Elevated C-Reactive Protein Associates With Early-Stage Carotid Atherosclerosis in Young Subjects With Type 1 Diabetes

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OBJECTIVE — To evaluate whether low-grade inflammation contributes to early-stage advanced carotid atherosclerosis in young subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS — The mean and maximum (max) intima-media thicknesses (IMT) of the carotid artery were assessed using ultrasound B-mode imaging in 55 patients with type 1 diabetes (22 men and 33 women, aged 22.1 ± 3.6 years (± SD), duration of diabetes 14.2 ± 5.7 years) and 75 age-matched healthy nondiabetic subjects (28 men and 47 women). High-sensitive C-reactive protein (hs-CRP) levels were measured with a latex-enhanced immunonephelometer.

RESULTS — The patients with type 1 diabetes had significantly higher hs-CRP levels (median 0.35, range 0.05–1.47 mg/l vs. median 0.14, range 0.05–1.44 mg/l; $P = 0.001$) as well as significantly higher mean IMT and max IMT than the nondiabetic subjects (mean IMT 0.76 ± 0.09 vs. 0.72 ± 0.04 mm, $P = 0.003$; max IMT 0.84 ± 0.11 vs. 0.77 ± 0.06 mm, $P < 0.0001$). Hs-CRP levels were significantly correlated with the mean and max IMT of patients with type 1 diabetes and with the max IMT of nondiabetic patients. Multivariate regression analyses for both diabetic and nondiabetic subjects as a single group showed that hs-CRP levels are independently correlated with the mean IMT and max IMT levels ($P = 0.002$ and $P = 0.023$, respectively) as well as with diastolic blood pressure, sex, and duration of diabetes.

CONCLUSIONS — Our data indicate that hs-CRP levels are elevated in young patients with type 1 diabetes, possibly corresponding with early-stage advanced carotid atherosclerosis.

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One line of evidence suggests that cardiovascular disease (CVD) caused by atherosclerosis is the major cause of mortality and morbidity in patients with type 1 diabetes (1,2). This emphasizes the importance of interventions that help patients with type 1 diabetes reduce their risk of CVD.

Intima-media thickness (IMT) of the carotid artery has been used as a subclinical index of early atherosclerosis (3,4). Several studies have shown an association between an increased carotid IMT and CVD in elderly subjects (5,6). We have shown that young patients with type 1 diabetes exhibit a much more advanced stage of carotid atherosclerosis than nondiabetic subjects (7). Other reports have shown that BMI, age, male sex, triglycerides, and nephropathy interact independently of IMT in patients with type 1 diabetes (8,9). However, the risk factors for early-stage carotid atherosclerosis in young subjects with type 1 diabetes have not yet been fully evaluated.

Recently, inflammation has been considered, at least in part, to lead to the development and progression of atherosclerosis (10). Acute-phase C-reactive protein has been used as a marker of systemic inflammatory changes in patients with sepsis or connective tissue disease. A high-sensitive C-reactive protein (hs-CRP) assay was developed that can detect slight but significant increases in CRP levels within the normal range. Hs-CRP is considered to be a consistent marker for evaluating the extent of CVD in clinical studies (11–13). Furthermore, the association between subtle increases in hs-CRP concentration and the development of carotid atherosclerosis has been recently reported in a longitudinal study (14).

Increased concentrations of circulating acute-phase proteins have been reported in patients with type 2 diabetes (15,16) and in patients with type 1 diabetes aged >30 years (17,18). However, there have been few studies to determine the level of hs-CRP in young patients with type 1 diabetes. In the present study, we investigated whether hs-CRP levels are elevated in young patients with type 1 diabetes and determined whether low-grade inflammation is related to early-stage atherosclerosis.

RESEARCH DESIGN AND METHODS

Study population

A total of 55 type 1 diabetic patients (22 men and 33 women, aged 22.1 ± 3.6 years (±SD), duration of diabetes 14.2 ± 5.7 years) undergoing periodic follow-up examinations at the Diabetes Clinic of Osaka University Hospital and the Osaka Police Hospital were enrolled in this study. All patients with diabetes were treated with at least three or four daily

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Abbreviations: AER, albumin excretion rate; CVD, cardiovascular disease; hs-CRP, high-sensitive C-reactive protein; IMT, intima-media thickness; LDL-c, LDL cholesterol; max, maximum.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

insulin injections. The daily insulin dose was 0.89 ± 0.20 units/kg (range 0.46–1.35 units/kg). As control subjects, we also enrolled 75 healthy nondiabetic individuals (28 men and 47 women aged 23.5 ± 3.8 years). None of the subjects had any clinical evidence of infection, connective tissue disease, liver dysfunction, or angiopathy. None of the subjects were taking antihypertensive, antiplatelet, or lipid-lowering medication at the time of the study. After a full explanation of this study, written informed consent was obtained from each subject. The study was approved by the Ethical Committee for Human Studies at Osaka University Graduate School of Medicine.

Fasting blood samples were collected and serum total cholesterol and HDL cholesterol, serum triglyceride, serum uric acid, serum creatinine, blood urea nitrogen, plasma glucose, and HbA_{1c} levels were measured using standard laboratory protocols. LDL cholesterol (LDL-c) levels were calculated using the Friedewald formula (19).

The subjects submitted urine samples that had been collected at home over the previous 24 h. Written instructions and careful explanation regarding the procedure for urine collection were given to each subject. Most of the patients with diabetes were familiar with the method for collecting urine at home. Nevertheless, a urine sample was discarded if there was any doubt with regard to its collection. The 24-h urine samples collected from each subject were used to determine the value of the urinary albumin excretion rate (AER; albumin/creatinine ratio). In the patients with diabetes, presence of retinopathy was diagnosed by ophthalmologists based on the findings of funduscopy. Smokers were classified as having a current smoking habit.

Measurement of hs-CRP concentration

Blood samples were collected in tubes containing citric acid and stored at −80°C after centrifugation. Hs-CRP concentrations were measured using a latex-enhanced immunonephelometer (range 0.05–10 mg/l; Dade Behring, Newark, DE) (18,20). The coefficient of variation for repeated CRP measurements was 11% over all ranges.

Measurement of IMT

To estimate early stages of atherosclerosis, ultrasonographic scanning of the carotid artery was performed using an echotomographic system (Toshiba, Tokyo, Japan) with an electrical liner transducer (midfrequency 8.0 MHz). Scanning of the extracranial common carotid artery, the carotid bulb, and the internal carotid artery in the neck was performed bilaterally from three different longitudinal projections (i.e., anterior oblique, lateral, and posterior oblique) as well as the transverse projections, as reported in our previous studies (7,21–24). All of the images were photocopied. The detection limit of this echo system using 8.0 MHz was 0.1 mm. The IMT defined by Pignoli et al. (3,4) was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. The first line represented the lumen-intima interface, and the second line is produced by the collagen-containing upper layer of the tunica adventitia. At each longitudinal projection, the site of the greatest thickness including a plaque lesion was sought along the arterial walls nearest the skin and farthest from the skin from the common carotid artery to the internal carotid artery. Three determinations of IMT were conducted at the site of the thickest point, maximum IMT (max IMT) and two adjacent points (located 1 cm upstream and 1 cm downstream from this site). These three determinations were averaged (mean IMT). The greatest value among the six max IMTs and six mean IMTs (three from the left and three from right) was used as the representative value for each individual. All ultrasound scans were performed by an experienced sonographer (A.K.), and an experienced physician (N.K.) performed determination of IMT on the photograph. These two were unaware of the subject's study group and clinical characteristics. Reproducibility of the IMT measurement was examined 1 week later in 30 participants with type 1 diabetes by the same sonographer and the same physician. The mean difference in IMT between these two determinations was 0.04 mm and the standard deviation was 0.07 mm, demonstrating good reproducibility for repeated measurements, as described previously (7,21–24).

Statistical analysis

Data are given as means ± SD. Means or proportions for clinical characteristics were computed for the case and control subjects, and the laboratory data were compared using Student's *t* tests. Differences in proportions were tested using the χ^2 test. Because the CRP and AER distributions were skewed to the left, the median concentrations were computed for these parameters and the significance of any differences between the patients and control subjects using the Mann-Whitney *U* test. Single linear univariate correlations (Pearson's correlation coefficients) and forward and backward stepwise multivariate regression analyses were performed to evaluate the relationship between IMT and the following variables: sex, age, duration of diabetes, BMI, systolic blood pressure, diastolic blood pressure, smoking habit, insulin dose, HbA_{1c}, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, uric acid, creatinine, hs-CRP (logarithmically transformed data), fibrinogen, and microangiopathy (AER and presence of retinopathy). For the forward and backward stepwise multivariate regression analyses, the *F* value for the inclusion and exclusion of variables was set at 2.0. These statistical analyses were performed using Stat-View statistical software (Version 5.0 for Windows; Abacus Concepts, Berkeley, CA) and HALBOU statistical software (Gendai Sugaku-sha, Kyoto, Japan) on a personal computer. The threshold of statistical significance was defined as $P < 0.05$.

RESULTS — The patients' characteristics are summarized in Table 1.

Between the diabetic subjects and the nondiabetic subjects, no differences were seen in age, sex, systolic blood pressure, current smoking habit, total cholesterol, triglycerides, HDL cholesterol, or LDL cholesterol. The patients with type 1 diabetes had a significantly higher BMI, diastolic blood pressure, HbA_{1c} level, serum creatinine level, and fibrinogen level than the nondiabetic subjects. The concentrations of hs-CRP were significantly higher in the patients with type 1 diabetes than in the nondiabetic subjects (median 0.35, range 0.05–1.47 mg/l vs. median 0.14, range 0.05–1.44 mg/l; $P = 0.001$).

The mean IMT was significantly greater in patients with type 1 diabetes than in control subjects (0.76 ± 0.09 vs. 0.72 ± 0.04 mm, respectively; $P =$

Table 1—*Clinical characteristics of type 1 diabetic subjects and nondiabetic subjects*

Variables	Type 1 diabetic subjects	Nondiabetic subjects	*P*
n	55	75	—
Sex (men/women)	22/33	28/47	NS*
Age (years)	22.1 ± 3.6	23.5 ± 3.8	NS
Duration of diabetes (years)	14.2 ± 5.7	—	—
BMI (kg/m^2)	22.4 ± 2.8	21.1 ± 2.7	0.011
Systolic blood pressure (mmHg)	118 ± 13	114 ± 10	NS
Diastolic blood pressure (mmHg)	74 ± 8	68 ± 8	<0.0001
Smoking (yes/no)	8/47	13/62	NS*
Insulin dose (IU · kg^{-1} · day^{-1})	0.89 ± 0.20	—	—
HbA_{1c} (%)	7.9 ± 1.4	4.6 ± 0.2	<0.0001
Total cholesterol (mmol/l)	4.4 ± 0.8	4.2 ± 0.6	NS
Triglycerides (mmol/l)	0.81 ± 0.28	0.70 ± 0.29	NS
HDL cholesterol (mmol/l)	1.55 ± 0.36	1.66 ± 0.34	NS
LDL cholesterol (mmol/l)	1.79 ± 0.43	2.20 ± 0.52	NS
Creatinine (μmol/l)	80.4 ± 12.4	54.8 ± 9.7	<0.0001
Uric acid (μmol/l)	244 ± 82	277 ± 60	NS
AER (mg/g Cr)	16.0 ± 36.6	7.8 ± 5.8	NS†
	6.0 (1.5–223)	5.65 (2.7–22.9)	
Fibrinogen (g/l)	2.25 ± 0.41	1.81 ± 0.33	<0.0001
Hs-CRP (mg/l)	0.44 ± 0.36	0.26 ± 0.29	0.001†
	0.35 (0.05–1.47)	0.14 (0.05–1.44)	
Mean IMT (mm)	0.76 ± 0.09	0.72 ± 0.04	0.003
Max IMT (mm)	0.84 ± 0.11	0.77 ± 0.06	<0.0001
Retinopathy (NDR/BDR/PDR)	33/17/5	—	—

Data are means ± SD or median (range). Student's *t* test was performed. *χ^2 test. †Mann-Whitney *U* test. NDR, no diabetic retinopathy; BDR, background diabetic retinopathy; PDR, proliferative diabetic retinopathy.

0.003). The max IMT was also significantly greater in patients with type 1 diabetes than in control subjects (0.84 ± 0.11 vs. 0.77 ± 0.06 mm, respectively; $P < 0.0001$).

In the patients with type 1 diabetes, positive correlations were observed between the mean IMT and sex, systolic blood pressure, current smoking habit, serum creatinine level, and hs-CRP concentration. In the nondiabetic subjects, positive correlations were observed between the mean IMT and BMI and between the mean IMT and the diastolic blood pressure (Table 2 and Fig. 1*A*).

A multivariate regression analysis showed that hs-CRP concentration ($P = 0.00001$), current smoking habit ($P = 0.006$), serum creatinine level ($P = 0.009$), and systolic blood pressure ($P = 0.025$) were variables that interacted independently of mean IMT in patients with type 1 diabetes. In the nondiabetic subjects, BMI ($P = 0.036$) was an independent risk factor (Table 2).

In patients with type 1 diabetes, positive correlations were observed between max IMT and sex, systolic blood pressure, and hs-CRP concentration. In nondiabetic subjects, positive correlations were observed between max IMT and age, sex, BMI, diastolic blood pressure, current

Table 2—*Correlation between mean IMT and variables in the subjects*

	Type 1 diabetic subjects					Nondiabetic subjects				
	Univariate*		Multivariate			Univariate*		Multivariate		
	r	*P*	β	*F*	*P*	*r*	*P*	β	*F*	*P*
Age (years)	0.236	0.089	—	—	—	0.162	0.210	—	—	—
Sex (men/women)	—	0.009†	—	—	—	—	0.905	—	—	—
Duration of diabetes (years)	0.198	0.157	—	—	—	—	—	—	—	—
BMI (kg/m^2)	0.051	0.720	—	—	—	0.279	0.029†	0.0043	4.621	0.036†
Systolic blood pressure (mmHg)	0.309	0.024†	0.002	5.413	0.025†	0.105	0.431	—	—	—
Diastolic blood pressure (mmHg)	0.231	0.096	—	—	—	0.270	0.039†	0.0012	3.216	0.079
Smoking (yes/no)	—	0.011†	0.079	8.271	0.006†	—	0.407	—	—	—
HbA_{1c} (%)	−0.152	0.279	—	—	—	0.183	0.260	—	—	—
Total cholesterol (mmol/l)	0.014	0.920	—	—	—	−0.112	0.413	—	—	—
Triglycerides (mmol/l)	0.108	0.486	—	—	—	0.055	0.699	—	—	—
HDL cholesterol (mmol/l)	−0.163	0.246	—	—	—	0.009	0.955	—	—	—
LDL cholesterol (mmol/l)	0.127	0.418	—	—	—	−0.175	0.309	—	—	—
Creatinine (μmol/l)	0.325	0.018†	0.189	7.455	0.009†	−0.310	0.075	—	—	—
Uric acid (μmol/l)	0.241	0.083	—	—	—	0.002	0.991	—	—	—
AER (mg/g Cr)	0.177	0.220	—	—	—	−0.370	0.100	—	—	—
Fibrinogen (g/l)	0.030	0.831	—	—	—	−0.038	0.860	—	—	—
log Hs-CRP (mg/l)	0.429	0.002†	0.119	24.01	0.00001†	0.089	0.503	—	—	—
R^2	—	—	0.491	—	—	—	—	0.142	—	—

*Pearson's univariate correlation coefficients. A stepwise multivariate regression analysis was performed. Sex: men = 1, women = 0; smoking: yes = 1, no = 0. β: Partial regression coefficient, †$P < 0.05$.

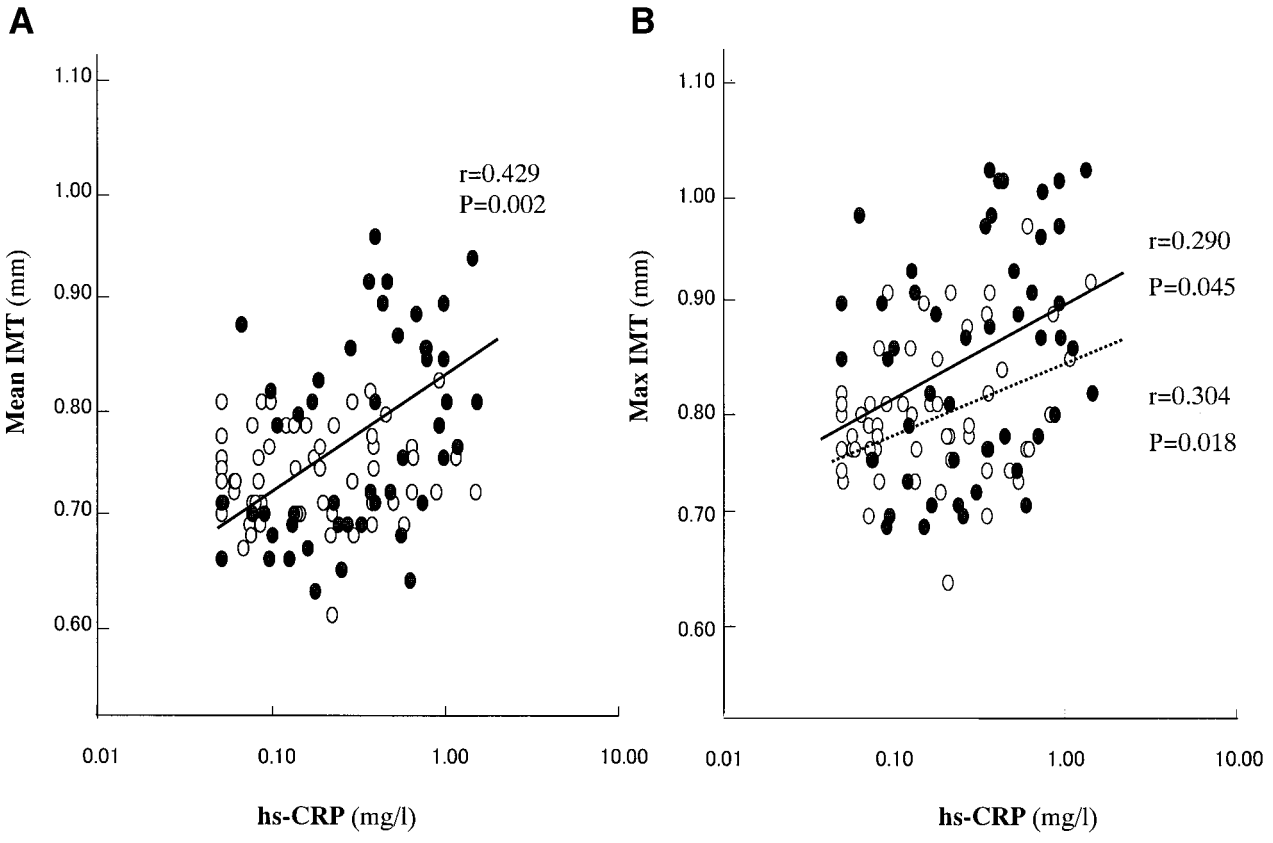

Figure 1—A: *Relationship between hs-CRP and mean IMT in patients with type 1 diabetes (closed circles;* r = *0.429,* P = *0.002) and nondiabetic subjects (open circles).* B: *Relationship between hs-CRP and max IMT in patients with type 1 diabetes (closed circles;* r = *0.290,* P = *0.045) and nondiabetic subjects (open circles;* r = *0.304,* P = *0.018).*

Table 3—*Correlation between max IMT and variables in the subjects*

	Type 1 diabetic subjects					Nondiabetic subjects				
	Univariate*		Multivariate			Univariate*		Multivariate		
Variables	*r*	*P*	β	*F*	*P*	*r*	*P*	β	*F*	*P*
Age (years)	0.203	0.146	0.006	2.661	0.110	0.296	0.019†	0.0048	5.571	0.022†
Sex (men/women)	—	0.042†	0.071	6.938	0.012†	—	0.042†	—	—	—
Duration of diabetes (years)	0.240	0.083	—	—	—	—	—	—	—	—
BMI (kg/m^2)	0.134	0.342	—	—	—	0.297	0.020†	—	—	—
Systolic blood pressure (mmHg)	0.324	0.018†	—	—	—	0.116	0.385	—	—	—
Diastolic blood pressure (mmHg)	0.259	0.061	—	—	—	0.260	0.047†	—	—	—
Smoking (yes/no)	—	0.113	—	—	—	—	0.040†	—	—	—
HbA_{1c} (%)	−0.223	0.109	—	—	—	0.116	0.477	—	—	—
Total cholesterol (mmol/l)	0.034	0.812	—	—	—	−0.104	0.448	—	—	—
Triglycerides (mmol/l)	0.121	0.435	—	—	—	0.151	0.283	—	—	—
HDL cholesterol (mmol/l)	−0.088	0.535	—	—	—	−0.191	0.220	—	—	—
LDL cholesterol (mmol/l)	0.141	0.370	—	—	—	−0.165	0.339	—	—	—
Creatinine (μmol/l)	0.224	0.107	—	—	—	−0.185	0.296	—	—	—
Uric acid (μmol/l)	0.124	0.376	—	—	—	0.084	0.700	—	—	—
AER (mg/g Cr)	0.114	0.433	—	—	—	−0.272	0.080	—	—	—
Fibrinogen (g/l)	0.127	0.367	—	—	—	−0.168	0.437	—	—	—
log Hs-CRP (mg/l)	0.290	0.045†	0.084	6.544	0.014†	0.304	0.018†	0.040	5.125	0.027†
R^2	—	—	0.247	—	—	—	—	0.174	—	—

*Pearson's univariate correlation coefficients. A stepwise multivariate regression analysis was performed. Sex: men = 1, women = 0; smoking: yes = 1, no = 0. β: Partial regression coefficient, †$P < 0.05$.

Table 4—*Multivariate regression analyses of mean IMT, max IMT, and other variables in all subjects*

		Mean IMT					Max IMT				
		Univariate*		Multivariate			Univariate*		Multivariate		
Variables		*r*	*P*	β	*F*	*P*	*r*	*P*	β	*F*	*P*
Age (years)	22.9 ± 3.7	0.153	0.103	—	—	—	0.167	0.074	—	—	—
Sex (men/women)	50/80	—	0.012†	0.023	3.152	0.079	—	0.004†	0.027	2.905	0.091
Type (diabetic/nondiabetic)	55/75	—	0.003†	—	—	—	—	<0.0001†	—	—	—
Duration of diabetes (years)	14.2 ± 5.7	0.326	0.0003†	—	—	—	0.417	<0.0001†	0.002	5.400	0.022†
BMI (kg/m^2)	21.6 ± 2.8	0.189	0.044†	—	—	—	0.279	0.003†	—	—	—
Systolic blood pressure (mmHg)	116 ± 11	0.284	0.002†	—	—	—	0.303	0.001†	—	—	—
Diastolic blood pressure (mmHg)	71 ± 8.4	0.315	0.0007†	0.002	6.661	0.011†	0.368	<0.0001†	0.002	4.361	0.039†
Smoking (yes/no)	21/109	—	0.018†	—	—	—	—	0.034†	0.031	2.462	0.120
HbA_{1c} (%)	6.5 ± 2.0	0.165	0.115	—	—	—	0.236	0.026†	—	—	—
Total cholesterol (mmol/l)	4.3 ± 0.8	0.016	0.871	—	—	—	0.038	0.692	—	—	—
Triglycerides (mmol/l)	0.75 ± 0.29	0.130	0.205	—	—	—	0.192	0.060	—	—	—
HDL cholesterol (mmol/l)	1.60 ± 0.36	−0.159	0.121	—	—	—	−0.177	0.085	—	—	—
LDL cholesterol (mmol/l)	1.99 ± 0.52	−0.074	0.520	—	—	—	−0.125	0.274	—	—	—
Creatinine (μmol/l)	69.8 ± 16.7	0.304	0.004†	—	—	—	0.374	0.0003†	—	—	—
Uric acid (μmol/l)	254 ± 77	0.173	0.132	—	—	—	0.051	0.660	—	—	—
AER (mg/g Cr)	13.6 ± 31 6.0 (1.5–223)	0.181	0.134	—	—	—	0.128	0.289	—	—	—
Fibrinogen (g/l)	2.11 ± 0.44	0.107	0.356	—	—	—	0.233	0.413	—	—	—
log Hs-CRP (mg/l)	0.33 ± 0.33 0.19 (0.05–1.47)	0.339	0.0003†	0.046	10.02	0.002†	0.364	<0.0001†	0.041	5.347	0.023†
R^2	—	—	—	0.203	—	—	—	—	0.307	—	—

Data are means ± SD and/or median (range). *Pearson's univariate correlation coefficients. A stepwise multivariate regression analyses was performed. Sex: men = 1, women = 0; smoking: yes = 1, no = 0; type: type 1 diabetics subjects = 1, nondiabetic subjects = 0. †$P < 0.05$. HDL-c, HDL cholesterol.

smoking habit, and hs-CRP concentration (Table 3 and Fig. 1*B*).

A multivariate regression analysis showed that hs-CRP concentration ($P = 0.014$) and sex ($P = 0.012$) were variables that interacted independently of max IMT in patients with type 1 diabetes. In nondiabetic subjects hs-CRP concentration ($P = 0.027$) and age ($P = 0.022$) were independent risk factors.

Another forward and backward stepwise multivariate regression analysis was performed to evaluate the significance of the existence of type 1 diabetes (type 1 diabetes was set as 1 and nondiabetes was set as 0) and the duration of diabetes (duration of a nondiabetic subject was set as 0 years) (Table 4).

This analysis showed that the hs-CRP concentration ($P = 0.002$) and diastolic blood pressure ($P = 0.011$) interacted independently of the mean IMT. Hs-CRP concentration ($P = 0.023$), duration of diabetes ($P = 0.022$), and diastolic blood pressure ($P = 0.039$) also interacted independently of the max IMT.

CONCLUSIONS — This study is the first to report that an elevated hs-CRP concentration is positively correlated with an increase in the mean and maximum severity of carotid atherosclerosis (mean IMT and max IMT) in young patients with type 1 diabetes. Furthermore, the hs-CRP response was also positively correlated with the max IMT of the carotid artery in nondiabetic subjects. A multivariate regression analysis investigating max IMT in a combined group of both diabetic and nondiabetic subjects strengthened these findings: hs-CRP concentration was the primary risk factor for max IMT in diabetic and nondiabetic subjects, regardless of the presence of type 1 diabetes, duration of diabetes, sex, BMI, diastolic blood pressure, or age.

Recently, Schalkwijk et al. (17) reported elevated hs-CRP concentrations in patients with type 1 diabetes aged >30 years. Kilpatrick et al. (18) confirmed this observation and noted that six subjects with coronary heart disease possessed significantly higher hs-CRP concentrations than those without coronary heart disease. We evaluated carotid atherosclerosis in patients with type 1 diabetes and clearly showed that the increase in hs-CRP concentrations is correlated with an increase in the maximum and mean IMT values of patients with type 1 diabetes.

We found that the hs-CRP concentration, which is a marker of acute-phase proteins, is higher in type 1 diabetic youths than in nondiabetic subjects. In human studies, increased circulating acute-phase proteins have been reported in type 2 diabetes (15,16) and also in adult subjects with type 1 diabetes (17,18). There are several possible mechanisms by which chronic low-degree inflammation might be induced in diabetes. In a hyperglycemic condition, the concentration of advanced glycation end products increases. Advanced glycation end products have been shown to activate macrophages, increase oxidative stress, and upregulate the synthesis of interleukin-1, interleukin-6, and tumor necrosis factor, resulting in the production of CRP

(25). Another possibility is that increases in CRP concentrations are related to adipose tissue–derived cytokines (26,27). In this study, there was a strong correlation between BMI and hs-CRP concentration in addition to the correlation with diabetic duration and hs-CRP (data not shown). Schalkwijk et al. (17) and Frohlich et al. (27) also showed a positive correlation between BMI and hs-CRP concentration. However, the role of adipose tissue as a possible cause of the chronic inflammatory condition in youths with type 1 diabetes requires further investigation.

Only a few studies have evaluated the association between CRP concentration and development of carotid atherosclerosis in elderly subjects (14,28). A previous cross-sectional study described an association between CRP concentrations and severity of carotid atherosclerosis; however, the multivariate regression analysis failed to show a correlation between these two factors (14). Also, Folsom et al. (28) reported a weak association between hs-CRP concentration and carotid IMT. In these studies, the subjects were elderly individuals who often had several risk factors including obesity, hyperlipidemia, and hypertension. In our study, however, the subjects were young and did not have any of these risk factors, with the exception of hyperglycemia. Therefore, the slight but significant increase in hs-CRP concentration may affect the early stage of carotid atherosclerosis in these young subjects.

In this study, hs-CRP concentration was correlated with both mean and max IMT in patients with type 1 diabetes. In nondiabetic subjects, however, hs-CRP was correlated with max IMT but was not correlated with mean IMT. The mean IMT was calculated as the average of the thickest point (max IMT) and two adjacent points (located 1 cm away from the max IMT point). Therefore, a focal atheromatous change, such as a single fatty streak, would increase the max IMT but might not substantially increase the mean IMT.

This study clearly shows that elevated hs-CRP concentrations are correlated with the early stage of carotid atherosclerosis in young patients with diabetes. Therefore, low-grade inflammation may be a risk factor for the early stage of carotid atherosclerosis, especially in young patients with type 1 diabetes. To evaluate this possibility, prospective studies are required.

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