Glucose Tolerance, Insulin Secretion, and Insulin Sensitivity in Nonobese and Obese Japanese Subjects

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OBJECTIVE — To investigate the relative contributions of insulin secretion and insulin resistance to the development of glucose intolerance in Japanese subjects.

RESEARCH DESIGN AND METHODS — A cross-sectional study of 756 Japanese subjects (530 nonobese, 226 obese) was performed. A 75-g oral glucose tolerance test (OGTT) was given, and subjects were classified according to the World Health Organization (WHO) criteria (normal glucose tolerance [NGT], impaired glucose tolerance [IGT], and diabetes). Early-phase insulin secretion was assessed by the insulinogenic index (the ratio of the increment of insulin to that of plasma glucose [PG] 30 min after a glucose load [ΔIRI0–30 min/ΔPG0–30 min]). Total insulin secretion was assessed by mean immunoreactive insulin (IRI) during the OGTT, and insulin resistance was assessed by use of the homeostasis model [HOMA(*R*)].

RESULTS — Early-phase insulin secretion was significantly decreased in IGT, compared with patients with NGT, in both the nonobese and obese subjects (0.70 ± 0.05 vs. 0.37 ± 0.03, $P < 0.01$ and 1.36 ± 0.19 vs. 0.73 ± 0.08, $P < 0.01$, respectively). However, mean IRI and HOMA(*R*) in both nonobese and obese subjects with IGT and NGT were not statistically different. Subjects with diabetes showed a significant decline in early-phase and total insulin secretion and a significantly higher level of insulin resistance than did subjects with IGT. When the fasting plasma glucose (FPG) exceeded 100 mg/dl, early-phase insulin decreased progressively. The graphed relationship between FPG and mean IRI did not show an inverted U-shape, and mean IRI decreased progressively when FPG exceeded 110–130 mg/dl. The pattern of changes in insulin secretion and insulin resistance associated with the progression of glucose intolerance was similar in both the nonobese and obese subjects.

CONCLUSIONS — The worsening from NGT to IGT in Japanese subjects may be associated with a decrease in early-phase insulin secretion in nonobese as well as in obese subjects. Hyperinsulinemia in IGT is not common. We suggest that impaired early-phase insulin secretion may be the initial abnormality in the development of glucose intolerance in Japanese people. Insulin resistance may be a consequence of hyperglycemia and/or obesity.

Insulin deficiency and insulin resistance are involved in the pathogenesis of NIDDM. The relative importance of each factor may differ from case to case. For example, insulin-sensitive and insulin-resistant variants of NIDDM have been reported (1,2). In Pima Indians and whites, insulin resistance is believed to be the primary defect in NIDDM (3–5). DeFronzo et al. (6,7) reported a "Starling's curve of the pancreas," which means that fasting and glucose-stimulated insulin concentrations form an inverted U-shaped curve when plotted against plasma glucose concentration. A longitudinal study in Pima Indians also demonstrated a "Starling's curve of the pancreas" (8). A worsening of glucose intolerance may therefore be associated with insulin resistance. In contrast, some investigators have reported the relative importance of an insulin deficiency (9–13). One reason for this difference in results is a difference in ethnic groups tested (14). Among Japanese subjects, Taniguchi et al. (15,16) reported impaired glucose tolerance (IGT) and NIDDM coexistent with normal insulin sensitivity. Kadowaki et al. (17) reported that insulin deficiency is a strong predictor of the development of NIDDM. As a result, we suggest that insulin deficiency may be an important factor in the development of glucose intolerance in Japanese people.

To investigate the relative importance of insulin secretion and insulin action on the development of glucose intolerance, we examined a large number of Japanese subjects with various degrees of glucose tolerance. If insulin deficiency was a major contributor to glucose intolerance, a "Starling's curve of the pancreas" might not be observed. Because NIDDM is classified as being of the nonobese and obese types, and because obesity affects both insulin secretion and insulin resistance, we assessed nonobese and obese subjects separately.

RESEARCH DESIGN AND METHODS

— All subjects visited the Health Care Center or the Department of Internal Medicine of Sasebo Chuou Hospital between 1993 and 1996. A physical checkup, routine collection of biochemical data, and a 75-g oral glucose tolerance test (OGTT) were performed. At the time of blood sampling, informed consent was obtained from each individual, according to protocol approved by the ethics committee of Sasebo Chuou Hospital. Clinical characteristics of the study subjects are presented in Table 1. The subjects (n = 756) included 444 men and 312 women, aged 15–70 years, and were classified into two groups according to BMI (nonobese, BMI

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Abbreviations: ANOVA, analysis of variance; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; IVGTT, intravenous glucose tolerance test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization.

Table 1—*Clinical characteristics of nonobese and obese subjects*

	Nonobese subjects			Obese subjects		
	NGT	IGT	Diabetes	NGT	IGT	Diabetes
n (M/F)	173 (108/65)	130 (83/47)	227 (137/90)	55 (35/20)	63 (35/28)	108 (46/62)
Age (year)	47.3 ± 1.4	57.2 ± 1.1†	56.3 ± 1.1†	44.7 ± 2.6	53.7 ± 1.7†	54.4 ± 1.3†
BMI (kg/m²)	21.2 ± 0.2	21.8 ± 0.2	21.6 ± 0.2	27.6 ± 0.3	27.8 ± 0.4	27.4 ± 0.2
FPG (mg/dl)	96.5 ± 0.9	105.5 ± 1.4†	140.5 ± 2.8†‡	98.6 ± 1.7	109.7 ± 1.6*	138.2 ± 3.5†‡
Fasting IRI (μU/ml)	5.2 ± 0.2	5.5 ± 3.3	5.8 ± 3.2	9.5 ± 0.7	9.6 ± 0.6	9.2 ± 0.4

Data are means ± SE or *n* (M/F). *$P < 0.05$ vs. NGT; †$P < 0.01$ vs. NGT; ‡$P < 0.01$ vs. IGT.

<25 kg/m², *n* = 530; obese, BMI ≥25 kg/m², *n* = 226). Normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes were diagnosed according to the World Health Organization (WHO) criteria (18). Nonobese subjects were classified as follows: NGT, *n* = 173; IGT, *n* = 130; diabetes, *n* = 227. In the same way, obese subjects were classified as follows: NGT, *n* = 55; IGT, *n* = 63; diabetes, *n* = 108. In both nonobese and obese subjects, mean age in the NGT group was significantly lower than in the IGT and diabetes groups. Age in IGT and diabetes groups was comparable. In nonobese subjects, the values for BMI were comparable in the NGT, IGT, and diabetes groups (21.2 ± 0.2, 21.8 ± 0.2, and 21.6 ± 0.2 kg/m², respectively). In obese subjects, the values for BMI were also comparable in the NGT, IGT, and diabetes groups (27.6 ± 0.3, 27.8 ± 0.4, and 27.4 ± 0.2 kg/m², respectively). Fasting plasma glucose (FPG) levels were increased according to the degree of glucose intolerance (96.5 ± 0.9, 105.5 ± 1.4, and 140.5 ± 2.8 mg/dl in nonobese subjects and 98.6 ± 1.7, 109.7 ± 1.6, and 138.2 ± 3.5 mg/dl in obese subjects, respectively). Fasting immunoreactive insulin (IRI) levels were lower in nonobese subjects than in obese subjects, but IRI levels in the NGT, IGT, and diabetes groups were comparable.

Patients who were under treatment for diabetes were excluded from this study, as were patients with heart or renal failure, chronic liver disease, or endocrine disease.

A 75-g OGTT was carried out after an overnight fast of 12–14 h. Subjects ingested carbohydrate equivalent to 75 g of glucose (Torelan-G, Shimizu Pharmaceuticals, Shimizu, Japan), and blood samples were taken at 0, 30, 60, 90, and 120 min. Plasma and serum were stored at −20°C for later assay of plasma glucose and serum insulin.

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 were 1.2 and 1.5%, respectively. Immunoreactive insulin (IRI) was measured in duplicate with a Phadeseph insulin radioimmunoassay (RIA) kit (Shionogi, Osaka, Japan). Coefficients of variation were 4% for insulin >30 μU/ml and 7% for insulin <30 μU/ml.

An insulinogenic index was used as an index of early-phase insulin secretion in the OGTT (19–22). The insulinogenic index was defined as the ratio of the increment of insulin to that of plasma glucose 30 min after a glucose load (ΔIRI 0–30 min/ΔPG 0–30 min). Mean IRI during the OGTT (0–120 min) was used as total insulin secretion. Insulin resistance was assessed by the *R* value of the homeostasis model (HOMA) of Matthews (23). Briefly, HOMA(*R*) was calculated by the formula HOMA(*R*) = insulin/($22.5e^{-\ln \text{glucose}}$), where the unit for insulin is microunits per milliliter and the unit for glucose is millimoles per liter. Although the reproducibility of HOMA is low, *R* values correlate well with values obtained by euglycemic clamp (23). We therefore believe that HOMA(*R*) may be useful in epidemiological studies and for routine measurement of insulin resistance.

Data are means ± SE. Statistical analysis was conducted by one-way analysis of variance (ANOVA) and a post hoc multiple-comparison test. Data were analyzed by a Power Macintosh 7600 using the SPSS statistical package. Differences were considered statistically significant at a level of $P < 0.05$.

RESULTS

Early-phase insulin secretion

Values of the insulinogenic index are shown in Table 2 and Fig. 1. The worsening in glucose tolerance was associated with a decrease in the insulinogenic index. In nonobese subjects, the worsening from NGT to IGT was associated with a significant decrease in the insulinogenic index (0.70 ± 0.05 vs. 0.37 ± 0.03, $P < 0.01$). The worsening from IGT to diabetes in these subjects was also associated with a significant decrease in the insulinogenic index (0.37 ± 0.03 vs. 0.15 ± 0.02, $P < 0.01$). In obese subjects, although values of the insulinogenic index were higher than those in nonobese subjects, the worsening in glucose tolerance was also associated with a decrease in the insulinogenic index. A worsening from NGT to IGT and from IGT to diabetes was associated with significant decreases in the insulinogenic index (1.36 ±

Table 2—*Early-phase insulin secretion, total insulin secretion, and insulin resistance in nonobese and obese subjects with NGT, IGT, or diabetes*

	Nonobese subjects			Obese subjects		
	NGT	IGT	Diabetes	NGT	IGT	Diabetes
ΔIRI0–30/ΔPG0–30	0.70 ± 0.05	0.37 ± 0.03*	0.15 ± 0.02*‡	1.36 ± 0.19	0.73 ± 0.08*	0.20 ± 0.02*‡
Mean IRI (μU/ml)	35.9 ± 1.2	39.4 ± 1.8	23.5 ± 1.0*‡	55.0 ± 3.7	60.8 ± 3.6	35.4 ± 2.0*‡
HOMA(*R*)	1.22 ± 0.05	1.44 ± 0.08	1.97 ± 0.08*‡	2.29 ± 0.17	2.63 ± 0.17	3.13 ± 0.16*†

Data are means ± SE: *$P < 0.01$ vs. NGT; †$P < 0.05$ vs. IGT; ‡$P < 0.01$ vs. IGT.

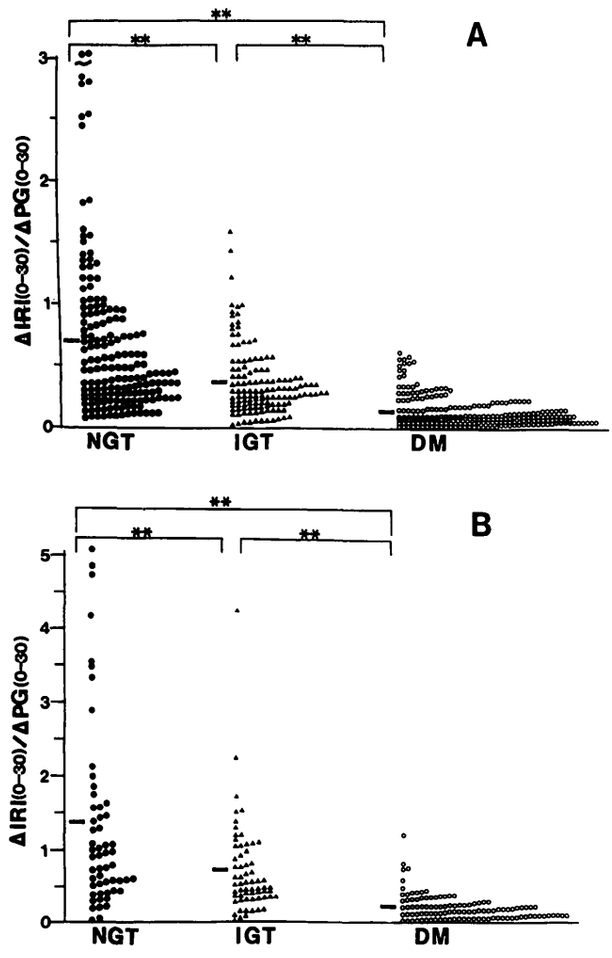

Figure 1—*Insulinogenic index (ΔIRI0–30/ΔPG0–30) in subjects with NGT (●), IGT (▲), or diabetes (○). A: nonobese subjects. B: obese subjects. Bars show mean values.* **P < *0.01.*

0.19 vs. 0.73 ± 0.08, $P < 0.01$ and 0.73 ± 0.08 vs. 0.20 ± 0.02, $P < 0.01$, respectively). Tomono et al. (24) assumed that subjects with an insulinogenic index below 0.4 manifest early-phase insulin deficiency. According to that criterion, 74 nonobese subjects with NGT (42.8%), 90 with IGT (69.2%), and 214 with diabetes (94.3%) were in the early phase of insulin deficiency. Among the obese subjects, 8 with NGT (14.5%), 20 with IGT (31.7%), and 97 with diabetes (89.8%) were in the early phase of insulin deficiency.

Total insulin secretion

Values for mean IRI during the OGTT are shown in Table 2 and Fig. 2. Values for mean IRI were higher in obese than nonobese subjects. In both nonobese and obese subjects, however, the mean IRI values of NGT did not differ significantly from those of IGT (35.9 ± 1.2 vs. 39.4 ± 1.8 μU/ml, $P = 0.07$ in the nonobese and 55.0 ± 3.7 vs. 60.8 ± 3.6 μU /ml, $P = 0.19$ in the obese subjects, respectively). The worsening from IGT to diabetes was associated with a decrease in mean IRI in both groups (39.4 ± 1.8 vs. 23.5 ± 1.0 μU/ml, $P < 0.01$ in the nonobese and 60.8 ± 3.6 vs. 35.4 ± 2.0 μU/ml, $P < 0.01$ in the obese subjects). Neither the fasting (Table 1) nor the glucose-stimulated insulin levels provided evidence of marked hyperinsulinemia in the subjects studied.

Insulin resistance

Values for HOMA(*R*), shown in Table 2 and Fig. 3, were higher in the obese than in the nonobese subjects. The worsening from NGT to IGT tended to be associated with an increase in HOMA(*R*), but this difference did not reach statistical significance (1.22 ± 0.05 vs. 1.44 ± 0.08, $P = 0.06$ in nonobese subjects and 2.29 ± 0.17 vs. 2.63 ± 0.17, $P = 0.17$ in obese subjects). The worsening from IGT to diabetes was associated with a significant increase in insulin resistance as estimated by HOMA(*R*) in both nonobese and obese subjects (1.44 ± 0.08 vs. 1.97 ± 0.08, $P < 0.01$ and 2.63 ± 0.17 vs. 3.13 ± 0.16, $P < 0.05$, respectively). We assumed that subjects whose HOMA(*R*) value was above the 90th percentile for the nonobese NGT group were insulin resistant [HOMA(*R*) >1.97]. According to that criterion, 16 nonobese subjects with NGT (9.2%), 21 with IGT (16.2%), and 100 with diabetes (44.1%) were in an insulin-resistant state. Among obese subjects, 28 with NGT (50.9%), 43 with IGT (68.3%), and 75 with diabetes (69.4%) were in an insulin-resistant state.

Relationship of FPG to insulin secretion and insulin resistance

The 530 nonobese subjects were classified by FPG level as follows: 61–80 mg/dl (*n* = 17), 81–90 mg/dl (*n* = 73), 91–100 mg/dl (*n* = 113), 101–110 mg/dl (*n* = 85), 111–120 mg/dl (*n* = 73), 121–130 mg/dl (*n* = 44), 131–140 mg/dl (*n* = 33), 141–160 mg/dl (*n* = 37), 161–180 mg/dl (*n* = 18), 181–200 mg/dl (*n* = 10), 201–220 mg/dl (*n* = 13), 221–240 mg/dl (*n* = 7), and >240 mg/dl (*n* = 7). Figure 4 shows the relationship of FPG to insulin secretion and insulin sensitivity in the nonobese subjects. Values for early-phase insulin secretion, as estimated by the insulinogenic index, decreased progressively when the FPG levels exceeded 100 mg/dl. Total insulin secretion, as estimated by mean IRI, did not show an inverted U-shape when graphed, and decreased progressively when the FPG levels exceeded 110–120 mg/dl. Values for HOMA(*R*) increased progressively with elevation of the FPG level. When FPG exceeded 130 mg/dl, HOMA(*R*) exceeded the 90th percentile for nonobese subjects with NGT [HOMA(*R*) >1.97].

The 226 obese subjects were also classified by FPG levels as follows: 61–90 mg/dl (*n* = 21), 91–100 mg/dl (*n* = 45), 101–110 mg/dl (*n* = 38), 111–120 mg/dl (*n* = 35), 121–130 mg/dl (*n* = 27), 131–140 mg/dl (*n* = 17), 141–160 mg/dl (*n* = 19), 161–180 mg/dl (*n* = 11), 181–200 mg/dl (*n* = 6), and >200 mg/dl (*n* = 7). Figure 5 shows the relationship of FPG to insulin secretion and insulin sensitivity in obese subjects. Levels of both insulin secretion and insulin resistance were apparently higher than those in the nonobese subjects, but the patterns of relationship to FPG were similar. Values of

the insulinogenic index decreased progressively when FPG levels exceeded 100 mg/dl. As in nonobese subjects, mean IRI did not show an inverted U-shape when graphed, and decreased progressively when FPG levels exceeded 120–130 mg/dl. Values for HOMA(*R*) increased progressively with elevation of FPG levels.

CONCLUSIONS — The present cross-sectional study of Japanese subjects demonstrated that the worsening from NGT to IGT is associated with impaired early-phase insulin secretion. Significant hyperinsulinemia or increased insulin resistance was not detected in subjects with IGT, as those with NGT. These patterns of change in insulin secretion and insulin action were observed in both nonobese and obese subjects. We conclude, therefore, that IGT in Japan is characterized by impaired early-phase insulin secretion to glucose load. Yoneda et al. (21) reported that IGT was associated with impaired early-phase insulin secretion in the OGTT and intravenous glucose tolerance test (IVGTT) in relatively small numbers of nonobese Japanese subjects (21). Our results support the view that impairment of early-phase insulin secretion may be an important factor in the development of glucose intolerance in both nonobese and obese Japanese subjects. Mitrakou et al. studied the pathophysiology of impaired insulin secretion in IGT (9). They found that subjects with IGT show reduced suppression of hepatic glucose output owing to diminished early-phase insulin secretion. They suggested that late hyperinsulinemia may be the consequence of inadequate early insulin secretion, rather than of insulin resistance. Indeed, our results showed that insulin resistance was not evident in Japanese subjects with IGT, and insulin resistant individuals constituted only 16.2% of our nonobese subjects with IGT [HOMA(*R*) >1.97].

In our study, when FPG levels were elevated, a decrease in early-phase insulin secretion appeared earlier than did a decrease in mean IRI or an increase in insulin resistance (Figs. 4 and 5). Early-phase insulin secretion decreased progressively when FPG level exceeded 100 mg/dl. A decrease in mean IRI during OGTT was observed when FPG level exceeded 110–130 mg/dl. In both nonobese and obese Japanese subjects, a "Starling's curve of the pancreas" was not recognized. We suggest, therefore, that an early abnormality in the development of glucose intolerance in Japanese subjects is impaired early-phase insulin secretion. Recently, Chen et al. (25) studied Japanese-American men longitudinally and concluded that impaired early-phase insulin secretion may be present earlier than visceral adiposity in subjects who subsequently develop NIDDM. Because the cross-sectional and longitudinal data show similar results, it is possible that impaired early-phase insulin secretion is a genetic abnormality in the development of NIDDM in Japanese subjects.

The worsening from IGT to diabetes in our study was associated with a greater decrease in early-phase insulin secretion, a significant decrease in total insulin secretion, and a significant increase in insulin resistance. The relative importance of impaired β-cell function in the transition from IGT to NIDDM was previously demonstrated by several investigators (26–28). The importance of β-cell dysfunction in the development of NIDDM is increasingly being recognized in insulin-resistant ethnic groups among Pima Indians, Mexican-Americans, and Swedes (12,29–31). Therefore, it seems most likely that further deterioration in glucose tolerance is related to progression of β-cell dysfunction.

In the nonobese and obese subjects, similar patterns of a decrease in insulin secretion and increase in insulin resistance associated with the progression of glucose intolerance were observed. Plasma insulin levels and levels of insulin resistance were, however, higher in the obese subjects than in the nonobese subjects, probably because of the effects of obesity (32). Obesity may, therefore, be the most significant factor in any investigation of the relationship between insulin secretion and insulin resistance.

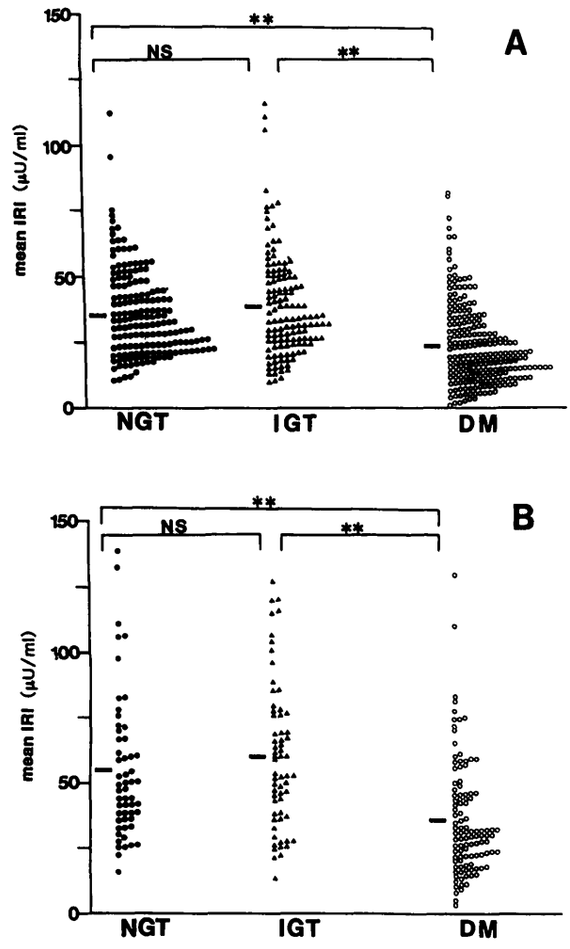

Figure 2—*Mean IRI during OGTT in subjects with NGT (●), IGT (▲), or diabetes (○). A: nonobese subjects. B: obese subjects. Bars show mean values.* **P < *0.01.*

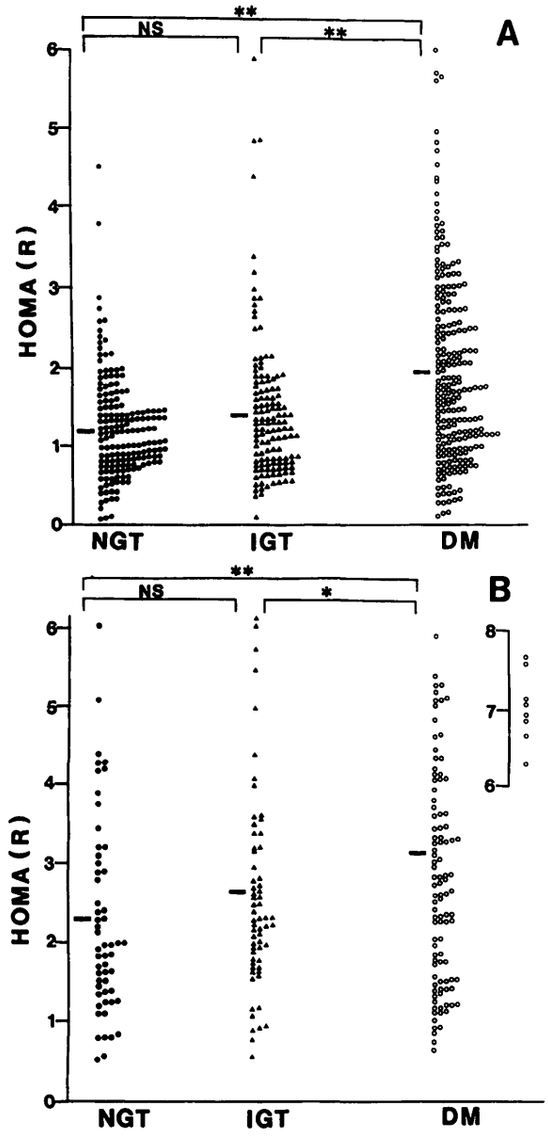

Figure 3—*Insulin resistance estimated by HOMA(R) in subjects with NGT (●), IGT (▲), or DM (○). A: nonobese subjects. B: obese subjects. Bars show mean values. *P < 0.05, **P < 0.01.*

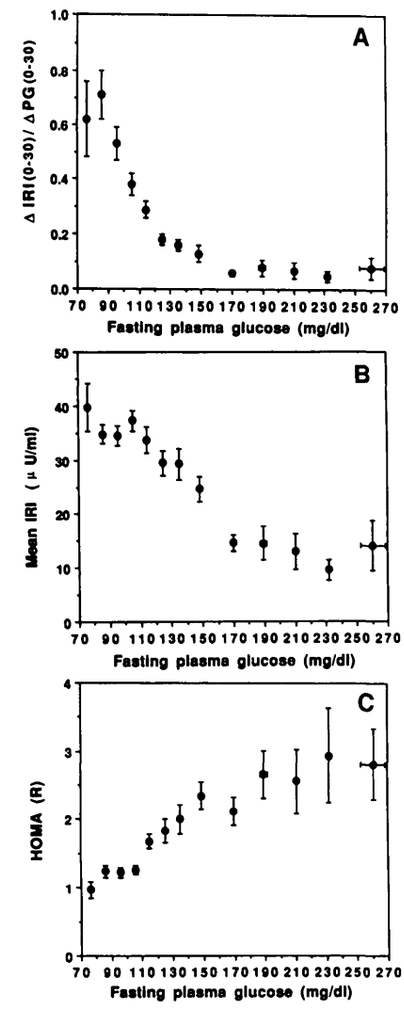

Figure 4—*Relationships between FPG and insulinogenic index (A), (ΔIRI0–30/ΔPG0–30), mean IRI during OGTT (B), and HOMA(R) in nonobese subjects (C). Data are means (●) ± SE (error bars).*

Our study has some limitations. First, we used HOMA(*R*) for measuring insulin resistance, an indirect method that depends on FPG and fasting IRI. Although the reproducibility of HOMA(*R*) is low, correlation of this value with values obtained by euglycemic clamp is high (23). Phillips et al. (22) reported that HOMA(*R*) correlated well with directly measured insulin resistance and concluded that this value is useful in population studies. Second, NGT subjects in our study were not age-matched to those with IGT or diabetes. Because aging reduces glucose tolerance by decreasing insulin secretion and insulin sensitivity (33), we have to take notice of this point.

However, if our NGT subjects were older, their insulin sensitivity may decrease more. Therefore, the difference in insulin sensitivity between NGT and IGT may be more small. Chen et al. (33) reported that the first-phase insulin in IVGTT did not correlate with age, and second phase insulin correlated with age inversely. Therefore, difference in age may not influence the early-phase insulin secretion. Third, and most important, the study design was cross-sectional. While cross-sectional studies provide information about the characteristics that may affect the development of NIDDM, they do not, however, provide information about the subjects who will actually develop NIDDM. Kadowaki et al. (17) studied Japanese subjects with IGT longitudinally and found that an impairment of the early-phase insulin secretion was independently related to the development of NIDDM. To our knowledge, however, no prospective study of a Japanese population that included measurements of both insulin secretion and insulin resistance has been reported.

In conclusion, we demonstrated that an impairment of early-phase insulin secretion may be the initial abnormality in the

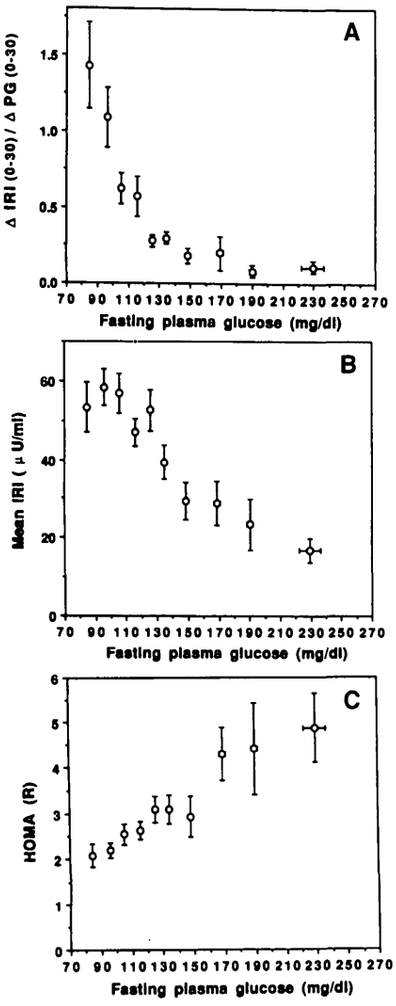

Figure 5—*Relationships between FPG and insulinogenic index* (A), *(ΔIRI0–30/ΔPG0–30), mean IRI during OGTT* (B), *and HOMA*(R) *in obese subjects* (C). *Data are means* (○) ± *SE (error bars).*

development of glucose intolerance in Japan. Contrary to results with Pima Indians and whites, marked hyperinsulinemia in IGT was uncommon in our subjects. Insulin resistance may be a consequence of significant hyperglycemia and/or obesity in NIDDM. The patterns of change in insulin secretion and insulin resistance associated with the progression of glucose intolerance were similar in the nonobese as well as obese Japanese subjects.

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