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ORIGINAL PAPER

Carotid intima-media thickness and stiffness in relation to type 2 diabetes in Chinese

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Abstract We investigated carotid intima-media thickness (IMT) and quantitative carotid stiffness (QCS) index in relation to plasma glycosylated hemoglobin A_{1C} (HbA_{1C}) and duration of diabetes mellitus in 337 Chinese diabetic patients. In categorical analyses, carotid IMT was 710 μm in subjects with a duration of diabetes mellitus ≤2 years, 760 μm in subjects with a duration of diabetes mellitus more than two years and with plasma $HbA_{1C} < 6.5\%$ ($P < 0.05$), and 790 μm in subjects with a duration of diabetes mellitus more than two years but with plasma $HbA_{1C} \geq 6.5\%$ ($P < 0.01$). The corresponding values for QCS values were 4.5, 4.6 and 5.1 ($P < 0.05$), respectively. In multiple stepwise regression analyses carotid IMT was significantly associated with the duration of diabetes mellitus, systolic blood pressure and serum concentration of total cholesterol, whereas QCS was significantly associated with age, HbA_{1C}, systolic and diastolic blood pressure ($P < 0.05$). In conclusion, carotid IMT as a structural measure of arterial wall is increased in patients with a longer history of diabetes mellitus, whereas QCS as functional index is mainly influenced by the quality of blood glucose control.

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Introduction

Arterial diseases, such as coronary heart disease and stroke, are major complications of type 2 diabetes mellitus and in diabetic patients account for up to 60–70% of deaths. Carotid intima-media thickness (IMT) is a marker of preclinical generalized atherosclerosis and a powerful predictor of stroke and coronary heart disease. Over the last decade, high-resolution B-mode ultrasound has been proven to be a valid and reliable method to detect and monitor the intima-media thickening of carotids [1–3]. With the echo-tracking technique, the stiffness of carotids can be automatically measured, and a quantitative carotid stiffness (QCS) can be generated. Intima-media thickness is a structural measure of the carotids, whereas stiffness index such as QCS reflects arterial function [4–6].

Previous studies have mainly focused on the association between hyperglycaemia and atherosclerotic diseases, but produced inconsistent results [6,7]. In the present study, we investigated in type 2 diabetic patients carotid IMT and QCS in relation to the duration of the disease and plasma glycosylated hemoglobin A_{1C} (HbA_{1C}).

Results

Characteristics of the subjects

The 337subjects included 131 men and 206 women with an average age (± SD) of 57.4 ± 7.3 years (Table 1). Overall, the study sample included 64 (19%) smokers. The duration

Table 1 Characteristics of patients in study

Characteristic	Newly diagnosed	Duration > 2 years	
		HbA_{1C} < 6.5%	HbA_{1C} ≥ 6.5%
Number	60	148	129
Age (years)	56.9 ± 8.2	58 ± 7.4	57 ± 6.7
Femal/Male	42/18	87/61	77/52
Current smoking (%)	15	16.9	23.3
Duration (years)	1.02 ± 0.5	7.55 ± 5.4**	8.80 ± 3.4**
Body mass index (kg/m2)	24.7 ± 3.2	24.3 ± 3.2	25.0 ± 3.3
Systolic blood pressure (mmHg)	126.6 ± 16.2	128.8 ± 1.4	130.0 ± 16.1
Diastolic blood pressure mmHg)	80.4 ± 10.8	80.2 ± 8.9	80.4 ± 8.8
HbA_{1C} (%)	6.3 ± 1.1	5.8 ± 0.5**	7.7 ± 1.1**☆☆
Total cholesterol (mmol/l)	5.3 ± 1.0	5.1 ± 1.0	5.4 ± 1.1☆
Triglycerides (mmol/l)	1.7 ± 1.1	1.5 ± 1.5	2.0 ± 2.0☆
LDL cholesterol (mmol/l)	3.3 ± 1.0	3.1 ± 0.7	3.2 ± 0.8
HDL cholesterol (mmol/l)	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3
CIMT (um)	710 ± 170	760 ± 190*	790 ± 180**
QCS	4.5 ± 1.9	4.6 ± 1.5	5.1 ± 1.6*☆

Data are n,%,or means ± SD. * $P < 0.05$, ** $P < 0.01$ vs. newly diagnosed group, ☆ $P < 0.05$, ☆☆ $P < 0.01$ vs. group with duration > 2 years and HbA_{1C} < 6.5%. HDL, high density lipoprotein; LDL, low density lipoprotein

of diabetes mellitus was ≤ 2 years in 60 subjects and more than 2 years in 277 subjects, of whom 148 and 129 had plasma HbA_{1C} < 6.5% and ≥ 6.5% , respectively.

Despite significant differences in the duration of diabetes mellitus and plasma HbA_{1C} among these three groups, these subjects had similar characteristics such as age, sex distribution, body mass index, systolic and diastolic pressure, and serum lipids (Table 1). Only the proportions of patients on insulin and sulfonylureas were statistically different among the three groups (Table 2).

Categorical analysis

Carotid IMT was 710 μm in subjects with duration of diabetes mellitus ≤ 2 years, 760 μm in subjects with duration of diabetes mellitus more than two years and

Table 2 Use of anti-diabetic, antihypertensive and lipid lowering drugs

Medication (%)	Newly diagnosed (n = 60)	Duration > 2 years		P
		HbA1C < 6.5% (n = 148)	HbA1 ≥ 6.5% (n = 129)	
Anti-diabetic agents				
Insulin	15.0%	27.0%	42.6%	0.000
Sulfonylureas	26.7%	52.7%	51.9%	0.002
Biguanides	40.0%	36.5%	46.5%	0.236
Thiazolidinedions (insulin sensitizer)	3.3%	6.8%	8.5%	0.419
α-glycosidase inhibitors	21.7%	32.4%	24.0%	0.164
Antihypertensive agents				
Angiotensin converting enzyme inhibitors	13.3%	20.3%	16.3%	0.440
Calcium channel blockers	20.0%	18.2%	10.9%	0.146
Angiotensin receptor blockers	6.7%	8.9%	5.4%	0.550
Diuretics	1.7%	4.1%	3.1%	0.674
β-blockers	3.3%	2.0%	3.1%	0.807
Lipid lowering agents				
Statins	3.3%	8.8%	3.9%	0.145
Fibrates	5.0%	5.4%	3.1%	0.634

plasma $HbA_{1C} < 6.5\%$ ($P < 0.05$), and 790 μm in subjects with duration of diabetes mellitus more than two years but with plasma $HbA_{1C} \geq 6.5\%$ ($P < 0.01$, Table 1). QCS value in the group with a duration of diabetes mellitus more than two years and with plasma $HbA_{1C} \geq 6.5\%$ was higher than those in the newly diagnosed group and the group with duration of diabetes mellitus more than two years and with plasma $HbA_{1C} < 6.5\%$ ($P < 0.05$). After adjustment for age, sex, and the use of insulin, sulfonylureas, thiazolidinedions, α-glycosidase inhibitors, angiotensin converting enzyme inhibitors, and Calcium channel blockers, the results did not materially change (Figs. 1 and 2).

Continuous analysis

In single regression, carotid IMT was positively and significantly associated with the duration of diabetes mellitus ($r = 0.14$, $P = 0.009$), systolic ($r = 0.18$, $P = 0.001$) and diastolic blood pressure ($r = 0.12$, $P = 0.026$) and serum total cholesterol ($r = 0.15$, $P = 0.007$), and QCS was positively and significantly associated with systolic blood pressure ($r = 0.22$, $P < 0.001$), age ($r = 0.30$, $P < 0.001$), and HbA_{1C} ($r = 0.18$, $P = 0.001$).

In multiple stepwise regression analyses with a model including age, body mass index, systolic and diastolic blood pressure, plasma HbA_{1C} concentration, serum concentrations of triglycerides and total, HDL and LDL cholesterol, current smoking, the duration of diabetes mellitus, using of insulin, sulfonylureas, thiazolidinedions, α-glycosidase inhibitors, angiotensin converting enzyme inhibitors and calcium channel blockers as independent variables, only the duration of diabetes mellitus, systolic blood pressure and serum concentration of total cholesterol appeared to be significantly ($P < 0.05$) associated with carotid IMT, while age, plasma HbA_{1C}, systolic and diastolic blood pressure appeared to be significantly ($P < 0.05$) associated with QCS (Table 3).

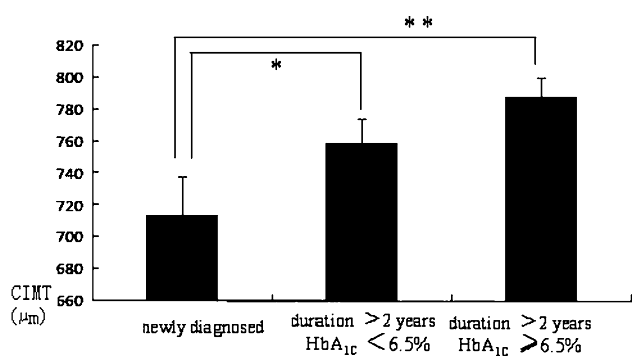

Fig. 1 Carotid intima–media thickness (CIMT) grouped by duration and HbA_{1C} after adjustment for age, sex, and the use of insulin, sulfonylureas, thiazolidinedions, α-glycosidase inhibitors, angiotensin converting enzyme inhibitors and Calcium channel blockers. Values are means ± SD, *$P < 0.05$, **$P < 0.01$

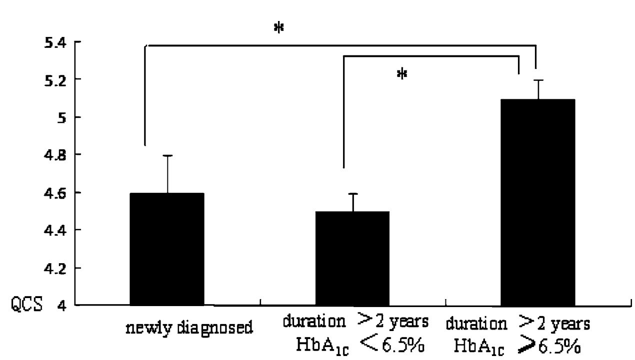

Fig. 2 Quantitative carotid stiffness (QCS) grouped by duration and $GHbA_{1C}$ after adjustment for age, sex, and the use of insulin, sulfonylureas, thiazolidinedions, α-glycosidase inhibitors, angiotensin converting enzyme inhibitors and Calcium channel blockers. Values are means ± SD, *$P < 0.05$, **$P < 0.01$

Discussion

In the present study, we found that carotid IMT was significantly associated with the duration of diabetes mellitus, and was 65 μm greater in subjects with a history of diabetes mellitus more than two years than the newly diagnosed diabetic patients. Patients with a higher HbA_{1C}, compared to those with lower HbA_{1C} had slightly but non-significantly increased carotid IMT. The functional arterial measurement QCS was also significantly increased in subjects with a history of diabetes mellitus more than two years only in the presence of a higher HbA_{1C}. These

Table 3 Multiple stepwise regression analyses with a model including age, systolic and diastolic blood pressure, current smoking, duration, body mass index, HbA_{1C}, Total cholesterol, Triglycerides, LDL cholesterol, HDL cholesterol, the use of insulin, sulfonylureas, thiazolidinedions, α-glycosidase inhibitors, angiotensin converting enzyme inhibitors and calcium channel blockers

Characteristic	CIMT		QCS	
	Standardized coefficient Beta	*P*	Standardized coefficient Beta	*P*
Duration(years)	0.123	0.023		
Total cholesterol (mmol/l)	0.143	0.008		
age			0.267	0.000
Systolic blood pressure (mmHg)	0.130	0.017	0.324	0.000
Diastolic blood pressure (mmHg)			–0.207	0.011
HbA1c (%)			0.198	0.000

results suggest that the structural arterial measurement is dependent on the duration of diabetes mellitus, whereas the functional measurement is mainly influenced by the HbA_{1C} level, which reflects the quality of blood glucose control.

Our findings are in line with the results of several previous studies. The Asymptomatic Carotid Artery Progression Research Group found that carotid IMT increased by 0.006 mm/year in nondiabetic subjects with coronary risk factors [8]. Studies in type 2 diabetic patients revealed that carotid IMT increased by 0.02 mm/year [9, 10]. However, the Italian Burneck study observed that impaired glucose tolerance or even diabetes was only of moderate relevance in early atherogenesis [11]. The structural changes in arterial wall is probably the consequence of long-term hyperglycaemia, but is less influenced by the blood glucose control. However, in our cross-sectional analysis, the latter factor showed significant impact on the functional measurement of the arterial wall. Tropeano and colleagues also found that pulse wave velocity, an arterial stiffness index, was higher in type 2 diabetic patients than subjects with normal fasting glucose [6].

The disease history or duration is a major determinant of arterial functional and structural measurements or indices. However, these measurements are differentially influenced by therapeutic interventions such as anti-diabetic treatment. Indeed, arterial stiffness as a functional measure in comparison with the structural measurement such as IMT is more susceptible to the current status of blood glucose control.

Our study should be interpreted within the context of its limitations. The number of participants especially the newly diagnosed diabetic subjects is relatively small. The possibility of a chance finding cannot be entirely excluded. Furthermore, the duration of diabetes mellitus is only a rough measure of the disease process, because we calculated the duration according to the time of the participant being diagnosed as diabetes.

In conclusion, our findings suggest that the structural and functional measurements of the arterial wall are differentially influenced by the duration of diabetes mellitus and plasma HbA_{1C}. These findings might have implications for clinical practice and research. QCS, a functional measure of the carotids, is probably more suitable to evaluate the impact of blood glucose control, whereas carotid IMT is probably an appropriate tool for long-term follow-up of diabetic patients.

Materials and methods

Subjects

The Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine approved the study protocol. From October 2006 to February 2007, 547 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. We excluded 210 patients because of missing clinical information (n = 121) and because of having a history of ischaemic heart disease or stroke (n = 89). Thus, the present analysis included 337 subjects.

Clinical and biochemical assessments

Blood pressure was measured with a standard mercury sphygmomanometer after at least 10 min rest in the sitting position. A standardized questionnaire was used 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 [12]. Body mass index was calculated as weight in kilograms divided by height in meter squared.

Carotid IMT and QCS measurements

One trained sonographer, unaware of the disease status of the subjects, performed carotid IMT measurements using a high-resolution B-mode tomographic ultrasound system (Shimadzu SDU-1200, Japan) with a linear 7.5–10 MHz transducer. This operator measured carotid IMT on the fall wall of the right and left common carotid arteries, 1.5 cm proximal to the bifurcation. The transducer was manipulated so that the lumen diameter was maximized in the longitudinal plane. Carotid IMT was measured on-line at the end of diastole as the distance from the leading edge of the first echogenic line to that of the second echogenic line. The first and second lines represent the lumen–intimal interface and the collage-contained upper layer of tunic adventitia, respectively [7]. The measurements of the right and left common carotid IMT were averaged for analysis.

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: QCS = ln (Ps / Pd) / (As / Ad-1), where Ps and Pd are systolic and diastolic blood pressures , and As and Ad 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. We performed reproducibility study in 20 subjects. The coefficient of variation was 3.1% for IMT and 4.3% 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 analysis of variance (ANOVA) and Chi-square test, respectively. In order to allow for covariates and confounders, we performed analysis of covariance and multiple linear regression analysis.

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