Metabolic Syndrome, ESRD, and Death in CKD

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Summary

Background and objectives Previous studies reported an association between metabolic syndrome , incident CKD, and proteinuria. This study examined the associations between metabolic syndrome and its components with ESRD and death among those patients with stages 3 and 4 CKD (estimated GFR=15–59 ml/min per 1.73 m²).

Design, setting, participants, & measurements Patients with stages 3 and 4 CKD (n=25,868) who had data relating to metabolic syndrome and were followed in our health care system were identified using an electronic medical record-based registry. Cox proportional hazards models and competing risk analyses were used to study the associations between metabolic syndrome, its components (elevated BP, low HDL cholesterol, elevated serum triglycerides, impaired glucose metabolism, and obesity), and all-cause mortality and ESRD while adjusting for demographics, comorbid conditions, use of relevant medications, and renal function.

Results Sixty percent of the study population (n=15,605) had metabolic syndrome. In the multivariate-adjusted analysis, presence of metabolic syndrome was associated with an increased risk for ESRD (hazard ratio=1.33, 95% confidence interval=1.08, 1.64) but not death (hazard ratio=1.04, 95% confidence interval=0.97, 1.12) during a mean follow-up of 2.3 years. Among the individual components of metabolic syndrome, impaired glucose metabolism, elevated triglycerides, and hypertension were associated with increased risk for ESRD, whereas low HDL cholesterol and impaired glucose metabolism were associated with higher risk of death.

Conclusions Presence of metabolic syndrome is associated with ESRD but not death in patients with stages 3 and 4 CKD.

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Introduction

CKD and metabolic syndrome are major public health problems (1,2). Metabolic syndrome is a constellation of cardiovascular risk factors linked with obesity and insulin resistance, with an estimated prevalence of 20%–25% in the general population, and it is associated with an increased risk of coronary artery disease, stroke, and mortality (3–5). In the past, various diagnostic criteria have been proposed by different organizations for metabolic syndrome (6–8). Recent consensus definition for metabolic syndrome consists of elevated BP, dyslipidemia (low HDL cholesterol and elevated serum triglycerides), elevated fasting glucose (impaired fasting glucose or type 2 diabetes), and central obesity (9). Previous observational studies and their meta-analysis reported an association between metabolic syndrome and incident CKD, microalbuminuria, and proteinuria among different ethnic groups (10–13).

Studies examining the association between metabolic syndrome and the progression of CKD are limited. A secondary analysis of the African American Study of Kidney Disease and Hypertension trial showed a 31% increased risk of CKD progression or death with metabolic syndrome (14). A population-based study from Taiwan showed that the impact of metabolic syndrome on CKD progression is significant only in early-stage CKD (stages 1–3) but not late-stage and diabetic CKD patients (15). Thus, the association between metabolic syndrome and CKD progression remains unclear and has not been explored in a diverse population. Therefore, we examined the associations between metabolic syndrome, ESRD, and death among those patients with stages 3 and 4 CKD (estimated GFR [eGFR]=15–59 ml/min per 1.73 m²) followed in our health care system.

Materials and Methods

We conducted an analysis using our preexisting Electronic Health Record-based CKD registry. The development and validation of this registry at Cleveland Clinic have been described in detail previously (16).

Study Population

Patients who had at least one outpatient encounter with a Cleveland Clinic health care provider and two eGFR values<60 ml/min per 1.73 m² (the Chronic Kidney Disease Epidemiology Collaboration equation) >90 days apart were included (17). Patients ages<18 years and patients who were already diagnosed with ESRD needing dialysis or renal transplant were excluded. Patients who met the inclusion/exclusion criteria from

January 1, 2005 to September 15, 2009 were included in this analysis.

Definitions and Outcome Measures

Renal Function. We applied the Chronic Kidney Disease Epidemiology Collaboration equation to patients who had two serum creatinine levels measured 90 days apart as of January of 2005 in our health care system. All creatinine measurements were performed by the modified kinetic Jaffe reaction using a Hitachi 747–200 Chemistry Analyzer (1996–2001) or a Hitachi D 2400 Modular Chemistry Analyzer thereafter (Roche Diagnostics, Indianapolis, IN) in our laboratory. Urinary protein studies were not available for the entire study population. Therefore, to be comprehensive and reflect clinical practice, patients who had urine dipstick measurements, urine albumin-to-creatinine ratio, urine protein-to-creatinine ratio, and 24-hour urine studies were included to assess whether they had proteinuria. The following cutoffs were considered in determining whether someone had proteinuria: presence of $\geq 1+$ proteinuria in dipstick studies, >30 mg/g in urine albumin-to-creatinine ratio and urine protein-to-creatinine ratio studies, and >30 mg proteinuria in 24-hour studies. Urine dipstick studies were performed using multistix reagent strips (SIEMENS). Urine albumin was measured by immunoturbidimetric assay with antigen excess check, and urine creatinine was measured using a multistep enzymatic procedure that produces a quinone imine chromogen on the Roche Modular platform in our laboratory.

Demographics, Comorbid Conditions, and Laboratory Parameters. Demographic variables, such as age, sex, and race/ethnicity, were extracted from the Electronic Health Records. Comorbid conditions were defined using prespecified criteria and previously validated (16). Serum triglycerides and HDL cholesterol were measured using an enzymatic colorimetric test run on the Roche Modular platform for all the study participants at different sites in our health care system. Within- and between-run precision of human serum for triglyceride is stated at 1.5% and 1.8%, respectively, and within- and between-run precision of human serum for HDL cholesterol is stated at 0.95% and 1.3%, respectively. In our health care system, lipid profiles are customarily obtained in the fasting state using a standard protocol.

Metabolic Syndrome. Metabolic syndrome was defined as the presence of three or more of the following components: body mass index (BMI) ≥ 30 kg/m^2, serum triglyceride level ≥ 150 mg/dl, HDL ≤ 50 mg/dl in women and ≤ 40 mg/dl in men, hypertension (BP $>130/85$ mmHg or on antihypertensive medications), and impaired glucose metabolism (presence of diabetes, use of oral hypoglycemics, or blood glucose level ≥ 200 mg/dl) (9). Because fasting blood glucose was not available, we included both the drug treatment for diabetes and physician diagnosis of diabetes in addition to blood glucose values to identify those patients with impaired glucose metabolism as suggested in the consensus definition (9). Similarly, it is recommended to consider BMI ≥ 30 kg/m^2 as a risk factor in the absence of waist circumference data, because this value approximates a waist circumference >102 cm in men and >88 cm in women.

Outcome Measures. The primary outcomes of interest were all-cause mortality and ESRD, which were ascertained from linkage of our registry with the Social Security Death Index and United States Renal Data System. Patients were followed from their date of inclusion in the registry until September 15, 2009.

Statistical Analyses

Baseline characteristics between CKD patients with and without relevant data relating to metabolic syndrome components were compared using chi-square and t tests for categorical and continuous variables, respectively. Similarly, baseline characteristics between CKD patients with and without metabolic syndrome were also compared. To evaluate whether survival and ESRD among persons with CKD were associated with metabolic syndrome, we used Kaplan–Meier plots and log-rank tests with entry into the registry as time of origin. Because ESRD and death are competing events, we fitted cumulative incidence functions that adjust for competing risks and compared these results with the traditional cause-specific analysis. In addition, a separate analysis that included all deaths (both before and after ESRD) was also conducted.

Cox proportional hazards models were used to assess the associations between metabolic syndrome, death, and ESRD while adjusting for age, sex, race, smoking, malignancy, congestive heart failure, cerebrovascular disease, coronary artery disease, chronic obstructive pulmonary disease, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, LDL cholesterol, hemoglobin, albumin, and eGFR. We checked the proportional hazards assumption of metabolic syndrome by inspection of log-negative log survival plots. We tested two-way interactions between metabolic syndrome and prespecified covariates in the adjusted model: age, sex, race, and eGFR. The interactions were not statistically significant, except for the interaction term for age in the ESRD model; 1% of patients had missing LDL, 18% of patients had missing hemoglobin, and 17% of patients had missing albumin data. Mean value imputation was used to include these patients in the adjusted model. An indicator for missing data on each variable was included as well. In the study population, 13,599 patients had at least one urinary protein measure, and a separate multivariate analysis, including proteinuria along with other previously mentioned variables, was also conducted. Lastly, we performed a logistic regression analysis to examine whether presence of metabolic syndrome was associated with proteinuria after adjusting for the covariates described above.

All data analyses were conducted using Unix SAS version 9.2 (SAS Institute, Cary, NC) and R 2.12.2 (The R Foundation for Statistical Computing, Vienna, Austria). The cmprsk package was used for competing risk analysis. This study was approved by the Cleveland Clinic Institutional Review Board.

Results

Baseline Patient Characteristics

Of 43,546 patients in our CKD registry (as of September 15, 2009), 25,868 (59%) patients had relevant data relating to the different components of metabolic syndrome and were included in this analysis. The primary reason for excluding other patients was lack of lipid profile measurement (Figure 1). About 60% of the study population

(*n*=15,605) had metabolic syndrome. The mean age was 72.3±11.2 years, with 54% being women and 12% being African Americans. Patients who had data relating to metabolic syndrome were significantly different from patients without data relating to metabolic syndrome on demographics, comorbid conditions, medication use, and number of hospital encounters except for African-American race (Table 1). Patients with and without metabolic syndrome differed on age, comorbid conditions, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, hospital encounters, and antihyperlipidemic agents (Table 1).

Metabolic Syndrome, ESRD, and Mortality

Among those patients without data relating to metabolic syndrome (*n*=17,678), there were 413 ESRD events and 4150 pre-ESRD death events during a median follow-up of 2.2 years (mean=2.2 years). Among those patients with metabolic syndrome data, during a median follow-up of 2.4 years (mean=2.3 years), 3345 participants died before ESRD, and 481 reached ESRD. Overall (pre- and post-ESRD), 3504 patients died. The Kaplan–Meier (data not shown) and competing risk analyses (Figure 2) showed no significant difference in overall mortality between those patients with and without metabolic syndrome. However, there were significantly higher rates of ESRD among those patients with metabolic syndrome than those patients without metabolic syndrome in both Kaplan–Meier (data not shown) (log rank *P*<0.001) and competing risk analyses (*P*<0.001) (Figure 2). Results were similar in both analyses.

In the Cox proportional hazards model, after covariate adjustment, presence of metabolic syndrome was not associated with pre-ESRD death, but it was associated with an increased hazard for ESRD (hazard ratio[HR]=1.33, 95% confidence interval [95% CI]=1.08, 1.64) (Table 2). An

analysis of covariate-adjusted overall mortality (pre- and post-ESRD) provided similar results to the analysis including only pre-ESRD death, with an HR for patients having metabolic syndrome of 1.06 (95% CI=0.98, 1.13).

Associations between Individual Components and Outcomes

Among the individual components of metabolic syndrome, elevated serum triglycerides (HR=1.07, 95% CI=1.00, 1.15), impaired glucose metabolism (HR=1.67, 95% CI=1.36, 2.00), and hypertension (HR=1.83, 95% CI=1.04, 3.25) were associated with an increased risk for ESRD. Impaired glucose metabolism (HR=1.18, 95% CI=1.10, 1.27) and low HDL cholesterol (HR=1.10, 95% CI=1.02, 1.18) were associated with an increased hazard for death, whereas obesity (HR=0.85, 95% CI=0.79, 0.93) and hypertension (HR=0.81, 95% CI=0.68, 0.97) were associated with a lower hazard for death (Figure 3).

Interaction with Age

We found a significant interaction of age with metabolic syndrome in the ESRD model, indicating that the association between metabolic syndrome and ESRD increased with age (*P*<0.001). For example, for a CKD patient of 70 years (mean age of our study population), there was an estimated 50% increased hazard for ESRD (95% CI =1.18, 1.93), whereas this risk was not significant for those patients ages 50 years (HR=1.11, 95% CI=0.85, 1.45). The test of interaction between age and metabolic syndrome was not significant for mortality (*P*=0.91), suggesting that the association between metabolic syndrome and mortality does not differ by age in our study population.

Subgroup Analyses

In a subgroup of patients who had at least one urinary protein study (*n*=13,599, 52%), the association between metabolic syndrome and ESRD was attenuated and no longer statistically significant with adjustment for proteinuria (HR=1.28, 95% CI=0.98, 1.60). There was no association between metabolic syndrome and all-cause mortality (pre-ESRD) in this model (HR=1.04, 95% CI=0.94, 1.40). Presence of proteinuria was significantly associated with ESRD (HR=2.87, 95% CI=2.19, 3.76) and mortality (HR=1.45, 95% CI=1.31, 1.60) in these models.

Metabolic Syndrome and Proteinuria

Metabolic syndrome was associated with significantly higher odds of having proteinuria after covariate adjustment (odds ratio=1.84, 95% CI=1.68, 2.03).

Discussion

Metabolic syndrome is widely prevalent among those patients with stages 3 and 4 CKD. In our study, the presence of metabolic syndrome was associated with ESRD but not death. The associations between individual components of metabolic syndrome and outcomes also varied. These findings have significant clinical importance, because individual components of metabolic syndrome, metabolic syndrome itself, and CKD in the US population and across the globe are increasing (2).
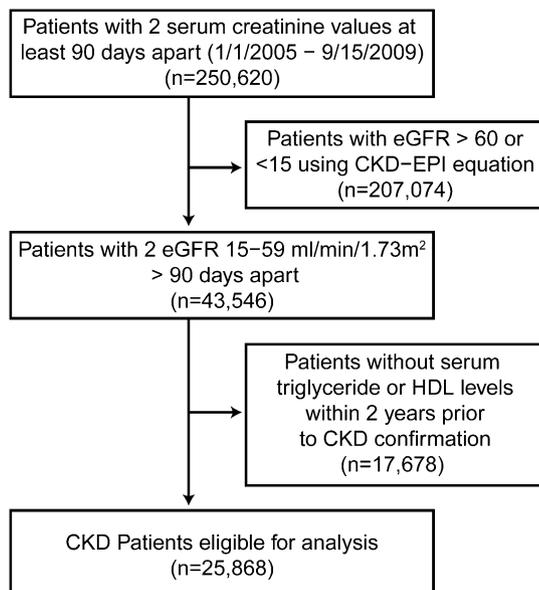

Figure 1. | **Flow chart showing details of how patients were selected from our CKD registry for this analysis.**

Table 1. Characteristics of patients with and without metabolic syndrome at the time of being classified as CKD

Variable	Metabolic Syndrome Present (n=15,605)	Metabolic Syndrome Absent (n=10,263)	Metabolic Syndrome Data Not Available (n=17,678)
Age (yr)	71.0±10.9	74.4±11.3	73.1±12.5
Man, n (%)	7212 (46.2)	4638 (45.2)	7752 (43.9)
African Americans, n (%)	1899 (12.2)	1214 (11.8)	2100 (11.9)
Diabetes, n (%)	6969 (44.7)	709 (6.9)	1458 (8.2)
Hypertension, n (%)	15,422 (98.8)	9303 (90.6)	13,631 (77.1)
Coronary artery disease, n (%)	4699 (30.1)	2355 (22.9)	1610 (9.1)
Cerebrovascular disease, n (%)	1791 (11.5)	1089 (10.6)	840 (4.8)
Congestive heart failure, n (%)	1614 (10.3)	766 (7.5)	941 (5.3)
Malignancy, n (%)	2957 (18.9)	2100 (20.5)	5168 (29.2)
Smoking (%)			
No	13,216 (84.7)	8697 (84.7)	10,474 (59.2)
Smoke	1172 (7.5)	667 (6.5)	1045 (5.9)
Missing	1217 (7.8)	899 (8.8)	6159 (34.8)
CKD stages			
Stage 3a (GFR=45–59 ml/min per 1.73 m^2)	10,399 (66.6)	7269 (70.8)	10,273 (58.1)
Stage 3b (GFR=30–44 ml/min per 1.73 m^2)	4012 (25.7)	2373 (23.1)	5463 (30.9)
Stage 4 (GFR=15–29 ml/min per 1.73 m^2)	1194 (7.7)	621 (6.1)	1942 (11.0)
Number of encounters in Electronic Health Record	56.3±43.2	47.3±37.8	31.6±36.3
Body mass index (%; kg m^2)			
<18.5	56 (0.36)	166 (1.6)	301 (1.7)
18.5–24.9	1940 (12.4)	3571 (34.8)	4592 (26.0)
25–29.9	4483 (28.7)	4783 (46.6)	5522 (31.2)
30–34.9	4939 (31.7)	785 (7.6)	3133 (17.7)
35–39.9	2219 (14.2)	268 (2.6)	1395 (7.9)
≥40	1501 (9.6)	146 (1.4)	976 (5.5)
Missing	467 (3.0)	544 (5.3)	1759 (10.0)
Albumin (g/dl)	4.2±0.42	4.2±0.40	3.9±0.55
Hemoglobin (g/dl)	13.0±1.7	13.1±1.6	12.6±1.9
Serum triglycerides (mg/dl)	278.8±226.4	143.7±84.2	NA
HDL cholesterol level (mg/dl)	39.7±11.0	55.4±14.7	NA
Use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (%)	12,024 (77.1)	6000 (58.5)	8311 (47.0)
Use of antihypertensives (%)	14,471 (92.7)	8159 (79.5)	11,943 (67.6)
Use of statins (%)	11,584 (74.2)	5818 (56.7)	6109 (34.6)
Use of fibrates (%)	2018 (12.9)	289 (2.8)	687 (3.9)
Proteinuria,[a] n (%)	2648 (30)	834 (17.5)	2105 (29.1)

All variables are $P<0.05$ comparing metabolic syndrome data available versus not available, except African American. Continuous variables compared using t test, and categorical variables compared using chi-square test.
[a]Data missing for 52% of study population.

We noted a higher prevalence (60%) of metabolic syndrome in CKD patients similar to the data from the Chronic Renal Insufficiency Cohort study (prevalence rate of 65%), because these patients have higher prevalence of the individual risk factors of metabolic syndrome (18). In the secondary analysis of the African American Study of Kidney Disease and Hypertension trial (n=842), metabolic syndrome was associated with a 31% increased risk (95% CI=1.03, 1.70) for the composite study end point of decrease in GFR of 50% or 25 ml/min per 1.73 m^2, ESRD, or death (14). However, the associations were attenuated when adjusted for proteinuria (HR=1.16, 95% CI=0.90,

1.50). Recent data from Taiwan reported that the association between metabolic syndrome and kidney disease progression is significant only in the nondiabetic early-stage CKD population and not stages 3 and 4 CKD population (15). Our analysis shows that, in a diverse CKD population, metabolic syndrome is associated with ESRD. However, we also noted that the association between metabolic syndrome and ESRD was attenuated when adjusted for proteinuria. Metabolic syndrome and its components lead to the development of proteinuria, which in turn, leads to progression of kidney disease and development of ESRD (19,20). Hence, it may not be appropriate to adjust
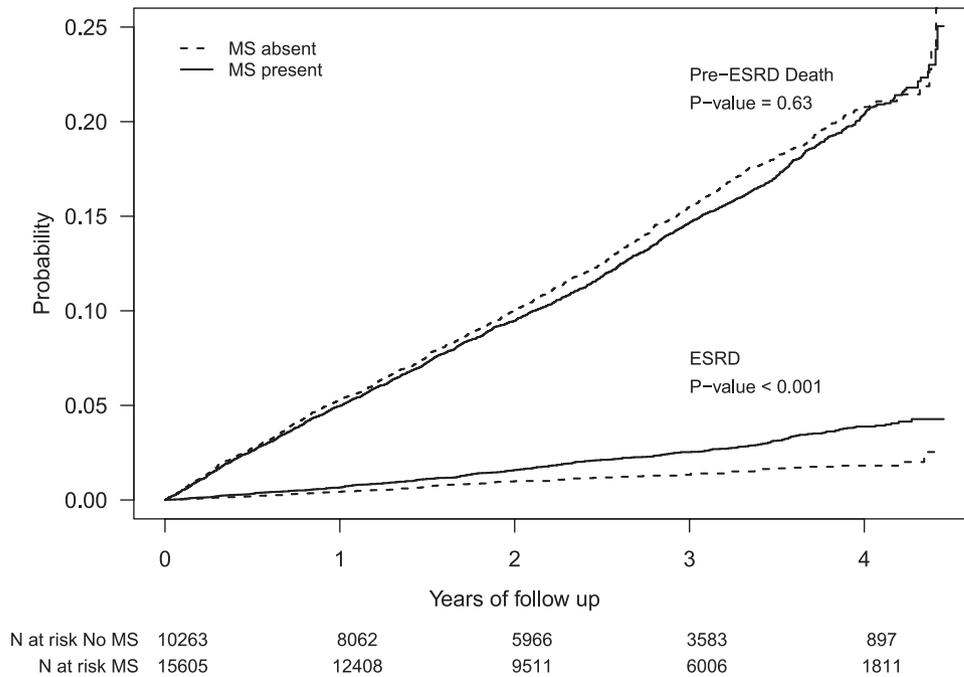
Figure 2. | Cumulative incidence curves for ESRD and death in those patients with and without metabolic syndrome (MS).

for proteinuria in this analysis (causal pathway), and thus, the results of the analysis adjusted for proteinuria should be interpreted with caution. In addition, proteinuria data were not available for 48% of patients, and the effect estimate (although not statistically significant) still suggests that there is potential for harmful renal effects of metabolic syndrome in this cohort (HR=1.28, 95% CI=0.98, 1.60).

Numerous experimental and population-based studies have shown that insulin resistance and hypertension are associated with glomerular injury and glomerulosclerosis (21–23), and thus, as expected, impaired glucose metabolism and hypertension were associated with an increased risk for ESRD in this analysis. However, the relationship between other components, such as elevated serum triglycerides and ESRD, low HDL cholesterol, and all-cause mortality, is novel. Previous studies have examined the relationship between low HDL cholesterol, elevated serum triglycerides, and incident kidney disease (24,25). Although Hanai et al. (26) reported an association between

low HDL cholesterol and progression of kidney disease, the observed relationship between serum triglycerides>150 mg/dl and ESRD in this study has not been reported before. We recently reported an increased risk for death among patients ages<65 years with serum triglycerides≥200 mg/dl (27). Cumulatively, these results might suggest the need for additional studies in this area. Low HDL cholesterol levels have been associated with increased cardiovascular disease and mortality in the general population, but interventional studies aimed to increase HDL levels failed to show any benefits (28,29). Hence, additional studies are warranted on this topic before any valid conclusions are drawn about HDL cholesterol and outcomes in CKD.

Obesity contributes to the development of CKD through different mechanistic pathways that include glomerular hyperfiltration, activation of the renin-angiotensin system, insulin resistance, and direct lipotoxicity (30). There was no association between obesity and ESRD in this analysis, and

Table 2. Associations between metabolic syndrome and all-cause mortality (pre-ESRD) and ESRD among stages 3 and 4 CKD patients (n=25,868)

Metabolic Syndrome Present Versus Absent	Unadjusted HR (95% CI)	Model A × HR (95% CI)	Model B × HR (95% CI)	Model C × HR (95% CI)
ESRD (n=481)	1.89 (1.54, 2.33)	1.60 (1.30, 1.98)	1.53 (1.24, 1.89)	1.33 (1.08, 1.64)
All-cause mortality (n=3345)	0.96 (0.90, 1.03)	1.17 (1.09, 1.25)	1.07 (0.99, 1.15)	1.04 (0.97, 1.12)

HR, hazard ratio; 95% CI, 95% confidence interval; model A, adjusted for age, sex, and race; model B, adjusted variables included in model A plus smoking, malignancy, congestive heart failure, cerebrovascular disease, coronary artery disease, chronic obstructive pulmonary disease, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, LDL cholesterol, hemoglobin, and albumin; model C, adjusted variables included in model B plus baseline estimated GFR.
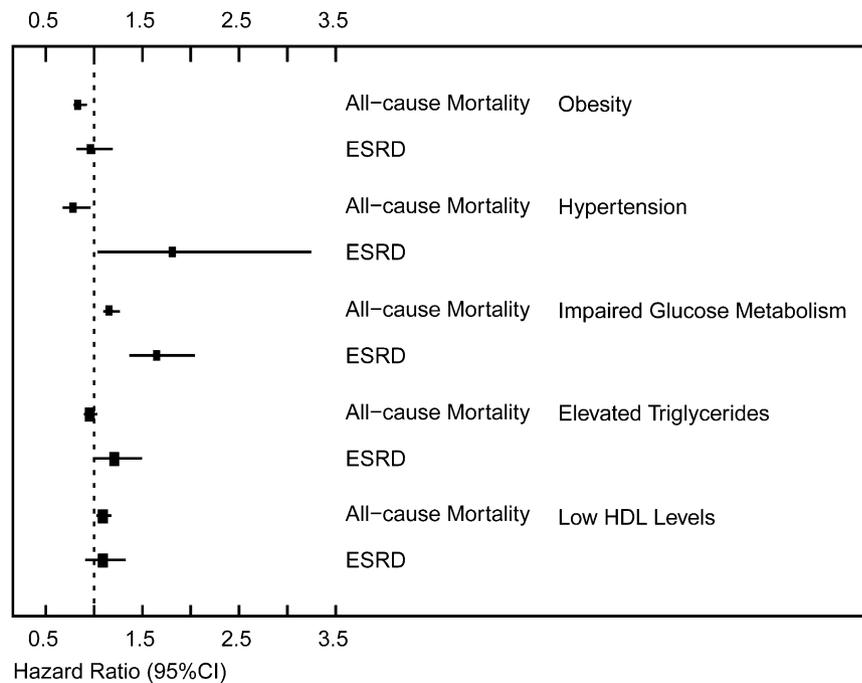
Figure 3. | Associations of individual components of metabolic syndrome with ESRD and mortality.

obesity was associated with a lower risk for all-cause mortality. Visceral or abdominal adiposity, as measured by waist circumference, is associated with inflammation and might be a better predictor for mortality than BMI, which does not distinguish between fat and fat-free mass. Recently, Kramer *et al.* (31) reported differential associations between BMI and waist circumference with mortality in a large cohort of participants with CKD, and each 1-kg/m² increase in BMI was associated with 3% lower risk of death. Similar associations have been reported in renal transplant recipients (32). We did not have waist circumference details given the nature of the study population; however, the revised definitions of the National Cholesterol Education Program-Adult Treatment Panel III suggest using BMI to define metabolic syndrome when waist circumference data are not readily available, and this definition has been used in previous studies.

Several factors, including aging, genetic and environmental factors, and Western lifestyle that includes a high calorie diet and sedentary lifestyle, contribute to the increasing prevalence of metabolic syndrome. Low physical activity levels are common in those patients with CKD and are associated with death in the CKD population (33–35). Although available data support adopting exercise and intentional weight loss in this population, the quality of the available evidence on this topic is suboptimal (36,37). Our results add to the existing body of literature about the harmful effects of metabolic syndrome and support the need for studying the effects of increasing levels of physical activity and adopting a healthier lifestyle in this population (38).

Strengths of this analysis include the large sample size, diverse population, availability of both dialysis and mortality data for the study cohort, and use of competing risk models. Apart from the inherent bias of an observational study, our study is subject to other limitations. Mean follow-up was 2.3 years, and a longer follow-up might have shown a risk for mortality among those patients with metabolic syndrome. A significant interaction was noted in the Cox proportional hazards model of ESRD, suggesting that metabolic syndrome confers a higher risk for ESRD in older but not younger populations. This finding might be attributed to the nature of the CKD registry, and the inception point for the outcomes analysis was the date of inclusion in the CKD registry and not when the patient developed metabolic syndrome. We could not ascertain whether the blood glucose results available were fasting, thereby reducing the number of patients with impaired glucose metabolism or insulin resistance.

A significant portion of the potential study population did not have information to assess the presence of metabolic syndrome and were excluded from the analysis. It is possible that these patients are systematically different from our study population, and as such, results may lack complete external validity. Furthermore, although we were able to adjust for several confounding variables, we lacked data relating to physical activity, diet, socioeconomic status, family history of cardiovascular and kidney disease, and whether the components of metabolic syndrome were well controlled, which might influence the results. The lack of association between metabolic syndrome and mortality in this study should be interpreted with caution. It could be attributed to the inverse association noted with BMI, hypertension, and higher use of cardioprotective medications, such as statins and renin angiotensin blockers, in this population.

In summary, metabolic syndrome is widely prevalent and associated with ESRD but not mortality in a diverse

nondialysis-dependent CKD population. The associations between the individual components of metabolic syndrome and outcomes varied, showing a need for additional investigation into the mechanisms. Furthermore, long-term studies to examine the relationship between metabolic syndrome and mortality in CKD patients are also warranted. Additionally, whether interventions, such as lifestyle modifications, can improve the risk associated with metabolic syndrome on kidney disease progression in those patients with CKD warrants additional study.

Disclosures
None.

References

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038–2047, 2007
2. Mozumdar A, Liguori G: Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. *Diabetes Care* 34: 216–219, 2011
3. Galassi A, Reynolds K, He J: Metabolic syndrome and risk of cardiovascular disease: A meta-analysis. *Am J Med* 119: 812–819, 2006
4. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM: Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol* 49: 403–414, 2007
5. Wu SH, Liu Z, Ho SC: Metabolic syndrome and all-cause mortality: A meta-analysis of prospective cohort studies. *Eur J Epidemiol* 25: 375–384, 2010
6. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 285: 2486–2497, 2001
7. World Health Organization: Definition, Diagnosis, and Classification of Diabetes Mellitus and Its Complications. Report of a WHO Consultation. Available at: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf. Accessed January 28, 2011
8. The International Diabetes Federation Consensus Worldwide Definition of the Metabolic Syndrome. Available at: http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf. Accessed January 28, 2011
9. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr;
International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity: Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; american heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation* 120: 1640–1645, 2009
10. 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
11. Locatelli F, Pozzoni P, Del Vecchio L: Renal manifestations in the metabolic syndrome. *J Am Soc Nephrol* 17[Suppl 2]: S81–S85, 2006
12. Alexander MP, Patel TV, Farag YM, Florez A, Rennke HG, Singh AK: Kidney pathological changes in metabolic syndrome: A cross-sectional study. *Am J Kidney Dis* 53: 751–759, 2009
13. Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD: Metabolic syndrome and kidney disease: A systematic review and meta-analysis. *Clin J Am Soc Nephrol* 6: 2364–2373, 2011
14. Lea J, Cheek D, Thornley-Brown D, Appel L, Agodoa L, Contreras G, Gassman J, Lash J, Miller ER 3rd, Randall O, Wang X, McClellan W; AASK Study Investigators: Metabolic syndrome, proteinuria, and the risk of progressive CKD in hypertensive African Americans. *Am J Kidney Dis* 51: 732–740, 2008
15. Lee CC, Sun CY, Wu IW, Wang SY, Wu MS: Metabolic syndrome loses its predictive power in late-stage chronic kidney disease progression—a paradoxical phenomenon. *Clin Nephrol* 75: 141–149, 2011
16. Navaneethan SD, Jolly SE, Schold JD, Arrigain S, Saupe W, Sharp J, Lyons J, Simon JF, Schreiber MJ Jr, Jain A, Nally JV Jr: Development and validation of an electronic health record-based chronic kidney disease registry. *Clin J Am Soc Nephrol* 6: 40–49, 2011
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009
18. Townsend RR, Anderson AH, Chen J, Gadebegku CA, Feldman HI, Fink JC, Go AS, Joffe M, Nessel LA, Ojo A, Rader DJ, Reilly MP, Teal V, Teff K, Wright JT, Xie D: Metabolic syndrome, components, and cardiovascular disease prevalence in chronic kidney disease: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Nephrol* 33: 477–484, 2011
19. The Microalbuminuria Collaborative Study Group: Predictors of the development of microalbuminuria in patients with Type 1 diabetes mellitus: A seven-year prospective study. *Diabet Med* 16: 918–925, 1999
20. Umegaki H, Haimoto H, Hoshide S, Kario K: Strong association between insulin resistance with urinary albumin excretion in older adults. *J Am Geriatr Soc* 59: 1361–1362, 2011
21. Conway BR, Rennie J, Bailey MA, Dunbar DR, Manning JR, Bellamy CO, Hughes J, Mullins JJ: Hyperglycemia and renin-dependent hypertension synergize to model diabetic nephropathy. *J Am Soc Nephrol* 23: 405–411, 2012
22. Simons JL, Provoost AP, Anderson S, Troy JL, Rennke HG, Sandstrom DJ, Brenner BM: Pathogenesis of glomerular injury in the fawn-hooded rat: Early glomerular capillary hypertension predicts glomerular sclerosis. *J Am Soc Nephrol* 3: 1775–1782, 1993
23. Hoehner CM, Greenlund KJ, Rith-Najarian S, Casper ML, McClellan WM: Association of the insulin resistance syndrome and microalbuminuria among nondiabetic native Americans. The Inter-Tribal Heart Project. *J Am Soc Nephrol* 13: 1626–1634, 2002
24. Lee PH, Chang HY, Tung CW, Hsu YC, Lei CC, Chang HH, Yang HF, Lu LC, Jong MC, Chen CY, Fang KY, Chao YS, Shih YH, Lin CL: Hypertriglyceridemia: An independent risk factor of chronic kidney disease in Taiwanese adults. *Am J Med Sci* 338: 185–189, 2009

25. Muntner P, He J, Astor BC, Folsom AR, Coresh J: Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: Results from the atherosclerosis risk in communities study. *J Am Soc Nephrol* 16: 529–538, 2005

26. Hanai K, Babazono T, Yoshida N, Nyumura I, Toya K, Hayashi T, Bouchi R, Tanaka N, Ishii A, Iwamoto Y: Gender differences in the association between HDL cholesterol and the progression of diabetic kidney disease in type 2 diabetic patients. *Nephrol Dial Transplant* 27: 1070–1075, 2012

27. Navaneethan SD, Schold JD, Arrigain S, Thomas G, Jolly SE, Poggio ED, Schreiber MJ Jr, Sarnak MJ, Nally JV Jr: Serum triglycerides and risk for death in Stage 3 and Stage 4 chronic kidney disease. *Nephrol Dial Transplant* 27: 3228–3234, 2012

28. deGoma EM, Leeper NJ, Heidenreich PA: Clinical significance of high-density lipoprotein cholesterol in patients with low low-density lipoprotein cholesterol. *J Am Coll Cardiol* 51: 49–55, 2008

29. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W; AIM-HIGH Investigators: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 365: 2255–2267, 2011

30. Wahba IM, Mak RH: Obesity and obesity-initiated metabolic syndrome: Mechanistic links to chronic kidney disease. *Clin J Am Soc Nephrol* 2: 550–562, 2007

31. Kramer H, Shoham D, McClure LA, Durazo-Arvizu R, Howard G, Judd S, Muntner P, Safford M, Warnock DG, McClellan W: Association of waist circumference and body mass index with all-cause mortality in CKD: The REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis* 58: 177–185, 2011

32. Kovesdy CP, Czira ME, Rudas A, Ujszaszi A, Rosivall L, Novak M, Kalantar-Zadeh K, Molnar MZ, Mucsi I: Body mass index, waist circumference and mortality in kidney transplant recipients. *Am J Transplant* 10: 2644–2651, 2010

33. Navaneethan SD, Kirwan JP, Arrigain S, Schreiber MJ, Sehgal AR, Schold JD: Overweight, obesity and intentional weight loss in chronic kidney disease: NHANES 1999-2006. *Int J Obes (Lond)* 36: 1585–1590, 2012

34. Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T: Physical activity and mortality in chronic kidney disease (NHANES III). *Clin J Am Soc Nephrol* 4: 1901–1906, 2009

35. Hawkins MS, Sevick MA, Richardson CR, Fried LF, Arena VC, Kriska AM: Association between physical activity and kidney function: National Health and Nutrition Examination Survey. *Med Sci Sports Exerc* 43: 1457–1464, 2011

36. Afshinnia F, Wilt TJ, Duval S, Esmaeili A, Ibrahim HN: Weight loss and proteinuria: Systematic review of clinical trials and comparative cohorts. *Nephrol Dial Transplant* 25: 1173–1183, 2010

37. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S: Weight loss interventions in chronic kidney disease: A systematic review and meta-analysis. *Clin J Am Soc Nephrol* 4: 1565–1574, 2009

38. Heiwe S, Jacobson SH: Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev* 10: CD003236, 2011