Prevalence of Carotid Atherosclerosis in Diabetic Patients

Ultrasound high-resolution B-mode imaging on carotid arteries

RYUZO KAWAMORI, MD, PHD
YOSHIMITSU YAMASAKI, MD, PHD
HIROYUKI MATSUSHIMA, MD
HIDEKO NISHIZAWA, MD
KATSUNORI NAO, MD, PHD
HIDETAKA HOUGAKU, MD
HIROAKI MAEDA, MD
NOBUO HANDA, MD, PHD
MASAYASU MATSUMOTO, MD, PHD
TAKENOBU KAMADA, MD, PHD

OBJECTIVE — To quantitatively assess atherosclerosis of the carotid artery in subjects with and without diabetes.

RESEARCH DESIGN AND METHODS — Ultrasound high resolution B-mode imaging of carotid arteries was conducted on 71 nondiabetic subjects without hyperlipidemia or hypertension and 295 diabetic patients to determine IMT of the arterial wall.

RESULTS — IMT was linearly related with age in nondiabetic (IMT = [0.0087 × age] + 0.3318) and diabetic subjects (IMT = [0.0155 × age] + 0.32450). The regression coefficient for age was significantly greater in diabetic than nondiabetic subjects. IMT (mean ± SD) of diabetic subjects aged 20–29 was significantly greater than that of nondiabetic subjects aged 20–29 (0.73 ± 0.27 vs. 0.52 ± 0.07 mm, $P < 0.01$). Multivariate regression analysis of 275 NIDDM patients indicated smoking, hyperlipidemia, duration of diabetes, hypertension, and age were factors determining thickness of the carotid arterial wall.

CONCLUSIONS — Diabetes, along with age, hyperlipidemia, smoking, and hypertension, aggravates carotid atherosclerosis.

FROM THE FIRST DEPARTMENT OF MEDICINE, OSAKA UNIVERSITY MEDICAL SCHOOL, 1-1-50 FUKUSHIMA, FUKUSHIMA-KU, OSAKA, JAPAN.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO DR. RYUZO KAWAMORI, FIRST DEPARTMENT OF MEDICINE, OSAKA UNIVERSITY MEDICAL SCHOOL, 1-1-50 FUKUSHIMA, FUKUSHIMA-KU, OSAKA, 553, JAPAN.

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IMT, INTIMAL PLUS MEDIAL THICKNESS; IDDM, INSULIN-DEPENDENT DIABETES; NIDDM, NON-INSULIN-DEPENDENT DIABETES; ACE, ANGIOTENSIN-CONVERTING ENZYME; HDL, HIGH-DENSITY LIPOPROTEIN; LDL, LOW-DENSITY LIPOPROTEIN.

Patients with diabetes mellitus suffer unduly from premature and severe atherosclerosis (1–3). The Framingham Study (1) pointed out a previously unknown factor in diabetic patients that may be the cause of much of the higher incidence of cardiovascular complications. Diabetic individuals have higher serum concentrations of lipid and more hypertension, obesity, and thus the pathogenesis of advanced atherosclerosis is complicated and difficult to understand.

To check the course of cardiovascular and cerebrovascular diseases, the detection of early atherosclerosis by noninvasive and quantitative methods is mandatory. Among noninvasive methods, high-resolution B-mode ultrasonography (4–9) can visualize directly both luminal and vessel wall characteristics, thus making possible the early detection of atherosclerotic changes in extracranial carotid arteries. This study was conducted to quantitatively assess atherosclerosis of the carotid artery in diabetic patients, and normal nondiabetic subjects without risk factors and to investigate relationships between carotid atherosclerosis and risk factors such as diabetes, hyperlipidemia, hypertension, obesity, and smoking.

RESEARCH DESIGN AND METHODS

Assessment of atherosclerosis

Ultrasonographic scanning of carotid arteries was done with an echotomographic system (EUB-450, Hitachi Medico, Japan) with an electrical linear transducer (midfrequency of 7.5 MHz). Axial resolution of this system was at least 0.3 mm. The scanning of extracranial carotid arteries in the neck was conducted bilaterally at 3 different (anterior-oblique, lateral, and posterior-oblique) longitudinal projections and at the transverse projection, as reported previously (9). By these projections, the common carotid artery, carotid bulb, and parts of

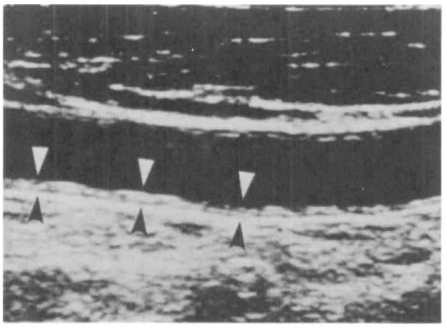

Figure 1—*Typical B-scan pattern of carotid artery of a diabetic patient. Arrows indicate sites at which thickness of intimal plus medial complex was determined.*

internal and external carotid arteries were scanned. All images were photographed. The scanning period averaged 30 min.

The IMT as defined by Pignoli et al. (4,5) was measured as the distance from the leading edge of the first echogenic line to that of the second echogenic line, as shown in Fig. 1. The first line represents the lumen-intimal interface, and the second line, the collagen-contained upper layer of tunic adventitia. At each longitudinal projection, three determinations of IMT were made at the site of greatest thickness and two other points, 1-cm upstream and 1-cm downstream from the site of greatest thickness (Fig. 1). The values were averaged. The greatest value of the six averaged IMT (three from the left and three from the right) was used as the representative value for each individual.

All scanning was conducted by physicians (K.N., H.M., and H.N.). The reproducibility of measurement of IMT was assessed by additional scanning 1 wk later of 10 diabetic patients (IMT was 1.273 ± 0.339 mm at the first scanning) and 8 nondiabetic subjects (IMT was 0.4667 ± 0.031 mm at the first scanning). The first and second scannings were done by different sonographers (K.N. and H.M., respectively). IMT on the photograph was determined by yet again a different physician (H.N.). Mean differences in IMT between the first and second measurements on diabetic and nondiabetic participants were 0.01 and 0.01 mm, respectively. SDs were 0.06 and 0.04 mm, respectively, demonstrating good reproducibility of measurements.

Two hundred ninety-five diabetic patients (20 IDDM patients aged 21 to 66 yr and 275 NIDDM patients aged 31 to 89 yr; 170 men and 125 women) were selected from outpatients attending Osaka University Hospital. Seventy-one hospital employees or nondiabetic individuals coming to Osaka University Hospital aged 20–79 yr without hyperlipidemia, hypertension, cardiovascular disease, or cerebrovascular disease served as control subjects.

All diabetic patients were free from neurological signs and clinical history of cerebrovascular diseases. Patients with positive history for coronary artery disease or ischemic arterial disease of the lower limbs also were used. Two patients had old myocardial infarction but none had angina pectoris. One patient had intermittent claudication of the lower limbs. Fifty-four patients were treated by diet therapy alone, 130 received oral hypoglycemic agents (acetohexamide, gliclazide, and glibenclamide), 44 were given once-a-day intermediate-acting insulin injection, and 47 received multiple-insulin-injection therapy. The characteristics of NIDDM patients are presented in Table 1.

Patients with hypertension and/or hyperlipidemia also were administered antihypertensive drugs (calcium blockers, ACE inhibitors, β-blockers, and diuretics) and hypolipidemic drugs (fibrates, ion-exchange resins, and nico-

Table 1—*Clinical characteristics of NIDDM patients*

	Treatment			
	Diet	OHA	CIT	MIT
Sex (men/women)	44/26	84/69	22/18	20/12
Age (yr)	59.4 ± 10.8	60.8 ± 9.5	58.9 ± 12.2	52.2 ± 11.6*†‡
Duration of diabetes (yr)	8.8 ± 7.2	13.4 ± 8.5*	17.7 ± 9.2*†	14.3 ± 9.6*‡
HbA_{1c} (%)	8.4 ± 1.8	9.0 ± 1.3	9.4 ± 1.8	9.6 ± 2.0
Pack-years of smoking	19.8 ± 35.6	17.3 ± 27.1	15.0 ± 24.5	12.1 ± 22.2
Systolic blood pressure (mmHg)	133.4 ± 15.9	134.3 ± 15.5	135.1 ± 16.1	132.9 ± 16.2
Diastolic blood pressure (mmHg)	79.1 ± 10.8	76.9 ± 10.0	76.8 ± 8.5	75.8 ± 8.2
Total cholesterol (mg/dl)	220.6 ± 48.6	204.9 ± 40.6*	203.6 ± 38.8	200.9 ± 39.0*
HDL cholesterol (mg/dl)	54.2 ± 17.8	54.2 ± 15.4	55.3 ± 22.0	59.6 ± 20.7
LDL cholesterol (mg/dl)	131.1 ± 40.1	125.0 ± 38.0	123.0 ± 40.3	120.9 ± 41.8
Triglyceride (mg/dl)	154.8 ± 111.9	138.5 ± 93.4	129.9 ± 57.8	116.1 ± 61.2*
IMT (mm)	1.24 ± 0.42	1.27 ± 0.33	1.24 ± 0.41	1.15 ± 0.39

Data are means ± SD.

OHA, treatment with oral hypoglycemic agents; CIT, treatment with once-a-day intermediate-acting insulin injection; MIT, treatment with multiple-insulin injection.

*$P < 0.05$ vs. diet.

†$P < 0.05$ vs. OHA.

‡$P < 0.05$ vs. CIT.

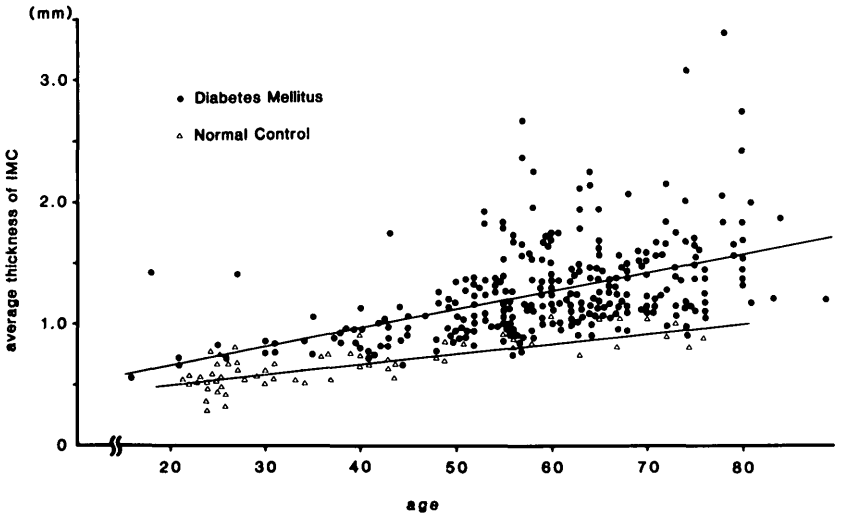

Figure 2—*Relation between IMT and age in normal, nondiabetic subjects (△) and diabetic patients (●). Positive correlation between IMT and age was shown in normal subjects and diabetic patients. Maximum IMT in normal subjects was 1.08 mm.*

tinic acid derivatives). Treatment for symptomatic coronary artery or peripheral artery disease was continued.

Blood pressure was measured with a mercury sphygmomanometer. After a supine rest of 5 min, three measurements in the sitting position were made, and the mean value was used. Blood was withdrawn after overnight fasting for analysis of total and HDL cholesterol, serum triglyceride, and HbA_{1c} by standard laboratory techniques (10–13). LDL cholesterol was estimated by the Friedwald equation (14). Patients were considered hypertensive (n = 119) if taking antihypertensive agents, and/or if systolic blood pressure >160 mmHg, and/or if diastolic blood pressure was >95 mmHg. Hyperlipidemia was considered present for patients (n = 156) taking hypolipidemic drugs and/or if the serum cholesterol level was >220 mg/dl, if LDL cholesterol was >150 mg/dl, or if HDL cholesterol was <40 mg/dl. The life-long exposure to smoking (pack-years) was estimated as the product of years smoked, and the mean number of cigarettes smoked daily at the time of examination. Nonsmokers included those who had stopped smoking for at least 1 yr; otherwise, subjects were classified as smokers.

Statistical analysis

Data were expressed as mean ± SD. The unpaired Student's t-test or nonparametric method was used for statistical analysis. Multivariate regression analysis was conducted with the HALBAU (Gendai-Sugaku-Sha, Japan) statistical package (15) for a personal computer (PC-9801 VM2, NEC, Japan).

RESULTS— In nondiabetic subjects, IMT increased with age (Fig. 2). Mean IMTs were 0.52 ± 0.07, 0.62 ± 0.11, 0.71 ± 0.10, 0.85 ± 0.10, 0.87 ± 0.11, and 0.92 ± 0.09 mm in nondiabetic subjects 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 yr of age, respectively. Maximum IMT in all nondiabetic subjects was 1.08 mm (Fig. 2). In the diabetic patients, IMT increased with age (Fig. 2); the values were 0.73 ± 0.27, 0.86 ± 0.10, 0.97 ± 0.21, 1.20 ± 0.31, 1.28 ± 0.33, 1.47 ± 0.42, and 1.72 ± 0.48 mm in those aged 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80 yr, respectively. Diabetic patients showed significantly greater IMTs than nondiabetic subjects for any age-group. In nondiabetic subjects, IMT (y) was closely related to age (x) (y = 0.0087 x + 0.3318) as in diabetic patients (y = 0.0155 x + 0.3450). With hyperlipidemia (1 = present, 0 = absent) as another independent factor for carotid atherosclerosis, IMT still was seen to be related to age in diabetic subjects (y = [0.0146 × age] + [0.0990 × HL] + 0.3259). The regression coefficient for age was significantly greater in diabetic patients than in nondiabetic subjects (0.0146 ± 0.00166 vs. 0.0087 ± 0.00087, $P < 0.0001$). Multivariate regression analysis on both nondiabetic patients and diabetic subjects as a group also showed a linear regression of IMT and age (partial coefficient = 0.0141; $P < 0.0001$). Diabetes and hyperlipidemia increased IMT by 0.135 ($P < 0.01$) and 0.111 ($P < 0.01$), respectively. Hypertension increased IMT by 0.0650, which was not statistically significant. Male sex increased IMT by 0.0393. Body mass index showed no association with IMT (partial coefficient = 0.0091, $P < 0.5$).

Another multivariate regression analysis was done only on NIDDM patients to determine relationships between IMT and possible risk factors, such as age; duration of diabetes; smoking; total, LDL, or HDL cholesterol; systolic or diastolic blood pressure; sex; and HbA_{1c} (Table 2). Age, LDL cholesterol, pack-years of smoking, duration of diabetes, and systolic blood pressure were associated independently with IMT. HbA_{1c} was not correlated significantly with IMT.

CONCLUSIONS— IMT, as determined by B-mode imaging, has been shown to be comparable with that of the intimal plus medial complex measured in pathological and histological examination. Patients with type IIa hyperlipidemia show significantly greater thickness of the intimal plus medial complex than normal subjects (6,7). A follow-up

Table 2—*Possible risk factors of thickness of intimal plus medial complex of carotid arteries in NIDDM patients*

Factors	Correlation coefficient	Partial correlation coefficient	Partial regression coefficient	F (probability)
Age (yr)	0.435	0.3954	0.01522	49.49 (0.0000)
LDL cholesterol (mg/dl)	0.130	0.1958	0.00175	10.65 (0.0013)
Pack-years of smoking	0.182	0.1811	0.00241	9.06 (0.0029)
Duration (yr)	0.226	0.1357	0.00558	4.85 (0.0286)
Systolic blood pressure (mmHg)	0.227	0.1097	0.00254	3.25 (0.0724)
HDL cholesterol (mg/dl)	−0.126			
Total cholesterol (mg/dl)	0.041			
Triglyceride (mg/dl)	−0.066			
Sex (men = 1, women = 0)	0.021			
HbA_{1c} (%)	0.01581			
Diastolic blood pressure (mmHg)	0.036			

Multivariate study was on 275 NIDDM patients.

study after 24 mo (8) indicated age, cigarette years of smoking, blood leukocyte count, and platelet aggregability as predictors of atherosclerosis progression. Our recent study on patients with risk factors for atherosclerosis suggested increased prevalence of carotid atherosclerosis in the Japanese, based on plaque scores as a quantitative index of carotid atherosclerotic lesions. A multivariate study indicated that age, male sex, and hyperlipidemia were independent risk factors and diabetes was a possible risk factor for carotid atherosclerosis. However, atherosclerosis of the carotid arteries in human diabetic patients was not evaluated fully. In this study, for examination of milder atherosclerotic lesions expected even in younger diabetic patients, IMT was measured to determine risk factors contributing to atherosclerosis in diabetic individuals.

As an index of carotid atherosclerosis, the greatest of six averaged values instead of the average of six values was used because anterior projection may miss the carotid sinus where plaque legion is frequently present, and the average of six values may underestimate carotid atherosclerosis.

In normal, nondiabetic subjects, IMT increased with age (7,9). In normal, nondiabetic subjects, it was ≤1.1 mm. Previous studies showed IMT in normal, nondiabetic subjects to be <1.1 mm (6) or <1.0 mm (9). Thus, measurements of IMT by B-mode imaging are quite close, regardless of who makes them.

The diabetic patients showed advanced atherosclerosis of the carotid arteries. Multivariate analysis indicated the partial coefficient for age to be 0.0146 mm/yr in diabetic patients, this being significantly greater than in normal subjects. The partial coefficient for diabetes was similar to that for hyperlipidemia (0.1351 vs. 0.1113, respectively). Thus, possibly diabetes itself may be a strong independent risk factor of atherosclerosis comparable to hyperlipidemia. Diabetic patients with a high incidence of hyperlipidemia may have a condition of 20–30 yr advanced atherosclerosis in carotid arteries compared with normal, nondiabetic subjects, as shown in Fig. 2.

Multivariate analysis on NIDDM patients alone showed systolic blood pressure to be a risk factor of atherosclerosis of the carotid arteries, indicating the possible association of hypertension with advanced diabetes. This stronger association of systolic than diastolic pressure with IMT agrees with the study on the risk of death from coronary heart disease (16–18), but disagrees with other studies (7,9,19). This result possibly may be because of differences in the manner in which studies were conducted (17). Smoking was associated significantly with IMT, in agreement with the follow-up study (8).

The diabetic patients aged 20–29 yr showed significantly greater IMT than normal subjects aged 20–29 by 0.21 mm. Pignoli et al. (5) showed high linearity of IMT by B-mode imaging with thickness of the intimal plus medial complex as determined histologically in subjects aged 20–25 yr. Minimal IMT determined was 0.5 mm in their study. Early changes in atherosclerosis in the carotid artery are thus detectable by B-mode imaging. In our first in vivo study, young diabetic subjects were found to have advanced atherosclerosis of the carotid arteries.

Increased arterial wall thickness was demonstrated in the carotid arteries of subjects with diabetes. Diabetes, along with age, hyperlipidemia, smoking, and hypertension are strong independent risk factors of carotid atherosclerosis. Diabetic patients without neurological symptoms were used in this study. Only a systematic follow-up of patients with thickness of the carotid artery wall will indicate whether this abnormality is associated with increased subsequent clinical manifestations of atherosclerotic diseases. The data will provide prognostic indicators of the clinical manifestations.

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