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URINARY IMMUNOGLOBULIN G AS A PARAMETER FOR EARLY DETECTION OF CHRONIC KIDNEY DISEASE IN PATIENTS WITH METABOLIC SYNDROME

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ABSTRACT

Background and aim: *Both metabolic syndrome (MetS) and chronic kidney disease (CKD) are silent major global health issues and are major risk factors of cardiovascular and all cause death. Patients with MetS are at a significantly higher risk for CKD. Urinary IgG is an important marker protein for early glomerular damage and increased urinary IgG levels was found to be useful predictor of diabetic kidney disease in normoalbuminuric patients. We aimed to assess urinary immunoglobulin G (IgG) levels as a predictor of early CKD in subjects with MetS.*

Methods: *A cross-sectional study with 81 adult individuals were enrolled. All participants were divided into 2 groups: with MetS (56 in MetS group) and without MetS (25 in non-MetS group), with MetS being identified using the NCEP-ATPIII criteria. Patients with known CKD, DM, neoplasm, infection or autoimmune diseases and pregnant women were excluded. Anthropometric, clinical and biochemical measures including urinary albumin/creatinine ratio (ACR), serum fasting plasma glucose, creatinine, lipid profiles, Haemoglobin A1c and fasting plasma Insulin were performed for all participants. IgG concentrations were measured by using human enzyme-linked immunosorbent assay (ELISA) and correlated these levels with urinary ACR and estimated glomerular filtration rate (GFR). CKD was identified by albuminuria and estimating GFR using the CKD-EPI equation. Logistic regression models were used to estimate the chances of elevated urinary IgG levels associated with MetS and its components.*

Results: *Showed that as compared with the non-MetS group, the adjusted odds ratios (ORs) of elevated urinary IgG levels were 7.7 in MetS group. Unadjusted analysis showed that the ORs of elevated urinary IgG levels were associated with elevated waist circumference, hypertension, elevated FBG and reduced HDL-c but not with elevated TG. In the adjusted model, ORs of elevated urinary IgG levels were 19.16 (OR: 19.16; 95% CI: 4.40-83.5, P<0.001) for elevated waist circumference, 3.53 (OR: 3.53; 95% CI: 1.03-12.2, P<0.05) for low HDL-c. TG/ HDL-c ratio, urinary ACR and HOMA-IR were significantly higher in the MetS group than in the non-MetS group (all P<0.05). Elevated urinary IgG levels was significantly correlating with urinary ACR (P<0.019) and showed statistically high significant negative correlation with absolute values eGFR.*

Conclusion: *It is suggested that elevated urinary IgG levels could be a predicting biomarker for CKD in MetS normoalbuminuric subjects. From MetS components, mainly abdominal obesity accounted for the greatest strength of association with elevated urinary IgG levels. More attention should be focused on visceral obesity during risk management in order to prevent CKD and further research into the mechanism behind is needed.*

Keywords: *metabolic syndrome, chronic kidney disease, urinary immunoglobulin*

INTRODUCTION

Metabolic syndrome (MetS) and chronic kidney disease (CKD) are both major global health challenges. Furthermore, both CKD and MetS are major risk factors for cardiovascular and all-cause death[1]. At least seven of the top ten causes of mortality in 2019 were linked to MetS and its associated chronic diseases[2]. In the current COVID-19 pandemic, patients with MetS are also at a higher risk of severe morbidity and mortality[3].

Metabolic syndrome has a significant impact on people's health and health-care costs. It is critical to recognize the increased prevalence of MetS since, with intervention; the syndrome's course can be halted and even reversed[4]. Those with MetS are at significantly higher risk for developing CKD, and the level of risk is linked to the number of MetS criteria itself[5]. Therefore, Kidney function may be advisable to be monitored on a regular basis in people with MetS

CKD is common around the world, affecting around 10% to 14% of the overall population with increasing age-dependent prevalence of up to 47% in persons older than 70 years[6]. CKD burden is not limited to the disease itself, extending to ESKD and CKD-related CVD and other complications. In order to reduce the burden of CKD, it is critical to identify which people are most at risk so that they can be evaluated and treated as soon as possible. It is hoped that early

detection and treatment will limit the proportion of patients with CKD progressing to ESKD and consequently the requirement for renal replacement therapy will be reduced[7].

Because the first indicators of kidney injury appear in the tubular cells, and subsequently the urine in the lumen, urinary biomarkers may offer potential advantages in comparison to blood biomarkers. As a result, they are more sensitive to changes in renal function, typically showing abnormal results within the first day of renal compromise[8].

Because proteinuria, serum creatinine and subsequently calculated GFR are insensitive, relying on them may result in a significant time lapse during which effective interventions could be investigated and implemented. As a result, new validated biomarkers for CKD progression and CVD risk are needed[9].

Recently, intensive prospective and cross-sectional studies demonstrated that increased urinary IgG level was found to be useful predictor of diabetic kidney disease in normoalbuminuric patients with type 2 DM, suggesting their potential for use as markers in predicting early-stage diabetic kidney disease[10].

Furthermore, urinary IgG was found to have a substantial positive correlation with glomerular injury. Therefore, it is a crucial marker protein for detecting early glomerular filtration membrane selective barrier damage[11]. Thus, the objective of this study was to report the association between the presence of MetS and its individual components, and CKD.

Aim of the work: The current study evaluated urinary immunoglobulin G levels as a predictor of early chronic kidney disease in subjects with MetS. We investigated urinary IgG levels that could be useful to detect subclinical CKD associated with the status of MetS, individual components of MetS, and number of MetS components.

The study correlated these levels with urinary albumin/creatinine ratio and estimated GFR as established markers for kidney damage.

Study design: This is a single-center cross-sectional study. Participants were enrolled from those attending the Internal medicine outpatient clinics, Fayoum University hospital between March 2020 and August 2021. 81 adult participants were included, and agree to participate in the study after due clarification. All participants were divided into 2 groups: with MetS (56 in MetS group) and without MetS (25 in non-MetS group), with MetS being identified using the **NCEP ATP III** criteria[12, 13] and revised in 2005[34] as having three or more of the following traits, including traits you're taking medication to control: - Large waist: A waistline that measures at least 35 inches (89 cm) for women and 40 inches (102 cm) for men. - High triglyceride blood level: ≥150 mg/dl (1.7 mmol/L). - Reduced HDLc: < 40 mg/dL (1.04 mmol/L) in men or < 50 mg/dl (1.3 mmol/L) in women. - Increased blood pressure ≥ 130 mmHg systolic and/or ≥ 85 mmHg diastolic and/or with pre-

existed individual history of hypertension and/or with taking antihypertensive therapy. - Elevated FBG ≥ 100 mg/dl (5.6 mmol/L).

Patients with known CKD, DM, neoplasm, severe cardiovascular, cerebrovascular or liver diseases, infection or autoimmune diseases and Females on hormonal replacement therapy and pregnant women were excluded.

METHODS

We used a semi-structured questionnaire collecting information on socio-demographic characteristics, medical history, lifestyle features, and current medical treatment, physical examination including anthropometric data, blood pressure measurement, and conducting biochemical tests of blood and urine.

Anthropometric measurements including height using a 'drop down' tape measure, body weight using a digital screen scale and waist circumference were recorded. **Body mass index (BMI)** was calculated by the formula: **BMI=Body weight (kg)/ Height (m^2),** and categorized based on the WHO classification into: Underweight <18.5 kg/m^2, Normal weight 18.5-24.9 kg/m^2, Overweight 25-29.9 kg/m^2 and Obese ≥ 30 kg/m^2

Waist circumference measurements was measured with an inelastic tape measure at the midpoint between the lower margin of the last palpable rib and the top of iliac crest at the end of a normal expiration with the patient standing according to the WHO guidelines. Abdominal obesity was defined according to the waist circumference equal to or greater than 102 cm in men and 89 cm in women. Blood pressure was measured by the researcher with a mercury sphygmomanometer applied to the arm, with the participant in a sitting position, after at least 10 min. of rest. The average of three measurements was recorded.

Mean peripheral blood pressure (MBP) was calculated as: **MBP = DBP + 1/3(SBP – DBP).**

Biochemical Measurements: All venous blood samples were collected from participants and biochemical parameters were analyzed using commercial kits. The techniques and the classification criteria of the values found were those of reference of the laboratory. **Serum Fasting plasma glucose** (after overnight 8 hours fasting of participants)**, serum creatinine, lipid profiles** (after overnight 12 hours fasting of participants) [total cholesterol, triglyceride, high-density lipoprotein (HDL- c), low-density lipoprotein (LDL-c)] were measured using a spectrophotometric technique by Chemistry Analyzer (MINDRAY BS-200, Diamond Diagnostics, Massachusetts, MA, USA) and were represented as mg/dL.

- **Haemoglobin A1c** (HbA1c) was measured using the high performance liquid chromatography (HPLC) (Bio-Rad Laboratories, Inc., USA). **Fasting plasma Insulin (mU/L)** was measured by an automatic biochemical

analyzer using the chemiluminescent microparticle immunoassay (Abbott Laboratories, Dallas, Bio-Rad Lyphochek Immunoassay, USA). Homeostatic model IR index (HOMA-IR) was calculated by the formula: **HOMA-IR= FBG (mmol/ L) × Insulin (mU/L)/22.5**

- Other biochemical parameters analyzed included **random blood glucose, serum albumin, urea, complete blood counts, ALT, AST and TSH.**
- Spot urine samples were obtained for the measurement of **immunoglobulin G concentrations** by using human enzyme-linked immunosorbent assay (ELISA) kits (normal value is 0 - 10,000 pg/ μL [< 10 mg/l]). Spot urine samples from the first micturition after rising was obtained for the measurement of urinary albumin and creatinine concentrations by the Chemistry Analyzer.

Albuminuria was defined as urinary **albumin-to-creatinine ratio (ACR)** ≥ 30 mg/gr according to KDIGO 2012 criteria[14] and was recognized as a marker of increased glomerular permeability and renal damage. The enrolled subjects were also classified based on urinary ACR. The distribution of albuminuria in our data included the three stages: **A1:** ACR < 30 mg/gr (normal to slightly increased); **A2:** ACR 30–300 mg/gr (moderately increased [microalbuminuria]) and **A3:** ACR > 300 mg/gr (severely increased [macroalbuminuria]).

The eGFR was calculated using The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. The classification of our subjects based on eGFR category included: **G1:** eGFR ≥ 90 mL/min/1.73 m^2; **G2:** eGFR = 60–90 mL/min/1.73 m^2; **G3:** eGFR = 30–60 mL/min/1.73 m^2; **G4:** eGFR = 15–30 mL/min/1.73 m^2; **G5:** eGFR < 15 mL/min/1.73 m^2. Chronic kidney disease was defined according to KDIGO 2012 criteria as eGFR < 60 mL/min/1.73 m^2 or **albuminuria (ACR ≥ 30 mg/g)** for time duration more than 3 months[14].

The study protocol was approved by the Medical Ethics Committee of Fayoum University. The study adhered to the tenets of the Declaration of Helsinki and was reviewed and approved by the Medical Ethics Committee of faculty of medicine, Fayoum University. **Informed consents were obtained from all participating subjects analyzed in this study.** All the data were input into Excel and statistical analysis performed using SPSS 20.0 software. The mean values between two groups were compared using the t-test, and the comparison of mean values among multiple groups was made using one-factor ANOVA for quantitative variables, mann-whitney and kruskal-wallis tests were used instead for –not normally distributed quantitative variables, chi-square test was used to compare qualitative variables between groups

The correlation was analyzed using spearman correlation the logistic regression analysis was used to identify the risk factors of CKD. Odds Ratios (ORs)

and 95% confidence intervals from logistic regression were used to estimate the association between metabolic syndrome components and CKD.

RESULTS

Totally, 81 persons were enrolled in this study, including 56 in the MetS group and 25 in the non-MetS group. Among them, 41 males (50.6%) and 40 females (49.4%). Males were 50% in MetS group and 52% in non-MetS group (*P* = 0.86)**.** The average age was 44.54 ± 10.6 years in MetS group and 40 ± 8.1 years in non-MetS group (*P* = 0.06)**.** Totally, 25% of the subjects in MetS group were taking antihypertensive therapy compared to 4% in non-MetS group (*P < 0.03*).

The distribution of metabolic syndrome components included 7 persons with no MetS component, 38 with 3 MetS components and 9 participants with one, two and four MetS components. Separately, the most prevalent component of MetS in the study population was**:** increased blood pressure observed in 58 participants (71.6%), followed by visceral obesity in 56 subjects (69.1%), high FBG in 42 participants (51.9%), reduced HDL-c in 39 participants (48.1%) and elevated triglycerides in 28 participants (34.6%) respectively.

Table 1 showed that BMI, waist circumference, hypertension, FBG, RBG, HbA1c, TG, TG/ HDL-c ratio, serum creatinine, urinary ACR, ALT, AST and HOMA-IR were significantly higher in the MetS group than in the non-MetS group. While, the levels of HDL-c and eGFR were significantly lower in the MetS group than in the non-MetS group.

Table 1. *Characteristics in MetS Group and non-MetS Group*

	MetS group		Non-MetS group		
	Mean	**±SD**	**Mean**	**±SD**	***P* value**
Age (years)	44.54	10.6	40	8.1	0.061
BMI (kg/m²)	34.68	7.72	29.55	5.63	**0.004***
Urinary IgG (pg/µL)	10000	841.376	8725	2150.024	**<0.001***
Urinary ACR	26.2411	26.66697	16.0000	4.23281	**0.012***
Urinary ACR >30	8 (14.3%)	0			
Serum Creatinine (mg\dl)	0.880	0.1764	0.726	0.1455	**<0.001***
estimated GFR (ml/min/1.73 m²)	93.93	21.022	114.32	15.296	**<0.001***
Classified eGFR, n (%) <60 **60-90 >90**	4 (7.2%) 24 (42.8%) 28 (50 %)		0 0 25 (100%)		
HOMA-IR	4.89	4.9	2.17	1.03	**0.008***
RBG (mg\dl)	185.73	97.317	114.56	12.393	**<0.001***
HbA1c (%)	6.49	1.412	5.28	0.437	**<0.001***
TG/ HDL-c ratio	4.0525	3.09727	1.5359	0.723	**<0.001***
TG/ HDL-c ratio >2.67, n (%)	33(58.9%)		2(8.9%)		**<0.001***
Hemoglobin (gm\dl)	12.641	1.2680	12.924	1.0553	0.333
Serum ALT (mg\dl)	34.02	6.323	24.20	9.055	**<0.001***
Serum AST (mg\dl)	30.62	6.231	25.48	7.550	**0.002***
Serum Albumin (mg\dl)	4.716	0.302	4.628	0.398	0.277
Blood urea (mg\dl)	28.77	8.393	23.20	6.850	**0.005***
Total Cholesterol (mg\dl)	210.65	52.618	191.78	37.986	0.131
LDL-c (mg\dl)	136.35	45.574	120.52	33.587	0.145
Thyroid stimulating hormone	1.75	0.744	4.16	3.687	0.061
Serum Fasting Insulin (mIU\mL)	15.536	16.9649	9.292	2.7171	0.072

*: $P < 0.05$ between the MS group and the non-MS group; BMI: Body mass index; CKD: Chronic kidney disease; eGFR: estimated glomerular filtration rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; RBG: random blood glucose; HDL-c: High density lipoprotein-cholesterol; LDL-c: low density lipoprotein-cholesterol; TSH: thyroid stimulating hormone; TG: Triglycerides.

Moreover, urinary IgG was significantly higher in the MetS group than in the non-MetS group *(P < 0.001).* These findings indicated that the subjects with MetS were strongly associated with CKD and the probability of CKD exposure was 7.7 times in MetS group in comparison with non- MetS group as shown in table 2.

Table 2. *The urinary immunoglobulin G (IgG) levels in metabolic syndrome (MetS) Group and non-metabolic syndrome (non-MetS) Group (the association of metabolic syndrome status with CKD, based on evaluating urinary IgG levels)*

Elevated urinary IgG	MetS group	Non-MetS group	OR (95%CI)	*P* value
Number	42	7	7.7 (2.67-22.3)	< 0.001*
Percent %	75.0%	28.0%		

*: *P < 0.05* significant between the MetS group and the non-MetS group; CI, confidence interval; CKD: Chronic kidney disease; MetS, metabolic syndrome; OR, odds ratio; Urinary IgG: immunoglobulin G.

Relationship of MetS components and elevated urinary IgG: The association between MetS components and prevalence of CKD based on evaluating urinary IgG concentrations were explored. Analysis showed that elevated urinary IgG concentrations was associated with elevated waist circumference, hypertension, elevated FBG and reduced HDL-c but not with elevated TG as shown in table 3.

Table 3. *Relationship of metabolic syndrome (MetS) components with elevated urinary immunoglobulin G concentration*

		Urinary IgG Concentration (pg/µL)		*P* value
		Elevated IgG(49)	Average IgG(32)	
Elevated Waist Circumference, n (%)	YES	44 (78.6%)	12 (21.4%)	<0.001
	No	5 (20%)	20 (80%)	
SBP > 130 or DBP > 85 (mmHg) or history of hypertension, n (%)	YES	40 (69%)	18 (31%)	0.013*
	No	9 (39.1%)	14 (60%)	
FBG (>100 mg\dl) n (%)	**YES**	**30 (71%)**	**12 (28.6%)**	0.037*
	No	**19 (48.7%)**	**20 (51.3%)**	
Triglycerides (>150mg\dl)	YES	18 (66.7%)	9 (33.3%)	0.422
	No	31 (57.4%)	23 (42.6%)	
HDL-c (< 40 mg\dl in men) (<50 mg\dl in women)	YES	28 (71.8%)	11 (28.2%)	0.045*
	No	21 (50%)	21 (50%)	

*: *P < 0.05* significant; OR, odds ratio; CI, confidence interval; ACR: Urinary Albumin Creatinine Ratio; CKD: Chronic kidney disease; eGFR: estimated glomerular filtration rate; FBG: Fasting blood glucose; SBP: Systolic blood pressure; DBP:

Diastolic blood pressure; MetS, metabolic syndrome; Urinary IgG: immunoglobulin G; HDL-c: High density lipoprotein-cholesterol.

Unadjusted analysis showed that the odds ratio for elevated urinary IgG concentrations was associated with elevated waist circumference, hypertension, elevated FBG and reduced HDL-c but not with elevated triglycerides as shown in table 4. After adjusting for age and gender, it showed that except elevated triglycerides and elevated FBG, all the other elements including hypertension, reduced HDL-c and elevated waist circumference were strongly associated with elevated urinary IgG concentrations (Table 4).

While after further correcting the impact of age, gender, smoking, and other MetS components, the ORs for elevated urinary IgG concentrations remained strongly associated with elevated waist circumference and reduced HDL-c (Table 4).

Notably, from the four MetS components that were associated with increased elevated urinary IgG concentrations, elevated waist circumference showed the highest OR *(P < 0.001)* whether adjusted or not as shown in Table 4.

Table 4. *The elevated urinary immunoglobulin G (IgG) levels associated with the presence of each MetS component*

	Unadjusted			**Adjusted for age and sex**			**Adjusted for age, sex &other MetS components**		
	P value	OR	95% CI	P value	OR	95%CI	P value	OR	95% CI
Visceral Obesity	**<0.001***	14.7	4.55-47.23	**0.001***	18.01	4.8-66.48	**0.000***	19.168	4.40-83.5
Increased BP	**0.016***	3.45	1.26-9.45	**0.03***	3.2	1.12-9.19	0.136	2.749	0.728-10.4
FBG (>100 mg\dl)	**0.039***	2.63	1.05-6.58	0.077	2.37	0.9-6.1	0.381	1.739	0.504-5.9
Triglycerides (>150mg\dl)	0.326	1.6	0.619-4.23	0.314	1.68	0.6-4.6	0.663	0.756	0.214-2.66
Reduced HDLc	**0.047***	2.6	1.01-6.4	**0.044***	2.64	1.029-6.8	**0.045***	3.538	1.03-12.2

*: *P < 0.05* significant; OR, odds ratio; CI, confidence interval; BP: blood pressure, CKD: Chronic kidney disease; FBG: Fasting blood glucose; MetS, metabolic syndrome; IgG: immunoglobulin G; HDL-c: High density lipoprotein-cholesterol.

Table 5 showed that elevated urinary IgG concentrations significantly correlated with albumin creatinine ratio as established marker for kidney damage.

Table 5. *Correlation of urinary immunoglobulin G (IgG) elevation with established markers of chronic kidney disease (CKD)*

		Urinary IgG Concentration (pg/µL)		*P* value
		Elevated IgG (49)	Average IgG (32)	
Urinary Albumin Creatinine Ratio	< 30	41 (56.2%)	32 (43.8%)	**0.019***
	> 30	8 (100%)	0	
Estimated GFR (ml/min/1.73 m²)	> 90	28 (52.8%)	25 (47.2%)	**0.03***
	60-90	17 (70.8%)	7 (29.2%)	
	< 60	4 (100%)	0	

*: *P < 0.05* significant; eGFR: estimated glomerular filtration rate; CKD: Chronic kidney disease; IgG: immunoglobulin G; Urinary ACR: Urinary Albumin Creatinine Ratio.

Table 6 showed that there was a statistically high significant positive correlation of urinary IgG level with waist circumference, RBG and serum creatinine. Besides, statistically high significant negative correlation of urinary IgG level with absolute values of eGFR.

Table 6. *Correlation between urinary immunoglobulin G (IgG) level and other quantitative variables*

Variable		Urinary IgG concentration	Variable		Urinary IgG concentration
Age	*r*	0.073	Waist Circumference (cm)	*r*	**0.301****
	P value	0.503		***P value***	**0.006**
Fasting Blood Glucose (mg/dl)	*r*	0.216	Triglycerides (mg/dl)	*r*	0.091
	P value	0.052		***P value***	0.419
Random Blood Glucose (mg/dl)	*r*	**0.234***	High density lipoprotein-cholesterol, HDL-c (mg/dl)	*r*	- 0.153
	P value	**0.036**		***P value***	0.110
Serum Creatinine (mg/dl)	*r*	**0.227***	Low density lipoprotein-cholesterol, LDL-c (mg/dl)	*r*	0.369
	P value	**0.041**		***P value***	**0.386****
estimated GFR (ml/min/1.73 m²)	*r*	**-0.229***	Body Mass Index (kg/m²)	*r*	**<0.001**
	P value	**0.039**		***P value***	0.091

*: Correlation is significant at *P < 0.05* level; **: Correlation is significant at *P < 0.01* level; eGFR: estimated glomerular filtration rate; Urinary ACR: Urinary Albumin Creatinine Ratio.

DISCUSSION

Early detection of CKD enables for more rapid interventions in order to control disease progression and management of risk factors. This will translate into better patients' prognoses as well as financial benefits related to reducing healthcare costs[9]. MetS has been shown to significantly increase the risk of ischemic heart disease, stroke, DM, Alzheimer's disease (and other dementias), kidney disease and cancers[15]. Consequently, MetS has now become a major public health concern worldwide[16].

CKD is a silent disease; hence most CKD patients are asymptomatic during the early stages of the disease. This poses a challenge for healthcare providers to start treatment or preventative measures. The problem with CKD diagnosis is that it is still done based on measurements of albuminuria and calculations of eGFR. The present staging system is controversial, particularly in terms of the methodology applied to diagnose and prognosticate CKD[17]. From this background, in this single-center cross-sectional study, we aimed to investigate the association of the MetS status with CKD, based on evaluating urinary IgG levels as suggested early biomarker for chronic kidney damage. Correlate urinary IgG levels with established predictors of CKD namely albuminuria and eGFR.

In our data, among MetS subjects, the prevalence of moderately or severely increased albuminuria (ACR ≥ 30 mg/gr) was 14% and a low eGFR (<90 mL/min/1.73 m^2) was found in 20 patients (35.7%) one of them with eGFR (< 60 mL/min/1.73 m^2). This is because we excluded subjects with known DM and subjects with known CKD.

We found that seven of our subjects had moderately or severely increased albuminuria despite having an eGFR > 60 mL/min/1.73 m^2 (G1 and G2 stages). Indeed, the kidney damage defined by the presence of albuminuria (ACR ≥ 30 mg/gr) can be combined by a normal or raised GFR, in agreement with previous reports[18]. Thirty-four of our enclosed MetS subjects had a normal renal function determined by an ACR < 30 mg/gr in conjunction with an eGFR > 90 mL/min/1.73 m^2.

The BMI, waist circumference, hypertension, FBG, RBS, HbA1c, TG, TG/ HDL-c ratio, serum creatinine, urinary ACR and HOMA-IR were significantly higher in the MetS group than in the non-MetS group. While, the levels of HDL-c and eGFR were significantly lower in the MetS group than in the non-MetS group. These findings were concordant with other studies conducted with the adult population and that used the same diagnostic criteria for MetS[19].

Our results showed a significant association between MetS and higher urinary IgG levels compared to non-MetS. Also, the association between MetS and increased albuminuria was significant. In agreement, previous studies reported an elevated risk for CKD due to the presence of MetS[20, 21].

In the meantime, in this study, we observed that the subjects who had higher urinary IgG levels presented with more MetS components (mainly those with 3 and 5 components) than the subjects who had 0 - 2 MetS components). Despite of that, there was no linear significant positive correlation trend between the number of MetS components and the prevalence of CKD, unlike earlier cross-sectional studies[22, 23]. On the other hand, comini et al. demonstrated results in line with ours[19].

When evaluated by a number of components rather than by a single component, MetS has previously been shown to be a substantial independent risk factor for CKD defined by eGFR < 60 mL/min/1.73 m^2 [24, 25]. Consistent with previous studies, Thomas et al. found that individuals with up to five components had a higher risk of developing CKD than those who didn't have any, possibly due to an additive negative impact of the cluster of MetS components rather than single components[26].

These findings highlight that periodically monitoring MetS status in people is important for public health and medical care since these people are rarely treated, despite the fact that they are at a significant risk of developing CVD, CKD, and all-cause death in the future. This is especially essential given that a lifestyle change could successfully resolve MetS status.

Indeed, in the present study, we noted that the subjects in MetS group had significantly higher HOMR-IR, together with significantly higher waist circumference and BMI, implicating a higher insulin resistance (IR) in MetS group than in non-MetS group.

Insulin resistance (IR) is becoming better recognized as a key factor in the development of early kidney disease independent of the presence of diabetes. MetS-related renal function deterioration may be linked to IR**(27)**. Reducing IR can provide a theoretical basis for prevention and intervention of the CKD occurrence and progression, implying that early monitoring and treatment of MetS individuals, as well as improving IR, is advantageous to our CKD prevention and treatment**(21)**.

Furthermore, the role of IR in MetS establishment could explain the observed strong relationship between MetS presence and renal illness aetiology. Although the total number of diabetic individuals manifested MetS, Raikou et al. found that some participants with hypertension nephrosclerosis had not exhibited MetS, possibly due to rising IR in diabetics rather than hypertensive individuals**(25)**.

It has been proposed that IR plays a crucial role in the onset and progression of kidney damage in the MetS population, with the mechanism being that hyperinsulinemia enhances oxidative stress, protein glycosylation oxidation, and lipid peroxidation, promoting renal impairment progression. The primary mechanism of IR-induced glomerular and tubulointerstitial injury may be connected to the inappropriate activation of the renin-angiotensin-aldosterone axis. As a result, IR could be an important therapeutic target for patients with CKD**(21)**.

As noted here, this study showed a significant correlation of MetS and its components with CKD. This finding is in line with those of previous studies**(21)**. Furthermore, the unadjusted association between higher urinary IgG levels and separated MetS components showed that visceral obesity, high FBG, hypertension and low HDL-c were significant factors.

Unadjusted analysis showed that the risk for CKD was associated with elevated waist circumference, hypertension, elevated FBG and reduced HDL-c but not with elevated TG. These findings were consistent with other adult population conducted studies and that applied the updated NCEP ATP III criteria for MetS diagnosis(19). Most studies suggested that elevated FBG levels or blood pressure were the strongest predictors of CKD in MetS[23, 25]Among the MetS components, high TG, low HDL-c and hyperglycemia were independently associated with the occurrence and development of CKD according to Hu et al.(21).

In our adjusted model for age and gender, we found that elevated waist circumference, hypertension and reduced HDL-c could be significant factors for CKD, based on evaluated IgG concentrations. While after further correcting the impact of age, gender, and other MetS components, the risk for CKD remained strongly associated with elevated waist circumference and reduced HDL-c.

Notably, from the four MetS components that were associated with increased risks of CKD. The elevated waist circumference showed the highest ORs whether adjusted or not. The subgroup analysis showed that visceral obesity, particularly, remained strongly associated with CKD, independent of diabetes and hypertension.

Regardless of overall adiposity or increased BMI, central obesity is an important factor in MetS that causes IR and is linked to CKD. As a result, visceral obesity should be concerned in addition to the other metabolic syndrome components while managing the risk of CKD.

Indeed, in our data, visceral obesity was the strongest predictor of CKD in MetS. This is concordant with previous reports. These reports have confirmed that obesity is associated with increased risk of developing CKD. This risk extends to metabolically healthy individuals, demonstrating that obesity per se contributes to CKD independent of the MetS. Recently, developments in the obesity related kidney disease pathophysiology indicate that abnormal lipid metabolism and chronic inflammation contribute to renal cell injury[28, 29].

In this study, we found that high triglycerides was not a significantly predictor of CKD. Contrary to this study, Hu et al. and Xie et al. reported that elevated TG was to be the most significant independent risk factor for incident CKD[21, 30].

Hu et al. suggested that the mechanism of hypertriglyceridemia induced incident CKD, defined by rapid deterioration of GFR, may be related to lipotoxicity and lipid overload(21).

Xie et al. found that, in patients with hypertension, hypertriglyceridemia, elevated FBG and hypertension grades were all significantly associated with the CKD prevalence. Elevated TG, in particular, was strongly linked to CKD, independent of diabetes and hypertension severity[30]. This controversy could be explained by the complexity and incomplete understanding of the interrelationships between each component of MetS and CKD.

In our adjusted model, MetS subjects with FBG >100 mg/dl showed higher urinary IgG levels than those subjects with FBG <100 mg/dl. This goes in harmony with Narita et al., who found that, in early stages of diabetic nephropathy, increased intraglomerular hydraulic pressure induces a concomitant increase in certain urine proteins including IgG but without simultaneous increased albuminuria[31]. Moreover, Kamal et al. found that, in early stages of diabetic nephropathy IgG appears in urine even before microalbuminuria[32].

Until date, it is difficult to conclude a causal link between MetS components and renal functional decline. It has been hard to ascertain which of these separate pathways contributes to the CKD risk.

This study showed, however, that TG/HDL-c ratio was significantly higher in the MetS group than in the non-MetS group. This result goes in harmony with those of previous investigations that suggested the TG/HDL-c ratio as an independent risk factor for CKD[33].

This study showed that urinary IgG levels were significantly correlating with albuminuria and estimated GFR as established markers for kidney damage. Elevated urinary IgG levels was significantly correlated with urinary ACR and showed statistically high significant negative correlation with absolute values eGFR. Although we excluded subjects with known DM and/or known CKD, however, it is possible to observe the positive correlation between higher urinary IgG levels and albuminuria and negative correlation between urinary IgG levels and absolute values of estimated GFR. In fact, previous studies reported the correlation between increased elimination of urinary IgG and CKD known markers namely albuminuria besides low eGFR[10].

The study suggested that MetS status and its individual components of abdominal obesity, high FBG, hypertension and reduced HDL-c, as well as the number components, may be independently associated with CKD. The strength of the study is that to our knowledge, this was the first study to evaluate the role of urinary IgG levels in detecting the risk of CKD in subjects with MetS. Our results also suggest that monitoring urinary IgG levels changes in MetS may be an important approach to identifying populations at higher risk of renal dysfunction and may help to prevent CKD in clinical practice.

CONCLUSION

It is suggested that elevated urinary IgG could be used as a biomarker for early detection of renal disease in MetS subjects with normal albuminuria. Abdominal obesity per se may be an important risk factor for CKD.

Larger studies are needed to determine the sensitivity, specificity, and cut-off value of urinary IgG as a predictor of early CKD in MetS patients. Particularly, these aspects were shown to be variable across studies. Repeated evaluations of MetS status and identification of those at risk of developing CKD will give evidence for future interventional research. These studies should determine whether treating the MetS components has a prophylactic effect on the progression of CKD. More attention should be focused on visceral obesity during risk management in order to prevent CKD and further research into the mechanism behind is needed. Further prospective studies are warranted to confirm our results, contribute to more evidence regarding the diagnostic accuracy of urinary biomarkers and validate their predictive value of CKD in MetS subjects.

The main limitation of this study is the relatively small sample size, by which the possibility of bias might exist. In addition, since its cross-sectional design conducted in a single center, it did not prove causal relationship between metabolic syndrome components and CKD. However, we could conclude that there was a strong independent association between them. Despite statistical adjustment methods used in the study, the results could still be influenced by confounding factors linked to metabolic syndrome.

REFERENCES

1) Gurka M.J., Guo Y., Filipp S.L., et al. Metabolic syndrome severity is significantly associated with future coronary heart disease in type 2 diabetes. Cardiovasc. Diabetes. 2018,17(1):17-7.
2) WHO Global Health Estimates. 2020. The Top 10 Causes of Death.
3) Zulhendri, F.; Ravalia, M.; Kripal, K.; Chandrasekaran, K.; Fearnley, J.; Perera, C.O. Propolis in Metabolic Syndrome and Its Associated Chronic Diseases: A Narrative Review. Antioxidants 2021, 10, 348. https://doi.org/10.3390/ antiox10030348
4) Van der Pal K.C., Koopman A.D.M., Lakerveld J., van der Heijden A.A., Elders P.J., et al. The association between multiple sleep-related characteristics and the metabolic syndrome in the general population: The New Hoorn study. Sleep Med. 2018 Dec; 52:51-57.

5) Kolaitis A., A. Ceasovschih, V. Sorodoc, A. Stoica, O. Sirbu, L. Sorodoc. Particularities of chronic kidney disease in patients with metabolic syndrome. Atherosclerosis. 2020 Dec 31;10(315) e185.
6) Philip D. Evans, Maarten W. Taal. Epidemiology and causes of chronic kidney disease. Medicine 2015; Volume 43, Issue 8, Pages 450-453.
7) Klein S.J., Brandtner A.K., Lehner G.F., et al. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Intensive Care Medicine 2018; 44:323-36.
8) Lousa, I.; Reis, F.; Beirão, I.; Alves, R.; Belo, L.; Santos-Silva, A. New Potential Biomarkers for Chronic Kidney Disease Management – A Review of the Literature. Int. J. Mol. Sci. 2021, 22, 43. https://dx.doi.org/10.3390/ijms22010043
9) Qin Yongzhang, Shuang Zhang, Xiaofang Shen, Shunming Zhang, Jingyu Wang, et al. Evaluation of urinary biomarkers for prediction of diabetic kidney disease: a propensity score matching analysis. Ther Adv Endocrinol Metab 2019, Vol. 10: 1–11.
10) Gao J., Wang F., Kuang X., et al. Assessment of chronic renal injury from melamine-associated pediatric urolithiasis: an eighteen-month prospective cohort study. Ann Saudi Med. 2016; 36(4): 252-257.
11) NCEP-ATP III, 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) final report. Circulation 2002; 106: 3143-3421 [PMID: 12485966].
12) Ford E.S., Giles W.H., Dietz W.H. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002; 287: 356-9.
13) KDIGO. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013; 3:1-150.
14) Chen, H.; Zheng, X.; Zong, X.; Li, Z.; Li, N.; Hur, J.; Fritz, C.D.L.; Chapman, W., et al. Metabolic syndrome, metabolic comorbid conditions and risk of early-onset colorectal cancer. Gut 2020. [CrossRef]
15) Joshi, P.; Ghosh, K.; Natarajan, V.S.; Mandal, P. Impact of healthcare access and socio-economic conditions on prevalence of metabolic syndrome: Evidence from 2015 brfss. Int. J. Bus. Excell. 2020, 21, 429-443. [CrossRef]
16) Mohammad Zulkarnain Bidin, Anim Md Shah, Stanslas, Christopher Lim Thiam Seong. Blood and urine biomarkers in chronic kidney disease: An update. Clin Chim Acta. 2019 Aug; 495: 239-250. doi: 10.1016/j.cca. 2019. 04.069

17) Mota, E.; Popa, S.G.; Mo¸ta, M.; Mitrea, A.; Penescu, M.; Tu¸tă, L.; et al. Prevalence of chronic kidney disease and its association with cardio-metabolic risk factors in the adult Romanian population: The PREDATORR study. Int. Urol. Nephrol. 2015, 47, 1831-1838.
18) Comini L.O., de Oliveira L.C., Borges L.D., Dias H.H., Batistelli C.R.S., da Silva L.S., et al. Individual and Combined Components of Metabolic Syndrome with Chronic Kidney Disease in Individuals with Hypertension and/or Diabetes Mellitus Accompanied by Primary Health Care. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2020: 13 : 71-80.
19) Alswat, K.A.; Althobaiti, A.; Alsaadi, K.; Alkhaldi, A.S.; Alharthi, M.M.; et al. Prevalence of Metabolic Syndrome Among the End-Stage Renal Disease Patients on Hemodialysis. J. Clin. Med. Res. 2017, 9, 687-694.
20) Hu Ying, Shi L.X., Zhang Q., Peng N.C. Increased risk of chronic kidney diseases in patients with metabolic syndrome: a 3-year prospective cohort study. Curr Med Sci. 2019; 39: 204-210.
doi: 10.1007/s11596-019-2020-8. [PubMed] [CrossRef] [Google Scholar]
21) Chen J., Kong X., Jia X., et al. Association between metabolic syndrome and chronic kidney disease in a Chinese urban population. Clin Chim Acta. 2017; 470:103-108. doi: 10.1016/j.cca.2017.05.012
22) Huh J.H., Yadav D., Kim J.S., et al. An association of metabolic syndrome and chronic kidney disease from a 10-year prospective cohort study. Metabolism. 2017, 67(2):54-61.
23) Zammit, R.A.; Katz, J.M.; Derby, C.; Bitzer, M.; Lipton, B.R. Chronic Kidney Disease in Non-Diabetic Older Adults: Associated Roles of the Metabolic Syndrome, Inflammation, and Insulin Resistance. PLoS ONE 2015, 10, e0139369.
24) Raikou, Vaia D. and Gavriil, Sotiris. Metabolic Syndrome and Chronic Renal Disease. Diseases 2018, 6, 12; doi:10.3390/diseases6010012
25) Thomas G., Sehgal A.R., Kashyap S.R., Srinivas T.R., Kirwan J.P., Navaneethan S.D. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2011;6: 2364-2373.
doi: 10.2215/CJN. 02180311.
26) Whaley-Connell A., Sowers J.R. Insulin Resistance in Kidney Disease: Is There a Distinct Role Separate from That of Diabetes or Obesity? Cardiorenal Med. 2017,8(1):41-49.
27) Garofalo C., Borrelli S., Minutolo R., Chiodini P., De Nicola L., Conte G. A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. Kidney Int. 2017 May; 91(5):1224-1235.

28) Nehus Edward. Obesity and chronic kidney disease. Curr Opin Pediatr. 2018 Apr; 30(2):241-246.
29) Xie Kun, Liwen Bao, Xiaofei Jiang, Zi Ye, Jianping Bing, Yugang Dong, et al. The association of metabolic syndrome components and chronic kidney disease in patients with hypertension. Lipids in Health and Disease. 2019 Dec; 18:229.
30) Narita T., H. Sasaki, M. Hosoba et al., "Parallel increase in urinary excretion rates of immunoglobulin G, ceruloplasmin, transferrin, and orosomucoid in normoalbuminuric type 2 diabetic patients," Diabetes Care 2004; 27 (5): 1176-1181.
31) Kamal, Nafesa M., Ahmed M. Elsayed, Essam Amin, Amal Zedan. Urinary immunoglobulin G versus microalbuminuria as an indicator of diabetic nephropathy in type 2 diabetic patients. Egypt J Intern Med. 2018 July 25;30: 58-62.
32) Ho Chih-I, Jau-Yuan Chen, Shou-Yen Chen, Yi-Ming Weng, Yu-Chung Tsao, Wen-Cheng Li. Relationship between TG/HDL-C ratio and metabolic syndrome risk factors with chronic kidney disease in healthy adult population. Clinical Nutrition. 2015; 34(5): 874-880.
33) Grundy S.M., Brewer H.B., Cleeman J.I., Smith S.C., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004; 109: 433-438 [PMID: 14744958 DOI: 10.1161/01. CIR.0000111245.75752.C6]
34) National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am. J. Kidney Dis. 2002, 39, S1-S266.