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JOURNAL OF THE AMERICAN HEART ASSOCIATION

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*Arterioscler Thromb Vasc Biol* 2003;23;295-301; originally published online Dec 5, 2002;

DOI: 10.1161/01.ATV.0000050142.09911.0B

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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# Association Between Insulin Resistance and Carotid Arteriosclerosis in Subjects With Normal Fasting Glucose and Normal Glucose Tolerance

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**Objective**—We examined the possible association between insulin resistance and carotid arteriosclerosis in subjects who had both normal fasting glucose and normal glucose tolerance after intake of a glucose load.

**Methods and Results**—Our subjects were individuals who underwent general health screening at our institute, which included carotid ultrasound and oral glucose tolerance testing. Of the 1238 subjects enrolled in our study, 738 (60%) were classified as normal, defined as a normal fasting glucose level and normal glucose tolerance, and 334 (27%) and 166 (13%) were classified as borderline and diabetic, respectively, according to the criteria of the Japan Diabetes Society. The homeostasis model assessment of insulin resistance (HOMA-IR) was used as the index to measure insulin resistance. In normal-type subjects, univariate analysis showed that insulin resistance, but not insulin secretion, was associated with the presence of carotid plaque. Multivariate analysis showed that HOMA-IR was positively associated with carotid plaque in normal-type subjects, with an odds ratio of 1.19 (95% confidence interval, 1.00 to 1.41;  $P < 0.05$ ).

**Conclusions**—These data suggest the possibility that the presence of higher insulin resistance could be a risk factor for carotid arteriosclerosis in subjects with normal fasting glucose and normal glucose tolerance. (*Arterioscler Thromb Vasc Biol.* 2003;23:295-301.)

**Key Words:** carotid ultrasound ■ atherosclerosis ■ diabetes ■ insulin resistance ■ risk factor

Several prospective epidemiological studies have suggested that there may be an association between insulin resistance and/or hyperinsulinemia and subsequent cardiovascular disease and stroke.<sup>1-5</sup> Furthermore, some studies have reported an association between insulin resistance and early carotid arteriosclerotic lesions,<sup>6,7</sup> the development of which is a known risk factor for myocardial infarction and stroke.<sup>8</sup> In interpreting these data, one needs to exercise caution, because an observed association may be dependent on other well-known atherogenic risk factors, such as other metabolic and hemodynamic disorders that may cluster in the subjects with increased insulin resistance and that compose the insulin-resistance syndrome.<sup>9</sup> Indeed, a large cross-sectional, population-based study in Sweden suggested that the association between insulin resistance in nondiabetic subjects and atherosclerosis was explained by its covariance with established risk factors.<sup>9</sup>

Patients with impaired glucose tolerance who may have features of the insulin resistance syndrome,<sup>10</sup> as well as diabetes, are at increased risk for developing atherosclerosis.<sup>11,12</sup> A recent study showed that subjects with impaired glucose tolerance had a risk of carotid stenosis 3-fold higher

than did subjects with normal glucose tolerance, even after adjustment for several confounding risk factors.<sup>13</sup> Therefore, we wanted to know whether we could isolate subjects at high risk for developing atherosclerotic complications, not from nondiabetic subjects but from subjects even without impaired glucose tolerance. To date, there has been little published information concerning whether increased insulin resistance is an independent risk factor for atherosclerotic diseases in subjects with both normal fasting glucose levels and normal glucose tolerance. The purpose of this study was to determine whether there was a possible association between insulin resistance and carotid arteriosclerosis by analyzing the population-based, cross-sectional data of these subjects.

## Methods

### Subjects

Between August 1994 and April 1999, 1238 subjects underwent general health screening tests at the Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital, which included both high-resolution B-mode carotid ultrasound and oral glucose tolerance testing. In Japan, regular health checkups for employees are legally mandated. Therefore, the majority of these subjects did

Received September 26, 2002; revision accepted November 20, 2002.

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*Arterioscler Thromb Vasc Biol.* is available at <http://www.atvbaha.org>

DOI: 10.1161/01.ATV.0000050142.09911.0B

not have serious health problems. Within this study period, a total of 16 383 subjects underwent general health screening at our institute, and only 8% (1238) of these underwent general health screening that included both high-resolution B-mode carotid ultrasound and oral glucose tolerance testing; these individuals make up the study population of the present work. The enrolled subjects were significantly older, had a significantly higher body mass index (BMI), and were more likely to be men, compared with the total population (data not shown). Therefore, it could be said that there was some selection bias when the participant was scheduled to undergo carotid ultrasonography together with oral glucose testing, though, it was neither the decision nor recommendation by the physicians.

### Carotid Ultrasound

Carotid artery status was studied with a high-resolution, B-mode ultrasound system (Sonolayer SSA270A, Toshiba) equipped with a 7.5-MHz transducer (PLF-703ST, Toshiba). The carotid arteries were examined bilaterally at the levels of the common carotid artery, the bifurcation, and the internal carotid arteries from transverse and longitudinal orientations by trained sonographers. The intima-media thickness was measured by a computer-assisted method by experienced sonographers who were unaware of the subjects' clinical and laboratory findings. Plaque was defined as a clearly isolated focal thickening of the intima-media layer with a thickness  $\geq 1.3$  mm at the common or internal carotid artery or the carotid bulb. Carotid wall thickening was judged to be present when the intima-media thickness, which was measured at the far wall of the distal 10 mm of the common carotid artery, was  $\geq 1.0$  mm.

### Glucose Tolerance Test and Classification of the Subjects

No subjects in the present study were being treated with either oral medications or insulin for diabetes. All subjects underwent an oral 75-g glucose tolerance test, for which their levels of plasma glucose and serum insulin were measured before administration of the glucose load and 30, 60, and 120 minutes later. With the data obtained during the test, subjects were classified into 1 of 3 categories according to the criteria of the Committee for the Classification and Diagnosis of Diabetes Mellitus of the Japan Diabetes Society.<sup>14</sup> Normal-type subjects were defined as having a fasting plasma glucose (FPG)  $< 110$  mg/dL ( $< 6.1$  mmol/L) and a 2-hour plasma glucose  $< 140$  mg/dL ( $< 7.8$  mmol/L), whereas diabetic-type subjects were defined as having an FPG  $\geq 126$  mg/dL ( $\geq 7.0$  mmol/L) and/or a 2-hour plasma glucose  $\geq 200$  mg/dL ( $\geq 11.1$  mmol/L). Borderline-type subjects included those who were of neither the diabetic nor normal type. Normal-type subjects met the criteria of having normal fasting glucose (NFG)<sup>15</sup> and normal glucose tolerance (NGT),<sup>16</sup> whereas borderline-type subjects included those with both impaired fasting glucose<sup>15</sup> and impaired glucose tolerance.<sup>16</sup>

### Risk Factors

BMI was calculated as weight (kg)/height (m<sup>2</sup>). Subjects were said to be hypertensive if they had a systolic blood pressure  $\geq 140$  mm Hg, a diastolic blood pressure of  $\geq 90$  mm Hg, or both.

### Laboratory Tests

Blood samples were taken from our subjects after an overnight fast. Total cholesterol (TC), HDL cholesterol (HDL-C), and triglycerides (TGs) were determined enzymatically, and hemoglobin A<sub>1c</sub> was determined by a latex agglutination immunoassay. The subjects' homeostasis model assessment of insulin resistance (HOMA-IR), which is a measure of the degree of their insulin resistance, was calculated as [fasting insulin ( $\mu$ U/mL)  $\times$  fasting glucose (mg/dL)]/405.<sup>17</sup> The correlation coefficient of HOMA-IR versus fasting insulin in normal-type subjects was 0.993. The insulinogenic index, an index of early-phase insulin secretion and thus, beta cell function, was defined as the ratio of the increment of serum insulin to that of plasma glucose 30 minutes after a glucose load, ie, ( $\Delta$ insulin 0 to 30 minutes)/( $\Delta$ plasma glucose 0 to 30 minutes), which was expressed in ( $\mu$ U/mL)/(mg/dL).

### Statistical Analysis

The  $\chi^2$  test, ANOVA, and univariate and multivariate logistic regression analyses performed with Statistica version 5J and Stat-View version 5.0 software, were used to analyze the data in this study. Age, BMI, TC, HDL-C, TGs, and hemoglobin A<sub>1c</sub> were included as continuous variables, and others were included as categorical variables. Statistical significance was taken at  $P < 0.05$ . Results were expressed as the mean  $\pm$  SD unless otherwise stated.

## Results

### Study Subjects

Of the 1238 participants in this study, 738 (60%) were normal-type, 334 (27%) were borderline type, and 166 (13%) were diabetic-type subjects. The baseline characteristics and laboratory data for each group are shown in Table 1. The mean age in the normal-type, borderline-type, and diabetic type subjects were 57.4 (24 to 82), 59.2 (24 to 88), and 60.0 years (27 to 79 years), respectively. HOMA-IR was lowest in normal-type subjects, with a range of 0.50 to 8.07 (median, 1.25), followed by borderline-type subjects, with a range of 0.62 to 12.4 (median, 1.96), and was highest in diabetic-type subjects, with a range of 0.71 to 11.1 (median, 2.78). The insulinogenic index was highest in normal-type subjects, followed by borderline-type subjects and then diabetic-type subjects. Carotid plaque was present in 22%, 28%, and 30% of normal-type, borderline-type, and diabetic-type subjects, respectively ( $P < 0.05$  by  $\chi^2$  test). Carotid intima-media thickness was the smallest in the normal-type subjects, followed successively by borderline-type and diabetic-type subjects, but these differences did not reach statistical significance. The prevalence of carotid artery wall thickening (intima-media thickness  $\geq 1.0$  mm) in normal-type, borderline-type, and diabetic-type subjects was 14%, 16%, and 20%, respectively (NS by  $\chi^2$  test).

### Univariate Analyses Examining the Association Between Insulin Resistance and Carotid Plaque

Results of the univariate analysis are shown in Table 2. Hemoglobin A<sub>1c</sub>, but not fasting glucose, was associated with carotid plaque in normal-type subjects. HOMA-IR was positively associated with carotid plaque in the population as a whole, as well as in the normal-type subjects, with odds ratios of 1.12 (95% confidence interval, 1.03 to 1.21,  $P < 0.01$ ) and 1.21 (95% confidence interval, 1.04 to 1.41,  $P = 0.014$ ), respectively. In contrast, the insulinogenic index was not significantly associated with carotid plaque in either the entire group of subjects as a whole or in normal-type subjects. A similar analysis was performed to assess the possible association between HOMA-IR and carotid intima-media thickening; however, there was no significant association between these variables in either the group as a whole or in normal-type subjects (Table 3).

### Relation Between Insulin Resistance and Atherogenic Risk Factors in Normal-Type Subjects

Before performing multivariate analyses, we assessed the relation between HOMA-IR and atherogenic risk factors in normal-type subjects. HOMA-IR showed weak but positive correlations with systolic blood pressure (0.26,  $P < 0.0001$ ), TC (0.07,  $P < 0.05$ ), and TGs (0.19,  $P < 0.0001$ ) and a nega-

TABLE 1. Baseline Characteristics

	All (n=1238)	Normal (n=738)	Borderline (n=334)	Diabetic (n=166)	P
Clinical characteristics					
Age, y	58.2±10.1	57.4±10.5	59.2±9.8	60.0±8.5	0.0042
Sex, female/male	329/909	260/478	53/281	16/150	<0.0001
BMI, kg/m <sup>2</sup>	23.6±3.1	23.0±2.9	24.4±3.0	24.7±3.3	<0.0001
Systolic blood pressure, mm Hg	128±21	123±19	134±20	137±23	<0.0001
Diastolic blood pressure, mm Hg	78±13	75±12	82±13	83±14	<0.0001
Hypertension, %	341 (27)	146 (20)	121 (36)	74 (45)	<0.0001
Never smoker, %	484 (39)	338 (46)	104 (31)	42 (25)	0.0050
Current smoker, %	506 (41)	279 (38)	142 (43)	85 (51)	0.0004
Ex-smoker, %	248 (20)	121 (16)	88 (26)	39 (23)	<0.0001
Laboratory data					
Lipid metabolism					
Total cholesterol, mmol/L	5.4±0.9	5.4±0.9	5.4±0.9	5.3±0.8	0.72
Triglycerides, mmol/L	1.6±1.2	1.3±0.9	1.9±1.3	2.1±1.4	<0.0001
HDL-cholesterol, mmol/L	1.4±0.4	1.5±0.5	1.3±0.4	1.2±0.3	<0.0001
Glucose metabolism					
Fasting glucose, mmol/L	5.9±1.2	5.3±0.4	6.0±0.5	8.0±1.9	<0.0001
30-min glucose, mmol/L	9.3±2.3	8.2±1.5	9.8±1.5	12.9±2.7	<0.0001
1-h glucose, mmol/L	9.5±3.7	7.5±2.1	10.7±2.3	15.8±3.5	<0.0001
2-h glucose, mmol/L	7.9±3.7	6.0±1.1	8.4±1.3	15.2±4.4	<0.0001
Fasting insulin, μU/mL	7.4±4.9	6.5±4.4	8.4±5.2	9.3±5.1	<0.0001
30-min insulin, μU/mL	41.3±30.2	43.8±30.1	44.2±32.9	24.4±15.7	<0.0001
1-h insulin, μU/mL	49.0±34.7	47.2±31.5	59.1±42.2	36.2±24.7	<0.0001
2-h insulin, μU/mL	42.1±30.1	33.3±19.3	59.3±40.4	46.2±30.5	<0.0001
Hemoglobin A <sub>1c</sub> , %	5.3±0.7	5.1±0.4	5.3±0.4	6.5±1.1	<0.0001
HOMA-IR	1.98±1.50	1.57±1.20	2.26±1.42	3.38±2.09	<0.0001
Insulinogenic index (μU/mL per mg/dL)	0.67±1.01	0.80±1.20	0.60±0.60	0.22±0.51	<0.0001
Carotid ultrasonographic data					
Carotid plaque, %	305 (25)	160 (22)	95 (28)	50 (30)	0.013
Intima-media thickness, mm	0.78±0.45	0.76±0.48	0.80±0.45	0.82±0.25	0.24
Intima-media thickening	195 (16)	107 (14)	55 (16)	33 (20)	0.21

tive correlation with HDL-C (-0.17,  $P<0.0001$ ) in this group. Notably, the correlation between HOMA-IR and hemoglobin A<sub>1c</sub> was not statistically significant (0.036,  $P=0.32$ ). Similarly, no statistically significant correlation was observed between the insulinogenic index and atherogenic risk factors, such as systolic blood pressure (0.027,  $P=0.47$ ), TC (0.005,  $P=0.89$ ), TG (-0.12,  $P=0.74$ ), HDL-C (-0.059,  $P=0.11$ ), and hemoglobin A<sub>1c</sub> (0.045,  $P=0.22$ ).

### Multivariate Analyses of Insulin Resistance and Carotid Plaque

The association between HOMA-IR and carotid plaque was assessed by multivariate logistic regression analysis, which included the following variables: age, sex, systolic blood pressure, TC, HDL-C, TGs, hemoglobin A<sub>1c</sub>, and smoking status (Table 4). In this model, HOMA-IR remained a significant and independent predictor of carotid plaque in normal-type subjects, with an odds ratio of 1.19 (95% confidence interval, 1.00 to 1.41,  $P<0.05$ ). In contrast,

HOMA-IR was not associated with carotid intima-media thickening (odds ratio, 1.01; 95% confidence interval, 0.87 to 1.30,  $P=0.52$ ).

### Discussion

In this study, we investigated whether there was an association between insulin resistance, assessed by HOMA-IR, and the presence of carotid plaque in normal-type subjects, defined as those who had both NFG and NGT. Univariate analysis showed that HOMA-IR and hemoglobin A<sub>1c</sub> levels, but not fasting glucose, were positively associated with the presence of carotid plaque. Insulin resistance was found to be positively associated, though weakly, with blood pressure, TC, and TGs and negatively with HDL-C. Multivariate analysis with other confounding risk factors for atherosclerosis, including hemoglobin A<sub>1c</sub>, demonstrated that HOMA-IR was also independently associated with the presence of carotid plaque, with an odds ratio of 1.19 (95% confidence interval, 1.00 to 1.41,  $P<0.05$ ), indicating that the association

**TABLE 2. Univariate Analysis For Carotid Plaque**

	All		Normal		Borderline		Diabetic	
	Odds Ratio (95% CI)	<i>P</i>	Odds Ratio (95% CI)	<i>P</i>	Odds Ratio (95% CI)	<i>P</i>	Odds Ratio (95% CI)	<i>P</i>
Male sex	2.45 (1.735–3.48)	<0.00001	2.86 (1.85–4.447)	<0.00001	1.86 (0.88–3.94)	0.1	0.69 (0.23–2.06)	0.5
Age, per y	1.11 (1.09–1.13)	<0.00001	1.11 (1.09–1.14)	<0.00001	1.09 (1.06–1.13)	<0.00001	1.10 (1.05–1.15)	0.00008
BMI, per 1 kg/m <sup>2</sup>	1.05 (1.01–1.09)	0.034	1.08 (1.02–1.15)	0.01	1.00 (0.93–1.09)	0.95	0.94 (0.84–1.05)	0.28
Systolic blood pressure, per 1 mm Hg	1.02 (1.01–1.03)	<0.00001	1.02 (1.01–1.03)	0.00057	1.07 (1.02–1.11)	0.0015	1.02 (1.00–1.03)	0.024
Total cholesterol, per 1 mmol/L	1.12 (0.97–1.30)	0.12	1.16 (0.96–1.39)	0.12	0.97 (0.73–1.29)	0.84	1.37 (0.89–2.10)	0.14
HDL cholesterol, per 1 mmol/L	0.63 (0.46–0.87)	0.0047	0.99 (0.97–1.00)	0.01	0.90 (0.50–1.62)	0.72	0.86 (0.31–2.39)	0.8
Triglycerides, per 1 mmol/L	1.09 (0.980–1.22)	0.097	1.22 (1.03–1.45)	0.018	0.89 (0.72–1.10)	0.26	1.02 (0.79–1.30)	0.86
Fasting plasma glucose, per 1 mg/dL	1.00 (1.00–1.01)	0.16	1.01 (0.99–1.04)	0.34	0.99 (0.97–1.02)	0.57	1.00 (0.99–1.01)	0.42
Hemoglobin A <sub>1c</sub> , per 1%	1.34 (1.13–1.58)	0.00065	2.70 (1.68–4.33)	0.00003	1.59 (0.90–2.79)	0.1	0.96 (0.70–1.30)	0.78
Fasting insulin	1.04 (1.01–1.06)	0.005	1.04 (1.01–1.09)	0.02	1.00 (0.96–1.06)	0.68	1.02 (0.96–1.09)	0.45
HOMA-IR, per 1	1.12 (1.03–1.21)	0.0075	1.21 (1.04–1.41)	0.014	1.03 (0.87–1.22)	0.74	1.00 (0.85–1.17)	0.96
Insulinogenic index, per 1	0.96 (0.84–1.10)	0.58	1.02 (0.88–1.19)	0.76	0.89 (0.57–1.38)	0.59	0.65 (0.15–2.77)	0.55
Current smoker*	1.51 (1.11–2.06)	0.0068	1.50 (1.00–2.24)	0.046	1.12 (0.62–2.00)	0.7	2.09 (0.84–5.19)	0.11
Ex-smoker*	1.93 (1.35–2.76)	0.00025	2.04 (1.25–3.34)	0.0037	1.33 (0.70–2.52)	0.37	2.38 (0.85–6.67)	0.094

\*Never smoker was used as reference.

between insulin resistance and carotid atherosclerosis was independent of other atherogenic risk factors.

Although HOMA-IR, calculated with fasting glucose and fasting insulin levels, was used to assess the degree of insulin resistance in our subjects, the estimation of insulin resistance by this approach may be somewhat less accurate compared with the use of glucose clamping. However, it is not feasible to perform glucose clamp studies in the general health screening setting. Furthermore, there has been shown to be

good agreement between HOMA-IR and clamp-measured glucose disposal in subjects with various degree of glucose tolerance.<sup>18</sup> Therefore, HOMA-IR was considered a useful model for assessing insulin resistance in epidemiological studies<sup>18</sup> such as ours.

The prevalence of subjects with borderline-type (27%) and diabetic-type (13%) glucose metabolism in this study was somewhat higher than expected. This may be due, at least in part, to the reduction in FPG threshold used to screen for

**TABLE 3. Univariate Analysis For Carotid Intima-Media Thickening**

	All		Normal		Borderline		Diabetic	
	Odds Ratio (95% CI)	<i>P</i>	Odds Ratio (95% CI)	<i>P</i>	Odds Ratio (95% CI)	<i>P</i>	Odds Ratio (95% CI)	<i>P</i>
Male sex	1.79 (1.21–2.67)	0.0034	2.07 (1.26–3.38)	0.0033	0.96 (0.43–2.12)	0.91	1.82 (0.38–8.72)	0.44
Age, per y	1.08 (1.06–1.10)	<0.00001	1.11 (1.08–1.13)	<0.00001	1.05 (1.01–1.08)	0.005	1.03 (0.99–1.08)	0.15
BMI, per 1 kg/m <sup>2</sup>	1.02 (0.97–1.07)	0.44	1.03 (0.96–1.11)	0.37	1.01 (0.92–1.11)	0.86	0.95 (0.84–1.08)	0.43
Systolic blood pressure, per 1 mm Hg	1.01 (1.01–1.02)	0.00046	1.02 (1.01–1.03)	0.00076	1.00 (0.98–1.01)	0.64	1.02 (1.00–1.03)	0.04
Total cholesterol, per 1 mmol/L	1.04 (0.87–1.23)	0.69	1.01 (0.80–1.27)	0.94	1.20 (0.85–1.69)	0.3	0.90 (1.49–0.55)	0.69
HDL cholesterol, per 1 mmol/L	0.52 (0.35–0.78)	0.0012	0.52 (0.31–0.88)	0.012	0.71 (0.34–1.49)	0.36	0.36 (0.10–1.33)	0.12
Triglycerides, per 1 mmol/L	1.02 (0.89–1.16)	0.78	1.03 (0.83–1.27)	0.78	0.93 (0.73–1.19)	0.57	1.00 (0.74–1.65)	0.99
Fasting plasma glucose, per 1 mg/dL	1.01 (1.00–1.01)	0.063	1.04 (1.01–1.07)	0.015	1.01 (0.98–1.04)	0.54	1.00 (0.99–1.01)	0.79
Hemoglobin A <sub>1c</sub> , per 1%	1.06 (0.60–1.30)	0.59	0.76 (0.45–1.31)	0.32	0.60 (0.30–1.17)	0.13	1.10 (0.78–1.55)	0.58
Fasting insulin	1.04 (1.01–1.06)	0.005	1.04 (1.01–1.09)	0.02	1.01 (0.96–1.06)	0.68	1.02 (0.96–1.09)	0.45
HOMA-IR, per 1	1.06 (0.96–1.17)	0.23	1.10 (0.93–1.30)	0.25	0.97 (0.79–1.21)	0.8	0.99 (0.82–1.20)	0.93
Insulinogenic index, per 1	0.94 (0.80–1.11)	0.48	1.02 (0.86–1.21)	0.82	0.61 (0.30–1.22)	0.15	0.40 (0.03–5.24)	0.48
Current smoker*	1.12 (0.78–1.60)	0.54	1.09 (0.68–1.74)	0.73	0.61 (0.27–1.35)	0.21	4.00 (1.09–14.7)	0.035
Ex-smoker*	1.61 (1.07–2.42)	0.02	1.65 (0.95–2.89)	0.072	1.00 (0.34–2.96)	0.99	4.48 (1.10–18.3)	0.034

\*Never smoker was used as reference.

**TABLE 4. Multivariate Analysis For Carotid Plaque**

	Odds Ratio (95% CI)	P
Male sex	1.79 (0.98–3.28)	0.055
Age, per y	1.12 (1.09–1.15)	<0.00001
Systolic blood pressure, per 1 mm Hg	1.00 (0.99–1.01)	0.99
Total cholesterol, per 1 mmol/L	1.25 (0.98–1.61)	0.072
HDL cholesterol, per 1 mmol/L	0.88 (0.50–1.54)	0.64
Triglycerides, per 1 mmol/L	1.21 (0.95–1.55)	0.11
Hemoglobin A <sub>1C</sub> , per 1%	1.82 (1.04–3.19)	0.032
HOMA-IR, per 1	1.19 (1.00–1.41)	0.045
Current smoker*	1.67 (0.98–2.85)	0.057
Ex-smoker*	1.44 (0.77–2.70)	0.24

\*Never smoker was used as reference.

diabetes mellitus, from 7.8 to 7.0 mmol/L according to the American Diabetes Association,<sup>16</sup> which may result in a >2-fold increase in the number of newly diagnosed diabetic subjects.<sup>19</sup> Indeed, using the same criteria as in our study, Liao et al<sup>20</sup> showed that of 562 Japanese-Americans in King County, Washington, the number of the subjects with normal-type, borderline-type, and diabetic-type responses were 307 (55%), 212 (38%), and 77 (14%), respectively, which was similar to the distribution seen in our study population. When interpreting our data, which suggest that there is an association between insulin resistance and atherosclerosis, we need to exercise caution for 2 reasons. First, other metabolic and hemodynamic disorders included in the insulin resistance syndrome may cluster in subjects with increased insulin resistance,<sup>9</sup> making it difficult to assess the independent association between insulin resistance and arteriosclerotic diseases. Second, HOMA-IR provides useful information only when this parameter can predict a higher incidence of arteriosclerotic diseases independent of other factors such as plasma glucose and hemoglobin A<sub>1C</sub>. In our study, as in a previous report,<sup>21</sup> plasma glucose was not a predictor of carotid plaque. Furthermore, there was no statistically significant relation between hemoglobin A<sub>1C</sub> and HOMA-IR levels in normal-type subjects, both of which were independently associated with carotid plaque.

In this study, we assessed the possible association between insulin resistance, carotid plaque, and carotid-media thickening. There have been several previous reports in which the association between carotid intima-media thickness and insulin resistance has been investigated in a nondiabetic population. Some studies showed a lack of independent association between insulin resistance and carotid arteriosclerosis,<sup>9,22,23</sup> whereas others showed a positive association between these variables.<sup>24</sup> Snehathala et al<sup>22</sup> reported lack of an association between insulin resistance and carotid intima-media thickness in nondiabetic Asian subjects. Bonora et al<sup>23</sup> reported that carotid intima-media thickness was associated with insulin resistance in nondiabetic subjects, as determined by univariate analysis, but was not associated by multivariate analysis, although their number of enrolled subjects (n=58) was relatively small. Hedblad et al<sup>9</sup> showed that the association between insulin resistance and carotid intima-media thickness in nondiabetic subjects and atherosclerosis was explained by

its covariance with established risk factors. Although the target populations were different from those of our study (our subjects were limited to those who had both NFG and NGT, whereas nondiabetic subjects enrolled in the aforementioned studies may have included not only subjects in this category but also subjects with impaired fasting glucose or impaired glucose tolerance), similar results were obtained. On the other hand, some studies have shown an independent association between carotid intima-media thickness and insulin resistance. De Pergola et al<sup>24</sup> reported an independent association between insulin sensitivity and the thickness of the intima-media complex after adjusting the data for age, BMI, waist circumference, mean blood pressure levels, and plasma glucose and lipids. Similarly, Shinozaki et al<sup>25</sup> and Suzuki et al<sup>26</sup> reported that insulin resistance was independently and statistically significantly associated with carotid intima-media thickness in nondiabetic subjects. The conclusions of these 3 articles, which differ from ours, may be partially explained by the fact that their target populations were nondiabetic subjects and thus, may have included subjects with impaired glucose tolerance and/or increased fasting glucose; in addition, the latter 2 studies examined the relation between carotid intima-media thickness and insulin resistance in a subpopulation of subjects with vasospastic angina and essential hypertension, respectively.

Few articles have examined the possible relation between carotid plaque and insulin resistance with a study population limited to nondiabetic subjects. Shinozaki et al<sup>25</sup> reported that carotid plaque, which had been defined as a distinct area with >50% intima-media thickness than neighboring sites (usually >1.2 mm) in subjects with vasospastic angina was statistically significantly associated with insulin resistance. Although subjects with impaired glucose tolerance were also included in their study population, they reached a conclusion similar to ours.

It has been reported that increases in intima-media thickness are related to locally detected atherosclerotic plaque.<sup>27</sup> One may wonder why HOMA-IR was associated with carotid plaque but not with carotid intima-media thickness in normal-type subjects. A recent study in Japan found that the prevalence of intima-media thickness and plaque were not associated in very old (>90 years of age) subjects,<sup>28</sup> which suggests the possibility that carotid intima-media thickening and plaque may have some distinct pathophysiological features. In addition, the prevalence of carotid plaque has been reported to be higher than that of intima-media thickening in some studies, which may further support the notion that carotid intima-media thickening is not just a less-severe lesion of carotid plaque. We do not know the exact reason why HOMA-IR was associated with only carotid plaque, but a possible explanation may be that different risk factors may affect only carotid plaque or carotid intima-media thickness if the pathological features differ, at least in part, between these 2 conditions. Indeed, in our study population, multivariate analysis showed that blood pressure and serum levels of TC were associated with carotid plaque but not with carotid intima-media thickening.

Both insulin resistance<sup>29,30</sup> and diminished insulin secretion<sup>31,32</sup> are known to predict the future development of

diabetes. Recently, it has become possible to treat patients in the clinical setting with insulin-sensitizing drugs. Our data and those of others<sup>33</sup> suggest that insulin sensitization, rather than the promotion of insulin secretion, would be the better therapeutic strategy in light of the fact that elevated insulin levels could cluster with other atherogenic risk factors, and insulin resistance itself is also an independent risk factor for the development of carotid arteriosclerosis. Because ours was not a longitudinal study, we cannot predict what percentage of our normal-type subjects will go on to develop diabetes later in life. Whether administration of insulin-sensitizing drugs, as opposed to insulin secretagogues, to prediabetic and diabetic individuals can prevent atherogenic complications remains to be investigated in longitudinal, double-blind studies. Because insulin resistance as well as levels of TGs and HDL-C may be related to the size of LDL, which has been reported to be associated with carotid and femoral arteries,<sup>34</sup> the relation between HOMA-IR and carotid plaque observed in the present study may be explained by variations in the sizes of LDL particles. This possibility should also be clarified in future studies.

An increase in systolic blood pressure was found to be a risk factor for carotid plaque in normal-type subjects by univariate analysis but not by multivariate analysis in our study. On the other hand, we found that each 10 mm Hg increase in systolic blood pressure in borderline-type or diabetic-type subjects was associated with a 20% increase in carotid plaque ( $P=0.0012$ ). These findings suggest that control of blood pressure is 1 of the potentially modifiable risk factors for the development of arteriosclerosis in subjects with abnormal glucose metabolism, a similar conclusion that has been reached in the recent UK Prospective Diabetes Study.<sup>35</sup>

In conclusion, analysis of cross-sectional data obtained from subjects undergoing general health screening tests showed that insulin resistance, calculated as HOMA-IR, was positively associated with carotid plaque formation in subjects who showed both NFG and NGT. This association remained significant even when other atherogenic risk factors, including hemoglobin A<sub>1c</sub> levels, were factored in as covariates. Thus, HOMA-IR may be a useful index to predict carotid plaque formation in the subjects with both NFG and NGT.

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