Factors Responsible for Development From Normal Glucose Tolerance to Isolated Postchallenge Hyperglycemia

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OBJECTIVE — Isolated postchallenge hyperglycemia (IPH), defined as fasting plasma glucose (FPG) level <7.0 mmol/l and 2-h plasma glucose (PG) level ≥11.1 mmol/l, is a subtype of early-stage diabetes. This study evaluates the metabolic profiles of insulin secretion and insulin sensitivity in IPH to clarify the factors responsible for development of this form of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted cross-sectional analysis of 231 Japanese men aged 20–70 years. The subjects were classified into the following three groups, based on the results of a 75-g oral glucose tolerance test (OGTT): *1*) normal glucose tolerance (NGT), defined as FPG level <6.1 mmol/l and 2-h PG level <7.8 mmol/l ($n = 89$); *2*) impaired glucose tolerance (IGT), defined as FPG level <7.0 mmol/l and 2-h PG level of 7.8–11.1 mmol/l ($n = 94$); and *3*) IPH ($n = 48$). We compared the three groups for insulin secretion (insulinogenic index) and insulin sensitivity (index of insulin resistance using homeostasis model assessment [HOMA-IR]).

RESULTS — The insulinogenic index in IPH was the lowest of the three groups ($P < 0.001$ versus NGT). The HOMA-IR in the IGT and IPH groups were significantly higher than in the NGT group ($P < 0.001$), but both were similar. By linear regression analysis, the insulinogenic index rather than fasting insulin or HOMA-IR was the more significant factor in the 2-h PG level in IGT and IPH.

CONCLUSIONS — Subjects with IPH exhibited distinctly impaired early-phase insulin secretion and only mild insulin resistance, indicating that reduced insulin secretion is the primary determinant of deterioration from NGT to IGT and IPH in development of type 2 diabetes in these subjects.

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Postprandial hyperglycemia is recognized as an important risk factor for diabetic complications. According to long-term follow-up data from the Honolulu Heart Program and the Diabetes Intervention Study (1,2), postprandial hyperglycemia is a significant predictor of myocardial infarction and mortality. Postprandial hyperglycemia itself also may play an important role in the development of type 2 diabetes, reducing the secretory response of β-cells and impairing insulin-mediated glucose transport, exacerbating metabolic deterioration (3,4).

Postchallenge hyperglycemia after oral glucose tolerance test (OGTT) is an appropriate model of postprandial hyperglycemia. In previous studies (5–7), subjects with isolated postchallenge hyperglycemia (IPH) have been shown to have higher risk of cardiovascular disease and mortality. In addition, some studies have suggested that postchallenge hyperglycemia represents a phenotype of early-stage overt diabetes (8).

The metabolic characteristics of IPH are of clinical importance for the prevention of diabetic complications and for early intervention. In this cross-sectional study, we compared insulin secretion and insulin sensitivity in subjects with IPH, impaired glucose tolerance (IGT), and normal glucose tolerance (NGT) to determine the metabolic characteristics of IPH in Japanese men and to evaluate the factors responsible for the deterioration of postload glucose regulation in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

We recruited 379 consecutive Japanese men undergoing 75-g OGTT for closer evaluation because of family history of diabetes, positive result of urine glucose test, or HbA_{1c} level >5.0% at the initial examination for regular medical checkup, at Kyoto University Hospital, Ikeda Hospital, Kansai-Denryoku Hospital, and Kansai Health Management Center between 1991 and 2001. In all subjects, OGTT was performed within 3 months of the initial examination. All subjects were Japanese men aged 20–70 years who showed no signs of hypertension or hepatic, renal, or endocrine diseases, engaged in no heavy exercise, and were not taking any medications before the study. The study was designed in compliance

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Abbreviations: FPG, fasting plasma glucose; HOMA-IR, index of insulin resistance using homeostasis model assessment; IGT, impaired glucose tolerance; IGT/FH, IGT with fasting hyperglycemia; IPH, isolated postchallenge hyperglycemia; ISI, insulin sensitivity index; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Demographic/metabolic characteristics of the NGT, IGT, and IPH groups*

	NGT	IGT	IPH	Total
n	89	94	48	231
Age (years)	45.6 ± 1.1	52.9 ± 0.9‡	52.0 ± 1.0‡	49.9 ± 0.6
BMI (kg/m^2)	23.9 ± 0.3	24.1 ± 0.3	24.7 ± 0.5	24.2 ± 0.2
Systolic blood pressure (mmHg)	128 ± 2	128 ± 2	131 ± 4	128 ± 1
Diastolic blood pressure (mmHg)	78 ± 2	77 ± 1	78 ± 2	78 ± 1
FPG (mmol/l)	5.3 ± 0.0	6.0 ± 0.1‡	6.4 ± 0.1‡	5.8 ± 0.0
2-h PG (mmol/l)	5.8 ± 0.1	9.3 ± 0.1	13.0 ± 0.2‡	8.7 ± 0.2
Fasting insulin (pmol/l)	27 ± 1	38 ± 2†	37 ± 4†	33 ± 1
2-h insulin (pmol/l)	168 ± 15	259 ± 11‡	235 ± 28†	219 ± 11
HbA_{1c} (%)	5.5 ± 0.1	5.9 ± 0.1‡	6.4 ± 0.1‡	5.9 ± 0.0
Triglycerides (mmol/l)	1.28 ± 0.09	1.97 ± 0.24†	2.22 ± 0.22†	1.73 ± 0.11
Total cholesterol (mmol/l)	5.09 ± 0.10	5.26 ± 0.10*	5.45 ± 0.11	5.24 ± 0.06
HDL cholesterol (mmol/l)	1.28 ± 0.04	1.12 ± 0.03†	1.20 ± 0.05	1.20 ± 0.05

Data are means ± SE. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ versus NGT.

with the ethics regulations set out by the Helsinki Declaration.

Each standard OGTT was administered according to the National Diabetes Data Group recommendations (9), which require the subjects to fast overnight for 10–16 h. Blood samples for determination of blood glucose levels were collected 0, 30, 60, 90, and 120 min after oral administration of 75 g glucose. Blood samples for measurement of HbA_{1c}, insulin, total cholesterol, HDL cholesterol, and triglyceride levels were collected after an overnight fast.

Because our focus is on postload hyperglycemia, we selected subjects with NGT, IGT, and IPH from the original sample ($n = 379$). Definition of NGT and IGT were according to the 1998 World Health Organization (WHO) diagnostic criteria (10). The NGT group comprised the subjects with fasting plasma glucose (FPG) level <6.1 mmol/l and 2-h plasma glucose (PG) <7.8 mmol/l ($n = 89$). The IGT group comprised the subjects with FPG level <7.0 mmol/l and 2-h PG level of 7.8–11.1 mmol/l ($n = 94$). Subjects with FPG level <7.0 mmol/l and 2-h PG level ≥11.1 mmol/l comprised the IPH group ($n = 48$). The definition of IPH in the present study is consistent with recent large epidemiologic studies (6–8). The mean BMI of the subjects enrolled in this study ($n = 231$) is similar to that in Japanese diabetic or IGT subjects in a population-based study: IGT 24.1 vs. 24.4 kg/m^2 and diabetes (IPH) 24.7 vs. 24.3 kg/m^2, respectively (11).

For further analysis, the IGT group was divided into isolated IGT, defined as FPG <6.1 mmol/l ($n = 48$), and IGT with fasting hyperglycemia (IGT/FH), defined as FPG 6.1–7.0 mmol/l ($n = 46$), because recent studies have shown that the metabolic characteristics of subjects with IGT/FH are more deteriorated than in isolated IGT (12,13).

Measurements

PG was measured by glucose oxidase method using the Hitachi Automatic Clinical Analyzer 7170 (Hitachi, Tokyo, Japan). Serum insulin was measured by radioimmunoassay (Dainabot, Tokyo, Japan). Serum total cholesterol, HDL cholesterol, and triglyceride levels were measured as reported previously (14).

As the index of insulin secretion, we used the insulinogenic index, the change in the ratio of insulin to glucose level during the first 30 min of OGTT (30-min insulin level − fasting insulin)/(30-min PG − FPG) (15,16). As the measure of insulin resistance, we used the index of insulin resistance by homeostasis model assessment (HOMA-IR) calculated by the formula of FPG (mmol/l) × fasting insulin (mU/l)/22.5 (17). HOMA-IR is a reasonable measure of insulin resistance, correlating well with values obtained by glucose clamp and minimal model studies (18,19).

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences version 10.0J (SPSS, Chicago, IL). Age, BMI, systolic and diastolic blood pressure, FPG/2-h PG, HbA_{1c}, fasting insulin, triglycerides, total cholesterol, HDL cholesterol, insulinogenic index, and HOMA-IR were compared among the NGT, IGT, and IPH groups by general ANOVA. For comparison with NGT, unpaired Student's *t* test was performed as post hoc analysis. When the IGT group was divided into isolated IGT and IGT/FH, comparisons of the metabolic profiles among isolated IGT, IGT/FH, and IPH were performed using ANOVA. Linear regression analysis was performed in the IGT and IPH subjects with fasting and 2-h PG measurements as dependent variables and fasting insulin level, HOMA-IR, and the insulinogenic index as independent variables. *P* values <0.05 were considered statistically significant. Data are expressed as means ± SE.

RESULTS — The clinical and metabolic characteristics of the subjects are shown in Table 1. A total of 231 subjects were enrolled in the study. The average (± SE) age and BMI were 49.9 ± 0.6 years and 24.2 ± 0.2 kg/m^2, respectively. There was no significant difference in BMI and blood pressure among the groups. The mean age of the NGT group was significantly younger than the others ($P < 0.001$), but there was no significant difference in age between the IGT and IPH groups. The fasting insulin level in the IPH group was significantly higher than in the NGT group ($P < 0.01$) but similar to that in the IGT group. On the other hand, the 30-min insulin level was significantly lower in the IPH group than in the NGT group (199 and 159 pmol/l, respectively; $P < 0.001$). In the IPH group, the 2-h insulin level was significantly higher

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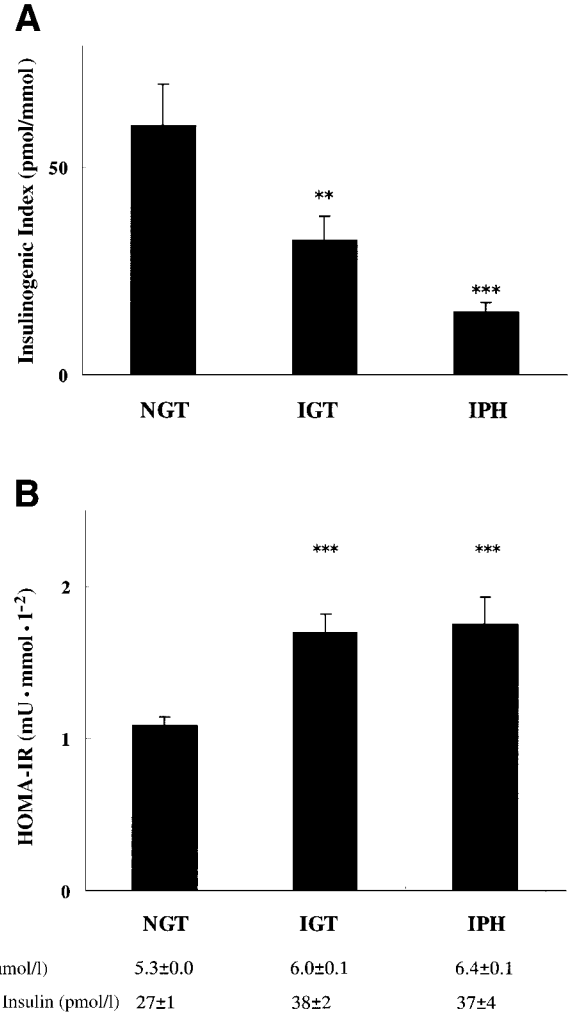

Figure 1—A: *Insulinogenic index in subjects with NGT, IGT, and IPH. Data are means ± SE.* **P < *0.01;* ***P < *0.001 versus NGT.* B: *HOMA-IR in subjects with NGT, IGT, and IPH. Data are means ± SE.* ***P < *0.001 versus NGT.*

than in the NGT group (235 and 168 pmol/l, respectively; $P < 0.05$) and marginally lower than in the IGT group (259 pmol/l; $P = 0.07$), although the IPH group had a higher 2-h PG level than the NGT and IGT groups. The IPH group had a significantly higher triglyceride level than the NGT group ($P = 0.001$), but there was no significant difference in total cholesterol or HDL cholesterol levels between the NGT and IPH groups.

Comparisons of the insulinogenic index among the groups are shown in Fig. 1*A*. The insulinogenic index in the IPH group was lower than the others ($P < 0.001$ versus NGT). Comparisons of HOMA-IR among the groups are shown in Fig. 1*B*. HOMA-IR in the IGT and IPH groups were similar, but both were significantly higher than the NGT group ($P < 0.001$).

Metabolic characteristics and comparisons of the isolated IGT, IGT/FH, and IPH groups are shown in Table 2. The insulinogenic index in the IPH group was significantly lower than the isolated IGT group ($P < 0.05$), but there was no significant difference between the isolated IGT and IGT/FH groups. On the other hand, HOMA-IR in the IGT/FH group was significantly higher than in the isolated IGT group ($P < 0.01$), but there was no significant difference between the IPH and isolated IGT groups.

Linear regression analysis of both FPG and 2-h PG levels and the fasting insulin, HOMA-IR, and insulinogenic index in IGT and IPH subjects is shown in Table 3. FPG correlated significantly with fasting insulin as a measure of insulin resistance ($P = 0.004$) but not with the insulinogenic index ($P = 0.074$). On the other hand, 2-h PG correlated well with the insulinogenic index ($P = 0.030$) but not with fasting insulin or HOMA-IR ($P = 0.396$ and 0.162, respectively).

CONCLUSIONS— In the present study, we have clarified the metabolic profile of IPH regarding insulin secretion and insulin resistance. Both insulin secretion and insulin action in IPH subjects are reduced significantly compared with NGT subjects. However, in contrast to similar insulin resistance, IPH subjects exhibit considerably less insulin secretion than IGT subjects. Moreover, when IGT is separated into isolated IGT and IGT/FH, IPH subjects show significantly lower insulin secretion than isolated IGT subjects,

Table 2—*Metabolic comparisons among the isolated IGT, IGT/FH, and IPH groups*

	Isolated IGT	IGT/FH	IPH
n	48	46	48
Age (years)	51 ± 1.3	55 ± 1.3*	52 ± 1.0
BMI (kg/m^2)	23.6 ± 0.4	24.4 ± 0.4	24.7 ± 0.5
Systolc blood pressure (mmHg)	124 ± 3	131 ± 3	131 ± 4
Diastolic blood pressure (mmHg)	75 ± 2	79 ± 2	78 ± 2
FPG (mmol/l)	5.6 ± 0.0	6.4 ± 0.0‡	6.4 ± 0.1‡
2-h PG (mmol/l)	9.0 ± 0.1	9.5 ± 0.1	13.0 ± 0.2‡
Fasting insulin (pmol/l)	32 ± 2	40 ± 4*	37 ± 4
HbA_{1c} (%)	5.5 ± 0.1	6.0 ± 0.1	6.4 ± 0.1‡
Triglycerides (mmol/l)	2.24 ± 0.41	1.61 ± 0.13	2.22 ± 0.22
Total cholesterol (mmol/l)	5.21 ± 0.15	5.33 ± 0.14	5.45 ± 0.11
HDL cholesterol (mmol/l)	1.07 ± 0.05	1.19 ± 0.05	1.20 ± 0.05
Insulinogenic index (pmol · mmol^{-1})	34 ± 8	30 ± 8	15 ± 2*
HOMA-IR (mU · mmol · l^{-2})	1.3 ± 0.1	1.9 ± 0.2†	1.8 ± 0.2

Data are mean ± SE. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ versus isolated IGT.

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Table 3—*Linear correlation analysis of FPG and 2-h PG levels with fasting insulin, HOMA-IR, and insulinogenic index in IGT and IPH subjects (n = 142)*

		Fasting insulin	HOMA-IR	Insulinogenic index
FPG	*r*	0.239	—	−0.160
	P	0.004	—	0.074
2-h PG	*r*	0.072	0.118	−0.195
	P	0.396	0.162	0.030

whereas insulin resistance is not significantly different. These results suggest that progression from NGT via IGT or isolated IGT to IPH in these subjects is due mostly to deterioration of early-phase insulin secretion and to a lesser contribution of insulin resistance.

For further clarification of the metabolic characteristics of IPH, we compared the insulinogenic index and HOMA-IR of IPH subjects with newly diagnosed overt diabetes from our original sample (FPG ≥7.0 mmol/l; $n = 118$). Subjects with IPH had higher insulinogenic index and lower HOMA-IR than those with overt diabetes (11.2 vs. 8.6 pmol · $mmol^{-1}$ and 1.76 vs. 2.19 mU · mmol · l^{-2}, respectively). These results suggest that IPH is a less metabolically deteriorated status than overt diabetes.

According to DeFronzo et al. (20), progression from NGT to type 2 diabetes with FPG <7.8 mmol/l correlates well with increased insulin resistance but less well with impairment of early-phase insulin secretion. The decline in β-cell function becomes apparent only after FPG exceeds 7.8 mmol/l. Gerich (21) has investigated insulin resistance in the prediabetic state and suggests the importance of impaired insulin secretion in progression to diabetes from NGT. The importance of insulin resistance at early stages of diabetes has been shown mostly in studies of obese subjects (22–24), who have higher insulin resistance. After excluding the influence of obesity in previous analyses, Gerich (25) showed that insulin resistance is frequently not the primary factor in the development of type 2 diabetes. The present study clearly shows, in nonobese Japanese diabetic subjects, that deterioration of β-cell function plays a very important role in progression from IGT to IPH.

Although HOMA-IR is a common index for evaluating insulin sensitivity and correlates well with both hepatic sensitivity measured by glucose tracer method and whole-body insulin sensitivity measured by glucose clamp method (17), it is believed to reflect hepatic insulin sensitivity more than peripheral insulin sensitivity (26). We also analyzed the insulin sensitivity of our study subjects by the insulin sensitivity index (ISI) composite proposed by Matsuda and DeFronzo (26), which is considered a more accurate measurement of systemic insulin resistance. The ISI composite is obtained from OGTT results and calculated by the formula of 10,000/square root (FPG × fasting insulin × mean OGTT glucose concentration × mean OGTT insulin concentration). There was no difference in insulin resistance between the IGT and IPH groups by this measurement (means ± SE were 7.3 ± 0.5 and 6.8 ± 0.6, respectively; $P = 0.557$).

In addition to the metabolic characteristics of IPH, the present study shows the metabolic characteristics of IGT in presence of fasting hyperglycemia. In subjects with IGT/FH, fasting insulin level and HOMA-IR were higher than in subjects with isolated IGT, whereas the insulinogenic index in subjects with IGT/FH was slightly lower than or similar to isolated IGT. These results indicate that deterioration from isolated IGT to IGT/FH is due to insulin resistance, in contrast to the deterioration to IPH. Linear regression analysis in IGT and IPH subjects also supports the theory that postload hyperglycemia is caused mostly by deterioration of insulin secretion and fasting hyperglycemia is caused by insulin resistance. Although the causes of fasting and 2-h hyperglycemia are controversial (12,13, 20,25), O'Rahilly et al. (23) and others have found that early insulin secretion is more closely related to FPG than to postload glucose level, whereas fasting hyperglycemia depends more on insulin resistance (13). The discrepancy may be due to the focus of the present study on subjects with IPH rather than those with IGT or diabetes. Ethnic and other population differences also may be a factor (27). The subjects of the present study, nonobese, middle-aged, Japanese men with early-stage type 2 diabetes, are more homogeneous than those of other studies, and other studies with lean and/or Japanese subjects also have shown that insulin secretion is an important factor in the development of postload hyperglycemia (28,29).

The present study is limited in that no insight is provided into the time course of the development of these abnormalities in insulin secretion and action. However, IPH clearly is characterized by considerably impaired early insulin secretion and mild insulin resistance, indicating that deterioration of insulin secretion is a strong determinant of progression from NGT via IGT or isolated IGT to IPH in this study population. However, insulin resistance is the stronger determinant of deterioration from isolated IGT to IGT/FH. The present study also indicates that results of 75-g OGTT may be clinically useful to classify patients for establishment of appropriate prevention and treatment in early-stage type 2 diabetes.

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