Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Risk factors in metabolic syndrome predict the progression of diabetic nephropathy in patients with type 2 diabetes

Shih-Ming Chuang [a,c,1], *Hong-Mou Shih* [b,d,1], *Ming-Nan Chien* [a], *Sun-Chen Liu* [a], *Chao-Hung Wang* [a], *Chun-Chuan Lee* [a,*]

[a] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Division of Nephrology, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Mackay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan*
[d] *Graduate Institute of Physiology, College of Medicine, National Taiwan University, Taipei, Taiwan*

ARTICLE INFO

Article history:
Received 18 December 2018
Received in revised form
21 March 2019
Accepted 12 April 2019
Available online 4 May 2019

ABSTRACT

Background: While metabolic syndrome can independently predict the development of diabetic kidney disease (DKD) in patients with type 2 diabetes, the risk factors for DKD progression have rarely been discussed. The purpose of this study is to evaluate the association between metabolic syndrome and the progression of DKD in patients with type 2 diabetes.

Material and methods: This retrospective observational cohort study lasted approximately five years. We defined metabolic syndrome using the criteria of the National Cholesterol Education Program Adult Treatment Panel III with the Asian definition of obesity. The progression of DKD was demonstrated by either the progression of albuminuria or worsening renal function. Progression of albuminuria was defined by the transition from normoalbuminuria (<30 mg/g) to microalbuminuria (30–300 mg/g) or from micro- to macroalbuminuria (>300 mg/g). Worsening renal function was defined by a reduction of eGFR to 50% of the baseline or the doubling of serum creatinine. We adopted multivariate Cox-regression analysis to determine the risk factors associated with DKD progression.

Results: This study consisted of 935 type 2 diabetic patients with a mean age of 64.62 years. We found progression of albuminuria in 172 patients (18.4%) and worsened renal function in 41 patients (4.4%). After Cox regression analysis, the multivariable-adjusted HR for the progression of albuminuria and worsened renal function was 1.65 (95% C.I.:1.07–2.53 P = 0.022) and 2.62 (95% C.I.:1.01–6.79 P = 0.047) respectively, for those with metabolic syndrome compared to those without metabolic syndrome.

Conclusion: The presence of metabolic syndrome independently predicts DKD progression in patients with type 2 diabetes.

* Corresponding author at: Division of Endocrinology and Metabolism, Department of Internal Medicine, Mackay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Taipei 10449, Taiwan.
E-mail address: lee5957.5957@mmh.org.tw (C.-C. Lee).

[1] S.C. and H.S. contributed equally to this work.

https://doi.org/10.1016/j.diabres.2019.04.022
0168-8227/

1. Introduction

Type 2 diabetes has been well recognized as the main cause of end-stage renal disease (ESRD) [1]. The U.S. Renal Database (USRDS) has shown that the incidence of metabolic syndrome is quite high, nearly two-thirds, at the beginning of dialysis. Type 2 diabetes has also been highly associated with metabolic syndrome and obesity [2]. A large cohort study of 5829 type 2 diabetic patients in Hong Kong with a follow-up period of 4.6 years found that metabolic syndrome independently predicted new onset of chronic kidney disease (CKD) in patients with type 2 diabetes [3]. Patients with metabolic syndrome are at an increased risk of cardiovascular disease (CVD) and cardiovascular mortality [4], and also share many other risk factors with CKD patients [5]. With regard to microalbuminuria, in the third National Health and Nutrition Examination Survey (NHANES III), microalbuminuria was associated with metabolic syndrome, leading the authors to suggest that microalbuminuria should be an integral part of the metabolic syndrome [6]. However, few longitudinal studies have discussed the association between metabolic syndrome and the progression of renal function. Longitudinal analysis have never determined whether metabolic syndrome predicts the progression of albuminuria and/or worsening of renal function in diabetic patients. Therefore, we conducted this observational cohort study to highlight the relationship between metabolic syndrome and the progression of albuminuria or worsening renal function in patients with type 2 diabetes.

2. Materials and methods

We included 1256 subjects with type 2 diabetes, ranging from 20 to 91 years of age, who had been followed up at the endocrinology outpatient department of the Taipei branch of MacKay Memorial Hospital between October 17, 2013 and February 7, 2015 for evaluation of glycemic control and diabetes complications in this study. Enrolled patients had normo- or microalbuminuria and estimated glomerular filtration rate (eGFR) > 15 mL/min per 1.73 m^2. We excluded pregnant women, patients who received renal replacement therapy, and patients with infectious or malignant diseases.

Participants underwent a routine medical history and physical examination, as well as blood sampling every 2 to 3 months at the outpatient clinic.

We collected the following data: age, blood pressure, anthropometry such as waist circumference and body mass index (BMI), and laboratory tests included fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), low-density-lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), liver enzymes, serum creatinine, eGFR and urine albumin-creatinine ratio (ACR). Personal history included smoking, drinking and duration of diabetes. A history of cardiovascular disease (CVD) was defined as a history of stroke/transient ischemic attack and/or coronary artery disease. Clinical evidence for coronary artery disease was defined as any of the following conditions: a history of myocardial infarction, previous coronary revascularization, or the presence of coronary artery stenosis evaluated by coronary angiography. Retinopathy was confirmed by an ophthalmologist through dilated ophthalmoscopy.

We defined metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII)'s modified criteria for Asians [7] with three of the following abnormalities: (1) central obesity or abdominal obesity (waist circumference >90 cm for men and >80 cm for women); (2) fasting TG level ≥150 mg/dL; (3) fasting HDL-C <40 mg/dL in men and <50 mg/dL in women; (4) fasting blood glucose ≥110 mg/dL or a diagnosis of diabetes; and (5) blood pressure ≥130/85 mmHg or a diagnosis of hypertension. Since all patients included in this study had diabetes, if patients had two or more of the other components of metabolic syndrome besides the glucose component, they were considered as having metabolic syndrome. Patients taking lipid lowering agents with fibrates and/or statins were recorded as fulfilling the lipid criterion, while patients using antihypertensive drugs were recorded as satisfying the blood pressure criterion.

3. Measurements

The waist circumference was measured at the midpoint between the lowest rib and the iliac crest. Urine albumin was measured using the immunoturbidimetric method and normalized by urine creatinine levels. Normoalbuminuria was defined as ACR < 30 mg/g, microalbuminuria was ACR between 30 and 299 mg/g, and macroalbuminuria was ACR > 300 mg/g [8]. eGFR was calculated using the following modified Modification of Diet in Renal Disease equation: 175 × Scr ^ − 1.154 × Age ^ − 0.203 × (0.742 if female).

4. Outcome

The end point of this study was defined as the progression of albuminuria or worsening renal function with CKD event. The progression of albuminuria was the end point for the transition of the stage from normo- to microalbuminuria or micro- to macroalbuminuria, as determined by at least two consecutive urine ACR studies to avoid misclassification. Patients with at least two ACR tests performed per year and a follow-up period of >1 year for urine ACR were included in the analysis.

The other end point was worsening renal function. For each individual, we collected at least one serum creatinine or eGFR each year and compared it to the patient's baseline creatinine or eGFR when enrolled in the study. The end point of worsening renal function was defined as the doubling of serum creatinine or eGFR reduction more than 50% from

baseline, as observed during follow-up, regardless of the frequency of creatinine measurements and albuminuria data during the follow-up period.

5. Statistical analysis

We performed statistical analysis using IBM SPSS version 21.0 (IBM, Armonk, New York). Baseline characteristics of the study participants were expressed as a percentage or mean ± standard deviation (SD), as appropriate according to data distribution. Student's *t*-test and X^2 test were adopted to analyze the differences in baseline characteristics between the groups with and without metabolic syndrome.

The cumulative incidence of the primary end point was estimated using Kaplan-Meier analysis. We adopted univariate and multivariate Cox proportional hazard model analysis to calculate the risk estimates for reaching the end point. The following variables were incorporated as covariates in the multivariate Cox regression analysis: gender, advanced age, longer diabetes duration (>10 years), high HbA1c level (>7%), TG, LDL-C, BMI, hypertension, use of renin-angiotensin system inhibitors (ACEI or ARB), eGFR, CKD (eGFR < 60), microalbuminuria (ACR > 30 mg/g), and metabolic syndrome at baseline. Prognostic factors were selected using the stepwise procedure. A p-value of <0.05 was considered statistically significant.

6. Results

This study consisted of a total of 935 type 2 diabetic patients with a sufficient follow-up period and relevant endpoints that met our research criteria. The mean ± SD age of these patients was 64.62 ± 9.73 years and 430 patients (46.0%) were men. Of these patients, 599 (64.1%) had metabolic syndrome. The demographic, clinical, and biochemical characteristics of the patients at baseline are shown in Table 1. Patients with metabolic syndrome were older, but there was no significant difference in DM duration, glycemic control, FPG, PPG, or HBA1C. Those with metabolic syndrome had higher BMI, TG, systolic blood pressure (SBP), and diastolic blood pressure (DBP) but lower HDL-C. Of particular note, metabolic syndrome patients also had higher serum creatinine and urine ACR levels at baseline.

We used Kaplan-Meier analysis to evaluate the incidence of progression of albuminuria and worsening renal function. The 5-year cumulative incidence of 50% reduction in eGFR or the doubling of serum creatinine was significantly higher in patients with metabolic syndrome compared to those without metabolic syndrome (log-rank test, p = 0.003) (Fig. 1). As for the progression of albuminuria, in the metabolic syndrome group, 21.4% patients (n = 128) developed albuminuria or progressed to a more advanced stage of albuminuria, compared to only 12.9% of patients (n = 43) in the group without

Table 1 – Clinical characteristics and laboratory data of type 2 diabetic patients with and without metabolic syndrome.

	MetS (N = 599)	No MetS (N = 336)	P
Age (years)	65.1 ± 9.6	63.8 ± 9.9	0.040
Gender (male, %)	45.4	47.0	0.635
Smoking (%)	9.8	13.3	0.146
DM duration (years)	10.9 ± 7.2	10.2 ± 6.9	0.206
>10 years (%)	54.9	55.1	0.947
BMI (kg/m^2)	26.6 ± 4.3	24.6 ± 3.7	<0.001
Central obesity (%)	76.0	58.9	<0.001
FPG (mg/dL)	149.2 ± 46.3	144.5 ± 41.3	0.107
PPG (mg/dL)	197.0 ± 66.0	196.7 ± 64.0	0.950
HbA1c (%)	7.4 ± 1.4	7.4 ± 1.4	0.766
A1c > 7% (%)	55.9	54.1	0.578
TC (mg/dL)	171.0 ± 35.2	174.9 ± 35.0	0.138
TG (mg/dL)	146.1 ± 108.2	88.4 ± 35.9	<0.001
LDL-C (mg/dL)	97.8 ± 27.8	100.0 ± 27.8	0.257
HDL-C (mg/dL)	44.7 ± 12.4	56.8 ± 13.4	<0.001
SBP (mmHg)	142.4 ± 17.2	135.4 ± 17.4	<0.001
DBP (mmHg)	78.8 ± 9.4	76.0 ± 9.8	<0.001
ACEI or ARB (%)	54.3	52.2	0.553
Cr (mg/dL)	0.9 ± 0.3	0.8 ± 0.3	<0.001
GPT (mg/dL)	27.8 ± 15.2	26.4 ± 23.2	0.287
eGFR (mL/min/1.73 m^2)	79.9 ± 26.7	88.8 ± 28.7	<0.001
CKD (eGFR < 60, %)	23.8	13.0	<0.001
ACR (mg/g)	38.3 ± 59.1	25.6 ± 42.2	<0.001
Normoalbuminuria (%)	67.90	79.90	<0.001
Microalbuminuria (%)	32.10	20.10	<0.001

Data are presented as mean value ± standard deviation or % MetS = metabolic syndrome; BMI = body mass index; FPG = fasting plasma glucose; PPG = post-prandial plasma glucose; HbA1c = glycosylated hemoglobin; TC = total cholesterol; TG = triglyceride; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure; GPT = glutamic-pyruvic transaminase; Cr = creatinine; eGFR = estimated glomerular filtration rate; ACR = urine albumin-creatinine ratio.

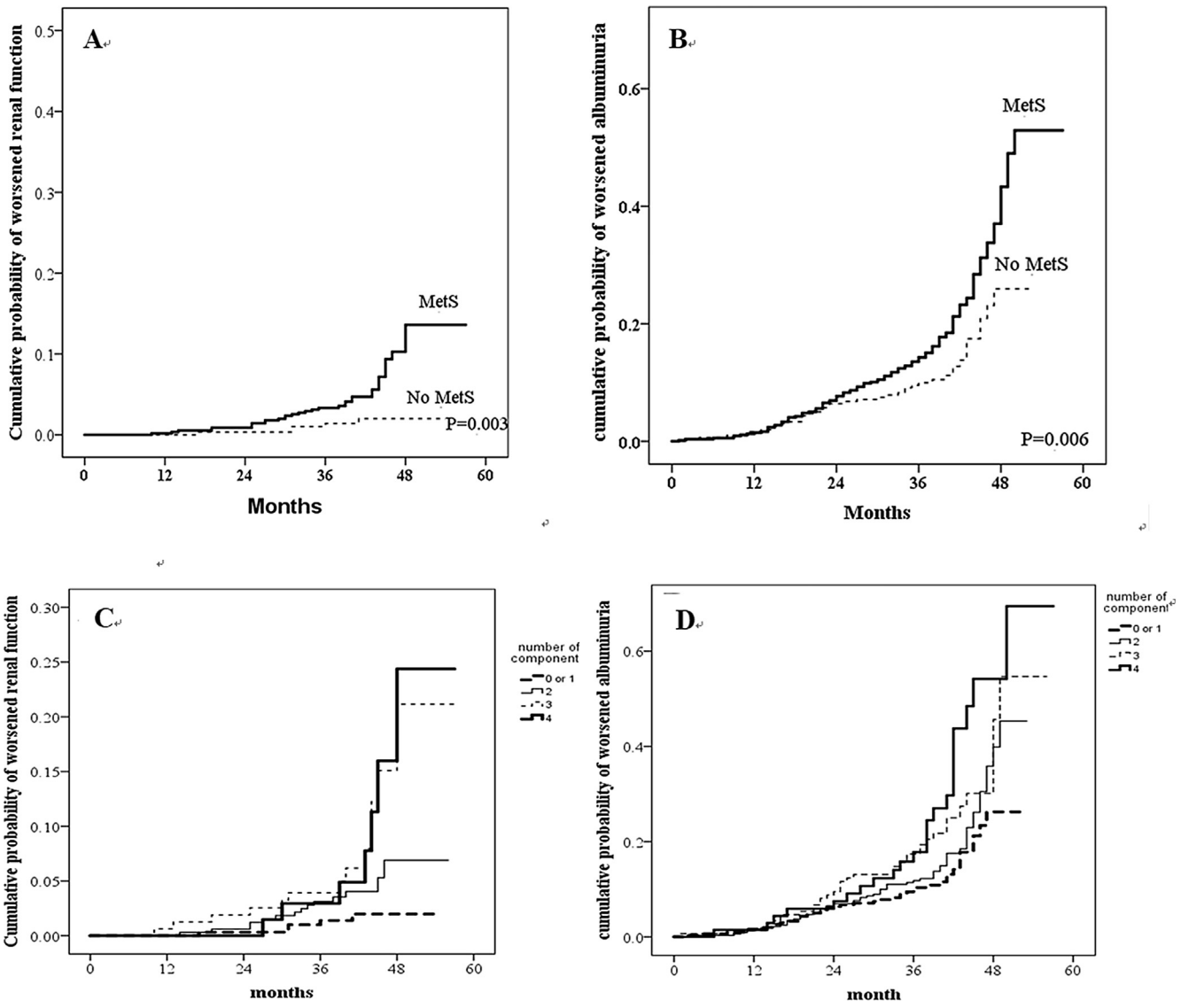

Fig. 1 – Kaplan-Meier estimates of probability of worsening renal function (Panel A) or progression of albuminuria (Panel B) in type 2 diabetic patients and cumulative probability of worsened renal function (Panel C) or progression of albuminuria (Panel D) according to the number of metabolic syndrome components.

metabolic syndrome. The cumulative incidence of progression of albuminuria increased sharply in patients with metabolic syndrome but to a lesser degree in those without metabolic syndrome (log-rank test, p = 0.006) (Fig. 1). Furthermore, we analyzed the association of these two endpoints with the number of metabolic syndrome components. As Fig. 1 shows, among patients with diabetes, increase in number of metabolic syndrome components was associated with a cumulative effect of worsening renal function and progression of albuminuria.

We used Cox regression analysis to explore the relationship between metabolic syndrome and DKD. In univariate Cox regression analysis, metabolic syndrome was significantly associated with progression of albuminuria (Table 2). After adjusting for confounding variables such as gender, age, DM duration, HbA1c level, TG, LDL, BMI, hypertension, use of ACEI or ARB, CKD and microalbuminuria, the multivariable-adjusted HR for patients with metabolic syndrome compared to those without metabolic syndrome was 1.65 (95% CI 1.07–2.53, p = 0.022). Subjects with two, three, and four metabolic syndrome components had HRs of 1.47 (0.92–2.32, P = 0.106), 1.91 (1.12–3.24, P = 0.017), and 2.29 (1.25–4.19, P = 0.007) respectively, compared to those with zero or one component of metabolic syndrome, excluding diabetes. The HRs increased as the number of metabolic syndrome components increased. On the other hands, metabolic syndrome was also significantly associated with worsening renal function (Table 3). Again, when accounting for confounding covariables, the association remained statistically significant (HR 2.62 95% CI 1.01–6.79 p = 0.047). Similarly, we also observed a gradual increase in HRs for deterioration in renal function with increasing number of

Table 2 – Cox proportional hazards models for the progression of albuminuria (transition to a more advanced stage of albuminuria) in type 2 diabetic patients.

	Univariate HR 95%(CI)	P-value	Multivariable HR 95%(CI)	P-value
Gender (male/female)	0.91(0.67–1.25)	0.554		
Elderly (>65 years)	1.38(1.01–1.89)	0.044		
DM duration (>10 years)	1.04(0.76–1.44)	0.798		
Higher HbA1c level (>7)	0.90(0.66–1.23)	0.497		
TG (per mg/dL)	1.01(1.00–1.02)	0.008		
LDL (per mg/dL)	1.00(0.99–1.00)	0.145		
BMI (kg/m^2)	0.99(0.96–1.03)	0.678		
Central obesity	1.72(1.26–2.34)	0.001		
Hypertension (SBP > 140)	1.34(0.97–1.83)	0.072		
ACEI or ARB use at baseline	1.01(0.74–1.38)	0.952		
CKD (eGFR < 60 mL/min/1.73 m^2)	2.15(1.53–3.01)	<0.001	2.05(1.40–3.01)	<0.001
Microalbuminuria (ACR > 30 mg/g)	1.35(0.97–1.88)	0.071		
Metabolic syndrome[†]				
2 components	1.31(0.88–1.95)	0.187	1.47(0.92–2.32)	0.106
3 components	1.84(1.17–2.89)	0.008	1.91(1.12–3.24)	0.017
4 components	2.54(1.52–4.23)	<0.001	2.29(1.25–4.19)	0.007

HbA1c = glycosylated hemoglobin; TG = triglyceride; LDL = low-density lipoprotein cholesterol; BMI = body mass index; SBP = systolic blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ACR = urine albumin-creatinine ratio.

[†] Comparsion to 0 or 1 component of metabolic syndrome except for diabetes.

Table 3 – Cox proportional hazards models for worsening renal function (doubling of serum creatinine or eGFR reduction >50%) in type 2 diabetic patients.

	Univariate HR 95%(CI)	P value	Multivariable HR 95%(CI)	P value
Gender (male/female)	0.78(0.41–1.47)	0.436		
Elderly(>65 years)	1.40(0.74–2.64)	0.299		
DM duration (>10 years)	2.59(1.22–5.52)	0.013	2.22(1.03–4.84)	0.043
Higher HbA1c level (>7)	2.39(1.16–4.90)	0.018	2.39(1.08–5.28)	0.031
TG (per mg/dL)	1.00(1.00–1.00)	0.012		
LDL (per mg/dL)	0.99(0.97–1.00)	0.020		
BMI (kg/m^2)	1.01(0.94–1.09)	0.715		
Central obesity	2.40(1.26–4.57)	0.008		
Hypertension (SBP > 140)	1.77(0.92–3.40)	0.086		
ACEI or ARB use at baseline	1.10(0.58–2.06)	0.779		
CKD (eGFR < 60 mL/min/1.73 m^2)	1.88(0.97–3.67)	0.063		
Microalbuminuria (ACR > 30 mg/g)	4.04(2.12–7.70)	<0.001	3.01(1.52–5.95)	0.002
Metabolic syndrome[†]				
2 components	2.56(0.92–7.11)	0.071	2.49(0.79–6.11)	0.249
3 components	5.47(1.95–15.34)	0.003	3.59(1.35–10.90)	0.031
4 components	5.60(1.78–17.67)	0.001	3.84(1.13–11.44)	0.011

HbA1c = glycosylated hemoglobin; TG = triglyceride; LDL = low-density lipoprotein cholesterol; BMI = body mass index; SBP = systolic blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ACR = urine albumin-creatinine ratio.

[†] Comparsion to 0 or 1 component of metabolic syndrome except for diabetes.

metabolic syndrome components excluding diabetes; 2.19 (0.79–6.11, P = 0.133) for two components, 3.59 (1.35–10.90, P = 0.031) for three components and 3.84 (1.13–11.44, P = 0.011) for four components.

7. Discussion

Our study demonstrated that the presence of metabolic syndrome independently predicted the progression of DKD, which was assessed by a 50% reduction in eGFR or doubling of serum creatinine and the transition to a more advanced stage of albuminuria in patients with type 2 diabetes. Our findings also demonstrated an increasing trend of DKD progression with increasing number of metabolic syndrome components, strengthening the association of DKD and metabolic syndrome. Furthermore, multivariate Cox regression analysis revealed that the association remained significant even after adjusting for other factors that may affect renal function.

Metabolic syndrome as a surrogate marker for visceral obesity is more closely associated with adverse metabolic risks (including hypertension, high triglyceride, low HDL and insulin resistance). Actually, type 2 diabetes itself was already found to have an independent and pivotal role in

predicting progression of DKD. Since all patients in our study were type 2 diabetes, we investigated whether the addition of the other four risk components had predicting significance. Previous research showed the cumulative effect of metabolic syndrome components, with increase in number of metabolic syndrome components resulting in a higher risk of CKD development [9,10]. Although hyperglycemia is the key modifiable risk factor that promotes the development of DKD, other components of metabolic syndrome such as hypertension, high triglyceride, and low HDL are also well-recognized modifiable initiators and promoters of DKD [11].

The central feature of metabolic syndrome is obesity. Although the association between obesity and renal dysfunction may primarily be due to metabolic abnormalities such as hypertension and dyslipidemia, a recent meta-analysis showed that obesity alone can increase the risk of CKD even without other metabolic abnormalities. If patients had other metabolic abnormalities, the risk of CKD increased compared to those without. Patients suffering from both obesity and metabolic abnormalities ultimately had the highest risk for CKD [12]. A Japanese study of more than 100,000 screened participants showed that high BMI was associated with a high risk of developing ESRD in men after additionally adjusting for hypertension and proteinuria [13]. Another study of more than 300,000 patients from the US with two decades of observation also revealed that higher BMI was an independent predictor for ESRD even after adjusting for blood pressure and diabetes [14]. Both these studies highlight the risk of renal dysfunction in obese patients. However, even within a normal range of BMI, there may still be an increased risk of abdominal fat accumulation, especially in some Asians [15]. Unlike typical obesity, central or abdominal fat accumulation was independently associated with metabolic syndrome [16]. In our present study on T2DM, central obesity is more relevant than BMI on renal outcomes, not only in progression of albuminuria, but also in worsening of renal function. Similar to our study, previous DKD studies showed that waist circumference, not BMI, together with arterial hypertension and dyslipidemia were associated with the risk of arteriosclerosis, ultimately leading to local intrarenal hemodynamic changes and albuminuria in diabetes [10,17]. Therefore, metabolic syndrome as a surrogate for insulin resistance would be superior to BMI in confirming impaired renal function in patients with DKD.

Growing clinical evidence has supported the association between metabolic syndrome and the development of kidney disease. A cross-section study of 7832 American participants showed that metabolic syndrome was an important predictor of early renal insufficiency, and the odds ratio (OR) of CKD and microalbuminuria increased with the number of metabolic syndrome components [9]. Another study of 15,160 Chinese individuals also demonstrated that the risk of CKD increased as the number of metabolic syndrome components increased [18]. A meta-analysis of 30,146 participants confirmed a relationship between metabolic syndrome and the development of eGFR < 60 mL/min per 1.73 m^2 and microalbuminuria or proteinuria [19].

However, few studies have evaluated the association between metabolic syndrome and DKD. Diabetes is not only an important cause of CKD but is also a major component of metabolic syndrome. Therefore, we recruited type 2 diabetic patients to evaluate whether other metabolic syndrome components accelerate renal disease. We wondered whether the central feature of metabolic syndrome, obesity, had certain additional impacts on DKD progression. A prospective study with an EDIC study cohort demonstrated that waist circumference was associated with the development of microalbuminuria in type 1 diabetes, but no association between waist circumference and reduction of creatinine clearance was found. This finding was probably due to the difference in pathogenesis between type 1 and type 2 diabetes and the heterogeneity and unpredictable duration of the disease [20]. In fact, a prospective study of type 2 diabetic patients from Hong Kong showed that metabolic syndrome independently predicted the development of CKD after adjusting for traditional risk factors, including age, glucose control, duration of disease and proteinuria [3]. Our study further confirmed that the presence of metabolic syndrome not only predicted the progression of CKD but also a transition to a more advanced stage of albuminuria in type 2 diabetes.

Metabolic syndrome might increases the risk of CKD [3]. CKD itself is an independent determinant of atherosclerotic disease. It is now known that metabolic syndrome is associated with the development of cardiovascular disease [4], and these conditions often coexist and have a vicious circle. Even renal outcomes such as albuminuria and reduced eGFR strongly predicted cardiovascular outcomes in a cohort study [21,22]. The underlying pathology of the metabolic syndrome included increased oxidative stress, chronic inflammation, increased fibrogenic activity, and endothelial dysfunction. Additionally, in metabolic syndrome, the presence of hyperinsulinemia and adipocytokines produced by adipocytes may ultimately lead to podocyte injury and induce albuminuria and profibrotic states. Therefore, we propose that risk factors in metabolic syndrome play a vital role in the progression of DKD [23].

Beside metabolic syndrome, we found other statistically significant risk factors for progression of microalbuminuria such as age and triglyceride (Table 2). On the other hand, in our study, diabetes duration and LDL were also risk factors for worsening renal function (Table 3). Most results except LDL were rational and compatible with prior research results [24,25]. However, until now, the effect of LDL levels or LDL-lowering on CKD progression remains uncertain [26]. As for DKD, only one study of a DCCT / EDIC cohort mentioned that renal deterioration was associated with elevated LDL levels, but most were for type 1 diabetes patients with smaller LDL size and elevated triglyceride levels [27].

Regardless of the different definitions, the prevalence of metabolic syndrome is increasing in both Western and Asian countries. It is difficult to clarify the concept of type 2 DM only or type 2 DM with metabolic risk factors due to the close correlation between type 2 DM and metabolic syndrome. In our study, ATPIII criteria identified more people with metabolic syndrome because diagnosis could be made with diabetes and two or three other metabolic disorders, without the coexistence of central obesity, which is a prerequisite for diagnosis by IDF. Small differences in diagnostic criteria by IDF and ATPIII are noted when applied to the Chinese population [28]. In a Chinese population with type 2 diabetes, the diagnosis of metabolic syndrome cannot rely solely on the presence

or absence of central obesity. Another study found that subjects with or without central obesity and the same number of components of metabolic syndrome had the same incidence of diabetes [29]. Waist circumference may not accurately reflect visceral fat for East Asians. Participants in East Asia have a lower overall adiposity levels and are more likely to accumulate visceral adipose tissue than any other ethnic groups [30]. Therefore, we should not ignore the potential risks of subjects without central obesity.

To the best of our knowledge, this study is the first to demonstrate the association between metabolic syndrome and the progression of DKD, as assessed by a 50% eGFR reduction or doubling of serum creatinine and worsening albuminuria. Nevertheless, our study has several limitations. First, since our study only consisted of a single center cohort, our results lack external validity. However, biochemical measurements using the same standard method improved the reliability of our data. Second, we cannot exclude the possibility of other confounders, including such medications as new oral diabetic medications and SGLT2 inhibitors that may affect our results. Third, other underlying kidney diseases, such as hypertensive nephrosclerosis, obstructive uropathy, and glomerulonephritis, may also accelerate kidney dysfunction and the progression of albuminuria.

In conclusion, this observational cohort study supports the hypothesis that metabolic syndrome, independent of other covariates, is a predictor of declining renal function and worsening albuminuria in patients with type 2 diabetes.

Acknowledgments

The authors thank Dr. Ming-Chieh Tsai (Division of Endocrinology and Metabolism, Department of Internal Medicine, Mackay Memorial Hospital) for her excellent assistance in data collection. The authors also thank all the involved clinicians, nurses, and technicians for dedicating their time and skill to this study.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Funding

The authors received no funding from an external source.

Author Contributions

S.C. and H.S. collected and analyzed data and wrote the paper. M.C. and S.L. interpreted the data and revised the manuscript. S.C. and H.S. conceived the study. S.C., H.S and S.L. analyzed data. S.C.,C.L. and C.W. conducted the study and collected data. S.C and C.L. are the guarantors of this work and as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

[1] United States Renal Data System (USRDS) Annual Data Report 2016. https://www.usrds.org/2016/view/v2_01.aspx, 2017.
[2] Marchesini G, Forlani G, Cerrelli F, Manini R, Natale S, Baraldi L, et al. WHO and ATPIII proposals for the definition of the metabolic syndrome in patients with Type 2 diabetes. Diabet Med 2004;21:383–7. https://doi.org/10.1111/j.1464-5491.2004.01115.
[3] Luk AO, So WY, Ma RC, Kong AP, Ozaki R, Ng VS, et al. Metabolic syndrome predicts new onset of chronic kidney disease in 5,829 patients with type 2 diabetes: a 5-year prospective analysis of the Hong Kong Diabetes Registry. Diabetes Care 2008;31:2357–61. https://doi.org/10.2337/dc08-0971.
[4] Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care 2005;28:1769–78.
[5] Costa LA, Canani LH, Lisbôa HR, Tres GS, Gross JL. Aggregation of features of the metabolic syndrome is associated with increased prevalence of chronic complications in type 2 diabetes. Diabet Med 2004;21:252–5.
[6] Palaniappan L, Carnethon M, Fortmann SP. Association between microalbuminuria and the metabolic syndrome: NHANES III. Am J Hypertens 2003;16:952–8.
[7] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.
[8] Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, et al. Nephropathy in diabetes. Diabetes Care 2004;27:S79–83.
[9] Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med 2004;140:167–74.
[10] De Cosmo S, Trevisan R, Minenna A, Vedovato M, Viti R, Santini SA, et al. Insulin resistance and the cluster of abnormalities related to the metabolic syndrome are associated with reduced glomerular filtration rate in patients with type 2 diabetes. Diabetes Care 2006;29:432–4.
[11] Macisaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. Am J Kidney Dis 2014;63:S39–62. https://doi.org/10.1053/j.ajkd.2013.10.048.
[12] Zhang J, Jiang H, Chen J. Combined effect of body mass index and metabolic status on the risk of prevalent and incident chronic kidney disease: a systematic review and meta-analysis. Oncotarget 2017;8:35619–29. https://doi.org/10.18632/oncotarget.10915.
[13] Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int 2004;65:1870–6.
[14] Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006;144:21–8.
[15] Mathew H, Farr OM, Mantzoros CS. Metabolic health and weight: Understanding metabolically unhealthy normal weight or metabolically healthy obese patients. Metabolism 2016;65:73–80. https://doi.org/10.1016/j.metabol.2015.10.019. Epub 2015 Oct 23.

[16] Goodpaster BH, Krishnaswami S, Harris TB, Katsiaras A, Kritchevsky SB, Simonsick EM, et al. Obesity, regional body fat distribution, and the metabolic syndrome in older men and women. Arch Intern Med 2005;165:777–83.
[17] Isomaa B, Henricsson M, Almgren P, Tuomi T, Taskinen MR, Groop L. The metabolic syndrome influences the risk of chronic complications in patients with type II diabetes. Diabetologia 2001;44:1148–54.
[18] Chen J, Gu D, Chen CS, Wu X, Hamm LL, Muntner P, et al. Association between the metabolic syndrome and chronic kidney disease in Chinese adults. Nephrol Dial Transplant 2007;22:1100–6.
[19] Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2011;6:2364–73. https://doi.org/10.2215/CJN.02180311. Epub 2011 Aug 18.
[20] de Boer IH, Sibley SD, Kestenbaum B, Sampson JN, Young B, Cleary PA, et al. Central obesity, incident microalbuminuria, and change in creatinine clearance in the epidemiology of diabetes interventions and complications study. J Am Soc Nephrol 2007;18:235–43.
[21] So WY, Kong AP, Ma RC, Ozaki R, Szeto CC, Chan NN, et al. Glomerular filtration rate, cardiorenal end points, and all-cause mortality in type 2 diabetic patients. Diabetes Care 2006;29:2046–52.
[22] Tong PC, Kong AP, So WY, Yang X, Ng MC, Ho CS, et al. Interactive effect of retinopathy and macroalbuminuria on all-cause mortality, cardiovascular and renal end points in Chinese patients with type 2 diabetes mellitus. Diabet Med 2007;24:741–6.
[23] De Cosmo S, Menzaghi C, Prudente S, Trischitta V. Role of insulin resistance in kidney dysfunction: insights into the mechanism and epidemiological evidence. Nephrol Dial Transplant 2013;28:29–36. https://doi.org/10.1093/ndt/gfs290.
[24] Smulders YM, Rakic M, Stehouwer CD, Weijers RN, Slaats EH, Silberbusch J. Determinants of progression of microalbuminuria in patients with NIDDM.A prospective study. Diabetes Care 1997;20:999–1005.
[25] Ohno T, Kato N, Shimizu M, Ishii C, Ito Y, Tomono S, et al. Effect of age on the development or progression of albuminuria in non-insulin-dependent diabetes mellitus (NIDDM) without hypertension. Diabetes Res 1993;22:115–21.
[26] Haynes R, Lewis D, Emberson J, Reith C, Agodoa L, Cass A, et al. Effects of lowering LDL cholesterol on progression of kidney disease. J Am Soc Nephrol 2014;25:1825–33. https://doi.org/10.1681/ASN.2013090965.
[27] Jenkins AJ, Lyons TJ, Zheng D, Otvos JD, Lackland DT, McGee D, et al. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. Kidney Int 2003;64:817–28.
[28] Liu J, Grundy SM, Wang W, Smith Jr SC, Vega GL, Wu Z, et al. Ethnic-specific criteria for the metabolic syndrome: evidence from China. Diabetes Care 2006;29:1414–6.
[29] Lee IT, Chiu YF, Hwu CM, He CT, Chiang FT, Lin YC, et al. Central obesity is important but not essential component of the metabolic syndrome for predicting diabetes mellitus in a hypertensive family-based cohort. Results from the Stanford Asia-pacific program for hypertension and insulin resistance (SAPPHIRe) Taiwan follow-up study. Cardiovasc Diabetol 2012;11:43. https://doi.org/10.1186/1475-2840-11-43.
[30] Nazare JA, Smith JD, Borel AL, Haffner SM, Balkau B, Ross R, et al. Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the International Study of Prediction of Intra-Abdominal Adiposity and Its Relationship With Cardiometabolic Risk/Intra-Abdominal Adiposity. Am J Clin Nutr 2012;96:714–26.