Association of Aqueous Humor Cytokines With the Development of Retinal Ischemia and Recurrent Macular Edema in Retinal Vein Occlusion

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PURPOSE. We evaluated the association of angiogenic and inflammatory cytokine levels in the aqueous humor with development of retinal ischemia and recurrent macular edema in retinal vein occlusion (RVO) patients.

METHODS. This was a retrospective cross-sectional study, and patients with RVO (n = 41) and age-matched control subjects (n = 25) were included. The concentrations of angiogenic and inflammatory cytokines, including VEGF, PDGF-AA, IL-1α, IL-6, IL-8, MCP-1, TNF-α, and IP-10, in the aqueous humor were measured before intravitreal injection of bevacizumab using suspension array technology. After retinal hemorrhage disappeared, fluorescein angiography (FA) images were obtained. Based on FA data, RVO patients were divided into a nonischemic group and an ischemic group. We investigated the presence of recurrent macular edema using optical coherent tomography (OCT) during the follow-up period. We compared the levels of cytokines between RVO patients and control subjects, between nonischemic and ischemic groups, and between patients with and without recurrent macular edema.

RESULTS. The levels of VEGF, PDGF-AA, IL-1α, IL-6, IL-8, MCP-1, TNF-α, and IP-10 in the aqueous humor were significantly higher in the ischemic RVO group than in the control group. The levels of IL-8, PDGF-AA, TNF-α, and VEGF in the aqueous humor were significantly higher in the ischemic RVO group than in the nonischemic RVO group. We did not observe any association between cytokine levels and recurrent macular edema.

CONCLUSIONS. Angiogenic and inflammatory cytokines were overexpressed in RVO patients. Additionally, increased levels of IL-8, PDGF-AA, TNF-α, and VEGF in the aqueous humor at the onset of RVO were associated with the development of future retinal ischemia in RVO patients.

Keywords: aqueous humor, cytokines, retinal vein occlusion, retina ischemia

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy,1,2 and is characterized by vascular obstruction leading to intraretinal hemorrhage, fluid exudation, and varying degrees of retinal ischemia. The RVOs are classified as central RVOs (CRVOs), hemiretinal vein occlusions, and branch RVOs (BRVOs).3 The RVO often results in macular edema (ME), which is the main cause of visual impairment in patients with RVO. A common cause for visual impairment, secondary to macular edema, is vitreous hemorrhage caused by new vessel formation resulting from retinal ischemia.4

The pathogenesis of ME in RVO is known to be complex. Vascular damage is accompanied by complex cellular and inflammatory reactions, which include vascular dysfunction, damage to the blood–retinal barrier, and release of several angiogenic and inflammatory mediators.5 The balance of angiogenic and inflammatory mediators has been reported to be disturbed in the ocular fluid in RVO.6–9 Previous reports showed no correlation between cytokine levels in the aqueous humor and plasma7,10, thus, providing evidence that the source of these cytokines is intraocular. The role of inflammation in RVO is supported by some reports that intraocular and periocular steroid treatments reduce ME in patients with RVO.11–15 Retinal hypoxia has been implicated in the pathogenesis of ME secondary to RVO. Hypoxia causes increased expression of VEGF, a potent mediator of vascular permeability, which causes vascular leakage.5 Several studies have demonstrated the efficacy of intravitreally injected anti-VEGF agents, for example, bevacizumab (IVB), for treatment of ME caused by RVO.14,15 Many studies have evaluated the profiles of various cytokines in intraocular fluid,10,16 the relationship between intraocular cytokine levels and macular edema,7,17 and the association between cytokine concentrations and the effect of anti-VEGF therapy18,19 in RVO patients.

Although ME is the main reason for visual impairment in RVO patients, neovascularization caused by retinal ischemia also leads to visual impairment as a late complication of RVO, and results in vitreous hemorrhage and neovascular glaucoma (NVG). There are no predictive indicators for late complications caused by retinal ischemia, such as vitreous hemorrhage and NVG. Therefore, our study evaluated the relationship of various cytokines at the onset of RVO, and the development of future retinal ischemia and recurrent ME in RVO patients.
Aqueous Humor Cytokines in RVO (Ischemic or Nonischemic)

METHODS

This study was conducted retrospectively at the Department of Ophthalmology at Gangneung Asan Hospital. The protocol used in this study was approved by the Institutional Review Board of Gangneung Asan Hospital (#2013-012), and the study was conducted in accordance with the procedure outlined in the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research.

Study Subjects

We included patients who were treated with IVB from November 2011 to December 2012 for ME secondary to RVO (including BRVO and CRVO). The IVB was used as first-line therapy for ME secondary to RVO. Informed consent was obtained from the patients in accordance with the tenets of the Declaration of Helsinki. In total, 71 eyes of 71 patients with ME associated with RVO were treated with IVB during this period. Complete ophthalmic examinations were performed before IVB, including a best-corrected visual acuity (BCVA) test, slit-lamp examination, fundus examination, and measurement of IOP by Goldmann applanation tonometry. The BCVA was measured using a Snellen chart and converted to the logarithm of the minimum angle of resolution for comparison. Optical coherent tomography (OCT, Stratus; Zeiss Humphrey, San Leandro, CA, USA) also was performed.

After topical anesthesia under sterile conditions, a 26-gauge needle was inserted through the corneal limbus to withdraw 0.05 mL of aqueous humor and soften the globe. Immediately, 1.25 mg (0.05 mL) of bevacizumab was injected intravitreally at 3.5 mm from the limbus using a 30-gauge needle. The aqueous humor samples were collected in sterile tubes and immediately stored at −80°C in a deep freezer. Reference samples were obtained from age-matched patients undergoing cataract surgery. The exclusion criteria for the controls included a history of diabetes mellitus, other retinal disease, glaucoma, previous ocular surgery, laser coagulation, and recent history of any medications. We collected aqueous humor samples during cataract surgery by paracentesis. The aqueous humor samples were stored as described above.

Follow-up examinations were conducted at 1 day, 1 week, and 6 weeks after injection. At 6 weeks after injection, comprehensive ophthalmic examination, including BCVA, slit-lamp, fundus, IOP, and OCT analyses, was performed. The IVB was repeated based on the ME status according to OCT. When retinal hemorrhage decreased or was absorbed, fluorescein angiography (FA, Topcon TRC-50IX; Topcon, Tokyo, Japan) and OCT (Stratus; Zeiss Humphrey) examinations were performed. At 6 weeks after injection, the next visit was decided according to the patients’ condition. Patients who had follow-up visits at least 6 months after IVB were included. We included patients in this study if they met the following criteria: less than 2 weeks of impaired visual acuity; ME with OCT (Stratus, Zeiss Humphrey); and follow-up visits at least 6 months after IVB.

Patients were excluded from this study if they did not visit the retinal clinic after injection or if they had a history of pericocular steroid therapy and/or focal/grid laser treatment, high myopia (>-6.0 diopters), systemic or ocular inflammatory disease, a history of ocular surgery, a history of diabetes mellitus, or a history of uncontrolled hypertension.

Among the 71 patients, only 41 eyes of 41 patients met the inclusion criteria and were included in this study. Based on the presence of capillary nonperfusion on FA, the patients were divided into an ischemic group and a nonischemic group (Figs. 1, 2). Based on the presence of recurrent ME during the follow-up period, patients were divided into ME(+) and ME(−) groups. We compared the levels of cytokines in the aqueous humor for these groups.

Measurement of Inflammatory and Angiogenic Cytokines

The samples were analyzed using suspension array technology (xMAP; Luminex Corp., Austin, TX, USA). Capture bead kits (Beadlyte; Upstate Biotechnology, Lake Placid, NY, USA) were used for detection of VEGF, PDGF-AA, IL-1α, IL-6, IL-8, monocyte chemotactic protein-1 (MCP-1), TNF-α, and interferon gamma-induced protein-10 (IP-10). The kits were used according to the manufacturer’s instructions. Standard curves for each cytokine were generated using the reference cytokine concentrations supplied in this kit. All incubation steps were performed at room temperature in the dark. The samples were read on the suspension array system, and control samples were included in all runs.

Statistical Analysis

All data were analyzed using SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL, USA). The Mann-Whitney U test was used to compare the levels of cytokines between the controls and RVO patients, between CRVO and BRVO patients, between ischemic RVO and nonischemic RVO patients, and between ME(+) and ME(−) groups. The Wilcoxon signed rank test was used to assess changes in BCVA and CFT after bevacizumab injection. Spearman’s correlation analysis was used to evaluate the relationship between cytokine levels and central foveal thickness (CFT) or visual acuity.

RESULTS

A total of 41 eyes of 41 consecutive patients (17 men and 23 women) was finally included in this study, and 25 eyes of 25 subjects undergoing cataract surgery served as the controls. The mean age of the patients with RVO (BRVO, 27 eyes; CRVO, 14 eyes) and control patients was 58.6 ± 23.0 and 59.2 ± 6.3 years, respectively (P < 0.05, Table 1).

The mean follow-up period after IVB was 9.9 ± 4.0 months, and there were no notable local or systemic complications related to IVB. The mean baseline BCVA (logarithm of the minimum angle of resolution) was 0.70 ± 0.46, and the baseline CFT was 478.5 ± 124.4 μm. Six weeks after IVB, the mean BCVA improved to 0.40 ± 0.35 (P < 0.001, Wilcoxon signed rank test), and the mean CFT decreased to 256.7 ± 82.6 μm (P < 0.001, Wilcoxon signed rank test).

The concentrations of aqueous humor cytokines in the RVO and control groups are listed in Table 2. The levels of all measured cytokines were significantly higher in the aqueous humor of patients with RVO than in control subjects. The levels of all of the measured cytokines, except IL-1α, were significantly higher in CRVO patients than in BRVO patients.
After the retinal hemorrhage disappeared, FA and OCT examinations were performed in all RVO patients. Based on the FA findings, 27 patients were included in the nonischemic group, and 14 patients were included in the ischemic group, regardless of BRVO or CRVO (Figs. 1, 2).

When RVO patients with and without ischemia were compared, significant differences were found with regard to IL-8, PDGF-AA, TNF-α, and VEGF levels in the aqueous humor (Table 3). The IL-8, PDGF-AA, TNF-α, and VEGF levels were significantly higher in the ischemic group, regardless of RVO type. The levels of IL-6, IP-10, and MCP-1 also were higher in the ischemic group, although these differences did not reach statistical significance.

Although relatively few patients were included in each group, we also evaluated the differences in cytokines between the nonischemic and ischemic group separately for BRVO and

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**Figure 1.** Representative images of BRVO patients. (A) Left eye of a 57-year-old female. Retinal hemorrhage and cotton wool patches were observed at the initial visit (left). Retinal hemorrhage disappeared 4 months after the initial visit (middle), and retinal capillary nonperfusion (retinal ischemia) was observed on FA (right). (B) Left eye of a 57-year-old male. Retinal hemorrhage was present at the initial visit (left). The retinal hemorrhage disappeared 3 months after the initial visit (middle), and there was no visible retinal capillary nonperfusion (retinal ischemia) on FA (right).

**Figure 2.** Representative figures of CRVO patients. (A) Right eye of a 70-year-old female. Retinal hemorrhage and cotton wool patches were present at the initial visit (left). The retinal hemorrhage disappeared 6 months after the initial visit (middle), and retinal capillary nonperfusion (retinal ischemia) was noticed on FA, especially inferiorly (right). (B) Left eye of a 67-year-old male. Retinal hemorrhage was present at the initial visit (left). The retinal hemorrhage disappeared 6 months after the initial visit (middle), and there was no visible retinal capillary nonperfusion (retinal ischemia) on FA (right).
The hypoxic retinal tissue in RVO may release angiogenic mediators, such as VEGF and inflammatory mediators, thereby inducing macular edema, vitreous hemorrhage, and neovascular glaucoma.6,20

In our study, we present evidence of a disturbance in the balance of angiogenic and inflammatory cytokines in the eyes of patients with RVO compared to control subjects. The levels of some of these angiogenic and inflammatory cytokines, such as IL-6, IL-8, MCP-1, and TNF-α, were correlated significantly with initial visual acuity and ME on OCT. These results were similar to those of previous studies.7,10,16,17,21,22

Most previous studies focused on the relationship between cytokines and ME in RVO.19,23,24 However, neovascularization is a late complication of RVO, and leads to vitreous hemorrhage and neovascular glaucoma. In our study, we focused on the relationship between the future ischemic condition and the level of cytokines in the aqueous humor at the onset of RVO. Before starting this study, we postulated that the levels of VEGF and other inflammatory cytokines involved in angiogenesis and/or inflammation would be higher in the ischemic group. In particular, we considered that when RVO occurred, a stronger insult would result in more complete obstruction of the retinal vein and eventually increase the hypoxia in the retina. All the measured cytokines in this study showed higher concentrations in the ischemic group. The levels of IL-8, PDGF-AA, TNF-α, and VEGF were altered significantly. Although the differences were not significant, the concentrations of IL-6 and MCP-1 were much higher in the ischemic group. Moreover, the levels of these cytokines were correlated (Table 6). However, when we evaluated these cytokines in the BRVO and CRVO groups, ischemic BRVO patients showed elevated levels of IL-6, IL-8, MCP-1, PDGF-AA, TNF-α, and VEGF, whereas ischemic CRVO patients showed elevated levels of IL-6, PDGF-AA, TNF-α, and VEGF. Thus, the elevation in cytokine levels differed according to the RVO condition. However, only a few patients were included in each group; therefore, these results are not definite. In cases of ischemia, panretinal photocoagulation was performed in areas with capillary nonperfusion to prevent neovascularization, and no complications were associated with neovascularization during the study period.

The IL-6 is an important proinflammatory cytokine that directly or indirectly induces the production of various other inflammatory cytokines. It also is known to increase vascular permeability and angiogenesis by inducing the expression of VEGF.25 The level of IL-6 was higher in RVO patients than in control subjects, especially in CRVO. The IL-6 also was associated with the development of retinal ischemia in BRVO and CRVO.
TABLE 4. Aqueous Humor Levels (pg/mL) of Angiogenic and Inflammatory Cytokines in BRVO and CRVO (Presence or Lack of Nonperfusion)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nonperfusion, −, n = 17</th>
<th>Nonperfusion, +, n = 10</th>
<th>P Value</th>
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<tr>
<td>IL-1α</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.3</td>
<td>0.334</td>
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<tr>
<td>IL-6</td>
<td>5.9 ± 6.4</td>
<td>6.5 ± 3.6</td>
<td>0.023*</td>
</tr>
<tr>
<td>IL-8</td>
<td>17.6 ± 17.8</td>
<td>46.8 ± 34.1</td>
<td>0.001*</td>
</tr>
<tr>
<td>IP-10</td>
<td>200.7 ± 101.5</td>
<td>325.9 ± 193.8</td>
<td>0.066</td>
</tr>
<tr>
<td>MCP-1</td>
<td>643.1 ± 131.3</td>
<td>758.9 ± 95.5</td>
<td>0.040*</td>
</tr>
<tr>
<td>PDGF-AA</td>
<td>11.9 ± 2.6</td>
<td>14.6 ± 3.7</td>
<td>0.046*</td>
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<tr>
<td>TNF-α</td>
<td>0.2 ± 0.0</td>
<td>0.3 ± 0.1</td>
<td>0.006*</td>
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<tr>
<td>VEGF</td>
<td>123.3 ± 253.3</td>
<td>231.2 ± 334.3</td>
<td>0.059</td>
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<td>IL-1α</td>
<td>0.5 ± 0.5</td>
<td>0.7 ± 0.2</td>
<td>0.188</td>
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<tr>
<td>IL-6</td>
<td>13.8 ± 8.6</td>
<td>73.2 ± 71.2</td>
<td>0.049*</td>
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<tr>
<td>IL-8</td>
<td>50.5 ± 29.6</td>
<td>68.7 ± 30.2</td>
<td>0.049*</td>
</tr>
<tr>
<td>IP-10</td>
<td>458.9 ± 223.8</td>
<td>301.8 ± 258.2</td>
<td>0.436</td>
</tr>
<tr>
<td>MCP-1</td>
<td>798.6 ± 99.9</td>
<td>855.6 ± 43.5</td>
<td>0.374</td>
</tr>
<tr>
<td>PDGF-AA</td>
<td>14.6 ± 3.7</td>
<td>21.7 ± 5.3</td>
<td>0.024*</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.008*</td>
</tr>
<tr>
<td>VEGF</td>
<td>166.4 ± 202.1</td>
<td>743.8 ± 543.6</td>
<td>0.064</td>
</tr>
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</table>

* Statistically significant, Mann-Whitney U test.

The IL-8 has been recognized as a potent chemoattractant, and activator of neutrophils and T-lymphocytes.26 Furthermore, IL-8 has been reported to promote angiogenesis and tumor metastasis.27,28 The level of IL-8 was higher in RVO patients than in control subjects, especially in CRVO. It also was associated strongly with the development of retinal ischemia in BRVO.

Elner et al.29 reported that vitreous levels of IP-10 are higher in patients with inactive proliferative diabetic retinopathy (PDR) than in those with active PDR and suggested that IP-10 may be involved in the regression of PDR. The IP-10 is a potent inhibitor of angiogenesis, because of its inhibition of angiogenic factors.30 In this study, the level of IP-10 was higher in the RVO group, and this increase was associated with retinal ischemia. However, it is possible that this effect represented compensation for overexpression of angiogenic mediators.

The MCP-1 is produced by retinal endothelial cells and has been implicated in leukostasis in hypoxic retinas.31,32 It also has been shown to facilitate angiogenesis.33-35 The level of MCP-1 was higher in RVO patients than in control subjects and also increased in CRVO patients. The level of MCP-1 was associated with the development of retinal ischemia only in BRVO.

The PDGF is a potent mitogen and chemoattractant for the retinal pigment epithelium, and it promotes organogenesis, angiogenesis, and wound healing.35 The PDGF is highly expressed in lesions in many retinal diseases involving retinal pigment epithelial cell migration, such as proliferative vitreoretinopathy, choroidal neovascularization, and PDR. The level of PDGF-AA was higher in RVO patients than in control subjects and greatly increased in CRVO patients. The level of PDGF-AA also was associated with the development of retinal ischemia in BRVO and CRVO.

The TNF-α belongs to the group of proinflammatory cytokines produced by macrophages and T-cells.36 In the eye, TNF-α appears to participate in the pathogenesis of inflammatory, edematous, neovascular, and neurodegenerative diseases.37 The level of TNF-α was higher in RVO patients than in the control group and was associated strongly with the development of retinal ischemia in RVO patients, but not with recurrent ME.

The VEGF is produced by damaged retinal and choroidal cells when abnormal vascular perfusion causes ischemia.38 As expected, the level of VEGF was higher in RVO patients than in control subjects, and this increase was associated with the development of retinal ischemia in RVO patients. Our results are consistent with those of previous reports, and indicated that these angiogenic and inflammatory mediators are involved in RVO, particularly in ischemic RVO. However, we did not find any relationship between the cytokine level at the onset of RVO and the recurrence of ME during the follow-up period.

Our study has several limitations. First, this study was not designed as a controlled prospective study, but as a retrospective study. Second, the number of study participants was small, and the clinical and demographic characteristics of the study participants were not fully documented. Third, the duration of follow-up was limited, and the number of study participants was small. Fourth, the study did not include a control group.

TABLE 5. Aqueous Humor Levels (pg/mL) of Angiogenic and Inflammatory Cytokines in RVO (Presence or Lack of Recurrent Macular Edema)

<table>
<thead>
<tr>
<th>Variables</th>
<th>ME, +, n = 16</th>
<th>ME, −, n = 25</th>
<th>P Value</th>
</tr>
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<tr>
<td>IL-1α</td>
<td>0.4 ± 0.4</td>
<td>0.6 ± 0.4</td>
<td>0.295</td>
</tr>
<tr>
<td>IL-6</td>
<td>7.6 ± 6.7</td>
<td>15.8 ± 32.2</td>
<td>0.724</td>
</tr>
<tr>
<td>IL-8</td>
<td>41.2 ± 31.9</td>
<td>36.6 ± 32.5</td>
<td>0.563</td>
</tr>
<tr>
<td>IP-10</td>
<td>339.7 ± 209.8</td>
<td>265.9 ± 175.8</td>
<td>0.320</td>
</tr>
<tr>
<td>MCP-1</td>
<td>731.9 ± 137.4</td>
<td>720.5 ± 130.0</td>
<td>0.947</td>
</tr>
<tr>
<td>PDGF-AA</td>
<td>13.9 ± 3.9</td>
<td>14.4 ± 4.7</td>
<td>0.822</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.2 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.843</td>
</tr>
<tr>
<td>VEGF</td>
<td>180.5 ± 283.2</td>
<td>226.2 ± 349.7</td>
<td>0.638</td>
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TABLE 6. Correlation Matrix for Aqueous Humor Cytokines

<table>
<thead>
<tr>
<th>Variables</th>
<th>IL-6</th>
<th>IL-8</th>
<th>IP-10</th>
<th>MCP-1</th>
<th>PDGF-AA</th>
<th>TNF-α</th>
<th>VEGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>0.488*</td>
<td>0.002*</td>
<td>0.438*</td>
<td>0.005*</td>
<td>0.282*</td>
<td>0.095*</td>
<td>0.487*</td>
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<td>IL-8</td>
<td>0.791 &lt;0.001*</td>
<td>0.455 0.006*</td>
<td>0.800 &lt;0.001*</td>
<td>0.515 0.001*</td>
<td>0.794 &lt;0.001*</td>
<td>0.595 &lt;0.001*</td>
<td>0.473 0.001*</td>
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<tr>
<td>IP-10</td>
<td>0.487 0.003*</td>
<td>0.779 &lt;0.001*</td>
<td>0.581 &lt;0.001*</td>
<td>0.806 &lt;0.000*</td>
<td>0.666 &lt;0.001*</td>
<td>0.164 0.348</td>
<td>0.577 &lt;0.001*</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.486 0.003*</td>
<td>0.283 0.094</td>
<td>0.559 &lt;0.001*</td>
<td>0.164 0.348</td>
<td>0.556 &lt;0.001*</td>
<td>0.567 &lt;0.001*</td>
<td>0.562 &lt;0.001*</td>
</tr>
</tbody>
</table>

r, correlation coefficient.
* Statistically significant, Spearman correlation test.
Aqueous humor cytokines in RVO (Ischemic or Nonischemic)

aqueous humor, but we did not measure the RVO area. We compared the level of cytokines in ischemic BRVO versus nonischemic BRVO and in ischemic CRVO versus nonischemic CRVO, but the low patient number may have prevented us from obtaining significant results. We included RVO patients with recent onset (less than 2 weeks), but it still is possible that the concentration of cytokines could change during this period. It also is possible that intravitreal anti-VEGF antibody injection may accelerate or modify the development of ischemic lesions. Finally, the follow-up period was not long enough, as there is a possibility that nonischemic RVO may convert to ischemic RVO.

To our knowledge, this study is the first to address the association between aqueous humor levels of cytokines at the onset of RVO and the future development of ischemia in RVO. If a simple method becomes available to measure the levels of cytokines in the aqueous humor, it would aid ophthalmologists in the treatment of RVO patients and the identification of RVO patients who require close follow-up. A future prospective study with a large number of patients is necessary to determine the association between cytokine concentration and the development of retinal ischemia in RVO patients.

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References

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