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Differences in the Risk for Atherosclerosis in Subjects with Impaired Glucose Tolerance with and without Visceral Fat Accumulation : A Study in Japanese Middle-Aged Men

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ABSTRACT

We investigated the differences in risk of atherosclerosis in men with impaired glucose tolerance (IGT) with and without visceral fat accumulation. The study population comprised 150 male office workers with IGT diagnosed with 75-g oral glucose tolerance tests administered at their company's healthcare center. Subjects with a visceral fat area (VFA) $\geq$100 cm^2 (n=78) had significantly higher insulin levels at baseline and 1 hour after challenge and a higher area under the curve for insulin values than did subjects with VFA$<$100 cm^2 (n=72). However, glucose responses after glucose loading did not differ significantly between the groups. The mean number of risk factors related to metabolic syndrome (Japanese diagnostic criteria) was significantly greater in subjects with VFA$\geq$100 cm^2 (3.06$\pm$0.8) than in subjects with VFA$<$100 cm^2 (1.65$\pm$0.9, $P<0.001$). Of the 78 subjects with VFA$\geq$100 cm^2, 62 (86%) met the Japanese criteria for metabolic syndrome. Our findings suggest that IGT with visceral fat accumulation and IGT without visceral fat accumulation vary in the degree of associated insulin resistance and in the risk of atherosclerosis.

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Key words : impaired glucose tolerance, visceral fat accumulation, metabolic syndrome, adiponectin

INTRODUCTION

Although impaired glucose tolerance (IGT) is an established risk factor for atherosclerosis, several recent epidemiological studies, such as the Diabetes Epidemiology : Collaborative Analysis of Diagnostic Criteria in Europe study[1], the Funagata study[2], and the Risk Factors in IGT for Atherosclerosis and Diabetes study[3], have provided direct evidence that, of the "borderline" pathologic conditions, IGT, rather than impaired fasting glucose (IFG), is associated with the onset of atherosclerotic disease and arteriosclerosis. In this regard, we have reported[4] that IGT is more strongly associated with metabolic syndrome than is IFG. Additionally, obesity is less common among the Japanese than among whites, and many Japanese with IGT also have low insulin secretion. Thus, Japanese with IGT are thought to have fewer and milder atherosclerotic risk factors than do whites and are, therefore, less likely to have atherosclerosis.

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In our study, therefore, we analyzed Japanese subjects with IGT from our previous report[4] and investigated the possible differences in the pathology of IGT with and without visceral fat accumulation to gain insight into the diverse spectrum of IGT.

SUBJECTS AND METHODS

Subjects were recruited from among employees who had received routine care at the outpatient clinic of the Matsushita Electric Industrial Corporation. A total of 575 Japanese men with IFG levels of 110 to 125 mg/dl based on clinical data provided by the employer were eligible for participation. The subjects were excluded if they were known to have diabetes mellitus or were receiving drugs affecting glucose tolerance or for treating hyperlipidemia or hypertension. Glycemic status in this cohort had been reassessed by repeated oral glucose tolerance tests (OGTTs) 2 months after the first diagnosis, and 150 subjects (mean age, 48.4±4.0 years) who met American Diabetes Association diagnostic criteria[5] for IGT (isolated IGT ; IGT with IFG) were included in the study. All subjects decided to participate in the study voluntarily and gave written informed consent. The studies were performed in accordance with the Helsinki Declaration of 1975 as revised in 1983. The visceral fat area (VFA) was measured with computed tomography (CT) scans at the umbilical level, and subjects were subsequently divided into a VFA≥100 cm^2 group and a VFA <100 cm^2 group[6] and compared.

Metabolic syndrome was diagnosed primarily on the basis of the criteria of the National Cholesterol Education Program Adult Treatment Panel III (ATPIII)[7] and of the presence of visceral fat accumulation, which is defined as a VFA≥100 cm^2 as measured with CT scans at the umbilical level[6] (equivalent to a waist circumference of 85 cm). Metabolic syndrome was also diagnosed with the Japanese criteria, which are a VFA≥100 cm^2 and the presence of at least 2 of following 3 criteria[8] : triglyceride (TG) level ≥150 mg/dl or high-density lipoprotein cholesterol (HDL-C) <40 mg/dl or both, blood pressure (BP)≥ 130/85 mmHg, and fasting plasma glucose≥110 mg/dl.

After fasting overnight, the subjects were subjected to a 75-g OGTT early in the morning. Blood samples were drawn from a median cubital vein before the test and every 30 minutes for 2 hours. Plasma glucose levels were determined with the glucose dehydrogenase method. Insulin and adiponectin levels were determined with commercial enzyme immunoassay kits (LS Eiken Insulin Kit, Eiken Chemical, Tokyo, and adiponectin ELISA kit, Otsuka, Tokushima). High-sensitivity C-reactive protein (hs CRP) was measured with a latex nephelometry assay (N High Sensitivity CRP, Dade Behring Marburg GmbH, Marburg, Germany). Early-phase insulin secretion was calculated as the ratio of the change in serum insulin (ΔINS) 30 minutes after the glucose loading to the change in plasma glucose (PG) concentration (ΔPG) 30 minutes after the glucose load (ΔINS/ΔPG). Insulin secretion was also estimated with homeostasis model assessment (HOMA) β cells[9]. The incremental areas under the curve (AUC) for insulin and glucose values were calculated with the trapezoidal method for 0-, 30-, 60-, and 120-minute time points.

Insulin resistance was estimated with the HOMA-R method as described by Matthews et al.[9] Serum lipids (TG, total cholesterol [TC], and HDL-C) were measured enzymatically with enzyme reagents (L-Type TG H, Wako Pure Chemicals, Osaka ; L-Type CHO H, Wako Pure Chemicals ; Cholestest N HDL, Daiichi Pure Chemicals, Tokyo). The low-density lipoprotein cholesterol (LDL-C) concentration was then estimated from these 3 measurements using the Friedewald formula when TG levels were less than 400 mg/dl. Serum uric acid levels were measured with uricase peroxidase assay using an enzyme reagent (L-Type UA F, Wako Pure Chemicals). The glycosylated hemoglobin (HbA1c) concentration was measured with cation exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA, USA). The BP was measured at least twice, with the subjects in a seated position after at least 5 minutes of rest. The average of BP measurements was used for the analysis. Body mass index (BMI [kg/m^2]) was calculated from current body

weight and height. All subjects also underwent abdominal CT scans (CTW550 scanner, Hitachi Medical Co., Tokyo) at the umbilical level during this same time period. Abdominal VFA and subcutaneous fat area were measured, as described elsewhere[6,10].

Statistical analysis

All data are presented as means±SD. The reliability of intergroup differences was estimated with the unpaired *t*-test. Differences with a P value <0.05 were considered significant. Any differences observed in the frequency of each risk factor and metabolic syndrome detected between the VFA≥100 cm^2 group and the VFA<100 cm^2 group were tested for significance using the χ^2 test.

Results

Seventy-eight subjects were placed in the VFA≥100 cm^2 group and 72 in the VFA < 100 cm^2 group. The glucose response (Fig. 1) and the AUC for glucose (Table 1) after glucose loading did not differ significantly between the VFA≥100 cm^2 group and the VFA<100 cm^2 group. However, insulin levels at baseline and 1 hour after challenge (Fig. 1) and the AUC for insulin (Table 1) were significantly higher in the VFA≥100 cm^2 group (12.2±6.8 μU/ml, 86.4±53.1 μU/ml, and 141±82 μU•hr/ml, respectively) than in the VFA<100 cm^2 group (10.2±5.9 μU/ml, $P<0.05$; 67.8±41.1 μU/ml, $P<0.05$; and 116±61 μU•hr/ml, $P<0.05$).

Furthermore, BMI, systolic and diastolic BPs and levels of TC, TG, uric acid, HbA_{1c}, and HOMA-R were significantly higher and adiponectin and HDL-C levels were significantly lower in the VFA≥100 cm^2 group than in the VFA <100 cm^2 group (Table 1). Additionally, the incidences of TG≥150 mg/dl and BP ≥130/85 mmHg were significantly higher in the VFA ≥100 cm^2 group than in the VFA<100 cm^2 group (Table 2). The mean numbers of risk factors for metabolic syndrome detected per subject according to both the ATPIII criteria and the Japanese criteria were significantly greater in the VFA≥100 cm^2 group

Table 1. Laboratory test findings in Japanese subjects with IGT subdivided according to the degree of visceral fat accumulation

	VFA<100 cm^2	VFA≥100 cm^2
Number of patients	72	78
Age (years)	47.8±5.9	48.9±7.1
BMI (kg/m^2)	25.3±3.0	27.2±3.7***
VFA (cm^2)	71.0±20.8	138.7±33.8***
SFA (cm^2)	140.4±51.2	161.6±60.9*
V/S ratio	0.55±0.2	0.97±0.4***
Systolic BP (mmHg)	131.8±14.0	139.3±15.9**
Diastolic BP (mmHg)	81.1±9.5	86.1±10.4*
TC (mg/dl)	216.5±32.1	228.7±32.0*
LDL-C (mg/dl)	133.0±30.7	139.7±34.4
HDL-C (mg/dl)	55.2±14.5	52.3±12.3*
TG (mg/dl)	141.3±69.7	196.4±126.5*
Uric acid (mg/dl)	6.35±1.2	6.97±1.4*
HbA1c (%)	5.35±0.4	5.54±0.8*
HOMA-R	2.83±1.7	3.47±2.0*
HOMA-β cell	74.6±44.7	87.6±45.3
Insulinogenic index	0.56±0.4	0.62±0.5
AUC for glucose (mg•hr/dl)	353±35	359±33
AUC for insulin (μU•hr/ml)	116±61	141±82*
Adiponectin (μg/ml)	7.28±3.4	5.01±1.6**
hs CRP (ng/ml)	508±602	811±818

*$P<0.05$, **$P<0.01$, ***$P<0.001$
SFA, subcutaneous fat area; V/S ratio, VFA/SFA

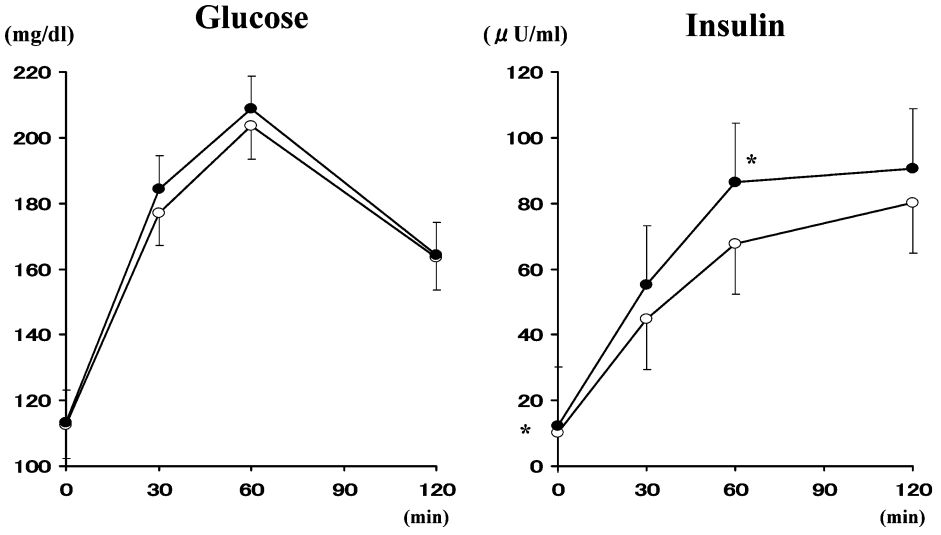

Fig. 1. Plasma glucose and insulin responses during OGTT in subjects with IGT with and without visceral fat accumulation. —●— ; IGT subjects with VFA≥100 cm², —○— ; IGT subjects without VFA<100 cm², Vertical bars represent SD.

Table 2. Number of risk factors and incidence of metabolic syndrome in Japanese subjects with IGT divided according to the degree of visceral fat accumulation

	VFA<100 cm²	VFA≥100 cm²
Number of patients	72	78
Incidence of TG ≥ 150 mg/dl (%)	31.9 (23/72)	53.8 (42/78)** (Odds ratio, 2.5)
Incidence of HDL-C < 40 mg/dl (%)	6.9 (5/72)	12.8 (10/78) (Odds ratio, 2.3)
Incidence of BP ≥ 130/85 mmHg (%)	61.1 (44/72)	78.2 (61/78)* (Odds ratio, 2.3)
Incidence of FPG ≥ 110 mg/dl (%)	68.1 (49/72)	70.5 (55/78) (Odds ratio, 1.1)
Number of risk factors in ATP III criteria (/case)	1.69±0.8	3.17±0.8***
Number of risk factors in Japanese criteria (/case)	1.65±0.9	3.06±0.8***
Incidence of MS in ATP III criteria (%)	14 (10/72)	86 (62/78)*** (Odds ratio, 24.0)
Incidence of MS in Japanese criteria (%)	—	76 (59/78)

*$P<0.05$, **$P<0.01$, ***$P<0.001$
FPG, fasting plasma glucose ; MS, metabolic syndrome

(3.17±0.8 and 3.06±0.8, respectively) than in the VFA <100 cm² group (1.69±0.8 and 1.65±0.9, Table 2).

The number of subjects who met the ATPIII diagnostic criteria for metabolic syndrome was significantly greater in the VFA≥100 cm² group (62 of 78 subjects, 86%) than in the VFA <100 cm² group (10 of 72 subjects, 14%). In addition, the prevalence of metabolic syndrome according to the Japanese diagnostic criteria was 76% (59 of 78 subjects) in the VFA ≥100 cm² group.

DISCUSSION

Our results suggest that the degree of insulin resistance, the severity and number of atherosclerotic

risk factors, and the prevalence of complicating metabolic syndrome varied greatly among subjects with IGT according to whether visceral fat accumulation was present. In addition to the risk factors associated with metabolic syndrome, uric acid levels were significantly higher in the VFA $\geq$100 cm^2 group than in the VFA $<$100 cm^2 group.

Hyperuricemia is reported a risk factor for cardiovascular disease[11] and a pathologic factor implicated in the pathogenesis of insulin resistance (syndrome X plus)[12]. Given the hypothesis that hyperuricemia and hypertriglyceridemia may be linked to insulin resistance with glycolytic glyceraldehyde 3-phosphate dehydrogenase working as an axis[13], high uric acid levels observed in the VFA $\geq$100 cm^2 group might be linked to high TG levels and high HOMA-R values.

On the other hand, adiponectin, an adipocytokine specific to adipocytes[14], has been reported to decrease with increased visceral fat accumulation[15], and hypoadiponectinemia has been closely associated with insulin resistance[16] and atherosclerosis[17,18]. In our study, too, adiponectin levels varied greatly in subjects with IGT depending on whether visceral fat accumulation was present, with this difference in adiponectin levels possibly involved, at least in part, in the varying degree of insulin resistance.

Because IGT is considered a prediabetic condition diagnosed primarily on the basis of blood glucose levels, insulin response varies greatly among subjects with IGT : some subjects exhibit a high response, and others show a low response. Subjects who exhibit a high insulin response may include many who are likely to meet the diagnostic criteria of metabolic syndrome, presenting with insulin resistance, visceral fat accumulation, hypertension, and dyslipidemia. Conversely, subjects who exhibit a low insulin response may include many who are likely to have IGT due to pancreatic β-cell dysfunction rather than insulin resistance. In this regard, Haffner et al.[19] have shown that insulin-resistant prediabetic patients are more likely than insulin-sensitive prediabetic patients to have multiple risk factors. In other words, although accumulating evidence suggests that IGT is closely associated with the onset of atherosclerotic disease or arteriosclerosis, persons with IGT but without visceral fat accumulation who show low insulin secretion are assumed to have milder and fewer atherosclerotic risks and to be less susceptible to the development of atherosclerosis. Our study results appear to support this view, as subjects with IGT and atherosclerotic risk factors also had a high BMI with visceral fat accumulation, high HOMA-R values, and higher AUC for insulin. Conversely, subjects with IGT but without visceral fat accumulation were found to have milder and fewer atherosclerotic risk factors. Our study results suggest that Japanese persons with IGT comprise a highly heterogeneous population. According to a study that stratified Japanese subjects with IGT by age[20], in subjects younger than 40 years, IGT is more typically associated with a significantly higher AUC for insulin, a higher insulinogenic index, and higher HOMA-R values than in other age groups. Therefore, IGT accompanied by visceral fat accumulation and presenting with insulin resistance is expected to increase in the years to come.

We therefore conclude that IGT with and without visceral fat accumulation varies in the degree of insulin resistance and in the risk for atherosclerosis. Of the two types of IGT examined, IGT accompanied by visceral fat accumulation may be directly associated with the development of cardiovascular disease in which atherosclerosis plays a key role as an underlying disease. This association supports the need for screening and early treatment for IGT with visceral fat accumulation, particularly in the presence of insulin resistance.

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