

Correlation Between the Intima-Media Thickness of the Carotid Artery and Aortic Pulse-Wave Velocity in Patients With Type 2 Diabetes

Vessel wall properties in type 2 diabetes

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OBJECTIVE — The aim of this study was to assess the relationship between atherotic (structural) and sclerotic (functional) changes in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Aortic distensibility and carotid intima-media thickness (IMT) were evaluated using carotid-femoral aortic pulse-wave velocity (a-PWV) and high-resolution B-mode ultrasonography in 271 patients with type 2 diabetes and 285 age-matched control subjects.

RESULTS — a-PWV and carotid IMT were significantly higher in the patients than in the control subjects in all age-groups ($P < 0.0001$, respectively). The carotid IMT and a-PWV were significantly correlated with age in both the patients with type 2 diabetes and control subjects. There was a significant positive relationship between the carotid IMT and a-PWV in both the patients ($r = 0.482$, $P < 0.0001$) and control subjects ($r = 0.424$, $P < 0.0001$). The slope of the regression line for the carotid IMT to the a-PWV was significantly steeper in the diabetic patients than in the control subjects ($P < 0.05$). Multiple regression analysis in all subjects showed that age, diabetic state, and cigarette smoking were independently common risk factors for the increase in carotid IMT and a-PWV. In the diabetic patients, the independent risk factors associated with the carotid IMT were age, hyperlipidemia, and duration of diabetes ($R^2 = 0.232$, $P < 0.0001$), while those associated with a-PWV were age and duration of diabetes ($R^2 = 0.334$, $P < 0.0001$).

CONCLUSIONS — The results indicated that diabetic patients showed more advanced changes in atherosclerosis than that in sclerosis as compared with age- and sex-matched control subjects. Such atherotic changes in diabetic patients may be associated with hyperlipidemia.

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Patients with diabetes have accelerated atherosclerotic vascular lesions. The risk for the coronary, cerebral, and peripheral arterial diseases is higher in diabetic patients than in nondiabetic subjects (1).

Atherosclerosis involves a combination of fatty degeneration (atherosis) and of vessel stiffening (sclerosis) of the arterial wall. Sclerotic changes have attracted less attention than atherosclerosis because of the greater difficulty entailed in their assess-

ment. For example, standard evaluation by histopathology and serial angiography is a sensitive method by which to determine the atheromatous but not sclerotic changes (2). In animal studies, a direct relationship has been established between regression of atherosclerosis and an increase in arterial distensibility (3).

The development of high-resolution B-mode ultrasonography has facilitated the noninvasive evaluation of structural changes in the arterial wall measured as the intima-media thickness (IMT) (4). Measurement of the far-wall IMT of the common carotid artery has become an important end point of atherosclerosis in epidemiological studies and cardiovascular clinical trials. It has been established that the extent of carotid atherosclerosis is strongly correlated with the presence of coronary artery disease and is a marker for an early phase of the atherosclerotic process (5). Indeed, the prevalence of carotid artery disease is higher in patients with type 2 diabetes than in control subjects (6). However, IMT only provides information about vessel wall anatomy. Other important aspects of atherosclerosis related to vessel function, such as wall composition or stiffness, can also be studied in diabetic subjects with other noninvasive techniques. Several studies have indicated decreased distensibility of the large arteries of patients with diabetes (7,8). Distensibility of the large arteries can be assessed by measuring the thoracic abdominal pulse-wave velocity, recorded as aortic pulse-wave velocity (a-PWV) (9). One study demonstrated that carotid arterial stiffness was associated with the morphological changes (10), while another suggested that it is relatively independent of IMT (11).

There have been no previous studies of the association between the structural and functional changes of the arterial wall in patients with type 2 diabetes. The aim of the present study was to assess the relationship between carotid IMT as an index of structural changes and a-PWV as that of

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Abbreviations: a-PWV, aortic pulse-wave velocity; IMT, intima-media thickness.

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

Table 1—Clinical characteristics of type 2 diabetic patients and control subjects

	Type 2 diabetic patients	Control subjects
n	271	285
Sex (M/F)	119/152	144/141
Age (years)	51.2 ± 9.9	49.8 ± 13.8
BMI (kg/m ²)	23.0 ± 3.3	22.5 ± 3.3
Cigarette-years	458 ± 574†	224.8 ± 398.9
Duration of diabetes (years)	10.7 ± 8.3	—
Fasting plasma glucose (mmol/l)	9.5 ± 3.6†	5.3 ± 0.6
HbA _{1c} (%)	9.0 ± 2.7	—
Total cholesterol (mmol/l)	5.40 ± 1.27*	5.12 ± 1.09
Triglyceride (mmol/l)	1.54 ± 0.88	1.34 ± 0.79
HDL cholesterol (mmol/l)	1.22 ± 0.39†	1.45 ± 0.44
LDL cholesterol (mmol/l)	4.19 ± 1.25†	3.68 ± 1.06
Systolic blood pressure (mmHg)	138.1 ± 25.5†	123.5 ± 19.1
Diastolic blood pressure (mmHg)	75.5 ± 11.8	74.0 ± 12.1
Diabetes therapy (diet/sulfonylurea/insulin)	74/134/63	—
Hypertension (−/+)	140/131†	0/285
Antihypertensive therapy (−/+)	171/100†	0/285
a-PWV (m/s)	9.02 ± 1.92†	7.19 ± 1.05
Carotid IMT (mm)	1.004 ± 0.372†	0.640 ± 0.182

Data are means ± SD. **P* < 0.05, †*P* < 0.001 vs. control subjects.

functional changes in arterial wall in patients with type 2 diabetes as compared with control subjects, and to investigate the risk factors for both the carotid IMT and a-PWV separately.

RESEARCH DESIGN AND METHODS

Subjects and clinical characteristics

There were 271 consecutive Japanese patients with type 2 diabetes recruited from inpatients of Osaka City University Hospital. They ranged in age from 18 to 75 years (119 men and 152 women). Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (12). Inclusion criteria were serum creatinin <106 mmol/l and no evidence of cardiovascular complications by clinical history or physical examination. As control subjects, 285 nondiabetic subjects (18–75 years of age) were recruited from a population participating in a local health check program in the Osaka Municipal Health Promotion Center investigating in the same period and living in the same area. Inclusion criteria were fasting plasma glucose <7.0 mmol/l, systolic blood pressure <160 mmHg, and diastolic blood pressure <90 mmHg; no history of myocardial infarction, cerebral infarction, or peripheral vascular disease; and no use of regular

medication. The experimental design was approved by our institutional ethical committee, and all subjects gave their informed consent to participate in this study.

Blood pressure was determined with a standard mercury sphygmomanometer and cuffs adapted to the arm circumference after the subject had rested for at least 15 min. The systolic blood pressure was taken as the point of appearance of Korotkoff sounds, and the diastolic blood pressure as the point of disappearance of the sounds. Results are reported as averages of three measurements. Hypertension was defined as 1) the taking of antihypertensive agents and/or a history of this disorder, 2) systolic blood pressure >160 mmHg, or 3) diastolic blood pressure >95 mmHg.

Information on smoking habits was obtained by a self-administered questionnaire. Exposure to smoking was estimated as the product of the number of years of smoking and the number of tobacco products smoked daily at the time of the study. The product was used in statistical analysis as cigarette-years.

Blood was withdrawn after an overnight fast for analysis of serum concentrations of glucose, total cholesterol, triglyceride, HDL cholesterol, and HbA_{1c} by standard laboratory methods. LDL cholesterol was estimated by the Friedewald equation (13). Patients were considered dyslipidemic if they were taking hyper-

lipidemic agents and/or if serum cholesterol was >5.69 mmol/l (220 mg/dl), HDL cholesterol was <1.03 mmol/l (40 mg/dl), or triglycerides were >1.70 mmol/l (150 mg/dl), according to the criteria of the Japan Atherosclerosis Society.

In patients with type 2 diabetes, the mean values of biochemical parameters and blood pressure obtained three times over a 6-month period were used for statistical analysis. In control subjects, biochemical parameters and blood pressure were obtained within 7 days of measurement of carotid IMT and a-PWV, and used for statistical analysis. The clinical and biochemical characteristics of the type 2 diabetic patients and control subjects are summarized in Table 1.

Measurement of a-PWV

a-PWV was measured in the supine position after 15 min of bed rest using a pulse-wave velocimeter (model PWV-200, Fukuda Denshi, Tokyo) (14). Briefly, amorphous sensors were placed on the skin at the right femoral and left carotid arteries to record pulse waves. Heart sounds S1 and S2 were detected by a microphone set on the right edge of the sternum at the second intercostal space. Electrocardiogram monitoring was performed with electrodes placed on the right and left arms and on the right leg. The PWV meter measured the time intervals between pulse waves at carotid and femoral sites (*T*) and between S2 and the notch of the carotid pulse wave (*T_c*). PWV of the aorta was calculated as follows:

$$a\text{-PWV} = 1.3L/(T + T_c)$$

where a-PWV is measured in meters per second and *L* is the measured distance between the carotid and femoral probes. The actual distance between the aortic orifice and the femoral site was calculated as 1.3 *L* (15). Because (*T* + *T_c*), the time for the pulse waves to travel from the aortic orifice to the femoral artery, is dependent on blood pressure, the a-PWV values were standardized for a diastolic pressure of 80 mmHg. a-PWV was measured for five consecutive pulses, and averages was used for analysis. The coefficient of variation for a-PWV was 4.2% for patients with type 2 diabetes and 4.5% for control subjects.

Ultrasonographic measurements of IMT of the carotid artery

Ultrasonographical B-mode imaging of the carotid artery was performed with a high

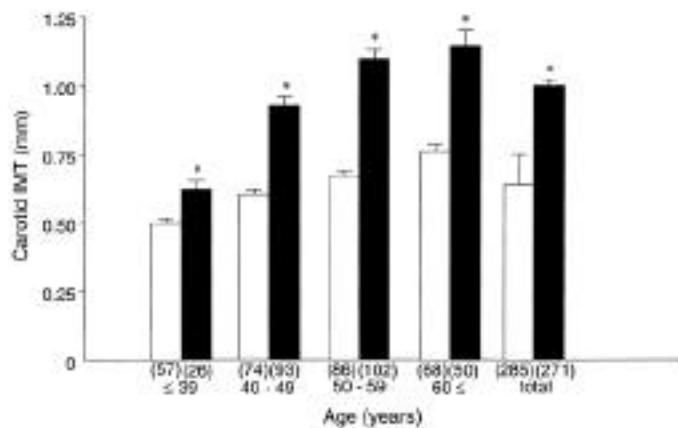


Figure 1—Bar graphs showing mean (SEM) values of the IMT of carotid artery (Carotid IMT) in control subjects ($n = 285$; □) and patients with type 2 diabetes ($n = 271$; ■) according to age. * $P < 0.0001$ vs. control subjects.

resolution real-time ultrasonograph with a 10-MHz in-line Sectascanner (SSD 650 CL, Aloka, Tokyo) (4,16). Each subject was examined in the supine position. The examination included ~4 cm of the common carotid artery and the carotid bulb. These regions were scanned bilaterally in the longitudinal and the transverse projections. The image was focused on the far wall of the artery. The site of the most advanced atherosclerotic lesion and the projection that showed the greatest distance between the lumen-intimal interface and the media-adventitia interface (IMT) was located in both the right and left carotid arteries (4). At each longitudinal projection, the IMT was conducted from the site of the greatest thickness. IMT was defined as the distance between the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. Three still images from the same section of the artery were measured, and the mean value was calculated. All measurements were made by the same examiner and under blind conditions. To assess intraobserver variability, 40 subjects (20 patients and 20 control subjects) were examined on two different occasions. The coefficient of variation for IMT was found to be 3.2% for patients and 3.6% for control subjects.

Statistical analysis

Data are expressed as means \pm SD. Values for clinical parameters were compared using one-way analysis of variance with Scheffé's F test. Multiple regression analyses were performed to assess the combined influence of

variables on carotid IMT and a-PWV values separately. First, to examine the effects of risk factors in all subjects (control subjects plus diabetic patients) on carotid IMT and a-PWV values, the following factors were considered as independent variables: age, BMI, cigarette-years, diabetes, hypertension, and dyslipidemia. Second, the following factors were considered in control subjects: age, sex, BMI, cigarette-years, fasting plasma glucose, total cholesterol, triglyceride, HDL cholesterol, and systolic and diastolic blood pressure. Lastly, the following factors were considered in patients: age, sex, BMI, cigarette-years, duration of diabetes, HbA_{1c}, total cholesterol, triglyceride, HDL chole-

sterol, and systolic and diastolic blood pressure. The relationships between IMT values and age and between a-PWV and IMT values in control subjects and patients separately were examined by linear regression analysis. To examine which change in arterial wall is more advanced, the slopes of the regression lines for the carotid IMT to the a-PWV were compared between the two groups. All statistical analyses were carried out with StatView IV on a Macintosh computer. A level of $P < 0.05$ was accepted as statistically significant.

RESULTS

Clinical characteristics of patients and control subjects

Of the diabetic patients, 63 (23%) had been treated with insulin injection, 134 (50%) had received antidiabetic agents, and 74 (27%) had been treated only with diet therapy. In addition, 188 (69%) had been treated for dyslipidemia and 131 (48%) for hypertension (Table 1).

There were no differences in age or the distribution of sex between the control subjects and type 2 diabetic patients (Table 1). Cigarette-years, systolic blood pressure, total cholesterol, and LDL cholesterol were significantly higher in the patients than in the control subjects. HDL cholesterol was lower in the patients than in the control subjects (Table 1). a-PWV and carotid IMT were significantly higher in the patients than in the control subjects ($P < 0.0001$, respectively) (Table 1).

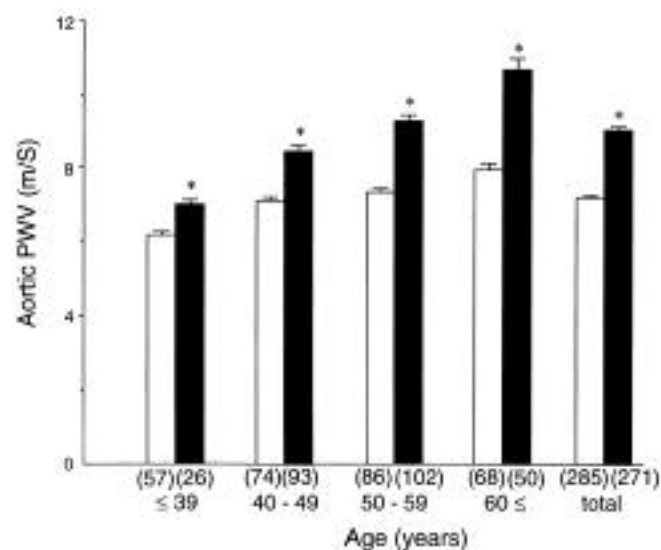


Figure 2—Bar graphs showing mean (SEM) values of the a-PWV in control subjects ($n = 285$; □) and patients with type 2 diabetes ($n = 271$; ■) according to age. * $P < 0.0001$ vs. control subjects.

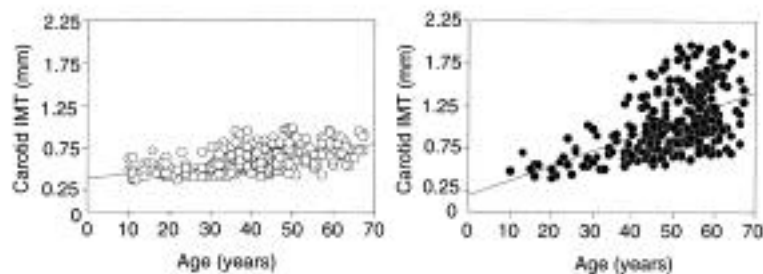


Figure 3—The relationship between carotid IMT and age in both control subjects ($n = 285$; \circ , $r = 0.546$, $P < 0.0001$) and patients with type 2 diabetes ($n = 271$; \bullet , $r = 0.515$, $P < 0.0001$).

Carotid IMT

The IMT values of the carotid artery in the patients <40 years of age (0.620 ± 0.167 mm, $n = 26$), 40–49 years of age (0.928 ± 0.308 mm, $n = 93$), 50–59 years of age (1.096 ± 0.366 mm, $n = 102$), or 60 to years of age (1.146 ± 0.414 mm, $n = 50$) were significantly higher than those in the age-matched control subjects (0.498 ± 0.106 mm, $n = 57$; 0.603 ± 0.130 mm, $n = 74$; 0.671 ± 0.166 mm, $n = 86$; 0.761 ± 0.205 mm, $n = 68$, respectively). The carotid IMT was significantly higher in the patients (1.002 ± 0.373 mm, $n = 271$) than in the control subjects (0.640 ± 0.182 mm, $n = 285$) ($P < 0.0001$, respectively) (Fig. 1). Women with type 2 diabetes showed no difference in the carotid IMT compared with the men counterparts (women vs. men, 1.011 ± 0.372 vs. 0.994 ± 0.376 , $P = 0.7103$). In control subjects, the carotid IMT was higher (but not significantly) in men than in women (0.659 ± 0.194 vs. 0.621 ± 0.167 , $P = 0.0747$).

a-PWV

The a-PWV values in the patients <40 years of age (6.98 ± 0.74 m/s, $n = 26$), 40–49 years of age (8.44 ± 1.42 m/s, $n = 93$), 50–59 years of age (9.27 ± 1.71 m/s, $n = 102$), or 60 years of age (10.66 ± 2.14 m/s, $n = 50$) significantly exceeded those in age-matched control subjects (6.17 ± 0.64 m/s, $n = 57$; 7.10 ± 0.74 mm, $n = 74$; 7.33 ± 0.84 m/s, $n = 86$; 7.96 ± 1.16 m/s, $n = 68$, respectively). The a-PWV was significantly higher in the patients than in the control subjects ($P < 0.0001$, respectively) (Fig. 2). Women with type 2 diabetes had significantly stiffer aortas compared with their male counterparts (women vs. men, 9.35 ± 2.00 vs. 8.77 ± 1.84 , $P = 0.0133$). In contrast, there was no difference in the a-PWV between men and women in the control subjects (7.16 ± 1.15 vs. 7.21 ± 0.95 , $P = 0.7272$).

Relationships between carotid IMT and age

The relationship between the carotid IMT and age showed correlation coefficients of $r = 0.515$ ($P < 0.0001$) in the patients with type 2 diabetes as well as in the control subjects ($r = 0.546$, $P < 0.0001$) (Fig. 3). The slope of the regression line for the carotid IMT to age was significantly steeper in the patients than in the control subjects ($P < 0.05$).

Relationships between a-PWV and age

The relationship between the a-PWV and age showed correlation coefficients of $r = 0.568$ ($P < 0.0001$) in the patients as well as in the control subjects ($r = 0.614$, $P < 0.0001$) (Fig. 4). The slope of the regression line for the a-PWV to age was significantly steeper in the diabetic patients than in the control subjects ($P < 0.05$).

Relationships between the carotid IMT and a-PWV

A significant positive correlation between the carotid and a-PWV was found in the control subjects ($r = 0.424$, $P < 0.0001$) (Fig. 5). We also observed a significant positive correlation between these values in the patients ($r = 0.482$, $P < 0.0001$) (Fig. 5).

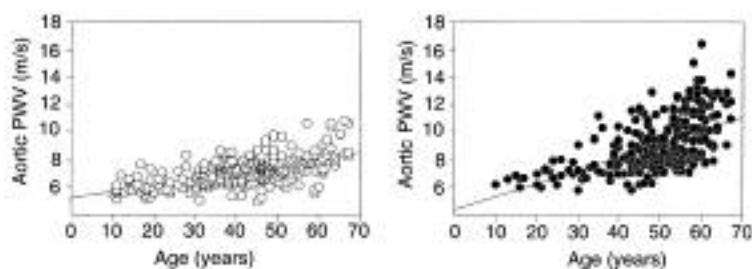


Figure 4—The relationship between a-PWV and age in both control subjects ($n = 285$; \circ , $r = 0.614$, $P < 0.0001$) and patients with type 2 diabetes ($n = 271$; \bullet , $r = 0.568$, $P < 0.0001$).

Moreover, the slope of the regression line for the carotid IMT to the a-PWV was significantly steeper in the diabetic patients than in the control subjects ($P < 0.05$).

Risk factors for increased carotid IMT and a-PWV in all subjects (model 1)

Multiple regression analysis in all subjects (control subjects and diabetic patients) demonstrated that age, the presence of diabetes, and smoking were risk factors for increased carotid IMT ($R^2 = 0.411$, $P < 0.0001$) (Table 3). Risk factors for increased a-PWV in all subjects were age, the presence of diabetes, hypertension, and smoking ($R^2 = 0.479$, $P < 0.0001$) (Table 2).

Risk factors for increased carotid IMT and a-PWV in the diabetic patients and control subjects (model 2)

Multiple regression analysis was conducted separately in diabetic patients and control subjects to assess the risk factors associated with increased carotid IMT and a-PWV. In control subjects, age was the only risk factor associated with increased a-PWV ($R^2 = 0.409$, $P < 0.0001$) (Table 2). Age, sex (male), decreased HDL cholesterol, and increased total cholesterol were risk factors for the increased carotid IMT ($R^2 = 0.396$, $P < 0.0001$) (Table 3). In diabetic patients, age and duration of diabetes were significantly independent risk factors for the increased a-PWV ($R^2 = 0.334$, $P < 0.0001$) (Table 2). Age, decreased HDL cholesterol, increased total cholesterol, and duration of diabetes were significant independent risk factors for the increased carotid IMT in diabetic patients ($R^2 = 0.232$, $P < 0.0001$) (Table 3).

CONCLUSIONS — We demonstrated that carotid IMT and a-PWV were significantly higher in patients with type 2 dia-

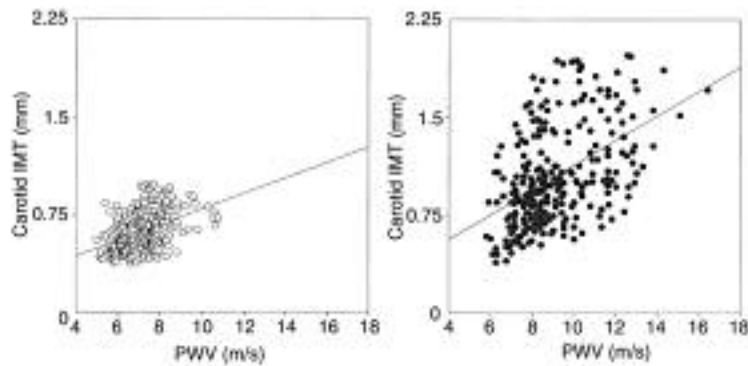


Figure 5—The relationship between the IMT of the carotid artery and a-PWV in control subjects ($n = 285$; ○, $r = 0.424$, $P < 0.0001$) and patients with type 2 diabetes ($n = 271$; ●, $r = 0.482$, $P < 0.0001$).

betes than in age-matched control subjects. Our observations indicated that both age and duration of diabetes were common risk factors for increased carotid IMT and a-PWV in patients with type 2 diabetes. In addition, hyperlipidemia, such as increased total cholesterol and decreased HDL cholesterol, was a risk factor associated with increased IMT in diabetic patients. Moreover, diabetic patients showed more advanced atherotic than sclerotic changes in the arterial wall compared with control subjects. Based on these findings, such advanced atherotic changes in diabetic patients may be attributed to additive or synergistic interaction between diabetes and hyperlipidemia. These results might explain why type 2 diabetes was originally recognized as the so-called metabolic syndrome, which included hyperlipidemia, hypertension, and insulin resistance (17,18).

We performed a multiple regression analysis in all subjects (model 1), which included age, sex, BMI, cigarette-years, presence of hypertension, presence of diabetes, and presence of hyperlipidemia, to determine the effects of hypertension and diabetes on the physical properties of large arteries, such as carotid IMT and a-PWV. Diabetes, age, and smoking were common risk factors for both increased carotid IMT and a-PWV in all subjects. In addition, hypertension also was a risk factor for increased a-PWV. Because diabetic patients are frequently hypertensive (19), it seems likely that the increased blood pressure may be a mechanical factor responsible for the observed arterial stiffening. These results suggest that both diabetes and the elevation of blood pressure were important factors for the increased a-PWV.

We divided the subjects into two groups, i.e., control subjects and diabetic patients, to assess the risk factors for increased carotid IMT and a-PWV in both groups separately. Duration of diabetes was an independent common risk factor for both increased carotid IMT and a-PWV in diabetic patients in the present study. Kawamori et al. (20) showed an independent association between duration of diabetes and carotid IMT in patients with type 2 diabetes. A causative link between glycemia and vessel stiffness was also suggested by Wright (21), who studied 340 patients with type 2 diabetes and found that for any given age and blood pressure value, a-PWV increased with abnormal glucose tolerance and dura-

tion of diabetes. These findings suggest that the diabetic state per se accelerates both atherotic and sclerotic changes of the arterial wall.

Ryden Ahlgren et al. (22) observed stiffer carotid arteries and aortas in women, but not in men, with type 1 diabetes than in nondiabetic individuals. Similar sex-specific results have been found for a-PWV in patients with type 2 diabetes (23). In the present study, the a-PWV was higher in women than in men with type 2 diabetes. However, in multiple regression analysis, sex (women) was not a significant independent risk factor for a-PWV in diabetic patients.

We assessed IMT of the carotid artery as an index of atherotic (structural) changes and PWV of the aorta as an index of sclerotic (functional) changes in the present study. Therefore, it is possible that the variation in these changes and in the risk factors may be due to measurement of different arteries. Although the size of the aorta is different from that of the carotid artery, the extent and severity of arteriosclerosis of the medium- and large-sized arteries have been reported to be correlated in autopsy studies (24–26). An extensive autopsy study performed in a well-defined population in a limited region of Malmö, Sweden, demonstrated a close association of arteriosclerosis among arteries of different sizes (25,27), showing the systemic nature of arteriosclerosis and its relationship with hypertension, age, and diabetes. On the other hand, it was

Table 2—Risk factors affecting a-PWV

	β	P value
All subjects		
Diabetes	0.432	<0.0001
Age	0.405	<0.0001
Hypertension	0.112	0.0012
Smoking	0.082	0.0298
		$R^2 = 0.479$ ($P < 0.0001$)
Control subjects		
Age	0.605	<0.0001
		$R^2 = 0.409$ ($P < 0.0001$)
Diabetic patients		
Age	0.488	<0.0001
Duration of diabetes	0.125	0.0207
		$R^2 = 0.334$ ($P < 0.0001$)

Parameters assessed in all subjects included age, sex, BMI, cigarette-years, diabetes, and the presence of hypertension and dyslipidemia. Parameters assessed in control subjects also included fasting plasma glucose, total cholesterol, triglyceride, HDL cholesterol levels, and systolic and diastolic blood pressure. In patients with type 2 diabetes, the parameters included all of these plus duration of diabetes and the level of HbA_{1c}. β , standard regression coefficient; R^2 , multiple coefficient of determination.

Table 3—Risk factors affecting carotid IMT

	β	P value
All Subjects		
Diabetes	0.452	<0.0001
Age	0.306	<0.0001
Smoking	0.128	0.0015
		$R^2 = 0.411 (P < 0.0001)$
Control Subjects		
Age	0.568	<0.0001
Sex	0.151	0.0118
HDL cholesterol	-0.203	0.0005
Total cholesterol	0.133	0.0179
		$R^2 = 0.396 (P < 0.0001)$
Diabetic patients		
Age	0.323	<0.0001
Total cholesterol	0.154	0.0216
HDL cholesterol	-0.135	0.0397
Duration of diabetes	0.145	0.0127
		$R^2 = 0.232 (P < 0.0001)$

Parameters assessed in all subjects included age, sex, BMI, cigarette-years, diabetes, and the presence of hypertension and dyslipidemia. Parameters assessed in control subjects also included fasting plasma glucose, total cholesterol, triglyceride, HDL cholesterol levels, and systolic and diastolic blood pressure. In patients with type 2 diabetes, the parameters included all of these plus duration of diabetes and the level of HbA_{1c}. β , standard regression coefficient; R^2 , multiple coefficient of determination.

shown recently that wall thickening of the large arteries is not necessarily associated with increased stiffness, indicating that other structural changes occur to regulate arterial elastic properties (28). The frequency of medial arterial calcifications that can lead to stiffening arterial wall is increased according to some studies in diabetic patients (29,30). However, the prevalence of medial arterial calcifications is highest in distal sites of the lower extremity (82% of the diabetic patients and 86% of the nondiabetic subjects) (30). Therefore, increased a-PWV in the diabetic patient cannot be explained by medial arterial calcification. Because of an inherent disadvantage of a cross-sectional study, the time relationship between structural and functional vessel wall changes cannot be answered in the present study. Despite the obvious correlations between structural and functional changes in diabetic patients and control subjects in the present study, the dissociation between these wall changes observed in some of the subjects suggests that arterial wall thickening and stiffening may partly express different atherosclerotic processes. The regression line for carotid IMT to a-PWV was steeper in the diabetic patients than in the control subjects, suggesting that atherosclerotic changes may be more advanced in diabetic patients than in control subjects.

In conclusion, our results demonstrated that both carotid IMT and a-PWV were increased in diabetic patients as compared with age-matched control subjects, that the risk factors for increased carotid IMT and a-PWV were partly different in diabetic patients, and that diabetic patients showed more advanced atherosclerotic changes in the arterial wall as compared with control subjects. Such atherosclerotic changes in diabetic patients may be associated with hyperlipidemia.

References

- Garcia MJ, McNamara PM, Gordon T, Kannel WB: Morbidity and mortality in diabetics in the Framingham population sixteen year follow-up study. *Diabetes* 23:105-111, 1973
- Blankenhorn DH, Krams DM: Reversal of atherosclerosis and sclerosis (the two components of atherosclerosis). *Circulation* 79:1-7, 1989
- Farrar DJ, Greed HD, Wagner WD, Bond MG: Reduction in pulse wave velocity and improvement of aortic distensibility accompanying regression of atherosclerosis in the Rhesus monkey. *Circ Res* 47:425-435, 1980
- Kawagishi T, Nishizawa Y, Konishi T, Kawasaki K, Emoto M, Shoji T, Tabata T, Inoue T, Morii H: High-resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. *Kidney Int* 48:820-826, 1995
- Wofford J, Kahl F, Howard G, McKinney W, Toole J, Crouse JI: Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. *Arterioscler Thromb* 11:1786-1794, 1991
- Chan A, Beach KW, Martin DC, Strandness DE Jr: Carotid artery disease in NIDDM diabetes. *Diabetes Care* 6:562-569, 1983
- Oxlund H, Rasmussen LM, Andreassen TT, Heickendorff L: Increased aortic stiffness in patients with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 32:748-758, 1989
- Christensen B, Neubauer T: Arterial wall stiffness in insulin-dependent diabetes mellitus. *Acta Radiol* 28:207-209, 1987
- Relf IRN, Lo CS, Myers KA, Wahlqvist ML: Risk factors for changes in aorto-iliac arterial compliance in healthy men. *Arteriosclerosis* 6:105-108, 1986
- Wada T, Kodaira K, Fujishiro K, Maie K, Tsukiyama T, Fukumoto T, Uchida T, Yamazaki T: Correlation of ultrasound-measured common carotid artery stiffness with pathological findings. *Arterioscler Thromb* 14:479-482, 1994
- Salomaa AR, Riley W, Kark JD, Nardo C, Folsom AR: Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: ARIC Study. *Circulation* 91:1432-1443, 1995
- American Diabetes Association: Screening for type 2 diabetes. *Diabetes Care* 21 (Suppl. 1):S20-S22, 1998
- Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low lipoprotein in plasma without the use of preparative ultracentrifuge. *Clin Chem* 18:499-502, 1972
- Shoji T, Nishizawa Y, Kawagishi T, Kawasaki K, Taniwaki H, Tabata T, Inoue T, Morii H: Intermediate-density lipoprotein as an independent risk factor for aortic atherosclerosis in hemodialysis patients. *J Am Soc Nephrol* 9:1277-1284, 1998
- Hasegawa M: Fundamental studies on pulse wave velocity of human aorta. *Jikeikai Med J* 85:742-760, 1970
- Kogawa K, Nishizawa Y, Hosoi M, Kawagishi T, Maekawa K, Shoji T, Okuno Y, Morii H: Effect of polymorphism of apolipoprotein E and angiotensin-converting enzyme genes on arterial wall thickness. *Diabetes* 46:682-687, 1997
- Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595-1607, 1988
- Ferrannini E: The metabolic syndrome. In *Target Organ Damage in the Mature Hypertensive*. Mogensen CE, Ed. London, Science, 1993, p. 231-249
- Sowers J, Khoury S, Standley P, Zemel M: Mechanisms of hypertension in diabetes. *J Hypertens* 4:177-182, 1991

20. Kawamori R, Yamazaki Y, Matsushima H, Nishizawa H, Nao K, Hougaku H, Maeda H, Hanada N, Matsumoto M, Kamada T: Prevalence of carotid atherosclerosis in diabetic patients. *Diabetes Care* 15:1290–1294, 1992
21. Wright JS: *Doppler Ultrasound Measurement of Aortic Compliance in Diabetic Patients and Community Controls*. PhD thesis. London, University of London, 1991
22. Ryden Ahlgren A, Lanne T, Wollmer P, Sonesson B, Hansen E, Sundkvist G: Increased arterial stiffness in women, but not in men, with IDDM. *Diabetologia* 38:1082–1089, 1995
23. Lehmann ED, Hopkins KD, Gosling RG: Increased aortic stiffness in women with NIDDM. *Diabetologia* 39:870–871, 1996
24. Wong M, Edelstein J, Wollman J, Bond G: Ultrasonic-pathological comparison of the human arterial wall: verification of intima-media thickness. *Arterioscler Thromb* 13:482–486, 1993
25. Sternby N: Atherosclerosis of peripheral arteries: an autopsy survey in Malmo, Sweden. *Acta Pathol Microbiol Scand* 194 (Suppl. 194):98–110, 1968
26. Arai C, Abe N, Takeuchi K, Saito M, Hasegawa M, Takayama Y, Masaaki T, Morishita T, Shirai T, Kawashimo H, Suzuki K: Comparison between antemortem PWV values and postmortem tissues in relation to atheroma, calcification, and intimal-medial elastin and collagen. *J Jpn Atheroscler Soc* 12:1419–1426, 1985
27. Wahlqvist ML, Lo CSM, Myers KA, Simpson RW, Simpson JM: Putative determinants of arterial wall compliance in NIDDM. *Diabetes Care* 11:787–790, 1988
28. Hayoz D, Rutschmann B, Perret F, Niederberger M, Tardy Y, Mooser V, Nussberger J, Waeber B, Brunner HR: Conduit artery compliance and distensibility are not necessarily reduced in hypertension. *Hypertension* 20:1–6, 1992
29. Neubauer B: A quantitative study of peripheral arterial calcification and glucose tolerance in elderly diabetics and non-diabetics. *Diabetologia* 7:409–413, 1971
30. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH: Medial arterial calcification and its association with mortality and complications of diabetes. *Diabetologia* 31:16–23, 1988