Pancreatic Beta-Cell Function and Insulin Sensitivity in Japanese Subjects With Impaired Glucose Tolerance and Newly Diagnosed Type 2 Diabetes Mellitus

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To clarify whether pancreatic beta-cell function and/or insulin resistance contributes to development of glucose intolerance in Japanese subjects, we investigated 551 subjects who underwent a 75-g oral glucose tolerance test (OGTT). Subjects were divided into 3 groups: normal glucose tolerance (NGT, n = 238), impaired glucose tolerance (IGT, n = 211), and newly diagnosed type 2 diabetes mellitus (n = 102). The diabetics were subdivided into 3 subgroups as follows: diabetes with normal fasting glucose (fasting plasma glucose [FPG] < 110 mg/dL), diabetes with impaired fasting glucose (FPG 110 to 125 mg/dL), and diabetes with diabetic fasting glucose (FPG ≥ 126 mg/dL). Insulinogenic index as early-phase insulin secretion, homeostasis model assessment (HOMA-beta and HOMA-resistance), and 4 different formulas of insulin sensitivity index were assessed by plasma glucose and insulin concentrations obtained at fasting or during a 75-g OGTT. Both early-phase insulin secretion and insulin sensitivity were low even in the IGT stage compared with NGT. The transition from IGT to diabetes was accompanied by a progressive deterioration of insulin reserve as well as insulin resistance. During the further progression in diabetes, insulinogenic index decreased additionally, whereas declines in insulin sensitivity were relatively small. In conclusion, both impaired insulin secretion and insulin resistance may contribute to the underlying mechanisms of glucose intolerance in Japanese subjects.

PREVIOUS STUDIES have demonstrated relative contributions of insulin resistance and/or pancreatic beta-cell failure to the pathogenesis of type 2 diabetes,[1-3] but which of these abnormalities is a primary defect for its pathogenesis has long been a matter of controversy. In examination of specific ethnic groups, insulin resistance has been reported to be a common physiologic defect underlying type 2 diabetes, with beta-cell failure and insulin deficiency occurring as secondary events.[4-6] On the other hand, some studies have found a lower early insulin secretory response even in prediabetic individuals.[7-9] However, these metabolic abnormalities may differ among ethnic groups.[10,11] Clearly, the Japanese population is lean relative to other populations. Notably, it has been known that Japanese subject with glucose intolerance are characterized by a decrease in the early-phase insulin response to a glucose load.[12-15] This information suggests that impaired pancreatic beta-cell function is probably the primary defect required for the development of type 2 diabetes in Japanese. Yet, no study has detailed insulin sensitivity together with pancreatic beta-cell function in Japanese subjects with newly presented type 2 diabetes mellitus compared to prediabetic individuals. Recently, several studies have demonstrated that the insulin sensitivity can be predicted from measurements in the fasting state and during an oral glucose tolerance test (OGTT).[16-20] In this study, we clarify whether pancreatic beta-cell function and/or insulin resistance contributes to the development of glucose intolerance in Japanese subjects.

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MATERIALS AND METHODS

Subjects

This study included 238 Japanese subjects with normal glucose tolerance (NGT), 211 with impaired glucose tolerance (IGT), and 102 with newly diagnosed type 2 diabetes mellitus. All underwent a diagnostic 75-g OGTT. Diabetes was diagnosed when hyperglycemia met the following criteria: casual plasma glucose ≥ 200 mg/dL, confirmed on a subsequent day by fasting plasma glucose (FPG) ≥ 126 mg/dL and/or an OGTT with the 2-hour postload value ≥ 200 mg/dL. All subjects with newly diagnosed diabetes had no type of diabetic microangiopathy, and subjects with previously known overt diabetes were excluded from the study. Furthermore, the diabetes subjects were subdivided into 3 groups as follows: diabetes with normal fasting glucose (DM-NFG), FPG less than 110 mg/dL; diabetes with impaired fasting glucose (DM-IFG), FPG 110 to 125 mg/dL; and diabetes with diabetic fasting glucose (DM-DFG), FPG ≥ 126 mg/dL.

This study was performed in accordance with the Helsinki Declaration, and written informed consent was obtained from each participant.

Oral Glucose Tolerance Test

A standard 75-g OGTT was performed after a 10-hour overnight fast. Plasma samples were obtained at 0, 30, 60, 90, 120, and 180 minutes after the glucose load. Plasma glucose was determined using a glucose oxidase autoanalyzer, and plasma immunoreactive insulin was measured by enzyme immunoassay (Entym Insulin Test, Roche, Basel, Switzerland). The plasma glucose response and total insulin secretion were evaluated by the area under the response curve for plasma glucose and insulin (AUC-glucose [0 to 180 minutes], and AUC-insulin [0 to 180 minutes]) calculated from the fasting, 30-, 60-, 90, 120-, and 180-minute plasma concentrations using the trapezoid rule.

Evaluation for Pancreatic Beta-Cell Function

The insulinogenic index, a widely used index of early-phase insulin response, was defined as the ratio of the increment of plasma insulin to that of plasma glucose at 30 minutes after glucose loading.[21] Homeostasis model assessment of beta-cell function (HOMA-B) proposed by Matthews et al[16] was caluculated as 20 × fasting plasma insulin/(FPG − 3.5).

Table 1. Clinical and Metabolic Characteristics of Subjects

	NGT	IGT	Type 2 DM
n	238	211	102
Age (yr)	61.6 ± 11.2	62.5 ± 10.4	62.6 ± 10.1
BMI (kg/m^2)	23.2 ± 3.1	24.4 ± 3.8*	25.2 ± 3.6†
SBP (mm Hg)	129 ± 19	131 ± 20	132 ± 18
DBP (mm Hg)	75 ± 13	74 ± 12	75 ± 11
Total cholesterol (mg/dL)	199 ± 41	199 ± 37	200 ± 37
Triglycerides (mg/dL)	123 ± 62	131 ± 83	166 ± 116†§
HDL-cholesterol (mg/dL)	52 ± 17	50 ± 15	47 ± 12*
Fasting glucose (mg/dL)	91.6 ± 7.2	97.7 ± 11.1†	116.1 ± 17.2†§
Fasting insulin (mU/L)	7.11 ± 4.15	8.05 ± 4.80*	7.85 ± 4.86
2-h glucose (mg/dL)	113.2 ± 18.1	163.7 ± 16.5†	242.2 ± 42.1†§
2-h insulin (mU/L)	41.8 ± 23.8	70.3 ± 46.0†¶	59.8 ± 43.2†

NOTE. Data are mean ± SD.

*$P < .05$ *v* NGT; †$P < .01$ *v* NGT; ‡$P < .05$ *v* IGT; §$P < .01$ *v* IGT; ¶$P < .05$ *v* DM; ‖$P < .01$ *v* DM.

Abbreviations: NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein.

Insulin Resistance and Sensitivity

Homeostasis model assessment of insulin resistance (HOMA-R) was used to calculate an index from the product of the fasting concentrations of plasma insulin and plasma glucose divided by 405.[16] Insulin sensitivity was also evaluated by 4 different formulas using 75-g OGTT values. The first formula of the insulin sensitivity index proposed by Matsuda and DeFronzo[17] was calculated as follows:

$$\text{ISI-M} = 10{,}000/\text{square root of } [(\text{mean plasma insulin} \times \text{mean plasma glucose during OGTT}) \times (\text{FPG} \times \text{fasting plasma insulin})].$$

The second formula used was proposed by Stumvoll et al[18]:

$$\text{ISI-S} = 0.157 - 4.576 \times 10^{-5} \times \text{I}(120) - 0.00519 \times \text{G}(90) - 0.000299 \times \text{I}(0).$$

The third formula used was proposed by Gutt et al[19]:

$$\text{ISI-G} = m/[\text{G}(0) + \text{G}(120)] \times 0.5/\log [\text{I}(0) + \text{I}(120) \times 0.5],$$

where m is the glucose uptake rate in peripheral tissues, calculated as $m = [75{,}000 \text{ mg} + (\text{G}(0) - \text{G}(120)) \times 0.19 \times \text{body weight}]/120 \text{ min}$.

The oral glucose insulin sensitivity (OGIS) index proposed by Mari et al[20] was calculated as follows:

$$\text{Cl(OGTT)} = \text{p4} \times [\{\text{p1 D}(0) - \text{V}[\text{G}(180) - \text{G}(120)]/60\}/\text{G}(120) + \text{p3 / G}(0)]/[\text{I}(120) - \text{I}(0) + \text{p2}]$$

$$\text{B} = [\text{p5 } (\text{G}(120) - \text{G(CLAMP)}) + 1] \times \text{Cl(OGTT)}$$

$$\text{OGIS index} = 0.5 \times \{\text{B} + \text{square root of } [\text{B}^2 + 4 \times \text{p5} \times \text{p6} \times (\text{G}(120) - \text{G(CLAMP)}) \times \text{Cl(OGTT)}]\}$$

where p1, p2, p3, p4, p5, and p6 are parameters (289, 270, 14,000, 440, 0.000637, and 117, respectively), D(0) is an oral glucose dose (expressed in g/m^2), V represents the total glucose distribution volume (assumed a value of 10 L/m^2), and G(CLAMP) is 90 mg/dL.

Statistical Analysis

Data are presented as the mean ± SD. Comparisons between groups were performed using analysis of variance (ANOVA) followed by post-hoc testing with Scheffé's test. Correlation between the measurements and the degree of diabetes (DM-NFG, DM-IFG, and DM-DFG) was tested with Spearman's nonparametric test. A *P* value less than .05 was considered significant.

RESULTS

Clinical and metabolic characteristics among NGT, IGT, and newly diagnosed type 2 diabetes mellitus (all-DM subjects) are shown in Table 1. No significant differences were seen between groups with respect to mean age, systolic and diastolic blood pressure, or total cholesterol. Body mass index was significantly higher in IGT and all-DM than in NGT. Triglycerides was significantly higher in all-DM than in NGT and IGT, whereas high-density lipoprotein (HDL)-cholesterol was significantly lower in all-DM than in NGT. FPG and 2-hour plasma glucose were significantly higher in IGT than in NGT, and were significantly higher in all-DM than in NGT and IGT. Fasting plasma insulin was significantly higher in IGT than in NGT, but no difference was seen between NGT and all-DM. The 2-hour plasma insulin was most prominent in IGT.

The values of total glucose and insulin responses, pancreatic beta-cell function, and insulin sensitivity among NGT, IGT, and all-DM subjects are shown in Table 2. The actual data for glucose and insulin responses during the OGTT are also illustrated in Figs 1 and 2. The AUC-glucose [0 to 180 minutes] increased significantly with worsening in glucose tolerance. Total insulin secretion evaluated by the AUC-insulin [0 to 180 minutes] was significantly higher in IGT than in both NGT and all-DM. The 30-minute increment in plasma insulin was significantly lower in IGT and all-DM than in NGT, and 60-minute plasma insulin was significantly lower in all-DM than in NGT and IGT. The plasma insulin values were greater in IGT at 90 and 120 minutes. Insulinogenic index decreased significantly with worsening in glucose tolerance, and HOMA-B was significantly lower in all-DM than in both NGT and IGT. The HOMA-R was significantly higher and ISI-M was significantly lower in both IGT and all-DM than in NGT. The ISI-S, ISI-G, and OGIS index were significantly lower in IGT than in NGT, and were significantly lower in all-DM than in both NGT and IGT. Figure 3s depicts the relationship between pancreatic

Table 2. Pancreatic Beta-Cell Function and Insulin Sensitivity Among Groups of Normal Glucose Tolerance, Impaired Glucose Tolerance, and Type 2 Diabetes Mellitus

	NGT	IGT	Type 2 DM
n	283	211	102
Total glucose and insulin responses			
Glucose AUC [0-180 min]	373 ± 44	477 ± 52†	645 ± 93†§
Insulin AUC [0-180 min]	124 ± 59	154 ± 84†‖	129 ± 81
Insurin secretion			
Insulinogenic index	0.797 ± 0.616	0.519 ± 0.411†	0.256 ± 0.208†§
HOMA-B	93.7 ± 58.5	93.4 ± 76.8	58.9 ± 41.5†§
Insulin resistance and sensitivity			
HOMA-R	1.62 ± 0.96	1.96 ± 1.23†	2.23 ± 1.37†
ISI-M	6.91 ± 3.38	5.43 ± 2.92†	5.31 ± 3.51†
ISI-S	951 ± 151	699 ± 209†	524 ± 200†§
ISI-G	83.2 ± 21.7	53.0 ± 12.3†	36.7 ± 9.9†§
OGIS index	529 ± 93	386 ± 55†	305 ± 44†§

NOTE. Data are mean ± SD.

*$P < .05$ *v* NGT; †$P < .01$ *v* NGT; ‡$P < .05$ *v* IGT; §$P < .01$ *v* IGT; ¶$P < .05$ *v* DM; ‖$P < .01$ *v* DM.

Abbreviations: AUC, area under the curve; HOMA-B, homeostasis model assessment of beta-cell function; HOMA-R, homeostasis model assessment of insulin resistance; ISI-M, insulin sensitivity index proposed by Matsuda et al; ISI-S, insulin sensitivity index proposed by Stumvoll et al; ISI-G, insulin sensitivity index proposed by Gutt et al; OGIS, oral glucose insulin sensitivity.

beta-cell function (insulinogenic index) and 4 formulas for insulin sensitivity (ISI-M, ISI-S, ISI-G, and OGIS index) in various degrees of glucose tolerance. This figure illustrates how abnormalities in insulin secretion and insulin action develop relative to each other during the development of glucose intolerance. It was shown that defects in insulin secretion occur at an early stage during the worsening of glucose tolerance (transition from NGT to IGT, 34% reduction in insulinogenic index; IGT to DM, 50%). On the other hand, decrease in insulin sensitivity was evident during the transition from NGT to IGT, as indicated by a 21% decrease in ISI-M, 26% in ISI-S, 36% in ISI-G, and 27% in OGIS index. But, declines in insulin sensitivity were relatively low during the further progression from IGT to DM (2% reduction in ISI-M, 25% in ISI-S, 32% in ISI-G, and 21% in OGIS index).

Moreover, subjects with newly diagnosed type 2 diabetes mellitus were subdivided based on the FPG diagnostic criteria; 40 were classified as DM-NFG, 34 as DM-IFG, and 28 as DM-DFG. Table 3 shows the values of total glucose and insulin responses, pancreatic beta-cell function, and insulin sensitivity among the 3 groups. The AUC-glucose [0 to 180 minutes] increased and the AUC-insulin [0 to 180 minutes] decreased significantly with further progression in diabetes, respectively. Both insulinogenic index and HOMA-B decreased significantly with further progression in diabetes. Although no significant differences in the HOMA-R, ISI-M, ISI-S, and ISI-G were seen among the 3 groups, the OGIS index significantly decreased with further progression in diabetes.

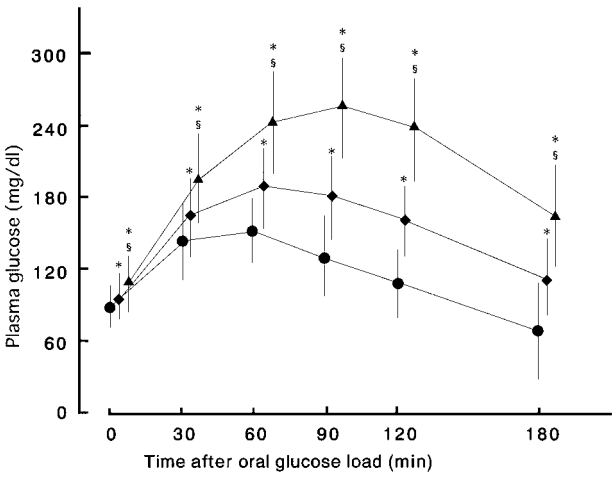

Fig 1. Plasma glucose concentrations during a 75-g OGTTin subjects with NGT (●), IGT (◆), and diabetes mellitus (▲). *$P < .01$ *v* NGT; §$P < .01$ *v* IGT.

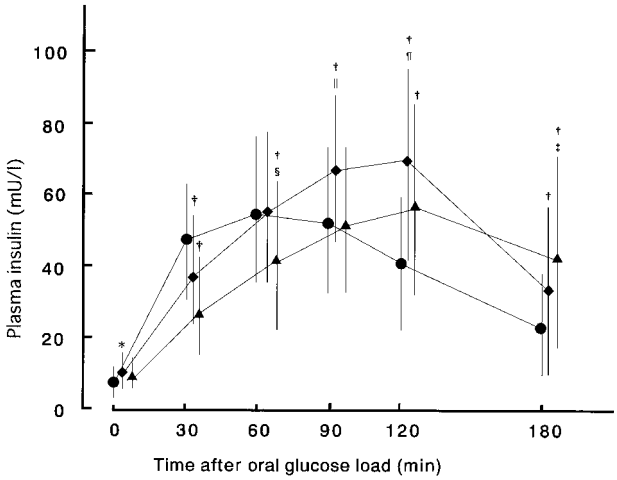

Fig 2. Plasma insulin concentrations during a 75-g OGTT in subjects with NGT (●), IGT (◆), and diabetes mellitus (▲). *$P < .01$ *v* NGT; †$P < .01$ *v* NGT; ‡$P < .05$ *v* IGT; §$P < .01$ *v* IGT; ¶$P < .05$ *v* DM; ‖$P < 0.01$ *v*. DM.

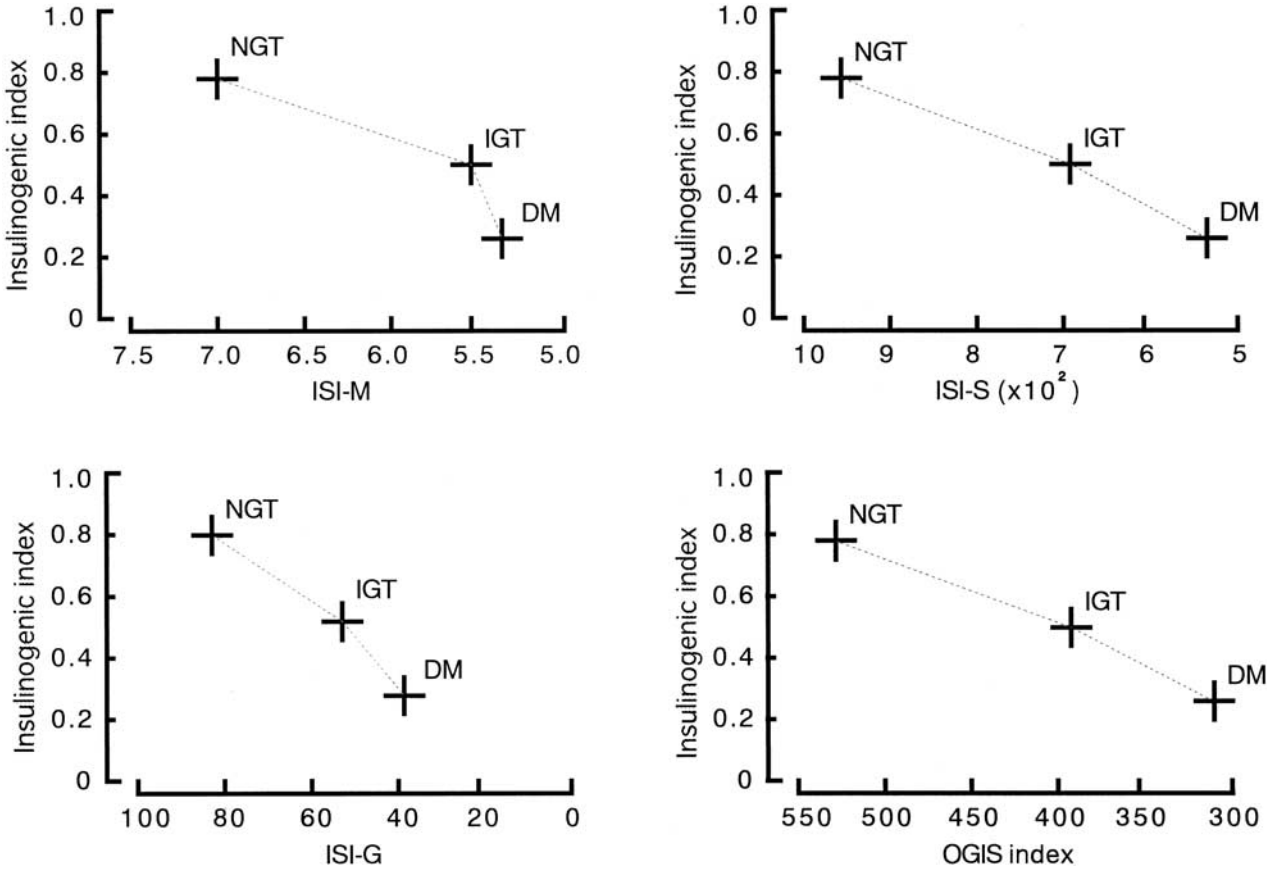

Fig 3. Relationships between insulinogenic index and insulin sensitivity in various degree of glucose tolerance: NGT, IGT, and DM. ISI-M, insulin sensitivity index proposed by Matsuda et al; ISI-S, insulin sensitivity index proposed by Stumvoll et al; ISI-G, insulin sensitivity index proposed bu Gutt et al; OGIS, oral glucose insulin sensitivity.

DISCUSSION

Together with changes in recent years from the traditional Japanese lifestyle to a Western lifestyle, the prevalence of IGT and type 2 diabetes has increased in Japan. In the Western countries, previous studies have demonstrated a link between insulin resistance (including compensatory hyperinsulinemia) and both IGT and early-stage diabetes.[22] Caucasians, Pima Indians, African-Americans, and Mexican Americans show relatively high insulin responses to an oral glucose load.[3,23,24] However, there is a general concept that there could be ethnic differences in the relative contributions of beta-cell failure versus decreased insulin sensitivity.[10,11] Which of these factors represents the primary abnormality is still a matter of controversy. In this context, Arner et al[25] have suggested that nonobese Swedes with type 2 diabetes have defects in insulin secretion rather than decreased insulin sensitivity, whereas obese diabetics have both impaired insulin action and secretion. Davies et al[26] also reported that Caucasians with newly diagnosed type 2 diabetes are predominantly insulin-deficient with defective beta-cell function rather than hyperinsulinemia. Furthermore, Haffner et al[3] reported that both decreased insulin secretion and insulin sensitivity contribute to the development of type 2 diabetes in Hispanics. On the other hand, most Japanese subjects with glucose intolerance are less obese than in such other ethnic groups. Yoneda et al[12] reported that Japanese non-obese subjects with IGT are characterized by marked impairment in early-phase insulin response to glucose, but insulin sensitivity was not analyzed in the study. Kosaka et al[13] reported that the insulin response to an oral glucose load is consistently decreased in established type 2 diabetes in most Japanese patients. Matsumoto et al[14] also reported that the worsening from NGT to IGT may be associated with a decrease in early-phase insulin secretion in non-obese and obese Japanese subjects, but that hyperinsulinemia is not common in IGT. Furthermore, prospective studies in Japan[27,28] suggested that low insulin response to glucose is a major risk factor for the development from IGT to type 2 diabetes. In the present study, insulinogenic index (it means early-phase insulin response) declined significantly during the development of glucose intolerance, as illustrated in Fig 3. As noted above, insulinogenic index was already too low even in the IGT stage compared with NGT in Japanese subjects.

The euglycemic hyperinsulinemic clamp is the generally accepted method to assess insulin sensitivity, but its invasiveness and high cost have limited its use in clinical practice. It seems likely that HOMA-R for measuring insulin resistance is

Table 3. Pancreatic Beta-Cell Function and Insulin Sensitivity Among the Three Groups of Type 2 Diabetes Mellitus Subjects Subdivided by the Degree of Fasting Plasma Glucose Levels

	Type 2 DM			
	FPG < 110 mg/dL	FPG 110-125 mg/dL	FPG ≥ 126 mg/dL	*P**
n	40	34	28	
Total glucose and insulin responses				
Glucose AUC [0-180 min]	604 ± 61	640 ± 69	709 ± 118	<.001
Insulin AUC [0-180 min]	152 ± 88	128 ± 80	97 ± 59	.0307
Insurin secretion				
Insulinogenic index	0.312 ± 0.226	0.265 ± 0.218	0.164 ± 0.123	.0471
HOMA-B	76.5 ± 46.1	59.9 ± 38.2	32.9 ± 20.5	<.001
Insulin resistance and sensitivity				
HOMA-R	1.97 ± 1.27	2.52 ± 1.48	2.27 ± 1.36	.1101
ISI-M	5.75 ± 4.42	4.82 ± 2.81	5.25 ± 2.75	.5032
ISI-S	519 ± 193	515 ± 214	543 ± 197	.3906
ISI-G	35.7 ± 8.4	37.1 ± 9.8	37.8 ± 12.1	.2856
OGIS index	318 ± 46	302 ± 39	289 ± 45	.0257

NOTE. Data are mean ± SD.

**P* value was tested by Spearman's nonparametric test.

an indirect method that depends on fasting glucose and insulin values. Recently, several investigators have demonstrated that the insulin sensitivity can be predicted from measurements in the fasting state and during an OGTT.[17-20] We have found a good correlation and a good agreement between these methods with almost the same numerical values and proposed the use of OGTT for the assessment of insulin sensitivity index.[29] In the present study, we demonstrated that the majority of subjects with glucose intolerance in Japan have a low insulin sensitivity index before the development type 2 diabetes mellitus, which is a new finding. In contrast, Matsumoto et al[14] reported that the worsening from NGT to IGT tended to be associated with an increase in insulin resistance (assessed by HOMA-R) in Japanese subjects, but this difference did not reach statistical significance ($P = .06$ in non-obese subjects and $P = .17$ in obese subjects). Our results showed that HOMA-R is significantly higher even in IGT than in NGT, and this evidence was confirmed by other insulin sensitivity indices: the ISI-M, ISI-S, ISI-G, and OGIS. Several factors may explain the discrepancy between the present and previous results. One reason is a difference in mean age of subjects, because aging reduces insulin sensitivity.[30] Our subjects were older than Matsumoto's subjects (61.6 ± 11.2 *v* 47.3 ± 1.4 years in NGT; 62.5 ± 10.4 *v* 57.2 ± 1.1 years, respectively). Second, Matsumoto et al assessed non-obese and obese subjects separately. The values for body mass index (BMI) were comparable in the NGT and IGT groups in both non-obese (21.2 ± 0.2 *v* 21.8 ± 0.2 kg/m^2) and obese (27.6 ± 0.3 *v* 27.8 ± 0.4 kg/m^2). Indeed, in our study, the mean value of BMI was slightly higher in IGT than in NGT (23.2 ± 3.1 *v* 24.4 ± 3.8 kg/m^2, $P < .05$), but the different was too small. It seems likely that the mean value of BMI in IGT does not indicate obviously obese. Furthermore, Taniguchi et al[31] also reported that IGT and type 2 diabetes mellitus in Japanese subjects coexistent with normal insulin sensitivity evaluated using a minimal model analysis, but this precise conclusion is difficult with a small number of study subjects.

In conclusion, the present study indicates that both insulin resistance and impaired beta-cell function contribute to the underlying mechanism of glucose intolerance in Japanese subjects.

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