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Insulin Secretion and Insulin Sensitivity at Different Stages of Glucose Tolerance: A Cross-Sectional Study of Japanese Type 2 Diabetes

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To evaluate the factors causing glucose intolerance in type 2 diabetes in Japan, insulin secretion and insulin sensitivity were compared across the range of glucose tolerance. Subjects were divided into 3 groups: normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (DM) according to the criteria of the World Health Organization (WHO). We examined insulin secretion and insulin sensitivity using fasting blood glucose and insulin levels and 75 g oral glucose tolerance test (OGTT). We used homeostasis model assessment (HOMA) β-cell and insulinogenic index (30 minutes) to estimate insulin secretion and HOMA-insulin resistance (IR) and insulin sensitivity index (ISI) composite for insulin sensitivity. Although insulin resistance plays an important role in the development of diabetes in many ethnic populations, the differences in insulin sensitivity between NGT and IGT and between IGT and DM are small in Japanese patients. On the other hand, as glucose intolerance increases, insulin secretion decreases most remarkably both between NGT and IGT and between IGT and DM in Japanese patients. Decreasing insulin secretion and decreasing insulin sensitivity both occur in developing type 2 diabetes in Japanese patients, but decreased basal and early-phase insulin secretion had more pronounced contribution to glucose tolerance than the indices of insulin sensitivity. Japanese type 2 diabetic patients are characterized by a larger decrease in insulin secretion and show less attribution of insulin resistance.

TYPE 2 DIABETES is characterized by both decreased insulin secretion and decreased insulin sensitivity, but the degree of contribution of these 2 factors in the etiology varies.[1,2] Impaired insulin secretion and impaired insulin sensitivity both occur in the development of type 2 diabetes, but the contribution of these factors differs in certain ethnic populations.[3-6] The prevalence of diabetes is increasing in Japan and is now comparable to other countries. However, there are some differences between Japanese and other ethnic populations. The mean body mass index (BMI) of epidemiologic studies of type 2 diabetes in Japanese is around 24, which is lower than the studies of other ethnic populations.[7-11] In previous studies, we have examined insulin secretion and sensitivity using 75 g oral glucose tolerance test (OGTT) and minimal model analysis.[4,12,13] There were some differences in factors responsible for glucose tolerance of Japanese subjects in comparison to the other studies. We have reported that lower insulin secretory capacity in Japanese subjects would be unlikely to compensate for only a slight decrease in insulin sensitivity.[14] However, to understand the profile of Japanese subjects at various stages of glucose tolerance, a large number of subjects had to be examined.

In the present study, we have investigated insulin secretion and insulin sensitivity of 684 Japanese subjects across the range of glucose tolerance: normal glucose tolerance (NGT) (fasting plasma glucose [FPG] level $<$ 6.1 mmol/L and 2-hour plasma glucose [PG] level $<$ 7.8); impaired glucose tolerance (IGT) (FPG level $<$ 7 and 7.8 $<$ 2-hour PG level $<$ 11.1); and type

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Table 1. Clinical Characteristics of the Subjects With Varing Degrees of Glucose Tolerance

	NGT	IGT	DM
N (M/F)	176 (125/51)	158 (112/46)	350 (248/102)
Age (yr)	49.1 ± 0.9	52.7 ± 0.7*	52.6 ± 0.4*
BMI (kg/m^2)	23.5 ± 0.2	23.9 ± 0.2	24.7 ± 0.2*†
FPG (mmo/L)	5.3 ± 0.03	5.8 ± 0.04*	8.1 ± 0.10*†
2-h PG (mmol/L)	5.9 ± 0.09	9.2 ± 0.08*	15.6 ± 0.23*†
Insulin-0 (μU/mL)	5.1 ± 0.19	5.7 ± 0.23	6.6 ± 0.22*†
Insulin-30	31.3 ± 1.78	24.8 ± 1.32*	15.1 ± 0.61*†
Insulin-60	43.7 ± 2.37	35.5 ± 2.15*	24.2 ± 1.04*†
Insulin-90	45.9 ± 3.76	43.9 ± 3.29	27.4 ± 1.26*†
Insulin-120	32.2 ± 2.03	41.1 ± 2.42*	29.3 ± 1.25†
Triglycerides (mg/dL)	120.4 ± 6.9	190.4 ± 33.5*	191.5 ± 13.5*
Total cholesterol (mg/dL)	205.8 ± 2.9	211.9 ± 3.0	211.4 ± 2.2
HDL-cholesterol (mg/dL)	56.3 ± 1.6	52.3 ± 1.6*	50.8 ± 0.8*

*Significant difference *v* NGT; †significant difference *v* IGT.

2 diabetes (DM) (FPG level $\geq$ 7 or 2-hour PG level $>$ 11.1).[15] The homeostasis model assessment (HOMA) β-cell and HOMA-insulin resistance (IR) indices calculated by HOMA were used to determine insulin secretion and sensitivity at the fasting state.[16-18] The insulinogenic index (30 minutes) and insulin sensitivity index (ISI) composite were determined by 75 g OGTT.[19-21] We compared these indices across the range of glucose tolerance from normal to type 2 diabetes to evaluate the causative factors.

SUBJECTS AND METHODS

OGTT (75 g) was used to divide 684 Japanese subjects into 3 groups: NGT, IGT, and DM according to the criteria of the World Health Organization (WHO) in 1998.[15] There were 102 isolated IGT subjects (FPG level $<$ 6.1 and 7.8 $<$ 2-hour PG level $<$ 11.1) in 158 IGT subjects. We recruited subjects from Kyoto University Hospital, Ikeda Hospital, Kanai Hospital, Kansai Health Management Center, and Kansai-Denryoku Hospital during 1990 to 2003. The subjects showed no signs of hypertension, hepatic or renal diseases, engaged in no heavy exercise, or took any medications before the study. Blood was drawn in the morning after a 12-hour fast. The plasma glucose was measured by the glucose oxidase method, and serum insulin was measured using 2-site immunoradiometric assay (Insulin Riabead I; Dainabot, 1990-1991 and Insulin Riabead II, Dainabot, 1992-2003, Tokyo, Japan). The assay results of the same samples with these 2 insulin assay methods showed a very high correlation ($r = 0.99$, $P < .0001$) in the usual assay range. The lipid profiles were measured as reported previously.[22]

The indices of basal insulin secretion and sensitivity were evaluated by HOMA and calculated as follows: HOMA-IR = FIRI $\times$ FPG/22.5, HOMA β-cell = 20 $\times$ FIRI/(FPG-3.5), where FIRI is fasting plasma insulin level(μU/mL) and FPG is fasting plasma glucose levels (mmol/L).[14-16] ISI composite was calculated according to the formula as follows: 10,000/(Glu 0 $\times$ Ins 0 $\times$ mean Glu 0$-$120 $\times$ mean Ins 0$-$120)$^{0.5}$.[19] Insulinogenic index (30 minutes) was estimated as follows: (Ins 30 $-$ Ins 0)/(Glu 30 $-$ Glu 0).[20,21]

Statistical Analysis

Statistical analysis was performed with the StatView 5 system (Abacus Concepts, Berkeley, CA). Unpaired student's *t* tests and simple regression analysis were used for the comparisons of clinical parameters. For the analysis of variance, Bonferroni test was used and $P < .05$ was considered significant. We used multiple regression analysis for the comparison of the relationship between area under the curve for glucose (G-AUC) and the indices of insulin secretion and sensitivity. The data are expressed as mean ± SEM.

RESULTS

Table 1 shows the characteristics of the subjects in this study. There was a 3.6-year difference between NGT and IGT, and no significant difference between IGT and DM in age. There was no significant difference between NGT and IGT, and only 0.8 difference between IGT and DM in BMI. The mean values of the HOMA-IR of NGT, IGT, and DM were 1.2, 1.5, and 2.4, respectively, only representing somewhat small differences between each of the groups, as shown in Fig 1A. The mean values of the ISI composite for NGT, IGT, and DM were 8.6, 7.1, and 5.8, respectively, also representing relatively small differences between the 3 groups (Fig 1B). In contrast, there was a dramatic decrease in HOMA β-cell among the 3 groups, as shown in Fig 2A, as there was also in the insulinogenic index, as shown in Fig 2B.

We then examined the relationship between the G-AUC and the indices of insulin secretion and sensitivity. The scattered plots of simple regression analysis between the G-AUC and the 4 indices are presented in Fig 3. There were significant relationships between G-AUC and the 4 indexes. Multiple regression analysis showed that HOMA-IR, HOMA β-cell, ISI composite, and insulinogenic index were independent factors to explain the variability of 60.7% of G-AUC ($P < .0001$). The

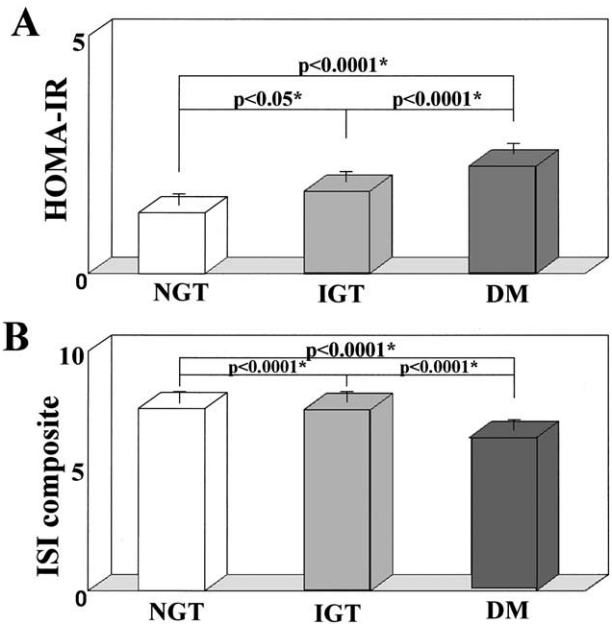

Fig 1. (A) Insulin resistance index at basal state was compared across the range of glucose tolerance. Insulin resistance increases with increasing glucose intolerance, but the differences are relatively small in Japanese subjects. (B) Insulin sensitivity decreases with increasing glucose intolerance according to the ISI composite, and the differences also are relatively small. *Significant differences assessed by analysis of variance.

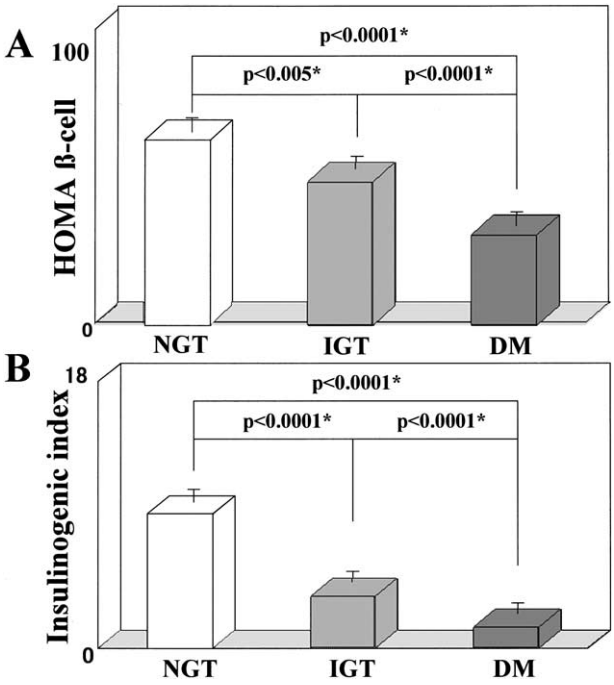

Fig 2. (A) Comparison of insulin secretion index in the basal state across the range of glucose tolerance. Insulin secretion decreases with increasing glucose intolerance. (B) Early-phase insulin secretion decreases remarkably with increasing glucose intolerance. *Significant differences assessed by analysis of variance.

correlation coefficients of these indices with G-AUC in simple regression analysis and β values and P values of multiple regression analysis are shown in Table 2. As estimates of basal insulin secretion and sensitivity, β value of HOMA β-cell was higher than HOMA-IR. As estimates of postchallenge insulin secretion and sensitivity, β value of insulinogenic index was considerably higher than ISI composite.

DISCUSSION

Indices of insulin secretion (HOMA β-cell) and insulin resistance (HOMA-IR) were evaluated from a fasting sample by HOMA.[16-18] These estimations correlated well with the insulin secretion and insulin sensitivity indices of minimal model analysis.[17] Matsuda and DeFronzo[19] have reported a new index of insulin sensitivity as an ISI composite, which has been validated by glucose clamp study. The insulinogenic index (30minutes) is a well-known measure of early-phase insulin secretion during OGTT.[20,21] Comparison of these 4 indexes across the range of glucose tolerance indicates that Japanese type 2 diabetic patients are characterized primarily by a decrease in insulin secretion and show less attribution of insulin resistance. BMI is a strong determinant of insulin resistance, and it is concordant with the evidence that the mean BMIs of representative epidemiologic studies of Japanese diabetic patients are from 23 to 25, lower than the studies of the other ethnic populations.[7-10]

These data indicate that the major factor in glucose intolerance that is characteristic of type 2 diabetes also differs in Japanese patients. Tripathy et al[11] found using OGTT in the Botnia study that the factors responsible for the development of glucose intolerance are decreased insulin secretion and sensitivity. Using HOMA-IR, insulin resistance increased nearly 2-fold from 1.7 as glucose intolerance increased from NGT to IGT and 3.6-fold in DM in that study. Using the same index, insulin resistance of Japanese subjects also increased from 1.2 to 1.5 as glucose intolerance increased from NGT to IGT and from 1.5 to 2.4 as glucose intolerance increased from IGT to DM, remarkably less than in the Botnia study. The difference of HOMA-IR in DM patients between Caucasian and Japanese becomes more than double as a number. Considering even the difference of insulin assay method and the existence of proinsulin, insulin resistance indices of Caucasian are remarkably higher than those of the Japanese. The HOMA-IR of Japanese subjects also is lower compared with that in other ethnic populations of previous studies.[23-27]

On the other hand, the reduction in insulin secretion in Japanese subjects is remarkable. The insulinogenic index (30minutes) of Japanese subjects decreased from 10.0 to 5.3 as glucose intolerance increases from NGT to IGT and from 5.3 to 1.7 as glucose intolerance increases from IGT to DM. In the Botnia study, insulin secretion decreased from 22 by half as glucose intolerance increased from NGT to IGT and by half as glucose intolerance increased from IGT to DM. The insulin secretion in Japanese subjects is considerably lower both than these and those reported in other populations.[28,29] These findings are in accord with those in the Japanese-American population, suggesting a common predisposition of Japanese populations.[30,31]). Multiple regression analysis revealed that HOMA-IR, HOMA β-cell, ISI composite, and insulinogenic index are independently associated with G-AUC. The correlation coefficients of insulinogenic index are considerably higher than the ISI composite (Table 2). In this study, the mean of all the subjects of fasting and 2-hour glucose levels were 6.8 mmol/L and 11.3 mmol/L, respectively, and their glucose intolerance was very mild. Compensately, increase in insulin secretion can make the fasting glucose levels stay near the normal range in these subjects. However, glucose intolerance, expressed as G-AUC during OGTT, appears after the challenge of glucose. Thus, indices using the results not only fasting levels, but after the glucose load, can detect a slight difference of glucose tolerance in subjects with mild glucose intolerance. Matsuda and DeFronzo[19] reported ISI composite is a good surrogate measure of whole body insulin sensitivity in comparison to clamp studies. We also have confirmed the validity of ISI composite using the minimal model analysis.[32]

The factors responsible for the ethnic differences in glucose tolerance are not yet fully clarified. Body fat distribution plays an important role in insulin resistance and glucose tolerance in some studies. We have reported not only visceral, but subcutaneous adiposity contributes to glucose intolerance suggesting the characteristic of Japanese patients.[33] Recently, the contribution of β-cell function to ethnic difference and genetic predisposition was described using precise estimation method of insulin secretion by simultaneous measurement of glucose, insulin, and C-peptide.[34,35] The analysis of body fat distribution and further estimation of insulin secretory capacity will give more explanations for ethnic differences in glucose tolerance.

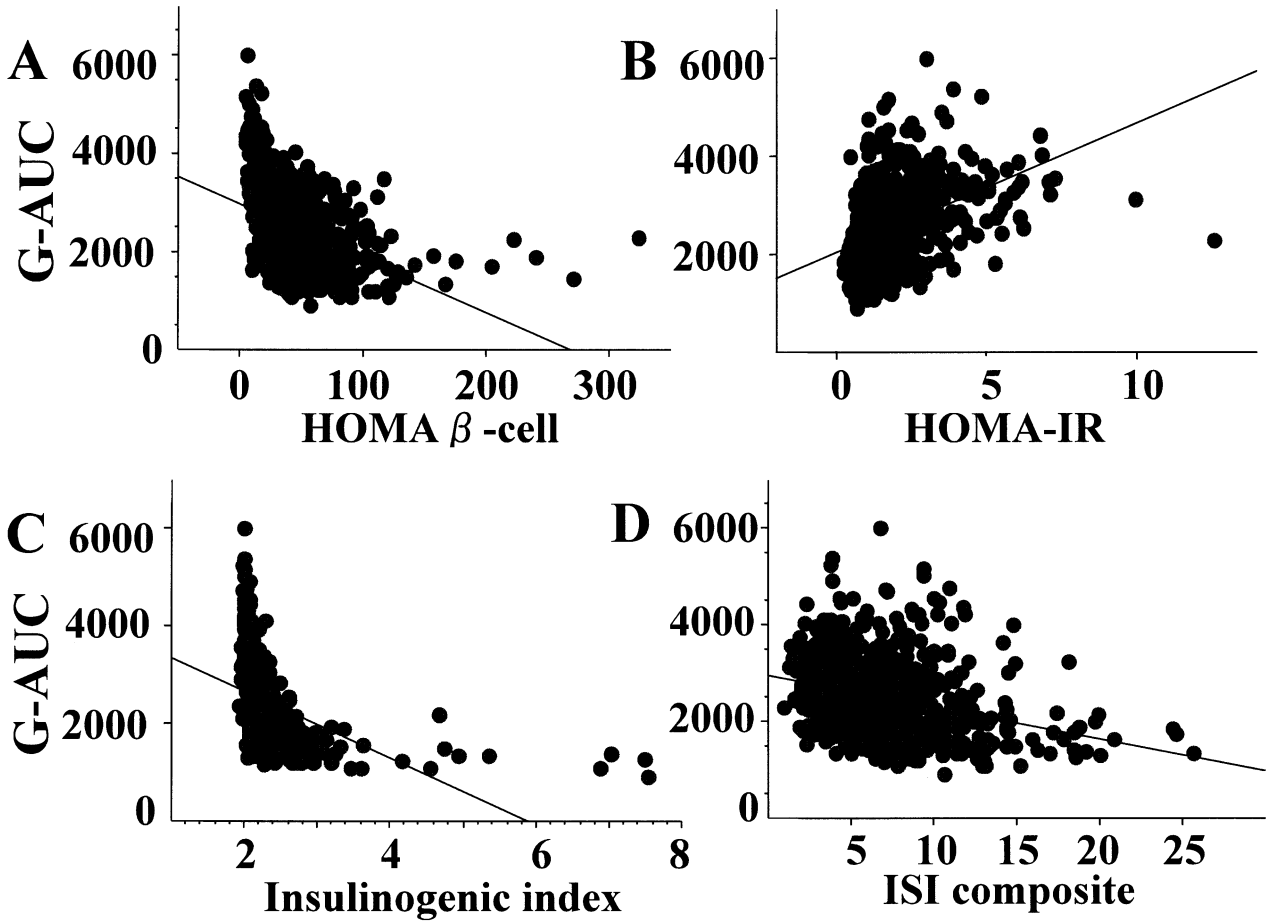

Fig 3. The relationship between G-AUC and the indices of insulin secretion and sensitivity. (A, B) As estimates of basal state, HOMA β-cell and HOMA-IR had significant relationships with G-AUC ($r = -0.45$, $P < .0001$, and $r = 0.41$, $P < .0001$, respectively). (C, D) As estimates of insulin secretion and sensitivy including postchallenge state, there were significant relationships between G-AUC and insulinogenic index ($r = -0.42$, $P < .0001$), and ISI composite ($r = -0.29$, $P < .0001$).

In addition, we compared the indices of insulin secretion and sensitivity between the subgroups of the prediabetic state to elucidate the profile of glucose tolerance (isolated IFG: 6.1 < FPG < 7 and 2-hour PG level < 7.8(n = 44) and isolated IGT: FPG level < 6.1 and 7.8 < 2-hour PG level < 11.1(n = 102)). Isolated IFG is characterized that they cannot keep fasting plasma glucose levels within normal limit at basal steady state, even if they have reserve capacity of insulin secretion after the glucose challenge. In these study subjects, we found HOMA β-cell of isolated IFG was significantly higher than that of isolated IGT (36.5 and 58.1, respectively, $P < .0001$), but there were no significant differences in other indices. It is considered that the difference between IFG and IGT is, at least in part, in the different disrupted balance of insulin secretion and sensitivity at the fasting state. We described the importance of early-phase insulin secretion for the elevation of 2-hour PG levels in Japanese subjects.[36] Further studies are necessary to clarify the different mechanisms of regulation between FPG and 2-hour PG levels.

Table 2. Relationship of the Indices of Insulin Secretion and Sensitivity With G-AUC

	Correlation Coefficients	Standardized β	*P* Value
HOMA β-cell	−0.45	−0.61	<.0001
HOMA-IR	0.41	0.53	<.0001
Insulinogenic index	−0.42	−0.20	<.0001
ISI composite	−0.29	−0.11	<.001

The incidence of type 2 diabetes has increased recently in Japan and is now comparable to that in other countries, but the causation of the glucose intolerance differs.[3,25,30,31] It is important in terms of prognosis and therapeutic strategy for each diabetic patient to consider the contribution of impaired insulin secretion and insulin resistance to glucose intolerance.[37] The present study clearly shows the clinical relevance of lower basal and impaired early-phase insulin secretion in type 2 diabetes in Japanese patients.

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