Original Article

Progression Factors of Carotid Intima-Media Thickness and Plaque in Patients with Long-Term, Early-Onset Type 1 Diabetes Mellitus in Japan: Simultaneous Comparison with Diabetic Retinopathy

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***Aim*: To evaluate carotid intima-media thickness (IMT) in patients with long-term early-onset type 1 diabetes, and investigate the associations between IMT, diabetic retinopathy and clinical characteristics.**
***Methods*: We evaluated anthropometric measurements, biochemical parameters and carotid IMT. Ultrasonography was performed on 73 patients diagnosed with type 1 diabetes before 30 years of age, and who have been living with diabetes for 20 years or more.**
***Results*: The mean max-IMT (maximal thickness of whole carotid artery) and IMT-Cmax (maximal thickness of common carotid artery) values were 0.94 mm and 0.67 mm; 21 patients had proliferative diabetic retinopathy and 21 patients had plaque (IMT ≥ 1.1 mm). Age, age at diagnosis of diabetes and adolescent HbA1c level (HbA1c at 18 years old or the earliest measurement available) were higher in patients with plaque than in those without. Max-IMT was greater in patients with proliferative retinopathy than in those without. Similarly, there were significant differences in current HbA1c level, and the prevalence of hypertension and dyslipidemia. In multivariate analysis, age and dyslipidemia were independently associated with max-IMT and IMT-Cmax.**
***Conclusions*: Age and dyslipidemia were associated with IMT. In contrast, glycemic control was closely associated with diabetic retinopathy, but weakly associated with IMT.**

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Key words; Type 1 diabetes mellitus, Intima-media thickness, Plaque, Diabetic retinopathy

Introduction

Cardiovascular diseases, as well as microvascular complications, have a major impact on the long-term prognosis and quality of life of diabetes patients. In recent years, funduscopic findings, urinary albumin:creatinine ratio and serum creatinine levels have been considered useful markers for microangiopathy, while carotid intima-media thickness (IMT) and stiffness of the carotid artery are considered to be predictive indicators of macrovascular disease[1-6].

Some studies have demonstrated an association between carotid IMT and cardiovascular disease in patients with type 1 diabetes mellitus[7-10]; however, few simultaneous comparative studies of microangiopathy with such indicators and macroangiopathy with carotid IMT as an indicator have been performed. Simultaneous assessment of macroangiopathy and microangiopathy in patients with long-term type 1 diabetes mellitus has rarely been reported in Japan[11].

In the present study, we aimed to evaluate carotid IMT as a predictive indicator of macrovascular diseases in patients with long-term, early-onset type 1 diabetes mellitus in Japan. We also investigated the associations between IMT and diabetic retinopathy and clinical characteristics, including cardiovascular risk.

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Research Design and Methods

Subjects

Of 1,370 patients with type 1 diabetes mellitus who had visited the Diabetes Center at Tokyo Women's Medical University as of December 2004[12], those diagnosed with early-onset type 1 diabetes, i.e; before 30 years of age, 20 years or more previously were included in this study. Patients with Stage 4 or 5 kidney disease[13], or cardiovascular or cerebrovascular diseases were excluded from this study. Seventy-three patients met these requirements and participated in this study from December 2004 to February 2007. The diagnosis of type 1 diabetes mellitus was based on the criteria of the Japan Diabetes Society[14], which is identical to that of the World Health Organization[15].

Informed consent was obtained from all subjects.

Protocol

Carotid IMT was measured by ultrasonography (discussed in more detail later). HbA1c, total cholesterol (TC) and high density lipoprotein-cholesterol (HDL-C) were measured using standard laboratory techniques. "Non HDL-C" was calculated by subtracting HDL-C from TC. Blood pressure was measured with a standard automated sphygmomanometer while patients were in a sitting position. Proliferative diabetic retinopathy was determined to be retinal neovascularization in accordance with the modified Airlie House System[16], and diabetic nephropathy was defined as a urinary albumin:creatinine ratio ≥30 mg/g Cr[17, 18]. "Smoking" included former smokers. "Adolescent HbA1c" was defined as an HbA1c level assessed at 18 years of age. If subjects were diagnosed as having diabetes after 19 years of age, or if the subjects were over 19 years of age at their initial visit to the Diabetes Center at Tokyo Women's Medical University, adolescent HbA1c was defined as the earliest HbA1c measurement available.

Subjects were considered hypertensive if they were taking antihypertensive agents, and/or if systolic blood pressure (SBP) was ≥140 mmHg, and/or diastolic blood pressure (DBP) was ≥90 mmHg. Dyslipidemia was considered if the subject was taking antihyperlipidemic agents, and/or if TC was ≥220 mg/dL, and/or HDL-C was <40 mg/dL.

Measurement of Carotid IMT

Ultrasonography of carotid arteries was performed using an echotomography system (SSA-550A; Toshiba, Tokyo, Japan) and a 7.5 MHz linear array transducer, as previously reported[1, 19, 20]. IMT was determined from the common carotid artery and carotid bulb to the internal carotid artery and was measured from the leading edge of the first echogenic line to that of the second echogenic line. The first line represented the collagen-containing upper layer of the adventitia. "Max-IMT" was defined as the maximal thickness of the whole bilateral carotid artery, and "IMT-Cmax" was defined as the maximum thickness of the common bilateral carotid artery. Max-IMT and IMT-Cmax represented the maximum wall thickness, including plaque lesions, and "plaque" was defined as IMT ≥1.1 mm.

Statistical Analysis

Statistical evaluation was performed with the StatView program for Windows (version 5.0; Abacus Concepts, Berkeley, USA), and data are presented as frequencies or the means ± SD. For all analyses, probability (p) values below 0.05 were considered to indicate statistical significance.

The associations among max-IMT, IMT-Cmax and clinical characteristics were analyzed by sex. We divided the subjects into two groups according to the presence or absence of plaque or proliferative diabetic retinopathy. The Mann-Whitney U-test and chi-square test were used to test for differences between the two groups with respect to clinical characteristics and cardiovascular risk factors. Stepwise multiple linear regression analysis was performed with max-IMT (or IMT-Cmax) as the dependent variable, and age, sex, age at diagnosis of diabetes, duration of diabetes, BMI, HbA1c, adolescent HbA1c, diabetic nephropathy, hypertension, dyslipidemia and smoking were included as independent variables.

Results

The clinical characteristics of the subjects, according to sex, are shown in **Table 1**. The mean age was 37.9 years (males: 37.2 years; females: 38.4 years), the mean age at diagnosis of diabetes was 11.0 years (males: 9.4 years; females: 12.0 years) and the mean duration of diabetes was 26.9 years (males: 27.8 years; females: 26.4 years). The mean HbA1c and adolescent HbA1c were 7.9% (males: 8.1%; females: 7.7%) and 9.5% (males: 9.4%; females: 9.6%), respectively, and the mean age at the measurement of adolescent HbA1c was 24.6 years. Twenty-one patients (males: 25.0%; females: 31.1%) had proliferative diabetic retinopathy and 17 patients (males: 25.0%; females: 22.2%) had diabetic nephropathy. The mean max-IMT and IMT-Cmax values were 0.94 mm (males: 1.02 mm; females: 0.89 mm) and 0.67 mm (males: 0.68 mm; females: 0.66 mm), respectively, and 21 patients (males:

Table 1. Clinical characteristics of the subjects ($n=73$)

	Male ($n=28$)	Female ($n=45$)	p
Age (years)	37.2 ± 6.7	38.4 ± 8.2	NS
Age at diagnosis of diabetes (years)	9.4 ± 6.6	12.0 ± 7.3	NS
Duration of diabetes (years)	27.8 ± 5.7	26.4 ± 5.2	NS
BMI (kg/m^2)	23.6 ± 3.0	23.1 ± 3.3	NS
HbA1c (%)	8.1 ± 1.5	7.7 ± 1.3	NS
Adolescent HbA1c (%)	9.4 ± 2.2	9.6 ± 2.2	NS
Total cholesterol (mg/dL)	198.8 ± 39.1	190.7 ± 29.0	NS
HDL-cholesterol (mg/dL)	66.8 ± 18.5	79 ± 19.6	<0.01
Non-HDL-cholesterol (mg/dL)	132 ± 38.8	111.4 ± 21.2	<0.05
Systolic blood pressure (mmHg)	133.8 ± 18.0	124.8 ± 13.7	<0.05
Diastolic blood pressure (mmHg)	83.8 ± 11.0	75 ± 10.6	<0.01
max-IMT (mm)	1.02 ± 0.45	0.89 ± 0.36	NS
IMT-Cmax (mm)	0.68 ± 0.15	0.66 ± 0.21	NS
Having plaque (%)	32.1	26.7	NS
Proliferative retinopathy (%)	25.0	31.1	NS
Diabetic nephropathy (%)	25.0	22.2	NS
Hypertension (%)	53.6	42.2	NS
Taking antihypertensive agents (%)	39.3	24.4	NS
Dyslipidemia (%)	39.3	26.7	NS
Taking antihyperlipidemic agents (%)	25.0	20.0	NS
Having smoked (%)	57.1	31.1	<0.05

Data are the means ± SD (range) or a percent, unless otherwise indicated. Non-HDL-cholesterol, Total cholesterol − HDL-cholesterol; max-IMT, maximal intima-media thickness of bilateral whole carotid artery; IMT-Cmax, maximal intima-media thickness of bilateral common carotid artery. NS, not statistically significant. Mann-Whitney U tests were used to compare the means between groups. Chi-square tests were used to compare the prevalence between groups.

32.1%; females: 26.7%) had plaque.

The associations between max-IMT, IMT-Cmax and clinical characteristics, according to sex, are presented in **Table 2**. Max-IMT was correlated with IMT-Cmax in both males and females (males: $p<0.05$, $r=0.408$; females: $p<0.0001$, $r=0.644$). In males, max-IMT was significantly correlated with adolescent HbA1c ($p<0.01$, $r=0.489$), and IMT-Cmax was significantly correlated with the duration of diabetes ($p<0.01$, $r=0.492$), systolic blood pressure ($p<0.05$, $r=0.405$) and diastolic blood pressure ($p<0.05$, $r=0.427$). In females, max-IMT was significantly correlated with age ($p<0.001$, $r=0.498$), age at diagnosis of diabetes ($p<0.01$, $r=0.417$) and systolic blood pressure ($p<0.05$, $r=0.319$), while IMT-Cmax was significantly correlated with age ($p<0.05$, $r=0.345$) and age at diagnosis of diabetes ($p<0.05$, $r=0.298$). In contrast, max-IMT and IMT-Cmax were not correlated with HbA1c in either males or females.

Table 3 shows a comparison of the clinical characteristics and cardiovascular risk factors in patients with and without plaque. The mean max-IMT was 1.44 mm (plaque group) and 0.74 mm (non-plaque group) ($p<0.0001$), and the mean IMT-Cmax was 0.80 mm (plaque group) and 0.61 mm (non-plaque group) ($p=0.0001$). Age and age at diagnosis of diabetes were higher in patients with plaque than in patients without plaque. Adolescent HbA1c was higher in patients with plaque than in patients without plaque ($p<0.05$), but there was no significant difference in HbA1c.

Table 4 shows a comparison of the clinical characteristics of patients with or without proliferative diabetic retinopathy. Max-IMT was thicker in patients with proliferative diabetic retinopathy than in those without ($p<0.05$). Similarly, there were significant differences in HbA1c, TC, non HDL-C, and the prevalence of hypertension, dyslipidemia, and antihyperlipidemic agent use between the two groups.

Table 5 shows stepwise multiple linear regression analysis performed with max-IMT (or IMT-Cmax) as dependent variables, and age, sex, age at diagnosis of diabetes, duration of diabetes, BMI, HbA1c, adolescent HbA1c, diabetic nephropathy, hypertension, dys-

Table 2. Associations between max-IMT, IMT-Cmax and clinical characteristics

	Male ($n=28$)				Female ($n=45$)			
	maxIMT		IMT-Cmax		maxIMT		IMT-Cmax	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age		NS		NS	0.498	<0.001	0.345	<0.05
Age at diagnosis of diabetes		NS		NS	0.417	<0.01	0.298	<0.05
Duration of diabetes		NS	0.492	<0.01		NS		NS
BMI		NS		NS		NS		NS
HbA_{1C}		NS		NS		NS		NS
Adolescent HbA_{1C}	0.489	<0.01		NS		NS		NS
Total cholesterol		NS		NS		NS		NS
HDL-cholesterol		NS		NS		NS		NS
Non-HDL-cholesterol		NS		NS		NS		NS
Systolic blood pressure		NS	0.405	<0.05	0.319	<0.05		NS
Diastolic blood pressure		NS		<0.05		NS		NS
IMT-Cmax	0.408	<0.05	0.427		0.644	<0.0001		
Max-IMT			0.408	<0.05			0.644	<0.0001

max-IMT, maximal intima-media thickness of bilateral whole carotid artery; IMT-Cmax, maximal intima-media thickness of bilateral common carotid artery; non-HDL-cholesterol, Total cholesterol−HDL-cholesterol, NS, not statistically significant.

Table 3. Comparison of clinical characteristics with or without plaque

	plaque (+) ($n=21$)	plaque (−) ($n=52$)	*p*
Sex (% males)	43	37	NS
Age (years)	43.9 ± 6.9	35.5 ± 6.6	<0.0001
Age at diagnosis of diabetes (years)	15.4 ± 7.9	9.2 ± 5.9	<0.01
Duration of diabetes (years)	28.5 ± 5.0	26.3 ± 5.5	NS
BMI (kg/m^2)	22.8 ± 3.5	23.5 ± 3.1	NS
HbA_{1C} (%)	7.8 ± 1.3	7.9 ± 1.4	NS
Adolescent HbA_{1C} (%)	10.5 ± 2.4	9.1 ± 2.0	<0.05
Total cholesterol (mg/dL)	200.8 ± 24.8	190.9 ± 35.9	NS
HDL-cholesterol (mg/dL)	76.9 ± 15.4	73.2 ± 21.6	NS
Non-HDL-cholesterol (mg/dL)	124.0 ± 20.7	117.5 ± 34.0	NS
Systolic blood pressure (mmHg)	129.9 ± 18.6	127.6 ± 14.9	NS
Diastolic blood pressure (mmHg)	76.4 ± 8.4	79.2 ± 12.5	NS
Max-IMT (mm)	1.44 ± 0.37	0.74 ± 0.15	<0.0001
IMT-Cmax (mm)	0.80 ± 0.21	0.61 ± 0.15	0.0001
Proliferative retinopathy (%)	42.9	23.1	NS
Diabetic nephropathy (%)	23.8	23.1	NS
Hypertension (%)	57.1	42.3	NS
Taking antihypertensive agents (%)	38.1	26.9	NS
Dyslipidemia (%)	47.6	25.0	NS
Taking antihyperlipidemic agents (%)	28.6	19.2	NS
Having smoked (%)	42.9	40.4	NS

Data are the means ± SD or a percent, unless otherwise indicated. Non-HDL-cholesterol, Total cholesterol−HDL-cholesterol; max-IMT, maximal intima-media thickness of bilateral whole carotid artery; IMT-Cmax, maximal intima-media thickness of bilateral common carotid artery; NS, not statistically significant. Mann-Whitney *U* tests were used to compare the means between groups. Chi-square tests were used to compare the prevalence between groups.

Table 4. Comparison of clinical characteristics with or without proliferative retinopathy

	Proliferative retinopathy		*p*
	(+) ($n=21$)	(−) ($n=52$)	
Sex (% males)	33	40	NS
Age (years)	40.1 ± 8.8	37.1 ± 7.0	NS
Age at diagnosis of diabetes (years)	11.9 ± 6.9	10.7 ± 7.2	NS
Duration of diabetes (years)	28.2 ± 4.5	26.4 ± 5.7	NS
BMI (kg/m^2)	22.7 ± 2.8	23.5 ± 3.3	NS
HbA1C (%)	8.4 ± 1.4	7.7 ± 1.3	< 0.05
Adolescent HbA1C (%)	10.3 ± 2.5	9.2 ± 2.0	NS
Total cholesterol (mg/dL)	209.2 ± 27.7	187.5 ± 33.4	< 0.01
HDL-cholesterol (mg/dL)	79.3 ± 20.4	72.2 ± 19.7	NS
Non-HDL-cholesterol (mg/dL)	129.9 ± 28.1	115.1 ± 31.0	< 0.05
Systolic blood pressure (mmHg)	130.9 ± 16.1	127.2 ± 15.9	NS
Diastolic blood pressure (mmHg)	77.6 ± 11.2	78.7 ± 11.7	NS
Max-IMT (mm)	1.13 ± 0.50	0.87 ± 0.32	< 0.05
IMT-Cmax (mm)	0.71 ± 0.16	0.65 ± 0.20	NS
Having plaque (%)	42.9	23.1	NS
Diabetic nephropathy (%)	38.1	17.3	NS
Hypertension (%)	66.7	38.5	< 0.05
Taking antihypertensive agents (%)	42.9	25.0	NS
Dyslipidemia (%)	52.4	23.1	< 0.05
Taking antihyperlipidemic agents (%)	42.9	13.5	< 0.001
Having smoked (%)	38.1	42.3	NS

Data are the means ± SD or a percent, unless otherwise indicated. Non-HDL-cholesterol, Total cholesterol − HDL-cholesterol; max-IMT, maximal intima-media thickness of bilateral whole carotid artery; IMT-Cmax, maximal intima-media thickness of bilateral common carotid artery; NS, not statistically significant. Mann-Whitney *U* tests were used to compare the means between groups. Chi-square tests were used to compare the prevalence between groups.

Table 5. Multiple linear regression models for max-IMT and IMT-Cmax using the stepwise model selection method

	β	R
Max-IMT		
Age	0.340	< 0.001
Dyslipidemia	0.243	< 0.01
		$R^2 = 0.213$
IMT-Cmax		
Age	0.266	< 0.01
Dyslipidemia	0.255	< 0.01
		$R^2 = 0.167$

max-IMT, maximal intima-media thickness of bilateral whole carotid artery; IMT-Cmax, maximal intima-media thickness of bilateral common carotid artery; β, standard partial regression coefficient; R, multiple correlation coefficient. Independent variables: age, sex, age at diagnosis of diabetes, duration of diabetes, BMI, HbA1C, adolescent HbA1C, diabetic nephropathy, hypertension, dyslipidemia, smoking.

lipidemia and smoking as independent variables. Age and dyslipidemia were independently associated with max-IMT and IMT-Cmax.

Discussion

In this study, we evaluated carotid IMT as an indicator of macrovascular disease in patients with long-term, early-onset type 1 diabetes mellitus in Japan, and investigated the associations between IMT and diabetic retinopathy as representing microangiopathy, and clinical characteristics, including cardiovascular risk. One of our main observations was that max-IMT and plaque were not correlated with current HbA1C, but were correlated with adolescent HbA1C (**Table 2**, **3**). In contrast, diabetic retinopathy was correlated with current HbA1C (**Table 4**). It was previously reported that glycemic control largely influenced the onset and progress of diabetic retinopathy[21-23]. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive diabetes therapy delayed the onset and slowed the progression of retinopathy, nephropathy and neuropathy in patients with type 1 diabetes mellitus, but the incidence of cardiovascular disease was not significantly different between the two treatment groups[24]; however, in the

Epidemiology of Diabetes Interventions and Complications (EDIC) study, the long-term follow-up of DCCT, intensive diabetes therapy during DCCT decreased the progression of IMT, and had long-term beneficial effects on the risk of cardiovascular disease in patients with type 1 diabetes mellitus[9, 25]. In our study, adolescent HbA1c, considered to represent past glycemic control, was associated with max-IMT and the presence of plaque. A history of long-term glycemic control influences the progression of IMT and development of cardiovascular disease in patients with type 1 diabetes mellitus.

In contrast, some studies have reported the IMT in subjects with type 2 diabetes or with impaired glucose tolerance (IGT). For example, Yamasaki *et al.* showed that subjects with IGT had significantly greater IMT than age-matched healthy males and there was no significant differences compared with age-matched patients with type 2 diabetes mellitus[26]. In a previous study, postchallenge plasma glucose was more strongly associated with carotid IMT than fasting plasma glucose in a cohort of subjects at risk for diabetes or in the early stage of diabetes[27]. These studies show that atherosclerosis was already present in subjects with IGT or in the early stage of type 2 diabetes mellitus. It may be inferred that the strength of the association between glycemic control and progression of atherosclerosis differs between type 1 and type 2 diabetes mellitus.

In our study, the factor that was most strongly correlated with max-IMT, IMT-Cmax and plaque was age (**Table 2**, **3**, **5**). This is in agreement with previous studies in which age was one of the strongest factors associated with the progression of atherosclerosis and IMT in patients with type 1 diabetes mellitus[7, 8, 10]. In contrast, in our study, there was no significant difference in age between patients with proliferative diabetic retinopathy and patients without proliferative diabetic retinopathy (**Table 4**). In Japanese patients with early-onset type 1 diabetes mellitus, the progression of IMT and plaque are strongly influenced by aging, and this influence is more important than glycemic control. On the other hand, the association between age and microangiopathy was relatively weak.

Dyslipidemia is a major risk factor for cardiovascular disease in patients with type 1 diabetes mellitus[28]. Dyslipidemia was also associated with max-IMT and IMT-Cmax in our study (**Table 5**). In the SEARCH for Diabetes in Youth, a recent population-based study in the United States, 19% of subjects had TC concentrations >200 mg/dL, 15% had LDL-C concentrations >130 mg/dL, 10% had triglyceride concentrations >150 mg/dL and 12% had HDL-C concentrations <40 mg/dL among youths with type 1 diabetes aged 10 years or older, but only 1% were receiving pharmacologic therapy for dyslipidemia[29]. Wadwa *et al.* reported that 47% of type 1 diabetic patients who had been diagnosed at <30 years of age and with a duration of type 1 diabetes ≥10 years had dyslipidemia, but 36% of those with abnormal lipid levels were on medication for dyslipidemia and only 15% were in control of their lipid levels[30]. These reports show naivety in the management of lipid levels in patients with type 1 diabetes mellitus. We must thesefore acknowledge the importance of managing lipid levels appropriately and treat dyslipidemia more actively.

Prior studies have reported that hypertension and smoking, in addition to dyslipidemia, are factors associated with the progression of IMT in patients with type 1 diabetes mellitus[8]. In our study, there was no significant difference in the prevalence of hypertension and smoking between patients with versus without plaque (**Table 3**). Meanwhile, the prevalence of hypertension and dyslipidemia in patients with proliferative diabetic retinopathy was higher than in patients without proliferative diabetic retinopathy (**Table 4**). T results from our study of Japanese patients, in addition to other studies of type 1 diabetes mellitus, suggested that these factors, as well as glycemic control, are associated with the progression of diabetic retinopathy[31-33].

There are a few limitations to our study. First, we defined dyslipidemia as TC ≥220 mg/dL, and/or HDL-C <40 mg/dL, and/or treatment with antihyperlipidemic agents. We could not differentiate precisely between hyper-low-density-lipoprotein (LDL) -cholesterolemia and hypo-HDL-cholesterolemia, because we did not measure LDL-cholesterol or fasting triglyceride, and some of our subjects were treated with antihyperlipidemic agents. Second, we did not analyze the association between carotid IMT and kidney function, although patients with chronic kidney disease at Stage 4 or 5 were excluded. The presence or absence of diabetic nephropathy was not associated with the progression of carotid IMT and plaque (**Table 3**, **5**), but we could not fully characterize the association between kidney function and the progression of carotid IMT and plaque. These issues need to be clarified in future studies.

In conclusion, our study found that age was closely associated with the progression of carotid IMT and plaque, while dyslipidemia was also associated with IMT in patients with long-term, early-onset type 1 diabetes in Japan. In contrast, glycemic control was strongly associated with diabetic retinopathy and

weakly associated with IMT and plaque. Preventing the onset and progression of diabetic complications is very important in patients with type 1 diabetes mellitus. This study indicates the necessity of interventions to manage risk factors such as dyslipidemia, in addition to glycemic control, to prevent long-term vascular complications of diabetes, including microvascular and macrovascular disease, in patients with long-term, early-onset type 1 diabetes mellitus.

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