Relationship of Regional Adiposity to Insulin Resistance and Serum Triglyceride Levels in Nonobese Japanese Type 2 Diabetic Patients

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The aim of this study was to investigate the relationships between insulin resistance and regional abdominal fat area, body mass index (BMI), and serum lipid profile in nonobese Japanese type 2 diabetic patients. A total of 63 nonobese Japanese type 2 diabetic patients aged 45 to 83 years were examined. The duration of diabetes was 8.4 ± 0.8 years. BMI, glycosylated hemoglobin (HbA_{1c}) levels, and fasting concentrations of plasma glucose, serum lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides), and serum insulin were measured. The low-density lipoprotein (LDL) cholesterol level was calculated using the Friedewald formula (LDL cholesterol = total cholesterol - HDL cholesterol - 1/5 triglycerides). Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR). Computed tomography (CT) was used to measure cross-sectional abdominal subcutaneous and visceral fat areas in all the patients. Adipose tissue areas were determined at the umbilical level. Subcutaneous and visceral abdominal fat areas were 136.5 ± 6.0 and 86.0 ± 4.1 cm_2, respectively. Univariate regression analysis showed that insulin resistance was positively correlated with subcutaneous (r = .544, P < .001) and visceral (r = .408, P = .001) fat areas, BMI (r = .324, P = .009), HbA_{1c} (r = .254, P = .001), serum triglycerides (r = .419, P < .001), and serum LDL cholesterol (r = .290, P = .019) levels and was negatively correlated with serum HDL cholesterol level (r = .254, P = .041). Multiple regression analyses showed that insulin resistance was independently predicted by the areas of subcutaneous (F = 6.76, P < .001) and visceral (F = 4.61, P < .001) abdominal fat and serum triglycerides (F = 8.88, P < .001) level, which explained 36.9% of the variability of insulin resistance. Moreover, the present study demonstrated that whereas BMI was positively correlated with visceral (r = .510, P < .001) and subcutaneous (r = .553, P < .001) fat areas, serum triglyceride level was positively associated with visceral (r = .302, P = .015), but not with subcutaneous (r = .222, P = .074) fat area. From these results, it can be suggested that (1) both subcutaneous and visceral abdominal fat areas are independently associated with insulin resistance and (2) visceral fat area, but not the subcutaneous one, is associated with serum triglyceride levels in our nonobese Japanese type 2 diabetic patients.

TYPE 2 DIABETES is a heterogeneous disorder characterized by insulin resistance and/or defective insulin secretion.[1,2] There seem to be ethnic differences in insulin resistance in type 2 diabetes. Haffner et al[3] recently reported that 92% of type 2 diabetic patients are insulin resistant in white populations. In contrast, Chaiken et al[4] previously showed that 60% of type 2 diabetic patients are insulin resistant in black Americans with a body mass index (BMI) less than 30 kg/m^2. Using the minimal model approach shown by Bergman,[5] we previously demonstrated that nonobese Japanese type 2 diabetic patients are divided into 2 variants; one with primary insulin resistance and the other with normal insulin sensitivity.[6-8] Thereafter, we used homeostasis model assessment insulin resistance (HOMA-IR) proposed by Matthews et al and found that 40% of Japanese type 2 diabetic patients are insulin resistant.[9,10]

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The mechanisms underlying insulin resistance in type 2 diabetes are not fully understood, but numerous studies in nondiabetic populations have addressed the importance of upper body fat distribution. Vague et al[11] were the first to show that upper body fat distribution had particularly adverse metabolic abnormalities. Higher concentrations of plasma glucose, insulin, and triglycerides were shown to be associated with increasing abdominal body fat in nondiabetic subjects.[12-15] In diabetic patients, however, very little has been documented on the associations between insulin resistance and body fat distribution.

Banerji et al[16] reported that visceral, but not subcutaneous abdominal fat volume, was associated with insulin resistance in black populations with type 2 diabetes. Thereafter, Abate et al[17] demonstrated that subcutaneous fat volume, but not intraperitoneal or retroperitoneal was associated with insulin resistance in non-Hispanic whites with type 2 diabetes. Nonobese Japanese type 2 diabetic patients are unique in that the prevalence of insulin resistance is much lower (40%) as compared with that in whites (92%) or black Americans (60%), suggesting an ethnic difference in the contribution of regional adiposity to insulin resistance in type 2 diabetes.[3,4,6-9] To the best of our knowledge, however, the relationship between insulin resistance and body fat distribution has not yet been investigated in nonobese Japanese type 2 diabetic populations. Thus, the first aim of the present study was to investigate the relationships between insulin resistance and subcutaneous or visceral fat area in nonobese Japanese type 2 diabetic patients.

In conjunction with BMI, serum triglyceride level is an important factor in the assessment of insulin resistance in Japanese type 2 diabetic patients.[9,18-20] Banerji et al[16] previ-

ously demonstrated that serum triglyceride levels are associated with visceral fat volume, but not with subcutaneous abdominal fat volume in black populations with type 2 diabetes. It is not yet fully clarified whether serum triglyceride levels are associated with subcutaneous or visceral abdominal fat accumulation in Japanese type 2 diabetic patients. Therefore, the second aim of the present study was to investigate the relationship between serum triglyceride levels and subcutaneous or visceral abdominal fat areas in nonobese Japanese type 2 diabetic patients.

MATERIALS AND METHODS

Sixty-three nonobese Japanese type 2 diabetic patients attending Kansai-Denryoku Hospital were recruited for the present study.[21] Type 2 diabetes mellitus was diagnosed based on the criteria of the World Health Organization (WHO).[22] They all had no history of obesity and had not received insulin therapy. The patients were treated with diet alone (27 patients) or diet in combination with sulfonylurea (gliclazide) (36 patients). They did not receive any medications affecting glucose metabolism. All subjects had ingested at least 150 g of carbohydrate for the 3 days preceding the study. None of the subjects had significant renal, hepatic, or cardiovascular disease. Eighteen of 63 patients had hypertension that was treated with angiotensin-converting enzyme inhibitors (10/18), calcium channel blockers (6/18), or both (2/18). They did not consume alcohol or perform heavy exercise for at least 1 week before the study.

Blood was drawn in the morning after a 12-hour fast. Plasma glucose was measured with glucose oxidase method, and serum insulin was measured using 2-site immunoradiometric assay (Insulin Riabead II; Dainabot Co, Osaka-city, Japan). The triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were also measured. The range of triglycerides was 30 to 337 mg/dL in our present study. The low-density lipoprotein (LDL) cholesterol level was calculated using the Friedewald formula.[23]

The estimate of insulin resistance by HOMA (HOMA-IR) was calculated with the formula: fasting serum insulin (μU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5.[10] Regarding the validity of HOMA-IR, our group[24] and Hermans et al[25] recently demonstrated that the HOMA-IR value is highly correlated with insulin resistance calculated by the minimal model approach in subjects with varying degrees of glucose tolerance. It may be argued that the use of sulfonylureas in patients with diabetes might significantly affect the estimate of insulin resistance by HOMA, as these drugs are known to decrease fasting plasma glucose without substantially changing fasting plasma insulin.[26] It seems, however, unlikely because Borona et al[27] and Emoto et al[28] showed that in the validation studies of HOMA, the correlation of insulin sensitivity estimated by such method and that measured by the glucose clamp was not substantially different in diet-treated and sulfonylurea-treated type 2 diabetes. Therefore, we estimated HOMA-IR in diet-treated and sulfonylurea-treated diabetic patients.

All subjects underwent computed tomography (CT) (TSX-012A, X-Vigor; Toshiba Co, Osaka-city, Japan) to measure cross-sectional abdominal subcutaneous and visceral fat areas using commercially available software (Fat Scan; N2 System Corp, Osaka, Japan).[29] The subjects were examined in the supine position, and CT scans were performed (120 kV, 200 mA, section thickness of 5 mm, scanning time of 2 seconds, field of view of 400 mm). Subcutaneous and visceral fat areas were measured on 1 cross-sectional scan obtained at the umbilicus. A region of interest of the subcutaneous and visceral fat layer was defined by tracing its contour, and their areas were measured using the attenuation range of CT numbers (in Hounsfield units) for fat tissue calculated.

Table 1. Correlation of Insulin Resistance to Measures of Variables in Diabetic Patients

	Univariate		Multivariate
	r	*P*	F
Subcutaenous fat area	.544	<.001	6.759
Visceral fat area	.408	.001	4.609
BMI	.324	.009	0.012
HbA_{1c}	.254	.040	0.933
Triglycerides	.419	<.001	8.880
LDL cholesterol	.290	.019	0.619
HDL cholesterol	−.254	.041	0.541
Total cholesterol	.227	.068	
Age	.134	.282	
Diabetes duration	−.069	.582	
Gender	−.204	.109	
Therapy for hypertension	.212	.096	
Therapy for diabetes	.030	.814	

Statistical Analysis

Data are presented as means ± SEM. Statistical analyses were conducted using the StatView 5 system (Statview, Berkeley, CA). Simple (Spearman's rank) correlation coefficient and stepwise multiple regression analyses were used to examine the relationships between insulin resistance and subcutaneous or visceral abdominal fat area, BMI, or the measures of variables including triglycerides. Furthermore, the relationship between serum triglycerides or BMI and regional abdominal fat area was also analyzed by Spearman's rank correlation coefficients. $P < .05$ was considered significant. In multivariate analysis, F value $\geq$ was considered significant.

RESULTS

The subjects studied were all Japanese type 2 diabetic patients (42 men and 21 women) with an age range of 45 to 83 years (61.5 ± 1.2) and a BMI of 20.1 to 26.8 kg/m^2 (22.8 ± 0.2). They were all nonobese.[21] The fasting plasma glucose was 145 ± 3 mg/dL and glycosylated hemoglobin (HbA_{1c}) was 6.9% ± 0.1%. Fasting plasma insulin level was 6.6 ± 0.4 μU/mL. Serum triglycerides and total and HDL cholesterol levels were 113 ± 7 mg/dL, 196 ± 4 mg/dL, and 56 ± 2 mg/dL, respectively. Serum LDL cholesterol level was 117 ± 3 mg/dL.

There was a wide variation in insulin resistance calculated from HOMA-IR in our diabetic patients (range, 0.64 to 9.67, 2.37 ± 0.16). Twenty-two of 63 (35%) patients had HOMA-IR greater than 2.5, indicating that they were insulin resistant.[20] Similar to the wide range of insulin resistance, there was also a wide variation in subcutaneous and visceral abdominal fat areas. Subcutaneous and visceral abdominal fat areas were 136.5 ± 6.0 cm^2 (range, 30.9 to 267.4 cm^2 and 86.0 ± 4.1 cm^2 (range, 29.0 to 179.1 cm^2), respectively. The ratio of subcutaneous to total abdominal fat area was 0.62 ± 0.01 (range, 0.41 to 0.82). There was a positive correlation between subcutaneous and visceral abdominal fat ($r = .411$, $P < .001$).

Table 1 demonstrates the correlation between insulin resistance and subcutaneous or visceral fat areas, BMI, or the measures of variables including serum triglycerides in our diabetic patients. Insulin resistance calculated from HOMA-IR was positively correlated with subcutaneous ($r = .544$, $P <$

.001) and visceral ($r = .408$, $P = .001$) fat area in our diabetic patients. Furthermore, insulin resistance was positively correlated with BMI ($r = .324$, $P = .009$), HbA_{1c} ($r = .254$, $P = .040$), serum triglycerides ($r = .419$, $P < .001$), and serum LDL cholesterol levels ($r = .290$, $P = .019$). In contrast, insulin resistance was negatively correlated with serum HDL cholesterol level ($r = .254$, $P = .041$). There was, however, no relationship between insulin resistance and measures of other variables including total cholesterol, age, gender, and medication status (Table 1).

Multiple regression analyses showed that insulin resistance was predicted by the area of subcutaneous ($F = 6.76$, $P < .001$) and visceral ($F = 4.61$, $P < .001$) abdominal fat and serum triglyceride levels ($F = 8.88$, $P < .001$), which explained 36.9% of the variability of insulin resistance in our nonobese Japanese type 2 diabetic patients. BMI ($F = 0.012$), HbA_{1c} ($F = 0.933$), and LDL ($F = 0.619$) and HDL ($F = 0.541$) cholesterol levels, however, were not independently associated with insulin resistance in our patients (Table 1).

Finally, the relationships between serum triglycerides or BMI and regional abdominal fat area were investigated. Serum triglyceride levels were associated with visceral fat area ($r = .302$, $P = .015$), but not with subcutaneous fat area ($r = .222$, $P = .074$). In contrast, BMI was positively correlated with both subcutaneous ($r = .553$, $P < .001$) and visceral fat ($r = .510$, $P < .001$) areas.

DISCUSSION

Our main observations in the present study were that both subcutaneous and visceral abdominal fat areas were independently associated with insulin resistance, but only visceral fat mass was positively correlated with serum triglyceride levels in nonobese Japanese type 2 diabetic patients.

Although there is some evidence supporting the view that regional abdominal fatness accounts for most insulin resistance in humans, correlation between insulin resistance and subcutaneous or visceral fat areas remain controversial. Abate et al[30] first demonstrated that subcutaneous truncal fat rather than intraperitoneal or retroperitoneal fat plays a major role in obesity-induced insulin resistance in nondiabetic patients. Goodpaster et al[31] later discovered a greater correlation of insulin-mediated glucose disposal with abdominal subcutaneous rather than visceral adipose tissue in nondiabetic patients with a BMI of 19.6 to 41.0 kg/m^2. Banerji et al[32] very recently showed that visceral, but not abdominal subcutaneous adipose tissue mass, is the principal adipose tissue determinant of insulin-mediated glucose disposal in nondiabetic Asian Indian men. On the other hand, only 2 reports are available on type 2 diabetic patients. Banerji et al[16] reported that visceral, but not subcutaneous abdominal fat volume, is associated with insulin resistance in black populations with type 2 diabetes. In contrast, Abate et al[17] recently demonstrated that subcutaneous fat volume, but not intraperitoneal or retroperitoneal, is associated with insulin resistance in non-Hispanic whites with type 2 diabetes. We first demonstrated in our study that insulin resistance was independently associated with subcutaneous and visceral abdominal fat areas in nonobese Japanese type 2 diabetic patients. The reason for the discrepancy among type 2 diabetic patients is unknown at present.

One possible explanation for the discrepancy may be due to the difference of the distribution of adipose tissue. Type 2 diabetic patients reported by Banerji et al[16] had a mean subcutaneous/total abdominal fat volume of 76% to 84%. In contrast, Abate et al[17] examined type 2 diabetic patients with the mean ratio of 49%. The mean ratio of subcutaneous to total abdominal fat area in our patients was intermediate (62%). Thus, the ratio of subcutaneous fat to total abdominal fat might affect the relationship between insulin resistance and regional abdominal adiposity in type 2 diabetic patients. Additional studies on large populations with broad variation in subcutaneous/total abdominal fat areas are required for further conclusion. Alternatively, there might be an ethnic difference in the effect of regional abdominal adiposity on insulin resistance in type 2 diabetic patients. It is reported that the distribution of adipose tissue (visceral/total fat) appears not to be markedly different among Asian Indian, African-American, or Swedish men when using comparable CT methods.[32-34]

Using the minimal model approach shown by Bergman,[5] we previously demonstrated that nonobese Japanese type 2 diabetic patients are divided into 2 variants: 1 with insulin resistance and the other with normal insulin sensitivity.[6-8] Although the BMI and serum triglyceride levels are important in identifying insulin-sensitive and insulin-resistant variants in Japanese type 2 diabetic patients, the serum triglyceride level is associated with insulin resistance in nonobese Japanese type 2 diabetic patients, while BMI is not.[9,20] This idea is supported in our recent study showing that bezafibrate, a triglyceride-lowering drug, reduces insulin resistance and plasma glucose levels without affecting BMI level in nonobese Japanese type 2 diabetic patients.[18,35,36] We recently documented that short-term physical training decreased serum triglycerides, insulin resistance, and glucose levels without affecting BMI levels in nonobese Japanese type 2 diabetic patients.[19]

There are several reports suggesting that serum triglyceride levels are associated with intra-abdominal adipose tissue mass in nondiabetic subjects. Fujioka et al[14] previously disclosed that intra-abdominal fat accumulation determined by axial CT contributes to dyslipidemia in obese subjects. Pouliot et al[37] showed that the amount of visceral adipose tissue is an important correlate of the alteration in lipid metabolism in obese men. The same group also reported similar results in premenopausal obese women.[38]

Our present study that visceral, but not subcutaneous abdominal fat area, is associated with serum triglyceride levels confirms the previous report in African-American type 2 diabetic patients shown by Banerji et al.[16] However, whether increased visceral abdominal fat accumulation is the cause of elevated triglyceride concentrations in nonobese Japanese type 2 diabetic patients is still an unsolved question. In this respect, in vitro studies of metabolism of adipocytes from different anatomical regions are of interst. Although no differences have been noted in basal rates of lipolysis and antilipolytic effects of insulin in adipose tissue, catecholamine-induced lipolysis has been reported to be uniformly higher in intraperitoneal fat than in subcutaneous abdominal fat.[39] It is considered that free fatty acids released from intraperitoneal fat tissue are drained into the portal system and directly into the liver, which raises serum triglyceride levels. Alternatively, the clinical characteristics

studied might explain the relationship between serum triglycerides and visceral adipose tissue area. Our patients and those reported by Banerji et al[40] were similar in terms of the range of BMI. The range of BMI in the patients shown by us and Banerji et al was 20.1 to 26.8 kg/m^2 and 24 and 28.5 kg/m^2, respectively, suggesting that the patients belonged to the midrange BMI group.[9]

In summary, although our present study was performed on a limited number of patients (n = 63), our results suggest that both subcutaneous and visceral abdominal fat areas are independently associated with insulin resistance, but only visceral abdominal fat area is associated with serum triglyceride levels in nonobese Japanese type 2 diabetic patients. A study on a larger population should be undertaken to clarify the relationship between insulin resistance and regional abdominal fat area and the role of visceral abdominal fat area on serum triglyceride levels in nonobese Japanese type 2 diabetic patients.

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