Insulin Resistance and Arteriosclerosis Obliterans in Patients With NIDDM

KAZUNARI MATSUMOTO, MD
SEIBEI MIYAKE, MD
MAYUMI YANO, MD
YUKITAKA UEKI, MD
YOSHIHIKO YAMAGUCHI, MD
SHOICHI AKAZAWA, MD
YUKO TOMINAGA, MD

OBJECTIVE — To investigate the risk factors for arteriosclerosis obliterans (ASO) in NIDDM, we measured insulin sensitivity and other risk factors including lipoprotein(a) [Lp(a)] in NIDDM patients with and without ASO.

RESEARCH DESIGN AND METHODS — A case-control study in 100 patients with NIDDM, 35 with and 65 without ASO, was performed. Insulin sensitivity was assessed by the short insulin tolerance test's *K* index (K_{ITT}). Duration of diabetes, a history of smoking, prevalence of hypertension, prevalence of coronary artery disease (CAD), serum C-peptide, 24-h urinary C-peptide, serum lipids, and Lp(a) were compared in the two groups.

RESULTS — Age, BMI, HbA_{1c}, and fasting plasma glucose were comparable in the two groups. Patients with ASO were significantly more insulin resistant than patients without ASO (K_{ITT} 2.16 ± 0.16 vs. 3.00 ± 0.13 %/min, $P < 0.0001$, respectively), had a longer duration of diabetes (10.3 ± 1.2 vs. 7.5 ± 0.8 years, $P < 0.05$), included a greater number of smokers (68.6 vs. 40.0%, $P < 0.01$), had a higher prevalence of CAD (60.0 vs. 16.9%, $P < 0.01$), and had a greater percentage of insulin therapy (48.6 vs. 29.2%, $P < 0.05$). However, urinary and serum C-peptide levels, serum lipids, and Lp(a) levels were comparable in the two groups. Multiple logistic regression analysis indicated that a history of smoking (odds ratio 3.70, $P = 0.011$), insulin resistance (odds ratio 3.68, $P < 0.001$), and an elevated Lp(a) level (odds ratio 1.03, $P = 0.020$) were independently related to ASO. When patients with CAD were removed from the logistic regression analysis, insulin resistance was most strongly related to ASO (odds ratio 20.9, $P < 0.001$).

CONCLUSIONS — Patients with ASO were characterized by a higher prevalence of CAD, a greater percentage of smokers, a greater percentage of insulin therapy, and a higher insulin resistance than were patients without ASO. Insulin resistance, especially, may be the most powerfully related to ASO. Lp(a) may play a minor role in the development of ASO.

The development of atherosclerosis is closely associated with such risk factors as hypertension, obesity, dyslipidemia, and diabetes.

Insulin resistance with compensatory hyperinsulinemia was recently reported to be an important risk factor for the development of atherosclerosis. Four prospective studies have shown hyperinsulinemia to be an independent predictor of coronary artery disease (CAD) (1–4). In peripheral artery disease, nondiabetic patients with arteriosclerosis obliterans (ASO) and ischemic strokes were reported to have insulin resistance with compensatory hyperinsulinemia (5,6). However, compensatory hyperinsulinemia was not often seen in diabetic subjects. The serum insulin concentration is not a good marker of insulin resistance in NIDDM because of the presence of an intrinsic β-cell defect beyond the acquired β-cell defect secondary to glucose toxicity (7–9).

An evaluation of the direct measurement of insulin resistance would be useful to studying the relationship between atherosclerosis and insulin resistance in diabetic subjects. By using the short insulin tolerance test's K index (K_{ITT}), Inchiostro et al. (10) established that NIDDM patients with CAD had a higher insulin resistance than did patients without CAD. Therefore, insulin resistance per se may be an important risk factor of CAD in nondiabetic as well as in diabetic subjects. Surprisingly, the participation of insulin resistance in peripheral artery diseases such as ASO and ischemic stroke has not yet been studied in diabetic subjects. The risk factor(s) for ASO are still unclear, especially in patients with NIDDM. To clarify this situation, we evaluated insulin resistance using the K_{ITT} method, lipids, and the clinical characteristics of 100 patients with NIDDM, with and without ASO. Additionally, because lipoprotein(a) [Lp(a)] is considered to be an independent risk factor for CAD (11–13), we evaluated Lp(a) in the same patients.

RESEARCH DESIGN AND METHODS

A total of 100 patients with NIDDM, 35 with and 65 without ASO, gave their informed consent to participate in this case-control study. NIDDM was diagnosed according to World Health Organization criteria (14). Excluded from study were patients who were >75 years of age, who had heart or renal failure, liver disease, endocrine disease, or intercurrent infections, or who required bed rest. Patients who were physically trained and patients who had taken hypolipemic drugs in the previous month were also excluded. All patients were admitted to Sasebo Chuou Hospital between June 1995 and September 1996. They were fed a standard weight-maintaining diet consisting of 25–35 kcal and 1.0–1.5 g of protein per kilogram of ideal body weight; 55–60% of the total energy was given as carbohydrates. The mode of the treatment of diabetes was preserved as outpatient treatment. The study protocol was approved by the ethics committee of Sasebo Chuou Hospital.

From the Department of Internal Medicine (K.M., S.M., M.Y., Y.U., Y.T.), Sasebo Chuou Hospital, Sasebo City; and the First Department of Internal Medicine (Y.Y., S.A.), Nagasaki University School of Medicine, Nagasaki, Japan.

Address correspondence and reprint requests to Kazunari Matsumoto, MD, Department of Internal Medicine, Sasebo Chuou Hospital, 15 Yamato-chou, Sasebo City, Nagasaki 857-11, Japan.

Received for publication 18 April 1997 and accepted in revised form 17 July 1997.

Abbreviations: API, ankle pressure index; ASO, arteriosclerosis obliterans; CAD, coronary artery disease; CV, coefficient of variation; IMT, intimal-medial thickness; ITT, insulin tolerance test; K_{ITT}, short insulin tolerance test's *K* index; Lp(a), lipoprotein(a).

Diagnosis of ASO

All patients were evaluated by the ankle pressure index (API). Patients with an API >1.0 were considered not to have ASO. Patients with API <1.0 underwent angiography (digital subtraction or magnetic resonance) and plethysmography. In such evaluations, 28 patients had API <1.0, and 25 patients were diagnosed as having ASO (Fontaine's class I–III). Only three patients with API <1.0 were diagnosed as not having ASO, and they were excluded from this study. Ten other patients with ischemic gangrene or a history of bypass graft or amputation were also diagnosed as having ASO (Fontaine's class IV). After the assignment of ASO patients, we chose patients matched for age, BMI, and glycemic control (HbA_{1c} and fasting plasma glucose) who did not have ASO (API >1.0) as a control group. The clinical characteristics of all patients are presented in Table 1.

Table 1—*Clinical characteristics of NIDDM patients with and without ASO*

	ASO (+)	ASO (−)
n (M/F)	35 (25/10)	65 (39/26)
Age (year)	65.3 ± 1.3	63.4 ± 0.9
Duration of diabetes (years)	10.3 ± 1.2*	7.5 ± 0.8
BMI (kg/m²)	23.1 ± 0.4	23.0 ± 0.4
Treatment (diet/OHA/insulin)	6/12/17*	20/26/19
HbA_{1c} (%)	8.6 ± 0.4	9.2 ± 0.4
FPG (mmol/l)	7.4 ± 0.4	7.7 ± 0.3
Fasting C-peptide (nmol/l)	0.58 ± 0.04	0.50 ± 0.03
Urinary C-peptide (nmol/day)	19.7 ± 2.3	19.6 ± 1.6
Smoking	24 (68.6)†	26 (40.0)
Prevalence of hypertension	18 (51.4)	27 (41.5)
Prevalence of CAD	21 (60.0)†	11 (16.9)
Intermittent claudication	17 (48.6)†	0 (0)
Absence of foot pulse	10 (28.6)†	0 (0)
History of foot ulcer	17 (48.6)†	0 (0)

Data are *n*, means ± SE, or *n* (%). *$P < 0.05$ and †$P < 0.01$ vs. ASO (−) patients.

Diagnosis of CAD and hypertension

CAD was diagnosed by a history of previous myocardial infarction with elevated cardiac enzymes and/or echocardiography with a 12-lead electrocardiogram. When hypokinesis of the cardiac wall and/or ST-T abnormalities in the electrocardiogram were found, those patients underwent coronary angiography. In the patients with ASO, 6 patients were diagnosed with CAD by a history of myocardial infarction, and 15 patients were diagnosed by angiography. In the patients without ASO, 4 patients were diagnosed with CAD by medical history, and 7 patients were diagnosed by angiography. Hypertension was diagnosed by World Health Organization criteria (systolic and/or diastolic blood pressure ≥160 mmHg and ≥95 mmHg) or by the administration of antihypertensive agents.

Study protocol

In principle, an insulin tolerance test (ITT) was performed within 2 weeks of admission. However, the ITT was postponed in patients who required treatment for ischemic gangrene until at least 3 months after the end of treatment. Exercise levels measured by the calorie counter (Kenz, Nagoya, Japan) for patients with and without ASO were comparable (224 ± 19 vs. 242 ± 14 kcal/day, $P = 0.45$).

Starting 2 days before the ITT, each patient was asked to provide two 24-h urine samples. Urine volume was measured, and aliquots were immediately frozen at −20°C until analyzed. On the day of the ITT, oral administration of hypoglycemic agents and insulin injections were withheld. The ITT was performed after an overnight fast of 12–14 h. A butterfly needle was inserted into the antecubital vein, with patency maintained by a slow drip of saline. Baseline samples were obtained at −3 min. A bolus of regular insulin (0.1 U/kg, Humalin R; Shionogi, Osaka, Japan) was infused, and blood samples were then obtained at 3, 6, 9, 12, and 15 min. At the end of the ITT, 40 ml of a 25% glucose solution was infused over 2 min to avoid the induction of hypoglycemia.

Analytical methods

Plasma glucose was measured in duplicate with an automatic analyzer (Kyoto-Daiichi Kagaku, Kyoto, Japan) by the glucose oxidase method. Intra- and interassay coefficients of variation (CVs) were 1.2 and 1.5%, respectively. C-peptide was measured in duplicate by use of a commercial radioimmunoassay kit (Daiichi, Tokyo, Japan). The intra- and interassay CVs were 6 and 9%, respectively. Total cholesterol and triglyceride were measured by enzymatic methods (Kokusai Shiyaku, Kobe, Japan). HDL cholesterol was determined after isolation by a precipitation method (Kyowa, Tokyo, Japan). CVs for intra- and interassay in total cholesterol, triglyceride, and HDL cholesterol were <3%. Lp(a) was measured with a commercial turbid immunoassay (TIA) kit (Daiichi, Tokyo, Japan). Intra- and interassay CVs were 5.5 and 10.4%, respectively.

K_{ITT}, an index of insulin sensitivity, was calculated from the formula $K_{ITT} = 0.693/t1/2$ (15). Plasma glucose $t1/2$ was calculated from the slope of least-square analysis of plasma glucose concentration from 3–15 min after bolus injection of insulin. K_{ITT} has been validated by comparison with a measurement of insulin sensitivity obtained by the glucose clamp method (15,16). An ITT performed with a 0.1 U/kg dose of insulin yielded reproducible results (17). The mean K_{ITT} value (± SE) for 10 normal subjects who had normal oral glucose tolerance in our hospital was 5.44 ± 0.29%/min.

Statistical analysis

Unpaired data were analyzed by the χ^2 test and the Mann-Whitney *U* test. K_{ITT} values within each Fontaine's class were analyzed by ANOVA and by a multiple-comparison test. Multiple logistic regression analysis was performed to evaluate the factors independently related to ASO. A forward stepwise logistic regression was chosen, with a cutoff level of significance of 0.05. Data are presented as means ± SE. Differences were considered statistically significant at $P < 0.05$. Data were analyzed by a Power Macintosh 7600 using the SPSS statistical package.

RESULTS

Clinical characteristics

Age, BMI, HbA_{1c}, and fasting plasma glucose were comparable in the patients with and without ASO (Table 1). However, the duration of diabetes was significantly longer in the patients with ASO than in the patients without ASO (10.3 ± 1.2 vs. 7.5 ± 0.8 years,

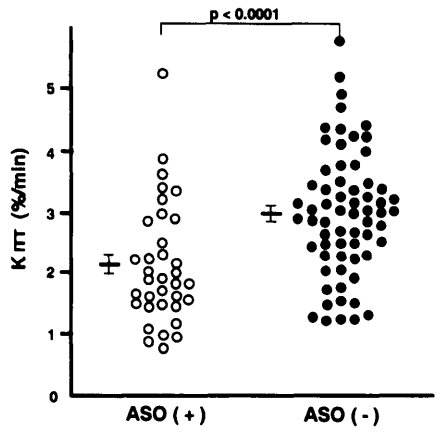

Figure 1—K_{ITT} *values in patients with (○) and without (●) ASO. The bar shows mean ± SE.*

$P < 0.05$). The percentage of patients on insulin treatment was significantly greater in the patients with ASO than in the patients without ASO (48.6 vs. 29.2%, $P < 0.05$). Fasting serum C-peptide and 24-h urinary C-peptide levels were comparable in patients with and without ASO (0.58 ± 0.04 vs. 0.50 ± 0.03 nmol/l and 19.7 ± 2.3 vs. 19.6 ± 1.6 nmol/day, respectively); therefore, neither group was considered to have the characteristics of hyperinsulinemia. The prevalence of smokers among patients with ASO was significantly higher than that among patients without ASO (68.6 vs. 40.0%, $P < 0.01$). The prevalence of CAD in patients with ASO was also significantly higher than that in patients without ASO (60.0 vs. 16.9%, $P < 0.01$). The prevalence of hypertension, however, was not statistically different in the two groups (51.4 vs. 41.5%, $P = 0.34$). Intermittent claudication, absence of foot pulse, and history of foot ulcer were found only in patients with ASO (48.6, 28.6, and 48.6%, respectively).

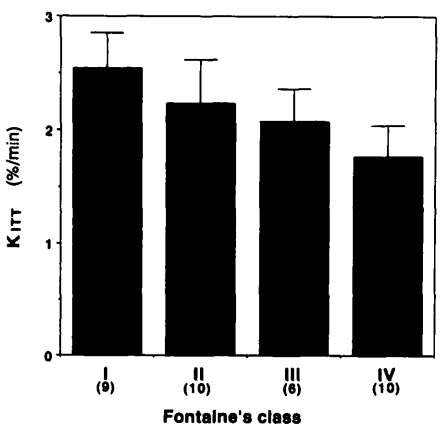

Figure 2—K_{ITT} *values in patients with ASO according to Fontaine's classification I to IV. Means ± SE are shown. Numbers in parentheses indicate number of patients.*

Table 2—*Lipid data in NIDDM patients with and without ASO*

	ASO (+)	ASO (−)
Total cholesterol (mmol/l)	4.83 ± 0.12	4.98 ± 0.11
Triglyceride (mmol/l)	1.32 ± 0.09	1.16 ± 0.05
HDL cholesterol (mmol/l)	1.10 ± 0.05	1.24 ± 0.05

Values are means ± SE.

Insulin resistance

Figure 1 shows individual K_{ITT} values in NIDDM patients with and without ASO. Patients with ASO showed significantly lower K_{ITT} values than did those without ASO (2.16 ± 0.16 vs. 3.00 ± 0.13%/min, $P < 0.0001$). Figure 2 shows the K_{ITT} values among patients with ASO according to Fontaine's classification. The K_{ITT} values in Fontaine's classes I, II, III, and IV were 2.54 ± 0.31, 2.23 ± 0.39, 2.08 ± 0.28, and 1.77 ± 0.27%/min, respectively. Insulin resistance tended to increase with the worsening of atherosclerosis, but the differences were not statistically significant by ANOVA ($F = 1.02$, $P = 0.40$).

Lipids and Lp(a)

Total cholesterol levels were comparable in patients with and without ASO (4.83 ± 0.12 vs. 4.98 ± 0.11 mmol/l, $P = 0.47$; Table 2). Triglyceride levels tended to be higher in patients with ASO than in patients without ASO, but the difference was not statistically significant (1.32 ± 0.09 vs. 1.16 ± 0.05 mmol/l, $P = 0.18$). The level of HDL cholesterol tended to be lower in patients with ASO than in those without ASO, but this difference also was not statistically significant (1.10 ± 0.05 vs. 1.24 ± 0.05 mmol/l, $P = 0.10$).

Figure 3 shows the individual Lp(a) values for NIDDM patients with and without ASO. The mean values of Lp(a) in patients with and without ASO were comparable (29.6 ± 4.0 vs. 22.7 ± 1.8 mg/dl, $P = 0.21$). The number of patients with an Lp(a) level >30 mg/dl was 12 (34.3%) in the patients with ASO and 16 (24.6%) in the patients without ASO, but this difference was not statistically significant ($P = 0.30$). Of 12 patients with an elevated Lp(a) >30 mg/dl in the ASO group, 6 had CAD, whereas only 1 of 16 patients with elevated Lp(a) in the group without ASO had CAD. Elevation of Lp(a) in patients with ASO may reflect the influence of CAD.

Multiple logistic regression analysis

To clarify whether insulin resistance may be an independent factor related to ASO, we performed a stepwise logistic regression analysis. The following independent variables were included in the model: age, duration of diabetes, BMI, HbA_{1c}, fasting plasma glucose, serum C-peptide, 24-h urinary C-peptide, total and HDL cholesterol, triglyceride, Lp(a), and K_{ITT} as continuous variables; sex, a history of smoking, prevalence of hypertension, and insulin therapy were included as categorical variables (Table 3).

Model 1 consisted of all patients (n = 100). This model found that only a history of smoking, insulin resistance (K_{ITT}), and Lp(a) were independently associated with ASO. A history of smoking was associated with a 3.70-fold increase in the odds of the presence of ASO. A 1-SD lower K_{ITT} value level was associated with a 3.68-fold increase in the odds of ASO. Similarly, a 1-SD elevation in Lp(a) level was associated with a 1.03-fold increase in the odds of ASO.

Model 2 consisted of the ASO patients and the control (without ASO) patients who did not have CAD (n = 89). This

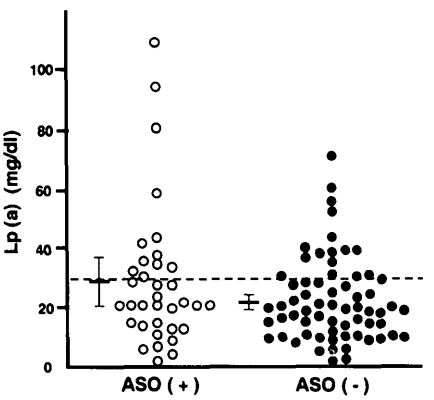

Figure 3—*Lp(a) levels in patients with (○) and without ASO (●). Dashed line indicates an Lp(a) level of 30 mg/dl. The bar shows mean ± SE.*

Table 3—*Independent factor(s) related to ASO in multiple logistic regression analysis*

	Odds ratio	95% CI	*P* value
Model 1 (*n* = 100)			
Smoking	3.70	1.04–4.35	0.011
K_{ITT}*	3.68	1.89–7.14	<0.001
Lp(a)	1.03	1.02–1.06	0.020
Model 2 (*n* = 89)			
Smoking	3.09	1.19–8.75	0.030
K_{ITT}*	2.84	1.60–5.00	<0.001
Lp(a)	1.03	1.00–1.06	0.043
Model 3 (*n* = 68)			
K_{ITT}*	20.9	3.84 –09.9	<0.001
Age	1.18	1.00–1.36	0.015
Lp(a)	1.08	1.02–1.14	0.004
Urinary C-peptide	1.07	1.00–1.15	0.042

Model 1 consisted of all patients. Model 2 consisted of the ASO patients and of the control patients who did not have CAD. Model 3 consisted of the ASO patients who did not have CAD and control patients who did not have CAD. *The negative of the K_{ITT} values were used in this analysis because K_{ITT} and ASO show inverse relationship.

model could remove the effects associated with CAD from control patients. Model 2 also indicated that smoking and insulin resistance were strongly associated with ASO (odds ratios were 3.09 and 2.84, respectively). Lp(a) also had a weak but significant relationship to ASO (odds ratio 1.03).

Model 3 consisted of the ASO patients without CAD and the control patients without CAD (*n* = 68). This model could remove the effects associated with CAD from all study patients. Model 3 indicated that insulin resistance, age, Lp(a), and urinary C-peptide were independently related to ASO. Insulin resistance, in particular, was associated with a 20.9-fold increase in the odds of ASO. Higher age and higher levels of Lp(a) and urinary C-peptide had weak but independent relationships to ASO (odds ratios were 1.18, 1.08, and 1.07, respectively). In model 3, a history of smoking was no longer independently related to ASO (*P* = 0.56).

CONCLUSIONS — The development of atherosclerosis has been linked to many conditions, such as metabolic disorders, altered hemodynamics, and the immune process (18–21). The presence of insulin resistance with compensatory hyperinsulinemia is thought by some to promote atherosclerosis. However, the severity of insulin resistance is clearly not parallel to insulin or C-peptide concentration in patients with NIDDM (22,23). Direct measurement of insulin sensitivity is required in patients with NIDDM. Only one study has demonstrated higher insulin resistance in NIDDM patients with CAD than in subjects without CAD (10). To our knowledge, the severity of insulin resistance in NIDDM patients with peripheral artery disease has not yet been studied. In the present study, we demonstrated that higher insulin resistance was present in NIDDM patients with ASO, and we showed by multiple logistic regression analysis that insulin resistance was independently related to ASO. NIDDM patients with and without ASO had been carefully matched for age, BMI, and glycemic control levels (HbA_{1c} and fasting plasma glucose), because these factors can affect insulin resistance (7,9,24,25). Furthermore, insulin secretion, as measured by urinary C-peptide and fasting serum C-peptide levels, was comparable in the NIDDM patients with and without ASO. Therefore, insulin resistance, rather than insulin, may be the important factor related to ASO in NIDDM. The Insulin Resistance and Atherosclerosis Study (IRAS) Group reported that insulin resistance, as measured by Bergman's minimal model (26,27), is closely related to atherosclerosis of the carotid artery, but measurements of serum insulin have failed to document a significant relationship (28). In the IRAS study, intimal-medial thickness (IMT), as measured by ultrasound imaging, was used as an index of atherosclerosis. There is no evidence, however, that changes in carotid IMT parallel similar changes in the coronary arteries (29). Even though a relationship between IMT and CAD is not evident, Laakso et al. (5) measured the IMT of femoral arteries and demonstrated a significant relationship between IMT and insulin resistance in nondiabetic subjects. These results suggest that insulin resistance may be closely related to CAD as well as to ASO. Additionally, monkeys with streptozotocin-induced insulinopenic, but insulin-resistant, diabetes have developed atherosclerosis (30). Therefore, insulin resistance, rather than hyperinsulinemia, may be the key factor that is related to atherosclerosis.

In our study, despite the evidence of greater insulin resistance in patients with ASO, glycemic control and intrinsic insulin secretion were similar to those of the patients without ASO. A possible reason for these curious results may be the difference in the mode of the treatment. Patients with ASO had a significantly greater percentage of insulin treatment. Therefore, we suggest that exogenous insulin may play a important role in the similar glycemic control in the two groups.

Smoking is significantly related to ASO in our study. However, when patients with CAD were removed from multiple logistic regression analysis, smoking was no longer independently related to ASO. Lehto et al. (31) reported that smoking could not predict the lower-extremity amputations in NIDDM patients. Therefore, smoking may be more relevant to CAD than to ASO. Smoking is reported to affect insulin resistance. Facchini et al. (32) have reported that smokers show insulin resistance with compensatory hyperinsulinemia. We suggest that insulin resistance may be common in patients with ASO and CAD, and that smoking may affect insulin resistance in part.

Although the significance of Lp(a) in CAD is controversial, Lp(a) is thought to be an independent risk factor for CAD by many investigators (33–36). James et al. (13), who studied large numbers of diabetic patients, demonstrated that Lp(a) levels >30 mg/dl were independently related to CAD but were not significantly related to such peripheral vascular diseases as ASO and ischemic stroke (13). The logistic regression model used in that study did not indicate the significance of Lp(a) in diabetic patients with peripheral vascular disease (13). In our study, Lp(a) levels were comparable in NIDDM patients with and without ASO, but they showed weak relationship in multiple logistic regression analysis. Based on the results of James et al. and the present study, we suggest that Lp(a)

may play a minor role in the development of ASO. The atherogenicity of Lp(a) may be specifically related to the coronary artery.

The serum lipid levels were comparable in NIDDM patients with and without ASO in our case-control study. It has been shown now, in various studies, that triglyceride and LDL and HDL cholesterol levels had a significant power toward atherosclerosis (4,10,18,19). The reason for this difference is unknown. However, a few possible explanations are as follows. First, we excluded the patients who had taken hypolipemic drugs in the month before this study. Second, the diabetes of the patients in this study was treated by diet, oral hypoglycemic agents, or insulin. Dyslipidemia due to diabetes is often improved by glycemic control only. Third, our study patients were not obese. It is well known that lipid abnormality is relevant to obesity (37). In a prospective study, Lehto et al. (31) failed to demonstrate the significance of lipid levels in NIDDM patients who had lower-extremity amputations. Furthermore, Laakso et al. (5) also failed to demonstrate the significance of lipid levels in their case-control study of ASO. Therefore, lipid levels may play a minor role in the development of ASO.

Our study has some limitations. First, our exclusion criterion for ASO was based on the API. Patients with API >1.0 were considered not to have ASO, and they did not undergo angiography or plethysmography. Therefore, it is possible that some individuals with ASO were misdiagnosed as being without ASO. According to Yao (38), few individuals with ASO have an API >1.0, so we believe that an incorrect diagnosis was unlikely in this study. Second, the relationship between insulin resistance and ASO was estimated by a cross-sectional method, so we could not demonstrate any direct and time-dependent causal effects of insulin resistance on the development of ASO. It is important to confirm these cross-sectional relationships in a prospective study.

In conclusion, we characterized patients with NIDDM and ASO as having a longer duration of diabetes, a higher incidence of smoking, a higher prevalence of CAD, a greater percentage of insulin therapy, and a more severe insulin resistance than patients without ASO. Smoking, insulin resistance, and Lp(a) were independently related to ASO. When patients with CAD were removed, insulin resistance was the most powerfully related to ASO. However, to confirm any relationship between insulin resistance and development of atherosclerotic disease in NIDDM, prospective studies are needed in a population of NIDDM patients initially free from ASO.

Acknowledgments — The authors thank Drs. H. Yamasaki and H. Takino, First Department of Internal Medicine, Nagasaki University School of Medicine, for helpful advice. The authors also thank Drs. T. Yamada and H. Yamaguchi, Department of Cardiovascular Surgery, Sasebo Chuou Hospital, for expert technical assistance.

References

1. Pyörälä K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care* 2:131–141, 1979
2. Welborn TA, Wearne K: Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentration. *Diabetes Care* 2:154–160, 1979
3. Ducimetiere P, Eschwege E, Papoz L, Richard JL, Claude JR, Rosselin G: Relationship of plasma insulin level to the incidence of myocardial infarction and coronary heart disease mortality in middle-aged population. *Diabetologia* 19:205–210, 1980
4. Despres JP, Lamaeche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ: Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 334:952–957, 1996
5. Laakso M, Sarlund H, Salonen R, Suhonen M, Pyörälä K, Salonen JT, Karhapaa P: Asymptomatic atherosclerosis and insulin resistance. *Arterioscler Thromb* 11:1068–1076, 1991
6. Shinozaki K, Naritomi H, Shimizu T, Suzuki M, Ikebuchi M, Sawada T, Harano Y: Role of insulin resistance associated with compensatory hyperinsulinemia in ischemic stroke. *Stroke* 27:37–43, 1996
7. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. *Diabetes Care* 13:610–630, 1990
8. Matsumoto K, Akazawa S, Abiru N, Yano M, Ishibashi M, Uotani S, Matsuo H, Kawasaki E, Yamasaki H, Yamamoto H, Yamaguchi Y, Nagataki S: Insulin response after treatment depends on fasting plasma glucose level in NIDDM. *Diabetes Res Clin Pract* 26:129–135, 1994
9. Ludvik B, Nolan JJ, Baloga J, Sacks D, Olefsky J: Effect of obesity on insulin resistance in normal subjects and patients with NIDDM. *Diabetes* 44:1121–1125, 1995
10. Inchiostro S, Bertoli G, Zanette G, Donadon V: Evidence of higher insulin resistance in NIDDM patients with ischemic heart disease. *Diabetologia* 37:597–603, 1994
11. Utermann G: The mysteries of lipoprotein (a). *Science* 246:904–910, 1989
12. Scanu AM, Fless GM: Lipoprotein (a): heterogeneity and biological relevance. *J Clin Invest* 85:1709–1715, 1990
13. James RW, Boemi M, Sirolla C, Amadio L, Fumelli P, Pometta D: Lipoprotein (a) and vascular disease in diabetic patients. *Diabetologia* 38:711–714, 1995
14. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group.* Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
15. Bonora E, Moghetti P, Zancanaro C, Cigolini M, Querena M, Cacciatori V, Corgnati A, Muggeo M: Estimates of in vivo insulin action in man: Comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies. *J Clin Endocrinol Metab* 68:374–378, 1989
16. Akinmokun A, Selby PL, Ramaiya K, Alberti KGMM: The short insulin tolerance test for determination of insulin sensitivity: a comparison with the euglycemic clamp. *Diabet Med* 9:432–437, 1992
17. Young RP, Critchley JAJH, Anderson PJ, Lau MS, Lee KK, Chan JC: The short insulin tolerance test: feasibility study using venous sampling. *Diabet Med* 13:429–433, 1996
18. DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dislipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
19. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
20. Ross R, Agius L: The process of atherogenesis: cellular and molecular interaction: from experimental animal models to humans. *Diabetologia* 35 (Suppl. 2):S34–S40, 1992
21. Uno H, Ueki Y, Murashima J, Miyake S, Tominaga Y, Eguchi K, Yano K: Removal of LDL from plasma by adsorption reduces adhesion molecules on mononuclear cells in patients with arteriosclerotic obliterans. *Atherosclerosis* 116:93–102, 1995
22. Laakso M: How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 137:959–965, 1993
23. DeFronzo RA: The triumvirate: β-cell, muscle, liver. *Diabetes* 37:667–687, 1988
24. Chen M, Bergman RN, Pacini G, Porte D: Pathogenesis of age-related glucose intolerance in man: insulin resistance and decreased β-cell function. *J Clin Endocrinol Metab* 60:13–20, 1985
25. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG: The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. *Diabetes* 34:222–234, 1985
26. Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensi-

tivity. *Am J Physiol* 236:E667–E677, 1979
27. Bergman RN: Toward physiological understanding of glucose tolerance: minimal model approach. *Diabetes* 38:1512–1527, 1989
28. Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R: Insulin sensitivity and atherosclerosis. *Circulation* 93:1809–1817, 1996
29. Taegtmeyer H: Insulin resistance and atherosclerosis: common roots for two common diseases? *Circulation* 93:1777–1779, 1996
30. Harano Y, Kojima H, Kosugi K, Suzuki M, Harada M, Nakano T, Hidaka H, Kashiwagi A, Torii R, Taniguchi Y, Nishimori T, Yasuda Y, Shigeta Y: Hyperlipidemia and atherosclerosis in experimental insulinopenic diabetic monkeys. *Diabetes Res Clin Pract* 16:163–173, 1992
31. Lehto S, Rönnemaa T, Pyörälä K, Laakso M: Risk factors predicting lower extremity amputations in patients with NIDDM. *Diabetes Care* 19:607–612, 1996
32. Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD, Reaven GM: Insulin resistance and cigarette smoking. *Lancet* 339:1128–1130, 1992
33. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL: Lp(a) lipoprotein as a risk factor for myocardial infarction. *JAMA* 256:2540–2544, 1986
34. Durrington PN, Ishola M, Arrol S, Bhatgnar D: Apolipoprotein (a), AI and B and parental history in men with early onset ischemic heart disease. *Lancet* i:1070–1073, 1988
35. Seed M, Hoppichler F, Reaveley D, McCarthy S, Thompson GR, Boerwinkle E, Utermann G: Relation of serum lipoprotein (a) and apolipoprotein (a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N Engl J Med* 322:1494–1499, 1990
36. Schaeffer EJ, Fava SL, Jenner JL, McNamura JR, Ordovas JM, Davis CE, Abolafia JM, Lippel K, Levy RI: Lipoprotein (a) levels and risk of coronary heart disease in men: the Lipid Research Clinics Coronary Primary Prevention Trial. *JAMA* 271:999–1003, 1994
37. Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, Superko HR, Fortmann SP, Albers JJ, Vranizan KM, Ellsworth NM, Terry RB, Haskell WL: Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med* 319:1173–1179, 1988
38. Yao JST: Haemodynamic studies in peripheral arterial disease. *Br J Surg* 57:761–766, 1970