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.

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.³⁴ 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 eyes⁵⁻⁷ and that vitreous levels of VEGF, interleukin (IL)-6, IL-8, and monocyte chemotactic protein (MCP)-1 are related to DME.⁸⁻¹⁰ 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.¹¹⁻¹³ 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.
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).

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.

### 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).
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, and 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 PDGAA-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.[15,19] 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

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**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)
Cytotoxic edema may progress to vasogenic edema with the latter representing a more severe type of macular edema. In agreement with previous studies, we found a significant difference in PDGF-AA aqueous levels and control groups. This difference could be occurred due to difference in PDGF-AA aqueous levels between the DME and control groups. 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. Hernandez et al., reported the increase of aqueous MCP-1 concentration among the diabetic retinopathy and according to its progression. Some studies report that aqueous levels of MCP-1 are higher in eyes with DME compared with normal controls. 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 present in the study. In vivo angiogenesis assays show that MCP-1 induced angiogenesis is as potent as that induced by VEGF. 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.

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. Elevated PDGF levels in the vitreous of patients with DME have been previously reported, and Lee et al., reported that aqueous levels of PDGF-AA are significantly higher in DME patients than in controls. 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 the vessel formation. 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 microvascular permeability. In agreement with previous studies, 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. 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. The pathogenesis of CME and SRD is related to prostaglandin or inflammatory cytokines as well as VEGF. Shimura et al., reported that adding triamcinolone to suppress prostaglandins and various cytokines have a better therapeutic effect than anti-VEGF treatment.

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.

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