Analysis of Early-Phase Insulin Responses in Nonobese Subjects With Mild Glucose Intolerance

HIROKO YONEDA, MD
HIROSHI IKEGAMI, MD, PHD
YOSHIHIRO YAMAMOTO, MD, PHD
EIJI YAMATO, MD, PHD
TEPYON CHA, MD, PHD
YOSHIHIKO KAWAGUCHI, MD
YASUHIRO TAHARA, MD, PHD
TOSHIO OGIHARA, MD, PHD

OBJECTIVE— To study the possible contribution of a B-cell defect in the development of glucose intolerance in nonobese subjects.

RESEARCH DESIGN AND METHODS— There were 41 normal, nondiabetic subjects; 18 subjects with IGT; and 21 patients with NIDDM. All subjects were nonobese (BMI <27 kg/m^2). Insulin secretory responses to an OGTT, IVGTT, and GST were studied.

RESULTS— Early-phase insulin responses to OGTT and IVGTT were decreased in subjects with IGT to levels comparable with those in NIDDM patients, whereas the response to GST was preserved in the subjects with IGT compared with NIDDM patients. The insulinogenic index of OGTT correlated well (r = 0.78) with early-phase insulin response to IVGTT, suggesting that the insulinogenic index in OGTT is related to the early-phase insulin response to IVGTT in nonobese subjects.

CONCLUSIONS— Impaired early-phase insulin response to glucose was associated with mild glucose intolerance, suggesting the importance of impaired insulin secretion in the development of glucose intolerance in nonobese subjects.

NIDDM appears to be caused by defects in both insulin secretion and action (1–4). Insulin secretion in patients with NIDDM is characterized by a decrease in the early-phase response to glucose (5). Early-phase insulin response to IVGTT was reported to be blunted in all subjects whose FPG levels were >6.4 mM (6). However, because chronic hyperglycemia itself makes the B-cell unresponsive to glucose (7), it is not clear whether decrease in early-phase insulin response to glucose is a cause or consequence of NIDDM. To clarify this point, it is necessary to study the characteristics of insulin response in prediabetic subjects, such as those with IGT.

In contrast to almost uniformly decreased early-phase insulin response to glucose in patients with NIDDM, that in subjects with IGT seems to be heterogeneous (5). Although some reports showed decreased early-phase insulin response to glucose, a considerable number (1–5) showed normal or increased insulin response to glucose. From these studies, it was suggested that impaired insulin action—rather than impaired insulin secretion—is the major cause of IGT (5,8). Subjects in these studies, however, were heterogeneous with respect to degree of obesity, and this may have affected heterogeneous results in insulin response in these studies. In fact, a recent study suggested that impaired insulin secretion is the major cause of NIDDM in nonobese subjects, whereas obese NIDDM is attributable to both impaired insulin action and secretion (9). Similarly, defective insulin secretion might be the major cause of IGT when only nonobese subjects are studied. Therefore, in this study, we focused on nonobese subjects and studied the B-cell response to glucose and nonglucose stimuli to clarify the characteristics of insulin response and their contribution to the development of glucose intolerance in nonobese subjects.

RESEARCH DESIGN AND METHODS

— Eighty one nonobese subjects (BMI <27 kg/m^2) were studied. The subjects were classified into three groups according to WHO criteria (10): normal (n = 41), IGT (n = 18), and NIDDM (n = 21). All subjects with normal glucose tolerance or IGT were recruited from either medical staff of our

FROM THE DEPARTMENT OF GERIATRIC MEDICINE, OSAKA UNIVERSITY MEDICAL SCHOOL, OSAKA, JAPAN.
ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO HIROSHI IKEGAMI, MD, PHD, DEPARTMENT OF GERIATRIC MEDICINE, OSAKA UNIVERSITY MEDICAL SCHOOL, 1-1-50 FUKUSHIMA, OSAKA 553, JAPAN.
RECEIVED FOR PUBLICATION 19 FEBRUARY 1992 AND ACCEPTED IN REVISED FORM 16 JULY 1992.

IGT, IMPAIRED GLUCOSE TOLERANCE; NIDDM, NON-INSULIN-DEPENDENT (TYPE II) DIABETES MELLITUS; BMI, BODY MASS INDEX; IVGTT, INTRAVENOUS GLUCOSE TOLERANCE TEST; OGTT, ORAL GLUCOSE TOLERANCE TEST; GST, GLUCAGON STIMULATION TEST; FPG, FASTING PLASMA GLUCOSE; WHO, WORLD HEALTH ORGANIZATION; IRI, IMMUNOREACTIVE INSULIN.

Downloaded from http://diabetesjournals.org/care/article-pdf/15/11/1517/441228/15-11-1517.pdf by guest on 02 October 2022

Table 1—*Clinical characteristics of the subjects studied*

	N	AGE (YR)	BMI (KG/M^2)	FPG (MM)	PLASMA GLUCOSE (MM)*
NORMAL	41	46 ± 13	22.4 ± 2.1	5.4 ± 0.7	6.4 ± 0.9
IGT	18	54 ± 10	22.2 ± 2.8	5.8 ± 0.8	9.3 ± 1.5
NIDDM	21	59 ± 12	21.8 ± 2.5	8.1 ± 2.0	15.8 ± 4.4

Values are means ± SD.
*Plasma glucose at 120 min during OGTT.

hospital or were otherwise healthy subjects who underwent OGTT as a part of a health screening program. They did not have a family history of NIDDM in first-degree relatives and were not taking any medication. Patients with NIDDM were recruited from patients in our hospital treated with diet alone (n = 8) or in combination with sulfonylureas (glibenclamide or gliclazide) (n = 13). Clinical characteristics of the subjects are shown in Table 1.

Each subject was subjected to three tests to study B-cell responses to different stimuli (i.e., an OGTT, an IVGTT, and an intravenous glucagon test, GST). Each test was performed at least 1 wk apart. All subjects were encouraged to eat a weight-maintaining diet, but no food was eaten for 12 h before the study. Those who were treated with sulfonylurea took no drug for 24 h before the study. OGTTs were performed according to WHO recommendations (10). IVGTTs were performed as follows: a pair of intravenous cannulae were inserted into the antecubital vein of both arms and were kept patent by flushing with saline. Glucose (0.5 g/kg body weight) in a 50% solution was infused over 2 min through one cannula. Zero time was taken as the point when glucose infusion was started. Blood samples were drawn from the other cannula at −5, 0, 3, 5, 7, 10, 15, 20, 30, 45, and 60 min. The B-cell response to GST was tested by infusing 1 mg of glucagon (Novo, Copenhagen, Denmark) intravenously. Blood samples were drawn at 0, 3, 6, 10, 20, 30, 45, and 60 min. Plasma glucose was determined by the glucose oxidase method. Plasma insulin and C-peptide were determined by a double-antibody technique. Insulinogenic index (11,12) was used as an index of early insulin response to OGTT. Insulinogenic index was defined as the ratio of the increment of insulin (pM) to that of plasma glucose (mM) 30 min after the glucose load. Statistical analysis was performed by Student's t test for unpaired data. Data are presented as mean ± SE.

RESULTS— Figure 1 shows plasma glucose and insulin levels during OGTTs. The total incremental area of the insulin response during OGTT in subjects with IGT was significantly smaller than that in normal subjects (388.1 ± 41.3 vs. 540.4 ± 55.6 pM/hr, $P < 0.05$). NIDDM patients also showed significantly lower total insulin response (271.6 ± 49.0 pM/hr) than normal subjects ($P < 0.01$). There was no significant difference between the IGT and NIDDM groups. The insulinogenic index of OGTT is shown in Fig. 2*A*. The insulinogenic index in subjects with IGT was significantly smaller than that in normal subjects (25.7 ± 7.5 vs. 98.4 ± 23.4 pM/mM, $P < 0.01$). The insulinogenic index in patients with NIDDM (15.0 ± 2.3 pM/mM) also was significantly smaller than that of normal subjects ($P < 0.01$). However, no significant difference was observed between the IGT and NIDDM groups.

Figure 3*A* shows the insulin responses to IVGTTs. Total insulin response to IVGTT in subjects with IGT

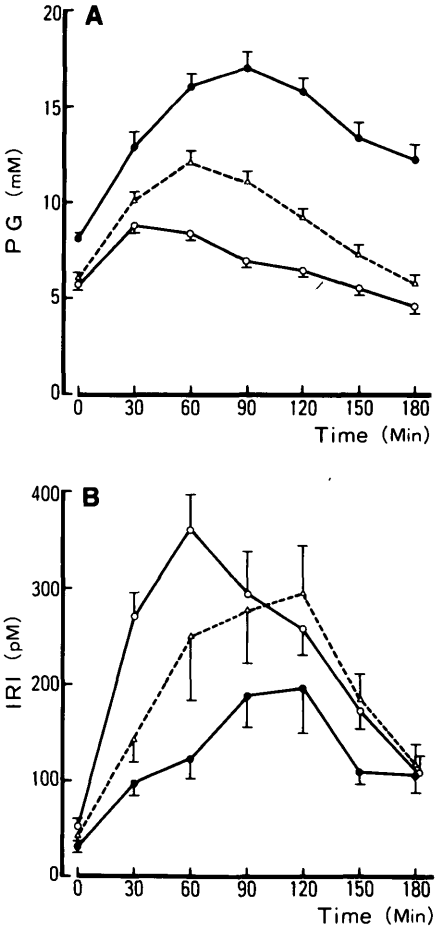

Figure 1—*Plasma glucose (A) and insulin (B) responses to OGTTs in normal subjects (○), subjects with IGT (△), and patients with NIDDM (●).*

was significantly lower than that in normal subjects (78.8 ± 11.4 vs. 159.4 ± 21.1 pM/hr, $P < 0.01$). Total insulin response in patients with NIDDM (35.6 ± 8.1 pM/hr) was significantly lower than that of normal subjects ($P < 0.01$) and subjects with IGT ($P < 0.01$). Because most subjects had peak insulin responses at 3 or 5 min after glucose infusion, summation of the increments of insulin at 3 and 5 min after injection was used as an index of early insulin response to IVGTT (Fig. 2*B*). Early-phase insulin response in subjects with IGT was significantly lower than that in normal subjects (222.6 ± 66.5

Downloaded from http://diabetesjournals.org/care/article-pdf/15/11/1517/441228/15-11-1517.pdf by guest on 02 October 2022

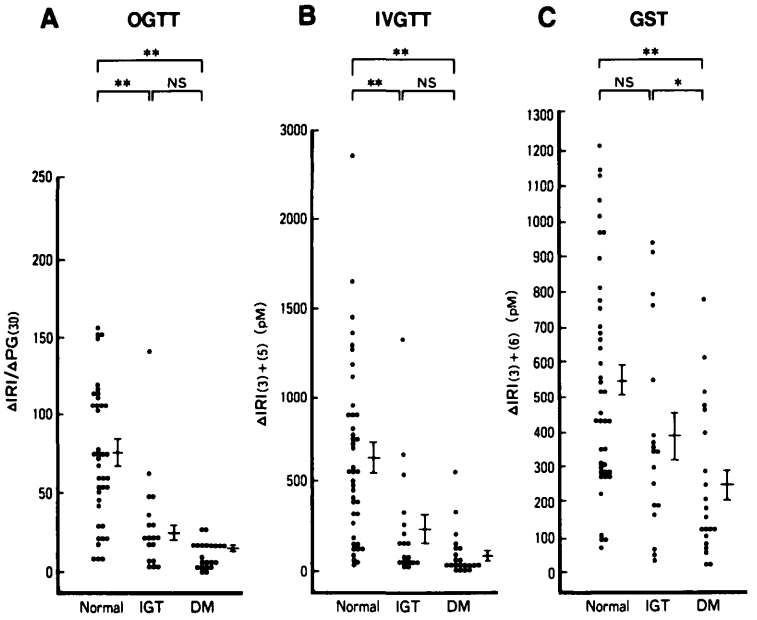

Figure 2—*Early-phase insulin responses to OGTTs (A), IVGTTs (B), and GSTs (C). *P < 0.05, **P < 0.01.*

vs. 653.4 ± 79.1 pM, $P < 0.01$). Early-phase insulin response in patients with NIDDM (88.8 ± 31.6 pM) was significantly lower than that in normal subjects ($P < 0.01$). However, no significant difference was noted between IGT and NIDDM groups.

Figure 3*B* shows the insulin responses to GST. Total insulin response to GST in subjects with IGT was significantly lower than that in normal subjects (285.5 ± 41.3 vs. 410.9 ± 36.5 pM/hr, $P < 0.05$). Total insulin response in patients with NIDDM (172.4 ± 33.3 pM/hr) was significantly lower than that in normal subjects ($P < 0.01$) and subjects with IGT ($P < 0.05$). Because most subjects had peak insulin responses at 3 or 6 min after glucagon infusion, summation of the increments of insulin at 3 and 6 min was used as an index of early insulin response to GST (Fig. 2*C*). Early-phase insulin response in subjects with IGT was lower than that of normal subjects (401.4 ± 59.5 vs. 540.6 ± 49.7), but the difference was not statistically significant. Early-phase insulin responses in patients with NIDDM (240.6 ± 48.4 pM) were significantly smaller than those of normal subjects ($P < 0.01$) and subjects with IGT ($P < 0.05$). Thus, early-phase insulin response to GST in the subjects with IGT was less impaired (74% of that in normal subjects) than that to oral glucose (26% of normal subjects) and intravenous glucose (34% of normal subjects).

To investigate further the difference in early insulin responses during the three tests, correlations between insulin responses to OGTT, IVGTT, and GST were studied. Significant correlation was found between insulin responses during OGTTs and IVGTTs ($r = 0.75$, $P < 0.001$). Significant correlation also

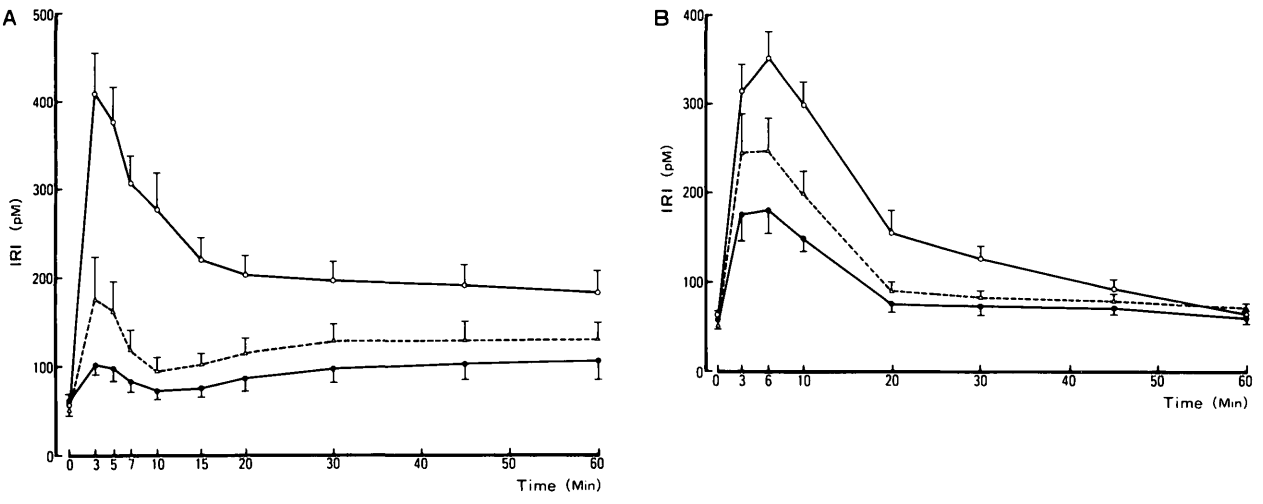

Figure 3—*Insulin responses to IVGTTs (A) and GSTs (B) in normal subjects (○), subjects with IGTs (△), and patients with NIDDM (●).*

Downloaded from http://diabetesjournals.org/care/article-pdf/15/11/1517/441228/15-11-1517.pdf by guest on 02 October 2022

was found between GSTs and IVGTTs ($r = 0.63$, $P < 0.001$), and between GSTs and OGTTs ($r = 0.51$, $P < 0.001$), but the correlation coefficient was smaller than that between OGTT and IVGTT.

CONCLUSIONS — This study demonstrated that early-phase insulin responses to OGTT and IVGTT were markedly decreased in nonobese subjects with IGT. These characteristics in early-phase insulin responses are similar to those in NIDDM subjects. There were no significant differences in the early-phase insulin responses to the OGTTs and the IVGTTs between IGT and NIDDM groups. In contrast, early-phase insulin response to GST was relatively preserved, and there was no significant difference between normal subjects and subjects with IGT. Thus, Japanese nonobese subjects with IGT are characterized by marked impairment in early-phase insulin responses to both oral and intravenous glucose, but near normal response to GST. Total insulin responses to oral glucose and intravenous glucose in the subjects with IGT also were significantly smaller than those in normal subjects.

In contrast to almost uniformly decreased insulin response to glucose in the subjects with IGT in this study, a considerable number of reports in Caucasians and Pima Indians showed normal or higher responses to OGTTs and IVGTTs (5,8,13,14). One reason for the difference in insulin responses to glucose might be the difference in degree of obesity. Mean BMI in Japanese normal populations was reported to be 23.3 in males and 21.8 in females (15). In contrast, mean BMI in Caucasian subjects with normal glucose tolerance was reported to be 25.5 in males and 24.6 in females (16), and that in IGT was 27.0 in males and 27.3 in females (17). In fact, sumo wrestlers with IGT, an extremely obese group of subjects in the Japanese population, were reported to have higher early-phase insulin responses than nonobese, normal subjects, and a considerable number of sumo wrestlers with IGT developed NIDDM despite high early-phase insulin responses to OGTT (18). Therefore, although insulin sensitivity was not analyzed in this study, it is reasonable to speculate that obesity and insulin resistance may be factors that contributed to the higher insulin responses to glucose in previous studies in Caucasian subjects with IGT (5) in contrast to the lower responses observed in this study with Japanese nonobese subjects with IGT. Consistent with this idea, Arner et al. (9) have reported that, even in Caucasians, nonobese patients with NIDDM were characterized by impaired insulin secretion, but not decreased insulin sensitivity.

Another possibility for the difference in insulin response in IGT between this study and in previous studies is the difference in the etiology of NIDDM. Glucose intolerance develops when insulin secretion cannot compensate for insulin resistance. One extreme of this situation is severe insulin resistance (with mildly impaired insulin secretion) and the other is markedly impaired insulin secretion with near normal insulin sensitivity. In fact, Banerji and Lebovitz (19) reported that NIDDM appears to consist of two subgroups: one with a predominant B-cell defect and the other with predominant insulin resistance. Glucose intolerance in most Japanese subjects may belong to the former subgroups, whereas that in Caucasian and the Pima Indian populations belongs to the latter group. These possibilities can be investigated by comparing insulin response with glucose in these populations using the subjects whose BMI and other parameters that affect insulin resistance are matched.

It has been reported previously that insulinogenic index is a good marker for the diagnosis of NIDDM (11,12,20), but it has not yet been studied whether insulinogenic index correlates with early-phase insulin response to an IVGTT. This study demonstrated that insulinogenic index is in good correlation with early-phase insulin response to IVGTT, suggesting that insulinogenic index in OGTT is related to the early-phase insulin responses to IVGTT, at least in nonobese subjects.

Insulin response to glucose and nonglucose stimuli are influenced by obesity, chronic hyperglycemia, and ambient plasma glucose levels. In this study, all these factors were eliminated by studying the nonobese subjects with mild glucose intolerance. When the effect of these factors on insulin secretion was eliminated, it was found that insulin response to glucose was impaired in the subjects with IGT. Because this study is cross-sectional, these data do not necessarily suggest that impaired insulin secretion is the cause of IGT and NIDDM. Previous prospective studies (12,20,21), however, suggested that low insulin response to glucose is a major risk factor for the development of NIDDM in subjects with IGT. Therefore, we speculate that impaired insulin secretion is an important precursor to the development of glucose intolerance in nonobese subjects. In addition, this study further suggests that it is important to control the factors that affect insulin secretion (such as obesity, chronic hyperglycemia, and ambient plasma glucose levels) in the assessment of the B-cell function.

References

1. Porte D Jr: β-cells in type II diabetes mellitus. *Diabetes* 40:166–80, 1991
2. DeFronzo RA: The triumvirate: B-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* 37:667–87, 1988
3. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595–607, 1988
4. Leahy JL: Natural history of β-cell dysfunction in NIDDM. *Diabetes Care* 13: 992–1010, 1990
5. DeFronzo RA, Ferrannini E, Koivisto V: New concepts in the pathogenesis and treatment of non-insulin-dependent diabetes mellitus. *Am J Med* 17:52–81, 1983

Downloaded from http://diabetesjournals.org/care/article-pdf/15/11/1517/441228/15-11-1517.pdf by guest on 02 October 2022

6. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensinck JW, Bierman EL, Porte D Jr: Relationship between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab* 42: 222–29, 1976
7. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. *Diabetes Care* 13:610–30, 1990
8. Lillioja S, Mott D, Howard BV, Bennett PH, Yki-Jarvinen H, Freymond D, Nyomba BL, Zurlo F, Swimburn B, Bogardus C: Impaired glucose tolerance as a disorder of insulin action: longitudinal and cross sectional studies in Pima Indians. *N Engl J Med* 318:1217–25, 1988
9. Arner P, Pollare T. Lithell: Different aetiologies of type 2 (non-insulin-dependent) diabetes mellitus in obese and non-obese subjects. *Diabetologia* 34:483–87, 1991
10. World Health Organization: *Diabetes Mellitus. Report of a WHO Study Group*, 1985 (Tech. Rep. Ser. 727)
11. Kosaka K, Hagura R, Kuzuya T, Kuzuya N: Insulin secretory response of diabetics during the period of improvement of glucose tolerance to normal range. *Diabetologia* 10:775–82, 1974
12. Kosaka K, Hagura R, Kuzuya T: Insulin responses in equivocal and definite diabetes, with special reference to subjects who had mild glucose intolerance but later developed definite diabetes. *Diabetes* 26:944–52, 1977
13. Jackson RL, Guthrie RA, Murthy DY, Lang J: The intravenous glucose tolerance test in chemical diabetes. *Metabolism* 22:247–53, 1973
14. Reaven GM, Olefsky JM: Relationship between heterogeneity of insulin responses and insulin resistance in normal subjects and patients with chemical diabetes. *Diabetologia* 13:201–6, 1977
15. Matsuzawa Y, Tokunaga K, Kotani K, Keno Y, Kobayashi T, Tarui S: Simple estimation of ideal body weight from body mass index with the lowest morbidity. *Diabetes Res Clin Pract* 10:S159–S164, 1990
16. Harris MI: Non-insulin-dependent diabetes mellitus in black and white Americans. *Diabetes Metab Rev* 6:71–90, 1990
17. Harris MI: Impaired glucose tolerance in the U.S. population. *Diabetes Care* 12: 464–74, 1989
18. Kuzuya T, Matsuda A: Glucose tolerance and insulin secretion in sumo wrestlers, and a follow-up study on the occurrence of diabetes. In *Diabetic Microangiopathy*. Abe H, Hoshi M, Eds. Tokyo, Japan, Univ. Tokyo Press, 1983, p. 405–14
19. Banerji MA, Lebovitz HE: Insulin-sensitive and insulin-resistant variants in NIDDM. *Diabetes* 38:784–92, 1989
20. Kadowaki T, Miyake Y, Hagura R, Akanuma Y, Kajinuma H, Kuzuya N, Takaku F, Kosaka K: Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 26:44–49, 1984
21. Kosaka K, Akanuma Y: Heterogeneity of plasma IRI responses in patients with IGT. *Diabetologia* 18:347–48, 1980

Downloaded from http://diabetesjournals.org/care/article-pdf/15/11/1517/441228/15-11-1517.pdf by guest on 02 October 2022