Glucose Intolerance Is Common in Japanese Patients With Acute Coronary Syndrome Who Were Not Previously Diagnosed With Diabetes

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OBJECTIVE — Postprandial hyperglycemia has emerged as a new glycometabolic condition associated with an excessive risk for coronary artery disease. We therefore attempted to evaluate the frequency of postchallenge hyperglycemia in patients with acute coronary syndrome (ACS) who were not previously diagnosed to have diabetes and did not have a fasting glucose concentration of ≥7 mmol/l or an HbA_{1c} level >6.0%. We further correlated the presence of postchallenge hyperglycemia with the extent of coronary atherosclerosis.

RESEARCH DESIGN AND METHODS — In all, 134 consecutive ACS patients who met the above inclusion criteria were studied. An oral glucose tolerance test was performed before discharge.

RESULTS — The mean age, fasting glucose, and HbA_{1c} were 60 years, 5.15 mmol/l, and 5.4%, respectively. Among ACS patients, impaired glucose tolerance (IGT) and diabetes were found in 50 (37%) and 13 patients (10%), respectively. The homeostasis model assessment for insulin resistance did not differ substantially among the normal glucose tolerance (NGT), IGT, and diabetic groups. Insulinogenic index, however, was lower and the number of stenosed vessels higher in diabetic patients compared with NGT patients.

CONCLUSIONS — Postchallenge hyperglycemia, caused primarily by impaired initial insulin secretion, is commonly found in Japanese ACS patients who have not been previously diagnosed with diabetes, and this phenomenon is considered to be associated with advanced coronary atherosclerosis. Therefore, the present study strongly supports the notion that oral glucose tolerance test assessment of postchallenge hyperglycemia is essential to identify any previously undiagnosed diabetes cases among Japanese ACS patients.

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Abbreviations: ACS, acute coronary syndrome; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment for insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IPH, isolated postchallenge hyperglycemia; IRI, immunoreactive insulin; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The number of diabetic patients in Japan is now estimated to be >6.8 million (1). Furthermore, the number of diabetic patients in Japan and other southeastern Asian countries is expected to increase at the fastest rate worldwide. This trend, together with its associated complications that involve a substantial utilization of resources, make diabetes an extremely important health problem in Japan.

Impaired insulin secretion or/and impaired insulin sensitivity play a pivotal role in the development of type 2 diabetes. Possible contributions of these two factors have been shown to be ethnicity dependent to some extent (2,3). In the Caucasian population, a decreased insulin sensitivity is a primary metabolic defect underlying glucose intolerance, whereas an impaired insulin secretion mainly accounts for glucose intolerance in the Japanese population, among other Asian populations (4,5). As a consequence, Caucasian diabetic patients are often accompanied by obesity and increased fasting glucose concentrations, whereas Japanese counterparts are relatively lean and having normal fasting glucose levels but increased postprandial hyperglycemia.

An increased prevalence of glucose intolerance has been previously reported in patients with acute coronary syndrome (ACS) in a European population (6). However, no corresponding information is available from Asian populations. In the present study, we therefore attempted to evaluate the frequency of postchallenge hyperglycemia in Japanese ACS patients who did not have a previous diagnosis of diabetes and did not have a fasting glucose concentration ≥7 mmol/l or HbA_{1c} >6.0%. We also correlated the presence of postchallenge hyperglycemia with the extent of coronary atherosclerosis.

RESEARCH DESIGN AND METHODS

— ACS patients admitted to the coronary care units of the Division

of Cardiology at Jikei University School of Medicine between 1 November 1997 and 31 December 2000 were recruited for this study. Among them, any patients with a previous diagnosis of type 2 diabetes or a fasting plasma glucose (FPG) ≥7 mmol/l or HbA_{1c} >6.0% were excluded. As a result, a total of 134 ACS patients, comprising 89 patients with acute myocardial infarction and 45 patients with unstable angina, were analyzed in this study. Myocardial infarction was defined by a combination of two of three typical characteristics: *1*) typical symptoms, *2*) an increased levels of cardiac enzymes (CK or CK-MB), or *3*) a typical electrocardiogram pattern involving the development of Q waves (7). The criteria for unstable angina included symptoms of angina at rest, a new-onset exertional angina, or a recent acceleration of angina (8). Hypertension was defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or use of antihypertensive agents. Hyperlipidemia was defined by LDL cholesterol ≥140 mg/dl and/or triglyceride ≥200 mg/dl or use of lipid-lowering agents. The study was approved by the Ethics Committee of the Jikei University School of Medicine. All study subjects gave their written informed consent to the study protocol.

Oral glucose tolerance test

A standard oral glucose tolerance test (OGTT) with 75 g of glucose was performed at least 2 weeks after admission to minimize any possible confounding effects of ACS on the glucose metabolism. Blood samples to determine the plasma glucose and insulin concentrations were taken at 0, 30, 60, and 120 min after the load. The interpretation of the OGTT data were based on the World Health Organization definition (9), also employing the concept of impaired fasting glucose (IFG) included in the American Diabetes Association criteria (10). In brief, the patients were classified as having diabetes when 2-h plasma glucose was >11.1 mmol/l; this category is identical to isolated postchallenge hyperglycemia (IPH) (11,12). Impaired glucose tolerance (IGT) was defined as an FPG level <7 mmol/l and a 2-h plasma glucose level of 7.8–11 mmol/l. Normal glucose tolerance (NGT) was defined as a FPG level <6.1 mmol/l and a 2-h plasma glucose <7.8 mmol/l. IGT was further classified into those who had normal FPG levels of <6.1 mmol/l (designated as IGT) and those with an increased FPG level of 6.1–6.9 mmol/l (designated as IFG/IGT). IFG was defined as an FPG level of 6.1–6.9 mmol/l and a 2-h plasma glucose level <7.8 mmol/l.

Insulin resistance expressed as the homeostasis model assessment for insulin resistance (HOMA-IR) was calculated under fasting conditions as plasma insulin (microunits per milliliter) × blood glucose (millimoles per liter)/22.5 (13). The insulinogenic index is equal to the increase in insulin secretion (immunoreactive insulin [IRI] at 30 min – IRI at 0 min) divided by that of plasma glucose (plasma glucose at 30 min – plasma glucose at 0 min) (14).

Coronary angiography

An analysis of the coronary angiograms was performed by an independent experienced observer. The presence of coronary artery disease was defined as ≥75% diameter narrowing. The coronary arteries were grouped as the left anterior descending or diagonal and septal branches, the left circumflex artery or obtuse marginal branch, and the right coronary artery or posterior descending and posterolateral branch to define one-, two-, and three-vessel disease (15), respectively.

Other methods

HbA_{1c}, total cholesterol, triglycerides, and HDL cholesterol were measured on the first morning after admission. Because all ACS subjects had plasma triglyceride levels <400 mg/dl, LDL was calculated according to the Friedewald formula.

Statistical analysis

All values are presented as means ± SD. Statistical analyses among the three groups (NGT, IGT, and diabetes) were performed by ANOVA or the χ^2 analysis followed by the Dunnett method, using NGT as the control group for the former. $P < 0.05$ was considered to be statistically significant. All statistical procedures were performed using SPSS 9.1 (SPSS, Chicago, IL).

RESULTS

Prevalence of IGT and diabetes

The study subjects included 114 men (85%) with a mean age of 60 ± 10 years and a mean BMI of 23.5 ± 3.2 kg/m^2. Hypertension, hyperlipidemia, and current smoking were commonly observed in 61, 71, and 66%, respectively. The HbA_{1c} level at admission was 5.4 ± 0.4% and a majority of the study subjects (90%) had a normal HbA_{1c} level of ≤5.8%. Table 1 and Fig. 1 show the patient classification based on OGTT. About half of the ACS patients (n = 71, 52.9%) were classified as having NGT; thus, the other half had postchallenge hyperglycemia including 50 patients with IGT (37.3%) and 13 patients with diabetes (or IPH 9.7%). As shown in Fig. 1, among IGT subjects, most patients (n = 45, 33.6% or 89% of all IGT) had normal FPG levels of <6.1 mmol/l with only five IFG/IGT patients (3.7 or 11% of all IGT). No IFG pattern was observed in this study. It is interesting to note that 93% of the ACS patients had normal FPG (<6.1 mg/dl), but among them, 45 (36%) patients had IGT and 8 (6%) had diabetes.

Metabolic profile among NGT, IGT, and diabetes

Pertinent clinical characteristics of the three groups of patients are presented in Table 1. Although the mean ages were significantly higher in the IGT and diabetes groups than in the NGT group, there were no significant differences among the groups in sex, diagnosis, BMI, prevalence of hyperlipidemia, current smoking, obesity, or family history. Furthermore, the total cholesterol, triglycerides, HDL, and LDL levels did not differ across the three groups. Hypertension, however, was more commonly found in the diabetic subjects than in the NGT or IGT subjects (P = 0.03). The mean FPG and HbA_{1c} were all within the normal range in all three groups. However, as expected, FPG and HgA_{1c} were lowest in the NGT subjects, highest in the diabetic subjects, and intermediate in the IGT subjects (P = 0.001). HOMA-IR results did not differ among the groups and were well below 2.5, the cutoff value representing insulin resistance.

OGTT patterns

The plasma glucose and insulin concentrations during OGTT are illustrated in Fig. 2. The plasma glucose levels in the NGT and IGT subjects were superimposed at 0 and 30 min but were higher in the IGT subjects thereafter (Fig. 2*A*). This difference may correspond to a delayed and decreased insulin response in IGT subjects compared with NGT subjects as shown in Fig. 2*B*. In contrast, the plasma

Table 1—*Clinical characteristics and metabolic data of patients with NGT, IGT, and diabetes*

	Total	NGT	IGT	Diabetes	*P* value
n	134	71	50	13	
Age (years)	59.5 ± 9.8	56.9 ± 9.9	62.1 ± 8.9*	63.6 ± 8.9†	0.005
Sex					
Male	114 (85)	61 (86)	40 (80)	13 (100)	0.189
Female	20 (15)	10 (14)	10 (20)	0	
Acute myocardial infarction	89 (66)	51 (72)	31 (62)	7 (54)	0.318
Unstable angina pectoris	45 (34)	20 (28)	19 (38)	6 (46)	
Hypertension	82 (61)	38 (54)	32 (71)	12 (92)	0.027
Hyperlipidemia	95 (71)	49 (69)	36 (72)	10 (77)	0.827
Smoking	88 (66)	46 (65)	33 (66)	9 (69)	0.951
Obesity	39 (29)	21 (30)	12 (24)	6 (46)	0.495
Family history	35 (26)	23 (32)	7 (14)	5 (38)	0.118
BMI (kg/m^2)	23.5 ± 3.2	23.6 ± 3.4	23.4 ± 2.8	24.6 ± 3.6	0.366
Total cholesterol (mmol/l)	5.44 ± 1.01	5.42 ± 1.04	5.49 ± 0.92	5.40 ± 1.24	0.919
Triglycerides (mmol/l)	1.52 ± 0.69	1.56 ± 0.72	1.48 ± 0.70	1.50 ± 0.51	0.827
HDL (mmol/l)	1.18 ± 0.36	1.20 ± 0.39	1.18 ± 0.30	1.07 ± 0.36	0.883
LDL (mmol/l)	3.55 ± 0.95	3.49 ± 0.91	3.62 ± 0.88	3.64 ± 1.38	0.723
FPG (mmol/l)	5.15 ± 0.58	4.94 ± 0.39	5.22 ± 0.55*	6.04 ± 0.69‡	0.0001
HbA_{1c} (%)	5.4 ± 0.4	5.3 ± 0.4	5.4 ± 0.4	5.7 ± 0.3*	0.001
Fasting insulin (pmol/l)	39 ± 23	39 ± 26	39 ± 21	36 ± 16	0.897
HOMA-IR	1.50 ± 0.96	1.45 ± 1.03	1.51 ± 0.88	1.64 ± 0.92	0.839
Insulinogenic index (pmol/mmol)	90 ± 97	107 ± 70	84 ± 132	29 ± 19†	0.071
Number of stenosed vessels	1.30 ± 0.78	1.13 ± 0.68	1.44 ± 0.80	1.77 ± 0.93†	0.008

Data are means ± SD or *n* (%). *P* value based on ANOVA or χ^2. *$P < 0.01$, †$P < 0.05$, ‡$P < 0.001$ vs. NGT group.

glucose levels were higher and insulin concentrations were lower in the diabetic subjects throughout the test period, except for the 2-h IRI level. However, even in the diabetic subjects, the mean fasting glucose level was within the normal range of 6.04 ± 0.69 mmol/l, which was consistent with IPH. To assess early-phase insulin secretion, the insulinogenic indexes were calculated. As shown in Table 1, impaired early-phase insulin secretion is evident in the diabetic subjects compared with the NGT or IGT subjects. A positive correlation between the FPG and 2-h plasma glucose concentrations was noted in the subjects with NGT ($r = 0.416$, $P < 0.01$) but not in the subjects with IGT ($r = 0.102$, $P = 0.482$) or diabetes ($r = 0.305$, $P = 0.310$).

Association between the glucose metabolism and coronary atherosclerosis

Coronary angiograms were performed on all study subjects except for two NGT and two IGT subjects. As shown in Table 1, the number of stenosed coronary vessels was significantly higher in the diabetic subjects (1.8 ± 0.9) than in the NGT subjects (1.1 ± 0.7, $P = 0.022$).

CONCLUSIONS — Glucose intolerance, including IGT and diabetes, has emerged as a major health hazard in Japan because it is causally associated with coronary artery disease. In the present study, we demonstrated a high prevalence of postchallenge hyperglycemia in Japanese patients with ACS. We furthermore revealed that postchallenge hyperglycemia was primarily caused by impaired initial insulin secretion, which was associated with more advanced coronary artery disease compared with subjects demonstrating NGT.

Norhammar et al. (6) recently reported that IGT or diabetes was common in patients with acute myocardial infarction. Similarly to our study, they investigated acute myocardial infarction patients who were not previously known to have diabetes and found 35 and 31% of patients to have IGT and diabetes, respectively. The prevalence of IGT in ACS patients was similar between the two

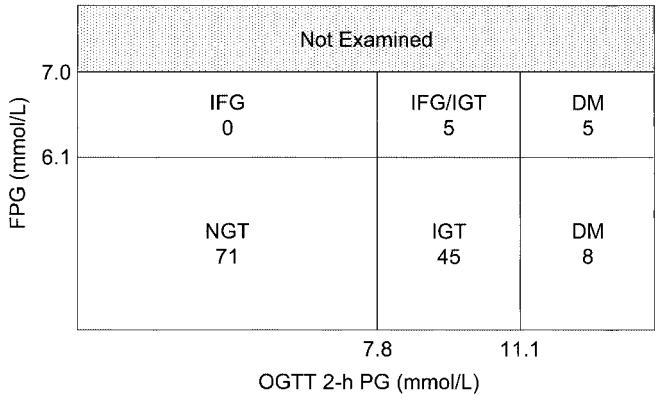

Figure 1—*Distribution of NGT and glucose intolerance based on the FPG and OGTT 2-h plasma glucose levels. Glucose intolerance includes IFG, IGT, IFG/IGT, and diabetic (DM) subjects.*

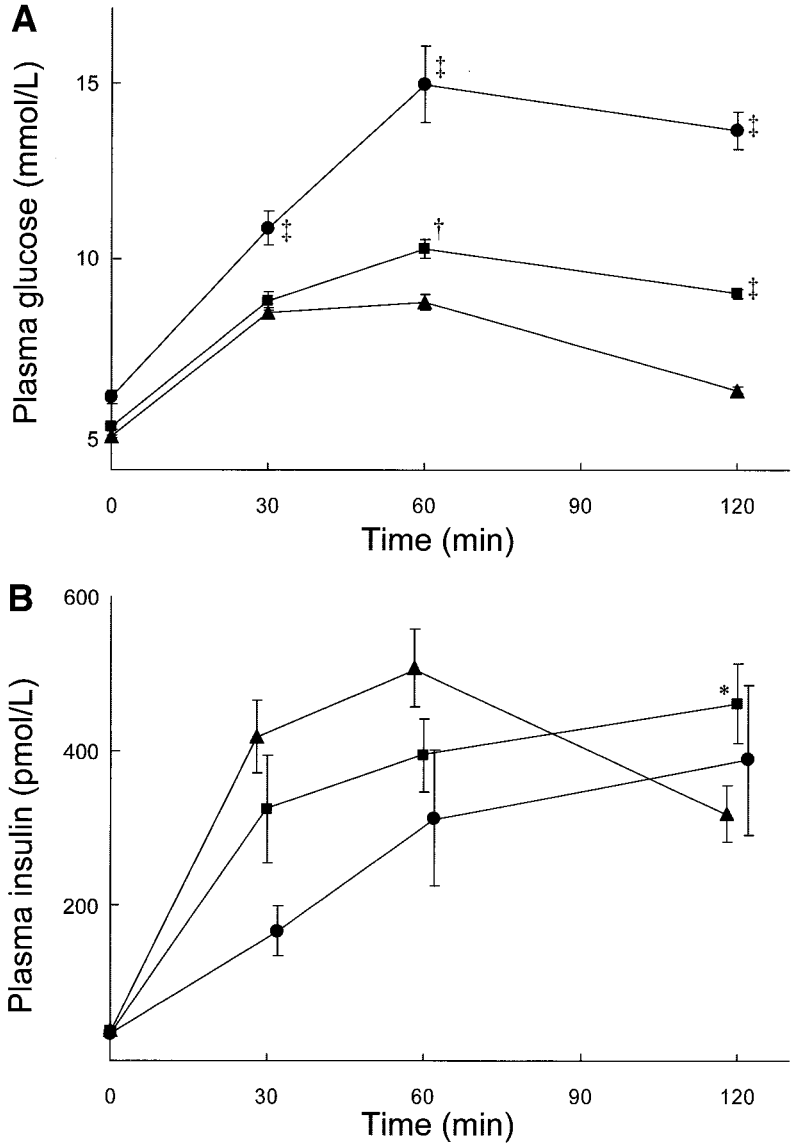

Figure 2—*The plasma glucose* (A) *and IRI* (B) *concentrations during OGTT in ACS patients with NGT* (▲)*, IGT* (■)*, and diabetes* (●)*. All data are given as means ± SEM.* *P < *0.05,* †P < *0.01,* ‡P < *0.001 vs. NGT group.*

studies, thus indicating that IGT in ACS patients is common irrespective of their ethnic background. However, a markedly lower prevalence of diabetes in our study (10%) relative to their study (31%) deserves discussion. Although both studies excluded patients who were known to have diabetes, we further excluded any patients who had a FPG level of ≥7 mmol/l or a HbA_{1c} level of >6.0%, whereas patients with blood glucose ≥11.1 mmol/l were excluded in their study. Our strict criteria are, therefore, likely to reduce the prevalence of diabetes rather than IGT, because the subjects with FPG ≥7 mmol/l are prone to show 2-h plasma glucose ≥11.1 mmol/l. The timing of OGTT after admission was also different. OGTT was conducted on days 4–5 in their study but at least 2 weeks after admission in our study. We chose this timing to avoid any confounding effects due to acute stress, inflammation, and left ventricular dysfunction, which may not fully subside by days 4–5. All together, our strict study design allowed us to focus on the issue of postchallenge hyperglycemia, thereby making a strong argument regarding whether postchallenge hyperglycemia is common in ACS patients in whom diabetes had been not been diagnosed based on a "snapshot" analysis (i.e., fasting glucose or HbA_{1c}).

Postchallenge hyperglycemia is a appropriate model of postprandial hyperglycemia and is associated with the increased risk for coronary artery disease (11,12,16). The Funagata diabetes study (17), a 7-year prospective study using a Japanese cohort population, demonstrated that IGT but not IFG was a risk factor for cardiovascular disease. The absence of IFG patients in the present study also supports the results of this study. Previous studies using Caucasian populations (18,19) found the fasting glucose criteria to be more likely detect obese diabetic patients. This, however, cannot be applied to Asian populations, including the present ACS patients who had a mean BMI of 23.5 kg/m^2. In the present study, the fasting glucose levels in our ACS patients were relatively normal and the fasting glucose levels did not correlate with the 2-h glucose levels in the ACS subjects with IGT ($r = 0.10$, $P = 0.48$) or diabetes ($r = 0.31$, $P = 0.31$). Therefore, the present study strongly supports the notion that an OGTT assessment of postchallenge hyperglycemia is essential in ACS subjects in whom diabetes had not been previously diagnosed, although they also have relatively normal fasting glucose concentrations.

In the present study, HOMA-IR, a parameter representing insulin resistance, did not differ among the groups, indicating that insulin resistance was not evident in our ACS patients. This also contrasted the results of previous studies in which insulin resistance was common in Caucasian ACS patients (20,21). Based on the OGTT data in Fig. 2, the IGT patients were characterized by an impaired prompt secretion of insulin, which was further exacerbated in diabetic patients. As shown in Table 1, a decreased insulinogenic index further supports this concept. Although we cannot rule out the possibility that our ACS patients with IGT or diabetes represent a metabolic status in which the β-cells can no longer compensate for insulin resistance, we favor the concept that impaired insulin secretion predominantly accounts for glucose intolerance in the Japanese population (2–5).

There are some limitations in the present study. We selected ACS patients in whom diabetes was not previously diagnosed and who did not have increased

fasting glucose or HbA_{1c} levels. Therefore, our study cohort may not represent the Japanese ACS population in general. In this regard, the exact prevalence of diabetes including postchallenge hyperglycemia may be different from our observations. Nonetheless, our conclusion that OGTT should be performed in ACS patients in whom diabetes has not been previously diagnosed is still considered to be valid because OGTT has rarely been performed in ACS patients of this category. Second, this study lacks a control group to which the ACS patients can be compared. Based on the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia study (22) that studied Asian cohorts, the prevalence of IGT and diabetes was 15.3 and 3.4%, respectively, which is about 33% of that observed in our ACS patients. A higher prevalence of glucose intolerance can therefore be interpreted as indicating that OGTT is more efficacious in ACS patients than in the general population to identify patients at increased risk.

In summary, the present study provides further evidence to support the previous finding that glucose intolerance is common in ACS patients in whom diabetes has not been previously diagnosed. Among the Japanese ACS patients, glucose intolerance is primarily caused by an impaired initial insulin secretion rather than insulin resistance, which is considered to be the main underlying defect in their Caucasian counterparts. An OGTT assessment of such patients before being discharged from the hospital is thus considered to be an essential step in identifying diabetic cases among Japanese ACS subjects.

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