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Characteristics of diabetic macular edema patients with serous retinal detachment

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Abstract

To determine characteristics of diabetic macular edema patients with serous retinal detachment (SRD).

We classified naïve diabetic macular edema (DME) patients with or without SRD, and compared their baseline characteristics; intravitreal bevacizumab (IVB) responsiveness; aqueous concentrations of IL (interleukin)-1β, -2, -8, -10, -17, placental growth factor (PlGF), and vascular endothelial growth factor (VEGF). In addition, factors associated with the existence of SRD were identified.

Of the 64 DME patients, 14 had SRD. The average levels of aqueous VEGF and PlGF were significantly higher in the SRD group than in the control group ($P = .022$ and $P = .041$, respectively). The best-corrected visual acuity (BCVA) and central subfield thickness (CST) did not differ significantly between the 2 groups at baseline or after 3 consecutive monthly IVBs. In multivariate logistic regression analysis, the level of aqueous VEGF was the only factor associated with the existence of SRD (odds ratio: 1.03; $P = .038$).

Rather than aqueous inflammatory cytokines, levels of aqueous VEGFs were associated with the occurrence of SRD in DME patients. In terms of prognosis, the existence of SRD was not related with BCVA or CST changes.

Abbreviations: BCVA = best corrected visual acuity, CIDME = center-involving diabetic macular edema, CME = cystoid macular edema, CST = central subfield thickness, DME = diabetic macular edema, DR = diabetic retinopathy, DRT = diffuse retinal thickening, EZ = ellipsoid zone, HF = hyperreflective foci, IL = interleukins, OCT = optical coherence tomography, PlGF = placental growth factor, SRD = serous retinal detachment, VEGF = vascular endothelial growth factors.

Keywords: center-involving diabetic macular edema, diabetic macular edema, diabetic retinopatathy, intravitreal bevacizumab, serous retinal detachment, vascular endothelial growth factors

1. Introduction

Diabetic macular edema (DME) is one of the most significant causes of visual disturbance in patients with diabetic retinopathy (DR).[1] DME may be caused by damage to the blood–retina barrier induced by metabolic changes and inflammation.[1,2] DME is affected by not only cells in the retina but also the expressions of various molecules, including interleukins (ILs), vascular endothelial growth factors (VEGFs), tumor necrosis factor-α, and matrix metalloproteinase.[2–4]

Classification of DME into several types using various imaging tools, including fluorescein angiography, optical coherence tomography (OCT), and OCT angiography, has been investigated to identify causes, predict prognosis, and select appropriate treatments.[5–8] Of these techniques, OCT is a fast and noninvasive tool to quantify macular profiles. Recent studies using OCT have morphologically classified DME as cystoid macular edema (CME), diffuse retinal thickening (DRT), or serous retinal detachment (SRD).[9] Of these morphological classifications, the prognosis and mechanism of SRD is controversial. Some studies have reported that DME with SRD has a better responsiveness or better prognosis after anti-VEGF treatments, suggesting that there could be an association between VEGF and SRD.[10,11] However, there are other studies that reported contradicting results showing no association between inflammation and SRD.[12–14]

Therefore, in this study, we grouped naïve DME patients according to the presence of SRD, and compared their systemic and ocular factors including the levels of VEGFs and inflammatory cytokines in the aqueous humor. Then, we identified factors associated with SRD.

2. Methods

The study protocol adhered to the tenets of the Declaration of Helsinki. The protocol was approved by the institutional review/ethics board of the Catholic University of Korea. All participants gave written informed consent for the use of their clinical records.

We enrolled treatment-naïve center-involving DME (CIDME) eyes of central subfield thickness (CST) ≥300 μm from June, 2016 to November, 2016.[15] The criteria of exclusion included macular edema due to other causes including an epiretinal membrane or vitreo-macular traction. We also excluded eyes with histories of uveitis or intraocular surgery.

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We measured glycated hemoglobin levels, and all patients took ophthalmic examinations, including measurements of the best corrected visual acuity (BCVA) and fundus examination. The CST was measured using OCT (Cirrus High-Definition OCT; Carl Zeiss Meditec, Dublin, CA) and axial length was measured using an IOL Master (Carl Zeiss Meditec). The hyperreflective foci (HF) were manually measured within 1500 μm, and ellipsoid zone (EZ) disruptions were manually measured within 1000 μm using a horizontal scan centered on the fovea.[6,16] EZ disruption was graded as 0 in case of intact, 1 in case of focal disruption ≤200 μm in length, and 2 in case of disruption >200 μm in length.

2.1. Assay of cytokines and growth factors

We collected aqueous fluid specimens before first intravitreal bevacizumab (IVB) injection, and measured the concentrations of IL-1β, -2, -8, -10, -17, placental growth factor (PlGF), and VEGF in 75 μL aqueous humor. The antibodies were immobilized on beads, and samples with 75 μL Calibrator Diluent RD6–52 (R&D Systems, Minneapolis, MN) were added to the preparations. And the samples were incubated for 2 hours after adding beads, for 1 hour after adding detection antibodies, and for half-hour after adding the streptavidin-phycoerythrin reagent. Samples were read using the Luminex xMAP system (Luminex, Austin, TX).[17]

2.2. Statistical evaluation

Statistical analyses were performed using SPSS statistical software for Windows, version 20.0 (SPSS, Chicago, IL). The *t* test, Mann–Whitney *U* test, and chi-square test were used to compare the values or the ratios of the patient subgroups. Logistic regression was employed to identify factors associated with SRD occurrence.

3. Results

We enrolled 64 treatment-naïve CIDME eyes of 64 patients. The mean age was 55.85 ± 9.35 years, and there were 30 men and 34 women. In the DR staging, 47 patients had proliferative DR (73.44%) and 17 patients had non-proliferative DR (26.56%). All the patients who showed proliferative DR had received panretinal photocoagulation. The mean BCVA (LogMAR) was 0.45 ± 0.27, and the mean CST was 416.03 ± 81.14 μm at baseline. Based on DME morphology, 33 patients had CME and 31 had DRT. The systemic and ocular characteristics of the patients are summarized in Table 1.

There were 50 eyes with DME without SRD and 14 eyes with SRD. There was a significant difference in sex distribution, but no significant differences were found in age, glycated hemoglobin level, duration of diabetes, DR stage, BCVA, or CST between the 2 groups. The OCT findings such as number of HF and EZ grade also showed no significant differences. The BCVA and CST after 3 consecutive monthly IVB injections did not significantly differ ($P = .238$ and $P = .314$, respectively). In the comparison of cytokine levels in the aqueous humor, VEGF and PlGF levels were significantly higher in the SRD group ($P = .022$ and $P = .041$, respectively) (Table 2).

The factors identified as associated with SRD are summarized in Table 3. In univariate and multivariate logistic analyses, VEGF level was the only factor associated with the existence of SRD (odds ratio [OR]: 1.01, $P = .009$ and OR: 1.03, $P = .038$, respectively).

Table 1

Demographics and clinical characteristics of DME patients.

Systemic factors		
Sex (male: female)		30:34
Age, y		55.85 ± 9.35
HbA1C (%)		7.49 ± 1.10
DM duration, y		9.0 (3.0;17.0)
OCT findings		
Number of HF		8 (5;11)
Cases of SRF		14 (21.88%)
CME: DRT		33:31
EZ	0	31 (48.44%)
Disruption	1	19 (29.69%)
Grade	2	14 (21.88%)
Aqueous humor		
IL-1β, pg/mL		3.49 (1.86;3.49)
IL-2, pg/mL		55.17 (45.62:67.94)
IL-8, pg/mL		17.71 (12.95;28.66)
IL-10, pg/mL		0.00 (0.00;0.74)
IL-17, pg/mL		2.56 (0.96;2.76)
VEGF, pg/mL		70.13 (37.40;103.61)
PlGF, pg/mL		1.52 (0.80;2.28)
Ocular factors		
Axial length, mm		23.21 (22.88;24.13)
Baseline BCVA (LogMAR)		0.5 (0.2; 0.7)
BCVA after IVBs (LogMAR)		0.3 (0.2; 0.5)
Baseline CST, μm		391.0 (361.0;460.0)
CST after IVBs, μm		343.5 (292.5;415.0)
DMR (NPDR:PDR)		17:47

Values are expressed as mean ± SD or median and interquartile range, as appropriate.
BCVA = best-corrected visual acuity, CME = cystoid macular edema, CST = central subfield thickness, DME = diabetic macular edema, DMR = DM retinopathy, DRT = diffuse retinal thickening, EZ = ellipsoid zone, HbA1c = glycated hemoglobin, HF = hyperreflective foci, IL = interleukin, IVB = intravitreal bevacizumab, NPDR = non-proliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, PlGF = placental growth factor, SRF = subretinal fluid, VEGF = vascular endothelial growth factor.

4. Discussion

Many studies have reported that DME is mediated by inflammation and VEGFs, and their actions are closely interconnected.[2,18] DME treatment by suppressing VEGF levels or the controlling inflammation has been spotlighted. Studies using imaging tools or biomarkers to find early and effective treatments among the various options have been reported.[16,19] This study also focused on finding more effective treatment regimen among various treatment options by using an imaging tool and biomarker; we are the first study to find that SRD in DME is associated with VEGF levels.

Several treatment options for DME are now available. Photocoagulation of the leaking point with a focal laser is used to treat non-CIDME patients.[20] Removal of traction, clearing the inflammatory cytokines and growth factors, and increasing the oxygen levels of the vitreous and retina via vitrectomy have also been used to treat refractory DME.[8,21–23] However, the main treatment of DME is intravitreal injection of anti-VEGF agents or steroids.[24–26] Many studies have shown that visual disturbances are associated with the degree of macular thickness, and long-lasting and chronic DME can compromise visual functions.[27–29] Thus, early and optimal treatments are required to recover and acquire a normal macular contour. If proper treatments are delayed, permanent visual disturbance can

Table 2

Demographics and clinical characteristics of DME patients depending on the existence of SRD.

	Without SRD (N = 50)	With SRD (N = 14)	*P*
Systemic factors			
Sex (male:female)	27:23	3:11	.038
Age, y	56.26 ± 8.86	54.43 ± 11.16	.521
HbA1C (%)	7.51 ± 1.08	7.44 ± 1.22	.847
DM duration, y	8.00 (3.00;17.00)	10.00 (5.00;17.00)	1.000
OCT findings			
Number of HF	8.00 (5.00;10.00)	6.50 (5.00;15.00)	.807
CME:DRT	24:26	9:5	
EZ disruption grade			
0	27 (54.00%)	4 (28.57%)	
1	14 (28.00%)	5 (35.71%)	.089
2	9 (18.00%)	5 (35.71%)	
Aqueous humor			
IL-1β, pg/mL	3.49 (1.86;3.49)	3.49 (1.86;3.49)	.469
IL-2, pg/mL	55.17 (45.62;63.85)	59.51 (45.62;75.72)	.151
IL-8, pg/mL	17.71 (14.70;28.49)	17.74 (11.99;35.48)	.808
IL-10, pg/mL	0.00 (0.00;0.69)	0.00 (0.00;1.52)	.497
IL-17, pg/mL	2.56 (0.96;2.56)	2.56 (2.56;4.18)	.052
VEGF, pg/mL	65.22 (37.47;79.18)	121.84 (37.18;206.58)	.022
PlGF, pg/mL	1.34 (0.65;2.05)	2.25 (1.34;6.14)	.041
Ocular factors			
Axial length, mm	23.23 (22.86;24.17)	23.18 (23.01;24.01)	.929
Baseline BCVA (LogMAR)	0.45 (0.20;0.70)	0.50 (0.30;0.70)	.621
BCVA after IVBs (LogMAR)	0.30 (0.10;0.50)	0.40 (0.20;0.50)	.238
Baseline CST, μm	389.00 (351.00;442.00)	419.00 (391.00;518.00)	.074
CST after IVBs, μm	341.50 (291.00;398.00)	384.50 (295.00;457.00)	.314
CST reduction, μm	46.00 (8.00;87.00)	45.50 (24.00;89.00)	.733
DMR (NPDR:PDR)	12:38	5:9	.495

Values are expressed as mean ± SD or median and interquartile range, as appropriate.

BCVA = best-corrected visual acuity, CME = cystoid macular edema, CST = central subfield thickness, DME = diabetic macular edema, DMR = DM retinopathy, DRT = diffuse retinal thickening, HbA1c = glycated hemoglobin, HF = hyperreflective foci, IL = interleukin, IVB = intravitreal bevacizumab, NPDR = non-proliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, PlGF = placental growth factor, SRD = serous retinal detachment, VEGF = vascular endothelial growth factor.

occur.[29,30] Thus, it is necessary to identify more relevant mechanisms in DME subtypes, so that customized treatments can be selected. Although SRD is one of the most common manifestations in DME, the mechanism of action is still unclear. We found SRD group had significantly higher aqueous levels of VEGF and PlGF ($P = .022$ and $P = .041$, respectively). Additionally, in the logistic analyses, the occurrence of SRD was significantly associated with VEGF levels (OR: 1.03; $P = .038$). The PlGF, a member of the VEGF family, is induced by ischemic reinal condition, and has a key role in angiogenesis and vasculogenesis in retina.[31] Based on these results, SRD seems to be more associated with VEGFs than with inflammation.

Although vitreous samples adequately reflect retinal status,[32] obtaining vitreous samples is invasive and difficult because few patients are treated with vitrectomy due to DME. In addition, posterior vitreous detachment or blood contamination could compromise data quality of vitreous samples. The aqueous humor, which can easily be obtained during intravitreal injection, can also reflect retinal status. The levels of many cytokines are increased under conditions such as retinal hypoxia or inflammation,[33,34] and most studies that have used aqueous humor samples have shown that the concentrations of various molecules from DME patients differ from those of controls.[17,35] However, few studies have investigated the associations between responsiveness of

Table 3

Results of logistic regression of the effects of SRD in DME patients.

	Univariate analyses*		Multivariate analyses*	
	Adjusted OR (95%CI)*	*P*-value	Adjusted OR (95%CI)*	*P*-value
IL-1β, pg/mL	0.84 (0.56, 1.25)	.386		
IL-2, pg/mL	1.03 (1.00, 1.06)	.104	1.03 (0.99, 1.08)	.216
IL-8, pg/mL	1.02 (0.99, 1.05)	.129	1.02 (0.99, 1.07)	.208
IL-10, pg/mL	1.72 (0.74, 3.90)	.192	1.84 (0.59, 5.91)	.284
IL-17, pg/mL	1.27 (0.94, 1.78)	.121	1.68 (0.95, 3.01)	.065
VEGF, pg/mL	1.01 (1.00, 1.02)	.009	1.03 (1.00, 1.07)	.038
PlGF, pg/mL	1.20 (0.99, 1.48)	.067	0.68 (0.37, 1.19)	.190

CI = confidence interval, DME = diabetic macular edema, IL = interleukin, OR = odds ratio, PlGF = placental growth factor, SRD = serous retinal detachment, VEGF = vascular endothelial growth factor.

* Adjusted for age, sex, and diabetic retinopathy stage.

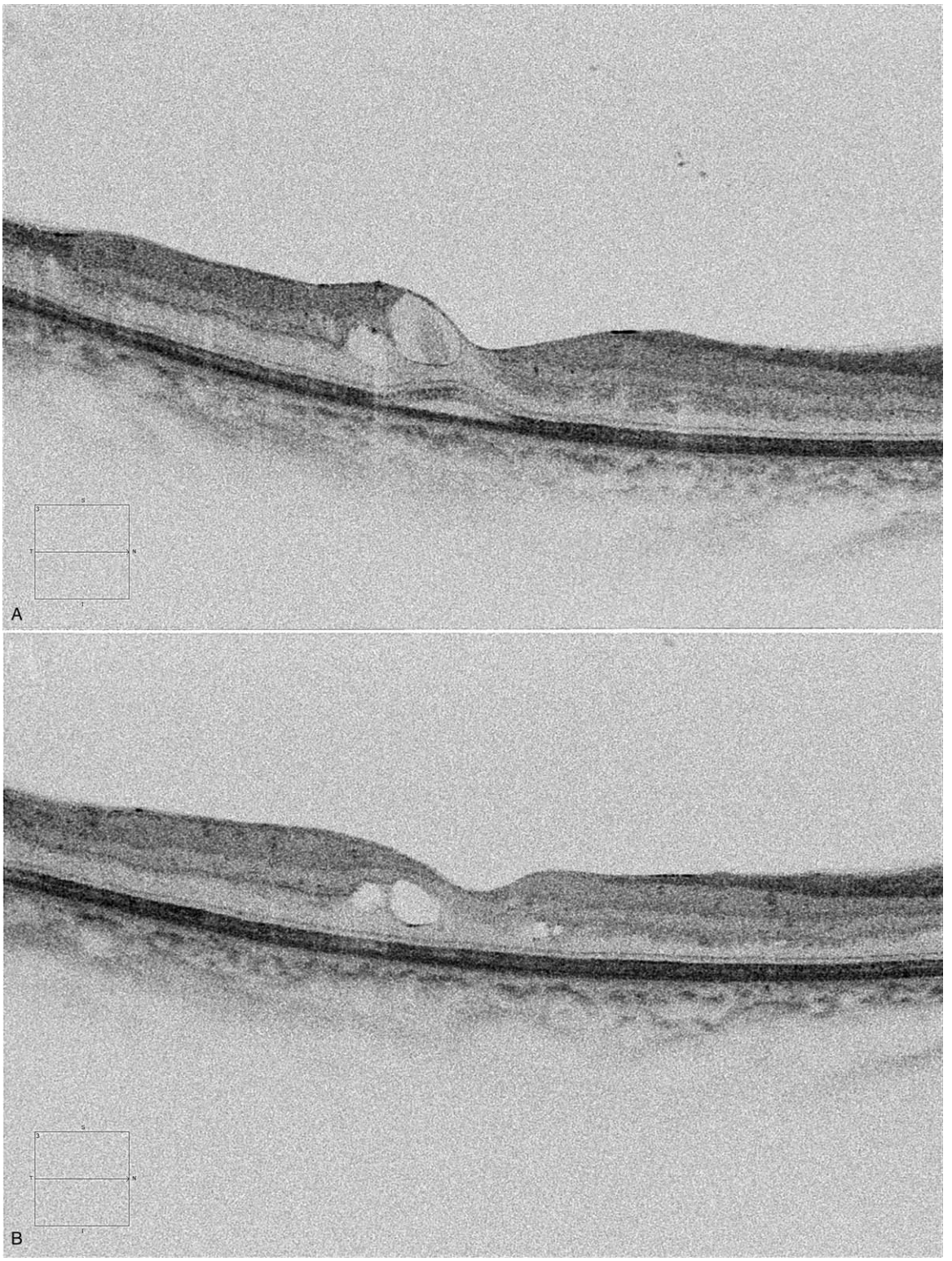

Figure 1. A representative patient who had diabetic macular edema (DME) with a serous retinal detachment (SRD) pattern. (A) The baseline spectral domain-optical coherence tomography image shows center-involving DME with an SRD pattern. (B) After 3 consecutive intravitreal bevacizumab injections, the SRD pattern disappeared and the DME decreased.

treatment and the levels of these biomarkers.[19] We suggest that aqueous humor samples can be used to identify the major mechanisms of DME. Our results could be useful in selecting appropriate treatments or predicting the prognoses of patients.

There is a consensus that the subretinal fluid in DME is resolved with anti-VEGF treatment,[10] but the prognosis regarding BCVA and CST is controversial. Some studies have reported that SRD patients showed better responsiveness or

prognoses in CST reduction or BCVA improvement with anti-VEGF treatments,[10,36,37] but others have reported no better responsiveness with the same treatments.[11,14] The mechanisms of SRD are also controversial. In contrast to our results, some studies have reported that there is an association between SRD and inflammation[12,38] and that steroid implants can result in a positive response.[39,40] On the other hand, other studies have shown that there is an association between systemic status or glycemic control and SRD.[41,42] Although there was no remaining SRD after 3 consecutive IVBs in all patients in the SRD group (Fig. 1), the degree of CST reduction in these patients did not differ from that of the DME patients without SRD in our study, and we did not detect a difference in glycated hemoglobin levels between the 2 groups. As the mechanism of DME is complicated and there is a lack of studies about the responsiveness of DME, more investigations and studies are needed to clarify the origin and responsiveness of SRD in DME.

Our study had some limitations. First, our sample size was relatively small and the follow-up duration was short. The aqueous levels showed no significant difference in SRD group may be attributable to the small number of control patients. We also judge that there is significantly higher ratio of women in SRD group by chance due to small sample size. Long-term changes in CST and BCVA must be evaluated with the treatments. In addition, although we made an effort to statistically factor in the systemic and ocular status of patients, other factors we did not consider might have affected our results. Second, the relationships between cytokine levels and other imaging techniques like fluorescein angiography or OCT angiography should be studied in terms of DME pathogenesis.[8]

In summary, the occurrence of SRD was associated with VEGF levels. Additional studies with more patients are required to confirm our results and to elucidate the pathogenesis of DME, which may provide the basis for novel therapeutic approaches.

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