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Plasma Level of Interleukin-6 Is an Indicator for Predicting Diabetic Macular Edema

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Purpose: To find a predictor in the pathogenesis of macular edema, we investigated ocular and systemic risk factors.

Methods: One hundred and fifty-nine patients with mild diabetic retinopathy who showed one or more soft exudates were recruited. We selected the possible predictors on the basis of relevant factors, including concentration of vascular endothelial growth factor, interleukin-6 (IL-6), transforming growth factor (TGF)-β_1, tumor necrosis factor (TNF)-α, and lipoprotein(a) in plasma, and serum level of von Willebrand factor and thrombomodulin.

Results: Macular edema was not detected in 94 eyes; focal macular edema was detected in 46 eyes; diffuse macular edema was detected in 18 eyes; and cystoid macular edema was present in 1 eye. The plasma level of IL-6 concentration and the state of the posterior vitreous detachment (PVD) correlated significantly with the severity of macular edema (odds ratios = 3.68, 1.70, respectively). Other risk factors were not significantly associated with macular edema. We estimated the probability of macular edema according to the IL-6 level in plasma and the state of the PVD, and were able to predict the probability of macular edema.

Conclusion: The results of the present study indicate that IL-6 concentration in plasma and the state of the PVD can be predictors of macular edema. **Jpn J Ophthalmol 2002;46: 78–83**

Key Words: Diabetic retinopathy, interleukin-6, macular edema, posterior vitreous detachment.

Introduction

Diabetic macular edema (macular edema) causes severe visual impairment with or without neovascularization, and the management of macular edema is very important for preserving the useful vision of diabetic patients and for maintaining a high quality of life.[1] The pathogenesis of diabetic macular edema has not been established. Macular edema is thought to be caused by a tractional force from the vitreous, the effects of various cytokines, and damage to the capillary endothelial cells due to abnormal diabetic metabolism. Macular edema is categorized into focal macular edema and diffuse or cystoid macular edema.[2,3] Focal macular edema is characterized by areas of focal leakage from specific capillary lesions. Diffuse macular edema is caused by a breakdown of the inner and outer blood–retinal barrier.[4] Various cytokines have been synergistically implicated in the pathogenesis of diabetic retinopathy,[5–10] and these cytokines are related to each other.[11] Vascular endothelial growth factor (VEGF) is known as a vascular permeability factor.[12,13] Transforming growth factor (TGF)-β_1 and hepatocyte growth factor were reported to be involved in the pathogenesis of proliferative diabetic retinopathy.[14,15] Some cytokines may affect the pathogenesis of macular edema. In addition, vitreomacular relationships are related to the development of diabetic macular edema.[16–19] Our final goal is to de-

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termine the factors relevant to macular edema in order to predict its occurrence, and to treat macular edema effectively in the very mild localized state. As the first step, we investigated the correlation between the severity of macular edema and ocular and systemic risk factors using cross-sectional data, and found that interleukin-6 (IL-6) concentration in plasma and the state of posterior vitreous detachment (PVD) were related to the severity of macular edema.

Materials and Methods

Study Subjects

One hundred and fifty-nine diabetic patients who showed one or more soft exudates and satisfied the entry criteria were recruited for this study from September 1998 to January 1999. Informed consent was obtained from all the patients at entry into the study. None of the patients had previously undergone laser treatment or ocular surgery. No patients had renal dysfunction, nor had they experienced severe physical complications. The mean age of the patients was 56.6 years (range, 28–80 years). Fifty patients (31.4%) were women and 109 (68.6%) were men (Table 1). The mean duration of diabetes was 14.9 years (range, 0–36 years). The baseline examination included a personal interview and physical examination. The personal interviews and the examinations were conducted by assigned physicians and assigned ophthalmologists. Fifty percent of the patients were taking insulin, 45% were taking oral hypoglycemic agents, and 5% were undergoing diet therapy at the time of enrollment. Sixty-seven (44%) had not smoked at any time in their lives. Fifty-one patients had a history of hypertension.

Table 1. Clinical Characteristics of Eyes and Patients (N = 159)

Characteristics	No.*	Value
Right	127	80%
Left	32	20%
ETDRS†		
35	48	30%
43	50	31%
47	29	18%
53	23	15%
61	3	2%
65	5	3%
71	1	1%
Sex		
Female	50	31%
Male	109	69%
Age (y)	159	56.6 ± 11.8‡
Diabetes duration (y)	159	14.9 ± 7.3‡
Hemoglobin A1c (%)	159	7.9 ± 1.3‡
Systolic blood pressure (mm Hg)	159	141.5 ± 20.3‡
Diastolic blood pressure (mm Hg)	159	83.3 ± 11.6‡
Body mass index (kg/m^2)	159	23.9 ± 3.5‡
Using diabetes drug	151	95%
Smoking status	86	56%
Alcohol habit	86	56%
History of hypertension	51	32%

*No.: Number of available data.
†ETDRS: Early Treatment Diabetic Retinopathy Study.
‡Mean ± SD.

Ophthalmologic Examinations

After the pharmacological dilation of pupils, tenfield color fundus photography, fluorescein angiography, and slit-lamp microscopic examination were performed on all patients.

Macular edema was defined as a thickening of the retina within 1 disc diameter from the center of the macula. Macular edema was classified into four types: no macular edema, focal edema, diffuse edema, and cystoid edema. The severity of macular edema was based on the worse eye of each patient.

The vitreous study was performed using a preset lens with a slit-lamp microscope. The state of the posterior vitreous membrane in the macular area was classified into three categories: posterior vitreous membrane detachment is absent, posterior vitreous membrane detachment is present except on macula with vitreo-macular adhesion, and posterior vitreous membrane is present in the macular area, in accordance with the modified Early Treatment Diabetic Retinopathy Study retinopathy severity system.[20–22]

Measurements of Systemic Factors

Several variables measured at baseline were assessed as risk factors for macular edema. We selected age, sex, duration of diabetes, treatment of diabetes, hemoglobin$_{A1c}$ (Hb_{A1c}) level, history of smoking, alcohol drinking habits, history of hypertension, systolic and diastolic blood pressure, body mass index, VEGF, IL-6, TGF-β_1, TNF-α, and lipoprotein (a) [Lp(a)] in plasma, and von Willebrand factor (vWF) and thrombomodulin (TM) in serum. Hb_{A1C} was measured by affinity chromatography (HPLC, Kyoto Chemical, Kyoto) (normal range, 4.3–5.8%). Systolic and diastolic blood pressure were measured with a mercury sphygmomanometer with the patient in the sitting position after a 10-minute rest. A classification of hypertension required a systolic blood pressure of $\geq$150 mm Hg, or the use of hypertension medication. Plasma level of Lp(a), and serum level of vWF and TM were measured using an autoanalyzer with an enzymatic technique.

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Sample Collection and Measurements

Plasma samples were collected from all patients after receiving informed consent. The blood samples were placed immediately on ice, clarified by centrifugation at 3000 *g* for 5 minutes at 4°C, and rapidly frozen at −80°C until assay. The institutional review board of Tokyo Women's Medical University approved the protocol for sample collection. The concentrations of VEGF, IL-6, TGF-β_1, and TNF-α were quantified using an ELISA kit (R& D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol. The examiners who participated in measurements of sample concentrations and the ophthalmological examiners were different. The results ensured that the levels of factors in vitreous fluid and plasma samples were within the detectable range of assay. The minimum detectable concentrations (sensitivity) for the assay kits were 15.6 pg/mL, 0.156 pg/mL, 0.38 ng/mL, 0.50 pg/mL, for VEGF, IL-6, TGF-β_1, TNF-α, respectively.

Statistical Methods

Analyses were performed using the SAS statistical software package (SAS Institute, Cary, NC, USA).[23] The data were presented as mean ± SD or geometric mean ± SD on the logarithmic scale for skewed variables. In this study, we analyzed the cross-sectional data as the first step for determining factors relevant to the severity of macular edema. To analyze the relationship between macular edema and risk factors, macular edema was classified into three types: no macular edema, focal macular edema, and diffuse or cystoid macular edema. The comparison of the three groups was performed with the Kruskal-Wallis test. Risk factors relevant to macular edema were analyzed with a proportional odds model with a 95% confidence interval. Two-tailed *P*-values of less than .05 were considered to indicate statistical significance. To predict macular edema, we selected certain ocular factors and systemic factors, and investigated the relevant factors vis-à-vis macular edema.[24] As ocular factors, we observed ocular tension and the presence of PVD. As systemic factors, we selected some clinical background data and the plasma level of various cytokines. Predicted probability of the severity of macular edema was calculated by the following formula:

$$\theta_{hik} = (\alpha_k + X'_{hi}\beta)/\{1 + \exp(\alpha_k + X'_{hi}\beta)\};$$

where θ represents cumulative probabilities, α denotes separate intercept parameters, β denotes regression parameters, *h* means level of IL-6, *i* means PVD, *k* means two logits, and X′ indicates design matrix.[24] This method of analysis involves developing a mathematical model in which a combination of the values of a group of explanatory variables (PVD and IL-6) was used to predict the value of a dependent variable (macular edema).

Results

State of Macular Edema and PVD

Ninety-four eyes had no macular edema, 46 eyes had focal edema, 18 eyes had diffuse edema, and 1 eye had cystoid macular edema. Seventy-nine eyes had no PVD, 38 eyes had complete PVD, and 39 eyes had PVD with vitreo-macular adhesion.

Plasma Levels of Various Cytokines

The geometric mean of VEGF, IL-6, TGF-β_1, and TNF-α was 45.3 pg/mL, 1.628 pg/mL, 6.41 pg/mL, and 1.90 pg/mL, respectively (Table 2). The geometric mean of Lp(a) and TM was 14 mg/dL and 15.8 U/mL, respectively, and the mean of vWF was 135.5%.

Univariate Analysis

The geometric mean of IL-6 in plasma was 1.45 in no macular edema, 1.77 in focal edema, and 2.33 in diffuse or cystoid edema ($P = .0380$, Kruskal-Wallis test) (Table 3). The plasma level of IL-6 and the presence of PVD significantly correlated with the severity of macular edema (odds ratios = 1.70, 3.68, respectively) (Table 4). Other factors did not correlate with the severity of macular edema.

Predicted Probability

Table 5 shows the predicted probability of macular edema according to IL-6 concentrations and PVD. Table 5 can be used to predict the occurrence

Table 2. Level of Cytokines and Other Factors in Plasma or Serum*

VEGF (pg/mL)	45.3	[21.2, 96.8]†
IL-6 (pg/mL)	1.628	[0.830, 3.195]†
TGF-β_1 (ng/mL)	6.41	[3.77, 10.88]†
TNF-α (pg/mL)	1.90	[1.10, 3.29]†
Lipoprotein (a) (mg/dL)	14	[6, 33]†
von Willebrand factor (%)	135.5 ± 43.6	
Thrombomodulin (U/mL)	15.8	[11.3, 21.9]†

*VEGF: vascular endothelial growth factor; IL-6: interleukin-6; TGF-β_1: transforming growth factor-β_1; TNF-α: tumor necrosis factor-α.

†These valuse represent geometric mean and values 1 SD below and 1 SD above mean on logarithmic scale.

Table 3. Cytokines and Macular Edema

Variable*	No.†	No Macular Edema	Focal Macular Edema	Diffuse or Cystoid Macular Edema	χ^2 statistic	*P*-Value
VEGF (pg/mL)	159	46.7 [21.9 99.5]‡	38.5 [17.6 83.9]	57.4 [29.4 112.2]	3.203	.2016
IL-6 (pg/mL)	146	1.45 [0.79 2.65]	1.77 [0.83 3.74]	2.33 [1.18 4.60]	6.538	.0380
TGF-β_1 (ng/mL)	157	6.21 [3.77 10.23]	6.29 [3.49 11.33]	7.76 [4.58 13.1]	2.362	.3070
TNF-α (pg/mL)	157	1.84 [1.03 3.28]	2.14 [1.34 3.43]	1.71 [1.00 2.93]	2.850	.2405

*VEGF: vascular endothelial growth factor; IL-6: interleukin-6; TGF-β_1: transforming growth factor-β_1; TNF-α: tumor necrosis factor-α.
†No.: Number of available data.
‡These values represent geometric mean and values 1 SD below and 1 SD above mean on logarithmic scale.

of macular edema using these two factors. Our analysis showed that IL-6 and the state of PVD can be considered as the significant predictive risk factors for macular edema. This reveals that when PVD is absent and IL-6 concentration is under 2.000 pg/mL, the probability of macular edema and of diffuse macular edema is 21.7 and 4.8; when PVD is present except in the macular area and IL-6 $\geq$ 4.000 pg/mL, these probabilities are 80.3 and 42.2, respectively.

Discussion

In our study, 41% of the patients had macular edema. Klein and associates reported that the incidence of macular edema was 18.6% in an older-onset group and 20.1% in a younger-onset group in their 10-year cohort study.[1] The incidence rates in our study were higher than in other studies because all our patients had retinopathy, and most of them had moderate or severe non-proliferative diabetic retinopathy, and they had not been treated by laser photocoagulation. The reason that we determine the severity of retinopathy is that the management of retinopathy and macular edema is difficult especially in such stages.

To our knowledge, this is the first report that macular edema is related to the plasma level of IL-6. Plasma levels of VEGF, TGF-β_1, and TNF-α were not related to macular edema. Various cytokines are considered to be involved in the pathogenesis of diabetic retinopathy.[5,6,25] VEGF in ocular fluid is reported to be related to the severity of diabetic retinopathy, and elevated VEGF in the retina causes a vascular permeability increase in diabetic patients.[26] Burgos et al. reported that the vitreous level of VEGF was not attributed to serum diffusion.[27] The VEGF levels in plasma were not found to be related to macular edema in our study.

IL-6 is a multifunctional cytokine that regulates immune response, acute-phase reactions, and hematopoiesis, and it may play a central role in host defense mechanisms.[28–30] IL-6 is secreted by many types of cells: macrophages, monocytes, fibroblasts, epithelial cells, endothelial cells, smooth muscle cells, and T and B lymphocytes.[31] IL-6 was reported to be involved in various diseases, for example, cardiac myxoma, rheumatoid arthritis, lymphoma, and leukemia. IL-6 has also been reported to be involved in the pathogenesis of proliferative diabetic retinopathy and proliferative vitreoretinopathy.[32,33] However, the relationship between the plasma level of IL-6 and macular edema had not been examined heretofore. We found that the correlation between the state of macular edema and the IL-6 level in

Table 4. Contributing Factors to Pathogenesis of Macular Edema According to Proportional Odds Model

Variable*	No. of Patients	ME(+)†	ME(−)†	Adjusted Odds Ratio‡	(95% CI)§	P-Value
PVD						
Absent	79	19	60	1.00		
Present	77	44	33	3.68	(1.81–7.50)	<.001
IL-6 level	144			1.70	(1.02–2.83)	.042

*PVD: posterior vitreous detachment; IL-6: interleukin-6.
†ME: macular edema.
‡Adjusted odds ratio was obtained by multivariate proportional odds model with best subset selection method.
§CI: confidence interval.

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Table 5. Predicted Probability of Macular Edema According to Risk Factors

Risk Factor		Predicted Probability			
		Diffuse or Cystoid Macular Edema		Macular Edema	
PVD	IL-6 (pg/mL)	%	95% CI	%	95% CI
Absent	<2.000	4.8	(2.3–9.6)	21.7	(13.4–33.2)
Absent	2–4.000	5.3	(2.0–13.5)	23.7	(11.1–43.6)
Absent	≥4.000	12.6	(5.0–28.4)	44.5	(23.4–67.7)
Macula area	<2.000	12.8	(6.2–24.5)	45.0	(29.0–62.0)
Macula area	2–4.000	14.1	(5.5–31.6)	47.8	(25.8–70.6)
Macula area	≥4.000	29.8	(13.3–53.9)	70.2	(46.3–86.5)
Except macula	<2.000	20.2	(10.4–35.6)	58.5	(40.4–74.6)
Except macula	2–4.000	22.1	(10.1–41.8)	61.2	(39.3–79.4)
Except macula	≥4.000	42.2	(21.6–66.0)	80.3	(59.8–91.8)

CI: confidence interval.

plasma is statistically significant. Morohoshi et al reported that hyperglycemia stimulated IL-6 synthesis and secretion by human peripheral monocytes.[34] In addition, hypoxia is considered to induce expression of IL-6.[35] The blood–retinal barrier plays an important part in the processes of retinal pathophysiology, and a significant breakdown of the blood–retinal barrier occurs in the early stages of retinal involvement in diabetes.[36] As IL-6 has been considered to play a role in blood–brain barrier permeability,[37–39] plasma IL-6 may be associated with blood–retinal barrier permeability. In the case of retinal edema, there is a predominantly extracellular accumulation of fluid, directly associated with an alteration of the blood–retinal barrier permeability to proteins. The relationship between the plasma level of IL-6 and macular edema has not been hitherto reported. The possible involvement of IL-6 was reported in various conditions, including cardiac myxoma, rheumatoid arthritis, and malignancies.[31] None of the patients who enrolled in our study had any of these diseases.

In our study, macular edema was also found to be related to the state of PVD. Vitrectomy can improve visual prognosis for patients with macular edema.[18,19] Clinical observations suggest that macular edema is induced by vitreous tractional force exerted on the macular area. Nasrallah and associates reported that vitreous traction may be an important factor in the development of diabetic macular edema; they stated that in eyes with macular edema and with vitreous adhesion in the macular area, the attached posterior vitreous may cause macular tangential traction.[16] In this study also, the relationship between the state of posterior vitreous detachment and macular edema was statistically significant. In our study, the category of no posterior vitreous membrane means there was normal macular function and the category of posterior vitreous membrane being present included vitreous-macular adhesions. So our results correspond to their reports.

We selected the PVD states and the IL-6 level as risk factors, and then estimated the probability of macular edema. From the results, we could predict the progression and/or grade of macular edema. These two factors may become important clinical markers of macular edema. In this report, we examined only cross-sectional data; we will next add follow-up data, and then investigate the correlation between the markers and macular edema.

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