Original Article

Comparison of aqueous concentrations of angiogenic and inflammatory cytokines based on optical coherence tomography patterns of diabetic macular edema

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Purpose: The purpose was to compare aqueous inflammatory and angiogenic cytokine levels in diabetic macular edema (DME). **Materials and Methods:** Aqueous samples were obtained from 50 eyes with DME and 12 normal eyes (control group). DME was classified according to the morphologic pattern based on optical coherence tomography: Diffuse retinal thickening (DRT; $n = 19$), cystoid macular edema (CME; $n = 17$), or serous retinal detachment (SRD; $n = 14$). Aqueous samples were collected just before intravitreal injection and at the beginning of cataract surgery in the control group. Interleukin (IL)-6, IL-8, interferon-induced protein (IP)-10, monocyte chemotactic protein (MCP)-1, platelet-derived growth factor (PDGF)-AA, and vascular endothelial growth factor (VEGF) levels were measured by multiplex bead assay. **Results:** The IL-6, IL-8, IP-10, and PDGF-AA levels differed significantly among the three groups of DME ($P = 0.014$, $P = 0.038$, $P = 0.021$, and $P = 0.041$, respectively). However, there were no differences between groups in aqueous concentration levels of MCP-1 and VEGF ($P = 0.205$ and $P = 0.062$, respectively). IL-6 ($P = 0.026$) and IL-8 ($P = 0.023$) correlated positively with central foveal thickness (CFT) in the CME group. None of the cytokine levels correlated significantly with CFT in any of the DRT and SRD groups. **Conclusions:** Aqueous concentrations of cytokines varied according to the morphologic pattern of DME, which might explain the variable response to treatments such as intravitreal bevacizumab or triamcinolone injection.

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.158069

Quick Response Code:

Key words: Cytokine, diabetic macular edema, optical coherence tomography

Diabetes mellitus (DM) is a globally epidemic disease with significant morbidity.[1] Diabetic retinopathy affects one in three persons with DM,[2] and the leading cause of vision loss is diabetic macular edema (DME). DME is caused by a breakdown of the blood-retinal barrier and the leakage of intraretinal fluid from abnormal retinal capillaries and microaneurysms.[3,4] The retinal changes induced by DM lead to ischemia and upregulation of angiogenic factors in the retina.

Cytokines are the classic mediators of inflammation and thus have been hypothesized to play a role in the development of DME. Vascular endothelial growth factor (VEGF) is a well-known potent angiogenic factor that is involved in the increased vascular permeability leading to macular edema and induces retinal neovascularization. Previous studies demonstrated that VEGF plays a major role in increasing vascular permeability in diabetic eyes[5-7] and that vitreous levels of VEGF, interleukin (IL)-6, IL-8, and monocyte chemotactic protein (MCP)-1 are related to DME.[8,9] Among the treatments available for DME, intravitreal injections of triamcinolone acetonide and anti-VEGF have proven to be safe, effective, and visually and anatomically beneficial in patients with DME.[10,11] The degree of improvement, however, varies. A few recently published studies about the effect of intravitreal bevacizumab injection based on the DME pattern demonstrated that intravitreal bevacizumab was more effective for the diffuse retinal thickening (DRT) type than in the other types of DME.[12,13] The mechanisms underlying these findings, however, have not been elucidated.

In the present study, DME was classified into three different patterns, as previously reported,[12,13] that is, DRT, cystoid macular edema (CME), and serous retinal detachment (SRD). To our knowledge, this study is the first to investigate the aqueous cytokine levels based on optical coherence tomography (OCT) patterns of DME. We designed a prospective study to compare the aqueous levels of inflammatory (IL-6, IL-8, interferon-induced protein [IP]-10, MCP-1, platelet-derived growth factor [PDGF]-AA), and angiogenic (VEGF) factors among the three different patterns of DME.

Materials and Methods

We conducted a prospective study of patients with DME between March 2012 and December 2012. Inclusion criteria were (1) age over 18 years with DME; (2) central foveal thickness (CFT) of at least 250 μm, as documented on OCT; (3) no previous intravitreal bevacizumab injection; or (4) only one intravitreal injection of 1.25 mg of bevacizumab at least 8 weeks before treatment of DME with recurrence of ME revealed by OCT. Exclusion criteria were (1) ocular disease other than diabetic retinopathy and cataracts, (2) previous ocular surgery other than cataract surgery, and (3) cataract surgery or intravitreal triamcinolone injection within 6 months

This study was supported by 2012 Research Grant from Kangwon National University.

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Manuscript received: 12.11.14; Revision accepted: 27.04.15

or laser photocoagulation within 3 months before entry into the study. A total of 50 aqueous humor samples from 50 DM patients and 12 controls were collected. The control group comprised patients who had undergone cataract surgery without a history of other ocular or systemic diseases. Approval for this retrospective review was obtained from the Institutional Review Board of our institution. A written informed consent was obtained from all the patients enrolled in this study. All patients received a complete ocular examination, including best-corrected visual acuity testing, intraocular pressure measurements, dilated fundus examination with slit lamp biomicroscopy, color fundus photography. CFT was measured with OCT (Cirrus HD-OCT, Carl Zeiss Meditec Inc., Dublin, CA, USA) using macular cube scans.

Optical coherence tomography scans were performed through dilated pupils. A macular cube 512 × 128 scan by Cirrus HD-OCT was performed to measure retinal thickness at the central fovea and classify DME according to the morphologic pattern. The macular cube 512 × 128 scan comprises 128 raster scans with 512 A-scans within a 6 mm × 6 mm macular area. DME was classified into three patterns, as follows [Fig. 1]. The DRT group was characterized by a sponge-like retinal swelling of the macula with reduced intraretinal reflectivity. The CME group was characterized by intraretinal cystoid spaces of low reflectivity with highly reflective septa separating cystoid-like cavities in the macular area. The SRD group was characterized by a shallow elevation of the retina, and an optically clear space between the retina and the retinal pigment epithelium. Our definition of DRT allowed for only pure DRT. If DRT was combined with CME or SRD, the pattern was classified as either CME or SRD, respectively; and when DRT, CME, and SRD were all present, the pattern was classified as SRD. Classification disagreements were resolved by open discussion. Patients were excluded if all three observers (MK, YUK, and SJL) did not agree on the same classification. CFT was defined as the mean retinal thickness in a 1-mm diameter circular zone centered on the fovea.

Undiluted aqueous samples (50–100 µl) were harvested just before intravitreal triamcinolone acetonide or bevacizumab injections in the DME group, and at the beginning of cataract surgery in the control group. Two retinal specialists (MK and SJL) obtained all samples under sterile conditions in the operating room. Aqueous humor was withdrawn through a limbal paracentesis site using a 30-gauge needle with a tuberculin syringe. Special care was taken to avoid touching the intraocular tissues and to prevent mixing of aqueous samples with other fluids. The specimens were immediately transferred to a sterile plastic tube and stored at −70°C until assayed. IL-6, IL-8, IP-10, MCP-1, PDGF-AA, and VEGF were measured in aqueous samples by the Luminex 100 multiplex array assay (Luminex Corporation, Austin, TX, USA).[14-16]

All data were collected in a Microsoft Excel 2007 spreadsheet. The results were expressed as the mean value, the median value, and the interquartile range. Statistical analyses were performed using a commercially available statistical software package (SPSS ver. 16.0; SPSS Inc., Chicago, IL, USA). Mann–Whitney U and Kruskal–Wallis Tests (nonparametric analysis of variance) were used to analyze the different cytokine concentrations between groups, and the Fisher exact test was used to compare noncontinuous variables. The data were analyzed through repeated-measures analysis of variance with a Bonferroni correction. To assess the relationship between cytokines and CFT, Spearman's rank-order correlation coefficients were calculated. A ($P < 0.05$) was considered statistically significant.

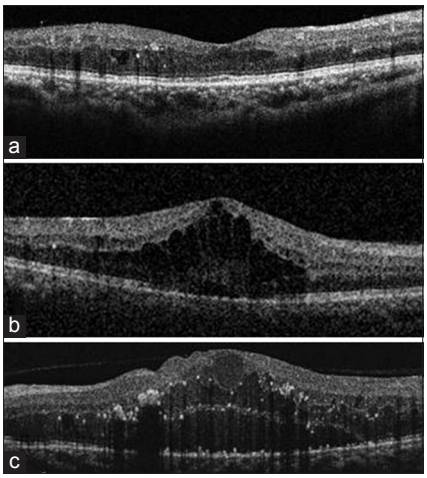

Figure 1: Three different patterns of diabetic macular edema determined based on optical coherence tomography. (a) Diffuse retinal thickening appears as a sponge-like retinal swelling with areas of reduced intraretinal reflectivity. (b) Cystoid macular edema exhibits intraretinal cystoid spaces. (c) Serous retinal detachment is associated with shallow elevation of the retina, and an optically clear space between the retina and the retinal pigment epithelium

Results

Fifty eyes of 50 patients were enrolled. Patient characteristics are summarized in Table 1. DRT was present in 19 eyes (38%), CME in 17 (34%), and SRD in 14 (28%). The baseline characteristics of each group based on the OCT pattern were not significantly different (Kruskal–Wallis Test): Age ($P = 0.434$), sex ($P = 0.664$), and best-corrected visual acuity ($P = 0.142$).

Aqueous concentrations of angiogenic and inflammatory cytokines in the three types of DME and control groups are shown in Table 2. The DME group showed significantly higher levels of IL-6 ($P < 0.001$), IL-8 ($P < 0.001$), IP-10 ($P < 0.001$), MCP-1 ($P < 0.001$), and VEGF ($P < 0.001$) compared with the control group. However, the PDGF-AA ($P = 0.055$) levels did not differ significantly between the DME and control groups.

The median aqueous humor level (interquartile range) of IL-6 was 39.4 pg/ml (17.1–60.0 pg/ml) in DRT group, 20.9 pg/ml, (12.2–43.3 pg/ml) in CME group, and 47.1 pg/ml, (41.1–71.0 pg/ml) in the SRD group. IL-6 levels were significantly different among the groups [Fig. 2] ($P = 0.014$). The SRD group had significantly higher levels of IL-6 compared with the CME group ($P = 0.002$). There was no difference, however, between the DRT group and CME group ($P = 0.156$), or between the DRT group and SRD group ($P = 0.152$).

The median aqueous humor level of IL-8 was 21.0 pg/ml (15.0–26.5 pg/ml) in DRT group, 29.5 pg/ml (21.7–34.7 pg/ml) in CME group, and 31.8 pg/ml (24.0–41.3 pg/ml) in the SRD group. IL-8 levels were significantly different among the groups [Fig. 3] ($P = 0.038$). The CME and SRD groups had significantly higher levels of IL-8 than the DRT group ($P = 0.023$ and 0.012, respectively).

Table 1: Patient background information in the three DME groups

	Control group (*n*=12)	DME group			*P* value	
		DRT group (*n*=19)	CME group (*n*=17)	SRD group (*n*=14)	Among 4 groups	Among 3 (DME) groups
Age (years)	66.6±8.0	66.5±10.3	62.4±7.9	65.0±10.2	0.602	0.434
Sex (male/female)	7/5	11/8	8/9	6/8	0.780	0.664
DM duration (years)	-	11.2	11.2	15.9	-	0.035
BCVA (logMAR)	-	0.52	0.65	0.8	-	0.142
CFT (μm)	-	393.2	503.4	598.7	-	<0.001
Type of diabeties (type 1/type 2)	-	5/14	5/12	5/9	-	0.844
Insulin use (no/yes)	-	13/6	11/6	9/5	-	0.961
Stage (NPDR/PDR)	-	10/9	7/10	5/9	-	0.600
HbA1C (%)	-	7.28	7.42	7.5	-	0.325
History of focal laser photocoagulations (no/yes)	-	14/5	7/10	6/8	-	0.091
History of panretinal photocoagulations (no/yes)	-	9/10	8/9	5/9	-	0.763

DME: Diabetic macular edema, DRT: Diffuse retinal thickening, CME: Cystoid macular edema, SRD: Serous retinal detachment, DM: Diabetes mellitus, BCVA: Best corrected visual acuity, CFT: Central foveal thickness, NPDR/PDR: Nonproliferative diabetic retinopathy/Proliferative diabetic retinopathy

Table 2: Aqueous concentrations (pg/ml) of angiogenic and inflammatory cytokines in the three types of DME group and control group

Variable	Control group (*n*=12)	DME group			*P* value		
		DRT group (*n*=19)	CME group (*n*=17)	SRD group (*n*=14)	Control vs DME	Control vs DRT vs CME vs SRD	DRT vs CME vs SRD
IL-6	17.7	39.4	20.9	47.1	<0.001	0.001	0.014
IL-8	10.8	21.0	29.5	31.8	<0.001	<0.001	0.038
IP-10	239.5	390.0	398.0	479.0	<0.001	<0.001	0.021
MCP-1	1166.1	2495.0	3123.2	4211.8	<0.001	<0.001	0.205
PDGF-AA	71.7	68.3	77.7	86.5	0.055	0.004	0.041
VEGF	38.4	68.5	79.2	94.4	<0.001	<0.001	0.062

MCP: Monocyte chemotactic protein, PDGF: Platelet-derived growth factor, VEGF: Vascular endothelial growth factor, DME: Diabetic macular edema, DRT: Diffuse retinal thickening, SRD: Serous retinal detachment, CME: Cystoid macular edema

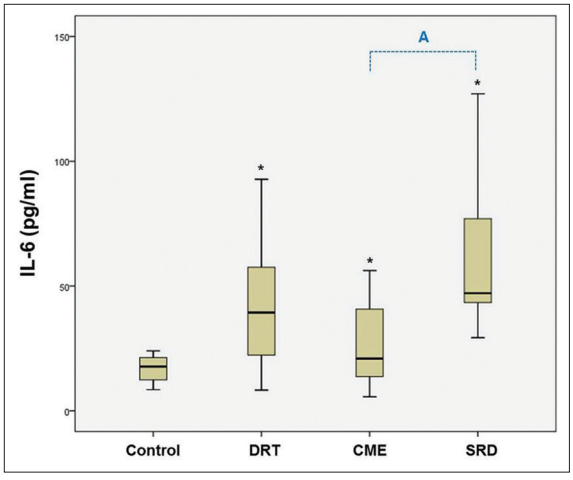

Figure 2: Aqueous levels of interleukin (IL)-6 in each of the three diabetic macular edema (DME) groups. The levels of IL-6 are significantly higher in three DME groups than in control group (*). The serous retinal detachment (SRD) group had significantly higher levels of IL-6 compared with the cystoid macular edema (CME) group (a, *P* = 0.002). There was no difference, however, between the Diffuse retinal thickening (DRT) group and CME group (*P* = 0.156), or between the DRT group and SRD group (*P* = 0.152)

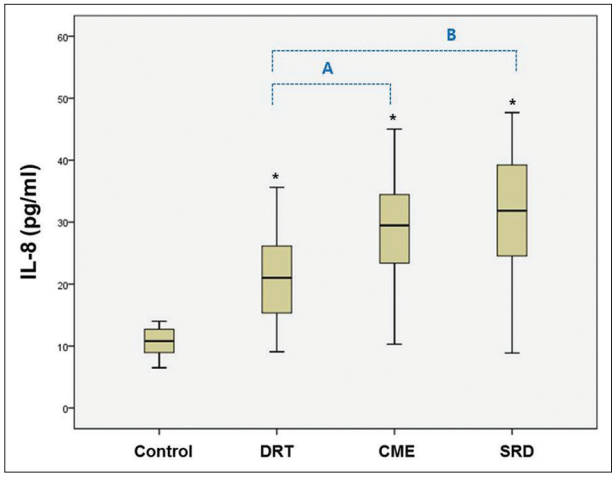

Figure 3: Aqueous levels of interleukin (IL)-8 in each of the three diabetic macular edema (DME) groups. The levels of IL-8 are significantly higher in three DME groups than in control group (*). The cystoid macular edema (CME) and serous retinal detachment (SRD) groups had significantly higher levels of IL-8 than the DRT group (a, *P* = 0.023 and b, *P* = 0.012, respectively). IL-8 levels did not differ significantly between the CME and SRD groups (*P* = 0.570)

IL-8 levels did not differ significantly between the CME and SRD groups ($P = 0.570$).

The median aqueous humor level of IP-10 was 390.0 pg/ml (294.0–459.0 pg/ml) in DRT group, 398.0 pg/ml (339.0–488.0 pg/ml) in CME group, and 479.0 pg/ml (433.0–770.8 pg/ml) in the SRD group. IP-10 levels were significantly different among the groups [Fig. 4] ($P = 0.021$). The SRD group had significantly higher IP-10 levels than the DRT group ($P = 0.007$). IP-10 levels, however, did not differ significantly between the DRT and CME groups ($P = 0.208$), or between the CME and SRD groups ($P = 0.092$).

The median aqueous humor level of PDGF-AA was 68.3 pg/ml (59.3–86.3 pg/ml) in DRT group, 77.7 pg/ml (72.7–80.9 pg/ml) in CME group, 86.5 pg/ml (70.6–110.6 pg/ml) in the SRD group. PDGF-AA levels were significantly different among the groups [Fig. 5] ($P = 0.041$). The SRD group had significantly higher levels of PDGF-AA than the DRT group ($P = 0.042$). PDGF-AA levels, however, did not differ significantly between the DRT and CME groups ($P = 0.066$), or the CME and SRD groups ($P = 0.128$).

There were no differences between groups in aqueous humor concentration levels of MCP-1 ($P = 0.205$) and VEGF ($P = 0.062$).

The relation of CFT and the aqueous levels of cytokines was analyzed in each group. IL-6 ($P = 0.026$) and IL-8 ($P = 0.023$) correlated positively with CFT in the CME group. None of the cytokine levels, however, correlated significantly with CFT in any of the DRT and SRD groups.

Discussion

According to our study, the level of inflammatory cytokines, such as IL-6, IL-8, IP-10, and PDGA-AA, in the aqueous humor differs depending on the DME pattern. The levels of inflammatory cytokines were higher in the CME or SRD groups than in the DRT group.

Several previous studies have investigated intraocular cytokine levels in patients with DME.[17-19] Recently, Sonoda *et al*., reported the relationship between the retinal morphologic changes and concentrations of intravitreal cytokines in eyes with DME.[20] To our knowledge, however, this is the first study to compare the aqueous inflammatory and angiogenic cytokine levels with respect to three different morphologic patterns of DME (DRT, CME, and SRD) classified using OCT.

Interleukin-6 is a cytokine that functions widely throughout the inflammatory cascade and is known to induce acute phase reactions and increase vascular permeability.[21] IL-6 is produced by a variety of cells, including fibroblasts, monocytes, T or B lymphocytes, vascular endothelial cells, and glial cells. Several studies have reported a role for IL-6 in inflammation in DME.[17-19] In our study, aqueous IL-6 levels were significantly higher in the SRD group than in the CME group, which may indicate that the role of inflammation in SRD is more influential than in CME. Sonoda *et al*., reported that the significant association of SRD with intravitreal IL-6 indicates that inflammation may play an important role in the development of SRD in DME.[20] Although the pathogenesis of SRD remains unclear, the deterioration of retina pigment epithelium function by inflammation or ischemia may cause the accumulation of intraretinal fluid and lead to SRD.[22] IL-6 levels did not differ, however, between the DRT and CME groups, or between the DRT and SRD groups.

Interleukin-8 is a pro-inflammatory and angiogenic cytokine produced by endothelial and glial cells in the ischemic retina.[23] Classically, IL-8 is known as a neutrophil chemotactic factor and T-cell activator in the innate immune system. In our study, aqueous IL-8 levels were significantly different among the four groups, with DRT, CME, and SRD groups having higher levels than the control group. Among the three DME groups, the CME and SRD groups had significantly higher levels of IL-8 than the DRT group. The DRT observed on OCT images appeared

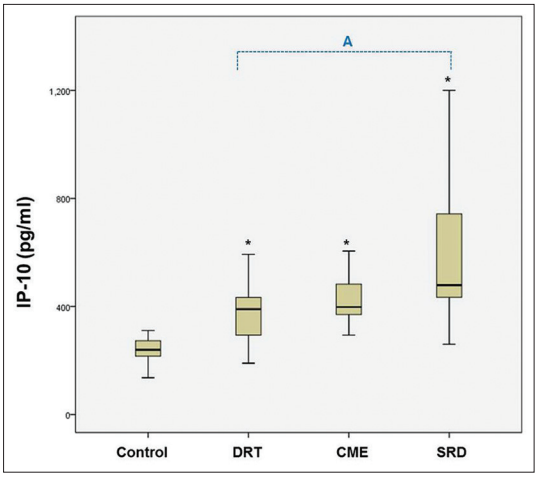

Figure 4: Aqueous levels of interferon-induced protein (IP)-10 in each of the three diabetic macular edema (DME) groups. The levels of IP-10 are significantly higher in three DME groups than in control group (*). The serous retinal detachment (SRD) group had significantly higher IP-10 levels than the Diffuse retinal thickening (DRT) group (a, $P = 0.007$). IP-10 levels, however, did not differ significantly between the DRT and cystoid macular edema (CME) groups ($P = 0.208$), or between the CME and SRD groups ($P = 0.092$)

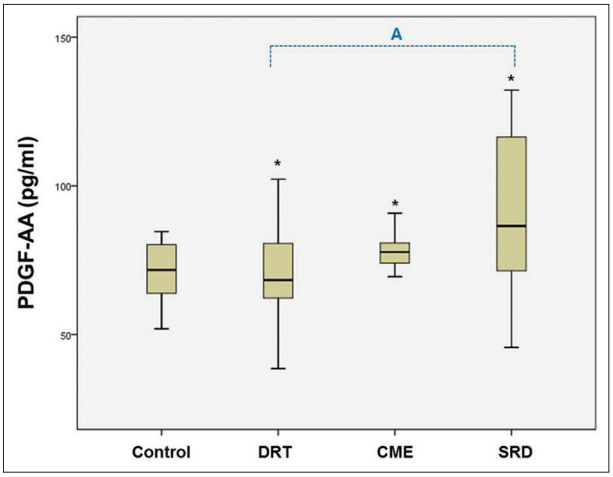

Figure 5: Aqueous levels of platelet-derived growth factor (PDGF)-AA in each of the three diabetic macular edema (DME) groups. The levels of PDGF-AA are significantly higher in three DME groups than in control group (*). The serous retinal detachment (SRD) group had significantly higher levels of PDGF-AA than the diffuse retinal thickening (DRT) group (A, $P = 0.042$). PDGF-AA levels, however, did not differ significantly between the DRT and cystoid macular edema (CME) groups ($P = 0.066$), or the CME and SRD groups ($P = 0.128$)

to reflect the intracytoplasmic swelling of Muller cells.[24] It is known that Muller cell cause diffuse thickening as the ability to eliminate fluid from retinal tissue decreases. Intracytoplasmic swelling of Muller cells due to ischemia results in cytotoxic edema.[25,26] Cytotoxic edema may progress to vasogenic edema with a subsequent release of a permeability disturbing substances, such as cytokines and VEGF from the ischemic retina.[27,28] Chronic macular edema leads to liquefaction necrosis of the Muller cells, which forms cystoid cavities leading to CME. Based on the IL-8 levels, this finding may indicate that the role of ischemia is more influential in CME than in DRT.

Interferon-induced protein (IP)-10 is induced in a variety of cells in response to interferon-γ and lipopolysaccharide. It promotes chemoattraction for monocytes and T lymphocytes but lacks the neutrophil chemoattractant and angiogenic properties of IL-8.[29] Earlier studies described elevated vitreous levels of IP-10 in patients with PDR.[30] In the present study, IP-10 levels were significantly higher in the three DME groups compared with the control group.

Monocyte chemotactic protein-1 is a chemotactic chemokine that induces monocyte and macrophage infiltration into tissue.[31,32] Hernandez *et al*., reported the increase of aqueous MCP-1 concentration among the diabetic retinopathy and according to its progression.[33] Some studies report that aqueous levels of MCP-1 are higher in eyes with DME compared with normal controls.[18,34] Our results are consistent with these previous studies, indicating that MCP-1 might have a role in DME. The aqueous MCP-1 levels, however, did not differ significantly among the three DME groups. Since the diabetic retinopathy progression does not always proportional to the severity of DME, this possibility could not differ from the three DME groups, as in the present study. *In vivo* angiogenesis assays show that MCP-1 induced angiogenesis is as potent as that induced by VEGF.[31] Previous studies showed that the angiogenic effects of MCP-1 are completely inhibited by a VEGF inhibitor, suggesting that MCP-1 induced angiogenesis is mediated through pathways involving VEGF.[31]

The platelet-derived growth factor is one of the most ubiquitous growth factors that stimulates cellular proliferation and directs cellular movement. Two different PDGF chains exist, designated as PDGF A and PDGF B, giving rise to three PDGF isoforms: PDGF-AA, -BB. and -AB.[35] Elevated PDGF levels in the vitreous of patients with DME have been previously reported,[36] and Lee *et al*., reported that aqueous levels of PDGF-AA are significantly higher in DME patients than in controls.[33] However, we could not find a significant difference in PDGF-AA aqueous levels between the DME and control groups. This difference could be occurred due to number of total eyes and experimental protocols. In addition, we found a significant difference in PDGF-AA aqueous levels between the SRD and DRT groups.

Vascular endothelial growth factor is an endothelial cell mitogen that induces an increase in vascular permeability and angiogenesis, which potently activate angiogenesis, enhance collateral vessel formation, and increase the permeability of the microvasculature. In agreement with previous studies,[37-39] VEGF concentration was elevated in the aqueous humor of patients with DME. Funatsu *et al*., reported that the aqueous level of VEGF correlates with the severity of macular edema graded by morphology.[37] They classified the morphology of macular edema as focal or cystoid, with the latter representing a more severe type of macular edema. Our results, however, are not consistent with this previous study. Aqueous VEGF levels did not differ significantly among the three DME groups. This finding, however, could be due to the relatively small sample size in the present study.

The results of several recently reported studies comparing the treatment effects of intravitreal triamcinolone acetonide and intravitreal bevacizumab in DME were consistent with our findings. Kim *et al*., reported that intravitreal injection of bevacizumab was more effective in the DRT type than in the CME or SRD types of DME.[12] The pathogenesis of CME and SRD is related to prostaglandin or inflammatory cytokines as well as VEGF,[40,41] so bevacizumab seems to have less of a therapeutic effect in this type because it suppresses only VEGF. Shimura *et al*., reported that adding triamcinolone to suppress prostaglandins and various cytokines have a better therapeutic effect than anti-VEGF treatment.[41]

Our study has several limitations. First, it is not appropriate to assume that a particular cytokine plays a role in pathogenesis based simply upon measurement of elevated aqueous levels. The release of a particular cytokine could be a result of the disease process, and not necessarily be the cause of the disease process. Second, the small sample size might limit the statistical power for detecting differences in the factors that influence the outcomes. Even though we tried to analyze correlations between the levels of cytokine and those of CFT, we did not find any associations, possibly because of the small sample size. Third, the levels of cytokines in the aqueous humor may reflect those in the vitreous fluid; analysis of vitreous fluid would more accurately reflect intraocular cytokine levels. Nevertheless, our study is the first to evaluate aqueous inflammatory cytokines and VEGF measurements based on OCT patterns of DME and might be helpful for predicting the treatment outcome of DME.

In summary, aqueous concentrations of cytokines varied according to the morphologic pattern of DME, which might explain the variable response to treatments such as intravitreal bevacizumab or triamcinolone injection. This study is not sufficient to reach definite conclusions, and to confirm our results, we are planning a study regarding the changes in aqueous humor cytokine levels, followed by the continuous intravitreal anti-VEGF or triamcinolone administration.

References

1. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124-36.
2. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, *et al*. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556-64.
3. Romero-Aroca P. Managing diabetic macular edema: The leading cause of diabetes blindness. World J Diabetes 2011;2:98-104.
4. Singh R, Ramasamy K, Abraham C, Gupta V, Gupta A. Diabetic retinopathy: An update. Indian J Ophthalmol 2008;56:178-88.
5. Selim KM, Sahan D, Muhittin T, Osman C, Mustafa O. Increased levels of vascular endothelial growth factor in the aqueous humor of patients with diabetic retinopathy. Indian J Ophthalmol 2010;58:375-9.
6. Funk M, Schmidinger G, Maar N, Bolz M, Benesch T, Zlabinger GJ, *et al*. Angiogenic and inflammatory markers in the intraocular fluid of eyes with diabetic macular edema and influence of therapy with bevacizumab. Retina 2010;30:1412-9.
7. Funatsu H, Yamashita H, Nakamura S, Mimura T, Eguchi S,

Noma H, *et al.* Vitreous levels of pigment epithelium-derived factor and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology 2006;113:294-301.

8. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. Ophthalmology 2009;116:73-9.
9. Roh MI, Kim HS, Song JH, Lim JB, Kwon OW. Effect of intravitreal bevacizumab injection on aqueous humor cytokine levels in clinically significant macular edema. Ophthalmology 2009;116:80-6.
10. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: Three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. Ophthalmology 2004;111:2044-9.
11. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, *et al.* Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: Results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. Ophthalmology 2007;114:743-50.
12. Kim M, Lee P, Kim Y, Yu SY, Kwak HW. Effect of intravitreal bevacizumab based on optical coherence tomography patterns of diabetic macular edema. Ophthalmologica 2011;226:138-44.
13. Shimura M, Yasuda K, Yasuda M, Nakazawa T. Visual outcome after intravitreal bevacizumab depends on the optical coherence tomographic patterns of patients with diffuse diabetic macular edema. Retina 2013;33:740-7.
14. Ozturk BT, Bozkurt B, Kerimoglu H, Okka M, Kamis U, Gunduz K. Effect of serum cytokines and VEGF levels on diabetic retinopathy and macular thickness. Mol Vis 2009;15:1906-14.
15. Maier R, Weger M, Haller-Schober EM, El-Shabrawi Y, Wedrich A, Theisl A, *et al.* Multiplex bead analysis of vitreous and serum concentrations of inflammatory and proangiogenic factors in diabetic patients. Mol Vis 2008;14:637-43.
16. Sato T, Kusaka S, Shimojo H, Fujikado T. Simultaneous analyses of vitreous levels of 27 cytokines in eyes with retinopathy of prematurity. Ophthalmology 2009;116:2165-9.
17. Oh IK, Kim SW, Oh J, Lee TS, Huh K. Inflammatory and angiogenic factors in the aqueous humor and the relationship to diabetic retinopathy. Curr Eye Res 2010;35:1116-27.
18. Sohn HJ, Han DH, Kim IT, Oh IK, Kim KH, Lee DY, *et al.* Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. Am J Ophthalmol 2011;152:686-94.
19. Suzuki Y, Nakazawa M, Suzuki K, Yamazaki H, Miyagawa Y. Expression profiles of cytokines and chemokines in vitreous fluid in diabetic retinopathy and central retinal vein occlusion. Jpn J Ophthalmol 2011;55:256-63.
20. Sonoda S, Sakamoto T, Yamashita T, Shirasawa M, Otsuka H, Sonoda Y. Retinal morphologic changes and concentrations of cytokines in eyes with diabetic macular edema. Retina 2014;34:741-8.
21. Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology 2003;110:1690-6.
22. Catier A, Tadayoni R, Paques M, Erginay A, Haouchine B, Gaudric A, *et al.* Characterization of macular edema from various etiologies by optical coherence tomography. Am J Ophthalmol 2005;140:200-6.
23. Lee YS, Choi I, Ning Y, Kim NY, Khatchadourian V, Yang D, *et al.* Interleukin-8 and its receptor CXCR2 in the tumour microenvironment promote colon cancer growth, progression and metastasis. Br J Cancer 2012;106:1833-41.
24. Yanoff M, Fine BS, Brucker AJ, Eagle RC Jr. Pathology of human cystoid macular edema. Surv Ophthalmol 1984;28 Suppl: 505-11.
25. Lee DH, Kim JT, Jung DW, Joe SG, Yoon YH. The relationship between foveal ischemia and spectral-domain optical coherence tomography findings in ischemic diabetic macular edema. Invest Ophthalmol Vis Sci 2013;54:1080-5.
26. Hannouche RZ, Avila MP. Detection of diabetic foveal edema with biomicroscopy, fluorescein angiography and optical coherence tomography. Arq Bras Oftalmol 2008;71:759-63.
27. Bringmann A, Uckermann O, Pannicke T, Iandiev I, Reichenbach A, Wiedemann P. Neuronal versus glial cell swelling in the ischaemic retina. Acta Ophthalmol Scand 2005;83:528-38.
28. Coscas G, Cunha-Vaz J, Soubrane G. Macular edema: Definition and basic concepts. Dev Ophthalmol 2010;47:1-9.
29. Ide N, Hirase T, Nishimoto-Hazuku A, Ikeda Y, Node K. Angiotensin II increases expression of IP-10 and the renin-angiotensin system in endothelial cells. Hypertens Res 2008;31:1257-67.
30. Praidou A, Klangas I, Papakonstantinou E, Androudi S, Georgiadis N, Karakiulakis G, *et al.* Vitreous and serum levels of platelet-derived growth factor and their correlation in patients with proliferative diabetic retinopathy. Curr Eye Res 2009;34:152-61.
31. Hong KH, Ryu J, Han KH. Monocyte chemoattractant protein-1-induced angiogenesis is mediated by vascular endothelial growth factor-A. Blood 2005;105:1405-7.
32. Kim MY, Byeon CW, Hong KH, Han KH, Jeong S. Inhibition of the angiogenesis by the MCP-1 (monocyte chemoattractant protein-1) binding peptide. FEBS Lett 2005;579:1597-601.
33. Hernández C, Segura RM, Fonollosa A, Carrasco E, Francisco G, Simó R. Interleukin-8, monocyte chemoattractant protein-1 and IL-10 in the vitreous fluid of patients with proliferative diabetic retinopathy. Diabet Med 2005;22:719-22.
34. Lee WJ, Kang MH, Seong M, Cho HY. Comparison of aqueous concentrations of angiogenic and inflammatory cytokines in diabetic macular oedema and macular oedema due to branch retinal vein occlusion. Br J Ophthalmol 2012;96:1426-30.
35. Fekete N, Gadelorge M, Fürst D, Maurer C, Dausend J, Fleury-Cappellesso S, *et al.* Platelet lysate from whole blood-derived pooled platelet concentrates and apheresis-derived platelet concentrates for the isolation and expansion of human bone marrow mesenchymal stromal cells: Production process, content and identification of active components. Cytotherapy 2012;14:540-54.
36. Praidou A, Papakonstantinou E, Androudi S, Georgiadis N, Karakiulakis G, Dimitrakos S. Vitreous and serum levels of vascular endothelial growth factor and platelet-derived growth factor and their correlation in patients with non-proliferative diabetic retinopathy and clinically significant macula oedema. Acta Ophthalmol 2011;89:248-54.
37. Funatsu H, Yamashita H, Noma H, Mimura T, Yamashita T, Hori S. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. Am J Ophthalmol 2002;133:70-7.
38. Abcouwer SF. Angiogenic Factors and Cytokines in Diabetic Retinopathy. J Clin Cell Immunol 2013;Suppl 1:1-12.
39. Cheung CM, Vania M, Ang M, Chee SP, Li J. Comparison of aqueous humor cytokine and chemokine levels in diabetic patients with and without retinopathy. Mol Vis 2012;18:830-7.
40. Alkuraya H, Kangave D, Abu El-Asrar AM. The correlation between optical coherence tomographic features and severity of retinopathy, macular thickness and visual acuity in diabetic macular edema. Int Ophthalmol 2005;26:93-9.
41. Shimura M, Nakazawa T, Yasuda K, Shiono T, Iida T, Sakamoto T, *et al.* Comparative therapy evaluation of intravitreal bevacizumab and triamcinolone acetonide on persistent diffuse diabetic macular edema. Am J Ophthalmol 2008;145:854-61.

Cite this article as: Kim M, Kim Y, Lee SJ. Comparison of aqueous concentrations of angiogenic and inflammatory cytokines based on optical coherence tomography patterns of diabetic macular edema. Indian J Ophthalmol 2015;63:312-7.

Source of Support: Nil. **Conflict of Interest:** None declared.