Association of Metabolic Syndrome in Nondiabetic Patients with Increased Risk for Chronic Kidney Disease: The Fat Lady Sings

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I n a recent editorial, we suggested that more data are required to determine if metabolic syndrome is associated with progressive chronic kidney disease (CKD) in the absence of overt diabetes (1). This is clearly an important issue; metabolic syndrome, characterized by abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, is present in approximately 23% of US adults (2) and is associated with increased risk of cardiovascular disease (3). If individuals with either self-reported diabetes or a fasting plasma glucose ≥126 mg/dl are excluded, metabolic syndrome prevalence remains at 19% (4), markedly expanding the numbers of patients at risk for CKD. Perhaps equally sobering is the increasing incidence of metabolic syndrome among adolescents (5). If metabolic syndrome also predicts cardiovascular disease and diabetes in this group, as we expect, the incidence of CKD will continue to rise and contribute to the chronic disease epidemic that causes death and disability and increases health care costs for Americans (http://www.cdc.gov/nccdphp/overview.htm).

In this issue of the Journal of the American Society of Nephrology, Chertow and colleagues provide further evidence to support the premise that metabolic syndrome, even after adjusting for diabetes status and BP control, independently contributes to CKD development (6). Using the Atherosclerosis Risk in Communities (ARIC) cohort dataset (7), their analyses suggest that metabolic syndrome, defined by the National Cholesterol Education Program (NCEP) guidelines (8), is independently associated with increased risk of incident CKD in nondiabetic adults. ARIC was a prospective study to investigate etiology of atherosclerotic disease and variation in cardiovascular risk factors by race, sex, and geography. The cohort was followed for 9 yr; serum creatinine was measured at baseline and at the last visit. Using the abbreviated Modification of Diet in Renal Disease study equation, Kurella et al. have estimated GFR (eGFR) in analytic cohort of 10,096 individuals, who had neither CKD nor diabetes at entry (6). Of all nondiabetic ARIC participants, 21% (n = 2110) met the NCEP criteria for metabolic syndrome at baseline. Ten percent of subjects with metabolic syndrome developed CKD (i.e., eGFR < 60 cc/min) compared with 4% of subjects without metabolic syndrome, a difference that remained statistically significant after correction for possible confounding variables and performance of interaction tests to check for modification of the metabolic syndrome-CKD relation. Even after adjusting for incident hypertension and diabetes during follow-up, the point risk estimates for incident CKD in metabolic syndrome patients remain increased, although the confidence interval range from 1.01 suggests marginal significance.

Strengths of the study are the large analytic dataset, the longitudinal design of the ARIC trial and the careful statistical analyses. Their analytic design used contemporaneous control subjects without metabolic syndrome, and observational studies with this design do not systematically overestimate magnitude of association between an exposure (in this case metabolic syndrome) and outcomes (i.e., CKD) compared with randomized designs (9). Although the ARIC study was prospective, association between metabolic syndrome and CKD was not a prespecified endpoint and conclusions from post hoc analyses of subgroups must be viewed with caution (10,11). Potential for selection bias or unintended confounding remains possible, even with multivariate analyses to adjust for imbalances in prognostically important covariates, as was done in this study.

Despite these reservations, Kurella and coworkers provide the strongest evidence to date that patients with metabolic syndrome, but without diabetes, are at increased risk for CKD. Importantly, their results corroborate conclusions derived from studies with cross-sectional designs, which suggested that metabolic syndrome was a risk for CKD independent of diabetes or hypertension. In an analysis using the Third National Health and Nutrition Examination Survey (NHANES III) dataset, risk of CKD, defined as eGFR < 60 cc/min, and microalbuminuria was increased in enrollees with metabolic syndrome but without diabetes (12). This same group also demonstrated increased prevalence of CKD in NHANES enrollees with fasting glucose levels ranging from 100 to 126 mg/dl but did not indicate how many of these individuals met NCEP criteria for metabolic syndrome (13). The study by Kurella et al. advances the field by focusing on GFR loss in nondiabetic patients with metabolic
syndrome, an important endpoint given the uncertainty of microalbuminuria as a biomarker for early CKD, and by demonstrating persistent CKD risk after simultaneously adjusting for incident diabetes and hypertension, two powerful predictors of CKD. Obesity has been linked to CKD (14) and body mass index (BMI) has been associated with ESRD incidence in Japanese men (15). However, the association between metabolic syndrome and increased CKD risk in the ARIC cohort remained significant after adjustment for BMI and other confounding demographic and clinical variables. Taken together, the results of a number of observational studies are concordant in suggesting that the presence of metabolic syndrome may be a risk for CKD pathogenesis, which is independent of diabetes and hypertension. Importantly, these studies highlight the possibility that combinations of less well-recognized CKD risk factors deserve scrutiny from both practitioners and investigators.

How does this information change practice? Most importantly, these studies remind us of the need to identify and treat factors for cardiovascular risk. Practically, each criterion of the NCEP metabolic syndrome definition identifies a risk factor for cardiovascular disease that requires intervention independent of its contribution to CKD pathogenesis. The evidence for risk factor management in patients with metabolic syndrome is compelling. Important recent studies demonstrate that alteration of lifestyle is a cost-effective approach to prevent type 2 diabetes (16–18), a major cause of cardiovascular disease, CKD, and ESRD (11). Given the prevalence of patients with metabolic syndrome but without diabetes, we need to more effectively identify individuals at risk for CKD. Even in the report from Chertow’s group (6), only 10% of ARIC subjects with metabolic syndrome develop CKD over nearly 10 yr. Methodologies to recognize the subgroups at risk would permit more efficient allocation of scarce health care resources. These types of tools have been developed to predict type 2 diabetes risk (19,20).

The mechanism by which metabolic syndrome causes kidney injury is intriguing and poorly understood. Inflammation has been implicated in metabolic syndrome pathogenesis (1,21,22), especially as a mechanism of insulin resistance. Nondiabetic patients with metabolic syndrome have impaired fasting glucose levels, consistent with insulin resistance. If these patients are at risk for CKD, as suggested by Chen et al. (12) and Kurella et al. (6), then insulin resistance may be responsible for increased CKD risk. Insulin resistance and hyperinsulinemia are associated with increased risk of CKD in NHANES III participants (23). Becker et al. recently reported that insulin sensitivity, assessed with the Homeostasis Model Assessment of Insulin Resistance [HOMA-IR], was impaired in patients early in the course of renal dysfunction (24). At a molecular level, endoplasmic reticulum (ER) stress may provide a link between inflammation and insulin resistance. The ER is an intracellular organelle that synthesizes and processes secretory and transmembrane proteins. Under pathologic stress, misfolded proteins accumulate in ER lumen and activate a signaling pathway called the unfolded protein response. Öczam et al. showed that this stress response suppresses insulin signaling by activating c-Jun N-terminal kinase (JNK). Activated JNK serine phosphorylates the insulin receptor substrate (IRS-1) (25), impairing insulin signaling. JNK activity is stimulated in diabetes in a number of tissues and intraperitoneal administration of a cell-permeable JNK-inhibitory peptide improved insulin resistance in diabetic mice (26). Increased insulin sensitivity may reduce CKD risk in nondiabetic, metabolic syndrome patients indirectly by preventing diabetes or perhaps directly by blocking kidney injury (27).

Over the last year, the fat lady has begun to sing. Epidemiologic evidence has accumulated and strengthened links between metabolic syndrome and CKD risk in nondiabetic patients. Given the additional association between metabolic syndrome and cardiovascular disease risk, we need to aggressively manage risk factors now. Finally, the association of metabolic syndrome and CKD highlights the promise and excitement of medical practice in the postgenome era. Integration of clinical and bench science will foster identification of subgroups of patients at risk for CKD and provide new treatments based on a more thorough understanding of CKD pathophysiology.

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References

9. Concato J, Shah N, Horwitz RI: Randomized, controlled