Original Article
Correlation between microalbuminuria and cardiovascular events

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Abstract: Objective: This study aimed to investigate the relationship between microalbuminuria (MAU) and cardiovascular events. Methods: A total of 1259 hospitalized patients who received urinary albumin detection were recruited from Tongji Hospital of Tongji University in 2012. They were divided into two groups according to the level of urinary albumin: normal albuminuria (NAU) group (n=907) and MAU group (n=352). General information and cardiovascular events were collected and further analyzed. Results: Patients in MAU group was elder than those in NAU group (P<0.01), and the prevalence of diabetes and/or hypertension in MAU group was significantly higher than that in NAU group (P<0.01). The prevalence of major cardiovascular events (unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction) and congestive heart failure requiring therapy in hospital in MAU group was significantly higher than that in NAU group (P<0.01). Logistic regression analysis showed patients in MAU group had higher risk for major cardiovascular events (OR 1.438, 95% CI 1.018-2.031) and congestive heart failure (OR 2.540, 95% CI 1.717 to 3.757). Conclusions: MAU increases the risk for major cardiovascular events and congestive heart failure. MAU is an independent risk factor of cardiovascular events. Patients with MAU (30-300 mg/24 h) should be treated timely to reduce the incidence of cardiovascular events and delay the progression of cardiovascular diseases, which is independent of presence of diabetes and/or hypertension.

Keywords: Microalbuminuria, cardiovascular events, risk factors, prevalence

Introduction

Microalbuminuria (MAU) is defined as the 24-h urine protein level higher than normal range but lower than the clinically detectable urine protein level. Currently, MAU refers to the urine protein level of higher than >20 μg/min but no more than 200 μg/min or 24-h urine protein between 300 mg and 30 mg. In clinical practice, physicians pay more attention to the MAU in diabetes patients and employ MAU to evaluate the renal impairment in these patients. However, recent studies reveal that MAU is closely related to some risk factors of cardiovascular diseases including age, smoking, hypertension, diabetes, dyslipidemia and lack of physical activity [1-3]. In addition, MAU is found to be associated with several risk factors of atherosclerosis (such as vascular endothelial cell injury and artery rigidity) [4-7]. There is evidence showing that the markers of systemic inflammation in MAU patients (C-reactive protein, white blood cell count, and fibrinogen) are significantly higher than those in subjects with normal albuminuria (NAU) [8]. These findings demonstrate that MAU may be used as a predictor of cardiovascular diseases.

Cardiovascular events significantly threaten the life and health of humans. To determine the correlation between MAU and cardiovascular events is helpful to take measures to reduce the incidence of these cardiovascular events. The present study aimed to investigate MAU and cardiovascular events in hospitalized patients, aiming to evaluate the correlation between them. Our findings may provide evidence for the screening of patients with high risk for cardiovascular events and the early prevention and treatment of these events, which is beneficial to reduce the harmfulness caused by these events and save limited medical resources.

Materials and methods

Subjects

From January 2012 to December 2012, a total of 1259 hospitalized patients who were older

Table 1. Clinical characteristic of patients in two groups

Clinical characteristics	NAU group (n=907)	MAU group (n=352)	P
Age (yr)	67.5±12.6	69.9±13.7	<0.01
Gender			>0.05
Male	468	182	
Female	439	170	
Triglyceride			>0.05
Normal	674	250	
Increased	233	102	
Total cholesterol			>0.05
Normal	750	278	
Increased	157	74	
Low-density lipoprotein cholesterol			>0.05
Normal	679	252	
Increased	228	100	
High-density lipoprotein cholesterol			>0.05
Normal	499	206	
Reduced	408	146	
Diabetes			<0.01
Yes	541	168	
No	366	184	
Hypertension			<0.01
Yes	488	148	
No	419	204	
Diabetes and Hypertension			<0.01
Yes	742	248	
No	165	104	

than 18 years and received MAU detection were recruited from Tongji Hospital of Tongji University. Exclusion criteria included proteinuria (urine protein of >300 mg/24 h), type 1 diabetes, primary urinary system diseases, secondary urinary system diseases (except for diabetic nephropathy), other cardiovascular diseases such as valvular heart diseases, active hepatitis and infection within prior 1 month and severe cerebrovascular events (such as brain infarction or hemorrhage) within prior 6 months.

Diagnostic criteria

MAU was defined as urine protein in 24 h between 300 mg and 30 mg. According to the criteria in The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), increased cholesterol is defined as total serum cholesterol (TC) of ≥5.20 mmol/L, increased triglyceride (TG) as TG of ≥1.70

mmol/L, increased low density lipoprotein cholesterol (LDL-C) as LDL-C of ≥3.1 mmol/L and reduced high density lipoprotein cholesterol (HDL-C) as HDL-C of <1.04 mmol/L. Diabetes is diagnosed according to the WHO criteria in 1999. Hypertension is diagnosed according to the WHO/ISH Guidance for the Treatment of Hypertension in 1999 and secondary hypertension should be excluded.

Study procedures

The medical record was reviewed, and the age, gender, TG, TC, HDL-C, LDL-C, fasting blood glucose (FBG), blood pressure (BP), urine protein level and cardiovascular events in past 5 years were recorded. The cardiovascular events included stable angina, heart failure requiring hospitalization, major cardiovascular events, and coronary revascularization. Major cardiovascular events included unstable angina, non-ST-segment elevation myocardial infarction (MI) and ST-segment elevation MI.

Statistical analysis

Statistical analysis was done with SPSS version 20.0. Quantitative data were expressed as mean ± standard deviation and compared with t test or analysis of variance. Qualitative data were expressed as rate or ratio, and compared with chi square test. Univariate analysis was employed to analyze the correlation of cardiovascular events with each factor. Factors with significance in univariate analysis were recruited into multivariate analysis with Logistic regression analysis. A value of P<0.05 was considered statistically significant.

Results

General information

A total of 1259 meeting the inclusion criteria were recruited into present study. There were 650 males and 609 females. The mean age was 68.1±12.9 years (range: 31-89 years). In addition, diabetes was found in 550 patients,

Table 2. Cardiovascular events in two groups

Cardiovascular events	NAU group (n=907)	MAU group (n=352)	P
Stable angina			
No	843	335	>0.05
Yes	64	17	
Congestive heart failure			
No	845	286	<0.01
Yes	62	66	
Major cardiovascular events			
No	795	286	<0.01
Yes	112	66	

Table 3. Coronary revascularization in patients with major cardiovascular events

Coronary revascularization	NAU Group (n=112)	MAU Group (n=66)	P
No	44	33	>0.05
Yes	68	33	

33.5% of whom (n=184) were diagnosed with MAU; hypertension was noted in 623 patients, 32.7% of whom (n=204) were diagnosed with MAU; 269 patients were diagnosed with diabetes and hypertension, of whom 104 patients (38.7%) had MAU. According to the presence of MAU, patients were divided into two groups: MAU group (n=352) and NAU group (n=907). Results showed patients in MAU group were significantly elder than those in NAU group; the prevalence of diabetes and/or hypertension in MAU group was markedly higher than that in NAU group (P<0.01) (**Table 1**).

Prevalence of cardiovascular events in two groups: In MAU group, the prevalence of major cardiovascular events and congestive heart failure was markedly higher than that in NAU group (P<0.01). However, the prevalence of stable angina was comparable between two groups (**Table 2**).

Coronary revascularization

Among patients with major cardiovascular events, the prevalence of coronary revascularization was similar between two groups (**Table 3**).

Correlation between MAU and major cardiovascular events

The age, gender, TG, TC, LDL-C, HDL-C, diabetes, hypertension, diabetes with hypertension,

and MAU served as independent variables and major cardiovascular events as a dependent variable for univariate analysis. Results showed age, gender, HDL-C, hypertension, diabetes with hypertension and MAU were closely related to major cardiovascular events. Further multivariate analysis with logistic regression revealed that MAU, age, gender, and hypertension were independent risk factors of major cardiovascular events. Advanced age, male gender, presence of hypertension and MAU increased the risk for major cardiovascular events (**Table 4**).

Correlation between MAU and congestive heart failure

The age, gender, TG, TC, LDL-C, HDL-C, diabetes, hypertension, diabetes with hypertension and MAU served as independent variables, and congestive heart failure as a dependent variable for univariate analysis. Results showed age, HDL-C, hypertension, and MAU were closely associated with congestive heart failure. Further multivariate analysis with logistic regression revealed that MAU, age, and hypertension were independent risk factors of congestive heart failure. Advanced age, presence of hypertension and MAU increased the risk for congestive heart failure (**Table 5**).

Discussion

The accelerated aging of population and increased living level increase the prevalence of MAU, which has been an important problem nowadays. According to the statistics of NHANES3, the prevalence of MAU is 7.8% in 22244 subjects surveyed in North America. The prevalence of MAU is as high as 28.8% in diabetes patients and 16% in hypertension patients. In general population without diabetes, hypertension or increased serum creatinine, the prevalence of MAU also reaches 5.1% [9]. A total of 979 patients (mean age [SD], 67.9 [10.8] years; 409 men and 570 women, 505 diabetics) were studied. The presence of microalbuminuria was found in 12.4% of hypertensive patients and in 21.4% of diabetic patients (p<0.001) [10]. MAPS of multiple Asian countries and regions showed the prevalence of MAU was 39.8% in 6801 patients with diabetes

Table 4. Logistic regression analysis of major cardiovascular events

Variables		β	P	OR	95% CI
Age	<60 years			1.000	
	60-70 years	0.728	0.009	2.071	1.203-3.566
	70-80 years	1.050	<0.001	2.858	1.688-4.840
	>80 years	1.233	<0.001	3.432	2.060-5.719
Male		0.530	0.002	1.698	1.206-2.392
Hypertension		0.452	0.009	1.571	1.121-2.203
MAU		0.363	0.039	1.438	1.018-2.031

Table 5. Logistic regression analysis of factors influencing congestive heart failure

Variables		β	P	OR	95% CI
Age	<60 years			1.000	
	60-70 years	0.041	0.921	1.042	0.463-2.343
	70-80 years	0.911	0.009	2.487	1.252-4.941
	>80 years	1.886	<0.001	6.595	3.535-12.304
Hypertension		0.667	0.002	1.948	1.288-2.945
MAU		0.932	<0.001	2.540	1.717-3.757

and hypertension (64% was Chinese) [11]. In another study in Beijing China, the prevalence of MAU was found to be 36.6% in 1004 patients with diabetes [12]. In a study on the relationship between MAU and cardiovascular events, 9043 subjects were followed up for a mean of 4.5 years, and results showed the risk for major cardiovascular events (MI, brain infarction and cardiovascular death) (RR 1.83, 95% CI 1.64-2.05), death of all causes (RR 2.09, 95% CI 1.84-2.38) and congestive heart failure requiring hospitalization (RR 3.23, 95% CI 2.54-4.10) increased significantly in MAU group. In a pooled analysis of all 9043 patients by Cox regression, the hazard for the primary outcome (all-cause death, hospitalization for heart failure) for every increment in the albumin: creatinine ratio (ACR) was determined. For every 0.4-mg/mmol increase in ACR, the hazard of the primary outcome increased by 5.9% (95% CI 4.9-7.0), all-cause death increased by 6.8% (95% CI 5.6-8.0), and hospitalization for heart failure increased by 10.6% (95% CI 8.4-13.0) after adjustment for age and sex and randomization to receive ramipril [13]. A review found that for people with both diabetes and hypertension, the presence of microalbuminuria was associated with a relative risk of all-cause mortality 2-8 times higher than that in similar individuals without microalbuminuria, and the car-diovascular mortality and morbidity was 2-4 times higher than in persons without microalbuminuria [14]. Estacio et al followed up 393 patients with type 2 diabetes and hypertension for 10 years. Their results showed the cardiovascular mortality was increased by 24.5% (95% CI 10.1% to 36.5%) in patients with an increase in urinary albumin excretion (UAE) of 2 logs at 1 year; but reduced by 4.7% in those with a decrease in UAE of 2 logs at 1 year (95% CI 1.4% to 7.8%) [15]. To date, no studies have been conducted to investigate the correlation between MAU and cardiovascular events in general population in China.

In the present study, a total of 1259 hospitalized patients were recruited from the Affiliated Tongji Hospital of Tongji University in 2012. Results showed the prevalence of MAU was 33.5% among diabetes patients and 32.7% among hypertension patients. However, the prevalence of MAU was as high as 38.7% in patients with diabetes and hypertension. The prevalence of MAU in the present study was higher than that reported in North America, but similar to that reported in Asia in epidemiological studies.

In our study, stable angina, congestive heart failure requiring hospitalization, major cardiovascular events and coronary revascularization were used as cardiovascular events. In MAU group, the prevalence of major cardiovascular events and congestive heart failure was significantly higher than that in NAU group, suggesting that MAU might be associated with major cardiovascular events and congestive heart failure. However, the prevalence of stable angina was comparable between two groups, which might be attributed that stable angina is a mild type of cardiovascular diseases. In addition, in patients with unstable angina, non-ST-segment elevation MI or ST-segment elevation MI, the prevalence of coronary revascularization was comparable between MAU group and NAU group. The coronary revascularization is related to not only the severity of diseases but the time of diagnosis, economic status, education level and family background. Thus, this result is required to be further studied. Logistic regres-

sion analysis was employed to analyze the factors influencing the major cardiovascular events and congestive heart failure. Results showed MAU patients had increased risk for major cardiovascular events (OR 1.438, 95% CI 1.018-2.031) and congestive heart failure (OR 2.540, 95% CI 1.717-3.757). Our findings were consistent with previously reported. Above findings indicate that MAU is one of independent risk factors of cardiovascular events. For patients with hypertension or diabetes or even general population, screening of MAU is useful to predict the risk for cardiovascular events.

It is crucial to correctly and comprehensively understand the clinical significance of MAU, and we may pay more attention to the early screening of MAU in subjects with high risk for cardiovascular diseases. A number of therapeutic options (tight blood sugar control, blood pressure reduction, lipid lowering) lead to a reduction of albuminuria and an improvement in cardiovascular prognosis. This has particularly been described for renin-angiotensin-aldosterone system-(RAAS-) blocking agents [16, 17]. LIFE study showed the urine albumin level in 568 patients with diabetes and hypertension who were treated with losartan was significantly lower than that in 609 control patients treated with atenolol. In addition, the cardiovascular mortality and all-cause mortality in losartan treated patients was significantly lower than that in control group [17]. Thus, when the urine albumin secretion is 30-300 mg/24 h, the risk factors for cardiovascular events should be carefully evaluated regardless of diabetes and hypertension, and active intervention to reduce urine albumin secretion is pivotal to reduce the incidence of cardiovascular events and delay the progression of cardiovascular diseases.

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