Race and the Insulin Resistance Syndrome

Holly Kramer, MD, MPH,[*] Lara Dugas, PhD,[*] and Sylvia E. Rosas, MD, MSc[†]

Summary: Type 2 diabetes remains an important cause of morbidity and mortality. The metabolic syndrome affects 25% of the adult US population based on the Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults from the National Cholesterol Education Program. Knowledge on the impact of obesity on metabolic health parameters has increased greatly over the past decade. This review discusses the limitations of the National Cholesterol Education Program metabolic syndrome definition and the racial disparities in the clinical presentation of the insulin resistance syndrome. We also examine the current literature with particular emphasis on albuminuria, nonalcoholic fatty liver disease, and intramyocellular lipid content. This review explores potential environmental and genetic reasons for differences in the manifestation of insulin resistance across racial/ethnic groups and highlights several promising areas for further study.

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Type 2 diabetes remains one of the top 10 leading causes of death worldwide[1] and the number one cause of end-stage kidney disease.[2] The global prevalence of type 2 diabetes in adults is 6.4%, affecting 285 million adults, and is expected to increase to 7.7%, affecting 439 million adults by 2030.[3] Within developing countries, type 2 diabetes is expected to increase by 69% during the years 2010 to 2030, largely as a result of urbanization, leading to decreased physical activity and higher caloric intake.[3] Regardless of industrialization of the country, type 2 diabetes is more prevalent among individuals with African ancestry compared with those without African ancestry.[4] For example, in both the United States and South Africa, diabetes prevalence is almost twice the prevalence rate of individuals without African ancestry living in these countries.[4,5] Diabetes-associated morbidities, including kidney disease, also are substantially higher among individuals with African ancestry compared with Caucasians.[6–8] Mortality directly resulting from diabetes is more than two-fold higher among African Americans compared with Caucasians.[6]

The greater prevalence of obesity among individuals of African descent, particularly those living in more industrialized settings, may in part explain these racial/ethnic differences.[9,10] However, differing frequencies in obesity do not account for racial disparities in patients with type 2 diabetes or other clinical manifestations of the insulin resistance syndrome. Although kidney disease, especially end-stage kidney disease associated with obesity and/or diabetes, is substantially higher among African Americans, nonalcoholic fatty liver disease is actually much more prevalent among Hispanics than any other group, including Caucasians. We explore potential reasons for the differing effects of insulin resistance across racial/ethnic groups and highlight several potential areas for additional research.

METABOLIC SYNDROME

Definition of Metabolic Syndrome

Over the past 50 years, substantial gains in life expectancy have been noted across all racial/ethnic groups in the United States and these gains were largely the result of population reductions in blood pressure and serum cholesterol levels mediated through diet and medications.[11–14] Over the next 50 years, health care's biggest challenge will be avoiding a reversal in life expectancy resulting from the sharp upward shift in obesity prevalence within the US population.[15] Visceral adipose tissue primarily drives the mortality risk associated with obesity because of the development of insulin resistance, which underlies the clustering of major cardiovascular risk factors including hypertension, dyslipidemia, and glucose intolerance. The clustering of these cardiovascular risk factors was first labeled *syndrome X* in 1988,[16] but then later was renamed *metabolic syndrome*.[17,18] The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) from the National Cholesterol Education Program (NCEP) subsequently defined metabolic syndrome as the presence of at least 3 of the following 5 criteria: central obesity (waist circumference: men, >102 cm; women, >88 cm);

[*]*Departments of Public Health Sciences and Medicine, Division of Nephrology and Hypertension, Loyola University Chicago Health Sciences Campus, Maywood, IL.*

[†]*Joslin Diabetes Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.*

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Address reprint requests to Holly Kramer, MD, MPH, Loyola University Chicago, Health Sciences Campus, Department of Public Health Sciences, 2160 S. First Avenue, Maywood, IL 60153. E-mail: hkramer@lumc.edu

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hypertriglyceridemia (triglyceride levels ≥150 mg/dL); low high-density lipoprotein (HDL) cholesterol (men, <40 mg/dL; women, <50 mg/dL); increased fasting glucose level (≥110 mg/dL); and hypertension (≥130/85 mm Hg).[19]

Metabolic syndrome definitions were designed to enhance the identification of individuals who may benefit from cardiovascular disease surveillance and intensive management of cardiovascular disease risk factors given the heightened risk of cardiovascular events and the development of type 2 diabetes among individuals with the metabolic syndrome.[20] Although the ATP III metabolic syndrome criteria show high specificity for the presence of insulin resistance, sensitivity is poor.[21–23] Indeed, the ATP III metabolic syndrome criteria do not address differences in race, sex, or age in the effects of adiposity on health.

EXPANDED DEFINITION OF THE METABOLIC SYNDROME

Low HDL, glucose intolerance, increased triglyceride levels, abdominal adiposity, and increased blood pressure all heighten cardiovascular risk,[18] and the metabolic syndrome may not be more than the simple sum of its parts. However, the impact of obesity on overall health is not limited to the five metabolic syndrome traits defined by the NCEP.[19] The World Health Organization's definition of metabolic syndrome released in 1988 included increased urine albumin concentration as one of the defining metabolic syndrome traits.[24] Albumin normally accounts for a very small fraction of the total urine protein excretion. In healthy states, spot urine albumin/creatinine ratios usually range from 2 to 10 mg/g.[25] Levels exceeding this threshold are associated with increased cardiovascular risk and mortality and end-stage kidney disease.[26] Redon et al[27] followed 187 hypertensive individuals without diabetes. After an average of 2.7 years of follow-up evaluation, 12% developed microalbuminuria. Those who progressed to microalbuminuria showed less controlled blood pressure and higher fasting glucose values compared with nonprogressors. Among 2829 adults in the Framingham Offspring Study who were followed for approximately 20 years, baseline fasting glucose and time-integrated fasting glucose values were the main significant predictors for the presence of microalbuminuria at the most recent examination after adjustment for blood pressure, antihypertensive medication use, body mass index (BMI), and smoking.[28] Several, but not all, studies have shown that increased urine albumin excretion is associated with visceral adiposity, especially in adults with type 2 diabetes.[29,30] However, both cross-sectional and longitudinal studies have reported a consistent and direct correlation between blood pressure and urine albumin excretion.[31] Because obesity impacts blood pressure, it may be extremely difficult to determine an independent effect of obesity on urine albumin excretion. Higher blood pressures likely mediate at least part of the link between obesity and increased urine albumin excretion.[32–34]

Obesity and Kidney Disease

In 2002, increased urine albumin concentration was included in the definition of chronic kidney disease (CKD).[35] However, the link between obesity and kidney disease is not limited to increased urine albumin excretion. Obesity, especially morbid obesity, strongly impacts the risk of all stages of CKD. Individuals with morbid obesity carry an approximately 600% higher risk of being on dialysis during their lifetime compared with individuals with a BMI in the ideal range (18.5-24.9 kg/m2).[36,37] It should not be surprising that observational studies consistently report moderate but significant associations between the NCEP-defined metabolic syndrome traits and both incident and prevalent CKD.[38–41] In a cross-sectional analysis of the Third National Health and Nutrition Examination Study, the odds of CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/m^2 or a spot urine albumin/creatinine ratio of 30-300 mg/g) increased linearly with the number of metabolic syndrome traits from 2.21 (95% confidence interval [CI], 1.16-4.24) with 2 traits to 5.85 (95% CI, 3.11-11.0) with 5 traits, compared with individuals with no traits.[39]

The strong link between obesity, insulin resistance, and increased urine albumin excretion is shown by decreases in urine albumin excretion after intentional weight loss. Weight loss and vigorous exercise improve insulin resistance and these effects largely are mediated by down-regulation of fatty acid mobilization.[42] Multiple studies have examined the impact of weight loss interventions on urine albumin or total protein excretion. These studies were summarized in a meta-analysis that pooled 13 studies with a total of 522 participants with weight loss interventions including dietary restriction, exercise, anti-obesity medications, and surgery.[43] Urine protein and albumin excretion (depending on the study) all decreased significantly with weight loss, regardless of the intervention. Urine protein excretion decreased on average by 110 mg (95% CI, 60-160 mg; $P < .001$) per kilogram of intentional weight loss, for both surgical and medical interventions. Urine albumin excretion decreased by 1.1 mg (95% CI, 0.5-2.4 mg; $P = .011$) per kilogram of weight loss.[43]

Non-alcoholic Fatty Liver Disease

Insulin resistance combined with adiposity leads to abnormal lipid accumulation in skeletal muscle and the