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Japanese IGT Subjects with High Insulin Response Are Far More Frequently Associated with the Metabolic Syndrome Than Those with Low Insulin Response

Yutaka Mori,[1] Kyouko Hoshino,[2] Kuninobu Yokota,[3] Yohta Itoh,[1] and Naoko Tajima,[3]

[1]Department of Internal Medicine, National Hospital Organization, Utsunomiya National Hospital, Kawachi, Tochigi, Japan; [2]Matsushita Tokyo Health Care Center, Matsushita Electric Industrial Corporation, Tokyo, Japan; and [3]Division of Diabetes and Endocrinology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan

Impaired glucose tolerance (IGT) represents a prediabetic state positioned somewhere between normal glucose tolerance and diabetes, which is also assumed to make individuals in this state highly susceptible to atherosclerotic disease. IGT also accounts for a highly heterogeneous population, with the condition varying from individual to individual. In this study, we stratified subjects with IGT by their insulin response and compare the pathology of IGT when it is associated with high or low insulin response to gain insight into the diverse pathology of IGT. Of the male corporate employees who underwent 75 g OGTT at the corporation's healthcare center, 150 individuals diagnosed with IGT (isolated IGT, combined IGT and IFG) comprised our study subjects. The study subjects were stratified into four quartiles by percentile AUC for insulin, and those in the 25th or less percentile were defined as the low insulin response group ($n = 37$), vs those in the 76th or greater percentile defined as the high insulin response group ($n = 38$), and these groups were compared. There was no significant difference observed between the two groups in regard to post-OGTT glucose response and area under the glucose curve. However, the high insulin response group was associated with higher BMI, subcutaneous fat area, uric acid levels, HOMA-β cell values, and Δinsulin/Δglucose (30 min) than the low insulin response group. The number of risk factors for the metabolic syndrome detected (as defined by the ATPIII diagnostic criteria) per subject was 2.84 ± 0.17 and 2.08 ± 0.20, respectively, in the high insulin response group and in the low insulin response group, with the number significantly ($p < 0.05$) higher in the high insulin response group. Furthermore, the incidence of the metabolic syndrome as defined by the ATPIII diagnostic criteria was 63.2% (24/38) in the high insulin response group vs 32.4% (12/27) in the low insulin response group, with the incidence significantly ($p < 0.01$) higher in the high insulin response group. Likewise, the incidence of the metabolic syndrome as defined by the Japanese diagnostic criteria was found to be significantly ($p < 0.05$) higher in the high insulin response group at 50% (19/38) compared to 27.0% (10/37) in the low insulin response group. Our study findings suggest that IGT subjects with high insulin response and those with low insulin response vary greatly in regard to the number of atherosclerotic risk factors complicated and the frequency with which they are associated with the metabolic syndrome. It is also shown in middle-aged Japanese males that of the two forms of IGT, IGT with high insulin response is more closely linked to the pathogenesis of atherosclerotic cardiovascular disease.

Key Words: IGT; high insulin response; low insulin response; metabolic syndrome; insulin resistance.

Introduction

Impaired glucose tolerance (IGT) has been known to be a risk factor for atherosclerotic disease, and recently there have emerged reports, such as the DECODE study *(1)*, the Funagata-machi study *(2)*, and the RIAD study *(3)*, demonstrating at first hand that IGT, but not IFG, is associated with the onset of atherosclerotic disease and arteriosclerosis. In this regard, we have also reported earlier that IGT is far more frequently associated with the metabolic syndrome than IFG *(4)*. Additionally, it is pointed out that fewer Japanese individuals tend to be obese than Caucasians, and that Japanese individuals with IGT are far more frequently associated with low rather than high insulin response. In these individuals with low insulin response are found milder atherosclerotic risk, fewer risk factors, and less advanced atherosclerosis than in Caucasians, suggesting that IGT in

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Author to whom all correspondence and reprint requests should be addressed: Yutaka Mori, MD, Department of Internal Medicine, National Hospital Organization, Utsunomiya National Hospital, 2160 Shimookamoto, Kawachi-machi, Kawachi-gun, Tochigi 329-1193, Japan. E-mail: moriyutakajp@yahoo.co.jp

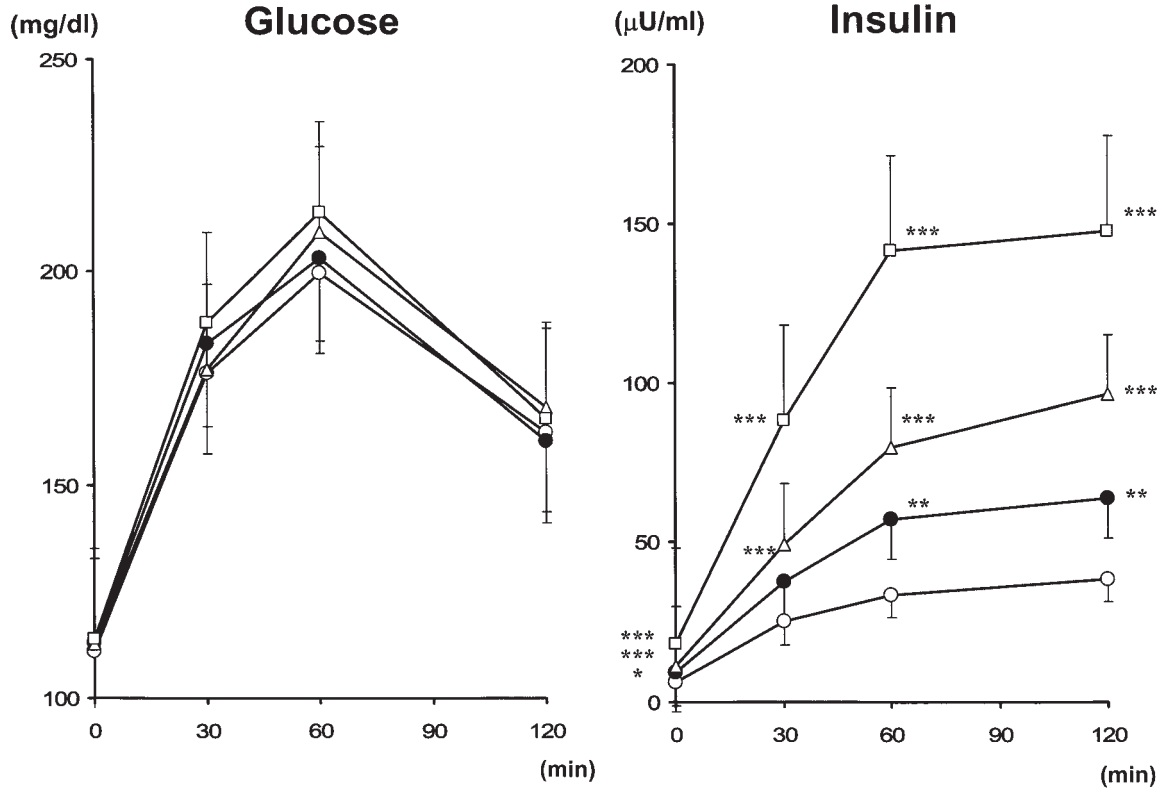

Fig. 1. Plasma glucose and insulin responses during OGTT in Japanese IGT subjects stratified by insulin response during 75 g OGTT; -○-, IGT subjects in the less than 25th percentile of AUC for insulin; -●-, IGT subjects in the 26th–50th percentile of AUC for insulin; -△-, IGT subjects in the 51th–75th percentile of AUC for insulin; -□-, IGT subjects in the 76th or greater percentile of AUC for insulin. Vertical bars represent SEM, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs IGT subjects in the less than 25th percentile of AUC for insulin (low response).

Japanese individuals is less associated with atherosclerosis than that in Caucasians. In this study, the subjects with IGT were stratified by insulin response during OGTT to compare the pathology of IGT in those with high insulin response and in those with low insulin response to gain insight into the diverse pathology of IGT in Japanese individuals.

Results

No significant difference was found between the high insulin response group ($n = 38$) and the low insulin response group ($n = 37$) in regard to post-OGTT glucose response and area under the glucose curve (Fig. 1). The high insulin response group was also associated with higher BMI, subcutaneous fat area, uric acid levels, HOMA-β cell values, and Δinsulin/Δglucose (30 min) than the low insulin response group, and the adiponectin levels tended to be lower in the high insulin response group than in the low insulin response group, while this difference failed to achieve statistical significance (Table 1). The high insulin response group was more frequently associated with visceral fat accumulation (VFA ≥ 100 cm^2) than the low insulin response group ($p < 0.05$). The high insulin response group also tended to be more frequently associated with the other risk factors (TG ≥ 150 mg/dL, HDL-C < 40 mg/dL, BP ≥ 130/85 mmHg, or FPG ≥ 110 mg/dL) than the low insulin response group, while the difference failed to reach significance (Table 2). The mean number of risk factors for the metabolic syndrome (as defined by the ATPIII diagnostic criteria) detected per subject was 2.84 ± 0.17 and 2.08 ± 0.20, respectively, in the high insulin response group and in the low insulin response group, with the number significantly ($p < 0.05$) higher in the high insulin response group (Table 2). Furthermore, the incidence of the metabolic syndrome as defined by the ATPIII diagnostic criteria was 63.2% (24/38) in the high insulin response group vs 32.4% (12/27) in the low insulin response group, with the incidence significantly ($p < 0.01$) higher in the high insulin response group (Table 2). Similarly, the incidence of the metabolic syndrome as defined by the Japanese diagnostic criteria was found to be significantly ($p < 0.05$) higher in the high insulin response group at 50% (19/38) compared to 27.0% (10/37) in the low insulin response group (Table 2).

Discussion

It has been noted that fewer Japanese individuals are associated with obesity than Caucasians, and that Japanese individuals with IGT are far more frequently associated with low rather than high insulin response, milder atherosclerotic risk, fewer risk factors, and less advanced atherosclerosis than Caucasians, suggesting that IGT in Japanese individuals is

Table 1
Laboratory Test Findings in Japanese Subjects with IGT Stratified by Insulin Response During 75 g OGTT

AUC for insulin	Less than 25th percentile (low response)	26th–50th percentile	51st–75th percentile	More than 76th percentile (high response)
Number	37	37	38	38
AUC for insulin*** (μU·h/mL)	58.4 ± 2.5	96.1 ± 1.9	135.9 ± 2.8	230.0 ± 11.0†††
Age	48.7 ± 0.9	49.1 ± 1.1	49.1 ± 1.1	46.7 ± 1.1
BMI***	24.3 ± 0.7	25.3 ± 0.4	26.7 ± 0.4	28.6 ± 0.5†††
VFA (cm^2)	95.1 ± 6.4	101.5 ± 7.1	111.6 ± 8.3	116.4 ± 6.6
SFA (cm^2)***	127.8 ± 8.3	140.5 ± 7.7	150.1 ± 7.8	186.5 ± 10.7†††
V/S ratio	0.795 ± 0.07	0.799 ± 0.08	0.798 ± 0.07	0.68 ± 0.05
Systolic BP (mmHg)	133.5 ± 2.5	133.8 ± 3.0	136.9 ± 2.2	138.4 ± 2.3
Diastolic BP (mmHg)	81.8 ± 1.6	82.5 ± 1.9	84.8 ± 1.6	85.7 ± 1.5
TC (mg/dL)*	213.1 ± 5.8	223.2 ± 5.5	220.8 ± 4.7	234.0 ± 4.9
LDL-C (mg/dL)	127.9 ± 5.1	136.6 ± 5.3	134.2 ± 6.1	146.8 ± 4.8
HDL-C (mg/dL)	54.8 ± 2.4	53.1 ± 2.3	53.7 ± 1.9	53.2 ± 2.2
TG (mg/dL)	152.0 ± 11.0	185.6 ± 22.3	172.1 ± 21.8	170.1 ± 11.2
Uric acid (mg/dL)**	6.19 ± 0.20	6.61 ± 0.20	6.65 ± 0.24	7.25 ± 0.19††
HbA1c (%)	5.39 ± 0.07	5.39 ± 0.07	5.42 ± 0.06	5.59 ± 0.17
HOMA-R***	1.67 ± 0.10	2.60 ± 1.20	3.12 ± 0.19	5.19 ± 0.34†††
HOMA-β cell***	45.7 ± 2.5	65.6 ± 4.1	83.2 ± 6.0	129.5 ± 7.6†††
ΔINS/ ΔPG***	0.33 ± 0.04	0.45 ± 0.04	0.61 ± 0.06	0.98 ± 0.09†††
AUC for glucose (mg·h/dL)	346.4 ± 5.3	352.0 ± 5.6	360.5 ± 5.3	365.4 ± 5.7
Adiponectin (μg/mL)*	7.31 ± 0.81	6.71 ± 0.99	5.62 ± 0.45	4.71 ± 0.35
Hs-CRP (ng/mL)	440.9 ± 93.5	782.7 ± 227.8	846.4 ± 257.8	627.4 ± 163.2

Mean ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ for trend, $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$ vs IGT subjects in the less than 25th percentile of AUC for insulin (low response).

VFA, visceral fat area; SFA, subcutaneous fat area; AUC, area under the curve.

Table 2
Number of Risk Factors and Incidence of the Metabolic Syndrome in Japanese Subjects with IGT Stratified by Insulin Response During 75 g OGTT

AUC for insulin	Less than 25th percentile (low response)	26th–50th percentile	51st–75th percentile	More than 76th percentile (high response)
Numbers of risk factors[1] (/subject)*	2.08 ± 0.2	2.43 ± 0.17	2.42 ± 0.18	2.84 ± 0.17†
Incidence of VFA ≧ 100 cm^2 (%)	14 / 37 (37.8%)	19 / 37 (51.4%)	21 / 38 (55.3%)	24 / 38 (63.2%)†
Incidence of TG ≧150 mg/dL (%)	15 / 37 (40.5%)	16 / 37 (43.2%)	12 / 38 (31.6%)	22 / 38 (57.9%)
Incidence of HDL< 40 mg/dL (%)	2 / 37 (5.4%)	6 / 37 (16.2%)	3 / 38 (7.9%)	4 / 38 (10.5%)
Incidence of ≧ BP 130/85 mmHg (%)	25 / 37 (67.6%)	21 / 37 (56.8%)	30 / 38 (78.9%)	29 / 38 (76.3%)
Incidence of FPG ≧110 mg/dL (%)	21 / 37 (56.8%)	28 / 37 (75.7%)	26 / 38 (68.4%)	29 / 38 (76.3%)
Incidence of MS[1] (%)	12 / 37 (32.4%)	17 / 37 (45.9%)	19 / 38 (50%)	24 / 38 (63.2%)††
Incidence of MS[2] (%)	10 / 37 (27.0%)	14 / 37 (37.8%)	16 / 38 (42.1%)	19 / 38 (50%)†

Mean ± SEM. $p < 0.05$, for trend, $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, vs IGT subjects in the less than 25th percentile of AUC for insulin (low response).

VFA, visceral fat area; AUC, area under the curve; MS[1], metabolic syndrome by the ATPIII criteria; MS[2], metabolic syndrome by the Japanese criteria.

less associated with atherosclerosis than that in Caucasians. Insulin response in Japanese individuals with IGT can generally be characterized by increased insulin response reflecting the presence of insulin resistance *(4)*. However, as IGT primarily represents a pathology diagnosed in conjunction with post-OGTT glucose response, IGT accounts for a diverse population composed of individuals who exhibit varying degrees of high to low insulin response. Of these individuals, those with high insulin response are worthy of particular attention in that they include many individuals who meet the diagnosis of the metabolic syndrome and present with the clinical features of insulin resistance, obesity, hypertension, and dyslipidemia. Conversely, it is assumed that those with low insulin response often present with IGT primarily due to reduced insulin response. In this regard, it is of note that Haffner et al. *(5)* showed that insulin-resistant prediabetic individuals are more frequently associated with clustering of multiple risk factors than insulin-sensitive prediabetic individuals. In agreement with the report of Haffner et al. *(5)*, our study also demonstrated that IGT individuals with high insulin response are associated with greater insulin resistance and more risk factors, and are more frequently associated with the metabolic syndrome than those with low insulin response, while they may exhibit similar post-OGTT glucose response.

In our study, all subjects receiving drug therapy for hyperlipidemia and hypertension were excluded, the reason being that lipid-lowering fibrates, blood pressure–lowering angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARB) have been shown to improve insulin resistance, as well as prevent diabetes from developing *(6,7)*, and are therefore thought to be capable of modifying insulin response following glucose loading, thereby potentially affecting the results of our study.

Additionally, the level of adiponectin, an adipocytokine specific to adipocytes *(8)*, in IGT individuals with high insulin response tended to be lower than in those with low insulin response, while short of reaching statistical significance. Given that hypoadiponectinemia has been shown to be closely associated with insulin resistance *(9)* and arteriosclerosis *(10,11)*, the adiponectin level that tended to be lower in those with high insulin response was assumed to have contributed at least in part to the observed insulin resistance in these individuals.

Our study findings also demonstrated that IGT in Japanese individuals represents a highly heterogeneous pathology particularly in relation to atherosclerotic risk factors. In this regard, a study in Japanese individuals with IGT *(12)* showed that when stratified by age, those younger than 40 yr of age are associated with overweight and greater insulin resistance compared to those 40 yr of age and older, suggesting that there will be an increase in the number of IGT subjects with high insulin response, as they are directly linked to atherosclerotic risks. While reports such as the Funagata-machi study have become available in recent years to demonstrate that IGT is associated with the pathogenesis of atherosclerotic disease and arteriosclerosis, as our study findings show, IGT in Japanese individuals as it is characterized by low insulin response appears to be less associated with severe insulin resistance, risk factors, and the metabolic syndrome, suggesting that atherosclerosis may be less advanced in Japanese individuals with IGT than in Westerners.

In summary, our study findings suggest that IGT subjects with high insulin response and those with low insulin response vary greatly in regard to the number of atherosclerotic risk factors complicated and the frequency with which they are associated with the metabolic syndrome. We therefore conclude that of the two forms of IGT, IGT with high insulin response is more closely linked to the pathogenesis of atherosclerotic cardiovascular disease, and that given the prevalence of insulin resistance, early therapeutic intervention appears to be a critically important issue in IGT individuals with high insulin response.

Subjects and Methods

Of the male employees having undergone 75 g OGTT at the Matsushita Electric Corporation's Tokyo Healthcare Center, our study subjects comprised 150 males who met the diagnosis of impaired glucose tolerance (IGT) by the American Diabetes Association's criteria (isolated IGT and combined IGT and IFG), and who decided to participate in the study and gave written informed consent. The subjects were excluded from the study if they had known diabetes mellitus (DM) or if they were receiving drug therapy that affected glucose tolerance, or for hyperlipidemia or hypertension.

The diagnostic criteria for the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) *(13)*, as well as visceral fat accumulation [defined as a viseral fat area (VFA) of 100 cm^2 or greater as measured by CT scans at the umbilical level *(14)*, which is equivalent to a waist circumference of 85 cm],were primarily used for the diagnosis of the metabolic syndrome, while the Japanese criteria for the metabolic syndrome *(15)* were also used, where the subjects with visceral fat accumulation who met any two of the three criteria (TG ≥ 150 mg/dL and/or HDL-C < 40 mg/dL, blood pressure ≥ 130/≥ 85 mmHg, and FPG ≥ 110 mg/dL) were diagnosed as having the metabolic syndrome. The study subjects were stratified into four quartiles by percentile AUC for insulin: those in the 0 to 25th percentile (n = 37), those in the 26th to 50th percentile (n = 38), those in the 51th to 75th percentile (n = 38), and those in the 76th or greater percentile (n = 38), and those in the 0 to 25th percentile was defined as the low insulin response group (n = 37), and those in the 76th or greater percentile as the high insulin response group (n = 38).

After fasting overnight, the subjects were subjected to an OGTT with 75 g glucose early in the morning. Blood samples were drawn from the median cubital vein before the test and

every 30 min over a period of 2 h. Plasma glucose levels were measured by glucose oxidase methods. Serum insulin and adiponectin levels were determined using commercial enzyme immunoassay kits (LS Eiken Insulin Kit, Eiken Chemical, Tokyo, Japan and adiponectin ELISA kit, Otsuka, Tokushima, Japan). High-sensitivity C-reactive protein (hs CRP) was measured by latex nephelometry assay (N High Sensitivity CRP, Dade Behring, Marburg GmbH, Marburg, Germany). Early-phase insulin secretion was calculated as a ratio of the increment of serum insulin (ΔINS) 30 min after the glucose load to plasma glucose (PG) concentration (ΔPG) 30 min after the glucose load (ΔINS/ΔPG). Insulin secretion was also estimated by HOMA-β cell *(15)*. The incremental areas under the insulin (AUC insulin) and glucose (AUC glucose) curve were calculated by the trapezoidal method for 0-, 30-, 60-, and 120-min time points.

The estimate of insulin resistance was based on a homeostasis model assessment (HOMA-R) as described by Matthews et al. *(16)*. Serum lipids (triglycerides, total cholesterol, HDL cholesterol) were measured enzymatically using enzyme reagents (L-Type TG H, Wako Pure Chemicals, Osaka, Japan; L-Type CHO H, Wako Pure Chemicals, Osaka, Japan; Cholestest N HDL, Daiichi Pure Chemicals, Tokyo, Japan). An estimate of the LDL-cholesterol (LDL-C) concentration was then made from these three measurements using the Friedewald formula when TG levels are below 400 mg/dL. Serum uric acid levels were measured by uricase POD assay using enzyme reagents (L-Type UA F, Wako Pure Chemicals, Osaka, Japan). The hemoglobin A1c (HbA1c) was measured by cation exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA, USA). Blood pressure was measured at least twice, with the subjects in a seated position after at least 5 min of rest. The average of blood pressure measurements was used for the analysis. Body mass index (BMI [kg/m^2]) was computed from current body weight and height. Abdominal computed tomography (CT; Hitachi model, CTW550, Hitachi Medical Co., Tokyo, Japan) scans at the umbilical level were also made for all subjects during this same time period. Abdominal VFA and subcutaneous fat area (SFA) were measured, as described elsewhere *(14,15,17)*.

Statistical Analysis

All numerical values were expressed as mean ± SEM. We applied one-way analysis of variance (ANOVA), and followed up with Scheffe's method as a post hoc test for any significant difference among the groups ($p < 0.05$). The level of $p < 0.05$ was considered to indicate statistical significance. χ^2 test was used to test for significance any differences between the high insulin response group and low insulin response group in the incidence of risk factors detected, as well as in the incidence of the metabolic syndrome detected.

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