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ORIGINAL PAPER

Carotid stiffness and microalbuminuria in patients with type 2 diabetes

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Abstract Microalbuminuria is associated with higher cardiovascular mortality, especially in diabetics. But the direct association between microalbuminuria and vascular wall properties is still not clear. We investigated quantitative carotid stiffness (QCS) index in relation to microalbuminuria in 260 Chinese diabetic patients. In categorical analyses, patients with elevated urinary albumin-to-creatinine ratio (uACR) had higher QCS than those with normal uACR ($P < 0.001$). The corresponding values for QCS values were 4.4 and 5.9, respectively. In multiple stepwise regression analyses, QCS was significantly associated with age, uACR, plasma glycosylated hemoglobin A_{1C} (HbA_{1C}), and current smoking ($P < 0.05$ for all). In conclusion, carotid stiffness as measured by QCS, a local functional measurement of the arterial wall, is increased in type 2 diabetes with microalbuminuria.

Keywords Carotid stiffness · Microalbuminuria · Type 2 diabetes mellitus

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Introduction

Atherosclerosis is a major complication of type 2 diabetes mellitus and accounts for up to 60–70% of death in diabetic patients [1–4]. Many researches have demonstrated that microalbuminuria is not only a predictor for the development of diabetic nephropathy [5–7] but also a risk factor for coronary artery disease (CAD) in diabetics and nondiabetics [8, 9]. It is associated with higher cardiovascular mortality, especially in diabetics [8]. Many biochemical parameters that indicate endothelial dysfunction and chronic inflammation such as soluble vascular cell adhesion molecule [10], C-reactive protein [11], and fibrinogen [12] have been shown to be significantly associated with microalbuminuria. These findings may support a hypothesis that microalbuminuria reflects generalized vascular damage [13, 14] which may promote atherosclerosis. However, the direct association between microalbuminuria and vascular wall properties is still not clear.

A number of researches studied the relation between microalbuminuria and arterial stiffness in diabetes by measuring pulse wave velocity (PWV), a systemic arterial stiffness parameter [15–18]. But in this study, we used a local arterial stiffness index. With the echo-tracking technique, the stiffness of carotids can be automatically measured, and a quantitative carotid stiffness (QCS) can be generated [19]. We investigated in type 2 diabetic patients QCS in relation to microalbuminuria.

Results

The 260 subjects included 89 men and 171 women with an average age (±SD) of 57.5 ± 7.2 years (Table 1). Overall, the study sample included 47 (18.1%) smokers. According

to the levels of uACR, the patients were divided into normoalbuminuria group (uACR $\leq$ 30 μg/mg creatinine, $n = 194$) and microalbuminuria (30 μg/mg creatinine < uACR < 300 μg/mg creatinine, $n = 66$).

Patients with elevated uACR had poorer diabetic control, had higher BMI, had greater waist and hip circumference, had higher levels of triglycerides, and had higher QCS than those with normal uACR ($P < 0.05$ for all; Table 1). After adjustment for age, sex, current smoking, duration of diabetes, HbA_{1C}, BMI, waist and hip circumference, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and systolic and diastolic blood pressure, the difference of QCS between these two groups was still significant ($P < 0.001$, Fig. 1).

In univariate analysis, QCS was positively and significantly associated with age ($r = 0.213$, $P = 0.001$), waist circumference ($r = 0.206$, $P = 0.001$), body mass index ($r = 0.126$, $P = 0.044$), systolic blood pressure ($r = 0.193$, $P = 0.002$), HbA_{1C} ($r = 0.232$, $P < 0.001$), and uACR ($r = 0.486$, $P < 0.001$) (Table 2).

In multiple stepwise regression analyses with a model including age, body mass index, systolic and diastolic blood pressure, waist and hip circumference, uACR, plasma HbA_{1C} concentration, serum concentrations of triglycerides and total, HDL and LDL cholesterol, current smoking, the duration of diabetes mellitus as independent variables, age, plasma HbA_{1C}, current smoking and uACR appeared to be significantly ($P < 0.05$) associated with QCS (Table 3).

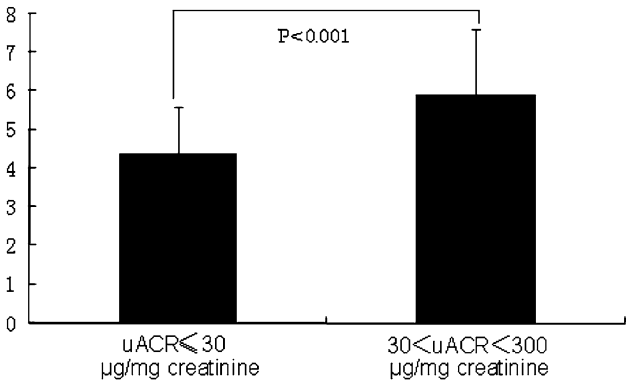

Fig. 1 Quantitative carotid stiffness (QCS) grouped by the levels of uACR after adjustment for age, sex, current smoking, duration of diabetes, HbA1C, BMI, waist and hip circumference, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, systolic and diastolic blood pressure. Values are means ± SD

Discussion

In the present study, we found that QCS was 1.5 higher in subjects with elevated uACR more than those with normal uACR, and microalbuminuria is an independent determinant of QCS after adjustment for conventional cardiovascular risk factors. These results suggest that microalbuminuria in diabetes may influence QCS which reflects the function of artery.

Our findings are in line with several previous studies, which have demonstrated that PWV, a systemic arterial stiffness index, is increased in patients with evaluated

Table 1 Characteristics of patients in study

Characteristic	uACR $\leq$ 30	30 < uACR < 300	*P*-value
Number	194	66	
Age (years)	57.1 ± 7.1	58.3 ± 7.7	0.242
Female/male	126/68	45/21	0.634
Current smoking (%)	19.6	13.6	0.248
Duration of diabetes (years)	7.1 ± 4.7	6.7 ± 5.1	0.785
Waist circumference(cm)	85.8 ± 8.3	90.0 ± 8.2	0.001
Hip circumference(cm)	95.8 ± 6.4	97.6 ± 6.7	0.001
Body mass index (kg/m^2)	24.5 ± 3.3	26.0 ± 3.3	<0.001
Systolic blood pressure (mmHg)	128.3 ± 16.7	132 ± 17.2	0.130
Diastolic blood pressure mmHg)	80.5 ± 9.3	80.8 ± 9.3	0.831
HbA_{1C} (%)	6.5 ± 1.2	7.2 ± 1.3	<0.001
Total cholesterol (mmol/l)	5.3 ± 1.1	5.4 ± 0.9	0.346
Triglycerides (mmol/l)	1.6 ± 1.5	2.3 ± 2.0	0.021
LDL cholesterol (mmol/l)	3.2 ± 0.9	3.2 ± 0.7	0.946
HDL cholesterol (mmol/l)	1.5 ± 0.3	1.6 ± 0.2	0.492
uACR (μg/mg creatinine)	11.7 ± 5.6	54.8 ± 27.4	<0.001
QCS	4.4 ± 1.2	5.9 ± 1.6	<0.001

Data are n, %, or means ± SD

HDL high density lipoprotein, *LDL* low density lipoprotein, *uACR* urinary albumin-to-creatinine ratio (μg/mg creatinine)

Table 2 Univariate correlation of QCS with other variables

Variable	QCS	
	Coefficient of correlation	*P*-value
Age (years)	0.213	0.001
Sex	−0.083	0.183
Current smoking (%)	0.108	0.082
Duration of diabetes (years)	−0.043	0.485
Waist circumference(cm)	0.206	0.001
Hip circumference (cm)	0.111	0.082
Body mass index (kg/m^2)	0.126	0.044
Systolic blood pressure (mmHg)	0.193	0.002
Diastolic blood pressure mmHg)	0.042	0.504
HbA_{1C} (%)	0.232	<0.001
Total cholesterol (mmol/l)	0.097	0.119
Triglycerides (mmol/l)	0.094	0.130
LDL cholesterol (mmol/l)	0.021	0.738
HDL cholesterol (mmol/l)	0.089	0.155
uACR (μg/mg creatinine)	0.486	<0.001

Table 3 Multiple stepwise regression analyses with a model including age, uACR, systolic and diastolic blood pressure, waist and hip circumference, current smoking, duration of diabetes, body mass index, HbA1C, Total cholesterol, Triglycerides, LDL cholesterol, and HDL cholesterol

Characteristic	QCS	
	Standardized coefficient beta	*P*-value
uACR (μg/mg creatinine)	0.448	<0.001
Current smoking	0.131	0.015
Age	0.210	<0.001
HbA1c (%)	0.161	0.004

uACR compared with those with normal ACR [15, 16]. However, the mechanism underlying the relationship is still not clear. Stehouwer et al. [17] found that microalbuminuria was linearly associated with impaired endothelium-dependent, flow-mediated vasodilation in elderly individuals with and without diabetes. It is possible that endothelial leakiness, as reflected by uACR, mirrors the endothelial dysfunction featuring the atherosclerotic process or arises from the action of yet unknown risk factors [20].

We also found patients with microalbuminuira had higher levels of plasma $HbA_{1C.}$ Furthermore, in multiple stepwise regression analysis, HbA_{1C} was an independent risk factor of QCS. Previous studies have demonstrated that glycation of structural protein, such as collagen and elastin, with the formation of advanced glycation end products (AGE) may contribute to the loss of arterial wall compliance. These same processes have been implicated in the genesis of albuminuria [21]. We presumed that the elevated HbA_{1C} is most likely an important mediator of the relationship between microalbuminuria and QCS.

Our study should be interpreted within the context of its limitations. The number of participants especially the subjects with microalbuminuria is relatively small. The possibility of a chance finding cannot be entirely excluded. A single morning spot urine sample rather than 24 h urine sample is used to get uACR. This may affect the accuracy of the results. Furthermore, antidiabetic, antihypertensive, and lipid lowering drugs have been already used in some patients. Thus, the relationship between the obtained values of blood pressure, lipid profiles, and HbA_{1C} with QCS were likely confounded by the treatment.

In conclusion, our findings suggest that microalbuminuria in type 2 diabetic patients may influence the local functional measurement of the arterial wall. Elevated HbA_{1C} is most likely an important mediator of this relationship. Further research is needed to confirm this finding.

Materials and methods

Subjects

The Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine approved the study protocol. From January 2008 to July 2008, 560 type 2 diabetic patients (diagnosed according to the 1999 World Health Organization criteria) were recruited via the outpatient clinic of the Department of Endocrine and Metabolism at Ruijin Hospital, Shanghai. All study participants gave written informed consent. Exclusion criteria were a history of ischemic heart disease, stroke, ketoacidosis or ketonuria, clinical or biochemical evidence of renal impairment (serum creatinine >150 μmol/l) and having macroalbuminuria (defined as albumin-to-creatinine (ACR) ≥300 μg/mg creatinine) ($n = 179$). Hundred and twenty one patients were excluded because of missing clinical information. Thus, the present analysis included 260 subjects.

Clinical and biochemical assessments

Blood pressure was measured with a standard mercury sphygmomanometer after at least 10 min rest in the sitting position. We used a standardized questionnaire to collect information on medical history including the duration of type 2 diabetes mellitus, lifestyle, and the use of medications.

Blood samples were obtained after an overnight fasting. Plasma HbA_{1C} was measured by high performance liquid chromatography (BRO-RAD Company, USA). Serum concentrations of total cholesterol and triglycerides were

measured by the enzymatic method, and high density lipoprotein (HDL) cholesterol was measured using a specific precipitation method (Beckman LX-20, Brea, CA, USA). Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald's formula [22]. A first-voided, early-morning spot urine sample was gained for calculation of urinary albumin-to-creatinine ratio (uACR). Body mass index was calculated as weight in kilograms divided by height in meter squared.

QCS measurements

One trained sonographer, blinded to all clinical and laboratory characteristics, performed QCS measurements. Ultrasound examinations of stiffness index QCS of the right and left common carotid arteries were performed in the supine position with slight hyperextension of the neck using an ultrasonic phase-locked echo-tracking system equipped with a high-resolution, real-time 10-MHz linear scanner (Esaote Picus, Italy). QCS was calculated using the blood pressure and diameter of the artery as follows: $\mathrm{QCS} = \ln (P_s/P_d)/(A_s/A_d - 1)$, where P_s and P_d are systolic and diastolic blood pressures, and A_s and A_d are the arterial cross-sectional area at systole and diastole, respectively. The measurements of the right and left common carotid QCS were averaged for analysis. The coefficient of variation was 3.3% for QCS.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0. Measurements with a skewed distribution were normalized by logarithmic transformation. Comparisons of means and proportions were performed with *t*-test. Correlation analysis that was appropriate for the normal (Pearson correlation) or nonnormal distribution (Spearman correlation) of the variable was used to test for association of QCS with a number of other parameters. To allow for covariates and confounders, we performed analysis of covariance and multiple linear regression analysis.

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