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The Metabolic Syndrome as a Risk Factor for Chronic Kidney Disease: More than a Fat Chance?

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The metabolic syndrome, also known as syndrome X or insulin resistance syndrome, is characterized by abdominal obesity, hyperglycemia, hypertension, hypertriglyceridemia, and reduced HDL cholesterol. In this issue of the *Journal of the American Society of Nephrology*, Wisse (1) describes the link between chronic inflammation of visceral adipose and the insulin resistance and pathologic features that characterize the metabolic syndrome. The prevalence of the metabolic syndrome in the United States is ~47 million and rising (2), as a result of the current obesity and diabetes epidemics. *Journal of the American Society of Nephrology* readers are well aware that chronic kidney disease (CKD) is also increasingly common, with an estimated 8 million people in the United States with GFR <60 ml/min (Third National Health and Nutrition Examination Survey). Many aspects of the metabolic syndrome phenotype are associated with CKD, suggesting that individuals with visceral obesity are at increased risk for progressive loss of renal function.

Several groups have examined the relationship between the metabolic syndrome and CKD. Hoehner *et al.* (3) correlated the metabolic syndrome profile and microalbuminuria in a cross-sectional study of American Indians from Wisconsin and Minnesota. After stratification, individuals with three or more metabolic syndrome traits had a 2.3-fold increased odds of having microalbuminuria compared with a control group without the syndrome. Palaniappan *et al.* (4) and Chen *et al.* (5) extracted data from the Third National Health and Nutrition Examination Survey database, which contains detailed clinical information from >6000 subjects. Both studies found a statistical association between metabolic syndrome and microalbuminuria. Chen *et al.* also discovered a significant correlation between number of metabolic syndrome factors and GFR <60 ml/min. Individual traits that confer greatest risk were hypertension and hyperglycemia (5), which is not surprising, because both factors predispose to CKD pathogenesis and/or progression (6,7).

We conclude from these reports that the metabolic syndrome is related to renal dysfunction, but a cause-and-effect relationship cannot be clearly established from these studies. Because of considerable overlap between clinical features of the metabolic syndrome and diabetes, CKD risk in individuals with the metabolic syndrome may reflect the presence of known risk factors for CKD initiation and progression—hypertension and diabetes—rather than an independent effect. One approach to identifying a distinction would be to compare the prevalence of CKD in metabolic syndrome cohorts who do or do not satisfy diagnostic criteria for diabetes. Until such a study is conducted, it is reasonable to view the renal risks and consequences of the metabolic syndrome and diabetes as indistinguishable.

Some data do suggest that the metabolic syndrome may independently cause CKD. In addition to identifying BP and hyperglycemia as risks for CKD in the metabolic syndrome, Chen *et al.* (5) observed that increased waist circumference significantly correlated with microalbuminuria and GFR decline, suggesting that obesity may be an independent risk for CKD. An association between obesity and the nephrotic syndrome was first recognized years ago (8). More recently, Iseki *et al.* (9) showed a statistical association between body mass index and incidence of ESRD in Japanese men, even after adjusting for comorbid risks, such as BP and proteinuria. A large renal pathology study demonstrated that obesity-related glomerulopathy, which is characterized by focal segmental glomerulosclerosis and glomerulomegaly, increased in incidence from 0.2 to 2% of all biopsy diagnoses during the 15-yr period of the study (10). None of the patients demonstrated a histologic pattern consistent with diabetic nephropathy, the presumed pathology associated with the metabolic syndrome. These studies raise the possibility that obesity, which is a cardinal feature of the metabolic syndrome, may lead to CKD. However, as mentioned earlier, this may be difficult to prove, in this case because obesity is also a risk for hypertension and diabetes (11).

Obesity and insulin resistance are prominent features of the metabolic syndrome, and both have been associated with secretion of inflammatory mediators and activation of inflammation-associated signaling pathways (12–15). The role of specific mediators in the pathogenesis of the metabolic syndrome, including leptin, IL-6, TNF-α, adiponectin, and acylation-stimulating protein, are discussed in detail in the review by Wisse (1) in this issue. Until recently, adipocytes were viewed as the most likely source of soluble, metabolic syndrome mediators, a notion that is corroborated by *in vitro* studies demonstrating adipocyte capacity to secrete proinflammatory cytokines (16). However, two groups have published studies within the past year implicating macrophages, which infiltrate fat tissue, as the principal site of obesity-related cytokine synthesis (17,18). Because many of these cytokines have been suggested to mediate renal disease pathophysiology (19), it is tempting to speculate that progressive kidney disease could also be regulated by proinflammatory cytokines in the context of the metabolic syndrome. Other potential mechanisms include physical compression of kidney parenchyma by

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adipose tissue, reduced birth weight and nephron number, enhanced glucocorticoid activity, or altered uric acid metabolism (20–22). We are hopeful that large National Institutes of Health–sponsored diabetic nephropathy initiatives, such as FIND (23) or the mouse consortium (www.niddk.nih.gov/fund/diabetesspecialfunds/consortia/AMDCC.pdf) will identify candidate molecules, which will elucidate novel pathogenetic pathways that may help to define unique mechanisms of renal injury associated with diabetes and the metabolic syndrome.

In the small subset of patients with metabolic syndrome and absence of glucose intolerance, we advocate close monitoring for subsequent development of diabetes, because these patients are at extremely high risk for diabetes and diabetes-related complications. In metabolic syndrome patients with hypertension and hyperglycemia, it is clear that aggressive BP and glucose control is warranted, for the prevention of renal as well as extrarenal disease manifestations of hypertension and diabetes. One cannot be as certain whether treatment of other components of the metabolic syndrome will necessarily have an impact on CKD progression. However, recent studies indicate that susceptibility to CKD increases with the number of metabolic syndrome traits (5), and other reports have linked obesity and dyslipidemia to CKD (24), thereby supporting the idea that aggressive obesity- and lipid-lowering therapies have the potential to ameliorate renal disease progression in the setting of the metabolic syndrome. More intensive investigation into the specific role of obesity and hyperlipidemia in CKD progression is warranted, particularly because the prevalence of diabetes, obesity, and ESRD continue to climb at alarming rates.

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