Original Article

Factors Associated with New Onset of Microalbuminuria in Patients with Type 2 Diabetes

Li-Fen Lu[1], Chao-Ping Wang[2], Teng-Hung Yu[2], Wei-Chin Hung[2],

Yau-Jiunn Lee[4], Yung-Chuan Lu[3]

Objectives: Microalbuminuria is often the first sign of renal dysfunction in patients with diabetes. Furthermore, the presence of microalbuminuria is associated with overt nephropathy and cardiovascular disease. The aim of this study was to investigate the incidence and baseline predictors for the development of microalbuminuria in patients with type 2 diabetes mellitus (T2DM).

Methods: In this longitudinal cohort study, we enrolled 739 normoalbuminuric patients with T2DM who were receiving routine clinical care at baseline. All of the patients were regularly examined for diabetes-associated complications.

Results: Of the enrolled patients, 262 (35.5%) progressed to microalbuminuria during follow-up (median, 3 years), with an incidence density of 9.17/100 people per year. Cox regression analysis showed that the baseline clinical and biochemical variables associated with the development of microalbuminuria were age, duration of diabetes, being illiterate, being a widow or widower, family history of T2DM, living alone, dependent economic situation, taking antihypertensive medication, anemia, stroke, elevated waist circumference, waist-to-hip ratio, systolic blood pressure plasma, triglyceride and creatinine concentration, Creatinine clearance estimated by modificated Cockcroft-Gault Equation (CCr-CGCR), urinary albumin to creatinine ratio (UACR), red blood cell count as well as hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration. After multivariate Cox regression analysis, the independent factors associated with the development of microalbuminuria were duration of diabetes, stroke, waist circumference, creatinine, and UACR.

Conclusions: A longer duration of diabetes, higher stroke rate, elevated waist circumference, as well as plasma creatinine level and UACR increased the risk of developing microalbuminuria in patients with T2DM after long-term follow-up. Except for the duration of diabetes, these factors are modifiable and should be identified early and followed closely.

Key words: microalbuminuria, incidence, risk factors, type 2 diabetes mellitus

From the [1]Division of Cardiac Surgery, Department of Surgery, and [2]Division of Cardiology, and [3]Division of Endocrinology and Metabolism, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung, and [4]Lee's Endocrinologic Clinic, Pingtung, Taiwan.

Received: November 5, 2015 Accepted: January 13, 2016

Address reprint request and correspondence to: Yung-Chuan Lu, Division of Endocrinology and Metabolism, Department of Internal Medicine, E-Da Hospital, No. 1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan.

Tel: +886-7-6150011 ext. 5914 or 5018, Fax: +886-7-6150940, E-mail: gene6623@yahoo.com.tw; gregory.yclu@msa.hinet.net

Introduction

The incidence of end-stage renal disease caused by diabetic nephropathy is currently worldwide. Diabetes represents the second leading cause of dialysis in most centers.[1,2] The earliest clinical sign of diabetic nephropathy is elevated urinary albumin excretion, referred to as microalbuminuria, which affects 20-40% of patients with type 2 diabetes.[3] Once microalbuminuria occurs, glomerular filtration rate begins to decline at an average rate of 10-12 mL/min/year.[3]

Microalbuminuria is defined as an albumin excretion rate of 20-199 g/min in a timed or 24 hours urine collection (equivalent to 30-299 mg/g creatinine in a random spot sample).[4] Microalbuminuria in diabetic patients is not only a predictor of the progression of diabetic nephropathy, but also a powerful independent risk factor for cardiovascular disease and all-cause mortality.[5-11] Thus, the prevention of elevated urinary albumin excretion is an important therapeutic target for the prevention of renal and cardiovascular events, and the identification of modifiable factors that affect microalbuminuria remains a key goal.

Although many studies have reported on the course of microalbuminuria in patients with type 1 diabetes and in certain racial groups with type 2 diabetes, only a few studies have explored this issue in Chinese patients with type 2 diabetes.[12,13] Furthermore, it appears that disease development at each stage of diabetic nephropathy is determined by somewhat different sets of risk factors. While the level of glycemic control is the most likely contributor to the occurrence of microalbuminuria,[14] its progression through the more advanced stages is determined by such risk factors as hypertension, hypercholesterolemia and certain unidentified genetic factors.[15] Moreover, the course of microalbuminuria is very complex and heterogeneous in patients with type 2 diabetes, mainly depending on individual, ethnic, genetic, environmental, and disease-specific conditions.[16-20] The aim of this longitudinal study was to determine the incidence of and predictors for the development of microalbuminuria in a Chinese population with type 2 diabetes without previous known proteinuria or kidney disease based on medical records. The results could be important in increasing physicians' awareness of the importance of regular urinary albumin screening when caring for patients with diabetes.

Subjects and Methods

Study participants

In this longitudinal observational study, we included outpatients with type 2 diabetes who regularly attended the diabetes clinic at Lee's Endocrinology Clinic in Pingtung and diabetes clinic of E-Da Hospital in Kaohsiung. The diagnosis of type 2 diabetes was based on World Health Organization criteria.[21] The inclusion criteria were a diagnosis of type 2 diabetes, regular follow-up at our clinic, and agreeing to participate by providing informed consent. Patients who had cancer, liver disease, fewer than two follow-up visits, either incipient or clinical nephropathy at baseline, and end-stage renal disease were excluded from this study. The initial cohort was followed from January 2002. During the follow-up period, each patient underwent standardized physical examinations, biochemical measurements after fasting, and measurements of urine albumin and urine creatinine within a period of 3 months. All participants received treatment based on the standard strategies for diabetes, hypertension, and hyperlipidemia during follow-up.

Study parameters and definitions

The urinary albumin concentration was measured by immunoturbidimetry (Beckman Instruments, Galway, Ireland). The detec-

tion limit was 2 mg/L, and the interassay and intraassay coefficients of variance were less than 8%. In the initial evaluation period, the patients were defined as being normoalbuminuric if they had a urinary albumin-to-creatinine ratio (UACR) of less than 30 mg/g regardless of duration of diabetes. In the follow-up period, to confirm the diagnosis of microalbuminuria, patients first observed to have microalbuminuria were asked to re-check the urine albuminuria within 3 to 6 months. The status of microalbuminuria was defined as a UACR of 30-300 mg/g in at least two consecutive overnight urine collections. Each urine specimen was tested for the presence of urinary infections for which the urine was discarded and a new sample was collected after treatment. Normal serum creatinine levels (0.8-1.4 mg/dL) and normal urinary sediment (absence of protein, red blood cells, hemoglobin, white blood cells, nitrites and casts) were used to exclude primary renal disease.

Plasma biochemical parameters and urinary microalbumin were measured after an overnight fast. Plasma triglycerides, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, uric acid, creatinine, and glucose were determined by standard commercial methods on a parallel-multichannel analyzer (Hitachi 7170A, Tokyo, Japan). Anthropometric parameters including body mass index and waist-to-hip ratio were measured. Waist and hip circumferences were measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest. The hips were measured at their widest point. Blood pressure was measured with the subject in sitting position by a trained nurse with a digital automatic blood pressure monitor (model HEM-907; Omron, Omron, Japan) after the subjects had rested for 5 minutes. The study protocol and procedure were approved by the Ethics Committee of E-Da Hospital (EDAH IRB No. EMRP03103N). Informed consents were obtained from all subjects.

Statistical analysis

Descriptive data were examined for all variables. For continuous variables, the results were presented as mean ± SD and as a percentage of the total for categorical variables. All statistical analyses were performed using SAS software, v10.0 (SAS Institute, Cary, NC). Baseline characteristics of the case and control subjects were compared by the Student's t test or χ^2 test. Cox regression univariate analysis was performed on each baseline variable. The patients were followed till they developed microalbuminuria, and the outcome was defined as the time elapsed before the development of microalbuminuria. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals. The variables with a p value < 0.25 in the univariate Cox regression were entered into the multivariate model. The proportional hazards assumption was verified by analysis of Schoenfeld residuals and assessment of a graph of the survival function versus the survival time. The incidence rate of microalbuminuria was expressed as cases/100 patients/year. Model discrimination was assessed by area under the receiver operating characteristic curves (AUC), which is a measure of overall predictive discrimination. All of the statistical analyses were two-sided, and a $p < 0.05$ was considered to be significant.

Results

During the follow-up period (median 3.0 years, range 1.0-10.0 years), 262 (35.5%) of the 739 normoalbuminuric patients at baseline fulfilled the criteria for microalbuminuria. The incidence density was 9.17/100 people per year.

The follow-up period and the duration of diabetes before the development of microalbuminuria were 3 (1-6) and 9 (6-13) years,

respectively. The final UACRs were 48.8 mg/g (22.6-174.8 mg/g) and 10.7 mg/g (7.6-16.8 mg/g) for patients who had microalbuminuria and persistent normoalbuminuria, respectively.

The baseline characteristics and clinical data for all of the patients are presented in Table 1. The patients who developed microalbuminuria had higher rates of illiteracy, being a widow or widower, no family history of type 2 diabetes mellitus (T2DM), living alone, being economically dependent, taking antihypertensive medication, and having anemia than those with persistent normoalbuminuria. In addition, the patients who developed microalbuminuria were older and had a longer duration of diabetes, larger waist circumference, higher systolic blood pressure and diastolic blood pressure, creatinine level, and UACR as well as lower Creatinine clearance estimated by modificated Cockcroft-Gault Equation (CCr-CGCR), red blood cell count, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration than those in patients with persistent normoalbuminuria (Table 2).

After individual Cox regression analysis, the baseline clinical and biochemical variables associated with the development of microalbuminuria were age, duration of diabetes, being illiterate, a widow or widower, having a family history of T2DM, living alone, being economically dependent, taking antihypertensive medication, having anemia, history of stroke, increased waist circumference, waist-to hip-ratio, systolic blood pressure, triglyceride and creatinine levels, CCr-CGCR, UACR, red blood cell count, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration. After multivariate Cox regression analysis, the independent factors associated with the development of microalbuminuria were duration of diabetes [HR 1.04 (1.01-1.07)], stroke [HR 2.49 (1.17-4.83)], waist circumference [HR 1.04 (1.01-1.07)], creatinine [HR 3.88 (1.52-9.79)], and UACR [HR 1.09 (1.07-1.11)] (Table 3 and 4).

Table 1. Basic characteristics and clinical measures of the study participants with and without microalbuminuria

Variable	Total (%)	New onset of microalbuminuria (%)	Non-microalbuminuria (%)	*p*-value
No	739	262	477	
Gender				
Women	56.2	58.8	54.7	0.287
Men	43.8	41.2	45.3	
Education				
Illiterate	19.4	23.9	17.0	0.024
Elementary school	26.1	24.2	27.2	0.395
Junior high school	16.9	16.9	17.0	0.993
High school	16.9	15.0	18.0	0.299
College	15.7	12.7	17.4	0.096
Marital status				
Single	4.7	3.9	5.2	0.433
Married	84.4	81.7	86.0	0.132
Divorced	0.4	0.0	0.7	0.556
Widow or widower	10.4	14.4	8.2	0.009
Family history of T2DM				
None	30.7	36.6	27.5	0.010
Unknown	19.0	18.3	19.3	0.748
Yes	50.3	45.0	53.3	0.033
Living Alone	3.4	6.1	1.5	0.008
Economic situation, ependent	42.6	49.5	37.7	0.013
Smoking	18.2	16.4	19.1	0.362
Drinking	15.9	14.5	16.6	0.449
Regular exercise	65.0	67.1	63.9	0.388
Antihypertensive medication	37.0	41.9	34.3	0.044
Statin	16.4	13.6	17.9	0.130
Oral hypoglycemic medication	96.4	96.9	96.2	0.605
Insulin therapy	8.3	9.7	7.5	0.296
Anemia	27.1	32.2	23.6	0.023
Hypertension	84.2	85.3	83.6	0.550
Hyperlipidemia	43.4	40.9	44.7	0.465
Coronary artery disease	23.0	25.1	21.8	0.320
Stroke	3.9	5.5	3.0	0.238

T2DM: Type 2 diabetes mellitus

The ability of duration of diabetes, stroke, creatinine, waist circumference, and UACR to predict the risk of microalbuminuria was then evaluated. The AUC for duration of diabetes was 0.583 (p = 0.006). For stroke, plasma

Table 2. Basic characteristics and biochemical measures of the study participants with and without microalbuminuria

Variable	Total	New onset of microalbuminuria	Non-microalbuminuria	*p*-value
No	739	262	477	
Age (years)	66.0 ± 12.4	68.2 ± 12.6	64.8 ± 12.1	0.0004
DMDU (years)	15.5 ± 5.8	16.3 ± 5.9	15.1 ± 5.7	0.005
Body mass index (kg/m^2)	25.3 ± 3.6	25.6 ± 3.5	25.2 ± 3.6	0.143
Waist circumference (cm)	89.6 ± 9.7	91.0 ± 9.7	88.8 ± 9.5	0.003
Waist to hip ratio	0.95 ± 0.1	0.95 ± 0.1	0.94 ± 0.1	0.410
Systolic BP (mmHg)	136 ± 21	140 ± 22	134 ± 19	0.0004
Diastolic BP (mmHg)	81 ± 12	82 ± 13	80 ± 11	0.016
HbA1C (%)	8.0 ± 2.1	8.0 ± 2.0	8.0 ± 2.1	0.662
Fasting sugar (mg/dL)	160.1 ± 55.8	158.8 ± 55.2	160.8 ± 56.1	0.631
Total cholesterol (mg/dL)	194.4 ± 38.7	193.6 ± 37.2	194.8 ± 39.5	0.670
Triglyceride (mg/dL)	145.5 ± 137.9	156.6 ± 199.4	139.4 ± 87.2	0.106
HDL-cholesterol (mg/dL)	46.3 ± 13.2	46.7 ±13.3	46.1 ± 13.2	0.536
LDL-cholesterol (mg/dL)	116.3 ± 31.5	114.8 ± 31.4	117.2 ± 31.6	0.321
Creatinine (mg/dL)	0.85 ± 0.2	0.87 ± 0.2	0.84 ± 0.2	0.042
CCr-CGCR (mL/min)	85.3 ± 27.7	81.6 ± 27.3	87.6 ± 27.4	0.005
UACR(mg/g)	10.4 ± 7.0	13.1 ± 7.5	9.0 ± 6.2	< 0.0001
White blood cell (10^9/l)	6.513 ± 1.6	6.542 ± 1.6	6.493 ± 1.6	0.716
Red blood cell (× 10^6/μL)	4.62 ± 0.6	4.56 ± 0.6	4.66 ± 0.6	0.049
Hemoglobin (g/dL)	13.5 ± 1.7	13.3 ± 1.7	13.7 ± 1.6	0.003
Hematocrit (%)	40.3 ± 4.3	39.8 ± 4.3	40.7 ± 4.3	0.009
Mean corpuscular volume (fL)	87.9 ± 7.6	87.8 ± 7.8	88.0 ± 7.4	0.767
MCH (pg/cell)	29.4 ± 3.2	29.3 ± 3.2	29.5 ± 3.2	0.441
MCHC (g/dL)	33.5 ± 1.2	33.3 ± 1.3	33.6 ± 1.2	0.012

Data presented as means ± SD; DMDU: Known duration of diabetes; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; CCr-CGCr: Creatinine clearance estimated by modificated Cockcroft-Gault Equation[13] (adjusted by age, sex, weight, creatinine); UACR: Urinary albumin to creatinine ratio

concentration creatinine, waist circumference, and UACR were added to this multivariate model: The AUC were increased to 0.597 for duration of diabetes and stroke, 0.598 for duration of diabetes, stroke, and creatinine, 0.616 (p = 0.005) for duration of diabetes, stroke, creatinine, and waist circumference, 0.702 (p < 0.0001) for duration of diabetes, creatinine, waist circumference, and UACR, and 0.705 (p < 0.0001) for duration of diabetes, stroke, creatinine, waist circumference, and UACR (Fig. 1).

Discussion

In this prospective study of normoalbuminuric patients with T2DM, 35.5% developed microalbuminuria after 9-year duration of diabetes and 3 (1-6) years of follow-up. The DEMAND (Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes) study reported that the overall prevalence of microalbuminuria among 24,151 patients with type 2 diabetes was 39%,[22] and the MAP (MicroAlbuminuria Prevalence) study reported the prevalence to be 40% among 5,549 Asian patients.[23] Hiroki et al. reported that the prevalence of microalbuminuria in a Japanese cohort of patients with T2DM was 32%.[24] In a study conducted in Saudi Arabia, the overall prevalence of microalbuminuria in both patients with type I and type II diabetes mellitus was 49.3%.[25] It has also been reported that the prevalence of microalbuminuria is 52% among all diabetic patients.[26] Taken together, these findings indicate that microalbuminuria is common.

Table 3. Cox proportional hazard model of baseline clinical risk factors for the development of microalbuminuria in 739 patients with type 2 diabetes who were followed for ten years

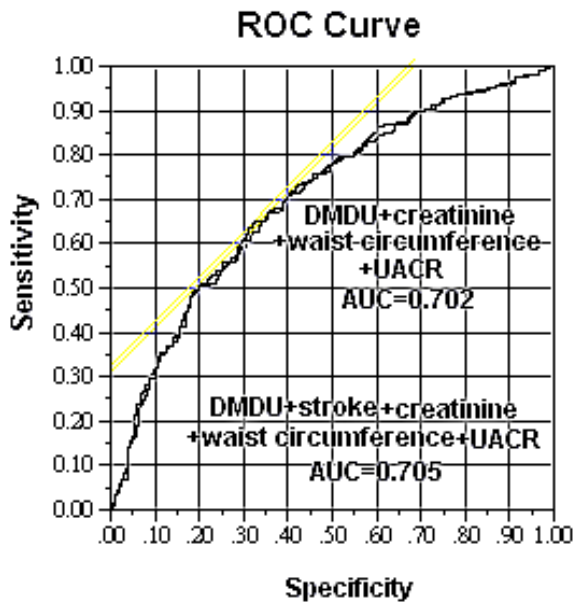
Baseline data	Univariate analysis hazard ratio (95% CI)	*p*-value	Multivariate model hazard ratio (95% CI)	*p*-value
Age	1.03 (1.02-1.04)	< 0.0001		
DMDU	1.04 (1.02-1.06)	0.0002	1.04 (1.01-1.07)	0.013
Gender	0.93 (0.73-1.19)	0.554		
Education (Illiterate)	1.52 (1.13-2.00)	0.006		
Marital status (Wifeless or widow)	1.77 (1.23-2.47)	0.003		
Family history of T2DM	0.77 (0.60-0.98)	0.033		
Living Alone	2.36 (1.24-4.06)	0.011		
Economic situation (dependent)	1.38 (1.04-1.84)	0.027		
Smoking	0.77 (0.55-1.06)	0.109		
Drinking	0.93 (0.65-1.30)	0.693		
Regular exercise	1.05 (0.81-1.37)	0.701		
Antihypertensive medication	1.33 (1.03-1.69)	0.027		
Statin	0.75 (0.51-1.05)	0.095		
Oral hypoglycemic medication	1.31 (0.69-2.89)	0.437		
Insulin therapy	1.19 (0.77-1.77)	0.411		
Anemia	1.46 (1.10-1.91)	0.009		
Hypertension	1.21 (0.87-1.74)	0.263		
Hyperlipidemia	0.99 (0.77-1.27)	0.914		
Coronary artery disease	1.23 (0.92-1.63)	0.157		
Stroke	3.16 (1.75-5.26)	0.0004	2.49 (1.17-4.83)	0.021

DMDU: Known duration of diabetes

Table 4. Cox proportional hazard model of baseline biochemical risk factors for the development of microalbuminuria in 739 patients with type 2 diabetes who were followed for ten years

Baseline data	Univariate analysis hazard ratio (95% CI)	*p*-value	Multivariate model hazard ratio (95% CI)	*p*-value
Body mass index	1.02 (0.98-1.05)	0.364		
Waist circumference	1.02 (1.00-1.03)	0.008	1.04 (1.01-1.07)	0.015
Waist to hip ratio	5.24 (1.22-21.80)	0.026		
Systolic BP	1.01 (1.01-1.02)	< 0.0001		
Diastolic BP	1.01 (0.99-1.02)	0.081		
HbA1C	1.05 (0.99-1.12)	0.129		
Fasting sugar	1.00 (0.99-1.00)	0.393		
Total cholesterol	1.00 (0.99-1.01)	0.345		
Triglyceride	1.00 (1.00-1.00)	0.029		
HDL-cholesterol	0.99 (0.99-1.01)	0.771		
LDL-cholesterol	1.00 (0.99-1.00)	0.904		
Creatinine	1.97 (1.10-3.47)	0.022	3.88 (1.52-9.79)	0.005
CCr-CGCR	0.99 (0.99-1.00)	< 0.0001		
UACR	1.08 (1.06-1.10)	< 0.0001	1.09 (1.07-1.11)	< 0.0001
White blood cell	1.02 (0.94-1.11)	0.602		
Red blood cell	0.75 (0.59-0.95)	0.017		
Hemoglobin	0.88 (0.81-0.95)	0.001		
Hematocrit	0.95 (0.93-0.98)	0.002		
Mean corpuscular volume	0.99 (0.98-1.01)	0.648		
MCH	0.98 (0.94-1.02)	0.270		
MCHC	0.88 (0.80-0.98)	0.024		

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular-hemoglobin concentration; CCr-CGCr: Creatinine clearance estimated by modificated Cockcroft-Gault Equation[13] (adjusted by age, sex, weight, creatinine); UACR: Urinary albumin to creatinine ratio



Parameter	AUC	Odds ratio (95% CI)	*p*-value
DMDU	0.583	6.64 (1.75-25.87)	0.006
DMDU + stroke	0.597	1.79 (0.82-3.96)	0.143
DMDU + stroke + creatinine	0.598	2.13 (0.95-4.78)	0.065
DMDU + stroke + creatinine + waist circumference	0.616	5.22 (1.66-16.76)	0.005
DMDU + creatinine + waist circumference + UACR	0.702	13.14 (6.64-26.47)	< 0.0001
DMDU + stroke + creatinine + waist circumference + UACR	0.705	13.89 (6.91-28.52)	< 0.0001

Fig. 1 Comparison of the receiver operating characteristic curves with area under the curves (AUC) for the risk of microalbuminuria with five factors (duration of diabetes, stroke, creatinine, waist circumference, and urinary albumin to creatinine ratio (UACR)). The AUC using the duration of diabetes was calculated first, then stroke was added to this model, followed by creatinine, waist circumference, and UACR.

In addition to the most common predictors of the progression to diabetic nephropathy and albumin excretion in patients with T2DM such as duration of diabetes, smoking,[22,27] blood pressure,[22,28] Estimated glomerular filtration rate (eGFR), HbA1c,[22,29] HDL cholesterol, apolipoprotein B, and fibrinogen,[29] the development of microalbuminuria in our population was determined by the duration of diabetes, stroke, waist circumference, plasma creatinine level, and UACR. Furthermore, we found that duration of diabetes, stroke, creatinine, waist circumference, and UACR predicted the development of microalbuminuria in multivariate analysis, with an AUC of 0.705. In addition, consistent with some previous reports[28,30,31] but in contrast to others,[22,24,27] HbA1c did not predict the development of microalbuminuria in our population.

In the current study, we found that microalbumin levels were linearly correlated to the duration of diabetes. In addition, we observed that elevated levels of microalbuminuria were significantly associated with an increased duration of disease (p = 0.005). Bahman et al. reported that the risk of developing microalbuminuria in patients who had had diabetes for 10-14 years was 4.1 times higher compared with those who had had diabetes for 0-4 years.[32] In addition, in the current study the levels of creatinine and UACR at baseline were associated with the development of microalbuminuria, which is consistent with other studies in which elevated initial levels of eGFR and UACR predicted the progression to new-onset albuminuria, major kidney-related events, and micro-and macroalbuminuria.[30,33]

Parving et al. demonstrated that increased body mass index was not related to the presence of micro- or macroalbuminuria, which may be because of the high prevalence of micro- and macroalbuminuria in Asian patients who have a relatively low body mass index.[22] However, in the present study, we found that waist circumference at baseline predicted the development of new-onset microalbuminuria. Pasko et al. reported that the increased duration of diabetes, systolic blood pressure, glycated hemoglobin (HbA1c), and waist circumference were risk factors for microalbuminuria in males, whereas poor glycemic control, prolonged diabetes and increased waist circumference were associated with microalbuminuria in females.[34] Consider-

ing the higher frequency of weight gain and obesity in patients with T2DM over the last decade, these clinical conditions that result in insulin resistance may be involved in the pathology of microalbuminuria.[35,36] Moreover, intensive insulin treatment, albeit beneficial in decreasing the risk of diabetic complications, can result in weight gain,[37] and the effects of weight gain may be intensified when not accompanied by good glycemic control.

In addition to the classical risk factors, others may influence the development of microalbuminuria.[38] In the present study, we also found that a history of stroke at baseline was associated with the development of new-onset microalbuminuria. Microalbuminuria is a common finding in patients with cerebrovascular diseases and is associated with an increased risk of stroke.[39] Das et al. found that microalbuminuria was present in 66% of ischemic stroke cases compared to only 8% of the control group, and that out of 50 ischemic stroke patients, 33 (66%) had microalbuminuria.[40] Patients with microalbuminuria tend to have higher levels of cholesterol and triglycerides, although no independent significant associations were observed in the multivariate model in the present study. A possible explanation for this result may be the use of statins in this group. In most studies, the prevalence of microalbuminuria was found to be positively associated with cholesterol and triglyceride levels.[41] In a prospective observational study, Gall et al. found that baseline cholesterol was an independent risk factor for the development of microalbuminuria.[42]

There are several limitations in this study. First, the study was not population-based and only patients followed at diabetes centers were included. This may have introduced referral bias that makes it difficult to extend our findings to the general diabetic population. Second, the albumin/creatinine ratio was determined by a dipstick on the basis of a single random urine sample. However, the large number of samples and the high frequency with which a single urine was collected showed a diagnostic abnormality should minimize the uncertainty associated with day-to-day differences in urinary albumin excretion. Third, the final UACR in patients who progressed to microalbuminuria were close to the normal range of albuminuria, and this group may have included patients who spontaneously reverted to normoalbuminuria. Despite these limitations, the high number of patients with microalbuminuria may have implications for future health policies. Because microalbuminuria is widely used as a sensitive risk marker to identify those at risk of renal dysfunction,[43] screening programs should be implemented at an early stage to prevent or postpone end-stage renal disease.

In conclusion, the present study indicates that a longer duration of diabetes and an elevated incidence of stroke, waist circumference, plasma creatinine level and UACR increased the risk of developing microalbuminuria in patients with T2DM after a long follow-up period. Except for the duration of diabetes, these risk factors are modifiable and should be identified early. We suggest that waist circumference, plasma creatinine level, and UACR should be closely monitored in patients with T2DM.

Acknowledgments

The authors would like to thank E-Da Hospital of the Republic of China, Taiwan, for financially supporting this research under grant no. EDAHP103045. The authors are also grateful to the staff and members of the diabetes care teams for their assistance with various measurements and other organizational aspects of this study.

References

1. Ritz E, Rychlik I, Locatelli F, et al: End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. Am J Kidney Dis

1999;34:795-808.
2. Raine AE: Epidemiology, development and treatment of end-stage renal failure in type 2 (non-insulin-dependent) diabetic patients in Europe. Diabetologia 1993;36:1099-104.
3. Remuzzi G, Schieppati A, Ruggenenti P: Nephropathy in patients with type 2 diabetes. N Engl J Med 2002;346:1145-51.
4. American Diabetes Association: Nephropathy in diabetes. Diabetes Care 2004;27:S79-S83.
5. Dinneen SF, Gerstein HC: The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: a systematic overview of the literature. Arch Intern Med 1997;157:1413-8.
6. Gerstein HC, Mann JF, Yi Q, et al: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. J Am Med Assoc 2001;286:421-6.
7. Garg JP, Bakris GL: Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. Vasc Med 2002;7:35-43.
8. Segura J, Campo C, Ruilope LM: Proteinuria: an underappreciated risk factor in cardiovascular disease. Curr Cardiol Rep 2002;4:458-62.
9. Adler AI, Stevens RJ, Manley SE, et al: Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003;63:225-32.
10. Mogensen CE: Microalbuminuria and hypertension with focus on type 1 and type 2 diabetes. J Intern Med 2003;254:45-66.
11. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, et al: Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation 2004;110:32-5.
12. Jia W, Gao X, Pang C, et al: Prevalence and risk factors of albuminuria and chronic kidney disease in Chinese population with type 2 diabetes and impaired glucose regulation: Shanghai diabetic complications study (SHDCS). Nephrol Dial Transplant 2009;24:3724-31.
13. Chung FM, Tsai JC, Chang DM, et al: Peripheral total and differential leukocyte count in diabetic nephropathy: the relationship of plasma leptin to leukocytosis. Diabetes Care 2005;28:1710-7.
14. Warram JH, Manson JE, Krolewski AS: Glycosylated hemoglobin and the risk of retinopathy in insulin-dependent diabetes mellitus. N Engl J Med 1995;332:1305-6.
15. Mathiesen ER, Ronn B, Jensen T, et al: Relationship between blood pressure and urinary albumin excretion in development of microalbuminuria. Diabetes 1990;39:245-9.
16. Dasmahapatra A, Bale A, Raghuwanshi MP, et al: Incipient and overt diabetic nephropathy in African Americans with NIDDM. Diabetes Care 1994;17:297-304.
17. Goldschmid MG, Domin WS, Ziemer DC, et al: Diabetes in urban African- Americans. II. High prevalence of microalbuminuria and nephropathy in African-Americans with diabetes. Diabetes Care 1995;18:955-61.
18. Mathiesen ER, Rønn B, Storm B, et al: The natural course of microalbuminuria in insulin-dependent diabetes: a 10-year prospective study. Diabet Med 1995;12:482-7.
19. Rudberg S, Osterby R: Decreasing glomerular filtration rate--an indicator of more advanced diabetic glomerulopathy in the early course of microalbuminuria in IDDM adolescents? Nephrol Dial Transplant 1997;12:1149-54.
20. Mrozikiewicz-Rakowska B, Maroszek P, Nehring P, et al: Genetic and environmental predictors of chronic kidney disease in patients with type 2 diabetes and diabetic foot ulcer: a pilot study. J Physiol Pharmacol 2015;66:751-61.
21. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012;35(Suppl 1):S64-S71.
22. Parving HH, Lewis JB, Ravid M, et al: Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int 2006;69:2057-63.
23. Weir MR: An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: the MicroAlbuminuria Prevalence (MAP) Study. Diabetologia 2005;48:17-26.
24. Hiroki Y, Koichi K, Masashi K: Microalbuminuria is common in Japanese type 2 diabetic patients: A nationwide survey from the Japan Diabetes Clinical Data Management Study Group (JDDM 10). Diabetes Care 2007;30:989-92.
25. Khalid SAG: Microalbuminuria among patients with diabetes type I and type II at the armed forces hospital in Jubail. Ann Saudi Med 2001;21:236-40.
26. Vivek A, Ranjit KS, Parduman S, et al: Incidence of microalbuminuria in hypertensive patients. Indian J Med Biochem 2004;8:57-61.
27. Aggarwal J, Kumar M: Prevalence of microalbuminuria among rural north Indian population with diabetes mellitus and its correlation with glycosylated haemoglobin and smoking. J Clin Diagn Res 2014;8:CC11-3.
28. Atta MG, Baptiste-Roberts K, Brancati FL, et al: The natural course of microalbuminuria among African Americans with type 2 diabetes: a 3-year study. Am J Med 2009;122:62-72.
29. Bruno G, Merletti F, Biggeri A, et al: Progression to overt nephropathy in type 2 diabetes: the Casale Monferrato Study. Diabetes Care 2003;26:2150-5.
30. Jardine MJ, Hata J, Woodward M, et al: Prediction of kidney-related outcomes in patients with type 2 diabetes. Am J Kidney Dis 2012;60:770-8.
31. Raine AE: Epidemiology, development and treatment of end-stage renal failure in type 2 (non-insulin-dependent) diabetic patients in Europe. Diabetologia 1993;36:1099-104.

32. Bahman PT, Abdul SAK, Liza LI, et al: Does microalbuminuria predict diabetic nephropathy. Diabetes Care 2001;24:1560-6.
33. Teimoury A, Iraj B, Heidari-Beni M, et al: Why 24-h urine albumin excretion rate method still is used for screening of diabetic nephropathy in Isfahan laboratories? Int J Prev Med 2014;5:341-7.
34. Pasko N, Toti F, Strakosha A, et al: Prevalence of microalbuminuria and risk factor analysis in type 2 diabetes patients in Albania: the need for accurate and early diagnosis of diabetic nephropathy. Hippokratia 2013;17:337-41.
35. Burgert TS: Glucose and insulin metabolism in obese youth. Pediatr Endocrinol Rev 2006;3 Suppl 4:555-9.
36. Wang Z, Wang FF, Zhu XJ, et al: Metabolic syndrome and microalbuminuria accompanied with hyperglycemia in community subjects. Zhonghua Yi Xue Za Zhi 2012;92:2526-9.
37. Reddy SV, Bhatia E: Intensive glycaemic control in type 2 diabetes mellitus: does it improve cardiovascular outcomes? Natl Med J India 2011;24:21-7.
38. Gross JL, de Azevedo MJ, Silveiro SP, et al: Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care 2005;28:164-76.
39. Beamer NB, Coull BM, Clark WM, et al: Microalbuminuria in ischemic stroke. Arch Neurol 1999;56:699-702.
40. Das S, Yadav U, Ghosh KC, et al: A clinical study of ischaemic strokes with micro-albuminuria for risk stratification, short-term predictive value and outcome. J Indian Med Assoc 2012;110:908-10,919.
41. Rosenson RS: Fenofibrate: treatment of hyperlipidemia and beyond. Expert Rev Cardiovasc Ther 2008;6:1319-30.
42. Gall MA, Hougaard P, Borch-Johnsen K, et al: Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. BMJ 1997;314:783-8.
43. Heerspink HJ, Holtkamp FA, de Zeeuw D, et al: Monitoring kidney function and albuminuria in patients with diabetes. Diabetes Care 2011;34 Suppl 2:S325-9.