Increased Risk Factors for Coronary Artery Disease in Japanese Subjects With Hyperinsulinemia or Glucose Intolerance

NOBUHIRO YAMADA, MD
HIDEYO YOSHINAGA, MD
NOBORU SAKURAI, MD
HITOSHI SHIMANO, MD
TAKANARI GOTODA, MD
YASUO OHASHI, PHD
YOSHIO YAZAKI, MD
KINORI KOSAKA, MD

OBJECTIVE — To understand the interrelationship of coronary artery disease (CAD) risk factors including hyperlipidemia, hypertension, and glucose intolerance to prevent and better manage this disease.

RESEARCH DESIGN AND METHODS — We performed a 100-g oral glucose tolerance test in 2,113 subjects, and we evaluated their plasma lipid levels, blood pressure (BP), and plasma glucose and plasma insulin responses.

RESULTS — Multiple regression analysis demonstrated a significant relationship of either BP, plasma triglyceride (TG), or high-density lipoprotein (HDL) cholesterol levels to plasma insulin and glucose response after the glucose load. Plasma cholesterol levels were related only to the plasma glucose response. In subjects matched for age, sex, and body mass index (BMI) with hyperinsulinemia or normoinsulinemia, the hyperinsulinemic subjects had a significantly higher mean BP and plasma TG level than the normoinsulinemic subjects (128.8/82.3 vs. 122.9/79.3 mmHg and 172.1 vs. 119.4 mg/dl), and the HDL-cholesterol level was significantly lower (43.9 vs. 47.8 mg/dl). Furthermore, subjects matched for age, sex, and BMI with glucose intolerance had a higher mean BP (128.4/81.8 vs. 123.5/78.7 mmHg) and higher plasma TG level (154.2 vs. 123.0 mg/dl) than those without glucose intolerance.

CONCLUSIONS — Based on these findings, subjects with hyperinsulinemia or glucose intolerance should be carefully managed to prevent CAD, because they have more numerous and more severe risk factors than subjects with normal plasma insulin levels or subjects without glucose intolerance.

From the 3rd Department of Internal Medicine (N.Y., H.S., T.G., Y.Y.), Department of Epidemiology (Y.O.), University of Tokyo; and Toranomon Hospital (H.Y., N.S., K.K.), Tokyo, Japan.

Address correspondence and reprint requests to Nobuhiro Yamada, MD, 3rd Department of Internal Medicine, University of Tokyo, Tokyo, Japan 113.

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CAD, coronary artery disease; HDL, high-density lipoprotein, LDL, low-density lipoprotein; BMI, body mass index; BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure; TG, triglyceride; OGTT, oral glucose tolerance test.

Patients with coronary artery disease (CAD) often have multiple risk factors including plasma lipid abnormalities, hypertension, and abnormal glucose tolerance (1–4). Recently, it has been suggested that hyperinsulinemia is related to hypertension, hypertriglyceridemia, and a low plasma high-density lipoprotein (HDL) cholesterol level, and that these risk factors may be caused by impaired insulin action (5–9). However, the relationship of glucose intolerance with coronary risk factors has not been fully understood. In the analysis of the relationship among coronary risk factors, it is important to minimize the factor of obesity, because both insulin sensitivity and glucose intolerance are significantly affected by body weight. The Japanese population has a relatively low body mass index (BMI) (22–23 kg/m^2) compared with the Caucasian population (5,8). Therefore, we analyzed a large population (n = 2,113) in Tokyo to clarify the relationship of coronary risk factors with the evaluation of glucose tolerance and insulin response after an oral glucose load. The findings provide evidence that subjects with hyperinsulinemia or glucose intolerance have higher plasma triglyceride (TG) levels, lower plasma HDL-cholesterol levels, and higher systolic blood pressure (sBP) and diastolic blood pressure (dBP) compared with subjects with normal plasma insulin levels or without glucose intolerance.

RESEARCH DESIGN AND METHODS

— We studied 2,113 subjects including 1,375 men and 738 women. These 2,113 subjects were selected from 2,631 subjects who visited Toranomon Hospital (Tokyo, Japan) for their general health examination, because they had not received any medication for diabetes, hypertension, or hyperlipidemia, had no abnormal liver or kidney functions, and had not received any operation. Toranomon Hospital is located in the center of Tokyo where we have government offices and large com-

Table 1—*Characteristics of study subjects and prevalences of hypertension, hyperinsulinemia, hypertriglyceridemia, low HDL cholesterolemia, and hypercholesterolemia*

Characteristics	
n	2,113
Sex (M/F)	1,375/738
Age (years)	53.7 ± 10.4
BMI (kg/m^2)	22.9 ± 2.9
BP (mmHg)	122 ± 18/77 ± 12
Plasma TG (mg/dl)	122 ± 84
Plasma cholesterol (mg/dl)	203 ± 37
Plasma LDL cholesterol (mg/dl)	129 ± 34
Plasma HDL cholesterol (mg/dl)	51 ± 14
Prevalences (%)	
Obesity	20.9
Hypertension	23.1
Hyperinsulinemia	11.0
Hypertriglyceridemia	24.4
Hypercholesterolemia	15.7
High LDL cholesterol	17.9
Low HDL cholesterol	23.0

Data are means ± SD.

panies; therefore, the majority of study subjects were office workers and the minority were people who live in this area. As part of their general health examination, all subjects stayed at the hospital for 2 days, and venous blood samples were drawn after a 15-h fast for analysis of the concentration of plasma TG, cholesterol, HDL cholesterol, and an oral glucose tolerance test (OGTT). Before and 30, 60, 90, 120, and 180 min after a 100-g load of oral glucose, the plasma glucose (10) and insulin (11) concentrations were determined. To evaluate plasma insulin response, a 100-g glucose rather than a 75-g glucose was loaded. Plasma TG (12), cholesterol (13), and HDL-cholesterol (14) levels were measured by enzymatic method, and the plasma insulin level was measured by radioimmunoassay.

Based on the determination of plasma insulin concentration, hyperinsulinemia (n = 233) was defined as both fasting and 2-h plasma insulin levels above the 80th percentile of respective plasma insulin distribution in study subjects after an oral glucose load (fasting level ≥11 μU/ml and post 2-h level ≥79 μU/ml), and normoinsulinemia (n = 1,442) was defined as both fasting and 2-h plasma insulin levels below the 80th percentile after an oral glucose load. Blood pressure (BP) was measured with a sphygmomanometer, with the subjects recumbent for at least 10 min. sBP ≥140 or dBP ≥90 mmHg was defined as hypertension (n = 489), sBP <130 mmHg and dBP <85 mmHg was defined as normal (n = 1,311), according to the fifth report of the National High Blood Pressure Education Program (15). Subjects with glucose intolerance (n = 408) were defined as 2-h plasma glucose levels above the 80th percentile of plasma glucose distribution in study subjects after an oral glucose load (post 2-h level ≥133 mg/dl), and other subjects were defined as nonglucose intolerant. BMI ≤21.5 and ≥25 kg/m^2 were defined as lean (n = 689) and obese (n = 441), respectively. A matched control group for the subjects with hyperinsulinemia was created by matching a subject with normoinsulinemia of similar age, sex, and BMI for each subject with hyperinsulinemia. Similarly, a matched control group consisting of age, sex, and BMI was created for the subjects with glucose intolerance.

Results were expressed as means ± SD unless otherwise stated. The unpaired Student's t test was used to compare mean group values. The multiple regression analysis was performed

Table 2—*Age, BMI, plasma lipid levels, and BP in subjects matched for age, sex, and BMI subclassed by plasma insulin levels*

	Normoinsulin	Hyperinsulin
n	216	216
Sex (F/M)	61/155	61/155
Age (years)	54.4 ± 9.9	54.4 ± 9.9
BMI (kg/m^2)	25.0 ± 2.6	25.0 ± 2.6
Lipids (mg/dl)		
TGs	119.4 ± 72.1	172.1 ± 116.9*
Cholesterol	204.4 ± 36.9	211.0 ± 39.6
LDL cholesterol	133.1 ± 34.4	135.4 ± 35.8
HDL cholesterol	47.8.1 ± 12.7	43.9 ± 11.3*
BP (mmHg)		
sBP	122.9 ± 18.1	128.8 ± 20.8†
dBP	79.3 ± 11.7	82.3 ± 13.7‡
Σ-plasma glucose (mg/dl)	711.8 ± 262.4	778.6 ± 212.4†
Σ-insulin (μU/ml)	201.3 ± 85.1	559.6 ± 200.0*

Data are means ± SD.
*$P < 0.001$.
†$P < 0.005$.
‡$P < 0.05$.

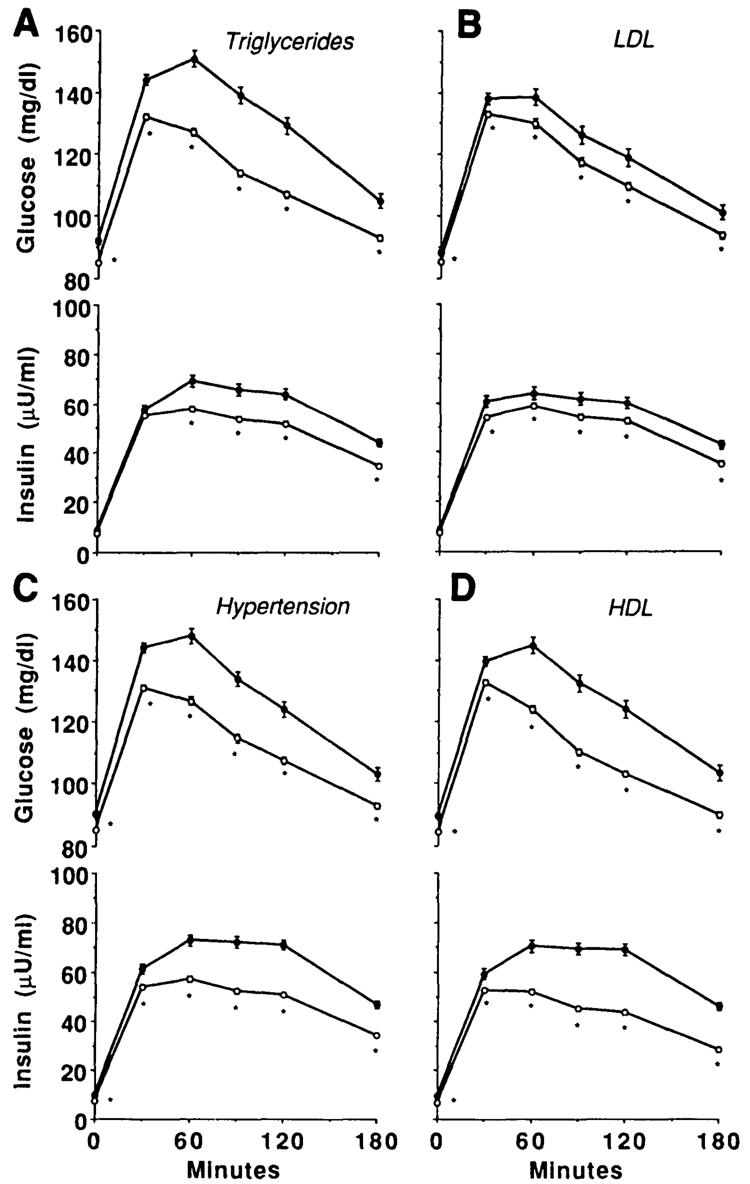

Figure 1—*Plasma glucose and insulin responses after a 100-g oral glucose load. In a panel of hypertension, hypertensive subjects (●——●, n = 489) were compared with normotensive subjects (○——○, n = 1,311). Similarly, subjects with hypertriglyceridemia (●——●, n = 516), low plasma HDL-cholesterol levels (●——●, n = 484), and high plasma LDL-cholesterol levels (●——●, n = 378) were compared with subjects with plasma TG levels <150 mg/dl (○——○, n = 1,597), plasma HDL-cholesterol levels ≥40 mg/dl (○——○, n = 1,629), and plasma LDL-cholesterol levels <130 mg/dl (○——○, n = 1,123), respectively. Values are means ± SE. *P < 0.05.*

with Statview II (version 1.02). Low-density lipoprotein (LDL) cholesterol was calculated as follows: LDL cholesterol = (cholesterol) − (HDL cholesterol) − (0.2 × TG).

RESULTS— Means ± SD in all subjects were as follows: 53.7 ± 10.4 years of age, a BMI of 22.9 ± 2.9 kg/m^2, plasma TG of 122 ± 84, cholesterol of 203 ± 37 mg/dl, LDL cholesterol of 129 ± 34 mg/dl, HDL cholesterol of 51 ± 14 mg/dl, and BP of 122 ± 18/77 ± 12 mmHg. The prevalences of hypertension, hyperinsulinemia, glucose intolerance, hypertriglyceridemia (≥150 mg/dl), hypercholesterolemia (≥240 mg/dl), high LDL cholesterolemia (≥160 mg/dl), and low HDL cholesterolemia (<40 mg/dl) in all subjects were 23.1, 11.0, 19.3, 24.4, 15.7, 17.9, and 23.0%, respectively (Table 1).

OGTT pattern in subjects with coronary risk factors

In hypertensive subjects, plasma insulin and glucose responses after an oral glucose load were much higher than in the normotensive subjects as shown in Fig. 1. Similar results were observed in hypertriglyceridemia and in low HDL cholesterolemia as shown in Fig. 1. A less significant difference was detected in the OGTT pattern between subjects with a plasma LDL-cholesterol level of ≥160 mg/dl and subjects with a plasma LDL-cholesterol level of <130 mg/dl. Hyperinsulinemic subjects were shown to be glucose intolerant compared with normoinsulinemic subjects (Fig. 2).

Coronary risk factors in subjects with hyperinsulinemia or glucose intolerance

Groups matched for age, BMI, and sex were selected from the total study subjects to analyze the relationship between hyperinsulinemia and coronary risk factors without effects of age, sex, and obesity. Hyperinsulinemic subjects in the matched group had significantly high plasma TG levels, low HDL-cholesterol levels, and high sBP and dBP levels compared with matched normoinsulinemic subjects (Table 2). No significant difference in the plasma cholesterol and LDL-cholesterol levels were found between the two groups (Table 2).

The relationship between glucose tolerance and coronary risk factors also was evaluated in age-, BMI-, and sex-matched subjects selected from all study subjects. The glucose intolerant subjects

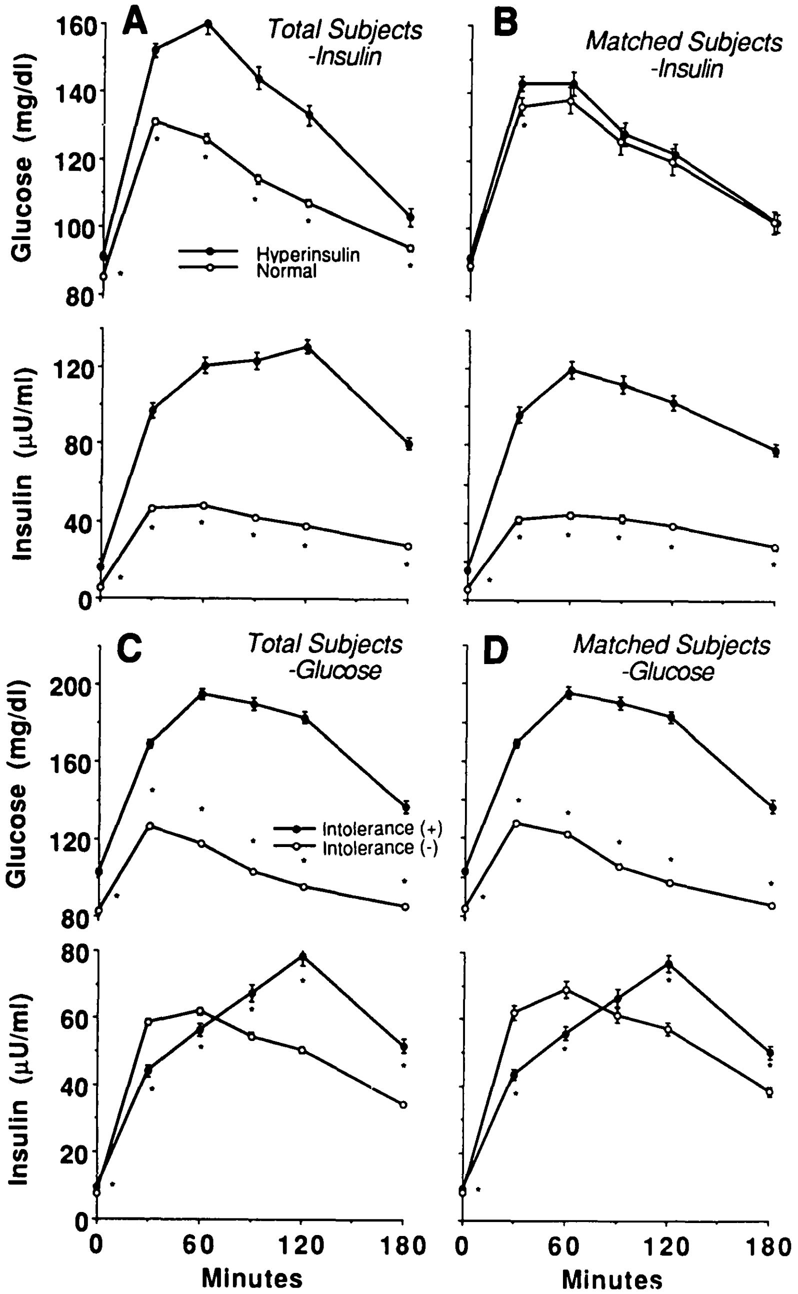

Figure 2—*Plasma glucose and insulin responses after a 100-g oral glucose load. A: Subjects with hyperinsulinemia (n = 233) and normoinsulinemia (n = 1,426) in all study subjects. B: Subjects with hyperinsulinemia (n = 216) and normoinsulinemia (n = 216) in groups matched for age, sex, and BMI. C: Glucose intolerant subjects (n = 408) and nonglucose intolerant subjects (n = 1,705) in all study subjects; D: Glucose intolerant subjects (n = 386) and nonglucose intolerant subjects (n = 386) in groups matched for age, sex, and BMI. Glucose intolerance was defined in terms of quintiles of 2-h blood glucose levels after the oral glucose load. Values are means ± SE. *P < 0.05.*

had significantly higher plasma TG levels and higher sBP and dBP levels compared with matched nonglucose intolerant subjects (Table 3). No significant difference was observed in the plasma cholesterol, LDL- and HDL-cholesterol levels between the two groups.

The relationship of the mean value of each risk factor to the Σ-insulin level or the severity of glucose intolerance was analyzed in all subjects. The magnitude of each risk factor became more severe according to the level of Σ-insulin as shown in Fig. 3. According to the severity of the glucose intolerance, all of the risk factors appeared to worsen in all subjects (Fig. 4).

Multiple regression analysis

sBP and dBP, plasma TG, cholesterol, LDL- and HDL-cholesterol levels were assigned to dependent values, and the sum of each plasma insulin level and plasma glucose level during OGTT (Σ-insulin and Σ-glucose, respectively), BMI, age, and sex were assigned to independent values (Table 4). BP, plasma TG, and HDL-cholesterol levels were significantly related to these independent variables, whereas the plasma cholesterol and LDL-cholesterol levels were not significantly related to Σ-insulin. BP was most significantly related to age and least related to Σ-insulin among variables, whereas the plasma TG and HDL-cholesterol levels were highly related to both Σ-insulin and Σ-glucose. Sex was significantly related to each risk factor for CAD as shown in Table 4. Plasma TG and BP levels were higher and plasma cholesterol, LDL-cholesterol levels, and HDL-cholesterol levels were lower in men than in women. As shown in Table 5, r^2 values of multiple regression analysis were better when both Σ-glucose and Σ-insulin were included than with Σ-glucose or Σ-insulin alone.

These relations were similar in subjects with BMI <25 kg/m^2, in subjects without glucose intolerance, and in subjects matched for age, sex, and BMI. Furthermore, we calculated the residual

Table 3—*Age, BMI, plasma lipid levels, and BP in subjects matched for age, sex, and BMI subclassed by glucose tolerance*

	Nonglucose intolerant	Glucose intolerant
n	386	386
Sex (F/M)	101/285	101/285
Age (years)	56.5 ± 9.4	56.5 ± 9.4
BMI (kg/m^2)	23.9 ± 2.9	23.9 ± 2.9
Lipids (mg/dl)		
TGs	123.0 ± 83.7	154.2 ± 103.3*
Cholesterol	205.2 ± 39.1	208.9 ± 39.0
LDL cholesterol	132.0 ± 35.8	131.7 ± 36.3
HDL cholesterol	49.6 ± 13.3	47.8 ± 14.1
BP (mmHg)		
sBP	123.5 ± 16.9	128.4 ± 19.1*
dBP	78.7 ± 11.6	81.8 ± 13.0*
Σ-plasma glucose (mg/dl)	624.1 ± 92.0	977.6 ± 301.6*
Σ-insulin (μU/ml)	296.9 ± 159.8	301.7 ± 193.1

Data are means ± SD.
*$P < 0.001$.

of Σ-insulin, Σ-glucose, BPs, plasma cholesterol, TG, HDL-cholesterol levels, and LDL-cholesterol levels by the regression of these seven factors on age, sex, and BMI to alleviate the influential factors of age, sex, and BMI. Results similar to those obtained from the multiple regression analysis were demonstrated. To know the effects of sex on the relationship between coronary risk factors and either plasma insulin or glucose response, Σ-insulin–sex and Σ-glucose–sex interactions were analyzed. We found a significant relationship only between HDL cholesterol and Σ-insulin–sex. Therefore, no significant variations by sex were observed in the relationship between coronary risk factors and either plasma insulin or glucose level, except between HDL cholesterol and Σ-insulin.

CONCLUSIONS— Data from the 100-g OGTTs of 2,113 subjects were analyzed to examine the relationship between coronary risk factors and plasma insulin response or glucose tolerance. As characteristic of the Tokyo population, these subjects have a relatively low BMI compared with the Caucasian population. The average BMI in our population was much less than that in Caucasian subjects, such as that reported by Zavaroni et al. (8) (22.9 vs. 24.7 kg/m^2), which indicates that the effects of obesity on coronary risk factors were much less in the Japanese population. Obese subjects (BMI ≥25 and ≥27 kg/m^2) in this study were 20.9 and 8.1% of total subjects, respectively.

We found that subjects with hypertriglyceridemia, a low HDL-cholesterol level, and hypertension have a relatively high insulin response and glucose intolerance after glucose load, whereas hyperinsulinemia was less significant in subjects with a high LDL-cholesterol level. These results indicate that risk factors other than plasma LDL cholesterol are significantly related to insulin resistance. To exclude the possible influence of obesity even in a population with relatively low BMI, we selected matched

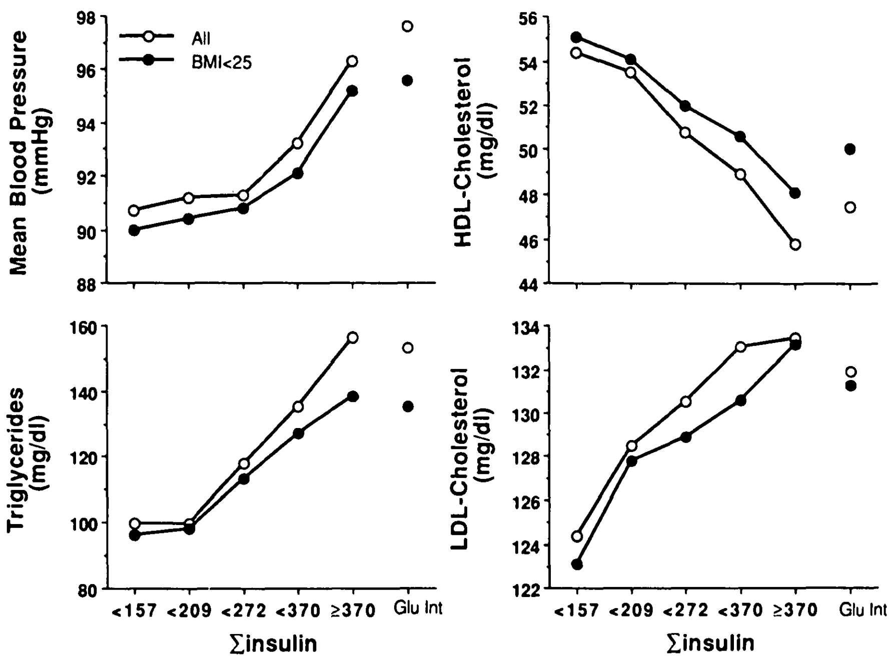

Figure 3—*Relationship of plasma insulin levels with mean BP (1/3 of sBP and 2/3 of dBP), plasma TG, HDL-cholesterol level, and LDL-cholesterol level in all subjects and in subjects with BMI <25 kg/m^2. Subjects were divided into five subgroups according to the level of Σ-insulin. Each value is the mean.*

Table 4—*Multiple regression analysis for insulin levels, BP, plasma lipids, and other relevant variables in total subjects*

Variables	*t* values	P values	Coefficient	SE
sBP				
Σ-insulin	2.92	0.004	0.007	0.002
Σ-glucose	4.98	0.001	0.009	0.002
BMI	6.81	0.001	0.895	0.131
Age	14.60	0.001	0.507	0.035
Sex	4.50	0.001	3.394	0.754
dBP				
Σ-insulin	2.45	0.014	0.004	0.002
Σ-glucose	3.97	0.001	0.005	0.001
BMI	7.35	0.001	0.684	0.093
Age	7.28	0.001	0.179	0.025
Sex	5.40	0.001	2.880	0.533
TGs				
Σ-insulin	8.15	0.001	0.091	0.011
Σ-glucose	8.73	0.001	0.070	0.008
BMI	8.46	0.001	5.201	0.615
Age	4.58	0.001	−0.743	0.162
Sex	10.62	0.001	37.429	3.524
HDL cholesterol				
Σ-insulin	4.70	0.001	−0.009	0.002
Σ-glucose	3.29	0.001	−0.004	0.001
BMI	13.88	0.001	−1.426	0.103
Age	3.91	0.001	0.106	0.027
Sex	13.19	0.001	−7.751	0.588
LDL cholesterol				
Σ-insulin	0.78	0.438	0.004	0.005
Σ-glucose	0.84	0.399	0.003	0.003
BMI	7.86	0.001	2.071	0.264
Age	8.58	0.001	0.597	0.070
Sex	8.45	0.001	−12.752	1.509
Cholesterol				
Σ-insulin	1.56	0.119	0.008	0.005
Σ-glucose	2.86	0.004	0.011	0.004
BMI	5.85	0.001	1.676	0.287
Age	7.92	0.001	0.600	0.076
Sex	8.18	0.001	−13.453	1.644

Σ-insulin, Σ-glucose, BMI, age, and sex are independent variables. sBP, dBP, TGs, HDL cholesterol, LDL cholesterol, and cholesterol are dependent variables.

Table 5—*r^2 values in each multiple regression analysis*

Variables	r^2 values
sBP	
Σ-insulin and Σ-glucose	0.165
Σ-insulin	0.155
Σ-glucose	0.161
dBP	
Σ-insulin and Σ-glucose	0.100
Σ-insulin	0.094
Σ-glucose	0.097
TGs	
Σ-insulin and Σ-glucose	0.204
Σ-insulin	0.175
Σ-glucose	0.179
HDL cholesterol	
Σ-insulin and Σ-glucose	0.231
Σ-insulin	0.227
Σ-glucose	0.223
LDL cholesterol	
Σ-insulin and Σ-glucose	0.091
Σ-insulin	0.091
Σ-glucose	0.090
Cholesterol	
Σ-insulin and Σ-glucose	0.083
Σ-insulin	0.079
Σ-glucose	0.083

Σ-insulin and Σ-glucose are independent variables. sBP, dBP, TGs, HDL cholesterol, LDL cholesterol, and cholesterol are dependent variables.

subjects with hyperinsulinemia or normoinsulinemia. Both groups in the matched subjects had a similar plasma glucose response after glucose loading compared with the total number of study subjects (Fig. 2), which suggests that the effects of glucose intolerance on coronary risks are not significantly different between the matched subjects with hyperinsulinemia and normoinsulinemia. Because significant differences were found in the plasma TG and HDL-cholesterol levels and BP between the matched groups, the pathophysiology of these factors are thought to be related to the hyperinsulinemic state or to insulin resistance, independent of BMI, age, sex, and glucose intolerance factors. We also demonstrated that glucose intolerance was an important determinant for plasma TG level and BP, from the analysis of subjects matched for age, sex, and BMI.

Furthermore, we performed multiple regression analysis to clarify the relationship of risk factors and hyperinsulinemia, glucose intolerance, age, BMI, or sex. Plasma TG and HDL-cholesterol levels and BP were related to hyperinsulinemia, glucose intolerance, age, BMI, or sex. Plasma cholesterol and LDL-cholesterol levels were not related to hyperinsulinemia. Age was the most important factor in the determination of BP, followed by BMI, and plasma insulin response was the least important. On the other hand, Zavaroni et al. (8) reported that the plasma insulin response was a more important determinant for BP than

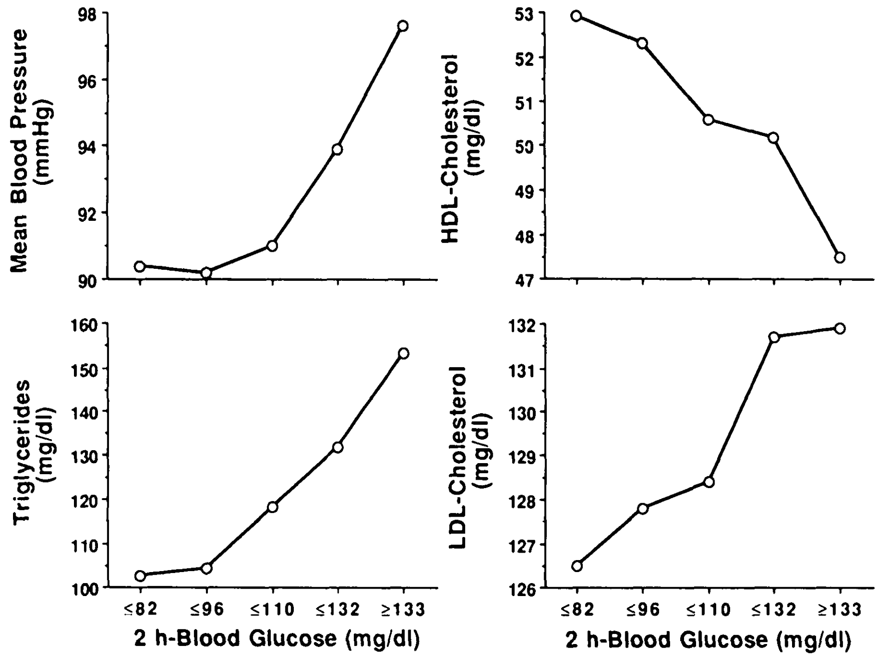

Figure 4—*Mean BP, plasma TG, HDL-cholesterol level, and LDL-cholesterol level in each quintile of the 2-h plasma glucose level after an oral glucose load. The sum of 1/3 of sBP and 2/3 of dBP (mmHg) was expressed as mean BP. Each value is the mean.*

either plasma glucose response after an oral glucose load or BMI in healthy subjects with normal glucose tolerance. Our analysis indicates that the plasma insulin level was a more significant determinant for plasma TG or HDL-cholesterol level than for BP, whereas factors other than the plasma insulin level were important determinants for plasma cholesterol and LDL-cholesterol levels. In relation to plasma insulin level, plasma TG, HDL cholesterol, and BP are considered to be a group of risk factors, and plasma cholesterol and LDL cholesterol are risk factors different from the others.

Many studies have reported a significant relationship between BP and hyperinsulinemia or insulin resistance (2,5–9,16) and a relationship between plasma lipid abnormalities and insulin resistance (7–9,17,18). Our results supported these previous studies by analyzing a large population with low BMI using the OGTT and clarified the relationship among risk factors. We divided the subjects into five subgroups by plasma insulin levels. The magnitude of each risk factor worsened according to the plasma insulin level, and subjects with glucose intolerance, whose mean Σ-insulin value (240 μU/ml) was much lower than that in hyperinsulinemic subjects, had relatively severe risk factors as shown in Fig. 3. This result suggests that the metabolic state caused by glucose intolerance and hyperinsulinemia is clearly involved in the pathophysiology of each risk factor for coronary atherosclerosis as reported previously (19–27), particularly in the pathophysiology of high plasma TG level and high BP, as demonstrated in the analysis of subjects matched for age, sex, and BMI (Table 3). In fact, the magnitude of each coronary risk factor became more severe in accordance with the severity of glucose intolerance (Fig. 4) and that of the Σ-insulin level (Fig. 3).

Multiple risk factors including hyperlipidemia and hypertension are commonly observed in patients with CAD. In this study, we established the close relationship of risk factors for CAD to either glucose intolerance, hyperinsulinism, or both through the analysis of OGTT in a large population. In conclusion, both the plasma insulin level and glucose intolerance were determinants for the severity of coronary risk factors. Careful management of both glucose intolerance and hyperinsulinism may reduce the risks for CAD and further prevent the disease.

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