Fasting tests of insulin secretion and sensitivity predict future prediabetes in Japanese with normal glucose tolerance

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ABSTRACT

Aims/Introduction: Reduced insulin sensitivity and secretion are important in the pathogenesis of type 2 diabetes. Their relationships to prediabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) have been previously studied with the oral glucose tolerance test (OGTT). We investigated whether or not baseline measures of insulin secretion and sensitivity obtained from fasting blood specimens were related to the development of prediabetes and how these measures compared with those based on the OGTT.

Materials and Methods: In 152 Japanese subjects with normal glucose tolerance, we measured baseline plasma glucose and insulin after an overnight fast and during a 75 g OGTT, insulin resistance index (homeostasis model assessment [HOMA-IR]), and insulin secretion (insulinogenic index [30 min insulin − fasting insulin] ÷ [30 min glucose − fasting glucose] or HOMA-β).

Results: At a 5–6 year (mean 5.7 years) follow-up examination, we confirmed 36 cases of prediabetes. After adjusting for age, sex, family history of diabetes, body mass index, and 2-h plasma glucose, the odds ratio comparing the lowest tertile (≤0.82) of insulinogenic index with the highest tertile (≥1.43) was 6.98 (95% confidence interval, 1.96–24.85) and was 10.72 (2.08–55.3) comparing the lowest tertile (≤76.3) of HOMA-β with the highest tertile (≥122.1), whereas the respective odds ratios of HOMA-IR were 3.74 (1.03–13.57) and 10.89 (1.93–61.41) comparing the highest tertile (≥1.95) with the lowest tertile (≤1.25).

Conclusions: Lower insulin secretion and sensitivity are independent risk factors for prediabetes. Clinically practical identification of those at risk for prediabetes is obtainable from HOMA-β and HOMA-IR, both of which are measured in fasting state. (J Diabetes Invest, doi: 10.1111.j.2040-1124.2010.00041.x, 2010)

KEY WORDS: Glucose intolerance, Insulin resistance, Epidemiology

INTRODUCTION

The prevalence of type 2 diabetes is rapidly growing worldwide[1,2]. Because impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are associated with a higher risk for future type 2 diabetes[3–6], they are also called prediabetes. In addition, IGT has been reported to be associated with an increased risk for cardiovascular disease, ophthalmic diabetic complications, and mortality[7–10]. Therefore, it may be important to detect subjects at high risk of development of prediabetes in order to prevent or delay onset of type 2 diabetes and its associated complications.

Although higher insulin resistance and lower insulin secretion are known to be key pathogenic factors in type 2 diabetes, only a few prospective studies have reported whether or not these are prospectively associated with an increased risk of prediabetes[11–13]. All have reported an association between lower insulin secretion and risk of IGT or IFG, but all also used the oral glucose tolerance test (OGTT) or a variant of it to assess insulin secretion. Because the OGTT is both time- and cost-consuming, a fasting test might be preferable when screening for those at risk for prediabetes among normal glucose tolerance (NGT) individuals. Homeostasis model assessment of β-cell function (HOMA-β) requires only a single measurement of insulin and glucose in the fasting state, but its ability to predict prediabetes has not been thoroughly studied. We therefore prospectively examined the relationship of insulin secretion, estimated as HOMA-β and insulinogenic index (Δinsulin [0–30 min] ÷ Δglucose [0–30 min]), and insulin resistance, measured as

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HOMA-IR, to the risk of IGT and/or IFG in Japanese men and women.

MATERIALS AND METHODS

Study Population

The study population consisted of native Japanese men and women with NGT enrolled between 1997 and 2003 at the Institute for Adult Diseases (IAD), Asahi Life Foundation, Tokyo, Japan. Subjects were excluded if they had diseases that might affect their ability to participate or influence glucose metabolism (endocrine, hepatic, pancreatic, pulmonary, neoplastic, neuromuscular or psychiatric diseases) or if they were receiving medications that could influence glucose metabolism, such as glucocorticoids.

Of 281 NGT subjects in the original baseline cohort, 85 subjects could not be contacted or refused to further participate, 15 moved and three died. Of the remaining 178 subjects, 14 were excluded because they were examined more than 7 years after their baseline examination, leaving 164 subjects who completed a 5–6-year (mean 5.7 ± 0.6 years) follow-up examination. For the current analysis, 12 subjects who developed diabetes during the follow-up period were also excluded. The study population for analyses therefore included 152 participants. The protocol for this research was reviewed by the institutional review board of Asahi Life Institute, and conforms to the provisions of the Declaration of Helsinki. Signed informed consent was obtained from all participants.

Data Collection

All evaluations were carried out at IAD, Asahi Life Foundation. The clinical examination consisted of a medical history, physical examination, anthropometric measurements and self-administered questionnaires. Plasma glucose and insulin were measured after an overnight 12-h fast and during a 75-g OGTT at 30, 60 and 120 min. Participants were classified as NGT, IFG, IGT or type 2 diabetes based on the American Diabetes Association 1997 criteria[14]. Plasma glucose was measured by an automated glucose oxidase method. Plasma insulin was measured by radioimmunoassay (RIA) from December 1997 to October 1998 at IAD and from October 1998 to November 2000 by solid phase RIA at SRL Inc (Tokyo, Japan). The conversion formula based on a comparison of the two assays on duplicate samples was SRL RIA insulin = 1.232 × IAD insulin (R^2 = 0.948). From November 2000, insulin was measured by enzyme immunoassay (EIA) at SRL. The conversion formula was SRL RIA insulin = 1.040 × SRL EIA insulin 0.706 (R^2 = 0.992). All the data are converted to SRL RIA insulin. Insulin sensitivity was estimated by homeostasis model assessment (HOMA-IR): (fasting glucose [mg/dL]) × [fasting insulin {μU/mL}] ÷ 405)[15]. To assess insulin secretion, we used the insulinogenic index (30–0 min insulin [μU/mL]) ÷ (30–0 min plasma glucose [mg/dL]), which provides a measurement of early insulin release during the OGTT, and HOMA-β (fasting plasma insulin [μU/mL] × 360 ÷ [fasting plasma glucose {mg/dL} – 63])[15]. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

Diagnosis of NGT, IFG, IGT and Type 2 Diabetes

Type 2 diabetes was diagnosed if fasting plasma glucose (FPG) was ≥126 mg/dL or 2-h glucose was ≥200 mg/dL or the subject was taking oral hypoglycemic medication or insulin. Isolated IGT was diagnosed if the subject had no history of diabetes and FPG was <110 mg/dL, but 2-h glucose was ≥140 and <200 mg/dL. Isolated IFG was diagnosed if the subject had no history of diabetes and FPG was ≥110 and <126 mg/dL, but 2-h glucose was <140 mg/dL. Subjects who met the criteria for both IGT and IFG (FPG of ≥110 and <126 mg/dL, and 2-h glucose of ≥140 and <200 mg/dL) were classified as IGT/IFG. Subjects with no history of diabetes, FPG < 110 mg/dL, and 2-h glucose <140 mg/dL were classified as NGT. These criteria, based on the earlier 1997 ADA criteria[14] and currently used by the Japan Diabetes Society, were applied at baseline and follow up.

Statistical Analyses

We used multiple logistic regression analysis to estimate the odds ratio (OR) for incidence of prediabetes in relation to baseline variables. The presence of effect modification was tested by the insertion of first-order interaction terms into appropriate regression models. Multicollinearity was assessed using the variance inflation factor (VIF). A value of VIF exceeding 10 is regarded as indicating serious multicollinearity and values above 4.0 might be a cause for concern. We calculated the 95% confidence interval (CI) for each OR. The areas under the receiver operator characteristic (ROC) curves for each multiple logistic regression model, which included the insulinogenic index or HOMA-β, were calculated and statistically compared. *P*-values presented are two-tailed. We carried out statistical analyses using the PASW Statistics version 17.0 (SPSS, Chicago, IL, USA) software package and Stata SE, version 10.0 (StataCorp, College Station, TX, USA).

RESULTS

Among 152 subjects with NGT at baseline who had follow-up examinations at 5–6 years (mean 5.7 ± 0.6 years), we confirmed 36 cases of IGT and/or IFG (26 isolated IGT, 6 isolated IFG and 4 IGT/IFG). The baseline anthropometric and metabolic characteristics of the 152 subjects are presented in Table 1. Subjects who developed prediabetes during the follow up tended to have higher mean levels of BMI, HOMA-IR, and fasting and 2-h plasma glucose, and a higher prevalence of family history of diabetes than those who did not. There were no statistically significant differences in HOMA-β and insulinogenic index levels between those who developed prediabetes and those who did not. The baseline characteristics of subjects who participated in follow up versus those who did not were not significantly different (data not shown).

Because beta-cell secretion is affected by prevailing insulin resistance, we took this into consideration in several different

Table 1 | Characteristics of study subjects at baseline according to whether prediabetes developed after 5–6 year follow up

Characteristics	Total (n = 152)	Glucose tolerance status at follow up		P
		NGT (n = 116)	Prediabetes (n = 36)	
Age (years)	58.8 ± 6.6	58.3 ± 6.3	60.3 ± 7.4	0.119
Female sex (%)	53.3	52.6	55.6	0.757
Body mass index (kg/m^2)	23.0 ± 2.9	22.7 ± 2.7	24.0 ± 3.5	0.022
Family history of diabetes (%)	11.2% (17/152)	7.8% (9/116)	22.2% (8/36)	0.016
Fasting plasma glucose, (mg/dL)	89.7 ± 7.1	88.6 ± 6.6	93.0 ± 7.5	0.001
2-h plasma glucose (mg/dL)	106.5 ± 20.2	103.6 ± 20.9	116.1 ± 14.4	0.001
Fasting plasma insulin (μU/mL)	7.78 ± 3.69	7.53 ± 3.74	8.58 ± 3.48	0.137
HOMA-IR	1.73 ± 0.86	1.66 ± 0.85	1.98 ± 0.85	0.046
Insulinogenic index	1.55 ± 2.00	1.68 ± 2.22	1.11 ± 0.88	0.132
HOMA-β	110.2 ± 56.2	111.1 ± 58.7	107.2 ± 47.5	0.718

Variables are expressed as mean ± SD or percentages.
IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Table 2 | Incidence of prediabetes according to homeostasis model assessment of β-cell function, insulinogenic index and HOMA-IR

		HOMA-IR		
	Total	Low (≤1.25)	Medium (1.25–1.95)	High (≥1.95)
Total		12.0% (6/50)	25.0% (13/52)	34.0% (17/50)
Insulinogenic index range				
Low (≤0.82)	31.4% (16/51)	8.7% (2/23)	50.0% (10/20)	50.0% (4/8)
Medium (0.82–1.43)	26.0% (13/50)	21.1% (4/19)	16.7% (2/12)	36.8% (7/19)
High (≥1.43)	13.7% (7/51)	0% (0/8)	5% (1/20)	26.1% (6/23)
HOMA-β				
Low (≤76.25)	24.0% (12/50)	13.2% (5/38)	60.0% (6/10)	50.0% (1/2)
Medium (76.25–122.13)	26.9% (14/52)	10.0% (1/10)	17.2% (5/29)	61.5% (8/13)
High (≥122.13)	20.0% (10/50)	0% (0/2)	15.4% (2/13)	22.9% (8/35)

HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

ways. To examine the relationship of HOMA-β and insulinogenic index to incidence of prediabetes by the levels of HOMA-IR, we stratified subjects according to tertiles of HOMA-IR (Table 2). In all of these strata, the highest tertile of HOMA-β and insulinogenic index had the lowest incidence of prediabetes. In contrast, after subjects were stratified according to tertiles of HOMA-β or insulinogenic index, higher levels of HOMA-IR were associated with greater incidence of IGT and/or IFG (Table 2).

We also carried out regression analysis to adjust for HOMA-IR and clarify the independent effects of insulinogenic index or HOMA-β on the incidence of IGT and/or IFG in two multivariate regression models (Table 3). Because insulinogenic index and HOMA-IR showed a nonlinear association with the incidence of prediabetes, to simplify the models we included insulinogenic index and HOMA-IR categorized by tertiles. After adjusting for age, sex, family history of type 2 diabetes, BMI and 120-min plasma glucose level, lower insulinogenic index and higher HOMA-IR were independently associated with the risk of developing prediabetes (Model 1, Table 3). Likewise, when HOMA-β was substituted for insulinogenic index, lower HOMA-β and higher HOMA-IR were also independently associated with an increased risk of incidence of prediabetes (Model 2, Table 3). Although HOMA-β and HOMA-IR both include fasting glucose and fasting insulin, they were independent risk factors when assessed by VIF. We examined the significance of the interaction terms between HOMA-IR and insulinogenic index or HOMA-β, but there was no significant improvement in fit. The interaction of sex with HOMA-IR, insulinogenic index, or HOMA-β was not significant. There was no multicollinearity in all models we examined.

The areas under the ROC curves for each multiple logistic regression model, which included the insulinogenic index (Model 1 of Table 3) or HOMA-β (Model 2 of Table 3), were calculated to compare which model was a better predictor. Model 2, which included HOMA-β, had almost the same areas under the ROC curves as Model 1, which included insulinogenic index (Figure 1; 0.797 and 0.800 are the areas under the ROC curves, respectively, P = 0.920).

Table 3 | Multivariate models of the incidence of prediabetes in relation to baseline insulin secretion and resistance

Variables in the model	Multiple-adjusted odds ratio (95% CI)	*P*
Model 1		
Insulinogenic Index		
Tertile 1 (≤0.82)	6.98 (1.96–24.85)	0.003
Tertile 2 (0.82-1.43)	3.73 (1.13–12.25)	0.030
Tertile 3 (≥1.43)	1.00	
HOMA-IR		
Tertile 1 (≤1.25)	1.00	
Tertile 2 (1.25–1.95)	2.13 (0.64–7.07)	0.215
Tertile 3 (≥1.95)	3.74 (1.03–13.57)	0.045
Female	1.12 (0.47–2.69)	0.801
Age	1.05 (0.99–1.13)	0.132
Body mass index	1.20 (1.01–1.43)	0.037
2-h glucose	1.03 (1.00–1.06)	0.027
Family history of diabetes	4.37 (1.26–15.23)	0.021
Model 2		
HOMA-β		
Tertile 1 (≤76.25)	10.72 (2.08–55.32)	0.005
Tertile 2 (76.25–122.13)	4.05 (1.19–13.84)	0.026
Tertile 3 (≥122.13)	1.00	
HOMA-IR		
Tertile 1 (≤1.25)	1.00	
Tertile 2 (1.25–1.95)	3.69 (0.87–15.59)	0.076
Tertile 3 (≥1.945)	10.89 (1.93–61.41)	0.007
Female	1.32 (0.54–3.18)	0.543
Age	1.05 (0.98–1.12)	0.149
Body mass index	1.20 (1.01–1.42)	0.038
2-h glucose	1.03 (1.01–1.06)	0.015
Family history of diabetes	2.87 (0.81–10.17)	0.103

HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

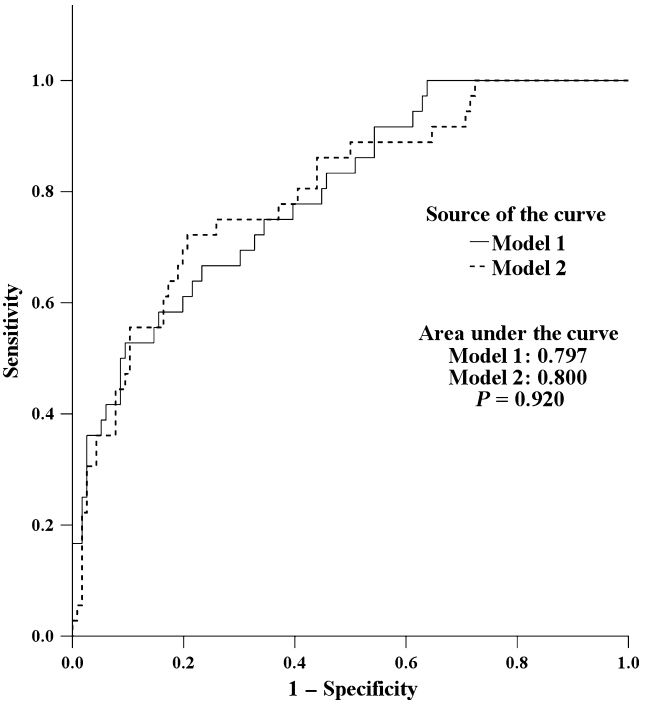

Figure 1 | Receiver operator characteristic (ROC) curve and areas under the ROC curves for Models 1 and 2.

DISCUSSION

In the present study, we showed that even among NGT subjects, both HOMA-IR and lower insulin secretion evaluated by insulinogenic index or HOMA-β were associated with an increased risk of IGT and/or IFG. This finding was independent of age, sex, family history of type 2 diabetes, and 120-min plasma glucose (OGTT). The multivariate model that included HOMA-β had almost the same predictive power as the model that included insulinogenic index.

A few previous studies have shown that insulin resistance and abnormal insulin secretion are both risk factors for the development of IGT[11–13]. Haffner *et al.* showed in the San Antonio Heart Study that decreased insulin secretion, assessed by low insulinogenic index using OGTT data, and increased insulin resistance, assessed by fasting serum insulin, predicted the development of IGT. Hayashi *et al.*[13] showed in an analysis of prospective OGTT data from the Japanese American Community Diabetes Study that both HOMA-IR and insulinogenic index were independent risk factors for incident IGT, even after adjusting for visceral adiposity as measured by computed tomography. Faerch *et al.* reported that prospective data from the Inter 99 Study showed reduced insulin secretion was present before the development of IFG and low insulin sensitivity was present before the development of IGT. However, there was no adjustment for BMI, insulin secretion, insulin sensitivity and other factors[11]. To our knowledge, ours is the first prospective study to show a significant relationship of insulin resistance and impaired β-cell function, both assessed by using only a fasting measurement, to incident IGT and/or IFG.

In the present study, 23.7% of the participants developed IGT and/or IFG during a mean 5.7 years of follow up. This rate is higher than shown in several previous studies[12,16,17], but is lower than in another report[18]. There are several possible reasons for these discrepancies, such as differences in age, BMI, race/ethnicity, study design (hospital-based or population-based), criteria for abnormal glucose tolerance and follow-up interval.

A limitation of the present study is that IGT and IFG could not be analyzed separately because of the low number of incident cases of IFG. These are different conditions[11,19,20] and might be associated with differences in the types or severity of complications associated with hyperglycemia[21]. Although the present study was carried out in Japanese, it is likely that similar results would be obtained in other ethnic groups, because the pathogenesis of glucose intolerance has been reported to be similar among four different ethnic groups: Caucasians, Blacks, Hispanics and Asians[22]. HOMA-β and HOMA-IR are known to be useful in assessing insulin secretion and resistance when

the fasting glucose level is not very high. Thus, our finding HOMA-β and HOMA-IR to be significant risk factors for prediabetes might be considered reliable, because the study subjects were NGT at baseline with normal fasting glucose.

Finally, there was a relatively low follow-up rate, although a comparison of baseline data showed no significant differences between those who dropped out and those who did not.

In conclusion, we have provided evidence that lower insulinogenic index or HOMA-β and higher HOMA-IR are significant risk factors for the future development of prediabetes among Japanese with NGT. Because HOMA-β can estimate insulin secretion in the fasting state, it is more practical than the insulinogenic index, which requires an OGTT. Further research is needed to identify whether or not the relationship of low insulin secretion and high insulin resistance with risk of IGT and IFG might differ between these two prediabetic states. Finally, further research might show whether intervention in people with NGT identified to be at high risk for prediabetes will prevent the development of future IGT and/or IFG.

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