Original Article

Differences in Insulin Action and Secretion, Plasma Lipids and Blood Pressure Levels between Impaired Fasting Glucose and Impaired Glucose Tolerance in Japanese Subjects

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We examined insulin action/secretion and cardiovascular disease risk factors in Japanese subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) who were not taking any medications known to affect glucose tolerance, blood pressure (BP) or plasma lipids (PLs). A total of 1,399 subjects received measurements of anthropometry, BP, PLs, and plasma glucose/insulin concentrations during 75 g-oral glucose tolerance test (OGTT). According to 2003 American Diabetes Association criteria, subjects were classified as having normal fasting glucose (NFG)/normal glucose tolerance (NGT) (*n*=1,173), IFG (*n*=128), IGT (*n*=55), and IFG/IGT (*n*=43). Insulin action was calculated using the HOMA-R (index of hepatic insulin resistance) and Matsuda index (reflects whole body insulin sensitivity). The ratio of the incremental area under the curve of insulin to that of glucose during OGTT ($\Delta AUC_{PI}/\Delta AUC_{PG}$) was used as an index of β-cell function. HOMA-R was higher in IFG (2.3±0.1) and IFG/IGT (2.5±0.2) than in NFG/NGT (1.8±0.03). The Matsuda index was lower in IFG (6.5±0.3), IGT (5.4±0.4) and IFG/IGT (5.1±0.5) than in NFG/NGT (9.6±0.2). $\Delta AUC_{PI}/\Delta AUC_{PG}$ was lower in IGT (0.6±0.05) and IFG/IGT (0.5±0.05) than in IFG (1.4±0.12) or NFG/NGT (1.2±0.03). Mean BP was higher in IGT (100±1.7 mmHg) than in NFG/NGT (91±0.3) or IFG (95±1.1). The plasma triglyceride level was higher in IGT (155±14 mg/dL) and IGT/IFG (173±12) than in IFG (132±7) or NFG/NGT (122±2). In conclusion, 1) whole body insulin sensitivity is decreased in IFG and IGT, with a greater reduction in IGT, 2) hepatic insulin resistance and preserved β-cell function are characteristics of IFG, and 3) higher BP and triglyceride levels are observed in IGT. IGT is more closely associated with risk factors for cardiovascular disease than is IFG. (*Hypertens Res* 2008; 31: 1357–1363)

***Key Words*: impaired fasting glucose, impaired glucose tolerance, cardiovascular disease risk factors**

Introduction

Impaired glucose tolerance (IGT) is an intermediate state in the transition from normal glucose tolerance (NGT) to type 2 diabetes. IGT subjects are at high risk for progression to type 2 diabetes, with an annual conversion rate of 5–10%, depending upon the ethnic group (*1–5*). In 1997, the American Diabetes Association (ADA) introduced another intermediate state, impaired fasting glucose (IFG) (*6*), in the transition from NGT to type 2 diabetes. IFG was meant to be analogous to IGT, since subjects with isolated IFG and isolated IGT had similar risk for progression to type 2 diabetes (*1–5*). However, only 45% of subjects with IFG had IGT; conversely,

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Table 1. Clinical Characteristics and Metabolic Measurements

	NFG/NGT	IFG	IGT	IFG/IGT	NFG/NGT *vs.* IFG	NFG/NGT *vs.* IGT	NFG/NGT *vs.* IFG/IGT	IFG *vs.* IGT	IFG *vs.* IFG/IGT	IGT *vs.* IFG/IGT
n	1,173	128	55	43						
Age (years old)	58±0.3	60±0.9	60±1.3	62±1.6						
Gender (male/female)	514/659	64/64	30/25	29/14			<0.01		<0.05	
BMI (kg/m^2)	23.1±0.1	23.8±0.3	23.9±0.4	24.3±0.5						
FPG (mg/dL)	85±0.2	105±0.5	92±0.7	108±1.2	<0.01	<0.01	<0.01	<0.01		<0.01
PG_{60} (mg/dL)	122±0.8	156±2.7	190±4.3	218±4.9	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
PG_{120} (mg/dL)	99±0.4	120±0.8	154±2.1	156±2.0	<0.01	<0.01	<0.01	<0.01	<0.01	
Mean PG (mg/dL)	107±0.5	134±1.5	157±2.4	175±2.7	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
FPI (μU/mL)	8.7±0.2	8.9±0.5	9.9±0.8	9.3±0.9						
PI_{60} (μU/mL)	41±0.9	58±3.6	60±5.0	55±4.4	<0.01	<0.01				
PI_{120} (μU/mL)	27±0.5	32±2.8	57±4.6	38±3.7	<0.05	<0.01	<0.01	<0.01		<0.01
Mean PI (μU/mL)	29±0.6	39±2.3	46±3.4	39±2.9	<0.01	<0.01	<0.05			
Systolic BP (mmHg)	125±0.5	131±1.7	140±2.9	131±3.2	<0.01	<0.01		<0.01		
Diastolic BP (mmHg)	74±0.3	75±0.9	79±1.3	77±1.7		<0.01				
Mean BP (mmHg)	91±0.3	94±1.0	100±1.7	95±2.0		<0.01		<0.05		
Total cholesterol (mg/dL)	188±0.9	194±2.8	196±3.8	190±4.4						
HDL cholesterol (mg/dL)	56±0.4	54±1.1	53±2.1	51±2.2						
LDL cholesterol (mg/dL)	108±0.9	113±2.7	112±4.0	104±4.0						
TG (mg/dL)	122±2.5	132±7.2	155±13.6	173±12.3		<0.01	<0.01			
TG/HDL cholesterol ratio	2.5±0.1	2.7±0.2	3.4±0.4	3.9±0.4		<0.01	<0.01		<0.01	

Data are means±SEM. *p* values indicate significance of differences among pairs of the groups analyzed by ANOVA. BMI, body mass index; FPG, fasting plasma glucose; PG, plasma glucose; $PG_{60\,(120)}$, PG at 60 (120) min; FPI, fasting plasma insulin; PI, plasma insulin; $PI_{60\,(120)}$, PI at 60 (120) min; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; NFG, normal fasting glucose; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose.

<25% of subjects with IGT had IFG (*2*, *3*, *7–11*). The partial overlap between IFG and IGT suggests that different pathophysiological mechanisms contribute to the disturbances in glucose homeostasis. However, the differences in pathophysiological mechanisms between IGT and IFG had not been fully defined. Some studies reported that the primary abnormality in IFG was insulin resistance, while IGT was more associated with impaired β-cell function (*12–19*). Other studies have reported opposite results (*20–24*). In 2003, the ADA introduced new diagnostic criteria for IFG based on the receiver operator curve analysis of several prospective epidemiological studies (*25*). As a result of this analysis, the criteria of the fasting plasma glucose (FPG) concentration for IFG was reduced from 110 to 100 mg/dL, and isolated IFG was defined as an FPG of 100–125 mg/dL with 2-h plasma glucose (PG) <140 mg/dL during the 75 g-oral glucose tolerance test (OGTT) (*25*). Using these new criteria, Abdul-Ghani *et al*. demonstrated that Mexican American and Caucasian subjects with IGT and IGT/IFG had significantly greater reductions in peripheral (muscle) insulin sensitivity and insulin secretion compared to subjects with IFG (*26*). However, the subject population was obese (body mass index [BMI] >30 kg/m^2) and 3/4 of the subjects were of Hispanic descent (*26*). Little information is available about differences in insulin action and insulin secretion in other ethnic groups with IFG, IGT, and IFG/IGT and in subjects whose BMI is in the normal weight range. Therefore, one aim of the present study was to examine insulin sensitivity and secretion in healthy, normal-weight Japanese subjects who were not taking any medications known to affect glucose tolerance, blood pressure, or lipids levels.

It has also been reported that IGT is associated with an increased prevalence of cardiovascular risk factors (*27–30*) and cardiovascular events (*30*, *31*), whereas IFG is less strongly associated with cardiovascular events and mortality (*30*, *31*). Therefore, a second aim of this study was to examine the association between cardiovascular risk factors (blood pressure and plasma lipids) and IFG, IGT, and IFG/IGT using the 2003 revised ADA criteria in Japanese subjects.

Methods

We have been carrying out a medical examination and epidemiological investigation of cardiovascular disease in the towns of Tanno and Sobetsu, Hokkaido, Japan since 1976 (*32*). From 2,027 citizens who had undergone medical examination and received measurements of anthropometry, blood pressure, plasma lipids, and PG/plasma insulin (PI) concen-

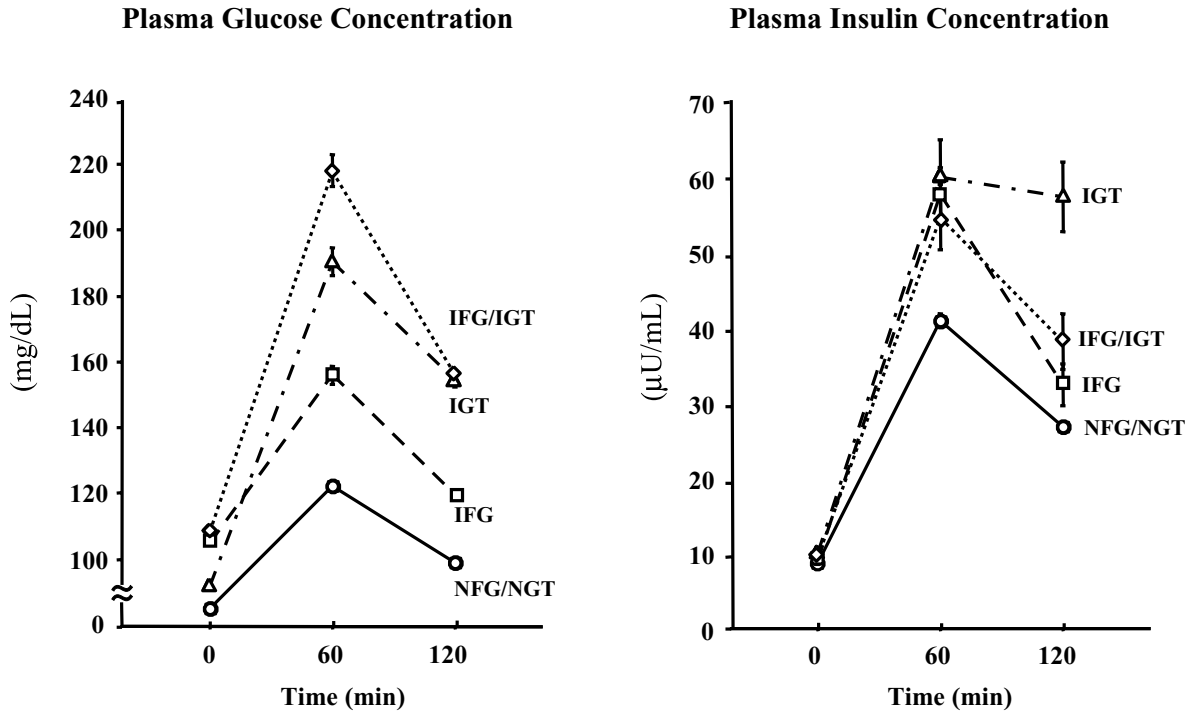

Fig. 1. *Plasma glucose (PG) and insulin (PI) concentrations during the 75 g-OGTT in subjects with normal fasting glucose and glucose tolerance (NFG/NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), and IFG plus IGT (IFG/IGT).*

trations during 75 g-OGTT in the town of Tanno and Sobetsu, we selected every healthy subject ($n=1{,}399$) who was not taking any medications known to affect glucose tolerance, blood pressure, and plasma lipids levels, and who did not have a history of diabetes. All study subjects were in good general health without evidence of cardiac, hepatic, renal or other chronic diseases as determined by medical history, complete blood cell count (CBC), routine chemistries and ECG. At 8 AM, after a 10-h overnight fast, height and weight were measured and BMI was calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 5 min in the reclining position with an automated blood pressure recorder (OMRON HEM 907; OMRON HEALTHCARE, Kyoto, Japan). Blood samples for measurement of fasting plasma lipids (total cholesterol, triglyceride [TG], high-density lipoprotein [HDL] cholesterol) were obtained through an indwelling catheter. Subjects then ingested 75 g of glucose and blood for measurement of PG and PI concentrations were obtained at 0, 60, and 120 min. Plasma total cholesterol, TG, and HDL cholesterol concentrations were measured enzymatically on an AU5200 autoanalyzer (OLYMPUS, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was calculated from the Friedewald equation. PG was measured using the glucose oxidase method, and PI was measured using RIA beads (Dinabot, Tokyo, Japan).

Insulin sensitivity indices were calculated from OGTT using the HOMA-R (*26*, *33*) and Matsuda index [10,000/ $\{(\text{FPG}\times\text{FPI})\times(\text{mean PG}\times\text{mean PI})\}^{1/2}$] (*26*, *34*). To evaluate β-cell function, the insulinogenic index was calculated as the incremental area under the curve (AUC) of PI ($\Delta\text{AUC}_{\text{PI}}$) divided by the incremental AUC of PG ($\Delta\text{AUC}_{\text{PG}}$) during a 0–120 min (total) time period of the OGTT (*26*, *35*). The insulin secretion/insulin resistance (disposition) index ($\Delta\text{AUC}_{\text{PI}}/\Delta\text{AUC}_{\text{PG}}\times$ Matsuda index) also was determined to provide a measure of β-cell function (*19*, *26*). Incremental AUCs of plasma insulin and glucose were calculated according to the trapezoid rule.

Statistical analysis was performed with StatView for Windows, v 5.0 (SAS Institute Inc., Cary, USA). Comparisons between groups were performed using analysis of variance with Scheffe post-hoc testing when appropriate. The χ^2 test was used for comparing proportions between groups. Stepwise multiple regression analysis was performed to examine the multiple correlations among variables. All data are presented as the mean value±SEM. Values of $p<0.05$ were considered statistically significant.

Results

The clinical characteristics and metabolic parameters of each group are summarized in Table 1. The IFG/IGT group had a higher percentage of males compared with the other three

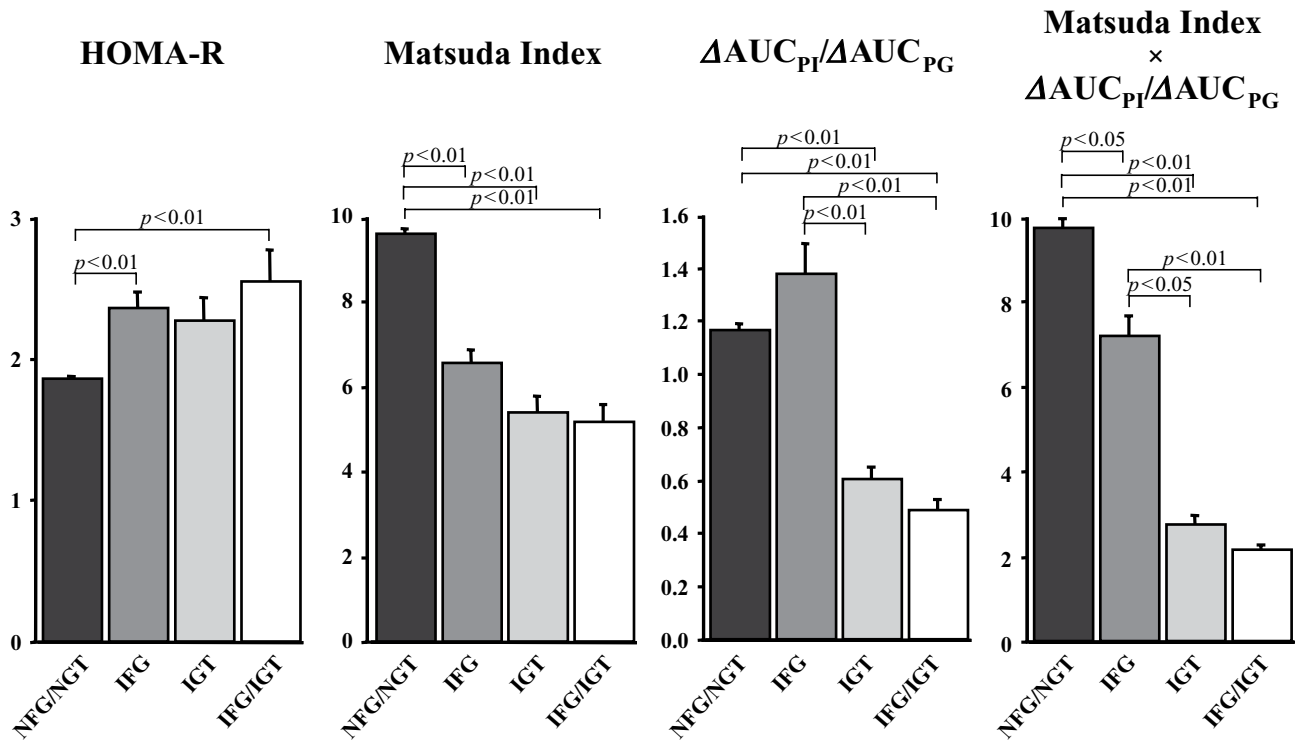

Fig. 2. *HOMA-R, Matsuda index [10,000/{(FPG × FPI) × (mean PG × mean PI)}$^{1/2}$], ratio of incremental area under the curve (AUC) of PI to incremental AUC of PG [$\Delta AUC_{PI}/\Delta AUC_{PG}$], and Matsuda index × $\Delta AUC_{PI}/\Delta AUC_{PG}$ during OGTT in subjects with normal fasting glucose and glucose tolerance (NFG/NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), and IFG plus IGT (IFG/IGT). p values indicate significant differences among the groups.*

groups. The four groups were similar in age, BMI, and fasting plasma levels of total-, HDL- and LDL-cholesterol. By definition subjects with isolated IFG and combined IFG/IGT had a significantly increased FPG compared to the normal fasting glucose (NFG)/NGT and isolated IGT groups. PG excursions during the OGTT rose progressively from NFG/NGT to IFG to IGT to IFG/IGT, and PG in each group was significantly higher than in the preceding group (Fig. 1 and Table 1). PI excursions during the OGTT were similar in IFG/IGT and IFG and both were significantly greater than in NFG/NGT. PI at 60 min (PI_{60}) during the OGTT was significantly higher in IFG and IGT than in NFG/NGT, while PI at 120 min (PI_{120}) and mean PI during the OGTT were significantly higher in IFG, IGT, and IFG/IGT than in NFG/NGT. The PI_{120} was significantly higher in IGT than in IFG and IFG/IGT. Blood pressure was significantly higher in IGT compared with NFG/NGT or IFG. Also, only SBP was significantly higher in IFG than in NFG/NGT. The prevalence of hypertension (SBP≥140 mmHg or DBP≥90 mmHg) in each group was 20% (235/1,173) in NFG/NGT, 29% (37/128) in IFG, 47% (26/55) in IGT, and 37% (16/43) in IFG/IGT, respectively. The TG concentration and TG/HDL cholesterol ratio were significantly higher in the IGT or IGT/IFG group than in the NFG/NGT group. Furthermore, the IGT/IFG group had a higher TG/HDL cholesterol ratio compared with the IFG group. The differences in metabolic parameters and blood pressure remained even after significant adjustment for gender, age, and BMI.

HOMA-R, an index of hepatic insulin resistance, was significantly higher in IFG (2.3±0.1) and IFG/IGT (2.5±0.2) than in NFG/NGT (1.8±0.04) (Fig. 2). The Matsuda index, a measure of whole body (especially muscle) insulin sensitivity, was significantly reduced in the IFG (6.5±0.3), IGT (5.4±0.4) and IFG/IGT (5.1±0.5) groups compared with the NFG/NGT group (9.5±0.2). $\Delta AUC_{PI}/\Delta AUC_{PG}$, an index of β-cell function, was significantly lower in IGT (0.6±0.05) and IFG/IGT (0.5±0.04) compared with IFG (1.4±0.1) or NFG/NGT (1.2±0.03). The insulin secretion/insulin resistance index of β-cell function ($\Delta AUC_{PI}/\Delta AUC_{PG}$ × Matsuda index) was significantly lower in the IFG (7.1±0.5) compared to the NGT group and was further and significantly reduced in the IGT (2.7±0.2) and IFG/IGT (2.1±0.2) groups compared with both the NFG/NGT (9.7±0.2) and IFG (7.1±0.5) groups.

The predictors of mean blood pressure, TG, and TG/HDL cholesterol ratio were examined in backward stepwise regression analysis using age, gender (male), BMI, FPG, PG_{60}, PG_{120}, FPI, PI_{60}, and PI_{120} during the OGTT as independent variables (Table 2). Increased age, BMI, PG_{120} and PI_{120}, and

Table 2. Multiple Regression Analyses for Blood Pressure, Triglyceride Level, and TG/HDL Cholesterol Ratio

Variables	Standard coefficient	SEM	*p* value
Positive predictors of mean blood pressure			
Age	0.129	0.026	<0.0001
Gender (male)	0.082	0.586	0.0014
BMI	0.170	0.105	<0.0001
PG_{120}	0.161	0.016	<0.0001
PI_{120}	0.082	0.015	0.0046
Positive predictors of triglyceride (TG) level			
Gender (male)	0.181	4.395	<0.0001
BMI	0.169	0.793	<0.0001
PG_{120}	0.064	0.114	0.0156
PI_{120}	0.147	0.071	<0.0001
Predictors of TG/HDL cholesterol ratio			
Gender (male)	0.201	0.110	<0.0001
BMI	0.200	0.020	<0.0001
FPI	−0.063	0.011	0.0199
PI_{60}	0.182	0.002	<0.0001
PI_{120}	0.074	0.003	0.0171

Evaluated parameters: age, gender, BMI, FPG, PG_{60}, PG_{120}, FPI, PI_{60}, and PI_{120} during 75 g-OGTT. TG, triglyceride; HDL, high-density lipoprotein; BMI, body mass index; PG_{120}, plasma glucose at 120 min; $PI_{60\,(120)}$, plasma insulin at 60 (120) min; OGTT, oral glucose tolerance test.

male gender were positive predictors of the increase in mean blood pressure (adjusted $r^2=0.12$, $p<0.0001$). When performing the same analysis for SBP or DBP, increased age, BMI, PG_{120} and PI_{120} were positive predictors of the increase in SBP (adjusted $r^2=0.12$, $p<0.0001$), and increased BMI, PG_{120} and PI_{60}, PI_{120} and male gender were positive predictors of the increase in DBP (adjusted $r^2=0.10$, $p<0.0001$). Increased BMI, PG_{120}, PI_{60}, and male gender were independent positive predictors of the increase in plasma TG (adjusted $r^2=0.11$, $p<0.0001$). BMI, PI_{60} and PI_{120}, decreased FPI, and male gender were independent positive predictors of the increase in TG/HDL cholesterol ratio (adjusted $r^2=0.15$, $p<0.0001$) (Table 2). Inversely, BMI, PI_{60} and PI_{120}, decreased FPI, and male gender were independent positive predictors of the decrease in HDL cholesterol (adjusted $r^2=0.13$, $p<0.0001$).

Discussion

In the present study, we investigated the pathophysiological disturbances in Japanese subjects with IFG, IGT, and IFG/IGT. HOMA-R was significantly higher in subjects with IFG with or without accompanying IGT compared to those with NFG/NGT. The HOMA-R index represents the product of the FPG and FPI concentrations (*33*). Since hepatic glucose production (HGP) is the primary determinant of the FPG concentration (*36*), and the fasting plasma insulin concentration is the primary regulator of HGP (*37*), HOMA-R primarily reflects hepatic insulin resistance. Thus, our results indicate that Japanese individuals with IFG are characterized by hepatic insulin resistance. The Matsuda index [10,000/{(FPG × FPI) × (mean PG × mean PI)}$^{1/2}$] was decreased in the IFG, IGT, and IFG/IGT groups compared to the NFG/NGT group, with a greater reduction in IGT ($p=0.03$) with or without IFG ($p=0.05$). The Matsuda index is strongly correlated with insulin-stimulated total body glucose disposal, which primarily reflects muscle insulin sensitivity, during the euglycemic insulin clamp (*26*, *34*). Thus, IGT can be characterized as a state of muscle insulin resistance. β-Cell function, expressed as $\Delta AUC_{PI}/\Delta AUC_{PG}$ and $\Delta AUC_{PI}/\Delta AUC_{PG} \times$ Matsuda index was more severely reduced in IGT with or without IFG compared with both NFG/NGT and IFG. Thus, Japanese subjects with IGT are characterized by both muscle insulin resistance and impaired insulin secretion. In contrast, IFG represents a state of hepatic insulin resistance with impaired early (0–60 min) but normal to slightly increased late phase (60–120 min) insulin secretion. These distinct metabolic disturbances in hepatic/muscle insulin sensitivity and β-cell function in nondiabetic healthy Japanese subjects with IFG, IGT, and IFG/IGT are similar to those reported in Mexican-American subjects (*26*). However, the severity of hepatic and muscle insulin resistance and the compensatory plasma insulin response following glucose ingestion is much higher in Mexican-Americans (see figure 1 and table 1 in Abdul-Ghani *et al*. (*26*)). The difference in severity in the insulin resistance and hyperinsulinemia most likely reflects the greater obesity and/or differences in genetic background in the Mexican-American *vs*. Japanese individuals.

We also compared the prevalence of cardiovascular risk factors in healthy Japanese subjects with IFG, IGT, and IFG/IGT. Of note, no subject was taking any medications known to affect glucose metabolism, blood pressure, or plasma lipid levels. Blood pressure was significantly higher in IGT than in either NFG/NGT or IFG. TG and the TG/HDL cholesterol ratio were significantly higher in IGT and IFG/IGT than in either NFG/NGT or isolated IFG. These findings in Japanese subjects are consistent with previous publications demonstrating an increased prevalence of cardiovascular risk factors and cardiovascular events in subjects with IGT, whereas IFG (defined by the 1997 ADA criteria) appears to be much less strongly associated with cardiovascular disease (*27–31*). The results in the present study, in which IFG and IGT were employed in healthy Japanese subjects, are consistent with the results of these previous reports. However, several studies have reported (using the 1997 ADA criteria) that both IFG and IGT were associated with an increased prevalence of cardiovascular risk factors (*38–40*). Using the 2003 ADA criteria for IFG, Kim *et al*. (*41*) did not observe an increased prevalence of cardiovascular risk factors. Because of these conflicting results, we performed multiple regression analysis to define which variables best predicted the presence of cardiovascular risk factors in our population of healthy Japanese subjects. Among the independent variables (age, gender, BMI, FPG, PG_{60}, PG_{120}, FPI, PI_{60}, and PGI_{120}), multiple stepwise regression analysis revealed that male gender, increased age, higher BMI, and elevated PG_{120} and PI_{120} were independently and positively associated with increased blood pressure. Many of the same variables (male gender, BMI, higher level of PG_{60} and PI_{120}) were independently and positively associated with elevated plasma TG levels and an increased TG/HDL cholesterol ratio. In summary, male gender, obesity, elevated postprandial but not fasting levels of PG and insulin concentrations are associated with cardiovascular risk factors (higher blood pressure and TG, increased TG/HDL cholesterol ratio) in pre-diabetic individuals.

In conclusion, subjects with IFG predominantly manifest hepatic insulin resistance leading to higher FPG and normal/near-normal indices of β-cell function, while subjects with IGT predominantly manifest peripheral (muscle) insulin resistance combined with impaired β-cell function leading to higher elevations in PG concentration during the postprandial state. Elevated blood pressure, plasma TG, and TG/HDL cholesterol ratio, components of the metabolic or insulin syndrome, are more commonly observed in Japanese subjects with IGT than in those with IFG.

References

1. Unwin N, Shaw J, Zimmet P, Alberti KGMM: Impaired glucose tolerance and impaired fasting glycemia: the current status on definition and intervention. *Diabet Med* 2002; **19**: 708–723.
2. Shaw J, Zimmet P, de Courten M, *et al*: Impaired fasting glucose or impaired glucose tolerance: what best predicts future diabetes in Mauritius? *Diabetes Care* 1999; **22**: 399–402.
3. Gabir MM, Hanson R, Dabelea D, *et al*: Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes. *Diabetes Care* 2000; **23**: 1113–1118.
4. de Vegt F, Dekker JM, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: The 1997 American Diabetes Association criteria *versus* the 1985 World Health Organization criteria for the diagnosis of abnormal glucose tolerance: poor agreement in the Hoorn Study. *Diabetes Care* 1998; **21**: 1686–1690.
5. Eschwège E, Charles MA, Simon D, Thibult N, Balkau B: Reproducibility of the diagnosis of diabetes over a 30-month follow-up: the Paris Prospective Study. *Diabetes Care* 2001; **24**: 1941–1944.
6. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20**: 1183–1197.
7. Dunstan D, Zimmet P, Welborn T, *et al*: The rising prevalence of diabetes mellitus and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 2002; **25**: 829–834.
8. Larsson H, Berglund G, Lindgarde F, Ahren B: Comparison of ADA and WHO criteria for diagnosis of diabetes and glucose intolerance. *Diabetologia* 1998; **41**: 1124–1125.
9. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–1985 World Health Organization diagnostic criteria. *Diabetes Care* 1997; **20**: 1859–1862.
10. Ko GT, Chan JC, Woo J, Cockram CS: Use of the 1997 American Diabetes Association diagnostic criteria for diabetes in a Hong Kong Chinese population. *Diabetes Care* 1998; **21**: 2094–2097.
11. The DECODE Study Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 1999; **354**: 617–621.
12. 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.
13. Guerrero-Romero F, Rodríguez-Morán M: Impaired glucose tolerance is a more advanced stage of alteration in the glucose metabolism than impaired fasting glucose. *J Diabetes Complications* 2001; **15**: 34–37.
14. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory disfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; **104**: 787–794.
15. Haeften TWV, Pimenta W, Mitrakou A, *et al*: Disturbance in β cell function in impaired fasting glycemia. *Diabetes* 2002; **51** (Suppl 1): S265–S270.
16. Ferrannini E, Gastaldelli A, Miyazaki Y, *et al*: Predominant role of reduced beta-cell sensitivity to glucose over insulin sensitivity in impaired glucose tolerance. *Diabetologia* 2003; **46**: 1211–1219.
17. Hanefeld M, Koehler C, Fuecker K, Henkel E, Schaper F,

Temelkova-Kurktschiev T: Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose, the risk factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study. *Diabetes Care* 2003; **26**: 868–874.

18. Pimenta WP, Santos ML, Cruz NS, Aragon FF, Padovani CR, Gerich JE: Brazilian individuals with impaired glucose tolerance are characterized by impaired insulin secretion. *Diabetes Metab* 2002; **28**: 468–476.
19. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA: the San Antonio Metabolism Study: Beta-cell dysfunction and glucose intolerance: results from the San Antonio Metabolism (SAM) study. *Diabetologia* 2003; **47**: 31–39.
20. Schianca GPC, Rossi A, Sainaghi PP, Maduli E, Bartoli E: The significance of impaired fasting glucose *versus* impaired glucose tolerance: importance of insulin secretion and resistance. *Diabetes Care* 2003; **26**: 1333–1337.
21. Weyer C, Bogardus C, Pratley R: Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 1999; **48**: 2197–2203.
22. Festa A, D'Agostino R, Hanley A, Karter AJ, Saad MF, Haffner SM: Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. *Diabetes* 2004; **53**: 1549–1555.
23. Davies MJ, Raymond NT, Day JL, Hales CN, Burden AC: Impaired glucose tolerance and fasting hyperglycaemia have different characteristics. *Diabet Med* 2000; **17**: 433–440.
24. Conget I, Fernandez Real JM, Costa A, Casamitjana R, Ricart W: Insulin secretion and insulin sensitivity in relation to glucose tolerance in a group of subjects at a high risk for type 2 diabetes mellitus. *Med Clin* 2001; **116**: 491–492.
25. Genuth S, Alberti KG, Bennett P, *et al*, The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; **26**: 3160–3167.
26. Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA: 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.
27. Kawamori R: Insulin resistance seen in non-insulin dependent diabetes mellitus and hypertension. *Hypertens Res* 1996; **19** (Suppl 1): S61–S64.
28. Rathmann W, Giani G, Mielck A: Cardiovascular risk factors in newly diagnosed abnormal glucose tolerance: comparison of 1997 ADA and 1985 WHO criteria. *Diabetologia* 1999; **42**: 1268–1269 (Letter).
29. Hanefield M, Temelkova-Kurktschiev T, Schaper F, Henkel E, Siegert G, Koehler C: Impaired fasting glucose is not a risk factor for atherosclerosis. *Diabet Med* 1999; **16**: 212–218.
30. The DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001; **161**: 397–404.
31. The DECODE Study Group on behalf of the European Diabetes Epidemiology Group: Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascuar and noncardiovascular diseases? *Diabetes Care* 2003; **26**: 688–696.
32. Tanaka S, Hayase A, Hashimoto A, *et al*: Hypertension and cardiovascular diseases in an epidemiological study in Hokkaido, Japan. *J Cardiovasc Pharmacol* 1990; **16** (Suppl 7): S83–S86.
33. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R: Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
34. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic glucose clamp. *Diabetes Care* 1999; **22**: 1462–1470.
35. Drivsholm T, Hansen T, Urhammer SA, *et al*: Assessment of insulin sensitivity and beta-cell function from an oral glucose tolerance test. *Diabetologia* 1999; **42** (Suppl 1): A185.
36. DeFronzo RA, Ferrannini E, Simonson DC: Fasting hyperglycemia in non–insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. *Metabolism* 1989; **38**: 387–395.
37. Sindelar DK, Chu CA, Venson P, Donahue EP, Neal DW, Cherrington AD: Basal hepatic glucose production is regulated by the portal vein insulin concentration. *Diabetes* 1998; **47**: 523–529.
38. De Pablos-Velasco PL, Martinez Marin FJ, Rodriguez Perez F, Ania BJ, Losada A, Betancor P: Prevalence and determinants of diabetes mellitus and glucose intolerance in a Canarian Caucasian population: comparison of the 1997 ADA and the 1995 WHO criteria: the Guia study. *Diabet Med* 2001; **18**: 235–241.
39. Larsson H, Berglund G, Lindgärde F, Ahrén B: Comparison of ADA and WHO criteria for the diagnosis of diabetes and glucose intolerance. *Diabetologia* 1998; **41**: 1124–1125.
40. Pallardo LF, Herranz L, Martin-Vaquero P, Garcia-Ingelmo T, Grande C, Janez M: Impaired fasting glucose and impaired glucose tolerance in women with prior gestational diabetes are associated with a different cardiovascular profile. *Diabetes Care* 2003; **26**: 2318–2322.
41. Kim SH, Chunawala L, Linde R, Reaven GM: Comparison of the 1997 and 2003 American Diabetes Association classification of impaired fasting glucose: impact on prevalence of impaired fasting glucose, coronary heart disease risk factors, and coronary heart disease in a community-based medical practice. *J Am Coll Cardiol* 2006; **48**: 293–297.