Are Patients Who Have Metabolic Syndrome without Diabetes at Risk for Developing Chronic Kidney Disease? Evidence Based on Data from a Large Cohort Screening Population

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Background and Objectives: Recently, metabolic syndrome (MS) was suggested to be an independent risk factor for chronic kidney disease (CKD). This study explored the relationship between MS and risk for development of CKD that is independent of diabetes.

Design, Setting, Participants, & Measurements: The study population consisted of 4607 adult (age >18 yr) individuals who did not have diabetes or CKD at baseline and were successfully followed for 3 yr in the Tehran Lipid and Glucose Study, a prospective, population-based study of risk factors for atherosclerosis and diabetes. Individuals with and without MS at baseline were compared regarding development of new CKD.

Results: A total of 1010 (21.9%) individuals met criteria for MS at baseline. During the follow-up, 38 (3.4%) individuals in MS group and 73 individuals (2.0%) of 3590 people in non-MS group developed CKD (OR = 1.88, 95% CI; 1.26–2.8). After exclusion of individuals with hypertension at baseline (n = 798), 406 people (10.7%) were defined as having MS. After follow-up, 62 (1.82%) people in the MS group and eight (1.98%) people in non-MS group developed CKD (OR = 0.925, 95% CI; 0.446–1.917; P = 0.844).

Conclusions: The results of this study suggest that MS is a cluster of multiple risk factors, and, as a cluster, it is a significant risk for CKD. The risk of MS for developing CKD is highly affected by the presence of diabetes and hypertension, and it seems that clustering of individual risk factors is more plausibly associated with risk for developing CKD than a unique biologic phenomenon.

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Chronic kidney disease (CKD) is a major risk factor for ESRD, cardiovascular disease, and premature death (1–5) and is increasingly recognized as an important public health problem in the United States. Data from the Third National Health and Nutrition Examination Survey (NHANES III) suggest that approximately 8.3 million (4.6%) of adult Americans (20 yr and older) have CKD (1). However, currently only 300,000 patients with CKD have ESRD (6), suggesting that the vast majority of patients with moderate CKD die of other causes, such as atherosclerotic events (7). Some data suggest that metabolic syndrome might be associated with higher risk for CKD. Prevalence of metabolic syndrome, which is characterized by abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, is approximately 20% in the adult US population. It has been estimated that 47 million US adults have metabolic syndrome (8). Cross-sectional as well as two recently reported longitudinal studies have suggested a relationship between the metabolic syndrome and risk for CKD (9–12). The strong impact of diabetes and hypertension in development of CKD in these studies raises the question of whether it is metabolic syndrome or diabetes and hypertension increase the risk for CKD.

In this study, we examined data from Tehran Lipid and Glucose Study (TLGS), a large, community-based, prospective cohort in Tehran, Iran. We hypothesized that among adult individuals with normal or near-normal kidney function at baseline, the metabolic syndrome would be associated with the development of CKD over time.

Materials and Methods

Study Population and TLGS Design

Details of TLGS and its rationale and design have been published previously (13–15). Briefly, TLGS is an ongoing longitudinal study conducted within the framework of a National Project of the Scientific Research Council of Iran. This population-based study includes an assessment of cardiovascular risk factors and disease in residents of Tehran. The study cohort consists of more than 15,000 individuals who were older than 3 yr at study entry. The sampling frame is chosen from urban district 13 of Tehran, a metropolitan city composed of 20 urban districts with a population of more than 7.2 million people. The rationale for choosing district 13 as the sample frame included the following: (*1*) The population that

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resides in that district is relatively stable compared with the other districts of Tehran; (*2*) the medical and health facilities in this district are under the supervision of Shahid Beheshti University of Medical Sciences, which also hosts the Endocrine Research Center, in which the study is designed and managed; (*3*) the health centers of district 13 enjoy a well-developed network of experienced volunteers, who play a critical role in the recruitment of individuals for the study; and (*4*) the age distribution of the population of district 13 are representative of the overall population of Tehran and Iran.

The TLGS is being conducted in multiple phases. Phase 1 included both a population survey and baseline health examinations. The primary objectives of this first phase were to measure the population prevalence of known cardiovascular risk factors, including dyslipoproteinemia, hyperglycemia, obesity, smoking, and hypertension. Using cluster random sampling, samples were selected as follows: (*1*) A list of all households under coverage by three health centers in east of Tehran was prepared; (*2*) households were specified according to each health center; (*3*) the proportion of households under coverage by each health center to the total number of households in the three health centers was determined; and (*4*) lists of all households selected were prepared, and their addresses were determined.

Samples were selected using the random multistage stratified cluster sampling method. Designated residents were sent an invitation requesting their participation. The crude response rate in the TLGS participants was approximately 57.5%. The reasons for no response were investigated, and there was no significant difference between responders and nonresponders (14). Selected people were visited for an interview and medical examination in the Lipid and Glucose Study Unit at the Endocrine Research Center of Shahid Beheshti University of Medical Sciences. Participants were first familiarized with the study objectives and were asked to sign a written consent and bring it to Lipid and Glucose Study Unit after the screening visit. In this section, trained physicians collected data on the medical history, BP, peripheral pulse, and thyroid examination. Trained technicians obtained anthropometric data such as height, weight, and hip and waist sizes. ECG was taken from those aged ≥30 yr. Data were collected through individual interviews and physical examinations and directly stored in a computer database (16). Blood samples were drawn after 10 to 12 h of fasting. Laboratory measurements included lipid profiles, fasting blood sugar, thyroid profile, and serum creatinine.

After baseline medical examinations, study participants are being contacted annually by telephone. Medical events are elicited by trained physicians. After identification of events, confirmatory data are being collected by study physicians by abstracting hospital records and performing in-home physical examinations. Finally, all medical event data are being adjudicated by an outcome committee that consists of an internist, an endocrinologist, a cardiologist, an epidemiologist, and other experts, when needed, to assign a specific outcome for every event.

The original TLGS cohort consists of more than 15,000 individuals who were older than 3 yr at study entry. We conducted our study on 11,001 TLGS participants who were older than 18 at entry. We excluded 596 individuals who had missing data for calculation of creatinine clearance, diabetes, or metabolic syndrome. Patients with CKD (n = 1464) and diabetes at baseline (n = 556) were excluded as well. Of the remaining 8385 people, 4607 were followed for at least 3 yr from 1999 to 2004 (Figure 1).

Definition of Metabolic Syndrome, Diabetes, CKD, and Hypertension

Metabolic syndrome was defined according to the National Cholesterol Education Program Third Adult Treatment Panel guidelines (17). The people who had at least three of the following findings received a diagnosis of metabolic syndrome: (*1*) Waist measurement >88 cm for women or >102 cm for men, (*2*) triglycerides ≥150 mg/dl, (*3*) HDL cholesterol <50 mg/dl for women or <40 mg/dl for men, (*4*) BP ≥130/85 mmHg or the use of BP medications, and (*5*) fasting glucose ≥110 mg/dl (5). Hypertension was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Eval-

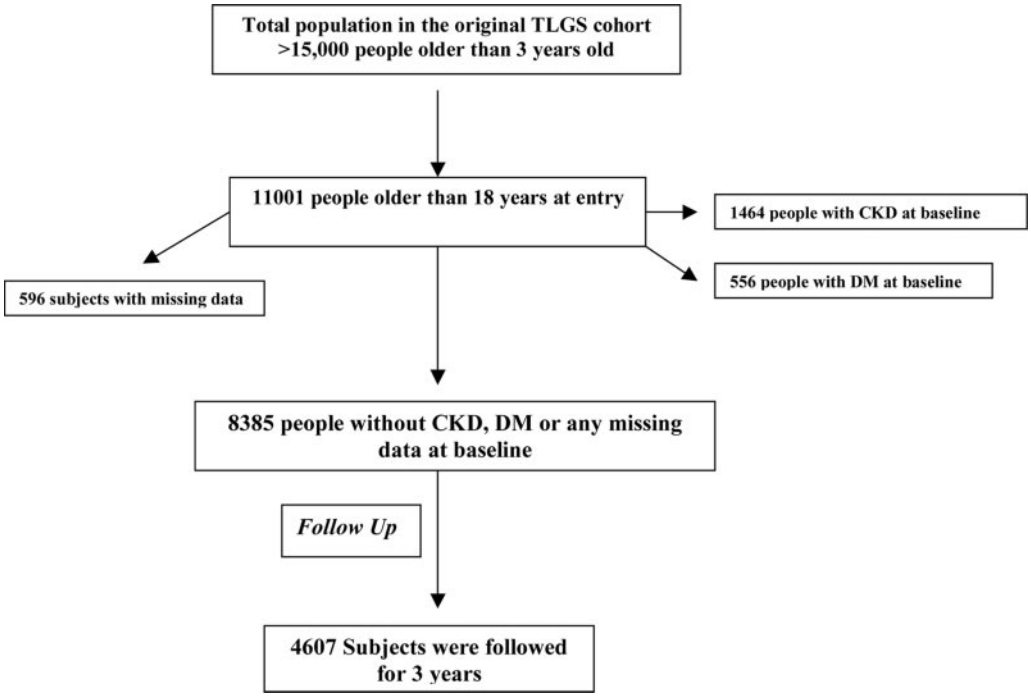

Figure 1. General picture of the studied population. CKD, chronic kidney disease; TLGS, Tehran Lipid and Glucose Study.

uation, and Treatment of High Blood Pressure criteria and also included patients who were taking antihypertensive agents (18). Diabetes was defined according to the American Diabetes Association (two measured fasting blood glucose levels >126 mg/dl) and also included the patients who were taking antiglycemic agents (19). Creatinine clearance was estimated using the Cockroft-Gault equation: Creatinine clearance (ml/min per 1.73 m^2) = [(140 − age in years) × (body weight in kilograms)]/(72 × serum creatinine in mg/dl). This value was multiplied by 0.85 in women. CKD was defined as creatinine clearance <60 ml/min per 1.73 m^2 (20).

Measurement of Other Risk Factors

Total cholesterol (TC) and triglycerides were assayed using enzymatic calorimetric tests with cholesterol esterase plus cholesterol oxidase and glycerol phosphate oxidase, respectively. HDL cholesterol was measured after precipitation of the apolipoprotein B–containing lipoproteins with phosphotungstic acid. LDL cholesterol was calculated from the serum TC, triglycerides, and HDL cholesterol concentrations expressed in mg/dl using Friedewald formula when triglyceride concentration was <400 mg/dl. (21) Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters.

Statistical Analyses

SPSS 10.0 statistical software package (SPSS, Chicago, IL) was used in statistical analysis. Statistical significance was set at $P \leq 0.05$. Difference for continuous variables was assessed by using the t test, whereas difference for categorical variables was assessed with the χ^2 test. Bivariate and logistic regression analyses were used to determine the odds ratio (OR) of incident CKD on the basis of metabolic syndrome.

Results

Baseline data for 4607 people who did not have diabetes and CKD at baseline and were followed for a minimum of 3 yr were analyzed (Table 1). Gender data revealed that 1924 individuals were male (41.8%) and 2683 were female (58.2%). Mean age of the population was 39.3 (SD 12.9). Of the total, 1010 (21.9%) patients at baseline met criteria for metabolic syndrome. Patients with metabolic syndrome were older than the group without metabolic syndrome at baseline. As expected, patients with metabolic syndrome had higher BP, BMI, triglyceride, total cholesterol, and LDL cholesterol and lower HDL cholesterol compared with the people without metabolic syndrome. Overall, a small percentage of the people were receiving medications, although after 3 yr of follow-up, more people were taking medications. Creatinine clearance was not significantly different at baseline between people with and without metabolic syndrome.

After 3 yr of follow-up, of the 4067 individuals without CKD and diabetes at baseline, 111 (2.4% of the total studies population) progressed to CKD stage 3, 38 (3.4% of the people with MS at base) of whom were in the metabolic syndrome group with a population of 1010, and 73 (2.0% of the people without MS at base) of whom were in the non–metabolic syndrome group, with a population of 3597 (OR 1.88; 95% confidence interval [CI] 1.26 to 2.8; $P = 0.002$; Table 2, Figure 2). When we used presence of four criteria for diagnosis of metabolic syndrome, 136 patients had a diagnosis of metabolic syndrome at baseline (Table 2). Seven (5.1%) patients in this group developed CKD. Of 4471 patients who did not have metabolic syndrome, on the basis of presence of four criteria, 104 (2.3%) developed CKD (OR 2.27; 95% CI 1.03 to 4.99; $P = 0.045$). After 3 yr of follow-up, 59 patients developed diabetes, and just one patient from this subgroup developed CKD.

Baseline characteristics of patients who developed CKD are summarized in Table 3. Of the parameters that were different between the CKD and non-CKD groups, it is important to note that the incidence of metabolic syndrome was significantly greater in the group that developed CKD.

In multivariate analysis, hypertension was the strongest predictor of CKD among the metabolic syndrome traits (OR 3.4; 95% CI 2.2 to 5.4; $P < 0.001$; Table 4). After adjustment on the basis of age and gender, the influence of hypertension was wiped out (OR 1.2; 95% CI 0.75 to 1.93; $P = 0.44$). To exclude the influence of hypertension, we examined the impact of metabolic syndrome on the development of CKD in 3809 people without hypertension. Of these, 406 (10.7%) were defined as having metabolic syndrome and 3403 (89.3%) did not have criteria for metabolic syndrome. After 3 yr of follow-up, 70 (1.83%) individuals developed new CKD, 62 (1.82%) of whom were in the metabolic syndrome group and eight (1.98%) of whom in the non–metabolic syndrome group (OR 0.925; 95% CI 0.446 to 1.917; $P = 0.844$; Table 5).

We also analyzed the data for 685 patients with CKD and without diabetes at baseline to determine whether metabolic syndrome would have any influence on this group. A total of 219 (32%) individuals in this group had metabolic syndrome at baseline. In 224 of 685 individuals with CKD at baseline, CKD stage improved from stage 3 (30 to 59 ml/min per 1.73 m^2) to stage II (60 to 89 ml/min per 1.73 m^2), and of those, 71 (31.7%) had metabolic syndrome at baseline. A total of 461 individuals stayed in CKD stage 3, including 148 (32.1%) with metabolic syndrome at baseline. In other words, there was not any difference regarding the prevalence of metabolic syndrome between the people who stayed in CKD stage 3 or improved to CKD stage 2 in people with CKD stage 3 at base line.

Discussion

TLGS is a screening population. Overall, in entry, despite having high prevalence of cardiovascular risk factors, the use of medications was low. For example, the prevalence of elevated BP in the TLGS population was 22%, although just 36% of the hypertensive individuals were receiving BP-lowering agents. Of those who were being treated for hypertension, only 40% had adequately controlled BP (14). The prevalence of high cholesterol and low HDL and high triglyceride is 19.3, 32, and 5.3%, respectively in the TLGS population (22). That the TLGS population is an undertreated population makes TLGS an ideal cohort for outcome epidemiologic studies. The results of this study support previous data that metabolic syndrome, even without diabetes, is a risk factor for development of CKD, but eliminating the effect of hypertension almost washed the effect of metabolic syndrome on development of CKD.

We used Cockroft-Gault, rather than the Modification of Diet in Renal Disease (MDRD) equation, because our population had relatively preserved kidney function and the MDRD equa-

Table 1. Characteristics of patients who had been followed for 3 yr at baseline and after 3 yr of follow-up[a]

Characteristic	Baseline Characteristics of Lost Individuals without Diabetes and CKD	Baseline Characteristics of All Followed Individuals without Diabetes and CKD	Characteristics of Individuals with MS at Baseline	Characteristics of Individuals without MS at Baseline	Follow-Up Characteristics	P[b]
n	3778	4607	1010	3597	4607	
Age (yr; mean [SD])	34.8 (12.7)	39.3 (12.9)	48.0 (12)	36.5 (12.2)	42.7 (12.8)	<0.001
Male gender (%)	42.1	41.8	47.6	40.1	41.8	<0.001
Hypertension (%)	13.5	17.2	59.8	5.2	15.4	<0.001
Obesity (BMI ≥30; %)	20.5	24.5 (M = 16, F = 30)	44.4 (M = 29, F = 57)	19 (M = 11, F = 24)	30.6	<0.001
SBP (mmHg; mean [SD])	115 (16)	117.3 (16.8)	135.6 (17.8)	122.2 (12.4)	115.4 (17.2)	<0.001
DBP (mmHg; mean [SD])	76.3 (10.3)	77.6 (10.3)	89.2 (8.8)	74.4 (8.2)	74.9 (10.4)	<0.001
BMI (mean [SD])	26.1 (5)	27.0 (4.7)	29.9 (4.0)	26.1 (4.5)	27.9 (4.8)	<0.001
Waist circumference (cm; mean [SD])	85.3 (12.8)	87.7 (12.4)	96.8 (9.8)	85.1 (11.7)	92.3 (12.3)	<0.001
Laboratory values						
triglycerides (mg/dl; mean [SD])	151.6 (108.6)	164.5 (105)	229 (126.7)	146.4 (90)	159.0 (102.8)	<0.001
total cholesterol (mg/dl; mean [SD])	195.5 (43.6)	205 (44.7)	225.6 (45.7)	199.2 (42.6)	191.7 (40.3)	<0.001
HDL cholesterol (mg/dl; mean [SD])	42.1 (10.8)	42.0 (10.6)	38.9 (8.7)	42.8 (10.9)	38.5 (10.0)	<0.001
LDL cholesterol (mg/dl; mean [SD])	123.7 (36.5)	130.4 (36.8)	142.6 (38.1)	127.2 (35.7)	122.7 (33.7)	<0.001
FBS (mg/dl; mean [SD])	89 (9.7)	90.0 (12.3)	96.3 (12.1)	88.2 (8.8)	92.4 (16.6)	<0.001
creatinine (mg/dl; mean [SD])	1.03 (0.15)	1.04 (0.15)	1.07 (0.16)	1.03 (0.15)	0.98 (0.15)	<0.001
CrCl (ml/min per 1.73 m^2; mean [SD])	89.9 (19.4)	87.8 (18.6)	87.9 (21.3)	87.8 (17.7)	103.4 (24.6)	0.854
CKD stages 1 and 2 (%)		100	100	100	97.6	
CKD stage 3 (%)		0	0	0	2.4	
CKD stages 4 and 5 (%)		0	0	0	0	
Medications (%)						
β blocker	3.4	5.3	13.7	3.1	8.1	<0.001
calcium-channel blocker	0.8	1.1	2.9	0.6	1.5	<0.001
diuretic agent	1.1	1.1	2.4	0.7	1.4	<0.001
ACEI	0.8	0.7	2.5	0.2	1.5	<0.001
vasodilator	0.5	0.4	1.2	0.1	0.6	<0.001
aspirin	1.4	2.3	6.1	1.3	4.3	<0.001
antihyperglycemic agent	0	0	0	0	0.6	–
lipid lowering	0.8	1.1	2.9	0.6	1.8	<0.001

[a]ACEI, angiotensin-converting enzyme inhibitors; BMI, body mass index; CKD, chronic kidney disease; CrCl, creatinine clearance; DBP, diastolic BP; FBS, fasting blood glucose; MS, metabolic syndrome; SBP, systolic BP.

[b]Comparison between the patients who had metabolic syndrome at baseline and the patients who did not have metabolic syndrome at baseline.

Table 2. Incidence of CKD after 3 yr of follow-up in MS and non-MS groups, based on three or four criteria for diagnosis of metabolic syndrome[a]

MS at Baseline	Non-MS at Baseline	New CKD after Follow-Up	New CKD in MS Group after Follow-Up	New CKD in Non-MS Group after Follow-Up	OR (95% CI)	*P*
1010[b]	3597	111 (2.4%)	38 (3.8%)	73 (2.0%)	1.88 (1.26 to 2.8)	0.002
136[c]	4471	111 (2.4%)	7 (5.1%)	104 (2.3%)	2.27 (1.03 to 4.99)	0.045

[a]CI, confidence interval; OR, odds ratio.
[b]Presence of three criteria for diagnosis of MS.
[c]Presence of four criteria for diagnosis of MS.

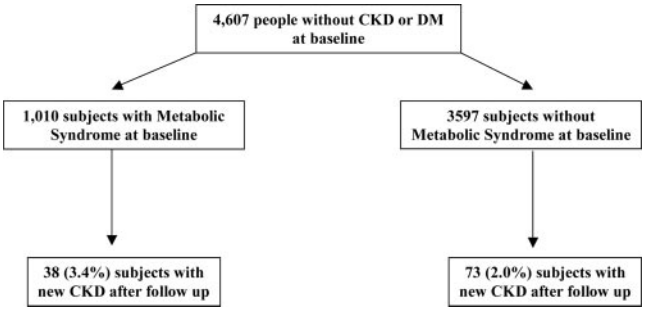

Figure 2. New-onset CKD in individuals with and without metabolic syndrome at baseline.

tion may not be as reliable for estimating GFR in the normal range. Originally, the MDRD equations (23,24) were derived from 1628 study participants who had mild to moderate renal failure (mean serum creatinine 2.3 mg/dl), and the Cockroft-Gault equation (25) was derived from 249 individuals with serum creatinine values ranging from 0.99 to 1.78 mg/dl, which more closely resembles our population. It has been shown that in healthy populations, the MDRD equation underestimates GFR (26) and performs less well as an estimate of GFR compared with the Cockroft-Gault equation (27).

The results of this study support the previous data that metabolic syndrome, even without diabetes, is a risk factor for development of CKD, but it also shows that after elimination of the effect of diabetes and hypertension, the risk for CKD drops. In other words, combination of multiple risk factors plays more of a role in the risk for CKD than any one individual risk factor. Increased prevalence of obesity in the United States makes the metabolic syndrome a common health problem in the future (28). However, data on the relationship between the metabolic syndrome and risk for CKD are limited. In the study by Hoehner *et al.* (29), which was a cross-sectional study on an American Indian population from Wisconsin and Minnesota, it was shown that the metabolic syndrome profile and microalbuminuria are correlated. Individuals with three or more metabolic syndrome traits had 2.3-fold increased OR for microalbuminuria compared with a control group without the syndrome. In two different studies, by Palaniappan *et al.* (30) and Chen *et al.* (10), data from the NHANES III database were examined. Both studies found an association between metabolic syndrome and microalbuminuria. Chen *et al.* also discovered a significant correlation between number of metabolic syndrome factors and GFR $\leq$60 ml/min per 1.73 m^2. Individual traits that confer greatest risk were hypertension and hyperglycemia (10) and had the greatest impact on the results of this study. We also showed that diabetes and hypertension play the major role in development of CKD in patients with metabolic syndrome. The strong impact of diabetes and hypertension on kidney is not surprising, and it has also been supported by the others (31,32).

Diabetes is a strong and known risk factor for development of CKD (33,34). Also, individuals with evidence of the metabolic syndrome are at risk for developing type 2 diabetes (35). 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 hypertension and diabetes, which are the two known risk factors for CKD initiation and progression, rather than an independent effect.

Hypertension plays an important role on development of CKD. That, expectably, individuals in the metabolic syndrome group in our study had a significantly higher prevalence of hypertension raises the question about the role of hypertension. In this study, after exclusion of hypertensive people, there was no difference regarding development of CKD between those with and without CKD. In other words, the people who had metabolic syndrome and did not have diabetes and hypertension did not have increased risk for developing new CKD. In the study by Kurella *et al.* (11), even after adjustment for diabetes status and BP control, metabolic syndrome independently contributed to CKD development. They estimated GFR in an analytic cohort of 10,096 individuals who had neither CKD nor diabetes at entry. Of all patients without diabetes, 21% (n = 2110) met the criteria for metabolic syndrome at baseline. Ten percent of individuals with metabolic syndrome developed CKD (estimated GFR $\leq$60 ml/min per 1.73 m^2) compared with 4% of individuals without metabolic syndrome. Even after correction for possible confounding variables, the difference remained significant. After adjustment for BP, the OR was dropped and the lower limit of OR became 1.08, which makes it very weak. The prevalence of nondiabetic metabolic syndrome was almost the same in the study by Kurella *et al.* and ours (21 *versus* 21.9%). The studied people by Kurella *et al.* had larger waist circumference in both metabolic syndrome and non–metabolic syndrome groups at baseline than ours (92.8 and 105.5 *versus* 85.1 and 96.8 cm in non–metabolic syndrome and metabolic syndrome groups, respectively). BMI

Table 3. Characteristics of individuals who developed CKD compared with individuals who did not develop CKD

Characteristic	Developed CKD	Did Not Develop CKD	*P*
n	111	4496	
Age (yr)	56.0 (10.7)	38.6 (12.6)	<0.001
Male gender (%; mean [SD])	41.4	41.7	0.945
Hypertension (%)	37.0	16.7	<0.001
SBP (mmHg; mean [SD])	131.7 (23.8)	116.9 (16.5)	<0.001
DBP (mmHg; mean [SD])	80.4 (11.9)	77.6 (10.3)	0.004
BMI (mean [SD])	26.0 (4.3)	26.9 (4.7)	0.043
Waist circumference (cm; mean [SD])	87.0 (11.8)	87.7 (12.4)	0.539
MS (%)	34.2	21.6	0.002
Laboratory values (mean [SD])			
triglycerides (mg/dl)	173.0 (92.8)	164.3 (105.3)	0.387
total cholesterol (mg/dl)	220.7 (49.4)	204.6 (44.5)	<0.001
HDL Cholesterol (mg/dl)	42.3 (9.9)	41.9 (10.6)	0.771
LDL Cholesterol (mg/dl)	143.4 (40.5)	130.0 (36.6)	<0.001
FBS (mg/dl)	92.2 (12.0)	89.9 (10.1)	0.021
creatinine (mg/dl)	1.04 (0.14)	1.04 (0.15)	0.795
CrCl (ml/min per 1.73 m^2)	66.0 (6.1)	88.32 (18.4)	<0.001

Table 4. OR for developing CKD after 3 yr of follow-up by individual MS traits

Trait	OR (95% CI)	*P*
Low HDL	1.002 (0.983 to 1.021)	0.843
Elevated triglycerides	1.000 (0.999 to 1.002)	0.608
Hypertension	3.447 (2.215 to 5.365)	<0.001
Impaired fasting glucose	1.018 (0.999 to 1.037)	0.067
Abdominal obesity	0.973 (0.995 to 0.991)	0.003

at baseline was also slightly higher in the metabolic syndrome group in the study by Kurella *et al.* than in ours. Also, there was significant difference in baseline kidney function between people with and without metabolic syndrome in the study by Kurella *et al.*, but the difference was NS in our studied population. They had an older population with a mean age of 53.7 than our population with a mean age of 39.3. There was 20% black population in the study by Kurella *et al.*, but our studied population consisted of just white individuals. They also had a longer follow-up period than we did. Probably the most important different between the studied population by Kurella *et al.* and ours, though, is higher systolic and diastolic BP in our population. The baseline systolic and diastolic BP were higher in both metabolic syndrome and non–metabolic syndrome groups in our population. Longer follow-up in the study by Kurella *et al.* can explain the higher incidence of CKD in their population compared with ours. Probably hypertension played a stronger role in development of CKD in our population than in the population of Kurella *et al.*, and obesity was more important in the Kurella *et al.* population. This may explain why after removing patients with hypertension from our population, the incidence of CKD in the follow-up population was not different between the metabolic syndrome and non–metabolic syndrome groups at baseline in our studied population. The study by Chen *et al.* (10) may explain the probable stronger role of obesity in development of CKD in the population of Kurella *et al.* This can be supported by the fact that, in that study, the effect of adjustment for BMI on decreasing the OR was more than the adjustment for hypertension.

In a recent Japanese cohort study by Ninomiya *et al.* (12), after 5 yr of follow-up, the risk for new CKD in people with metabolic syndrome was significantly higher than in the people without metabolic syndrome (OR 2.33; 95% CI 1.47 to 3.69). After elimination of those with diabetes, there still was significant risk for development of CKD. Even after adjustment for hypertension, the results stayed significant. It is important to know that in the last adjustment of that study, the patients with

Table 5. Incidence of CKD after 3 yr of follow-up, in MS and non-MS groups after exclusion of hypertensive individuals at baseline

MS at Baseline	Non-MS at Baseline	New CKD after Follow-Up	New CKD in MS Group after Follow-Up	New CKD in Non-MS Group after Follow-Up	OR (95% CI)	*P*
406 (10.7%)	3403 (89.3%)	70 (1.8%)	8 (1.97%)	62 (1.82%)	0.925 (0.446 to 1.917)	0.844

diabetes were not eliminated. This may explain the difference between the findings in their and our study. They also showed that with decreasing the number of metabolic syndrome criteria, the risk for CKD decreases.

The results of our study, in combination with those of Kurella *et al.* (11) and Ninomiya *et al.* (12), corroborate conclusions derived from studies with cross-sectional designs, which suggested that metabolic syndrome is a risk for CKD. It seems that clustering of the risk factors in metabolic syndrome, especially diabetes and hypertension, makes metabolic syndrome a risk for development of CKD. The mechanism by which metabolic syndrome causes kidney injury is not well understood. In fact, metabolic syndrome is a combination of multiple cardiovascular risk factors, all of which need to be treated (36).

Our study has multiple limitations. First, the results may be biased because of the people who did not show up for follow-up. Considering that the lost people over the course of follow-up had less cardiovascular risk factors makes this probable bias less highlighted. They were younger, less obese, and less hypertensive and had a better lipid profile compared with the people who were followed successfully (Table 1). Short period of follow-up and overall young study population are the other important limitations of our study. However, the large number of individuals studied and the presence of multiple untreated cardiovascular risk factors in the studied population are the two major strong points of the study.

Conclusions

Our findings support that metabolic syndrome is a cluster of multiple risk factors that is highly affected by the diabetes and hypertension. It seems that clustering of individual risk factors in metabolic syndrome (primarily diabetes and hypertension) is more plausibly associated with risk for development of CKD than a unique biologic phenomenon. To prevent the negative outcomes of metabolic syndrome, patients with hypertension and hyperglycemia should be treated aggressively to prevent CKD as well as other extrarenal disease manifestations of hypertension and diabetes. Because of the lack of intervention trials, it is difficult to be certain whether treatment of other components of the metabolic syndrome will necessarily have an impact on CKD progression.

Disclosures

None.

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See the related editorial, "Metabolic Syndrome: An Emerging Threat to Renal Function," on pages 869–871.