Insulin secretory capacity and insulin sensitivity in impaired fasting glucose in Japanese

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ABSTRACT

Aims/Introduction: Impaired fasting glucose (IFG) increases the risk of developing diabetes mellitus (DM). This study was carried out to characterize Japanese patients who have fasting glucose levels (FPG) between 100 and 109 mg/dL ($IFG_{100–109}$).

Materials and Methods: A total of 1383 Japanese participants were examined by oral glucose tolerance test. We compared insulin secretory capacity (insulinogenic index) and insulin sensitivity (ISI composite) of $IFG_{100–109}$/normal glucose tolerance (NGT; 100 ≤ FPG < 110 mg/dL and 2-h postchallenge glucose level (2-hPG) < 140 mg/dL) with NGT (100 mg/dL < FPG and 2-hPG < 140 mg/dL) and $IFG_{110–125}$/NGT (110 ≤ FPG < 126 mg/dL and 2-hPG < 140 mg/dL). In addition, $IFG_{100–109}$ patients were analyzed in three subgroups according to glucose intolerance by 2-hPG.

Results: Of the three categories of $IFG_{100–109}$, $IFG_{100–109}$/DM had the lowest insulinogenic index despite an ISI composite showing only a small decline from $IFG_{100–109}$/NGT through $IFG_{100–109}$/IGT (100 ≤ FPG < 110 mg/dL and 140 ≤ 2-hPG < 200 mg/dL) to $IFG_{100–109}$/DM (100 ≤ FPG < 110 mg/dL and 200 mg/dL < 2-hPG). By multiple regression analysis, the insulinogenic index showed a significant relationship with 2-h PG levels. Both insulinogenic index and ISI composite were decreased significantly from NGT through $IFG_{100–109}$/NGT to $IFG_{110–125}$/NGT.

Conclusions: Although impaired early-phase insulin secretion plays the more important role in the elevation of postchallenge glucose in $IFG_{100–109}$ patients, both impaired early-phase insulin secretion and decreased insulin sensitivity are involved in the deterioration of FPG in Japanese. In addition, insulin secretory defect and decreased insulin sensitivity already have begun in patients with $IFG_{100–109}$. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00201.x, 2012)

KEY WORDS: Impaired fasting glucose, Insulin secretion, Insulin sensitivity

INTRODUCTION

The prevalence of type 2 diabetes is increasing dramatically throughout the world; early detection of developing glucose intolerance is important to delay and prevent the disease. The American Diabetes Association (ADA) has lowered the cut-off value of impaired fasting glucose (IFG) from 110 to 100 mg/dL in 2003. Subjects with fasting plasma glucose (FPG) from 100 to 109 mg/dL together with normal postchallenge glucose levels have been classified as normal glucose tolerance (NGT) by the criteria of the World Health Organization (WHO) and the Japanese Diabetes Society (JDS), but are classified as IFG by the 2003 ADA criteria[1–3]. Insulin secretory capacity and insulin sensitivity are regulated differently with regard to fasting and postchallenge plasma glucose[4,5], and therefore require separate evaluation. In addition, there are ethnic differences in the pathology of developing glucose intolerance. In our previous studies, impaired insulin secretion is shown to play an especially important role in both diabetic and pre-diabetic Japanese subjects[4,5], in contrast to the increasing insulin resistance that is the more important factor in Caucasian, Mexican American and Pima Indian populations[6,7]. In the present cross-sectional study, we analyzed 1383 Japanese patients with fasting plasma glucose between 100 and 109 mg/dL ($IFG_{100–109}$) to characterize and compare insulin secretory capacity, and insulin sensitivity of Japanese patients with $IFG_{100–109}$ in the development of glucose intolerance.

METHODS

Subjects

A total of 1835 Japanese patients undergoing 75-g oral glucose tolerance test (OGTT) as a result of positive urine glucose test, ≥5.5% glycated hemoglobin (HbA_{1c}) level, ≥100 mg/dL fasting plasma glucose (FPG) level, and family history of diabetes at initial examination for medical check-up at Kyoto University

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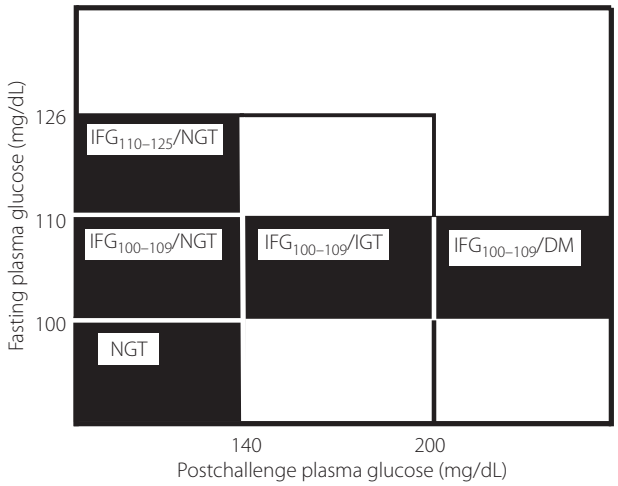

Figure 1 | Subgroups of impaired fasting glucose. DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Hospital, Ikeda Hospital, Kansai Electric Power Hospital, Kansai Health Management Center, Center for Preventive Medicine of St. Luke's International Hospital and Kyoto Preventive Medical Center from 1993 to 2009 were examined. Originally, 358 patients who had hypertension, hepatic or renal dysfunction, endocrine or malignant disease, or history of heavy exercise, gastrectomy, or medication known to affect glucose metabolism were excluded from 2193 patients. Among the 1835 patients, 470 patients were excluded because of fasting glucose levels ≥ 126 mg/dL and postchallenge glucose levels ≥ 140 mg/dL with FPG ≥ 110 mg/dL and FPG < 100 for the present study, and 1383 patients were included. The study was designed in compliance with the ethics regulations of the Helsinki Declaration, and the study protocol was approved by the ethics committee of St. Luke's International Hospital.

Standard OGTT with 75-g glucose was given according to the National Diabetes Data Group recommendations[8], which require patients to fast overnight for 10–16 h. Fasting, 0.5, 1, and 2-h blood samples were obtained for measurement of plasma glucose and serum insulin after oral administration of 75-g glucose. Blood samples for measurement of HbA_{1c}, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglyceride levels were collected after overnight fast.

The subjects that underwent 75-g OGTT were divided into two groups: one having normal postchallenge glucose (2-hPG < 140 mg/dL) and another having $IFG_{100–109}$ (100 ≤ FPG < 110 mg/dL). The subjects of each group also were divided into three groups as shown in Figure 1.

Group one had normal postchallenge glucose: NGT (n = 594); normal fasting glucose according to ADA (FPG < 100 mg/dL) with normal postchallenge glucose, $IFG_{100–109}$/NGT (n = 369); $IFG_{100–109}$ (100 ≤ FPG < 110 mg/dL) with normal postchallenge glucose, $IFG_{110–125}$/NGT (n = 160); and IFG (110 ≤ FPG < 126 mg/dL) with normal postchallenge glucose. Group two had $IFG_{100–109}$: $IFG_{100–109}$/NGT (n = 369); $IFG_{100–109}$ with normal postchallenge glucose, $IFG_{100–109}$/IGT (n = 225); $IFG_{100–109}$ with impaired glucose tolerance (IGT; 140 ≤ 2-hPG < 200 mg/dL), and $IFG_{100–109}$/diabetes mellitus (DM; n = 35); $IFG_{100–109}$ with postchallenge hyperglycemia (200 mg/dL ≤ 2-hPG; Figure 1).

Measurements

Plasma glucose level was measured by the glucose oxidase method using a Hitachi Automatic Clinical Analyzer 7170 (Hitachi, Tokyo, Japan). Serum insulin was measured by two-site radioimmunoassay (Insulin Riabead II; Dainabot, Tokyo, Japan), as reported previously[9]. HbA_{1c} was measured by HLC-723G7 (Tosoh, Tokyo, Japan). Coefficients of variation (CVs) were 0.56% for plasma glucose, <7% for insulin and <2% for HbA_{1c}. Serum total cholesterol and triglycerides levels were measured as reported previously[10].

Blood samples were collected at 0, 30, 60 and 120 min after OGTT, and plasma glucose and serum insulin levels were measured for all subjects. Blood samples for measurements of HbA_{1c}, total cholesterol, HDL-C and triglycerides were drawn after an overnight fast. The HbA_{1c} value was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated by the formula: HbA_{1c} (NGSP) = HbA_{1c} (JDS) + 0.4%, considering the relational expression of HbA_{1c} (JDS) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (NGSP)[2].

Early-phase insulin secretion and systemic insulin sensitivity during OGTT were evaluated by insulinogenic index[11–13], and Insulin sensitivity was determined by an OGTT based on the formula for the composite of insulin sensitivity index (ISI composite)[14]. Insulinogenic index < 0.4 is considered in Japanese to be decreased early-phase insulin secretion according to the 'Report of The Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus' by the Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus[2]. The calculations were as follows:

$$\text{Insulinogenic index (II)} = (\text{Ins}_{0.5} - \text{Ins}_0[\text{pmol/L}])/(\text{Glu}_{0.5} - \text{Glu}_0[\text{mmol/L}])^{11-13}$$

$$\text{ISI composite} = 10{,}000/([\text{Glu}_0 \times \text{Ins}_0] \times [\text{mean Glu}_{0-120} \times \text{mean Ins}_{0-120}])^{0.5},^{14}$$

We compared these two indices between IFG subgroups and NGT as shown in Figure 1 in this cross-sectional study.

Statistical Analysis

All of the statistical analyses were carried out using SPSS version 19.0 (SPSS Japan, Tokyo, Japan). Clinical characteristics of the study subjects are described using mean ± standard deviation, and general analysis of variance (ANOVA) was carried out for

between-group comparisons. The differences were established by *post-hoc* Bonferroni test for multiple comparisons. *P*-values <0.05 were considered statistically significant. Multiple stepwise regression analysis was done using AUC-G and 2-h PG as the dependent variables, and age, body mass index (BMI), ISI composite and insulinogenic index as the independent variables among the $IFG_{100–109}$ subgroups. In addition, simple regression analysis was applied between insulinogenic index and area under the curve of glucose (AUC-G), and also between insulinogenic index and 2-hPG, as the insulinogenic index showed the strongest relationship with these two factors.

RESULTS

Comparison of NGT, $IFG_{100–109}$/NGT and $IFG_{110–125}$/NGT

Clinical Characteristics

Table 1 shows the clinical and metabolic characteristics of the 1123 Japanese patients classified with NGT, $IFG_{100–109}$/NGT and $IFG_{110–125}$/NGT. The age and BMI (mean ± standard error) of the total of the three groups were 51.3 ± 0.4 years and 22.9 ± 0.2, respectively. The mean age of the NGT group was significantly lower than that of the other two groups ($P < 0.05$). The differences in BMI were significant among the three groups ($P < 0.05$, respectively). There was no significant difference in triglycerides, total cholesterol or HDL-C, although HbA_{1c} showed significant differences among the three groups ($P < 0.001$, respectively).

Insulin Secretion

The insulinogenic indices of the three groups are shown in Figure 2a; NGT 0.48, $IFG_{100–109}$/NGT 0.39, $IFG_{110–125}$/NGT 0.27. The insulinogenic index in the NGT group was significantly higher than that in the other groups ($P < 0.05$). The insulinogenic index in the $IFG_{100–109}$/NGT group was <0.4.

Table 1 | Clinical and metabolic characteristics of NGT, $IFG_{100–109}$/NGT and $IFG_{110–125}$/NGT

	NGT	$IFG_{100–109}$/NGT	$IFG_{110–125}$/NGT
n	594	369	160
Age (years)	48.6 ± 0.6	54.2 ± 0.6*	54.7 ± 0.7*
BMI (kg/m^2)	22.2 ± 0.1	23.1 ± 0.2	24.9 ± 1.2***
FPG (mg/dL)	90.3 ± 0.3	104.1 ± 0.2*	114.8 ± 0.3*,***
2-h PG (mg/dL)	104.5 ± 0.8	112.8 ± 0.9*	112.5 ± 1.5*
Fasting insulin (pmol/L)	33.3 ± 0.7	37.5 ± 1.0*	40.2 ± 1.6*
HbA_{1c} (%)	5.3 ± 0.0	5.7 ± 0.0*	5.9 ± 0.0*,***
Triglycerides (mmol/L)	1.26 ± 0.06	1.23 ± 0.05	1.28 ± 0.10
Total cholesterol (mmol/L)	5.28 ± 0.06	5.34 ± 0.05	5.38 ± 0.09
HDL cholesterol (mmol/L)	1.61 ± 0.03	1.63 ± 0.03	1.62 ± 0.05

Data are mean ± standard error. BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; PG, plasma glucose. *$P < 0.05$ (vs normal glucose tolerance [NGT]); **$P < 0.05$ (vs impaired fasting glucose $[IFG]_{100–109}$/NGT); ***$P < 0.001$ (vs $IFG_{100–109}$/NGT).

Insulin Sensitivity

Figure 2b shows the ISI composites: NGT 10.3, $IFG_{100–109}$/NGT 7.9, $IFG_{110–125}$/NGT 7.2. ISI composite in the NGT was significantly higher than in the other groups ($P < 0.001$).

Comparison of $IFG_{100–109}$/NGT, $IFG_{100–109}$/IGT and $IFG_{100–109}$/DM

Clinical Characteristics

Table 2 shows the clinical and metabolic characteristics of the 629 Japanese patients classified with $IFG_{100–109}$/NGT, $IFG_{100–109}$/IGT and $IFG_{100–109}$/DM. The age and BMI (mean ± standard error) of all of the patients were 55.2 ± 0.4 years and 23.5 ± 0.1, respectively. However, the BMI of $IFG_{100–109}$/NGT subjects were significantly lower ($P < 0.05$). There was a significant difference in age only between $IFG_{100–109}$/NGT and $IFG_{100–109}$/DM. The differences in triglycerides and total cholesterol were significant only between $IFG_{100–109}$/NGT and $IFG_{100–109}$/IGT ($P < 0.05$). There was no significant difference in HDL-C, except for HbA_{1c}, which showed significant differences among the three groups ($P < 0.001$, respectively).

Insulin Secretion

The insulinogenic indices of the three groups are shown in Figure 2c. The insulinogenic index showed a significant difference between $IFG_{100–109}$/NGT and the others ($P < 0.05$), and the insulinogenic index of $IFG_{100–109}$/DM (0.19) was nearly 50% compared with $IFG_{100–109}$/NGT (0.39). The insulinogenic index (II) in the $IFG_{100–109}$/NGT (0.39) group was <0.4.

Insulin Sensitivity

Figure 2d shows the ISI composite of the three groups. There was a significant difference only between $IFG_{100–109}$/NGT and $IFG_{100–109}$/IGT ($P < 0.001$), which showed a 9% decline from $IFG_{100–109}$/NGT (7.9) to $IFG_{100–109}$/DM (7.2).

Simple and Multiple Regression Analysis

We examined the relationship between the dependent variables AUC-G and 2-hPG, and the independent variables of age, BMI, ISI composite and insulinogenic index by multiple regression analysis. Insulinogenic index showed the strongest relationship with AUC-G and 2-hPG (β of 2 h-PG: age 0.11, BMI 0.10, II −0.215, ISI composite −0.164; and β of AUC-G: age 0.082, BMI 0.048, II −0.545, ISI composite −0.350). Figure 3a shows scattered plots of simple regression analysis of AUC-G with insulinogenic index and ISI composite. Insulinogenic index ($r = 0.454$, $P < 0.001$, *F*-value 16.3) had a stronger relationship with AUC-G than with ISI composite ($r = 0.232$, $P < 0.001$, *F*-value 35.7). Figure 3b shows scattered plots of simple regression analysis of 2-hPG with insulinogenic index and ISI composite. Insulinogenic index ($r = 0.165$, $P < 0.001$, *F*-value 17.5) was

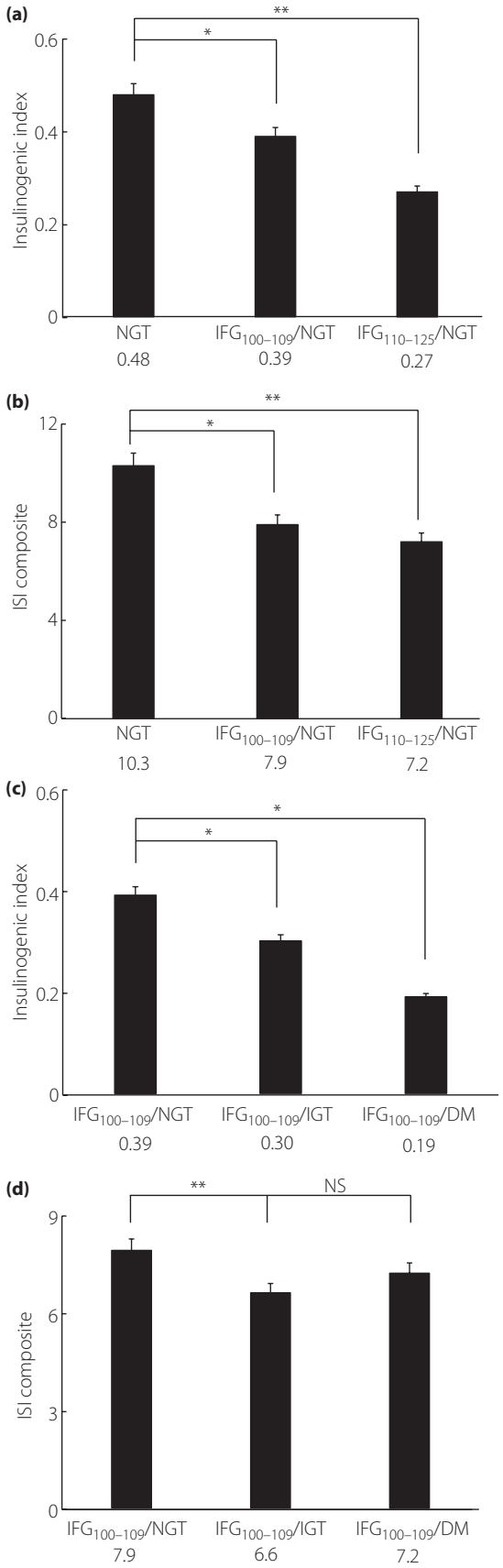

Figure 2 | Indices of insulin secretion and sensitivity. (a) Early-phase insulin secretion. Insulinogenic index in normal glucose tolerance (NGT) is highest and shows significant differences compared with the other two groups (NGT and impaired fasting glucose $(IFG)_{100–109}$/NGT: $P = 0.026$, NGT and $IFG_{110–125}$/NGT: $P \leq 0.001$). (b) Insulin sensitivity. Insulin sensitivity index (ISI) composite in NGT is significantly higher than the other groups. (NGT and $IFG_{100–109}$/NGT: $P \leq 0.001$, NGT and $IFG_{110–125}$/NGT: $P \leq 0.001$). (c) Early-phase insulin secretion. The difference of insulinogenic index is significant except between $IFG_{100–109}$/impaired glucose tolerance (IGT) and $IFG_{100–109}$/diabetes mellitus (DM; $IFG_{100–109}$/NGT and $IFG_{100–109}$/IGT: $P = 0.023$, $IFG_{100–109}$/NGT and $IFG_{100–109}$/DM: $P = 0.013$). (d) Insulin sensitivity. The difference of ISI composite is significant only between $IFG_{100–109}$/NGT and $IFG_{100–109}$/IGT ($IFG_{100–109}$/NGT and $IFG_{100–109}$/IGT: $P \leq 0.001$). *$P < 0.05$; **$P < 0.001$. NS, not significant.

Table 2 | Clinical and metabolic characteristics of $IFG_{100–109}$/NGT, $IFG_{100–109}$/IGT and $IFG_{100–109}$/DM

	$IFG_{100–109}$/NGT	$IFG_{100–109}$/IGT	$IFG_{100–109}$/DM
n	369	225	35
Age (years)	54.2 ± 0.6	56.3 ± 0.7	58.9 ± 1.9*
BMI (kg/m^2)	23.1 ± 0.2	24.0 ± 0.2	24.6 ± 0.8*
FPG (mg/dL)	104.1 ± 0.2	104.7 ± 0.3*	105.1 ± 0.5
2-h PG (mg/dL)	112.8 ± 0.9	161.8 ± 1.1**	223.8 ± 3.7****
Fasting insulin (pmol/L)	37.5 ± 1.0	44.6 ± 1.9**	41.2 ± 3.9
HbA_{1c} (%)	5.7 ± 0.0	5.8 ± 0.0**	6.2 ± 0.1****
Triglycerides (mmol/L)	1.23 ± 0.05	1.64 ± 0.11**	1.35 ± 0.13
Total cholesterol (mmol/L)	5.34 ± 0.05	5.54 ± 0.07*	5.54 ± 0.17
HDL cholesterol (mmol/L)	1.63 ± 0.03	1.53 ± 0.04	1.59 ± 0.12

Data are mean ± standard error. BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; PG, plasma glucose. *$P < 0.05$ (vs impaired fasting glucose $[IFG]_{100–109}$/normal glucose tolerance [NGT]); **$P < 0.001$ (vs $IFG_{100–109}$/NGT); ***$P < 0.001$ (vs $IFG_{100–109}$/impaired glucose tolerance [IGT]).

more related to 2-hPG than to ISI composite ($r = 0.150$, $P < 0.001$, F-value 14.5).

DISCUSSION

In the present study, we analyzed insulin secretory capacity and insulin sensitivity in a cross-sectional study in Japanese subjects who had $IFG_{100–109}$ ($IFG_{100–109}$; 100 ≤ FPG < 110 mg/dL). A reduction in the insulinogenic index, a measure of early-phase insulin secretion, has already begun in $IFG_{100–109}$/NGT subjects, for which the insulinogenic index was 0.39 (Figure 2a). The ISI composite, an index of systemic insulin sensitivity, is also decreased in the deterioration of FPG from NGT through $IFG_{100–109}$/NGT to $IFG_{110–125}$/NGT (Figure 2b). $IFG_{100–109}$/NGT subjects are classified into normal fasting glucose tolerance according to the 1998 WHO criteria and the criteria of the JDS,

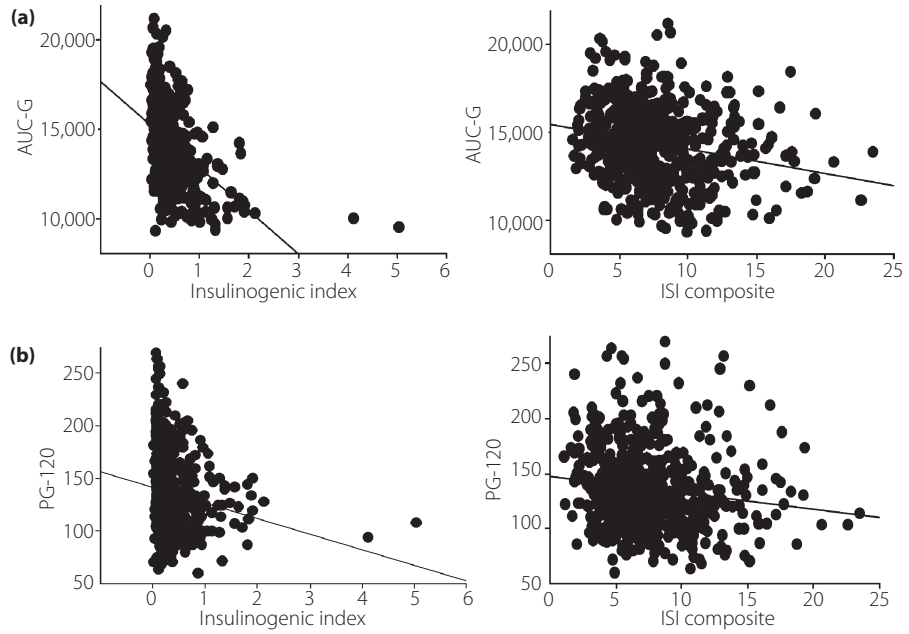

Figure 3 | (a) The relationship between area under the curve of glucose (AUC-G), and insulinogenic index and insulin sensitivity index (ISI) composite among the impaired fasting glucose $(IFG)_{100–109}$ groups. Insulinogenic index ($r = 0.454$, $P < 0.001$, F-value 16.3) was more related to AUC-G than ISI composite ($r = 0.232$, $P < 0.001$, F-value 35.7). (b) The relationship between 2-h postchallenge glucose level (PG-120), and insulinogenic index and ISI composite. Insulinogenic index ($r = 0.165$, $P < 0.001$, F-value 17.5) was more related to PG-120 than ISI composite ($r = 0.150$, $P < 0.001$, F-value 14.5).

although they are classified into IFG based on the 2003 ADA criteria. There are numerous studies of impaired fasting glucose that justify the new ADA criteria, but few studies focus on the borderline $IFG_{100–109}$ group regarding the relevance of insulin secretory capacity and insulin sensitivity in the development of disease. The present study showed deterioration of both early-phase insulin secretion and insulin sensitivity in $IFG_{100–109}$/NGT. To clarify the pathology, we evaluated $IFG_{100–109}$ subjects in three subgroups: $IFG_{100–109}$/NGT, $IFG_{100–109}$/IGT and $IFG_{100–109}$/DM. The mean insulinogenic indices were found to decrease from $IFG_{100–109}$/NGT through $IFG_{100–109}$/IGT to $IFG_{100–109}$/DM (0.39 [<0.40], 0.30 and 0.19, respectively), and those of $IFG_{100–109}$/IGT and $IFG_{100–109}$/DM were significantly lower than that of $IFG_{100–109}$/NGT. In contrast, the differences among ISI composites in $IFG_{100–109}$/NGT, $IFG_{100–109}$/IGT and $IFG_{100–109}$/DM were small. In addition, $IFG_{100–109}$/DM showed a stronger deterioration in insulin secretory capacity and insulin sensitivity than in $IFG_{110–125}$/NGT ($P < 0.05$). These results agree with those of our previous studies in Japanese subjects that show that impairment of early-phase insulin secretion plays the more important role in the deterioration of postchallenge glucose tolerance, whereas insulin resistance plays a lesser role[15].

It is notable that $IFG_{100–109}$/IGT and $IFG_{100–109}$/DM are included into $IFG_{100–109}$ if judged only by FPG. Although this study is not a population-based study, over 40% of the subjects with $IFG_{100–109}$ also were classified as IGT or DM. This suggests that DM, as well as IGT, might be overlooked when screening by FPG among subjects with $IFG_{100–109}$. IFG has been reported as high risk for developing type 2 diabetes. In a study of Japanese subjects, those with $IFG_{100–109}$ developed type 2 diabetes at twice the rate as NGT during 4 years[16]. Bonora *et al.*[17] found that diabetic incidence rates for 10 years of IGT, IFG and IFG/IGT were 3.9, 11 and 20.5 compared with that of NGT, respectively. Meigs *et al.*[18] found that 40% of isolated IFG progressed to diabetes. According to the Funagata study, the risk for type 2 diabetes in Japanese with isolated IFG is 20.5 compared with that in NGT[19]. IFG subjects, therefore, require checking of postchallenge plasma glucose levels by OGTT to prevent or delay diabetes.

Regarding insulin secretory capacity and insulin sensitivity, fasting and postchallenge plasma glucose levels are regulated differently[20]. Hyperglycemia in Japanese patients is typically as a result of factors that differ from those in other ethnic groups, impaired insulin secretion and sensitivity being most notable. We have previously reported that although impaired early-phase insulin secretion plays the more important role in deterioration from NGT through IGT to isolated postchallenge hyperglycemia in Japanese subjects[9], progression from NGT through IFG to isolated fasting hyperglycemia is associated with both impaired insulin secretion and decreased insulin sensitivity[21]. However, impaired insulin secretion is the more important factor in Japanese subjects, whereas increasing insulin resistance is the more important factor in Caucasians,

Mexican Americans and Pima Indians[7,22]. The mean BMI of Japanese diabetics is 23–25 according to various epidemiological studies, which is lower than that in other ethnic groups[4,23]. It has also been reported that the insulinogenic index in IGT is greater than that in NGT in Caucasians, in whom insulin secretion peaks at 121 mg/dL of plasma glucose[24] compared with 100 mg/dL in Japanese[25]. The diversities in these groups suggest the importance of characterizing both insulin secretion and sensitivity in the different stages of glucose intolerance. In the present study, for the prevention of type 2 diabetes and the selection of suitable treatments, we analyzed $IFG_{100–109}$, which has not been addressed with regard to insulin secretory capacity and insulin sensitivity. The present results in Japanese subjects with $IFG_{100–109}$ show that lesser reserve capacity of insulin secretion rather than greater insulin resistance is involved in deteriorating 2-hPG and AUC-G.

We have found that deterioration of both insulin secretory capacity and insulin sensitivity has already begun in $IFG_{100–109}$/NGT. In addition, early-phase insulin secretion plays an important role in the deterioration of postchallenge glucose levels among Japanese subjects with slightly impaired fasting glucose of $IFG_{100–109}$, whereas insulin sensitivity plays a more limited role. Over 40% of $IFG_{100–109}$ subjects were classified into IGT or diabetes according to 2-hPG during OGTT. Therefore, Japanese $IFG_{100–109}$ subjects classified into normal glucose tolerance according to the WHO criteria and the JDS criteria are recommended to be screened by OGTT to identify whether they are NGT, IGT or diabetes.

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REFERENCES

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539–553.
2. The Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Invest* 2010; 1: 212–228.
3. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; 26: 3160–3167.
4. Fukushima M, Usami M, Ikeda Y, *et al.* Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. *Metabolism* 2004; 53: 831–835.
5. Mitsui R, Fukushima M, Nishi Y, *et al.* Factors responsible for deteriorating glucose tolerance in newly diagnosed type 2 diabetes in Japanese men. *Metabolism* 2006; 55: 53–58.
6. Haffner SM, D'Agostino R, Saad MF, *et al.* Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites. The Insulin Resistance Atherosclerosis Study. *Diabetes* 1995; 45: 742–748.
7. Haffner SM, Stern MP, Hazuda HP, *et al.* Increased insulin concentrations in nondiabetic offspring of diabetic parents. *N Engl J Med* 1998; 319: 1297–1301.
8. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979; 28: 1039–1057.
9. Suzuki H, Fukushima M, Usami M, *et al.* Factors responsible for development from normal glucose tolerance to isolated post challenge hyperglycemia. *Diabetes Care* 2003; 26: 1211–1215.
10. Taniguchi A, Fukushima M, Sakai M, *et al.* Remnant-like particle cholesterol, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients. *Diabetes Care* 2000; 23: 1766–1769.
11. Harada N, Fukushima M, Toyoda K, *et al.* Factors responsible for elevation of 1-h postchallenge plasma glucose levels in Japanese men. *Diabetes Res Clin Pract* 2008; 81: 284–289.
12. Abdul-Ghani MA, Jenkinson CP, Richardson DK, *et al.* Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. *Diabetes* 2006; 55: 1430–1435.
13. Seltzer HS, Allen EW, Herron AL Jr, *et al.* Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes. *J Clin Invest* 1967; 46: 323–335.
14. Matsuda M, Defronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999; 22: 1462–1470.
15. Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. *Diabetes Res Clin Pract* 2004; 66: S37–S43.
16. Sato KK, Nakamura Y, Hayashi T, *et al.* Combined measurement of fasting plasma glucose and A1c is effective for the prediction of Type 2 diabetes. *Diabetes Care* 2009; 32: 644–646.
17. Bonora E, Kiechl S, Willeit J, *et al.* Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. *Diabetes* 2004; 53: 1782–1789.

18. Meigs JB, Muller DC, Nathan DM, *et al.* The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. *Diabetes* 2003; 52: 1475–1484.
19. Eguchi H, Kato T, Tominaga M. Significance of IGT and impaired fasting glucose on the risk of development of diabetes. The Funagata study. *Diabetes (Japan)* 1998; 41: A107–A109.
20. Faerch K, Borch-Johnson K, Holsy JJ, *et al.* Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? *Diabetologia* 2009; 52: 1714–1723.
21. Nishi Y, Fukushima M, Mitsui R, *et al.* Insulin secretion and insulin sensitivity in Japanese subjects with impaired fasting glucose and isolated fasting hyperglycemia. *Diabetes Res Clin Pract* 2005; 70: 46–52.
22. Saad MF, Knowler WC, Pettitt DJ, *et al.* A two-step model for development of non–insulin-dependent diabetes. *Am J Med* 1991; 90: 229–235.
23. Tripathy D, Carlsson M, Almgren P, *et al.* Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia Study. *Diabetes* 2000; 49: 975–980.
24. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* 1998; 37: 667–687.
25. Seino Y, Ikeda M, Yawata M, *et al.* The insulinogenic index in secondary diabetes. *Horm Metab Res* 1975; 7: 107–115.