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Insulin Resistance and Atherosclerosis in Branch Retinal Vein Occlusion

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Purpose: To investigate insulin resistance and atherosclerotic change in patients with branch retinal vein occlusion (BRVO).

Subjects: Sixty-three patients with BRVO, 859 age- and sex-matched control subjects without BRVO who received the 75-g oral glucose tolerance test (OGTT), and 53 control subjects, in whom carotid artery intima-media thickness (IMT) was measured by high-resolution ultrasonography, were included in this study.

Results: The area under the curve of immunoreactive insulin in plasma during the OGTT was higher in patients with BRVO than in control subjects without BRVO, both when comparing individuals with normal glucose tolerance ($P = .013$) and when comparing individuals with impaired glucose tolerance ($P < .005$). Patients with BRVO showed greater IMT than control subjects, but the differences were significant only in the group aged 50–59 years and in the group older than 70 years.

Conclusions: Insulin resistance may play some role in the onset or progression of BRVO. **Jpn J Ophthalmol 2003;47:351–355**

Key Words: Atherosclerosis, branch retinal vein occlusion, insulin resistance.

Introduction

Retinal vein occlusion, which can compromise vision, follows diabetic retinopathy as the second most common form of retinal vascular disease.[1] The pathogenesis of branch retinal vein occlusion (BRVO) is not well understood, but it is suspected of being associated with underlying atherosclerosis. In a few reports, hypertension, obesity, and hyperlipidemia were identified as major risk factors for retinal vein occlusion.[1,2] These factors are also associated with insulin resistance.[3] Recently, insulin resistance has become recognized as a risk factor for atherosclerosis, including ischemic cardiovascular and cerebral disease.[3–5] We therefore suspected that insulin resistance leads to the occurrence of BRVO by promoting atherosclerosis. Although a previous study suggested an association between central retinal vein occlusion and insulin resistance,[6] few reports have associated BRVO with either insulin resistance or atherosclerosis. This study was performed to investigate both insulin resistance and early atherosclerotic change in the carotid arteries of patients with BRVO.

Materials and Methods

Subjects included 63 patients who complained of visual disturbance that had been newly diagnosed as BRVO at the Takayanagi Eye Clinic between January 1998 and September 1999. The diagnosis of BRVO was made by an experienced ophthalmologist (Y.T.) based on ophthalmoscopic examination of the fundus revealing typical

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clinical features; specifically intraretinal hemorrhages in one quadrant with or without macular edema. Ten patients included in the study were already diagnosed as having diabetes. Two patients included in the study had a history of ischemic heart disease; another patient who was included had a history of ischemic cerebral disease. All patients were free of hepatic disorder (serum alanine aminotransferase activity <40 U/L, and serum aspartate aminotransferase activity <40 U/L), as well as severe renal dysfunction (serum creatinine concentration <150 μmol/L).

Control subjects for the study of insulin resistance were age- and sex-matched individuals who were suspected of having diabetes and had undergone a 75-g oral glucose tolerance test (OGTT) for diagnosis at Saiseikai Central Hospital in Tokyo between January 1994 and December 1996.[7] Control subjects for the study of early atherosclerosis involving the carotid arteries were 53 healthy paramedical personnel at Osaka University Hospital as well as elderly volunteers living in Osaka, Japan. All control subjects for the study of atherosclerosis were free of hypertension (systolic blood pressure <140 mm Hg, and diastolic blood pressure <90 mm Hg), hyperlipidemia (total cholesterol <220 mg/dL), and without any history of cardiovascular disease, or cerebrovascular disease.[8]

Oral Glucose Tolerance Test

After a 10- to 12-hour overnight fast, the OGTT was carried out in 40 patients with BRVO who did not have a past history of diabetes. After baseline blood sampling (0 minutes), subjects ingested carbohydrates equivalent to 75 g of glucose (Torelan-G, Shimizu Pharmaceuticals, Shimizu). Blood samples were taken at 0, 30, 60, and 120 minutes for measurement of plasma glucose and insulin concentrations. Plasma glucose was measured by the glucose oxidase method. Plasma insulin was measured by radioimmunoassay. BRVO patients and control subjects were divided into three groups, those with normal glucose tolerance (NGT), those with impaired glucose tolerance (IGT), and those with diabetes, using the 1998 World Health Organization criteria.[9] The area under the curve of plasma glucose (AUC-PG) during the OGTT was estimated by the linear trapezoidal method. The area under the curve of immunoreactive insulin in plasma (AUC-IRI) during the OGTT, also estimated by the linear trapezoidal method, was used as an index of insulin sensitivity.[4,10]

Measurement of Intima-media Thickness of the Carotid Arteries

Ultrasonographic scanning of carotid arteries was performed for all patients with BRVO using an echotomographic system (EUB-525; Hitachi Medico, Tokyo) with an electrical linear transducer (mid-frequency, 10.0 MHz). Extracranial carotid arteries in the neck were scanned bilaterally in three different longitudinal projections (anterior-oblique, lateral, and posterior-oblique) and in the transverse projection, as reported previously.[11] These projections provided images of the common carotid artery, the carotid bulb, and parts of the internal and external carotid arteries. All images were photographed. Scanning was performed by experienced ultrasonographers (O.O. and H.U.), and required an average of 20 minutes per patient. Carotid intima-media thickness was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans, with the first line representing the lumen-intimal interface and the second line representing the collagen-containing upper layer of the adventitia. In each longitudinal projection, the site with the greatest thickness was detected along the vessel from the common carotid artery to the internal carotid artery. Three measurements of the carotid artery intima-media thickness (IMT) were made at the site of the greatest thickness by visual examination and at two other points (1 cm proximal and 1 cm distal to this site). These three determinations were averaged. The greatest value among the six averaged IMTs (three from the left and three from the right) was used as the representative value (the absolute millimeter of IMT) for each individual. The reproducibility of these measurements has been demonstrated previously.[11,12]

Other Measurements

Blood pressure was measured with a mercury sphygmomanometer in the sitting position after 5 minutes of rest in that position. Blood was drawn for analyses of serum total cholesterol, high-density lipoprotein (HDL) cholesterol, serum triglycerides, and hemoglobin A_{1c} when the patient first presented to the clinic, and these data therefore were of a postprandial nature data. Total cholesterol, HDL cholesterol, triglycerides, and hemoglobin A_{1c} were determined by standard laboratory techniques. Weight and height were measured with subjects wearing light clothing and no shoes. Body mass index was calculated as weight (kg)/height $(m)^2$. Informed consent was obtained from all subjects.

Statistical Methods

Statistical analyses were performed using StatView-J 4.5 computer software (Abacus Concepts, Berkeley, CA, USA). Student *t* tests were used for comparisons between groups. Probability values <.05 were considered statistically significant.

Table 1. Characteristics of Patients with Branch Retinal Vein Occlusion

Sex (male/female)	28/35
Age (y)	62.3 ± 10.4
Body mass index (kg/m^2)	25.4 ± 3.7
Systolic blood pressure (mm Hg)	154.9 ± 22.1
Diastolic blood pressure (mm Hg)	83.3 ± 13.5
Total cholesterol (mg/dL)	208.4 ± 39.9
HDL cholesterol (mg/dL)	54.0 ± 14.3
Triglycerides (mg/dL)	135.3 ± 85.0
Hemoglobin A_{1c} (%)	5.3 ± 0.7

Except for sex, data are the mean ± SD. HDL: high-density lipoprotein.

Results

Characteristics of our patients with BRVO are shown in Table 1. Their ages ranged from 35–79 years. Current smoking was noted in 22 patients. Hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, and/or treatment with antihypertensive agents) were present in 47 patients. Twenty-nine patients had hyperlipidemia (serum total cholesterol concentration >220 mg/dL, triglyceride concentration >150 mg/dL, and/or treatment with antihyperlipidemic agents). Thirty patients were obese (body mass index >25 kg/m^2). Twelve BRVO patients had both hypertension and hyperlipidemia; 14 had both hypertension and obesity; 2 had both hyperlipidemia and obesity; and 10 had all three, hypertension, hyperlipidemia, and obesity.

By OGTT, 5 BRVO patients were diagnosed with diabetes, 11, with IGT, and 24 with NGT (Table 2). Plasma glucose concentrations did not differ significantly between BRVO and control subjects except for the value at 60 minutes in subjects with NGT. In both subjects with NGT and those with IGT, plasma insulin concentrations in patients with BRVO were higher than in controls, except just before glucose ingestion. At 30 minutes in NGT subjects and at 60 minutes in IGT subjects, these differences were statistically significant. For both individuals with NGT and those with IGT, the AUC-IRI in BRVO patients was significantly greater than in control subjects.

Results for IMT are presented in Table 3. Because IMT increases gradually with age,[11] subjects were grouped by decade. IMT was greater in patients with BRVO than in controls, *but* differences were significant *only* in the groups aged 50 to 59 years or older than 70 years.

Discussion

This study showed that AUC-IRI was significantly higher in NGT and IGT subjects with BRVO than in NGT and IGT control subjects without BRVO. In subjects with NGT or IGT, hyperinsulinemia, a higher AUC-IRI, appears to be closely correlated with insulin resistance.[3,4,10,13] Our data, therefore, suggest that insulin resistance with compensatory hyperinsulinemia may exist in both NGT and IGT subgroups of patients with BRVO. On the other hand, atherosclerotic change was not always evident in patients with BRVO. Our data therefore, suggest that some patients with BRVO show atherosclerotic changes and others do not.

The following two hypotheses can be advanced to explain these findings. First, insulin resistance closely related with atherosclerosis might cause the onset of BRVO.

Table 2. Plasma Glucose and Insulin During Oral Glucose Tolerance Test* in patients with Branch Retinal Vein Occlusion (BRVO)

	NGT			IGT		
	BRVO (n = 24)	Controls (n = 506)	$P^\dagger$	BRVO (n = 11)	Controls (n = 353)	$P^\dagger$
Glucose (mmol/L)						
Pre-ingestion	5.15 ± 0.41	5.23 ± 0.48	0.41	5.58 ± 0.63	5.58 ± 0.59	.99
30 min	8.76 ± 1.11	8.60 ± 1.40	0.60	10.14 ± 1.25	9.40 ± 1.50	.11
60 min	8.13 ± 1.43	8.82 ± 2.25	0.006	11.16 ± 2.36	10.81 ± 2.17	.60
120 min	6.17 ± 1.01	6.37 ± 0.90	0.35	8.96 ± 1.30	9.07 ± 0.90	.68
AUC-PG (mmol/L)	14.86 ± 1.67	15.38 ± 2.40	0.29	19.31 ± 2.76	18.78 ± 5.79	.47
Insulin (pmol/L)						
Pre-ingestion	35.0 ± 14.7	41.3 ± 19.7	0.13	53.0 ± 34.8	55.8 ± 58.6	.87
30 min	369.0 ± 192.4	259.7 ± 177.7	0.004	325.8 ± 178.2	242.7 ± 243.7	.091
60 min	397.6 ± 178.5	327.8 ± 194.8	0.086	664.8 ± 631.3	335.8 ± 243.7	<.001
120 min	303.0 ± 188.2	250.0 ± 159.5	0.12	567.6 ± 363.3	400.4 ± 275.5	.050
AUC-IRI (pmol/L)	643.0 ± 262.0	511.0 ± 253.9	0.013	958.6 ± 697.9	587.3 ± 373.0	<.005

Data are the mean ± SD. NGT: normal glucose tolerance, IGT: impaired glucose tolerance, AUC-PG: the area under the plasma glucose curve, AUC-IRI: the area under the plasma immunoreactive insulin curve.

*75 g.

†Student *t* test.

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Table 3. Carotid Artery Intima-media Thickness in Patients with Branch Retinal Vein Occlusion (BRVO)

Age (y)	BRVO (n = 63)	Controls (n = 53)	*P**
≤39	0.92 ± 0.14 (n = 2)	0.64 ± 0.12 (n = 12)	
40–49	0.94 ± 0.26 (n = 5)	0.73 ± 0.09 (n = 15)	.15
50–59	0.98 ± 0.26 (n = 11)	0.87 ± 0.09 (n = 13)	<.005
60–69	1.01 ± 0.21 (n = 25)	0.92 ± 0.12 (n = 7)	.31
≥70	1.13 ± 0.24 (n = 20)	0.94 ± 0.11 (n = 6)	.014

Data are the mean ± SD.
*Student *t* test.

BRVO almost invariably occurs at an arteriovenous crossing, where both artery and vein are bound by a common adventitial sheath. Contraction of the sheath and increased rigidity of the crossing artery are features of atherosclerosis likely to result in turbulent blood flow, endothelial cell damage, and thrombotic occlusion of the vein.[2] Histopathologic study disclosed that all crossing arterioles except one showed moderate or severe sclerosis in 8 eyes with BRVO.[14] Therefore, BRVO was associated with arteriolosclerosis. Recently, the association between retinal vein occlusion and asymptomatic cerebral infarction was reported.[15] This result indicated that retinal arteriolosclerosis was associated with systemic atherosclerosis. A previous study reported that insulin resistance increased IMT, which has been used for assessment of early atherosclerosis;[16,17] accordingly, insulin resistance with compensatory hyperinsulinemia is likely to favor progression of atherosclerosis, and atherosclerotic change could cause onset of BRVO. Hypertension, hyperlipidemia, and obesity also have been implicated as risk factors for BRVO,[1,2] and many BRVO patients in our study had these risk factors for atherosclerosis, which together with insulin resistance have been termed ''the insulin resistance syndrome,'' ''the deadly quartet,'' or ''syndrome X.''[3,13,18] Such pro-atherosclerotic conditions would favor causing the onset of BRVO. While BRVO appears to be a ''multiple-hit condition'' with a multifactorial pathogenesis, a number of the factors implicated appear linked to insulin resistance.

Thrombophilia and hypofibrinolysis have been reported to be causes of retinal vascular occlusion. Methylene-tetrahydrofolate reductase mutations, abnormalities of the protein C pathway, and antiphospholipid antibody syndrome are reported to be risk factors for BRVO associated with thrombophilia.[19–21] In addition, recent studies have linked insulin resistance to thrombophilia and hypofibrinolysis.[22–26] We could suggest another possibility that insulin resistance might cause the onset of BRVO via thrombophilia rather than or in addition to atherosclerotic change. Unfortunately, a limitation of our study was that we did not examine coagulation measurement and various risk factors for thrombophilia, so further examination of the relation between insulin resistance and thrombophilia in BRVO is necessary to evaluate this possibility. Treatment aimed at insulin resistance, such as alleviation of obesity, may prevent the onset or limit the severity of BRVO.

In conclusion, the present results suggest that insulin resistance is involved in an interactive manner in the onset or the progression of BRVO.

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