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Metabolic syndrome components as markers to prognosticate the risk of developing chronic kidney disease: evidence-based study with 6492 individuals

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ABSTRACT

Objective The global prevalence of metabolic syndrome (MetS) appears to be increasing and the impact of this condition on potential comorbidities such as cardiovascular disease is high. Chronic kidney disease (CKD) is also a potential comorbidity of MetS but the method of screening for this is somewhat controversial. Thus, predictive markers that can predict the risk of developing CKD are warranted for identification of patients with MetS at an increased risk.

Research methods/patients We investigated the occurrence of CKD in 6492 individuals, either with or without MetS.

Results Our results showed that the prevalence of CKD was markedly higher in those individuals with MetS, and increased progressively with the number of MetS components and age. Waist circumference, triglycerides and high-density lipoprotein cholesterol were significantly ($p<0.05$) associated with altered levels of urea nitrogen, glomerular filtration rate and creatinine, and were related to the increased risk of CKD (eg, OR 1.293 (95% CI 1.10 to 1.52; p=0.002)). The relative risk of CKD remained statistically significant for uric acid following multivariate analyses and adjusting for MetS-associated factors.

Conclusions Our data demonstrated the association of MetS components with CKD in our population and revealed that susceptibility to CKD was increased with the number of defining features of MetS. These findings prompt prospective studies to determine the impact of preventing and detecting MetS on the risk of developing CKD.

INTRODUCTION

Chronic kidney disease (CKD) is a common condition[1–3] that often progresses to end-stage renal disease.[3] CKD is associated with an increased risk of developing cardiovascular disease (CVD)[4] and metabolic syndrome (MetS).[5] Strategies for early detection and prevention could improve the outcome of the future burden of CKD and CVD, and their associated mortality.

MetS is characterised by abdominal obesity, dyslipidaemia, hypertension and impaired glucose tolerance, and is associated with an increased risk of developing CVD, diabetes and related diseases.[6] There is evidence for an association between MetS and CKD in adults from the USA,[7 8] China,[9] Thailand,[10] Nepal[11] and Japan.[5] Tanaka and colleagues investigated the prevalence of CKD and its relationship with metabolic risk factors. They showed that MetS was a significant determinant of CKD (adjusted OR 1.537 and 95% CI 1.277 to 1.850, $p<0.0001$), and there was a positive relationship between the number of features of MetS and the prevalence of CKD.[5]

The number of patients with MetS is increasing, therefore identification of patients who might develop CKD is warranted. Thus detection and treatment of MetS may be a strategy for prevention of CKD. Moreover, the relationship between MetS and CKD has not been extensively studied in the Iranian population, a group that has a high prevalence of MetS and obesity. Therefore we explored the association of MetS and risk of developing CKD in 6492 patients with and without MetS.

MATERIALS AND METHODS

Phenotypic definition of MetS

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and International Diabetes Federation (IDF) guidelines were used to define MetS.

Phenotypic definition of CKD

CKD was defined, using National Kidney Foundation guidelines, as a glomerular filtration rate (GFR) <60, which was calculated by MDRD (Modification of Diet in Renal Disease) formula, as described previously.[10]

Population

In total, 6492 individuals (2175 with and 4317 without MetS, respectively) were recruited from Mashhad University of Medical Science (MUMS); these individuals had no known history of infectious diseases or C reactive protein (CRP) concentrations of >10 mg/L and were without a family history of stroke, myocardial infarction and diabetes mellitus. Informed consent was obtained from all participants using protocols approved by the Ethics Committee of the MUMS.

Anthropometric and biochemical measurements

Anthropometric parameters (eg, height, body weight, body mass index (BMI), waist circumference (WC) and hip circumference) and biochemical factors

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Table 1 Clinical characteristics of the individuals with and without MetS

Characteristics	Without MetS (n=4317)	With MetS (n=2175)	p Value
Age, year	46.8±8.1	50.4±7.9	<0.001
Gender, N (%), men	2979 (46.2)	924 (27.8)	<0.001
Body mass index (kg/m^2)	26.6±4.4	30.3±4.3	<0.001
Weight (kg)	69.2±12	76.8±12.9	<0.001
Height (m)	1.6±0.12	1.58±0.10	<0.001
Total cholesterol (mg/dL)	186.3±36.5	201.1±42.1	<0.001
Low-density lipoprotein cholesterol (mg/dL)	115.3±33.6	118.2±39.7	<0.001
hs-CRP (mg/dL)	3.8±0.87–2.9	5.9±1.2–4.6	<0.001
High-density lipoprotein cholesterol (mg/dL)	44.5±10.2	39.6±8.3	<0.001
Systolic blood pressure (mm Hg)	116.4±15.7	132±19.3	<0.001
Diastolic blood pressure (mm Hg)	76.2±10.1	84.7±11.4	<0.001
Waist circumference (cm)	91.3±12.2	101.9±10.4	<0.001
Fasting plasma glucose (mg/dL)	83.7±2.6	110±5.2	<0.001
Triglyceride (mg/dL)	114.1±75.1	197.3±31.2	<0.001
Uric acid	4.5±1.58	4.9±1.45	<0.001
Elevated creatinine (%)	3.1±0.6	4.9±1.2	<0.001
Urea nitrogen (mg/dL)	12.9±4	13±4.5	0.429
eGFR (mg/min per 1.73 m^2)	89.3±24.3	88±27.1	0.05
CKD (%), ATP III	9.9±0.9	12.5±1.6	<0.001
CKD (%), IDF	7.6±1.3	11.6±2.2	<0.001

Values are expressed as mean±SD or median and IQR for normally or non-normally distributed variables, respectively. For normally distributed variables, the Student t test was used to compare the clinical characteristics and baseline demographics between the groups, while Bonferroni correction was considered for multiple comparisons. The Mann-Whitney U test was used for not normally distributed.
CKD was defined as estimated GFR<60 mL/min/1.73 m^2. GFR was calculated by MDRD formula [eGFR: 186×serum creatinine (mg/dL)$^{-1.154}$×age$^{-0.203}$×(0.742 if female)]. Elevated serum creatinine was defined as ≥1.14 mg/dL in men and ≥0.97 mg/dL in women, as described previously.[7]
ATP III, Adult Treatment Panel III; CKD, chronic kidney disease; GFR, glomerular filtration rate; hs-CRP, high-sensitivity C reactive protein; IDF, International Diabetes Federation; MDRD, Modification of Diet in Renal Disease; MetS, metabolic syndrome.

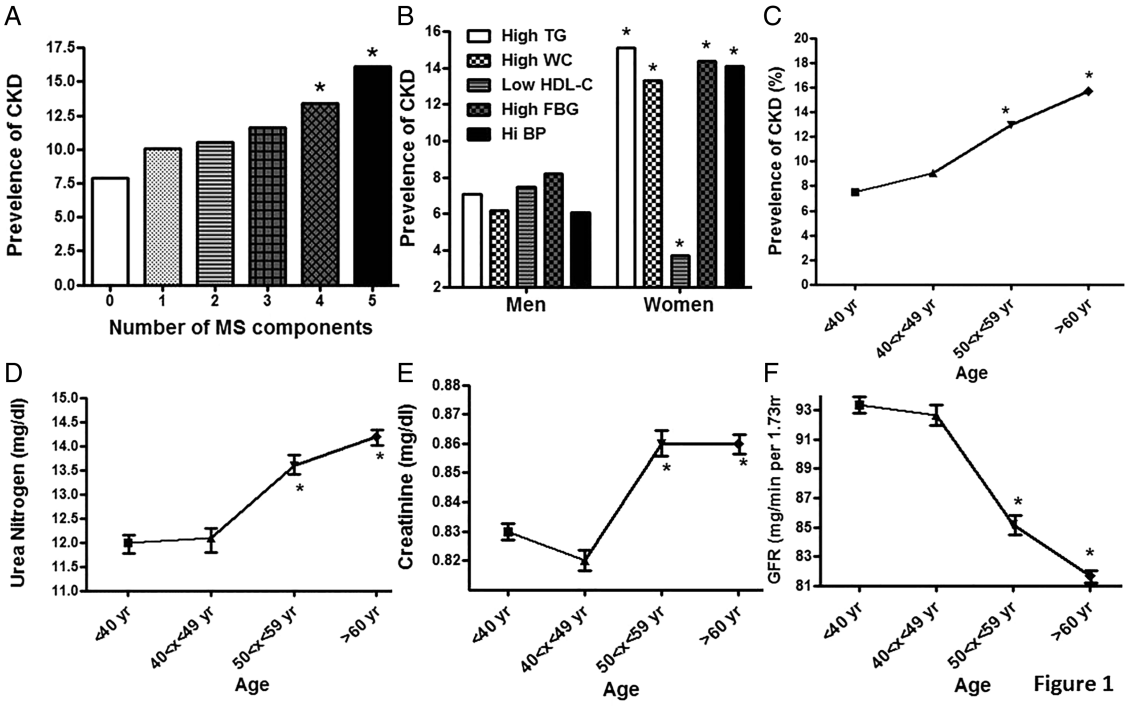

Figure 1 Prevalence of chronic kidney disease (CKD) in patients with metabolic syndrome (MetS). (A and B) Prevalence of CKD with the number of the MetS components and (C–F) age. CKD was defined as an estimated-glomerular filtration rate (GFR) <60 mL/min. The MetS components include waist circumference (WC) >102 cm in men or >88 cm in women; serum triglyceride (TG) >1.70 mmol/L (150 mg/dL); high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L (40 mg/dL) in men or <1.30 mmol/L (50 mg/dL) in women; blood pressure (BP) >130/85 mm Hg; or plasma glucose >6.11 mmol/L (110 mg/dL). *p<0.05 (FBG, fasting blood glucose).

(including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG), CRP, fasting blood glucose (FBG), urea nitrogen and creatinine) were measured as described previously.[12]

Statistical analysis

Data were calculated using SPSS V.20 software (SPSS Inc). Normality of distribution was determined using the Kolmogorov-Smirnov test. Descriptive statistics including mean, frequency and SD were determined for all variables, and expressed as mean±SD for normally distributed variables (or as the median±IQR for not normally distributed variables). For normally distributed variables, the Student t test was used to compare the clinical characteristics and baseline demographics, while Bonferroni correction was considered for multiple comparisons. The Mann-Whitney U test was used for continuous variables if they were not normally distributed. χ^2 or Fisher exact tests were used for categorical variables. Logistic regression analysis was used to calculate association of CKD and MetS factors. Multivariate analysis was then undertaken for the variables. All the analyses were two-sided and statistical significance was set at $p<0.05$.

RESULTS

Characteristics of the population

The characteristics of the population with and without MetS are reported in table 1. Not surprisingly, patients with MetS had a significantly ($p<0.05$) higher levels of BMI, TG, systolic/diastolic blood pressure, LDL-C, high-sensitivity (hs) CRP and FBG, while the levels of HDL-C were lower in the MetS group compared to the control group (table 1).

Relationship between MetS and the prevalence of CKD

In order to investigate the association of CKD with MetS, we determined the levels of estimated GFR (eGFR), creatinine and urea nitrogen in all samples. As shown in table 1, individuals with MetS had a significantly ($p<0.05$) higher level of creatinine compared to the control group. However, this difference in urea nitrogen level was not statistically significant between groups ($p=0.429$). Moreover, patients with MetS had a trend towards a significantly ($p=0.05$) lower eGFR level compared to the patients without MetS (table 1).

As shown in table 1, the prevalence of CKD was significantly ($p<0.001$) higher in the MetS group with respect to the control group. In particular, we observed that 12.5% of the patients with MetS had CKD. In addition, there was a significant dose–response association between the number of MetS components and the prevalence of CKD ($p<0.05$, figure 1A, B). Generally, the prevalence of CKD was higher in women than in men (figure 1B). We also observed that the prevalence of CKD increased by age (figure 1C–E). Levels of urea nitrogen and creatinine were significantly enhanced by increasing of age (figure 1C, D), while the eGFR level was reduced ($p<0.05$; figure 1E).

Moreover, we observed that the mean levels of urea nitrogen and eGFR were significantly higher in patients with hypertriglyceridemia than in those with normal TGs, while the creatinine level was markedly associated with blood pressure, WC, BMI and hs-CRP in the MetS group. The eGFR level had an inverse relationship with high blood pressure in patients with MetS (table 2). In addition, WC was significantly ($p<0.05$) related to the urea nitrogen, GFR and creatinine levels (table 2).

To further explore the association of CKD with MetS, univariate and multivariate analyses were employed (table 3). These analyses showed that CKD was associated with specific components of MetS (including HDL-C, WC) as well as with age, gender and MetS, using ATP III as well as IDF definitions. Of note, MetS defined by ATP III and IDF was significantly correlated with increased prevalence of CKD with ORs of 1.293 (95% CI 1.10 to 1.52; $p=0.002$) and 1.526 (95% CI 1.231 to 1.892; $p<0.001$), respectively. Moreover, logistic regression analysis was conducted with respect to age, sex, TC and BMI to investigate the association of CKD with MetS factors. This analysis illustrated the association of only uric acid with an increased susceptibility to CKD (table 3).

DISCUSSION

The present study demonstrates a significant association between certain MetS components and increased prevalence of CKD in the general adult population of Iran. Moreover, we observed that CKD prevalence increased progressively with the presence of an increasing number of MetS components and age.

Several studies have shown the relationship between insulin resistance and MetS, and risk of CKD.[5 7–10] In particular, Chen *et al*[7] reported that MetS was associated with a 2.60-fold and

Table 2 Relationship between CKD and MetS compounds in the MetS group

	CKD		
MetS-associated factor	**Urea nitrogen**	**Creatinine**	**eGFR**
Normal TG	12.7±4	0.84±0.2	84.4±23.8
Hypertriglyceridemia	13.2±4.5	0.85±0.2	89.8±28
p Value	0.027	0.326	<0.001
Normal SBP	12.9±4.6	0.83±0.2	90.1±29.2
High SBP	13.1± 4.6	0.85±0.2	87±26
p Value	0.278	0.043	0.019
Normal HDL-C	13±4.8	0.85±0 .2	92.1±31
Low HDL-C	13± 4,5	0.84±0 .2	87±26.4
p Value	0.861	0.847	0.011
Normal FBG	13±4.2	0.87±0.2	88.73±24.5
High FBG	13.25±4.4	0.85±0.2	89.88±28.9
p Value	0.837	0.165	0.216
Normal WC	13.3±4	0.9±0.2	91.1±25.4
High WC	12.7±4	0.83±0.2	86±25.2
p Value	<0.001	<0.001	<0.001
Normal BMI	13.23±4.5	0.86±0.2	87.6±27.1
BMI >30	12.9±4.6	0.83±0.2	88.45±27.2
p Value	0.09	0.017	0.471
Normal TC	13.01±4.5	0.84±0.2	87.94±26.1
High TC	13.34±4.7	0.83±0.2	88.72±31.7
p Value	0.227	0.422	0.661
Normal LDL-C	12.85±4.5	0.85±0.2	88.33±27.2
High LDL-C	13.42±4.6	0.84±0.3	87.56±27
p Value	0.005	0.565	0.519
Normal hs-CRP	13±4.4	0.86±0.2	87.3±26.5
High hs-CRP	13.1±4.7	0.82±0.2	89.1±28
p Value	0.586	0.002	0.122

Values are expressed as mean±SD or median and IQR for normally or non-normally distributed variables, respectively. Student t test was used to compare the CKD-associated markers and TG, SBP, HDL-C, FBG and WC. The MetS components (high/low) defined by WC >102 cm in men or >88 cm in women; serum TG >1.70 mmol/L (150 mg/dL); HDL-C <1.04 mmol/L (40 mg/dL) in men or <1.30 mmol/L (50 mg/dL) in women; blood pressure >130/85 mm Hg; or plasma glucose >6.11 mmol/L (110 mg/dL).
BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride, WC, waist circumference.

Table 3 Association between MetS-associated factors and OR for the presence of CKD

	Univariate		Multivariate*	
	OR	p Value	OR	p Value
Low HDL-C	1.13 (1.1 to 1.5)	0.001	1.12 (0.9 to 1.3)	0.231
High TG	1.14 (0.9 to 1.3)	0.105	1.17 (0.9 to 1.4)	0.099
High WC	1.36 (1.2 to 1.6)	<0.001	0.89 (0.7 to 1.1)	0.363
High FBG	1.16 (0.9 to 1.4)	0.138	1.04 (0.8 to 1.3)	0.736
High TC	1.16 (0.9 to 1.4)	0.233	1.01 (0.7 to 1.3)	0.079
High BMI	1.09 (0.9 to 1.2)	0.305	0.84 (0.6 to 1.1)	0.24
High LDL-C	1.11 (0.9 to 1.3)	0.206	1.14 (0.8 to 1.4)	0.271
Age	1.04 (1.0 to 1.0)	<0.001	1.3 (1.0 to 1.04)	<0.001
Gender, women	2.18 (1.8 to 2.6)	<0.001	3.26 (2.6 to 4.02)	<0.001
MetS (ATP III)	1.29 (1.1 to 1.5)	0.002	0.99 (0.8 to 1.2)	0.979
MetS (IDF)	1.52 (1.2 to 1.89)	<0.001	1.05 (0.78 to 1.4)	0.700
Uric acid	1.03 (0.9 to 1.1)	0.174	1.07 (1.0 to 1.1)	0.003
hs-CRP	0.99 (0.9 to 1.0)	0.521	0.99 (0.9 to 1.0)	0.130

This association was calculated by binary logistic regression model.
*With respect to age, sex, total cholesterol, BMI, SBP, DBP and urea nitrogen.
ATP III, Adult Treatment Panel III; BMI, body mass index; CKD, chronic kidney disease; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C reactive protein; IDF, International Diabetes Federation; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

1.89-fold increased risk of CKD and microalbuminuria, respectively, in US adults. Tanaka *et al*[5] showed this correlation in a hospital-based screening programme in Okinawa, Japan. Ninomiya *et al*[13] followed up 1440 individuals without CKD in Japan, and found that MetS remained an independent risk factor for the occurrence of CKD (OR 2.08; 95% CI 1.23 to 3.52).

To the best of our knowledge, this is the first study showing the relationship between MetS and risk of CKD in a province of Iran that has a high prevalence of MetS. Our findings indicate that the prevalence of CKD was enhanced by increasing of age and a number of MetS-associated factors. We also found that elevated TG, WC and blood pressure were statistically associated with an increased level of urea nitrogen and creatinine, respectively, while a low HDL-C and high TG/blood pressure/WC were related to an altered GFR level. Consistent with these results, accumulating data are showing that high TG level is a risk factor for developing proteinuria, and low HDL-C levels in men predicts a decline in renal function.[14] In a prospective investigation with more than 12 000 participants, high TG and low HDL-C were significant risk factors for increasing serum creatinine.[15] Additionally, Chen *et al*[7] showed that increased WC was significantly related to microalbuminuria and reduced GFR, suggesting that obesity might be an independent risk for CKD, which is in agreement with our data. We also observed that MetS was markedly associated with an increased OR of CKD (OR of MetS: 1.293, 95% CI 1.10 to 1.52; p=0.0021), however, this association was statistically significant for uric acid in the multivariate-adjusted models, which is consistent with previous studies.[16 17] This can be explained, at least in part by the progressive loss of GFR, that patients with CKD have decreased renal clearance of uric acid and thus higher serum uric acid levels.[18] Moreover, another study by Obermayr *et al* evaluated the association between uric acid level and incident kidney disease in 21 475 healthy volunteers who were followed prospectively for a median of 7 years. It showed that increased levels of uric acid independently enhanced the risk of new-onset kidney disease.[19]

A major strength of the present study is that it was performed in a large number of patient samples and provides a new insight regarding the relationship between certain MetS components and risk of renal function in a representative sample of the Iran population. This could suggest that prevention and treatment of MetS should be given priority to help in reducing the prevalence of CKD and its associated diseases. Conversely, the main limitation of this study is measuring GFR indirectly using serum creatinine. But serum creatinine levels and GFR estimated have been widely utilised in clinical practice for the assessment of CKD, thus our findings might be applicable to clinical and public health practice.

In conclusion, our data revealed that the prevalence of CKD was associated with an increasing number of MetS components in an Iranian population. In addition, there is a graded association between the levels of uric acid and number of MetS components and CKD risk, supporting future prospective and interventional studies to determine the impact of preventing and treating MetS, and reduced uric acid on the risk of developing CKDs.

What is already known on this subject?

- The global prevalence of metabolic syndrome appears to be increasing and the impact of this condition on potential comorbidities such as cardiovascular disease or chronic kidney disease is high.
- There is evidence for a relationship between metabolic syndrome and chronic kidney in adults from the USA, China, Thailand, Nepal and Japan; however, this relationship has not been extensively studied in the Iranian population, a group that has a high prevalence of metabolic syndrome and cardiovascular disease.

What this study adds

- The present study demonstrates a significant association between some of metabolic syndrome components and increased prevalence of chronic kidney disease in the general adult population of Iran.
- Our findings indicate that the prevalence of chronic kidney was increased by ageing and by a number of metabolic syndrome-associated factors.
- Our data suggest that prevention and treatment of metabolic syndrome should be given priority for reducing the prevalence of chronic kidney and its associated diseases.

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Contributors AK-R, AA, ME, MN, MRA, HE, MM, MRP and MG-M conceived and designed the experiments. DZ, AK-R, AA, ME, MRA, ME, MM, MM, MRP and MG-M performed the experiments. DZ, AK-R, MRA, HE and MG-M analysed the data. AK-R, ME, MN, MRA, MM, MRP, GAF and MG-M contributed reagents/materials/analysis tools. DZ, AK-R, AA, ME, MN, MRA, ME, MS, SRM, MM, MM, HE, MM, MRP, GAF and MG-M contributed to writing of the manuscript.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study has been approved by the Ethics Committee of the Mashhad University of Medical Science and conducted according to the Declaration of Helsinki.

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