Molecular Vision 2013; 19:2418-2425 <http://www.molvis.org/molvis/v19/2418>
Received 3 August 2013 | Accepted 22 November 2013 | Published 24 November 2013

Aqueous cytokines as predictors of macular edema in non-diabetic patients following uncomplicated phacoemulsification cataract surgery

Liqun Chu, Bingsong Wang, Bing Xu, Ning Dong

Department of Ophthalmology, Beijing Shijitan Hospital, Capital Medical University, Beijing, People's Republic of China

Purpose: To ascertain whether cytokines in the aqueous humor can predict macular edema (ME) in non-diabetic patients following uncomplicated phacoemulsification cataract surgery.

Methods: Undiluted aqueous humor samples were obtained from 288 consecutive non-diabetic patients (288 eyes; 132 men and 156 women) who underwent cataract surgery. Macular edema was defined as an increase in the foveal center point thickness (FCPT) more than 30% from the preoperative baseline using optical coherence tomography 4 weeks after cataract surgery. The concentrations of 27 cytokines were measured in aqueous humor samples using the multiplex bead immunoassay.

Results: No major intraoperative complications occurred. The incidence of ME was 8.13% (23 patients) 4 weeks after cataract surgery. Compared to the ME (-) patients, the concentrations of interleukin-1β (IL-1β; p=0.016), IL-6 (p=0.013), monocyte chemotactic protein-1 (MCP-1; p=0.030), and vascular endothelial growth factor (VEGF; p=0.033) in the ME (+) patients were significantly higher. In addition, the aqueous humor levels of IL-1β (r=0.376), IL-6 (r=0.418), MCP-1 (r=0.348), and VEGF (r=0.375) positively correlated with the postoperative FCPT. However, the aqueous humor levels of IL-10 (p=0.017) were significantly lower in patients with ME and were negatively correlated with the postoperative FCPT (r=–0.424).

Conclusions: IL-1β, IL-6, MCP-1, VEGF, and IL-10 may be potential predictors of postoperative macular thickness in non-diabetic patients following uncomplicated phacoemulsification cataract surgery.

Cataracts are the most common eye disease that may lead to blindness and severe visual impairment among adults aged 50 years or older in China. More than 5 million cataract operations are performed annually in China, suggesting that cataract extraction is the most frequently performed ophthalmic surgery. At present, the incidence of postoperative complications is decreasing with the development of phacoemulsification and posterior chamber intraocular lens implantation. However, anterior segment inflammation and macular edema (ME) are the most common complications of uneventful cataract surgery [1]. ME is one of the main causes of unfavorable visual outcomes following uncomplicated cataract surgery and can result in permanent visual loss [2]. The reported incidence of ME ranges from 4% [3] to 11% [4] following uncomplicated phacoemulsification cataract surgery.

ME can be observed angiographically (seen using fluorescein angiography in patients who do not suffer from a detectable visual impairment) or clinically (associated with decreased visual acuity) [5]. Although the pathogenesis of ME is likely multifactorial and remains unknown, it appears to be associated with postoperative inflammation induced by prostaglandins or other inflammatory mediators [3,6]. Inflammatory mediators break down the blood–retinal barrier and the blood–aqueous barrier, leading to increased vascular permeability [7]. A previous study measured the concentrations of vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6) in aqueous humor in patients with nonproliferative diabetic retinopathy with enzyme linked immunosorbent assay during cataract surgery [8] and demonstrated that high VEGF levels in the aqueous humor predict a significant risk of postoperative exacerbation of ME [8]. However, the limitations of the previous study on aqueous humor cytokines include the examination of a limited number of cytokines. Exploring a greater number of cytokines would provide broader insight into the inflammatory mechanisms involved. Recently, the multiplex bead immunoassay has been used to detect cytokines in tears and the aqueous humor because of the capacity of this assay to simultaneously quantify multiple cytokines in small sample volumes [9-12].

Therefore, in this study, we used the multiplex bead immunoassay to evaluate the concentrations of 27 cytokines in the aqueous humor at the beginning of cataract surgery and correlate their expression levels to the development of ME 4

Correspondence to: Ning Dong, Department of Ophthalmology, Beijing Shijitan Hospital, Capital Medical University, Beijing, 100038, People's Republic of China; eye_dongning@163.com

weeks after surgery. In addition, our study explores whether cytokine concentrations in the aqueous humor can predict ME after phacoemulsification.

METHODS

The present study used a comparative cross-sectional design and recruited participants between January 2012 and January 2013. The survey included 288 consecutive non-diabetic patients (288 eyes; 132 males and 156 females) who underwent cataract surgery from Beijing Shijitan Hospital, Capital Medical University, Beijing, People's Republic of China. The mean age of the patients was 71.6 years (range, 58–88 years). The study was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University, Beijing, People's Republic of China, and the study was performed in accordance with the Declaration of Helsinki. Each participant received detailed information and provided informed written consent before being included in the study.

Subjects with blood pressure above 140/90 mmHg or who were receiving any antihypertensive medications were considered hypertensive. Hypercholesterolemia was defined as a fasting total plasma cholesterol level above 200 mg/dl. Hypertriglyceridemia was classically defined as a fasting plasma triacylglycerol (triglycerides, TG) level above 200 mg/dl. Inclusion criteria for all patients were the absence of any retinal or optic nerve disease. Exclusion criteria included the following: (1) a history of ocular surgery; (2) subcapsular posterior cataract; (3) diabetes; (4) age-related macular disease; (5) and intraoperative complications such as posterior capsule rupture, vitreous loss, or lens fragments in the vitreous.

Patients underwent preoperative ophthalmologic examination and a physical examination that included best-corrected visual acuity (BCVA), electroretinogram (ERG), slit lamp-assisted biomicroscopy of the anterior segment, fundus examination, and optical coherence tomography (OCT), which was used to measure the foveal center point thickness (FCPT). The BCVA was measured with a Snellen chart at the preoperative examination 1 day and 4 weeks postoperatively. The OCT examination (Stratus OCT3; Carl Zeiss Meditec, Dublin, CA) was performed by an experienced operator through a dilated pupil. Each study eye underwent OCT testing fewer than 2 weeks before cataract surgery. OCT images were generated with the use of six radial-line scans, 6.00 mm each in length. The maximal foveal center point thickness (in micrometers) was measured at the center point of the fovea by manually placing computerized calipers at the vitreous–retina and retina–retinal pigment epithelium interfaces [13].

Surgical technique: All cataract surgeries were performed using the phacoemulsification technique and the insertion of a foldable hydrophilic acrylic intraocular lens (Acrysof IQ IOL, Alcon, Fort Worth, TX) in the capsular bag. A total of 0.3 mg TobraDex ointment (tobramycin 0.3% and dexamethasone 0.1%; Alcon) was used at the end of the surgery in all patients. All patients were instructed to administer TobraDex eye drops (tobramycin 0.3% and dexamethasone 0.1%; Alcon) four times daily for 2 weeks after surgery and two times daily until 4 weeks post-cataract surgery. In addition, all patients were instructed to administer 0.1% diclofenac sodium eye drops four times daily for 4 weeks after surgery. All patients were followed for at least 4 weeks after surgery.

Aqueous humor sampling: At the time of cataract surgery, a limbal paracentesis was made with a sterile tuberculin syringe. Undiluted aqueous humor samples (0.1–0.2 ml) were aspirated into a syringe. The samples were immediately frozen and stored at −80 °C until analysis.

Postoperative evaluation: Postoperative follow-up visits were scheduled for 1 day and 4 weeks post-cataract surgery. The following assessments were performed 1 day post-cataract surgery: BCVA, slit lamp-assisted biomicroscopy, fundus examination, and intraocular pressure. The following assessments were performed 4 weeks post-cataract surgery: BCVA, slit lamp-assisted biomicroscopy, intraocular pressure, fundus examination, and OCT.

Definition of postoperative macular edema: ME was defined as an increase in the center point thickness of more than 30% from the preoperative baseline on OCT 4 weeks after cataract surgery [2,13]. All patients were divided into either the ME group [ME (+)] or the non-ME group [ME (-)].

Multiplex analysis of cytokines in the aqueous humor: The Bio-Plex Pro magnetic color bead-based multiplex assay (Bio-Plex Human Cytokine 27-plex panel; Bio-Rad, Hercules, CA) was used to measure the concentrations of 27 human aqueous humor cytokines: interleukin-1β (IL-1β), IL-1rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, basic fibroblast growth factor (b-FGF), eotaxin, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GMCSF), interferon-gamma (IFN-γ), interferon-induced protein-10 (IP-10 or CXCL10), monocyte chemotactic protein-1 (MCP-1 or CCL2), macrophage inflammatory protein-1α (MIP-1α or CCL3), macrophage inflammatory protein-1β (MIP-1β or CCL4), platelet-derived growth factor-BB (PDGF-BB), regulated upon activation normal T-cell expressed and secreted (RANTES), tumor necrosis factor-alpha (TNF-α), and VEGF. The analysis procedure was conducted according to the manufacturer's instructions. Standard curves were generated by using the

Table 1. Baseline characteristics of patients with ME (-) and ME (+).

Characteristics	ME (-)	ME (+)	*P* value
Number	23	23	-
Gender			0.552[a]
Male (%)	11 (47.8)	9 (39.1)	
Female (%)	12 (52.2)	14 (60.9)	
Age (SD)	70.8 (8.47)	73.6 (7.43)	0.215[b]
Hypertension (%)	14 (60.9)	13 (56.5)	0.765[a]
Hypercholesterolemia (%)	7 (30.4)	9(39.1)	0.536[a]
Hypertriglyceridemia (%)	5 (21.7)	8 (34.8)	0.326[a]
Blood glucose level, mmol/l (SD)	4.98 (0.73)	5.27 (0.67)	0.139[b]
Type of cataract			0.552[a]
Cortical (%)	9 (39.1)	11 (47.8)	
Nuclear (%)	14 (60.9)	12 (52.2)	
Iris color			0.300[a]
Dark (%)	16 (69.6)	19 (82.6)	
Light (%)	7 (30.4)	4 (17.4)	

[a]Pearson $\chi 2$ test;[b]Student *t* test.

reference cytokine sample supplied in the kit and the Bio-Plex 200 System (software version 6.0; Bio-Rad Laboratories) and were used to calculate the cytokine concentrations in aqueous humor samples.

Statistical analysis: Data were recorded as the mean±standard deviation (SD) or as the median and range. The BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR). The statistical analyses were performed using SPSS for Windows Version 17.0 (Chicago, IL). The Pearson χ^2 test was used to compare the proportion of the qualitative variables. The Student *t* test and the Mann–Whitney U test were used to compare the means of the quantitative variables between two independent groups. Pearson correlation coefficients were used to assess the relationship between the concentrations of the assayed cytokines and the foveal center point thickness 4 weeks post-cataract surgery. A p value less than 0.05 was accepted as statistically significant.

RESULTS

Patient demographics: A total of 288 consecutive non-diabetic patients (288 eyes) were enrolled, and there were no cases of intraoperative vitreous loss or suprachoroidal hemorrhage. At the final follow-up examination, 283 patients (283 eyes) completed 4 weeks of follow-up (98.3% completion), and the five patients who did not complete the protocol were excluded from the study. In the entire study population, 23 patients (23 eyes; 9 men and 14 women) had an increase in the center point thickness of more than 30% from the preoperative baseline on OCT 4 weeks after cataract surgery. The incidence of ME was 8.13%. Table 1 shows the demographic and clinical characteristics of the patients, including the 23 consecutive ME (+) patients and 23 ME (-) patients (23 eyes; 11 men and 12 women) who were randomly selected from the ME (-) group by a random number table. There were no significant differences in age, hypertension, blood glucose level, cholesterol, triglycerides, type of cataract, and iris color between the ME (+) and ME (-) groups.

Postoperative clinical characteristics: The mean BCVA before surgery was 0.50±0.22 (logMAR) in the ME (-) group and 0.47±0.21 (logMAR) in the ME (+) group. Table 2 shows the BCVA 1 day and 4 weeks after surgery. The postoperative BCVA was not significantly different between the ME (-) and ME (+) groups.

The mean foveal center point thickness before surgery was 161.03±22.56 µm in the ME (-) group and 163.39±18.72 in the ME (+) group. Table 3 shows the FCPT 4 weeks after surgery. At 4 weeks, there was an increase of 17.39 µm and 62.7 µm in the FCPT of the ME (-) and ME (+) groups, respectively. The postoperative FCPT differed significantly between the ME (-) and ME (+) groups.

Table 2 and Table 3 show the average increase in center point thickness at 4 weeks for eyes with ME was 62.7 µm, which resulted in a nearly 1-line loss of vision (0.05 logMAR

Table 2. Preopertive, 1-day and 4-week post–cataract surgery BCVA for eyes with ME (-) and ME (+).

Time	logMAR BCVA		
	ME (-), n=23	ME (+), n=23	*P* value[a]
Preoperative	0.50±0.22	0.47±0.21	0.687
1-day	0.09±0.15	0.07±0.15	0.618
4-week	0.04±0.16	0.12±0.11	0.067

logMAR=logarithm of the minimum angle of resolution; BCVA=best-corrected visual acuity. [a]Student *t* test.

units) compared to eyes without ME, which gained approximately 1 line of vision (0.05 logMAR units). However, the patients with ME did not suffer from a serious visual impairment during the 4 weeks after cataract surgery.

Cytokine concentrations in the aqueous humor: Table 4 shows the concentrations of the assayed cytokines. Positive detection rates were more than 80% for 21 cytokines. The positive detection rates for the other six cytokines were IL-13 (66%), TNF-α (50%), IL-17 (36%), G-CSF (28%), IFN-γ (26%), and MIP-1α (18%); these cytokines were not included in the statistical analysis because of the low detection rates.

Compared to the ME (-) group, the concentrations of IL-1β (p=0.016), IL-6 (p=0.013), MCP-1 (p=0.030), and VEGF (p=0.033) in the ME (+) patients were significantly higher. However, the IL-10 concentrations in the samples from the ME (+) patients (p=0.017) were significantly lower. There were no significant differences in the other cytokine concentrations between the ME (-) and ME (+) patients.

Association between cytokine concentrations and foveal center point thickness: Table 5 shows the relationship between the concentrations of the assayed cytokines and the postoperative FCPT. The aqueous humor levels of IL-1β (r=0.376), IL-6 (r=0.418), MCP-1 (r=0.348), and VEGF (r=0.375) correlated positively with postoperative FCPT. In addition, the aqueous humor level of IL-10 (r=–0.424) was negatively correlated with the postoperative FCPT.

DISCUSSION

The incidence of ME peaks at approximately 4 to 6 weeks after uneventful cataract surgery [4,14]. The incidence of angiographic ME has been reported to range from 4% [3] to 11% [4] following uncomplicated phacoemulsification cataract surgery; however, the prevalence of clinical ME is much lower and ranges from 0.1% to 2.35% [15-17]. The different rates may be caused by several factors, such as the type of cataract, surgical technique, time of phacoemulsification, variation in follow-up times, and rates of complications [6]. In the current study, 23 patients (23 eyes; nine men and 14 women) had an increase in the center point thickness of more than 30% from the preoperative baseline on OCT 4 weeks after cataract surgery, and the incidence of ME was 8.13% [2,13]. The average increase in center point thickness at 4 weeks for eyes with ME was 62.7 µm, which resulted in a nearly 1-line loss of vision (0.05 logMAR units) compared to eyes without ME, which gained approximately 1 line of vision (0.05 logMAR units). However, the patients with ME did not suffer from a serious visual impairment during the 4 weeks after cataract surgery. There may be several explanations for these results. First, no clinical ME was associated with decreased visual acuity because our cataract surgeries were routine and uncomplicated phacoemulsification cataract surgeries. In addition, all surgeries were performed by the same experienced expert. Second, our follow-up observation period was only 4 weeks, and the incidence of significant clinical ME may increase after 4 weeks. Therefore, our study

Table 3. Preopertive and 4-week post–cataract surgery foveal center point thickness for eyes with ME (-) and ME (+).

Time	Foveal center point thickness (µm)		
	ME (-), n=23	ME (+), n=23	*P* value[a]
Preoperative	161.03±22.56	163.39±18.72	0.773
4-week	178.42±22.01	226.09±26.26	<0.001

[a]Student*t* test.

Table 4. The concentrations of cytokines in aqueous humors of eyes with ME (-) and ME (+).

Cytokine	ME (-), n=23		ME (+), n=23		*P* value[a]
	Median	Range	Median	Range	
IL-1β	2.0	0–38	5.0	0–34	0.016
IL-1rα	15.1	0–323	17.2	0–356	0.560
IL-2	1.7	0–118	1.9	0–136	0.768
IL-4	1.4	0–133	1.7	0–124	0.850
IL-5	1.3	0–151	2.1	0–121	0.752
IL-6	13.0	0–26	17.0	0–42	0.013
IL-7	4.7	0–95	2.2	0–86	0.130
IL-8	6.6	0–86	8.0	0–106	0.112
IL-9	2.9	0–87	2.6	0–102	0.620
IL-10	7.0	0–33	5.0	0–13	0.017
IL-12	8.3	0–86	9.6	0–102	0.531
IL-13	-	-	-	-	-
IL-15	1.3	0–58	1.7	0–96	0.733
IL-17	-	-	-	-	-
b-FGF	13.2	0–165	11.1	0–178	0.780
Eotaxin	5.7	0–103	6.1	0–116	0.813
G-CSF	-	-	-	-	-
GM-CSF	6.7	0–88	7.5	0–79	0.673
IFN-γ	-	-	-	-	-
IP-10	1.1	0–26	0.9	0–19	0.732
MCP-1	79.5	23–276	134.0	24–269	0.030
MIP-1α	-	-	-	-	-
MIP-1β	32.8	0–213	33.5	0–232	0.630
PDGF-BB	3.1	0–66	3.8	0–71	1.000
RANTES	5.3	0–83	5.9	0–93	0.661
TNF-α	-	-	-	-	-
VEGF	38.0	11–298	76.0	13–246	0.033

[a]Mann–Whitney U test

on the incidence of ME after uneventful cataract surgery must continue.

The pathophysiology of ME involves the accumulation of transudate in the outer plexiform and the inner nuclear layers of the retina; the microcysts coalesce into cysts [5].

Table 5. Correlations between concentrations of cytokines in aqueous humors and 4-week post–cataract surgery foveal center point thickness.

Cytokine	Correlation coefficients	*P* value[a]
IL-1β	0.376	0.003
IL-6	0.418	0.001
IL-10	−0.424	0.001
MCP-1	0.348	0.007
VEGF	0.375	0.003

[a]Pearson correlation coefficient

The pathogenesis of ME is associated with the destruction of the blood–retinal barrier and the blood–aqueous barrier induced by prostaglandins or other inflammatory mediators [3,6,7]. Elevated levels of angiogenic factors, inflammatory cytokines, chemokines, and growth factors in the aqueous humor may play a role in the breakdown of the vascular barrier [18-22].

Aqueous humor analysis provides useful tools in understanding the pathophysiology and treatment response to many ocular conditions. However, aqueous humor samples consist of small volumes, limiting the usefulness of the analysis with traditional enzyme linked immunosorbent assay techniques. In the current study, multiplex bead immunoassay was used to analyze the aqueous humor levels of cytokines and chemokines in non-diabetic patients following uncomplicated phacoemulsification cataract surgery. Multiplex assays measure the concentrations of multiple cytokines simultaneously in small sample volumes, such as those of the aqueous humor, serum, and tears [23,24]. Using multiplex assays, we simultaneously measured the concentrations of 27 cytokines in human aqueous humor samples. To our knowledge, this sample is comparatively large, and this is the first investigation of these 27 aqueous cytokines as predictors of ME in non-diabetic patients following uncomplicated phacoemulsification cataract surgery.

In our study, positive detection rates were more than 80% for 21 cytokines. Compared to the ME (-) patients, the concentrations of IL-1β (p=0.016), IL-6 (p=0.013), MCP-1 (p=0.030), and VEGF (p=0.033) were significantly higher in the ME (+) patients. In addition, the aqueous humor levels of IL-1β (r=0.376), IL-6 (r=0.418), MCP-1 (r=0.348), and VEGF (r=0.375) correlated positively with postoperative FCPT.

IL-1β is a proinflammatory cytokine and angiogenic mediator [25]. IL-1β upregulates several inflammatory mediators, including IL-1β itself, TNF-α, cyclooxygenase 2 (COX-2), prostaglandins, inducible nitric oxide synthase (iNOS), and chemokines [26]. Meanwhile, experimental studies have demonstrated the in vivo angiogenic activity of IL-1β, and its influence on the development of ocular neovascularization [27,28]. In the current study, the IL-1β concentrations in the ME (+) patients were significantly higher than those of the ME (-) group. Our study suggests a possible role of IL-1β in the development of ME after cataract surgery, and we will need to prove if using IL-1β receptor antagonists or otherwise neutralizing IL-1β can inhibit the development of ME.

IL-6 is synthesized by various cells, including epidermal cells, fibroblasts, macrophages, vascular smooth muscle, vascular endothelial cells, and glial cells [29,30]. Furthermore, IL-6 is a multifunctional, proinflammatory cytokine that increases vascular permeability and angiogenesis through inducing VEGF [29,30]. MCP-1 (CCL2) is a member of the C-C chemokine family, which regulates the migration and infiltration of monocytes/macrophages [31]. This protein was a well-known proinflammatory cytokine, and aqueous MCP-1 levels were elevated in human and animal eyes after phacoemulsification [32]. In our study, the IL-6 and MCP-1 concentrations from the ME (+) patients were significantly higher than those of the ME (-) patients. There is evidence that inflammation is an important molecular mechanism in the development and progression of ME after uncomplicated phacoemulsification cataract surgery.

VEGF 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 [33]. In accordance with previous results, levels of VEGF in the aqueous humor have markedly increased in postoperative exacerbation of patients with ME [8]; therefore, aqueous cytokines may be a predictor of ME in non-diabetic patients after cataract surgery.

IL-10, which is produced by monocytes and macrophages, is a primary anti-inflammatory cytokine. IL-10 limits inflammation by reducing the synthesis of proinflammatory cytokines, such as IL-1 and TNF-α, by suppressing cytokine receptor expression and inhibiting receptor activation [34]. In addition, IL-10 prevents angiogenesis by downregulating VEGF expression [35]. In our study, the IL-10 concentrations of samples from the ME (+) patients (p=0.017) were significantly lower. Our results suggest that low levels of circulating IL-10 (anti-inflammatory and antiangiogenic activity) are involved in the pathogenesis of ME after cataract surgery.

The limitations of our study should be mentioned. First, our study was limited to non-diabetic patients with uncomplicated phacoemulsification cataract surgery and a relatively short follow-up observation period in which the prevalence of ME was comparatively low and the prevalence of clinical ME was none after cataract surgery. In addition, the concentration of the cytokines was not determined from vitreal samples. The cytokine levels in the vitreous humor usually show higher concentrations, and analysis of the vitreal samples would more accurately reflect the intraocular cytokine concentrations and the condition of the macula. However, in contrast to vitreous samples, obtaining aqueous fluid samples from the anterior chamber is easier, faster, and less risky. Finally, multiplex bead immunoassay has a limitation if the cytokine levels are low. Thus, the positive detection rates for the six cytokines were not higher than 80%, and these

cytokines were not included in the statistical analysis because of the low detection rates in the current study.

In conclusion, the present study showed that the aqueous humor levels of IL-1β, IL-6, MCP-1, and VEGF were increased in patients with post-cataract surgery ME and were positively correlated with FCPT 4 weeks following cataract surgery in non-diabetic patients. In addition, the aqueous humor levels of IL-10 were significantly lower in patients with post-cataract surgery ME and were negatively correlated with postoperative FCPT. These results indicate that the aqueous humor levels of IL-1β, IL-6, MCP-1, VEGF, and IL-10 may be potential predictors of postoperative exacerbation of ME in non-diabetic patients following uncomplicated phacoemulsification cataract surgery.

REFERENCES

1. Vukicevic M, Gin T, Al-Qureshi S. Prevalence of optical coherence tomography-diagnosed postoperative cystoid macular oedema in patients following uncomplicated phaco-emulsification cataract surgery. Clin Experiment Ophthalmol 2012; 40:282-7. [PMID: 21718410].
2. Dieleman M, Wubbels RJ, van Kooten-Noordzij M, de Waard PW. Single perioperative subconjunctival steroid depot versus postoperative steroid eyedrops to prevent intraocular inflammation and macular edema after cataract surgery. J Cataract Refract Surg 2011; 37:1589-97. [PMID: 21855759].
3. Bélair ML, Kim SJ, Thorne JE, Dunn JP, Kedhar SR, Brown DM, Jabs DA. Incidence of cystoid macular edema after cataract surgery in patients with and without uveitis using optical coherence tomography. Am J Ophthalmol 2009; 148:128-35. [PMID: 19403110].
4. Perente I, Utine CA, Ozturker C, Cakir M, Kaya V, Eren H, Kapran Z, Yilmaz OF. Evaluation of macular changes after uncomplicated phacoemulsification surgery by optical coherence tomography. Curr Eye Res 2007; 32:241-7. [PMID: 17453944].
5. Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol 2012; 23:26-32. [PMID: 22134362].
6. Gulkilik G, Kocabora S, Taskapili M, Engin G. Cystoid macular edema after phacoemulsification: risk factors and effect on visual acuity. Can J Ophthalmol 2006; 41:699-703. [PMID: 17224950].
7. Benitah NR, Arroyo JG. Pseudophakic cystoid macular edema. Int Ophthalmol Clin 2010; 50:139-53. [PMID: 20057303].
8. Funatsu H, Yamashita H, Noma H, Shimizu E, Mimura T, Hori S. Prediction of macular edema exacerbation after phacoemulsification in patients with nonproliferative diabetic retinopathy. J Cataract Refract Surg 2002; 28:1355-63. [PMID: 12160804].
9. Liu J, Shi B, He S, Yao X, Willcox MD, Zhao Z. Changes to tear cytokines of type 2 diabetic patients with or without retinopathy. Mol Vis 2010; 16:2931-8. [PMID: 21203348].
10. 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. [PMID: 22511846].
11. Banerjee S, Savant V, Scott RA, Curnow SJ, Wallace GR, Murray PI. Multiplex bead analysis of vitreous humor of patients with vitreoretinal disorders. Invest Ophthalmol Vis Sci 2007; 48:2203-7. [PMID: 17460280].
12. Ang M, Cheung G, Vania M, Chen J, Yang H, Li J, Chee SP. Aqueous cytokine and chemokine analysis in uveitis associated with tuberculosis. Mol Vis 2012; 18:565-73. [PMID: 22509092].
13. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology 2007; 114:881-9. [PMID: 17275910].
14. Buyukyildiz HZ, Gulkilik G, Kumcuoglu YZ. Early serous macular detachment after phacoemulsification surgery. J Cataract Refract Surg 2010; 36:1999-2002. [PMID: 21029910].
15. Rossetti L, Autelitano A. Cystoid macular edema following cataract surgery. Curr Opin Ophthalmol 2000; 11:65-72. [PMID: 10724830].
16. Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. J Cataract Refract Surg 2007; 33:1550-8. [PMID: 17720069].
17. Loewenstein A, Zur D. Postsurgical cystoid macular edema. Dev Ophthalmol 2010; 47:148-59. [PMID: 20703048].
18. 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. [PMID: 13129863].
19. 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. [PMID: 19784389].
20. Funk M, Schmidinger G, Maar N, Bolz M, Benesch T, Zlabinger GJ, Schmidt-Erfurth UM. 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. [PMID: 20711086].
21. Sohn HJ, Han DH, Kim IT, Oh IK, Kim KH, Lee DY, Nam DH. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. Am J Ophthalmol 2011; 152:686-94. [PMID: 21782151].
22. Jonas JB, Jonas RA, Neumaier M, Findeisen P. Cytokine concentration in aqueous humor of eyes with diabetic macular edema. Retina 2012; 32:2150-7. [PMID: 22617833].
23. Sharma RK, Rogojina AT, Chalam KV. Multiplex immunoassay analysis of biomarkers in clinically accessible

quantities of human aqueous humor. Mol Vis 2009; 15:60-9. [PMID: 19145248].

24. Corrales RM, Villarreal A, Farley W, Stern ME, Li DQ, Pflugfelder SC. Strain-related cytokine profiles on the murine ocular surface in response to desiccating stress. Cornea 2007; 26:579-84. [PMID: 17525655].
25. Gustavsson C, Agardh CD, Agardh E. Profile of intraocular tumour necrosis factor-α and interleukin-6 in diabetic subjects with different degrees of diabetic retinopathy. Acta Ophthalmol (Copenh) 2013; 91:445-52. [PMID: 22520269].
26. Rothwell NJ, Luheshi GN. Interleukin 1 in the brain: biology, pathology and therapeutic target. Trends Neurosci 2000; 23:618-25. [PMID: 11137152].
27. Demircan N, Safran BG, Soylu M, Ozcan AA, Sizmaz S. Determination of vitreous interleukin-1 (IL-1) and tumour necrosis factor (TNF) levels in proliferative diabetic retinopathy. Eye (Lond) 2006; 20:1366-9. [PMID: 16284605].
28. Zhou J, Wang S, Xia X. Role of intravitreal inflammatory cytokines and angiogenic factors in proliferative diabetic retinopathy. Curr Eye Res 2012; 37:416-20. [PMID: 22409294].
29. 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. [PMID: 13129863].
30. Lotz M. Interleukin-6: a comprehensive review. Cancer Treat Res 1995; 80:209-33. [PMID: 8821579].
31. Penny LA. Monocyte chemoattractant protein 1 in luteolysis. Rev Reprod 2000; 5:63-6. [PMID: 10864849].
32. Kawai M, Inoue T, Inatani M, Tsuboi N, Shobayashi K, Matsukawa A, Yoshida A, Tanihara H. Elevated levels of monocyte chemoattractant protein-1 in the aqueous humor after phacoemulsification. Invest Ophthalmol Vis Sci 2012; 53:7951-60. [PMID: 23132797].
33. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE, Nguyen HV, Aiello LM, Ferrara N, King GL. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994; 331:1480-7. [PMID: 7526212].
34. Rubio-Perez JM, Morillas-Ruiz JM. A review: inflammatory process in Alzheimer's disease, role of cytokines. Scientific-WorldJournal 2012; 2012:756357-[PMID: 22566778].
35. Silvestre JS, Mallat Z, Duriez M, Tamarat R, Bureau MF, Scherman D, Duverger N, Branellec D, Tedgui A, Levy BI. Antiangiogenic effect of interleukin-10 in ischemia-induced angiogenesis in mice hindlimb. Circ Res 2000; 87:448-52. [PMID: 10988235].

Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 24 November 2013. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.