level of adiposity.[12] Thus, fasting insulin levels are higher in nonobese African American women than in White women, whereas the frequency of insulin resistance is similar in frequency in men of both races.[12] Although African Americans appear to have increased insulin levels, these may be due to ethnic differences in insulin secretion and reduced hepatic extraction rather than insulin resistance. Despite the lower incidence of metabolic syndrome in African Americans, which is driven by lower rates of dyslipidemia, African Americans still have higher rates of premature cardiovascular deaths, primarily related to increased rates of diabetes and hypertension.

INDIVIDUAL COMPONENTS OF METABOLIC SYNDROME ARE LINKED TO CHRONIC KIDNEY DISEASE RISK

The individual components of metabolic syndrome have been linked to CKD. For example, obesity has been associated with focal segmental glomerulosclerosis and glomerulomegaly. In a study of 102 nonobese subjects (BMI <30 kg/m^2), higher BMI was associated with a higher GFR ($P < .001$), which suggests that increases in BMI may lead to hyperfiltration and increase susceptibility to renal damage.[13] Elevated triglyceride and low HDL cholesterol levels may increase the risk for CKD, and statins may slow CKD progression.[14]

A number of recent studies now strongly support including proteinuria as part of metabolic syndrome, especially in African Americans and other ethnic minority groups. The relevance of nonnephrotic levels of urine protein in hypertensive renal disease had not previously been appreciated. Data from the African American Study of Kidney Disease and Hypertension (AASK) trial revealed that small amounts of albuminuria (<1 g/day) predicted the increased risk for a clinical composite outcome (CKD progression, ESRD, death) in patients with hypertensive renal disease. Among AASK participants, for every 2-fold increase in baseline proteinuria, GFR declined by an additional .54 mL/minute/year and risk of ESRD increased by 80%.[15] Both the baseline level and the initial change in proteinuria from baseline to 6 months were strong predictors of subsequent progression of hypertensive kidney disease in African Americans, and this relationship extended to participants with microalbuminuria. The level of baseline GFR, however, was not predictive of the subsequent rate of GFR decline after accounting for baseline proteinuria, which suggests that CKD progression is driven by proteinuria independently of GFR.

Table 1. Baseline demographics and select cardio-metabolic characteristics in the AASK cohort (adapted from ref 15)

Variable	+MS (*n*=351)	−MS (*n*=491)	*P* value
Age	54.5 (10.5)	54.8 (10.7)	.8
Males	211 (60)	310 (63)	.4
Current smokers	102 (29)	137 (28)	.7
ETOH use	89 (25.5)	137 (28)	.4
BMI (kg/m^2)	33.5 (6.3)	28.6 (6.1)	**<.0001**
HDL (mg/dL)	40.1 (12.4)	54 (15.8)	**<.0001**
TRIG (mg/dL)	186 (95.6)	107.7 (46.1)	**<.0001**
GLUC (mg/dL)	101.3 (20.6)	90.2 (14.8)	**<.0001**
SBP (mmHg)	148.4 (24)	151.6 (24)	.06
DBP (mmHg)	95.5 (14.1)	95.5 (14.2)	.97
BUN (mg/dL)	24.9 (10.5)	24.5 (10.3)	.6
GFR (mL/min/1.73m^2)	45.5 (13.6)	46 (12.7)	.6
U P/Cr	0.38 (0.57)	0.30 (.57)	**.04**
Hematocrit (mg/dL)	39.7	39.3	.30
Uric acid (mg/dL)	8.7 (1.98)	8.1 (1.92)	**<.0001**
Phosphorus (mg/dL)	3.5 (0.6)	3.55 (.66)	.07
Beta blocker group	146 (41.6)	185 (37.7)	

Data are means ± SD with *P* values for continuous variables and *n* (%) with *P* values for categorical variables.
MS=metabolic syndrome; BMI=body mass index; HDL=high density lipoprotein; TRIG=triglycerides; GLUC=glucose; SBP=systolic blood pressure; DBP=diastolic blood pressure; GFR=glomerular filtration rate; BUN=blood urea nitrogen; U P/Cr= urine protein to creatinine ratio; ETOH=alcohol use. Current smokers compared to never smokers. Significant variables are bolded.

The role of metabolic syndrome on CKD progression in the AASK study was recently examined by using a modified NCEP/ATP III criteria for metabolic syndrome.[16] Participants with metabolic syndrome had higher urinary protein-to-creatinine ratios and serum uric acid levels in addition to the expected higher levels of glucose and triglycerides, higher BMI, and lower HDL cholesterol levels that defined metabolic syndrome (Table 1). The unadjusted risk of reaching the composite outcome (GFR, ESRD, or death) in those with metabolic syndrome was increased by 31% and was significant without any covariate adjustment. When controlling for all covariates except proteinuria, the relationship remained strong and significant, but the effect of metabolic syndrome on the composite outcome was reduced to only 16% and was no longer significant when all covariates plus protein-to-creatinine ratio were considered (Table 2). This finding reinforces the idea that proteinuria, rather than metabolic syndrome, is an independent predictor of clinical outcomes in hypertensive renal disease progression. Of note in this analysis, waist circumference was used as a substitute for BMI as the measure of obesity, which could have influenced the results.

Table 2. Hazard ratio of metabolic syndrome with time to event analyses (GFR event, ESRD, and death) with and without adjustments for significant covariates (with and without proteinuria) and additional adjustments for BP goal group and antihypertensive drug group.

	HR (95% CI)	*P* value
MS unadjusted	1.31 (1.03–1.7)	.03
MS adjusted for other covariates, not UP/Cr	1.32 (1.03–1.7)	.03
Plus UP/Cr	1.16 (0.89–1.5)	.2
Above plus BP goal group/UP/Cr	1.16 (0.89–1.5)	.3
Above plus Drug group/UP/Cr	1.14 (0.88–1.5)	.3

Covariates adjusted for were: age, sex, smoking and alcohol status, GFR, BUN, hematocrit, uric acid, and phosphorus. Then additional adjustments for proteinuria, log base transformation UP/Cr - urine protein/creatinine ratio where indicated.
MS=Metabolic syndrome; BP=blood pressure; UP/Cr=urine protein/creatinine ratio; HR=hazard ratio; CI=confidence interval.

Among Native Americans, albuminuria >30 mg/g was more common in those with metabolic syndrome (defined by NCEP/ATP III guidelines) than in those without metabolic syndrome (15.7% vs 10.3%),[17] and no difference in the prevalence of renal insufficiency (GFR <60 mL/minute) was seen at baseline according to metabolic syndrome status. Even so, as in other studies, the authors concluded that metabolic syndrome in this nondiabetic population still predicted the incidence of CKD. Data from 5659 men and women aged 20–80 years from the NHANES III cohort showed a strong association between microalbuminuria and metabolic syndrome (OR 4.1, 95% CI 2.5–6.7 for men and OR 2.2, 96% CI 1.4–3.3 for women).[7] Their report showed that hypertension and high glucose levels were significantly associated with microalbuminuria, whereas low HDL cholesterol levels and hypertriglyceridemia were not.

Supporting the differential importance of the independent components of metabolic syndrome, an analysis of the NHANES II mortality followup cohort found that most metabolic syndrome-related death was driven by elevated blood pressure and elevated blood glucose levels. The relationship between BMI and dyslipidemia was particularly weak in African Americans (Table 3).[18] In addition, CKD was strongly associated with death in the NHANES III mortality followup cohort, especially among young African Americans.[19] These findings support the premise that CKD should be a defining element of the cardiorenal metabolic syndrome, especially for African Americans.

Table 3. Age- and sex-adjusted relative risk of CV death for individual components of metabolic syndrome across racial/ethnic groups (NHANES II)

Components of the Metabolic Syndrome	White RR (95% CI)	Black RR (95% CI)	Relative Risk (95% CI)*
Diabetes	3.1 (2.6–3.8)*	4.0 (2.5–6.5)*	3.23 (2.70–3.88)*
Hypertension	2.2 (1.9–2.6)*	3.0 (1.7–5.2)*	2.28 (1.94 –2.67)*
Obesity	1.1 (0.9–1.4)	1.3 (0.8–2.1)	1.14 (0.94–1.38)
Low HDL	1.2 (1.0–1.4)	1.2 (0.7–2.1)	1.20 (1.01–1.41)*
High Triglyceride	1.6 (1.3–2.0)*	2.0 (1.1–3.7)*	1.63 (1.34–2.00)*

RR=relative risk; CI=confidence interval; HDL=high density lipoprotein.
* $P<.05$
Table data adapted from Martins et al 2008.[18]

SUMMARY

A review of the available data leads to heightened concerns that the ongoing use of the NCEP metabolic syndrome definition without CKD as the defining profile for CVD risk markedly underestimates the true risk of premature death for all Americans, particularly for African American patients. Indeed, others have previously suggested that if CKD were included in metabolic syndrome definition and the syndrome were redefined as the cardiorenal metabolic syndrome, more people at risk for premature CVD could be identified and treated by their healthcare providers.[7] We propose that future investigations of risk factors that characterize incipient CVD risk should include more specific assessment of CKD as well as more specific measures of insulin resistance. In the interim, we recommend that therapy for patients with metabolic syndrome should address CKD to reduce the incidence and severity of adverse CVD events.

ACKNOWLEDGMENTS

Dr Norris receives support from NIH grants RR011145, RR019234, RR014616, and MD000182.

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