Stiffness Indexes β of the Common Carotid and Femoral Arteries Are Associated With Insulin Resistance in NIDDM

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OBJECTIVE — To investigate the association between arterial wall stiffness indexes β of the common carotid artery (CCA) and the femoral artery (FA) and insulin resistance in NIDDM subjects in a cross-sectional study.

RESEARCH DESIGN AND METHODS — We evaluated the arterial stiffness indexes β of CCA and FA using an ultrasonic phase-locked echo-tracking system in 60 NIDDM subjects attending the diabetes center in Osaka City University Hospital, compared with 120 age- and sex-matched control subjects. Insulin sensitivity indexes were evaluated using a euglycemic-hyperinsulinemic clamp.

RESULTS — Stiffness indexes β of both CCA and FA were significantly higher in NIDDM subjects than in control subjects (CCA 18.1 ± 0.9 vs. 11.7 ± 0.3, respectively, $P < 0.001$; FA 35.7 ± 2.3 vs. 23.7 ± 0.8, respectively, $P < 0.001$). The mean insulin sensitivity index in NIDDM subjects was 4.69 ± 0.29 mg · kg^{-1} · min^{-1} · mU^{-1} · l. The stiffness indexes β of both CCA and FA were inversely correlated with insulin sensitivity indexes (CCA $r = -0.393$, $P = 0.002$; FA $r = -0.329$, $P = 0.010$), as well as with age, duration of diabetes, and mean blood pressure. In stepwise multiple regression analyses, insulin sensitivity index and duration of diabetes were identified as significant independent variables for stiffness indexes β in both CCA and FA (CCA $R^2 = 0.249$, $P = 0.0003$; FA $R^2 = 0.336$, $P < 0.0001$).

CONCLUSIONS — Arterial stiffness indexes β of CCA and FA were associated with insulin resistance in NIDDM subjects.

Atherosclerotic disease is the most common cause of death among patients with diabetes. It has been proposed that insulin resistance and associated hyperinsulinemia play central roles in the pathogenesis of atherosclerotic disease, not only in diabetes, but also in nondiabetic pathological states, e.g., hypertension, obesity, and hyperlipidemia (1,2). Since the first report by Laakso et al. (3), there have been several reports on the direct association of insulin resistance and early atherosclerosis (4–6). Epidemiological studies by Howard et al. (4) and Bonora et al. (5) demonstrated that the early atherosclerotic change of the carotid artery, intimal-medial thickness (IMT) measured by ultrasonography, was associated with the insulin resistance index as assessed by a minimal model or insulin tolerance test. Kekäläinen et al. (6) failed to demonstrate the direct association of femoral arterial atherosclerosis and insulin resistance assessed by a minimal model. Therefore, it remains to be ascertained whether insulin resistance is associated with the early changes of atherosclerosis because the most reliable method of quantifying insulin sensitivity in vivo, the glucose clamp technique, is too labor-intensive to perform in a large number of subjects and because other methods are less precise (7–9).

Most previous studies on the early changes of atherosclerosis have addressed the early atherotic changes in the arterial wall, IMT. There have been few reports on the sclerotic changes in the arterial wall, which are represented by the stiffness index β as measured by the phase-locked echo-tracking system (10,11). One study demonstrated that carotid arterial stiffness was associated with the morphological change (12), and another suggested that it is relatively independent of IMT (13,14). The arterial stiffness of the common carotid artery (CCA) is higher in patients with diabetes (13,15), as well as in those with hypertension (16) and coronary heart disease (10). However, to the best of our knowledge, there have been no reports on the association between arterial stiffness and insulin resistance in diabetes.

We hypothesized that insulin resistance is associated with the development and progression of the increased arterial stiffness in NIDDM patients. To verify this hypothesis, our first purpose was to confirm the existence of the increased stiffness of CCA and the femoral artery (FA) when compared with age-matched healthy subjects and then to investigate the impact of insulin resistance on arterial stiffness in NIDDM patients. We evaluated the stiffness of CCA and FA using ultrasound techniques as the indexes of the early sclerotic changes in the arterial wall, and the insulin sensitivity index was assessed using a euglycemic-hyperinsulinemic clamp as the index of insulin resistance.

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Abbreviations: CCA, common carotid artery; FA, femoral artery; HGP, hepatic glucose production; IMT, intimal-medial thickness; SSPI, steady-state plasma insulin.

RESEARCH DESIGN AND METHODS

Study population

From patients attending our diabetes center at the Osaka City University Hospital, 60 NIDDM patients participating in the diabetes educational programs were selected for the present study. The diagnosis of diabetes was based on a previous history of diabetes or on World Health Organization criteria (17). Hypertension was defined as blood pressure >140/90 mmHg or the use of known agents for the treatment of hypertension; hyperlipidemia was defined as total cholesterol >200 mg/dl, LDL cholesterol 130 mg/dl, or the use of known agents for the treatment of hyperlipidemia (18). The mean age of the NIDDM subjects was 56.6 ± 10.0 years (mean ± SD), ranging from 28 to 71 years. The known duration of diabetes ranged from 1 to 30 years, with a mean duration of 10.9 ± 7.5 years. Percentages of patients with hypertension, hyperlipidemia, and chronic renal failure and of those who were current smokers were 51.7, 65.0, 20.0, and 56.7%, respectively. Of the patients, 16 were treated only with diet therapy, 27 with sulfonylureas, and 17 with insulin therapy. None of the 17 NIDDM patients treated with insulin therapy had anti-insulin antibodies. There were 21 NIDDM patients with hypertension being treated with calcium antagonists, and 10 being treated with ACE inhibitors. Patients who underwent dialysis therapy or who had other endocrinopathy, malignancies, or infections were excluded.

There were 120 healthy subjects who participated in a health check program at the Osaka Municipal Health Promotion Center and who were used as control subjects for the arterial stiffness indexes β of CCA and FA. Inclusion criteria were as follows: systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg; fasting plasma glucose level <5.5 mmol/l; and no history of myocardial infarction, cerebral infarction, intermittent claudication, or the use of medication. The mean age of the control subjects was 55.1 ± 9.1 years, ranging from 30 to 75 years. Of the subjects, 55% were men and 42.5% were current smokers. Informed consent for participating in this study was obtained from all NIDDM and healthy subjects.

Study protocol

The NIDDM subjects were admitted to our diabetes ward 1 week before the glucose clamp study. During admission, diet therapy (30 kcal · kg^{-1} of body wt · day^{-1}) was undertaken for all patients; the diet contained 50% carbohydrates, 30% fat, and 20% protein. Blood pressure was measured three times using a mercury sphygmomanometer on the right arm after a 15-min rest in the supine position before ultrasonographic examinations. The BMI was calculated by dividing the body weight (kilograms) by the square of the height (meters), and the smoking index was calculated by multiplying the number of cigarettes per day by years. The waist-to-hip ratio was calculated by measuring the waist circumference at the level of the umbilicus, and that of the hip at the greater trochanter.

Ultrasonography

Before the glucose clamp study, ultrasonographic examinations of the atherosclerosis of CCA and FA were performed by the same examiner (M.E.) in the supine position with slight hyperextension of the neck using an ultrasonic phase-locked echo-tracking system, which was equipped with a high-resolution real-time 7.5-MHz linear scanner (SSD 610; Aloka, Tokyo) (10,11). The bilateral carotid arteries were scanned at the level of the bifurcation and the CCA, and the scanning included ~4 cm of the CCA, the carotid bulb, and 1 cm each of the internal and external carotid arteries. The bilateral FAs were scanned distal to the inguinal ligament at the site where the artery divides into the superficial and the profound FAs, including ~4 cm proximal and 1 cm distal to the flow divider (19,20). The stiffness index β, an index of the elastic property of the arterial wall, was calculated from the blood pressure and the diameter of the artery as follows (10,11): Stiffness $\beta = [\ln (Ps/Pd)] \times Dd/(Ds - Dd)$, where *Ps* and *Pd* were the systolic and diastolic blood pressures, and *Ds* and *Dd* were the systolic and diastolic inner diameters of the artery, respectively. The stiffness index β is a unitless quantity that is adjusted by blood pressure.

Intraobserver variability

To estimate the intraobserver variability of the measurements of stiffness index β, 20 NIDDM subjects and 20 control subjects were examined twice with an interval of 7 days. The two measurements were performed by the same examiner, who had no knowledge of the first examination results or the subjects' clinical characteristics. The correlation coefficients for stiffness index β between the first and second measurements in NIDDM and control subjects were 0.973 and 0.966, respectively. The coefficients of variation for stiffness index β in NIDDM and control subjects were 4.3 and 4.1%, respectively.

Euglycemic-hyperinsulinemic clamp

The euglycemic-hyperinsulinemic clamp was performed in NIDDM subjects 10–12 h after an overnight fast, using an artificial pancreas model STG 22 (Nikkiso, Tokyo) according to the method of DeFronzo et al. (21). In brief, after baseline blood sampling, insulin (Humulin; Eli Lilly, Indianapolis, IN) was infused in a continuous fashion at a rate of 1.25 mU · kg^{-1} · min^{-1} after the priming insulin infusion during the first 10 min of the clamp at the same doses as previously reported (21). Blood glucose levels were determined every 5 min during the 120-min clamp study, and euglycemia (5.0 mmol/l) was maintained by infusion of variable amounts of 20% glucose solution. The total-body glucose disposal rate was evaluated as the mean of the glucose infusion rate during the last 30 min of the clamp. We calculated insulin sensitivity indexes by dividing the mean glucose infusion rate by the steady-state plasma insulin (SSPI) levels during the last 30 min of the clamp, as described elsewhere (22,23).

Biochemical analysis

Plasma glucose levels were measured by the glucose oxidase method, HbA_{1c} by high-pressure liquid chromatography (normal range 4.0–5.5%), and plasma insulin levels by immunoradiometric assay (Insulin RIA bead II kit; Dainabot, Tokyo). Serum creatinine, serum total cholesterol, triglyceride, HDL cholesterol, and free fatty acid levels were measured by enzymatic methods adapted to an autoanalyzer (Hitachi 7450; Hitachi, Tokyo).

Statistical analysis

Statistical analyses were performed with the Stat View IV system (Abacus Concepts, Berkeley, CA) for the Apple computer. All results were expressed as means ± SEM, unless otherwise indicated. Student's *t* tests or χ^2 tests were performed for comparison of the groups. Simple linear regression analyses and stepwise multiple regression analyses were performed to evaluate the relationships among stiffness indexes β and various clinical factors. A *P* value of <0.05 was considered significant.

Table 1—*Clinical characteristics of NIDDM and control subjects*

	NIDDM	Control
n	60	120
Age (years)	56.6 ± 10.0	55.1 ± 9.1
Sex (M/F)	39/21	66/54
Duration of diabetes (years)	10.9 ± 7.5	—
BMI (kg/m²)	23.1 ± 3.2	22.8 ± 2.2
Blood pressure (mmHg)		
Systolic	141 ± 30*	124 ± 16
Diastolic	76 ± 13	76 ± 10
Hypertension	31 (51.7)*	18 (15.0)
Current smokers	34 (56.7)	51 (42.5)
Smoking index (cigarette-years)	548 ± 664*	238 ± 340
Fasting plasma glucose (mmol/l)	8.4 ± 2.8*	5.5 ± 0.5
HbA_{1c} (%)	8.5 ± 2.3	—
Fasting plasma insulin (pmol/l)	40.8 ± 57.6	39.2 ± 25.2
Total cholesterol (mmol/l)	5.11 ± 1.28	5.15 ± 0.76
HDL cholesterol (mmol/l)	1.14 ± 0.37*	1.52 ± 0.49
Triglyceride (mmol/l)	1.42 ± 0.87	1.44 ± 0.86

Data are means ± SD, *n*, or *n* (%). *$P < 0.001$ vs. control group.

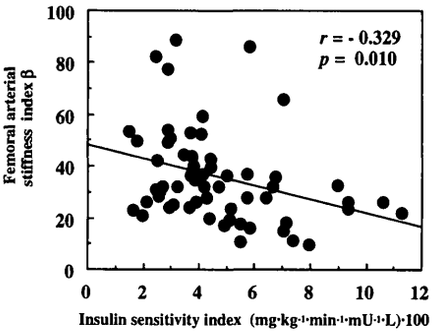

Figure 2—*Relationships between the arterial stiffness index β of FA and the insulin sensitivity index in 60 NIDDM subjects.*

RESULTS

Clinical characteristics of subjects

Clinical characteristics of NIDDM and control subjects are shown in Table 1. There were no significant differences in age, sex, or BMI between NIDDM and control subjects. The number of subjects with hypertension and the mean systolic blood pressure were significantly higher in NIDDM subjects than in control subjects ($P < 0.001$). The smoking index was significantly higher in NIDDM subjects than in control subjects, although there was no significant difference in the number of current smokers between the two groups. The mean HDL cholesterol level was significantly lower in NIDDM subjects than in control subjects ($P < 0.001$), although there were no significant differences in the mean total cholesterol or triglyceride levels between the two groups.

Stiffness indexes β for CCA and FA

Stiffness indexes β for both CCA and FA were significantly higher in NIDDM subjects than in control subjects (CCA 18.1 ± 0.9 vs. 11.7 ± 0.3, respectively, $P < 0.001$; FA 35.7 ± 2.3 vs. 23.7 ± 0.8, respectively, $P < 0.001$).

Insulin sensitivity indexes in NIDDM subjects

Steady-state blood glucose levels during the last 30 min of the clamp were maintained constant throughout at 5.0 mmol/l levels (4.99 ± 0.03 mmol/l), and the mean coefficient of variance was 1.29%, ranging from 0.4 to 2.9%. The mean SSPI level during the last 30 min of the clamp was 109.7 ± 3.7 mU/l. The mean insulin sensitivity index in NIDDM subjects was 4.69 ± 0.29, ranging from 1.51 to 11.30 mg · kg^{-1} · min^{-1} · mU^{-1} · l.

Associations of stiffness indexes β with insulin resistance

The stiffness indexes β of both CCA and FA showed significant inverse correlations with insulin sensitivity indexes, as shown in Figs. 1 and 2 (CCA $r = -0.393$, $P = 0.002$; FA $r = -0.329$, $P = 0.010$). Table 2 shows the simple linear regression analyses of the relationships among the stiffness indexes β of CCA and FA and various possible risk factors in NIDDM subjects. In addition to its relationship with insulin sensitivity index, the stiffness index β of

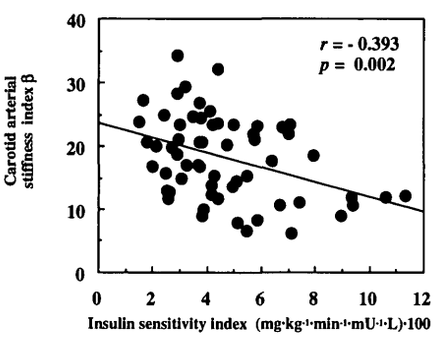

Figure 1—*Relationships between the arterial stiffness index β of CCA and the insulin sensitivity index in 60 NIDDM subjects.*

Table 2—*Simple linear regression analyses of the associations between the stiffness indexes β of the CCA and FA and clinical factors in 60 NIDDM subjects*

	CCA		FA	
	r value	*P* value	*r* value	*P* value
Age	0.557	<0.0001*	0.398	0.002*
Duration of diabetes	0.383	0.003*	0.412	0.001*
BMI	0.022	0.868	0.152	0.247
Smoking index	0.180	0.169	0.057	0.666
Mean blood pressure	0.201	0.024*	0.347	0.007*
Insulin sensitivity	0.393	0.002*	0.329	0.010*
HbA_{1c}	0.266	0.040*	0.164	0.211
Fasting plasma insulin	0.040	0.760	0.005	0.972
Total cholesterol	0.229	0.079	0.316	0.014*
Triglyceride	0.263	0.042*	0.382	0.003*
HDL cholesterol	0.014	0.914	0.066	0.617
1/Creatinine	0.273	0.035*	0.117	0.372

*$P < 0.05$.

Table 3—*Stepwise multiple regression analyses of clinical factors affecting the stiffness index β of the CCA in 60 NIDDM subjects*

	Model 1		Model 2	
	β value	*F* value	β value	*F* value
Age	0.561	29.176	—	—
Duration of diabetes	—	3.920	0.315	7.220
Mean blood pressure	—	2.423	—	0.622
Insulin sensitivity	—	3.889	−0.328	7.798
HbA_{1c}	—	0.830	—	3.061
Triglyceride	0.273	6.904	—	3.242
1/Creatinine	—	1.562	—	0.858
R^2	0.384 ($P < 0.0001$)		0.249 ($P = 0.0003$)	

F value to enter was set at 4.0 at each step.

CCA was significantly correlated with age, duration of diabetes, HbA_{1c}, and triglyceride and 1/creatinine levels. The stiffness index β of FA was significantly correlated with age, duration of diabetes, mean blood pressure, and total cholesterol and triglyceride levels. Because these factors may be associated with each other, stepwise multiple regression analyses were performed to extract the independent factor(s) among them (Tables 3 and 4). In these analyses, the stiffness indexes β for CCA or FA were regarded as the dependent variables, and the factors that showed significant correlations with the stiffness indexes β by simple regression analyses were regarded as the independent variables. In model 1, which included significant factors in Tables 3 and 4 as independent variables, age was demonstrated to be the strong independent contributing variable. In model 2, which did not include age as an independent variable, duration of diabetes and insulin sensitivity index were identified as significant independent variables for the stiffness index β in both CCA and FA.

CONCLUSIONS — The present study demonstrated that the arterial stiffness indexes β of both CCAs and FAs are exacerbated in NIDDM patients compared with age-matched control subjects. The stiffness index β for both CCA and FA was associated with insulin resistance in NIDDM patients. This is the first report in NIDDM patients to demonstrate the association between early sclerotic alterations of the CCAs and the FAs measured by ultrasonography and the insulin sensitivity indexes assessed by the euglycemic-hyperinsulinemic clamp.

The stiffness index β, representing the elastic properties of the arterial wall, was shown to increase with age, the existence of hypertension, and the severity of coronary atherosclerosis (10,11,13,16). The stiffness index β of CCA in humans is reported to be closely correlated with the pathological grading score of atherosclerosis in the CCA at autopsy (12). This stiffness index β in dogs was reported to be associated with an increase in collagen contents and a decrease in elastin contents (14). These previous reports demonstrated that the stiffness index β is considered to be an early indicator of the sclerotic change resulting from atherosclerosis.

To date, only a few reports have studied the arterial stiffness of CCA or FA in diabetic patients. It has been reported that the stiffness indexes β of FA in IDDM patients and the carotid artery in NIDDM patients were significantly higher than those in control subjects (13,24). However, it was also reported that the arterial stiffness index β of the carotid artery increased in women but not in men with IDDM (15). The present study demonstrated that the arterial wall stiffness index β of both CCA and FA was significantly higher on average in NIDDM patients than in age-matched control subjects. Our results were consistent with those of previous reports (13,24).

Insulin resistance is hypothesized to play a pathogenic role in atherosclerosis not only in diabetes, but also in hypertension and obesity (1,2). Previous epidemiological studies have demonstrated that ultrasonographic atherosclerosis indexes, IMT or stiffness index β of CCA, were associated with fasting plasma insulin levels as an indirect index of insulin resistance (13,25). Because it is too labor-intensive in human subjects to assess the insulin resistance by the glucose clamp technique, there have been few reports that demonstrate the direct association between atherosclerosis and insulin resistance. It was recently reported that IMT of the carotid artery was closely associated with insulin resistance when assessed by the minimal model technique or the insulin tolerance test (4,5). However, the insulin sensitivity indexes applied in these previous studies also have limitations in quantifying the precise insulin sensitivity in vivo (7,9). Only one report demonstrated the association between carotid arterial wall thickness and insulin resistance as assessed by the glucose clamp technique (26).

In the present study, age was strongly correlated with arterial stiffness, as previously reported (10,11). Aging concealed the impact of insulin resistance on arterial stiffness when it was included in the multiple regression analyses as an independent variable. However, in analyses that did not include aging, insulin resistance was identified as an independent factor for the arterial stiffness of CCA and FA. Therefore, our study indicates that insulin resistance may, at least partially, play an independent role in the development of the early stiffness of

Table 4—*Stepwise multiple regression analyses of clinical factors affecting the stiffness index β of the FA in 60 NIDDM subjects*

	Model 1		Model 2	
	β value	*F* value	β value	*F* value
Age	0.351	10.730	—	—
Duration of diabetes	0.230	4.409	0.323	8.318
Mean blood pressure	0.235	4.623	—	2.218
Insulin sensitivity	—	1.359	−0.239	4.596
HbA_{1c}	—	0.190	—	0.994
Triglyceride	0.290	7.345	0.325	8.726
Total cholesterol	—	0.460	—	0.513
R^2	0.427 ($P < 0.0001$)		0.336 ($P < 0.0001$)	

F value to enter was set at 4.0 at each step.

the arterial wall. Our results are compatible with those of previous reports that indicate the association between early atherosclerosis and insulin resistance (4,5,13).

There were two limitations of our present study. First, it was not determined whether anti-hypertensive drugs may affect arterial stiffness indexes β and insulin sensitivity indexes. Second, the incomplete suppression of hepatic glucose production (HGP) during the euglycemic glucose clamp may affect the insulin sensitivity indexes, since we did not directly measure HGP by isotope dilution technique. However, we assumed that HGP was fully suppressed when SSPI levels reached the level of ≧100 mU/l, as previously reported (27,28).

The mechanisms that could link atherosclerosis and insulin resistance remain to be clarified. It is well known that insulin has a vasodilatory effect in humans (29,30). Recently, it was reported that insulin resistance in obesity and diabetes is associated with the insulin-induced vasodilatory effect, which is mediated by endothelium-derived nitric oxide (31). The association between insulin resistance and endothelial dysfunction may account for the association between insulin resistance and early functional alterations of the arterial wall.

In conclusion, we demonstrated that the arterial wall stiffness indexes β of CCA and FA in 60 Japanese NIDDM patients increased compared with healthy subjects and that the sclerotic changes in these arteries were associated with insulin resistance in these patients. Further prospective studies in humans are necessary to ascertain whether insulin resistance may induce the early changes of atherosclerosis in diabetes.

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