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Diabetic retinopathy is associated with visceral fat accumulation in Japanese type 2 diabetes mellitus patients

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Abstract

The presence of diabetic retinopathy (DR) and increased of visceral fat accumulation (VFA) are associated with high mortality in type 2 diabetes mellitus patients. This preliminary study was therefore designed to test the hypothesis that DR is associated with insulin resistance and VFA in type 2 diabetes mellitus patients without insulin treatment. A total of 102 type 2 diabetes mellitus patients were divided into 2 groups: DR group (age, 60 ± 6 years [mean ± SD]; n = 31) and no diabetic retinopathy (NDR) group (59 ± 5 years, n = 71). The level of blood glucose was assessed by fasting plasma glucose, fasting immunoreactive insulin, homeostasis model assessment index, and hemoglobin A_{1c}. The fat distribution was evaluated by measuring the VFA by abdominal computed tomography at the umbilical level. The body mass index and waist circumference were higher in the DR group than in the NDR group ($P < .001$ and $P < .0005$, respectively). Plasma levels of triglyceride were higher, whereas high-density lipoprotein cholesterol was lower, in the DR group than in the NDR group ($P < .005$ and $P < .0001$, respectively). Fasting plasma glucose ($P < .0005$), insulin concentrations ($P < .0001$), homeostasis model assessment index ($P < .0001$), and VFA ($P < .0001$) levels were higher in the DR group than in the NDR group. Multivariate logistic analysis revealed that DR was independently predicted by high VFA and insulin resistance. The results of this preliminary study indicate that the presence of DR was associated with high VFA and insulin resistance in Japanese patients with type 2 diabetes mellitus.

1. Introduction

There is increasing evidence that micro- and macrovascular complications of diabetes share certain pathophysiologic mechanisms. This may explain why microangiopathy has been associated with macroangiopathy and with mortality [1,2].

For example, diabetic retinopathy (DR) has also been associated with increased cardiovascular and all-cause mortality risk, particularly in type 2 diabetes mellitus [3,4].

A central pattern of body fat distribution, rather than regional or generalized obesity, is now generally considered to play an important role in the metabolic syndrome, which involves insulin resistance, hyperinsulinemia, dyslipidemia, obesity, diabetes mellitus, and hypertension [5,6].

The data confirmed that, whereas the more expensive abdominal computed tomography (CT) precisely assesses visceral fat accumulation (VFA), the waist circumferences measurement or body mass index (BMI) provides less expensive means to assess VFA [7]. An increased VFA is a risk factor for cardiovascular disease [8,9] and is associated with insulin resistance in healthy subjects [10] and patients with type 2 diabetes mellitus [11]. Furthermore, the presence of DR is reported to be associated with insulin resistance in type 2 diabetes mellitus patients [12,13].

We hypothesized that increased severity of DR is associated with VFA and insulin resistance in type 2 diabetes mellitus patients. To test our hypothesis, we compared blood

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pressure (BP), dyslipidemia, metabolic profiles, and level of VFA in 2 groups of Japanese type 2 diabetes mellitus patients. One group consisted of DR patients, and the other group had no diabetic retinopathy (NDR). Evaluation of the independent predictors of DR in the patients in both groups was conducted.

2. Materials

2.1. Study population

We screened 210 subjects seen in the Department of Endocrinology of Oita Red Cross Hospital between April 2007 and December 2008 for the treatment of type 2 diabetes mellitus detected during medical examination. Of these, 102 patients (52 men and 50 women), with a mean ± SD age of 59 ± 5 years, fulfilled the inclusion criteria and were enrolled in the present study. The inclusion criteria were as follows:

1. Organic heart disease was not determined by treadmill exercise electrocardiography (ECG). Treadmill exercise ECG did not have ST-T abnormal changes.
2. An absence of causes of secondary hypertension (ie, primary aldosteronism, renal vascular hypertension, hyperthyroidism, pheochromocytoma).
3. No history of chronic disease, such as renal failure (creatinine >1.5 mg/dL), pulmonary disease, liver dysfunction (aminotransferase: aspartate aminotransferase >50 IU/L), arteriosclerotic obliterans, sleep apnea syndrome, and symptomatic cerebrovascular disease, was noted.
4. The patient was not currently receiving treatment with insulin. (For this reason, insulin therapy patients were not subjected to measurement by the homeostasis model assessment [HOMA] index.)

Of the 210 screened patients, 108 were excluded from further evaluation because of extenuating circumstances. The reasons for the exclusion were as follows: 65 patients being treated with insulin, 9 with renal failure, 7 with symptomatic cerebrovascular disease, 6 with angina pectoris, 5 with arteriosclerotic obliterans, 6 with sleep apnea syndrome, 5 with secondary hypertension (2 with primary aldosteronism, 2 with renal vascular hypertension, and 1 with hyperthyroidism), 3 with liver dysfunction (2 with hepatitis B an d 1 with hepatitis C), and 2 with lung cancer.

All subjects gave their written informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Oita University Hospital.

2.2. Patients and methods

The clinical characteristics of the patients in the 2 WML groups are summarized in Table 1. Twenty of the 31 patients in the DR group and 44 of the 71 patients in the NDR group met the criteria for essential hypertension. All of these patients were being treated with calcium channel antagonists, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers with diuretics. *Dyslipidemia* was defined as fasting triglyceride levels of at least 200 mg/dL or high-density lipoprotein cholesterol (HDL-C) concentration less than 45 mg/dL for women and less than 35 mg/dL for men [14]. There were 13 of the 31 patients in the DR group and 28 of the 71 patients in the NDR group who met the criteria for dyslipidemia.

2.3. Assessment of DR

Diagnosis of DR was made by ophthalmologists based on the presence of one or more of the following clinical features in the fundus: hemorrhages, hard or soft exudates, venous beading, intraretinal microvascular abnormalities, cotton wool spots, preretinal new vessels, fibrous proliferation, and scars of photocoagulation. In addition, participants were divided into the following 3 groups using the Davis classification: NDR, simple retinopathy, and either preproliferative or proliferative DR [15].

2.4. Definition of hypertension

Hypertension was defined by measurement of BP as the average of 3 measurements obtained with a mercury-column

Table 1
Clinical characteristics of studied patients

	NDR	DR	*P* value
Age (y)	59 ± 5	60 ± 6	NS
Sex (men/women)	34/37	18/13	NS
VFA (cm^2)	87 ± 30	162 ± 62	<.0001
Duration of diabetes (y)	9.8 ± 3.5	10.5 ± 4.1	NS
Hypertension (%)	62	65	NS
Dyslipidemia (%)	39	42	NS
Drug use (%)			
Sulfonylurea	38	39	NS
α-Glucosidase inhibitors	37	35	NS
Statin	31	32	NS
Calcium channel antagonists	41	39	NS
ACE inhibitors	23	26	NS
Angiotensin receptor blocker	38	42	NS
BMI (kg/m^2)	25.4 ± 2.2	27.3 ± 3.4	.0008
Waist circumference (cm)	84.3 ± 8.5	91.7 ± 9.8	.0004
Systolic BP (mm Hg)	130 ± 10	132 ± 13	NS
Diastolic BP (mm Hg)	77 ± 7	78 ± 8	NS
Heart rate (beat/min)	68 ± 6	70 ± 7	NS
Total cholesterol (mg/dL)	201 ± 29	208 ± 34	NS
Triglyceride (mg/dL)	132 ± 31	155 ± 39	.0025
HDL-C (mg/dL)	48 ± 10	42 ± 8	<.0001
LDL-C (mg/dL)	127 ± 32	137 ± 38	NS
FPG (mg/dL)	138 ± 19	151 ± 23	.0002
F-IRI (μU/mL)	6.6 ± 1.7	9.3 ± 2.5	<.0001
HOMA index	2.2 ± 0.6	3.5 ± 1.1	<.0001
Hemoglobin A_{1c} (%)	7.5 ± 1.3	7.8 ± 1.1	NS
Uric acid (mg/dL)	6.0 ± 1.5	6.7 ± 1.1	.0226
Creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.2	NS
Insulin resistant (%)	32	81	<.0001
High VFA (%)	30	74	<.0001

Data are mean ± SD. ACE indicates angiotensin-converting enzyme; NS, not significant.

sphygmomanometer after 10 minutes of physical resting by the patients. *Essential hypertension* was defined as diastolic BP of at least 90 mm Hg, systolic BP of at least 140 mm Hg, or self-reported use of antihypertensive medication [16].

2.5. Laboratory methods

Blood was extracted from the antecubital vein with the patient in the recumbent position at 7:00 AM after an overnight fast. All patients underwent routine laboratory tests including assays for serum electrolytes, serum total cholesterol, serum triglyceride, serum HDL-C, fasting plasma glucose (FPG), and fasting immunoreactive insulin (F-IRI). Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index: (fasting plasma insulin [in microunits per milliliter] × FPG [in millimoles per liter])/22.5 [17].

The subjects were divided into 2 groups according to HOMA index values. Values of at least 2.5 were indicative of insulin-resistant state, whereas values less than 2.5 were indicative of insulin-sensitive state [18]. All subjects underwent CT at the level of the umbilicus for cross-sectional measurement of abdominal visceral fat areas and were analyzed with Fat scan version 3 software (N2 Systems, Osaka, Japan). Details of the procedures have been described previously [19]. This method was validated by other determinations of VFA [20,21] and widely adopted as a practical method for evaluating regional adiposity. The VFA levels were divided into 2 groups: levels of at least 100 cm^2 were indicative of high VFA, whereas levels less than 100 cm^2 indicate normal VFA, the classification of which was previously validated [22].

2.6. Anthropometric and body composition measurement

The anthropometric and body composition characteristics of the patients were evaluated using the following parameters: height, body weight, BMI, and waist circumference. Body mass index was calculated as weight/(height^2) (kilograms per square meter). The waist circumference was measured midway between the lower rib margin and the iliac crest in standing subjects after normal expiration.

2.7. Statistical analysis

All data are presented as mean ± SD. First, subjects were divided into 2 groups: those with and those without DR (Table 1). For each variable in Table 1, the 2-sided test with level of significance .05 was performed to test the difference between the 2 groups. The Student *t* test was used for continuous variables, whereas, for categorical variables, the χ^2 test was carried out.

Logistic regression analysis was used to assess the influence of explanatory variables on DR. The explanatory variables included age, sex, BMI, VFA, waist circumference, duration of diabetes, hypertension, dyslipidemia, BP, heart rate, total cholesterol, triglyceride, HDL-C, low-density lipoprotein cholesterol (LDL-C), FPG, F-IRI, HOMA index, hemoglobin A_{1c}, uric acid, creatinine, and percentages of insulin resistant and high VFA. The sex, hypertension, dyslipidemia, and percentages of insulin resistant and high VFA were dichotomized as 1 (presence) and 0 (absence) by cutoff values defined in the previous section.

In the procedure of DR, positive was represented as 1 and negative as 0. To determine the factors among all explanatory variables used, a backward elimination procedure was used. In the procedure, the BMI, VFA, waist circumference, triglyceride, HDL-C, FPG, F-IRI, HOMA index, uric acid, and percentages of insulin resistant and high VFA were determined as significant factors influencing WML. All the analyses were performed using a standard statistical package (JMP 6.0; SAS Institute, Cary, NC).

3. Results

Patients with type 2 diabetes mellitus were classified into 2 groups on the basis of the presence or absence of DR. A total of 31 of the type 2 diabetes mellitus patients (30.4%) were in the DR group, and 71 (69.6%) were in the NDR group.

As shown in Table 1, the level of VFA was higher in the DR group than in the NDR group ($P < .0001$). The BMI values and waist circumference were larger in the DR group than in the NDR group ($P = .0008$ and $P = .0004$, respectively). The mean ages of the DR and NDR groups were similar; and there were no significant differences between the groups with respect to sex, duration of diabetes, or administered medications. With regard to lipid metabolism, serum triglyceride was higher and serum HDL-C was lower in the DR group than in the NDR group ($P = .0025$ and $P < .0001$, respectively), whereas serum total cholesterol showed no significant difference between the 2 groups. Regarding glucose metabolism, FPG, fasting insulin concentrations, and HOMA index were higher in the DR group than in the NDR group ($P = .0002$, $P < .0001$, and $P < .0001$, respectively).

The uric acid was higher in the DR group than in the NDR group ($P = .0226$). However, there was no significant difference in hemoglobin A_{1c}. Regarding the renal function, there was no significant difference in the serum creatinine concentration.

Furthermore, the percentage of insulin resistance and high VFA was higher in the DR group than in the NDR group ($P < .0001$ and $P < .0001$, respectively).

Univariate logistic regression analysis showed that the risk of DR was associated with BMI (odds ration [OR], 1.30; 95% confidence interval [CI] = 1.10-1.54; $P = .0020$), VFA (OR, 1.04; 95% CI = 1.02-1.05; $P < .0001$), waist circumference (OR, 1.09; 95% CI = 1.03-1.14; $P = .0013$), triglyceride (OR, 1.02; 95% CI = 1.01-1.03; $P = .0045$), HDL-C (OR, 0.88; 95% CI = 0.82-0.94; $P = .0002$), FPG (OR, 1.06; 95% CI = 1.02-1.09; $P = .0008$), F-IRI (OR, 2.10; 95% CI = 1.51-2.92; $P < .0001$), HOMA index (OR, 8.31;

Table 2
Univariate logistic regression analysis with DR as dependent variable in type 2 diabetes mellitus

	DR		
	OR	95% CI	*P* value
Age	1.06	0.97-1.15	NS
Sex (men)	1.51	0.64-3.53	NS
BMI	1.30	1.10-1.54	.0020
VFA	1.04	1.02-1.05	<.0001
Waist circumference	1.09	1.03-1.14	.0013
Duration of diabetes	1.02	0.91-1.14	NS
Hypertension	1.75	0.56-2.78	NS
Dyslipidemia	1.26	0.48-2.58	NS
Systolic BP	1.02	0.98-1.06	NS
Diastolic BP	1.03	0.96-1.08	NS
Heart rate	1.06	0.99-1.14	NS
Total cholesterol	1.01	0.99-1.02	NS
Triglyceride	1.02	1.01-1.03	.0045
HDL-C	0.88	0.82-0.94	.0002
LDL-C	1.01	0.99-1.02	NS
FPG	1.06	1.02-1.09	.0008
F-IRI	2.10	1.51-2.92	<.0001
HOMA	8.31	3.29-21.0	<.0001
Hemoglobin A_{1c}	1.11	0.73-1.69	NS
Uric acid	1.45	1.05-2.01	.0258
Creatinine	4.02	0.38-18.8	NS
Insulin resistant	8.70	3.13-24.2	<.0001
High VFA	6.85	2.64-17.7	<.0001

Significant predictors of DR were explored among 5 parameters: sex (female = 0, men = 1), hypertension (absent = 0, present = 1), dyslipidemia (absent = 0, present = 1), insulin resistance (insulin sensitivity = 0, insulin resistance = 1), and high VFA (normal VFA = 0, high VFA = 1).

95% CI = 3.29-21.0; $P < .0001$), uric acid (OR, 1.45; 95% CI = 1.05-2.01; $P = .0258$), the percentage of insulin resistant (OR, 8.70; 95% CI = 3.13-24.2; $P < .0001$), and the percentage of high VFA (OR, 6.85; 95% CI = 2.64-17.7; $P < .0001$) and that these were dependent on lipid and glucose metabolic parameters in type 2 diabetes mellitus patients (Table 2).

On the other hand, multivariate logistic analysis identified high VFA (OR, 4.83; 95% CI = 1.74 -13.4; $P = .0025$) and insulin resistant (OR, 6.39; 95% CI = 2.19-18.6; $P = .0007$) in type 2 diabetes mellitus patients as the independent and significant risk factors for DR (Table 3).

4. Discussion

In the present study, measurement of the metabolic parameters revealed that serum HDL-C level was lower, whereas the HOMA index and VFA levels were higher, in the DR group than in the NDR group. Multivariate logistic analysis determined high VFA levels and insulin resistance as independent risk factors for the presence of DR in type 2 diabetes mellitus patients.

The present study revealed that a greater proportion of type 2 diabetes mellitus patients in the DR had high VFA and insulin resistance.

There are several reports indicating that the presence of DR is associated with insulin resistance in type 1 [12] and type 2 diabetes mellitus [13].

Hadjadj et al [12] investigated the association between DR and insulin resistance score using a World Health Organization recommendation [22] (ie, hypertension, personal history of lipid disorders, personal history of type 2 diabetes mellitus, and obesity were considered). They found a significant DR in type 1 diabetes mellitus patients with insulin resistance. Parvanova et al [13] have reported that proliferative retinopathy is associated with insulin resistance using a hyperinsulinemic-euglycemic clamp in 115 patients with type 2 diabetes mellitus.

Although the specific mechanism that links DR and insulin resistance remains to be elucidated, several mechanisms could explain our observations. First, defective fibrinolysis caused by excess plasminogen activators inhibitor–1 activity and selective inhibition of some antiatherogenic effects of insulin may promote the occlusion of retinal capillaries and secondary ischemia-induced neovascularization [23]. Second, the ischemic damage can be further amplified by insulin resistance that has been related to a lower ability of insulin to induce vasodilatation through impaired nitric oxide endothelial production or accelerated inactivation [24].

The association between obesity and retinopathy has been investigated in several studies [25,26]. In the Hoorn study, 626 individuals were analyzed by age, sex, BP, lipids, and obesity to retinopathy in diabetic and nondiabetic patients. The BP, lipids concentrations (ie, total cholesterol, triglyceride), and BMI were associated with retinopathy [25]. In the Atherosclerosis Risk in Communities study, hypertensive retinopathy signs were related to larger waist circumference, an indicator of abdominal obesity [26]. However, in these reports, obesity was evaluated by BMI and waist circumference; they did not measure VFA evaluated by abdominal CT.

The underlying pathophysiologic mechanisms of the possible association between VFA and DR are not understood. In our opinion, there are several possible explanations for this observation. Several pathogenetic theories of DR exist based on the potential roles of aldose reductase activity, vasoproliferative factors, oxidative stress, platelet function, and blood viscosity. Of these, vasoproliferative factors, such as the vascular endothelial growth factor (VEGF), have recently gained intense interest. The concentration of VEGF has been found to be higher in the vitreous of eyes with DR

Table 3
Multivariate logistic regression analysis with DR as dependent variable in type 2 diabetes mellitus

	DR		
	OR	95% CI	*P* value
High VFA	4.83	1.74-13.4	.0025
Insulin resistant	6.39	2.19-18.6	.0007

[27]. Serum angiogenic factors, including VEGF, have been observed to be elevated in obese human [28]. Moreover, Arner [29] has suggested that the flux of lipid from the visceral fat depot to the liver might account for hepatic insulin resistance. In a canine model, development of insulin resistance occurred concomitant with visceral adiposity because of a modest fat content in the diet but without increased calories [30]. Steinberg et al [31] reported that insulin-resistant states such as diabetes and obesity are associated with decreased endothelium-dependent vasodilation [31], and arterial compliance may be a partially nitric oxide–dependent process [32]. In addition, insulin has been shown to induce vascular smooth muscle proliferation and migration in cell cultures [33].

Taken together, it is possible that DR, insulin resistance, and VFA interact and reinforce each other through mechanisms that may be associated with endothelial dysfunction.

There are several limitations to this study. Firstly, it is well known that in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study on type 1 diabetes mellitus patients, the reduction in the risk of progressive retinopathy resulting from intensive glycemic therapy resists for at least 4 years, despite increasing hyperglycemia [34]. It is possible that it is also the case in type 2 diabetes mellitus because the microvascular disease development process is likely to be similar for both type 1 and type 2 diabetes mellitus. However, we could not examine the glycemic status of all patients before study. Further studies are required to examine the relationship between worse prior glycemic control and DR in type 2 diabetes mellitus patients. Secondly, we excluded patients with secondary hypertension. For this reason, secondary hypertension is associated with impaired glucose tolerance (ie, primary aldosteronism, hyperthyroidism). Thirdly, as to antidiabetic medications, a considerable number of patients were being treated with sulfonylurea and/or α-glucosidase inhibitors, whereas only 1 patient in each group was treated with pioglitazone, an oral peroxisome proliferator–activated receptor γ agonist reported to reduce VFA in type 2 diabetes mellitus patients [35]. Furthermore, there are several studies that have demonstrated the relationship between DR and peroxisome proliferator–activated receptor γ [36,37]. Our small cross-sectional study did not allow us to statistically analyze and exclude the potential effects of such therapeutic regimen on the HOMA index and VFA. Fourthly, we used the HOMA index as a conventional indicator of insulin resistance. We excluded insulin-treated diabetic patients just for the reason of HOMA index calculation. It may be that a significant number of DR patients were excluded, which will decrease the power of the study. Further clinical investigators are needed to determine the relationship between insulin resistance as evaluated by glucose clamp method, VFA, and DR in type 2 diabetes mellitus patients. Finally, no patients enrolled in the present study underwent coronary angiography. Although ischemic heart disease could not be completely excluded, severe coronary artery disease was unlikely to be present in view of the normal results of the treadmill exercise ECG testing. It remains that the presence of cardiovascular disease alters the relationship between VFA and DR in type 2 diabetes mellitus patients. Further studies are required to examine if the presence of cardiovascular disease alters the relationship between VFA and DR in type 2 diabetes mellitus patients.

In conclusion, our findings suggest that the presence of DR is associated with elevated VFA and insulin resistance. High VFA levels and insulin resistance were independent predictors of DR in the Japanese patients with type 2 diabetes mellitus.

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