Insulin Secretory Dysfunction and Insulin Resistance in the Pathogenesis of Korean Type 2 Diabetes Mellitus

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Although insulin resistance has been shown to be a primary defect causing type 2 (non–insulin-dependent) diabetes mellitus in Pima Indians and Caucasians, insulin secretory defect has also been known to be an important factor in the development of type 2 diabetes. We undertook a study to investigate the initial abnormality of glucose intolerance in Koreans. A total of 370 Korean subjects were classified into 5 groups according to their degree of glucose intolerance (normal fasting glucose [NFG]/normal glucose tolerance [NGT], n = 95; impaired fasting glucose [IFG]/NGT, n = 29; NFG/impaired glucose tolerance [IGT], n = 60; IFG/IGT, n = 68; diabetes, n = 118). Insulinogenic index was used as an index of early-phase insulin secretion. Insulin resistance was assessed by the R value of the homeostasis model assessment [HOMA(R)]. Insulinogenic index significantly decreased in subjects with IFG/NGT and NFG/IGT compared with those with NFG/NGT. However, there was no significant difference in HOMA(R) between subjects with NFG/NGT and those with IFG/NGT or NFG/IGT. Insulinogenic index decreased significantly with the increase of plasma glucose 120-minute value at the earlier stage of glucose intolerance compared with HOMA(R). These results suggest that early-phase insulin secretory defect may be the initial abnormality in the development of type 2 diabetes in Korean subjects.

BOTH INSULIN deficiency and insulin resistance have been known to be involved in the pathogenesis of type 2 (non–insulin-dependent) diabetes mellitus. The relative importance of each factor may differ widely from patient to patient. DeFronzo et al[1] have stated that type 2 diabetes mellitus is largely due to insulin resistance, and only in some type 2 diabetic patients is the impairment of insulin secretion the initial lesion. On the other hand, Porte[2] viewed type 2 diabetes as a heterogeneous disorder in which islet dysfunction plays a critical role, while insulin resistance contributes to produce the final syndrome. Lillioja[3] stated that beta cell function may not be able to withstand the demands of insulin resistance in some ethnic groups. Although both factors are important and which one is the initial lesion does not diminish the importance of the other, investigation of the initial lesion in the development of glucose intolerance is undoubtedly important. The purpose of our study was to investigate which the initial lesion is in the development of glucose intolerance in Koreans, insulin resistance or impaired insulin secretion.

SUBJECTS AND METHODS

Subjects

All subjects were recruited from those who visited the Health Promotion Center or the Diabetes Clinic of Samsung Medical Center between 1996 and 1998. A complete physical examination, routine collection of biochemical data, and a 75-g oral glucose tolerance test (OGTT) was performed after an overnight fast of 12 to 14 hours. Subjects ingested 75 g of glucose, and blood samples were taken at 0, 30, 60, 90, and 120 minutes. Plasma and serum were stored at −20°C for later assay of plasma glucose and serum insulin. Subjects who were being treated for diabetes were excluded from the study as were those with heart or renal failure, chronic liver diseases, endocrine diseases, or those with type 1 diabetes (ketonuria or anti-glutamic acid decarboxylase [anti-GAD] II antibody positivity). The subjects (n = 370) included 248 men and 122 women, aged 17 to 74 years, and were classified into 5 groups according to their degree of glucose intolerance (normal fasting glucose [NFG; fasting plasma glucose value < 6.1 mmol/L]/normal glucose tolerance [NGT; 120-minute plasma glucose value during OGTT < 7.8 mmol/L], n = 95; impaired fasting glucose [IFG; fasting plasma glucose value 6.1 to 7.0 mmol/L]/NGT, n = 29; NFG/impaired glucose tolerance [IGT; 120-minute plasma glucose value during OGTT 7.8 to 11.1 mmol/L], n = 60; IFG/IGT[4], n = 68; diabetes; 120-minute plasma glucose value during OGTT > 11.1 mmol/L, n = 118).[5,6] All of the subjects with fasting plasma glucose values > 7.0 mmol/L showed 120-minute plasma glucose value during OGTT > 11.1 mmol/L. Informed consent was obtained from all of the participants, and this study was approved by the Internal Review Board (IRB) of Samsung Medical Center.

Analytical Procedures

Plasma glucose was measured in duplicate with an autoanalyzer (Hitachi, Tokyo, Japan) by the hexokinase method. Interassay coefficients of variation was 1.6%. Serum insulin was measured in duplicate with an immunoradiometric assay (IRMA) method (Medgenix, Niveles, Belgium). Intra- and interassay coefficients of variation were 2.2% and 5.8%, respectively, in cases of serum insulin level < 215 pmol/L and 3.9% and 4.5%, respectively, in cases of serum insulin level ≥ 215 pmol/L.

Analysis of Insulinogenic Index and HOMA(R)

An insulinogenic index was used as an index of early-phase insulin secretion during the OGTT.[7-10] The insulinogenic index was defined as the ratio of the increment of insulin to that of plasma glucose 30 minutes after a 75-g glucose load administered orally (Δinsulin, 0 to 30 minutes/Δplasma glucose (PG), 0 to 30 minutes). Insulin resistance was assessed by HOMA(R).[11] Briefly, HOMA(R) was calculated by the formula HOMA(R) = fasting serum insulin (μU/mL) × fasting plasma glucose (FPG) (mmol/L)/22.5. Although the reproducibility of HOMA is low, R values have been shown to correlate well with values obtained by euglycemic clamp studies.[11] Insulinogenic index and HOMA(R) were log transformed so that their distribution

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would be more normally distributed. These variables were back transformed in the table and figures presented.

Statistical Analyses

Values were expressed as means ± SD. The differences in the insulinogenic index and HOMA(R) among 5 groups were examined by 1-way analysis of variance (ANOVA) and post hoc multiple-comparison test. Data were analyzed with the SPSS statistical package (SPSS N.T. for Windows, Chicago, IL). Differences were considered statistically significant at the level of $P < .05$.

RESULTS

Changes in Insulinogenic Index and HOMA(R) With the Worsening of Glucose Tolerance

Clinical characteristics of the subjects are presented in Table 1. There was no significant difference in age, body mass index (BMI), and gender among the 5 groups. Fasting serum insulin in the diabetes group was significantly higher than that in NFG/NGT group (78.1 ± 38.2 *v* 65.1 ± 44.1 pmol/L, $P < .05$). However, there was no significant difference in fasting serum insulin among NFG/NGT, IFG/NGT, NFG/IGT, and IFG/IGT groups. There was no significant difference in HOMA(R) among NFG/NGT, IFG/NGT, and NFG/IGT groups. HOMA(R) of IFG/IGT and the diabetes group was significantly higher than that of NFG/NGT group, respectively (3.0 ± 1.8, 3.5 ± 1.7 *v* 2.2 ± 1.5, $P < .001$, Fig 1). Insulinogenic indices of the IFG/NGT and NFG/IGT groups were significantly lower than that of the NFG/NGT group, respectively (0.47 ± 0.51, 0.62 ± 0.65 *v* 0.89 ± 0.86, $P < .01$, Fig 1). Values of insulinogenic index in the IFG/IGT and diabetes groups were also significantly lower than that in the NFG/NGT group, respectively (0.40 ± 0.39, 0.21 ± 0.19 *v* 0.89 ± 0.86, $P < .001$, Fig 1).

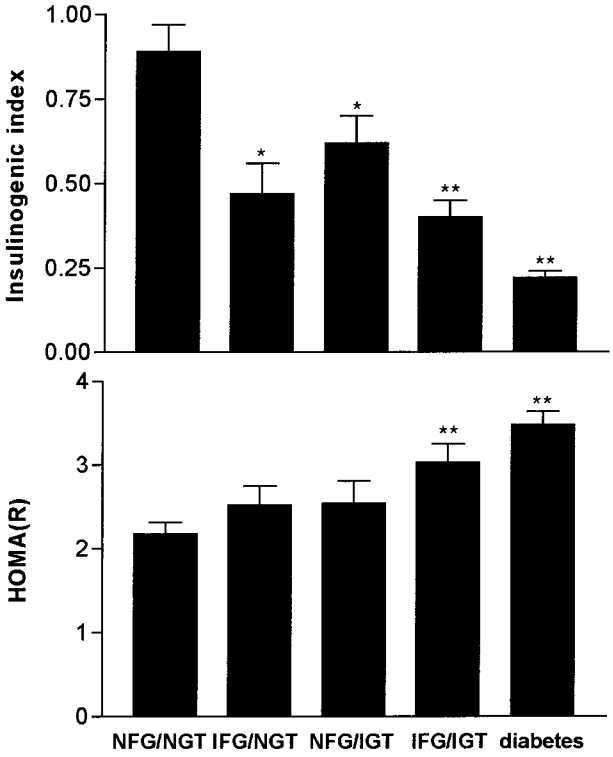

Fig 1. Insulinogenic index and HOMA(R) in the NFG/NGT, IFG/NGT, NFG/IGT, IFG/IGT, and diabetes groups. Insulinogenic index significantly decreased in subjects with IFG/NGT and NFG/IGT compared with those with NFG/NGT. However, there was no significant difference in HOMA(R) between subjects with NFG/NGT and those with IFG/NGT or NFG/IGT. * $P < .01$, ** $P < .001$ *v* NFG/NGT.

Relationship of PG 120 to Insulin Secretion and Insulin Resistance

Subjects were classified by PG 120 as follows: < 7.8 mmol/L (n = 124), group 1; 7.8 to 9.4 mmol/L (n = 63), group 2; 9.4 to 11.1 mmol/L (n = 65), group 3; > 11.1 mmol/L (n = 118), group 4 (Fig 2). There was no significant difference in age and BMI among groups (data not shown). There was no significant difference in HOMA(R) between groups 2 and 1 (2.61 ± 1.90 *v* 2.26 ± 1.42, not significant [NS]), but HOMA(R) of group 3 was significantly higher than that of group 1 (3.00 ± 2.03 *v* 2.26 ± 1.42, $P < .01$). Insulinogenic index of group 2 was significantly lower than that of group 1 (0.53 ± 0.60 *v* 0.79 ± 0.80, $P < .001$).

DISCUSSION

In the present study, there was no significant difference in insulin resistance assessed by HOMA(R) among subjects with NFG/NGT, IFG/NGT, and NFG/IGT. However, early-phase insulin secretion assessed by insulinogenic index was signifi-

Table 1. Clinical Characteristics of the Subjects

	NFG/NGT	IFG/NGT	NFG/IGT	IFG/IGT	Diabetes
No. (M:F)	95 (56:39)	29 (22:7)	60 (37:23)	68 (46:22)	118 (87:31)
Age (yr)	48.1 ± 11.9	51.8 ± 10.4	49.2 ± 10.4	51.2 ± 10.0	48.9 ± 10.3
BMI (kg/m^2)	25.3 ± 3.6	25.3 ± 3.7	25.3 ± 4.0	24.9 ± 2.8	25.3 ± 2.8
Systolic BP (mm Hg)	129.5 ± 17.5	129.8 ± 15.2	130.9 ± 20.0	129.0 ± 16.8	133.3 ± 17.5
Diastolic BP (mm Hg)	79.4 ± 11.0	81.3 ± 11.1	79.6 ± 13.3	78.9 ± 12.0	81.8 ± 11.3
Serum cholesterol (mmol/L)	5.0 ± 1.0	5.1 ± 0.8	5.1 ± 0.9	5.2 ± 0.8	5.3 ± 1.0*
Serum triglyceride (mmol/L)	1.8 ± 1.6	1.7 ± 0.9	1.9 ± 1.1	1.8 ± 0.9	2.1 ± 1.2
FPG (mmol/L)	5.38 ± 0.48	6.46 ± 0.41†	5.53 ± 0.39	6.77 ± 0.57†	7.14 ± 1.15†
PG 120 (mmol/L)	6.02 ± 1.03	6.28 ± 0.93	9.29 ± 0.99†	9.48 ± 1.01†	14.37 ± 2.76†
Fasting serum insulin (pmol/L)	65.1 ± 44.1	62.1 ± 29.2	72.9 ± 61.7	71.4 ± 40.5	78.1 ± 38.2*

NOTE. Data are means ± SD or no. (M:F).

* $P < .05$, † $P < .001$ *v* NFG/NGT group.

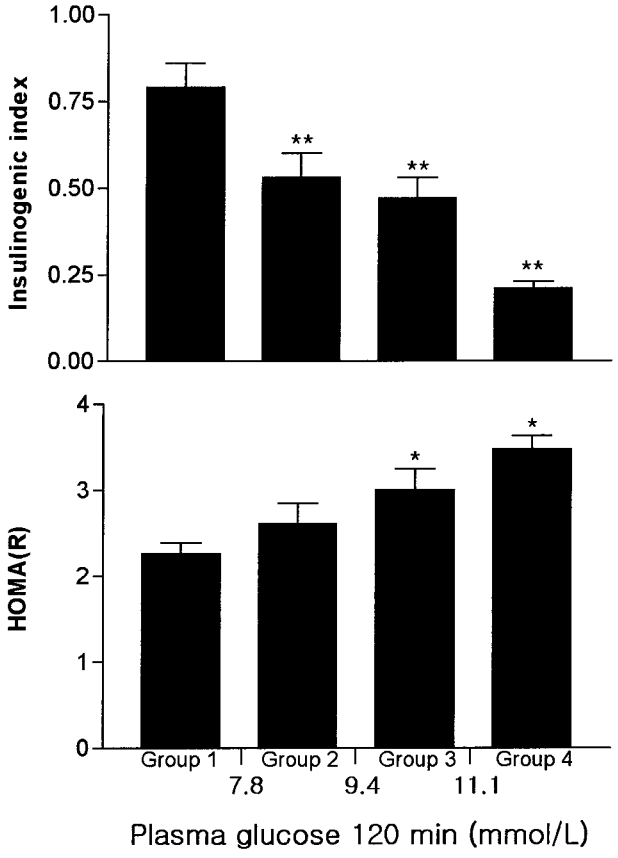

Fig 2. Changes of insulinogenic index and HOMA(R) with worsening of glucose tolerance. Insulinogenic index decreased significantly from NGT to mild cases of IGT. There was no significant difference in HOMA(R) between NGT and mild cases of IGT. * $P < .01$, ** $P < .001$ *v* group 1.

cantly decreased in subjects with IFG/NGT or NFG/IGT compared with those with NFG/NGT. We, therefore, suggest that the worsening from NGT to IGT is more closely related to impaired early-phase insulin secretion than insulin resistance in our subjects.

Previous studies have suggested the relative importance of insulin secretory defect in the development of glucose intolerance in Koreans. Lee et al[12] investigated 15,665 Korean diabetic subjects and found that 67.6% had a BMI below 25 kg/m^2, and only 3.3% had a BMI over 30 kg/m^2. Their study shows that the majority of Korean diabetic subjects are nonobese and suggests the etiologic difference of type 2 diabetes in Korean subjects compared with Caucasians. Shin et al[13] studied 1,193 Korean nondiabetic subjects at baseline who participated in a 2-year follow-up study on diabetes in Younchon County and reported that BMI was not a significant predictor of diabetes, which is also somewhat different from studies in Caucasians. It is of interest to note that the prevalence of type 2 diabetes in Far East Asian countries is now similar to that in western countries.[14-16] The prevalence of type 2 diabetes among the second-generation Japanese-Americans is even 2- to 4-fold higher than that among western populations despite the fact that the second-generation Japanese-Americans are less obese than the Caucasians.[17-19] These findings may imply that Far East Asian people are more prone to develop diabetes for their degree of obesity. As Korean people are genetically close to Japanese and in the midst of similarly rapid economic change, it is possible that similar mechanisms may be operative in the pathogenesis of glucose intolerance in Korea. There have been several reports on the relative importance of early-phase insulin secretory defect compared with insulin resistance in the development of glucose intolerance in Japanese people. Chen et al[20] studied Japanese-American men longitudinally and concluded that impaired early-phase insulin secretion might be present earlier than visceral adiposity in subjects who subsequently developed type 2 diabetes. Matsumoto et al[21] performed a cross-sectional study of 756 Japanese subjects and suggested that impaired early-phase insulin secretion assessed by the insulinogenic index during the OGTT may be the initial abnormality in the development of glucose intolerance in Japanese people.

The degree of obesity may be 1 of the factors that determine the relative importance between the insulin resistance and the insulin secretory defect. Most of the populations in whom insulin resistance is considered to be the primary pathogenetic factor of diabetes have shown a higher degree of obesity[22-30] compared with those with primary insulin secretory dysfunction.[20,21,31-33] When we divided our subjects into 2 groups by their degree of obesity, ie, nonobese (BMI, < 25 kg/m^2) and obese group (BMI, ≥ 25 kg/m^2), the insulinogenic index of the IGT group was significantly lower than that of the NGT group in both the nonobese and obese groups (0.74 ± 1.00 *v* 0.37 ± 0.38, $P < .001$ in the nonobese group; 0.86 ± 0.60 *v* 0.67 ± 0.67, $P < .001$ in the obese group). However, there was no significant difference in HOMA(R) between the NGT and IGT groups in both nonobese and obese subjects (1.8 ± 0.9 *v* 2.1 ± 1.1, NS in the nonobese group; 2.9 ± 1.6 *v* 3.8 ± 2.4, NS in the obese group). It is noteworthy that the early-phase insulin secretory defect was the sole determinant for the worsening of glucose tolerance from NGT to IGT without significant difference in insulin resistance, independent of the degree of obesity. Weyer et al[34] showed that the inability of insulin secretion to compensate for the decrease in insulin sensitivity distinguishes individuals who will develop diabetes from those who will retain NGT in Pima Indians. Our results support their observation and suggest that the defect in the compensatory insulin secretion is more important in the development of type 2 diabetes, independent of the degree of obesity and ethnicity.

We used HOMA(R) to measure insulin resistance in this study. Recently, Emoto et al[35] reported that the HOMA(R) strongly correlated with the insulin resistance index obtained by the glucose clamp study in type 2 diabetic patients treated with sulfonylurea, as well as in those with diet alone. Interestingly, in their multiple regression analysis, 64% of the variability in the insulin resistance index of the clamp study was contributed to age, BMI, and HOMA(R), which was calculated by the data from one blood sampling.[35] Therefore, HOMA(R) can be regarded as an acceptable index to compare the degree of insulin resistance among NGT, IGT, and diabetes groups. It should also be pointed out, however, that this was a cross-sectional study. The results of the current study should, there-

fore, be confirmed in other longitudinal studies and also be confirmed by more sophisticated methods, such as the glucose clamp technique or intravenous glucose tolerance test (IVGTT), which are now being performed in our laboratory. However, despite the limitations in our study, the fact that insulinogenic index was the sole differentia among NFG/NGT, isolated IFG, and isolated IGT strongly suggests the importance of early-phase insulin secretory defect in the pathogenesis of type 2 diabetes in Korean subjects. This is the first study that shows the relative importance of early-phase insulin secretory defect compared with insulin resistance in Koreans.

In conclusion, the impairment of early-phase insulin secretion may be the initial abnormality in the development of glucose intolerance in Korean subjects.

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