Metabolic Syndrome, CKD Progression, and Death: the Good, the Bad, and the Ugly

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Previous studies have reported an association between metabolic syndrome, proteinuria, incidence and progression of CKD, and ESRD among different ethnic groups (1–6). With an increasing sedentary lifestyle and high rates of obesity, the prevalence of metabolic syndrome stands at 34% (7). The burden of incident and prevalent CKD has also increased in the United States; thus, CKD and metabolic syndrome, in addition to obesity, are major public health problems. Metabolic syndrome is defined by central obesity, hyperglycemia, hypertension, and dyslipidemia (8,9). Diabetes and hypertension are the leading causes of both CKD and ESRD. Because both elevated blood glucose and BP are included in the definition of metabolic syndrome, it is not surprising that recent data suggest a link between metabolic syndrome and CKD. Moreover, metabolic syndrome in the general population increases risk of cardiovascular disease, stroke, and all-cause mortality, as do CKD and microalbuminuria (10). It has not been clear whether these effects of metabolic syndrome are driven by one or more individual factors, are due to clustering of risk factors, or perhaps result from some other concomitant factors. In addition, it is unclear whether the consequences of metabolic syndrome differ according to level of CKD.

In this issue of *CJASN*, Navaneethan and colleagues (11) tackle the subject of metabolic syndrome, CKD progression, and death in a large (n=25,868) and diverse population with stage 3–4 CKD. They used a preexisting electronic health record–based CKD registry. The definition of metabolic syndrome was modified from that used by the National Cholesterol Education Program, with body mass index (BMI) instead of waist circumference. This is an acceptable alternative used in the World Health Organization classification of metabolic syndrome and in other similar studies (9). Sixty percent of the cohort was defined as having metabolic syndrome. Multivariate analyses for several risk factors known to influence CKD progression and death showed that metabolic syndrome was associated with an increased risk for ESRD but not for death during a mean follow-up of 2.3 years. Subgroup analyses conducted in patients with urine protein measurements showed that the presence of proteinuria was associated with an increased risk of ESRD and death. Those with metabolic syndrome had much higher odds of proteinuria even after covariate adjustment; however, when the prior ESRD analyses were adjusted for proteinuria, there was no longer an association of metabolic syndrome with ESRD. We previously reported in a secondary analysis of the African-American Study of Kidney Disease and Hypertension (AASK) an association of 31% increased risk of CKD progression to ESRD or death in patients who met criteria for metabolic syndrome, but this was attenuated and no longer significant when adjusted for proteinuria (4). These findings, coupled with those from the current study, suggest that proteinuria may play an important role in the effect of metabolic syndrome on CKD progression. In fact, the World Health Organization classification of metabolic syndrome includes proteinuria as one of the criteria (9). Prior investigators have demonstrated a significant correlation between urinary albumin excretion and insulin resistance in patients with essential hypertension, those with type 2 diabetes, and young African Americans with borderline hypertension (12,13).

Navaneethan and colleagues' article substantiates an association of metabolic syndrome with CKD progression in a much larger and more diverse patient population. The public health relevance of these results is underscored by the fact that the prevalence of metabolic syndrome and its components, especially diabetes, is increasing over time, and the CKD burden thus may rise commensurately. Moreover, each of the individual components of the metabolic syndrome has been linked to CKD; thus, it is not surprising to find the observed link between the composite of metabolic syndrome and CKD. Diabetes and hypertension are well established risk factors for progression of CKD. Observational data and a recent meta-analysis suggest that elevated triglyceride and low HDL cholesterol levels are independent risk factors for the acceleration of CKD (14,15) and that the use of statins may slow progression of CKD (16). Several authors have reported that higher BMI is associated with lower GFR and CKD progression (17–19); however, Navaneethan and colleagues' study shows that higher BMI had no effect on ESRD. Although 46.6% of the AASK cohort had a BMI >30 kg/m^2 and thus were obese, no association was observed with BMI alone and the renal outcome (4). Nonetheless, this current report, like the AASK cohort, shows that in a more diverse population with established CKD, the presence of the metabolic syndrome composite is associated with

CKD progression. It also confirms that some of the individual components of metabolic syndrome—impaired glucose metabolism, elevated triglyceride levels, and hypertension—are associated with increased risk of ESRD.

Previous reports have explored the association of metabolic syndrome and CKD. Chen *et al.* reported that the presence of metabolic syndrome was a strong and independent risk factor for CKD and microalbuminuria; later, in a cross-sectional analysis, they noted a 2.6-fold increased prevalence of CKD among adults in the Third National Health and Nutrition Examination with the metabolic syndrome (1,2). Kurella *et al.* reported that metabolic syndrome predicted incident CKD (3). A total of 10,096 nondiabetic participants who were in the Atherosclerosis Risk in Communities study and had normal baseline kidney function composed the study cohort. The multivariate adjusted odds ratio of developing CKD in participants with metabolic syndrome was 1.43. After adjustment for the subsequent development of diabetes and hypertension during the 9 years of follow-up, the odds ratio for incident CKD among participants with metabolic syndrome was 1.24 but remained significant. In a large American Indian population, Lucove *et al.* reported that metabolic syndrome was significantly and independently associated with a 30% increased risk of CKD during 9 years of follow-up and that this risk was greater in persons who developed diabetes during the study (6).

Although Navaneethan and colleagues' study was adequately powered to detect a difference in the death outcome, and despite the association of proteinuria with death, the metabolic syndrome composite was not associated with an increased risk of death. However, individual components, such as low HDL cholesterol level and impaired glucose metabolism, were associated with an increased hazard for death, whereas obesity and hypertension were associated with a lower hazard for death. The lack of association of metabolic syndrome with death may be due to the inverse association of obesity and hypertension with death or to the effect of cardioprotective medications widely used in this high-cardiovascular-risk population. Perhaps longer-term follow-up (>2 years) would have yielded different results. Another plausible hypothesis is that metabolic syndrome or its individual components are expressed differently in more advanced stages of CKD. Studies suggest a paradoxical association with obesity and reduced mortality in hemodialysis patients and in the elderly and heart failure populations (20,21). This study confirms previous reports and suggests that in advanced CKD, obesity may be protective. This report introduces another population (CKD stage 3–4) that may not express the normal phenotype of obesity and worse survival. One limitation of both this study and the AASK cohort was the absence of waist circumference data to use as a surrogate for abdominal obesity, as defined by the National Cholesterol Education Program. However, both studies used an alternative measure of obesity, BMI, which has recognized limitations as an indicator of obesity, particularly in the elderly and in women; nevertheless, it has been widely used in the medical literature. Further investigation into the reasons for the protective effect of obesity and survival are urgently needed given the high morbidity and mortality, as well as aggressive measures used to eradicate obesity in the general population.

In summary, this report substantiates and strengthens the previous associations between metabolic syndrome and CKD progression, even after adjustment for other factors known to influence renal and death outcomes (with the exception of proteinuria). Strengths of these analyses include its very large and diverse population, with competing risk models applied, and multivariate adjustment for many known risk factors associated with cardiovascular disease and CKD progression, such as use of cardiac medications and presence of cardiovascular disease. Major weaknesses are related to the retrospective observational study design with possible selection bias, incomplete data on confounders, and lack of a prespecified study protocol. The findings of this report are important because of the escalation of CKD and ESRD rates, as well as the increasing prevalence of obesity, insulin resistance, and impaired glucose tolerance. Further studies are necessary to determine putative mechanisms of the effect of the metabolic syndrome on CKD progression and should include more specific measures of insulin resistance, as well as more detailed investigation into the role of proteinuria. Moreover, metabolic syndrome is a modifiable risk factor; thus, strategies to reduce its prevalence and severity may be a new target in treating CKD that warrants further study. In addition, further investigations into the differential effects of metabolic syndrome and obesity on renal disease progression and mortality across different levels of CKD are warranted.

Disclosures

None.

References

1. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, Whelton PK, He J: Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J Am Soc Nephrol* 14: 469–477, 2003
2. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J: The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 140: 167–174, 2004
3. Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 16: 2134–2140, 2005
4. Lea JP, Cheek D, Thornley-Brown D, Appel L, Agodoa L, Contreras G, Gassman J, Lash J, Miller E, Randall O, Wang X, McClellan W, for the AASK Investigators: Metabolic Syndrome, Proteinuria, and the Risk of Progressive Chronic Kidney Disease in Hypertensive African-Americans. *Am J Kidney Dis* 51: 732–740, 2008
5. Lea J, Greene E, Nicholas S, Agodoa L, Norris K: Cardiorenal metabolic syndrome in the African diaspora: Rationale for including chronic kidney disease in the metabolic syndrome definition. *Ethnicity Dis* 19: S2-11–S2-14, 2009
6. Lucove J, Vupputuri S, Heiss G, North K, Russell M: Metabolic syndrome and the development of CKD in American Indians: The Strong Heart Study. *Am J Kidney Dis* 51: 21–28, 2008
7. Ervin RB: Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. *Natl Health Stat Report* 13: 1–7, 2009
8. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15: 539–553, 1998
9. Ford ES, Giles WH: A comparison of the prevalence of the metabolic syndrome using two proposed definitions. *Diabetes Care* 26: 575–581, 2003
10. Galassi A, Reynolds K, He J: Metabolic syndrome and risk of cardiovascular disease: A meta-analysis. *Am J Med* 119: 812–819, 2006

11. Navaneethan SD, Schold JD, Kirwan JP, Arrigain S, Jolly SE, Poggio ED, Beddhu S, Nally JV Jr: Metabolic syndrome, ESRD, and death in CKD. Clin J Am Soc Nephrol 8: 945–952, 2013
12. Palaniappan L, Carnethon M, Fortmann SP: Association between microalbuminuria and the metabolic syndrome: NHANES III. *Am J Hypertens* 16: 952–958, 2003
13. Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities—the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 334: 374–381, 1996
14. Walker WG: Relation of lipid abnormalities to progression of renal damage in essential hypertension, insulin-dependent and non insulin-dependent diabetes mellitus. *Miner Electrolyte Metab* 19: 137–143, 1993
15. Samuelsson O, Aurell M, Knight-Gibson C, Alaupovic P, Attman PO: Apolipoprotein-B-containing lipoproteins and the progression of renal insufficiency. *Nephron* 63: 279–285, 1993
16. Fried LF, Orchard TJ, Kasiske BL: Effect of lipid reduction on the progression of renal disease: A meta-analysis. *Kidney Int* 59: 260–269, 2001
17. Toto RD, Greene T, Hebert LA, Hiremath L, Lea JP, Lewis JB, Pogue V, Sika M, Wang X; AASK Collaborative Research Group: Relationship between body mass index and proteinuria in hypertensive nephrosclerosis: Results from the African American Study of Kidney Disease and Hypertension (AASK) cohort. *Am J Kidney Dis* 56: 896–906, 2010
18. Gelber RP, Kurth T, Kausz AT, Manson JE, Buring JE, Levey AS, Gaziano JM: Association between body mass index and CKD in apparently healthy men. *Am J Kidney Dis* 46: 871–880, 2005
19. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS: Body mass index and risk for end-stage renal disease. *Ann Intern Med* 144: 21–28, 2006
20. Lea JP, Crenshaw D, Onufrak S, Newsome B, McClellan WM: The interaction of race and obesity on ESRD and death in an elderly high risk cardiovascular population. *Obesity (Silver Spring)* 17: 2216–2222, 2009
21. Glanton CW, Hypolite IO, Hshieh PB, Agodoa LY, Yuan CM, Abbott KC: Factors associated with improved short term survival in obese end stage renal disease patients. *Ann Epidemiol* 13: 136–143, 2003

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