# Original Article

# Development and Progression of Atherosclerotic Disease in Relation to Insulin Resistance and Hyperinsulinemia

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It is unclear whether the role of insulin resistance in the development of atherosclerotic cardiovascular disease is similar in populations in which the incidence of atherosclerotic diseases significantly differs from that in Western countries. The aim of this study was to determine the relationship between insulin resistance and the development of cardiovascular disease in the Japanese population. We conducted 75 g-oral glucose tolerance tests (OGTTs) on 1,928 inhabitants of two towns in Hokkaido, Japan. Subjects using antihypertensive agents and known diabetic patients were excluded from the study. Data from the remaining 1,227 subjects (540 males and 687 females; mean age 56.0 ± 10.8 years) were used for the analysis, and 1,051 subjects were seen in a follow-up care setting for a period of 8 years. The presence of insulin resistance was defined according to the guidelines reported our previous study: insulin levels of 64.0 mU/l or higher 2 h after the 75 g-OGTT. The insulin-resistant (IR) group had several risk factors such as hypertension, diabetes, treated or untreated hypercholesterolemia, hypertriglyceridemia, low high-density-lipoprotein (HDL) cholesterol levels, and obesity. During the follow-up period of 8 years, the incidence of coronary artery disease, which was adjusted for age, body mass index, sex, systolic blood pressure, fasting plasma glucose, total cholesterol, triglyceride, and HDL cholesterol was significantly (3.2 times) higher in the IR group than in the insulin non-resistant group. The results suggested that insulin resistance is an independent risk factor for coronary artery disease in Japanese subjects, as has also been demonstrated in the case of individuals in Europe and USA. (Hypertens Res 2005; 28: 665-670)

Key Words: insulin resistance, cardiovascular disease, risk factors

### Introduction

The incidence of cardiovascular disease is high in patients with multiple risk factor syndrome (or metabolic syndrome). Although the criteria for the diagnosis of multiple risk factor syndrome have not been standardized, there is a consensus that insulin resistance is an important factor underlying the association of this syndrome with atherosclerotic cardiovascular diseases. Insulin resistance is known to cause multiple pro-atherosclerotic effects on the hemostatic system as well

as on vascular endothelial function (1, 2). Furthermore, several studies using meta-analysis have indicated that hyperinsulinemia is associated with various atherosclerotic cardiovascular diseases, including the coronary artery disease (3-7). However, the incidence of atherosclerotic vascular diseases differs among different races; epidemiological studies conducted to date have revealed racial differences in the relationship between insulin resistance and atherosclerotic diseases (8, 9). No study has yet been conducted to clarify the impact of insulin resistance on the development and progress of atherosclerotic cardiovascular disease in the general Japa-

**Table 1. Baseline Characteristics** 

	Male	Female
Age (year)	57.2±11.3	55.1±10.3
BMI (kg/m <sup>2</sup> )	$23.2 \pm 3.0$	$23.3 \pm 2.9$
SBP (mmHg)	$125.2 \pm 15.8$	$123.3 \pm 16.5$
DBP (mmHg)	$75.4 \pm 9.0$	$73.4 \pm 9.0$
FPG (mg/dl)	$89.9 \pm 12.0$	$87.3 \pm 10.9$
TC (mg/dl)	$184.3 \pm 30.2$	196.3±34.6
TG (mg/dl)	$148.0 \pm 110.4$	111.1±62.9
HDL-C (mg/dl)	$52.6 \pm 14.0$	57.7±13.2

Values are expressed as means±SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density-lipoprotein cholesterol.

nese population.

In the present study, we aimed to determine the relationship of insulin resistance with established risk factors and with the incidence of cardiovascular events in the general Japanese population. We performed mass screening examinations, including a 75 g-oral glucose tolerance test (OGTT), for the inhabitants of two towns in Hokkaido, Japan, and followed these individuals for 8 years for cardiovascular events and mortality. Insulin resistance was diagnosed on the basis of blood insulin levels 2 h after administration of the 75 g-OGTT, according to the methods described in our previous study (10).

The present results support the hypothesis that insulin resistance is an important independent risk factor in coronary artery disease and its occurrence in the Japanese population.

#### Methods

# Study Subjects

The subjects of this study were 2,138 inhabitants of two towns in Hokkaido, who participated in a health examination program in 1991 and 1992 (9). The subjects inhabited a largely agricultural area. Subjects using anti-hypertensive agents and those undergoing medical treatment for diabetics were excluded from the analysis, because these morbid states exert an effect on insulin resistance. Data obtained from the remaining 1,227 subjects (540 males and 687 females; mean age 56.0±10.8 years) were used for analysis.

#### **Parameters**

Blood samples were obtained from the subjects in the early morning after an overnight fast, and the following factors were measured: fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG) and high-density-lipoprotein (HDL) cholesterol levels, and blood pressure (systolic and diastolic blood pressure [i.e., SBP and DBP]), which was

measured twice with the subject in a sitting position after a 5-min rest to calculate the mean blood pressure. A 75 g-OGTT was then performed on each subject to determine the blood insulin level 2 h after administration of the test (120 IRI). The cutoff point of 120 IRI≥64.0 mU/l was used to determine insulin resistance according to the report by Oimatsu *et al.* (10).

The following definitions of risk factors and cardiovascular diseases were employed: obesity was defined as a body mass index (BMI) of 25 kg/m<sup>2</sup> or higher (11) and according to the criteria of JNC-VI of the International Hypertension Society, hypertension was defined as a SBP of 140 mmHg or higher, or a DBP of 90 mmHg or higher (12). The 1997 criteria of the American Diabetes Society was used for the diagnosis of diabetes mellitus, namely, a FPG level of 126 mg/dl or higher, or a plasma glucose level 2 h after the administration of the 75 g-OGTT of 200 mg/dl or higher (13). Hypercholesterolemia was defined as a plasma cholesterol level of 220 mg/dl or higher. Hypertriglyceridemia was defined as plasma TG levels of 150 mg/dl or higher, and low HDL cholesterol was defined as blood HDL cholesterol levels of less than 40 mg/dl (14). Coronary artery disease was defined as myocardial infarction or angina pectoris. Cerebral vascular disease was defined as cerebral infarction or cerebral hemorrhage. We excluded subjects with subarachnoid hemorrhage and unclassified stroke from the analysis. Public health nurses, who were continuously engaged in local public health services, performed the follow-up examinations. The diagnosis of cases involving morbidity was confirmed by answers to questionnaires mailed to the doctors in charge of the cases in hospitals or in outpatient clinics, and electrocardiographies and brain CT scans were also reviewed in as many cases as possible. The nurses checked the death certificates in cases of mortality.

The present study was carried out in accordance with the Declaration of Helsinki (1981) of the World Medical Association, and the study protocol was approved by the Research Committee of Sapporo Medical University, Sapporo. Informed, written consent was obtained from all subjects after they had been provided with a complete explanation of the purpose, nature, and risks of all procedures used.

The data are shown as mean  $\pm$ SD. An unpaired t-test was used to test the differences between mean values in the two groups, and a p value of less than 0.05 was considered statistically significant. TG values were logarithmically transformed before the analysis. A simple correlation analysis was applied to test the relationship between the onset of disease and insulin resistance using a significance level of p<0.05. The  $\chi^2$  test was used to examine the relationship between insulin resistance and risk factors for atherosclerosis. Because there were significant differences in age between the insulin non-resistant (NR) group and the insulin-resistant (IR) group, we used the Mantel-Haenszel test to assess differences in the onset of cardiovascular disease and insulin resistance. Multiple logistic regression analysis was used to test the relation-

Table 2.	Baseline	Characteristics	in the	NR	Group	and	the IR	Group

		Male			Female		
	NR group	IR group	p-value	NR group	IR group	p-value	
Age (year)	57.1±11.4	58.8±10.1	0.381	54.9±10.3	58.5±9.4	0.041	
BMI (kg/m <sup>2</sup> )	$23.0\pm2.8$	$26.7 \pm 2.8$	< 0.001	$23.1 \pm 2.8$	$26.4 \pm 2.6$	< 0.001	
SBP (mmHg)	$125 \pm 15.7$	$128.4 \pm 17.0$	< 0.001	$122.6 \pm 16.2$	$137.7 \pm 15.6$	< 0.001	
DBP (mmHg)	$75.2 \pm 9.2$	$78.4 \pm 6.4$	0.008	$73.1 \pm 8.9$	$79.1 \pm 9.1$	< 0.001	
FPG (mg/dl)	$89.6 \pm 11.9$	$94.8 \pm 12.9$	0.011	$87.1 \pm 11.0$	$91.8 \pm 7.0$	< 0.001	
TC (mg/dl)	183.4±29.3	196.5±38.6	0.049	$195.3 \pm 34.2$	$214.3 \pm 37.3$	0.002	
log TG (mg/dl)	$4.788 \pm 0.528$	$5.056 \pm 0.528$	0.659	$4.578 \pm 0.428$	$5.008 \pm 0.537$	< 0.001	
HDL-C (mg/dl)	$52.9 \pm 13.9$	$48.4 \pm 14.6$	0.074	$58.0 \pm 13.2$	$51.4 \pm 13.2$	0.004	

Values are means ±SD. NR, insulin non-resistant; IR, insulin-resistant; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density-lipoprotein cholesterol.

Table 3. Frequency of Each Risk Factor in the IR Group and the NR Group

	NR group	IR group	p-value
Number	1,155	72	
Obesity (%)	24.1	74.6	< 0.001
Hypertension (%)	18.0	33.8	0.002
Diabetes mellitus (%)	1.0	5.6	0.012
High total cholesterol (%)	19.0	36.1	0.001
High triglyceride (%)	22.8	44.4	< 0.001
Low high-density-lipoprotein cholesterol (%)	12.9	29.6	< 0.001

Values are expressed as %. NR, insulin non-resistant; IR, insulin-resistant.

ship between the onset of cardiovascular disease and insulin resistance and/or other risk factors. The commercially available statistical package SPSS Version 12.0J was used for the statistical analyses.

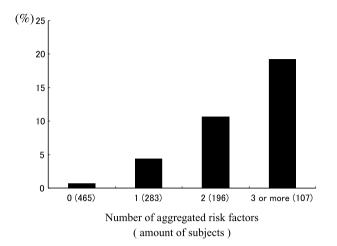
#### Results

A cross-sectional investigation was conducted in the first year of the current study. The baseline characteristics of subjects of each gender are shown in Table 1. As regards risk factors, the levels of the following factors were higher in men than in women: age, FPG, DBP, and TG. On the other hand, TC and HDL cholesterol levels were higher in women. There were no significant gender-related differences in SBP. The subjects were divided into an NR group (control group) and an IR group. In the IR group, 6.5% of the subjects were males and 4.4% were females. Among males, the IR group had significantly higher BMI, SBP, DBP, FPG, and TC values than the NR group. However, no significant difference was observed in terms of age, log TG, or HDL cholesterol between the two groups. Among females, the IR group had significantly higher age, BMI, SBP, DBP, FPG, TC, and log TG values than the NR group. Moreover, females in the IR group had lower HDL cholesterol levels than the NR group (Table 2). The prevalence of female or male subjects with obesity, hypertension, diabetes, or abnormalities in plasma lipid levels were significantly higher in the IR group than in the NR group (Table 3).

The association between insulin resistance and the aggregation of risk factors is shown in Fig. 1. The prevalence of insulin resistance (0.7, 4.4, 10.6, and 19.2%: p<0.001) was found to increase with the number of risk factors present (0, 1, 2, and 3 or more). In addition, 70.2% of the subjects in the IR group had two or more risk factors, whereas 70.6% of the subjects in the NR group had none or only one risk factor (data not shown).

During the follow-up period, coronary artery diseases developed in 43 subjects (acute myocardial infarction in 15 subjects and angina pectoris in 28 subjects), and cerebral vascular accidents occurred in 15 subjects (cerebral infarction in 11 subjects and cerebral hemorrhage in four subjects). The incidence of coronary artery disease in the IR group (16.1%) was significantly higher than that in the NR group (3.4%), but no significant difference was found between these two groups in terms of the incidence of cerebral vascular disease (3.6 vs. 1.3%, p=0.188) (Table 4).

Table 5 shows the results of the multiple logistic analyses of the determinants of coronary artery disease-associated morbidity during an 8-year follow-up period. The IR group had a 3.2-fold higher incidence of coronary artery disease than the NR group, even after corrections were made for age, gender, BMI, SBP, FPG, and TC. SBP, age, and sex were also shown to be significant risk factors in the present dataset.



**Fig. 1.** Percentages of IR and NR subjects according to the aggregation of risk factors. The percentage of IR subjects tended to be higher than that of NR subjects with respect to an increasing number of risk factors. Risk factors: obesity, hypertension, diabetes mellitus, high total cholesterol, high triglyceride, low high-density-lipoprotein cholesterol.

# **Discussion**

It is known that the following are potential markers of insulin resistance: the product of insulin levels and plasma glucose levels, as determined by the 75 g-OGTT (Σ BS/IRI, sum of the 0–120 min values), and the fasting insulin and FPG levels (HOMA values; 104/Ip×Gp, where Gp and Ip are maximum blood glucose level and maximum insulin level, respectively). A cutoff point of IRI≥64.0 mU/l at 120 min after the administration of the 75 g-OGTT was used as a marker of insulin resistance in the present study. This cutoff point has been demonstrated as a valid marker of insulin resistance, as the insulin level observed 120 min after glucose loading in the context of the 75 g-OGTT is known to correlate negatively with the M value obtained by the glucose clamp method, thus indicating that insulin secretion has been maintained (10). Age, gender, and medication potentially exert effects on insulin sensitivity, and diuretic agents,  $\alpha$  and  $\beta$  blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors have been shown to affect insulin resistance. However, since the subjects of the present study were primarily inhabitants of rural communities (excluding those subjects administered anti-hypertensive agents and diabetes medications), it is expected that the above factors had only limited effects on the results. The findings of the above mentioned meta-analysis revealed that the fasting insulin level or a cutoff value in the 80th percentile could be used for the determination of insulin resistance. According to the criteria for diagnosis used in the present study, 5.3% of the subjects suffered from insulin resistance. However, the criteria used in our study were stricter than those used in the studies conducted in Western countries, and it is therefore difficult to draw conclusions

regarding differences in the effects of insulin resistance on the development of coronary artery disease in the Western samples.

Zavaroni et al. examined subjects living in a workers' community; in that study, a glucose intolerant non-obese group suffering from hyperinsulinemia was compared to a group with normal insulin levels, and the results showed that before the onset of diabetes, the former group had higher levels of TG, low-density-lipoprotein (LDL) cholesterol, and blood pressure, as well as a higher incidence of coronary artery disease, than the latter group (15). Moreover, on the basis of the results of a follow-up study carried out over a period of 8 years, the San Antonio Heart Study revealed associations between fasting hyperinsulinemia and the onset of diabetes, low HDL cholesterol, and hypertension (16). It has also been reported that subjects with multiple risk factors had significantly higher fasting insulin levels than did those presenting with only a single risk factor. The results of the cross-sectional investigation in the first year of the present study showed that in the IR group, the incidence of hypertension, diabetes, and abnormal lipid metabolism was significantly higher than that in the NR group. The present results also suggested that insulin resistance is associated with atherosclerotic risk factors and also with the accumulation of these risk factors. These results are thus consistent with the findings of recent studies conducted in Western countries.

Several studies have been conducted to investigate the relationship between insulin resistance and the onset of coronary artery disease; differences between such studies were considered in terms of baseline characteristics such as age, male-tofemale ratio, drug usage, and length of follow-up period, as well as in terms of the criteria used for the diagnosis of insulin resistance by determination of the insulin level. Ruige et al. carried out a meta-analysis of 17 past major epidemiological studies in Western countries, and they showed that insulin resistance and hyperinsulinemia are independent risk factors in ischemic heart disease, and that race influences the relationship between the onset of coronary artery disease and insulin resistance (7). Racial differences have been shown to exist in the relationship between insulin resistance and atherosclerotic diseases. The IRAS study showed that the progression of atherosclerosis differs among races (17). Pima Indians, who have high insulin resistance, have a low incidence of coronary artery disease (8). A comparison of Japanese and Western samples revealed that the latter group had the capacity to secrete more insulin, and most of the Japanese diabetes patients studied did not have hyperinsulinemia (18). In Westerners, pancreatic insulin secretion function is maintained after the onset of type II diabetes. The condition of diabetes associated with hyperinsulinemia and insulin resistance differs greatly from that observed among Japanese. The results of our follow-up study of Japanese subjects showed that a significant relationship existed between insulin resistance and the incidence of coronary artery disease, even after the correction of risk factors for atherosclerosis, such as age,

	NR group	IR group	Odds ratio	p-value
Follow up	995	56		
Coronary artery disease	34	9	5.4 (4.6*)	<0.001 (<0.001*)
(Morbidity (%))	(3.4)	(16.1)		
Stroke	13	2	2.8 (2.1*)	0.188 (0.348*)

(3.6)

Table 4. Cardiovascular Event in the IR Group and the NR Group

(1.3)Values are expressed as % or number. NR, insulin non-resistant; IR, insulin-resistant. \*Adjusted for age.

Table 5. Multiple Logistic Analysis for Coronary Artery **Disease Morbidity** 

(Morbidity (%))

Odds ratio	95.0% CI	p-value
3.203	1.260-8.142	0.014
1.023	1.004-1.042	0.020
1.040	1.003 - 1.077	0.033
1.976	0.995-3.925	0.052
1.006	0.966 - 1.016	0.234
0.991	0.996-1.016	0.458
0.999	0.995 - 1.003	0.611
0.994	0.963 - 1.026	0.709
1.015	0.903-1.141	0.801
	3.203 1.023 1.040 1.976 1.006 0.991 0.999 0.994	3.203 1.260-8.142 1.023 1.004-1.042 1.040 1.003-1.077 1.976 0.995-3.925 1.006 0.966-1.016 0.991 0.996-1.016 0.999 0.995-1.003 0.994 0.963-1.026

Independent variables: coronary artery disease morbidity. Dependent variables: insulin resistance (IR/NR), age, sex, BMI, SBP, FPG, TC, TG, HDL-C. Odds ratios for continuous risk factors expressed for single value higher. NR, insulin non-resistant; IR, insulin-resistant; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, highdensity-lipoprotein cholesterol.

gender, blood pressure, blood glucose, and total cholesterol. Insulin resistance causes atherosclerosis by giving rise to risk factors for atherosclerosis. Moreover, insulin itself directly promotes atherosclerosis. Insulin resistance is classified as decreased tissue sensitivity to insulin or compensatory hyperinsulinemia. The pathological states caused by low insulin sensitivity include glucose intolerance and lipid metabolism disorders, such as hypertriglyceridemia, elevated very lowdensity-lipoprotein cholesterol, and low HDL cholesterol. Hyperinsulinemia can cause hypertension via an increase in sympathetic nerve activity, increased renin-angiotensin activity, sodium retention in the kidneys, increased Na<sup>+</sup>/H<sup>+</sup> pump activity, activation of insulin-like growth factor (IGF) receptors, and impaired endothelium-dependent vasodilation. We believe that insulin resistance is a marked risk factor for the development of coronary artery disease, even after subtraction of the influence of other risk factors, because increased Na<sup>+</sup>/H<sup>+</sup> pump activity, IGF receptor activation, and impaired endothelium-dependent vasodilation can be direct causes of atherosclerotic disease, and because plasminogen-activatorinhibitor-1 (PAI-1) can increase blood coagulability to accelerate atherosclerosis. PAI-1 levels are known to be elevated in

patients in an insulin-resistant state. However, these pathways are known to differ among races. Nonetheless, the results of the present study indicated that insulin resistance in Japanese, as well as in Westerners, is involved in the development of coronary artery disease, independent of the other risk factors for atherosclerosis.

Our results did not show a significant correlation between insulin resistance and the incidence of stroke. However, the Helsinki Policemen Study showed that insulin resistance is a predictor not only of coronary artery disease, but also of stroke (19). In our study, only a small number of subjects experienced cerebrovascular disorders. The following potential reasons for this were considered: the mean age of the subjects included in the analysis was 56, which is otherwise associated with a relatively low prevalence of cerebrovascular disorder; patients who were under treatment for hypertension and diabetes were excluded from the study, resulting in a sample with only a low risk of cerebrovascular disorder; and mild transient ischemic attack might have been missed in the present study. Moreover, in a previous study of Japanese subjects, it was found that the percentage of subjects with insulin resistance was significantly high but only in the atherothrombotic infarction group, and not in groups with other types of cerebrovascular disorder (20).

Studies performed in Western countries have reported that insulin resistance leads to the development of hypertension, diabetes, and abnormal lipid metabolism, all of which are known to lead to the progression of atherosclerosis and the development of cardiovascular diseases. As has been noted in these reports, insulin resistance leads to hypertension in Japanese subjects (21). In the present study, we investigated the relationship between insulin resistance and the development of cardiovascular disease in Japanese subjects who had undergone a number of screening examinations. Our results demonstrated that insulin resistance is associated with the development of coronary artery disease; this finding is similar to those of studies conducted in Europe and in USA. According to the present study, the expected frequency of patients suffering from cerebral vascular disease while also having insulin resistance was low, i.e., 0.8, and therefore it was impossible to arrive at a conclusion regarding the relationship between insulin resistance and the onset of cerebral vascular disease (22). In our study, the stroke incidence was 1.4%, which was also low compared with that expected for Japanese

people in general. It is thought that the reason for this relatively low value was that we analyzed a group from which patients with a previous history of hypertension or diabetes were excluded.

The number of Japanese with risk factors for atherosclerosis (*e.g.*, hypertension, diabetes, hyperlipidemia, and obesity) has been increasing in recent years due to changes in diet and habitual exercise. The incidence of either hyperinsulinemia or insulin resistance is also believed to be increasing in Japan. Therefore, the evaluation of insulin resistance will be important in the future for the prevention of atherosclerotic disease. An investigation of changes in insulin resistance should enable the determination of the risk for atherosclerotic disease in the Japanese population, and would contribute to the elucidation of racial differences in the relationship between insulin resistance and the development of atherosclerotic disease.

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