Relationship Between the Levels of Inflammatory Cytokines in the Aqueous Humor and Cataract in Fuchs Uveitis Syndrome-A Case Control Study

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Research article

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Abstract

Background

This study aims to compare the levels of intraocular cytokines between FUS eyes and the senile cataract eyes. The association between inflammatory cytokine levels and cataract severity in FUS is evaluated to find the possible mechanism of cataract in FUS eyes.

Methods

A retrospective study of 28 eyes with FUS was performed. Auxiliary examinations were performed, including ophthalmic examinations, laser flare-cell photometry, and levels of inflammatory cytokines in the aqueous humor were measured. The control group included 25 eyes with senile cataract. Data on the aqueous humor inflammatory cytokines were compared between the two groups. The association between the aqueous humor cytokine levels and severity of cataract was assessed.

Results

There were 28 eyes with FUS in 27 patients. Unilateral involvement was noted in 26 patients (96.30%). Stellate keratic precipitates (KPs) were noted in 16 eyes (57.14%). Heterochromia was observed in 21.43% of affected eyes. Posterior capsular opacification cataract was observed in 16 of the 28 eyes. Eyes with FUS had significantly higher aqueous humor cytokine levels (VEGF, IL-6, IL-8 and IL-10) compared with the control eyes ($P < 0.001$). There was a statistically significant positive correlation between the severity of cataract and IL-6 and IL-8 levels in the aqueous humor ($\tau = 0.675$ and 0.793, respectively; $P = 0.001$, $P < 0.001$, respectively).

Conclusions

Expression of VEGF, IL-6, IL-8 and IL-10 in the aqueous humor of FUS patients was significantly higher than in senile cataract eyes, and the aqueous levels of IL-6 and IL-8 were significantly positively associated with the severity of posterior capsular opacification of cataract. Our results imply that an inflammation mechanism may be involved in the early development of cataract in FUS.

Background

Fuchs uveitis syndrome (FUS) is an intraocular inflammatory condition which was first described in 1906 by[1]. FUS is an unilateral chronic recurrent non-granulomatous uveitis syndrome in about 90% of cases and accounts for 2 ~ 11% of uveitis, characterized by diffuse distribution of stellate keratic precipitates (KP), heterochromia, iris depigmentation, iris atrophy and early cataract formation[1]. Although the trigger

mechanism of FUS is unknown, many studies have shown that immunological factors may play a role in the development of FUS[2, 3, 4]. However, few studies have compared inflammatory cytokine levels in the aqueous humor of FUS patients and normal eyes until now.

The most common complication in FUS patients is complicated cataract. Due to the long-term effects of inflammation, the average incidence of cataract in FUS is around 50%[5, 6, 7, 8]. Cataract is a common complication of chronic or recurrent uveitis, which may be caused by intraocular inflammation, long-term use of corticosteroids, or a synergistic effect of both[9]. Vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines play a role in the development of cataract in patients with non-infectious uveitis. However, no study has assessed the association between inflammatory cytokine levels and the severity of cataract.

The aims of this study were to evaluate the clinical, demographic characteristics, aqueous humor inflammatory cytokines during follow-up in Chinese patients diagnosed with FUS, to compare the aqueous humor inflammatory cytokines in FUS and the senile cataract eyes and to The assess the association between the aqueous humor cytokine levels and the severity of cataract.

Methods

Study design and participants

We reviewed the medical records of 27 patients diagnosed with FUS who were admitted to our department, the Department of Ophthalmology, Beijing Chaoyang Hospital, Capital Medical University during May 2018 to May 2019. This study was performed in accordance with the standards of the Declaration of Helsinki and was approved by the Institutional Review Board (No. 2018-4-3-3). Written informed consent was obtained from the subjects after potential risks involved with the study were explained to them.

Diagnostic criteria: Diagnosis of FUS was principally based on the criteria of Kimura et al. [10]. The major criteria included the presence of (i) diffuse KPs (stellate or non-stellate), (ii) mild anterior chamber reaction defined as up to 2 + cells and flare, (iii) absence of posterior synechiae, and (iv) absence of ciliary congestion or red eye. The minor criteria for diagnosis included (i) heterochromia of the iris with/without iris depigmentary changes, (ii) presence of multiple nodules on iris, (iii) presence of vitreous opacities, and (iv) unilateral or bilateral involvement (one eye only was enrolled). Two of the four major criteria with or without the presence of minor criteria were required for diagnosis.

The demographic and clinical characteristics were obtained from each participant. Data included age, gender, ocular and medical history. Aqueous humor samples were obtained for routine diagnostic purposes from patients with classical clinical signs of FUS while the disease was active. The intraocular antibody synthesis of rubella virus (RV) was confirmed by using the antibody index (AI) described in the literature[11].

Regular ophthalmologic examinations

Regular ophthalmic examinations, including slit-lamp biomicroscopy, best-corrected visual acuity (BCVA) on the Snellen chart, intraocular pressure (IOP), and fundoscopy with dilated pupils. Some detailed ophthalmic characteristics, such as keratic precipitates, iris atrophy, iris nodules, anterior chamber reaction and vitreous reaction were also evaluated. Evaluation of aqueous cells was done by laser flare photometry (Model KOWA FM-600, Hamamatsu Factory, Japan). The main manifestation of complicated cataract in FUS patients is posterior capsular opacification (PCO). Posterior capsular opacification is classified from grade 0 to 5, according to the Lens Opacities Classification System III (LOCS III) [12].

Aqueous humor cytokine levels assessment

Aqueous humor samples were collected simultaneously. Patients were given topical anesthesia, and a 1-ml syringe was inserted at the peripheral cornea parallel to the iris. Aqueous humor samples of 100 μL were extracted. Six immune mediators were measured: Vascular endothelial growth factor (VEGF), transforming growth factor (TGF), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10) and vascular cell adhesion molecule (VCAM).

To serve as controls, 25 patients with senile cataract who underwent surgery for cataract removal and intraocular lens implantation were enrolled. The levels of cytokines in the aqueous humor of the control group were also examined. Rubella virus IgG antibodies in the aqueous humor were measured quantitatively with a commercial ELISA kit (Virion/serion GmbH, Würzburg, Germany) in aqueous humor. The antibody activities were expressed in international units per mL (IU/mL). The assay was conducted according to the manufacturer’s instructions. Data analysis was performed using SERION easy base 4PL software.

Statistical analysis

The Kolmogorov–Smirnov test was used to identify the normality of distribution. The independent t-test and Mann-Whitney U test were used to compare parameters between the two groups. Descriptive statistics were calculated as the mean and standard deviation for normally distributed variables, and the median, first quartile, and third quartile for non-normally distributed variables. To assess the difference in aqueous cytokine levels between FUS patients and the normal controls, box plots was created to allow visualization of the data. Kendall's tau-b rank correlation was used to evaluate associations between the aqueous humor cytokine levels and severity of cataract. All analyses were performed with SPSS Statistics, version 22.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered statistically significant 2-sided.

Results

Demographics and symptoms

The present study included 27 patients diagnosed with FUS. 15 (55.56%) of the patients were male, 12 (44.44%) of the patients were female. Mean age at diagnosis was 33.89 ± 13.50 years old. Mean follow-up time was 20.89 ± 8.90 months. The right eye was involved in 17 patients (62.96%) and the left eye was involved in 9 patients (33.33%), while 1 patients (3.70%) had bilateral involvement. Decreased visual acuity or blurred vision were the most common complaints at presentation (16 eyes, 57.14%). 11 patients (40.74%) had no symptoms. (Table 1).

Table 1
Baseline demographics and symptoms of all patients

Characteristic	FUS patients
Number of eyes	28
Age (year, mean ± SD)	33.89 ± 13.50
Sex (male : female)	15/12
Follow-up time (year, mean ± SD)	20.89 ± 8.90
Bilateral involvement (n,%)	1 (3.70%)
Ophthalmologic symptoms (n,%)	
Decreased visual acuity or blurred vision	16 (57.14%)
Floaters	10 (35.71%)
Posterior synechiae (n,%)	1 (3.70%)
Systemic diseases (n,%)	
Rheumatoid arthritis (n,%)	1 (3.70%)
Thyroid disease (n,%)	0
FUS: fuchs uveitis syndrome, SD = standard deviation.	

Ocular findings

Stellate KPs were found in 16 (57.14%) FUS patients. Anterior chamber (AC) reaction was observed in all of the affected eyes. Aqueous cells were observed in only 10 eyes, and aqueous flare was observed in 19 eyes. Although there were varying degrees of iris depigmentation in some patients, 6 of the eyes (21%) presented with heterochromia. 2 eyes (7.14%) had iris atrophy. Iris nodules were observed in 35.71% of the affected eyes. At diagnosis, 20 eyes (71.43%) presented with lens opacity: 14 (50.00%) had posterior subcapsular opacity, 5 (17.86%) were mature, and 1 (3.70%) was nuclear. Vitreous cells were noted in 7 eyes (25.00%). (Table 2).

Table 2
Ocular findings in 28 eyes of 27 patients at time of presentation

Finding	FUS patients
Stellate KPs (n,%)	16 (57.14%)
Anterior chamber reaction (n,%)	
Aqueous cells	10 (35.71%)
Aqueous flare	19 (67.86%)
Iris atrophy (n,%)	2 (7.14%)
Heterochromia (n,%)	6 (21.43%)
Iris nodules (n,%)	10 (35.71%)
Koeppe	8 (28.57%)
Busacca	2 (7.14%)
Lens opacity (n,%)	20 (71.43%)
Posterior subcapsular opacity	14 (50.00%)
Mature cataract	5 (17.86%)
Nuclear opacity	1 (3.70%)
Vitreous cells (n,%)	7 (25.00%)
Vitreous opacity (n,%)	14 (50.00%)
Mild	6 (21.43%)
Severe	8 (28.57%)
FUS: fuchs uveitis syndrome, KP: keratic precipitates.	

Complications

The most common complication during follow-up was cataract (16 eyes, 57.14%), followed by epiretinal membrane (4 eyes, 14.28%), corneal endothelial plaque (3, 10.71%) and chorioretinal lesion (3 eyes, 10.71%). Observed complications were presented in Table 3.

Table 3
Complications observed in patients with Fuchs' uveitis syndrome

Complication (n,%)	FUS patients
Corneal endothelial plaque	3 (10.71%)
Cataract	16 (57.14%)
Glaucoma	2 (7.14%)
Iris pigmentation on the IOL	2 (7.14%)
Glaucomatous optic disc	2 (7.14%)
Epiretinal membrane	4 (14.28%)
Chorioretinal scar	1 (3.70%)
Intravitreal hemorrhage	1 (3.70%)
Chorioretinal lesion	3 (10.71%)
FUS: fuchs uveitis syndrome, IOL: intraocular lens.	

Growth factors, aqueous humor cytokines and RV antibody levels

Growth factors and aqueous humor cytokines levels of 16 FUS eyes and 25 senile cataract eyes were showed in Table 4. Statistically significant differences were found between the two groups. The mean concentrations of VEGF in FUS eyes were higher than in the cataract eyes ($P = 0.018$). The median concentrations of IL-6, IL-8 and IL-10 were 36.35 (13.88, 102.50) pg/mL, 37.5 ± 33.6 pg/mL and 3.25 (1.20, 11.55) pg/mL, respectively. The FUS eyes had significantly higher aqueous humor cytokine levels (IL-6, IL-8 and IL-10) compared with the cataract eyes ($P < 0.001$). Levels of VCAM in FUS eyes were higher than in cataract eyes ($P < 0.001$). No statistically significant differences were found in TGF levels between the groups, as shown in Table 4. Viral antibody levels of RV were also shown in Table 4. 11 (69%) patients had a positive outcome for intraocular antibody production against RV, with IgG more than 20 IU/mL.

Table 4
Cytokines and viral antibody levels in all measured aqueous humor

Mediators (pg/mL)	FUS group (n = 16)	Cataract group (n = 25)	P value
VEGF (pg/mL), mean ± SD	27.1 ± 12.7	17.8 ± 11.1	P = 0.018∗
TGF (pg/mL), median (IQR)	11.30 (0,58.93)	0 (0,5.40)	P = 0.278†
IL-6 (pg/mL), median (IQR)	36.35 (13.88,102.50)	2.60 (0,12.15)	P < 0.001†
IL-8, (pg/mL), mean ± SD	37.5 ± 33.6	3.0 ± 2.1	P < 0.001∗
IL-10 (pg/mL), median (IQR)	3.25 (1.20,11.55)	0 (0,0)	P < 0.001†
VCAM (pg/mL), median (IQR)	1706.65 (1079.95,4918.23)	22.00 (9.50,85.30)	P < 0.001†
Viral antibody (positive) (n,%)			P = 0.758†
RV	11 (68.75%)		
VEGF: vascular endothelial growth factor, TGF: transforming growth factor, IL: interleukin, VCAM: vascular cell adhesion molecule, RV: rubella virus, SD: standard deviation, IQR: interquartile range.			
∗P values were calculated using the independent t-test.			
†P values were calculated using the Mann–Whitney U test.			

Correlation between aqueous humor cytokine levels and severity of PCO

The main manifestation of complicated cataract in FUS patients is PCO. A correlation analysis between severity of PCO and levels of VEGF, TGF, IL-6, IL-8 and IL-10 were shown in Table 5. There was a statistically significant positive correlation between the severity of PCO and IL-6 and IL-8 levels in aqueous humor ($\tau = 0.675$ and 0.793, respectively; $P = 0.001$, $P < 0.001$, respectively). But there were no correlation between the severity of PCO and VEGF, TGF and IL-10 ($\tau = 0.287$, 0.187 and 0.213, respectively; $P > 0.05$).

Table 5
Kendall's tau-b rank correlation analyses between cytokine levels and PCO grade

Cytokines	PCO grade	
	Kendall's tau-b rank correlation	
	τ	P
VEGF	0.287	P = 0.149
TGF	0.187	P = 0.363
IL-6	0.675	P = 0.001*
IL-8	0.793	P < 0.001*
IL-10	0.213	P = 0.284

PCO: posterior capsular opacification, VEGF: vascular endothelial growth factor, TGF: transforming growth factor, IL: interleukin, VCAM: vascular cell adhesion molecule, RV: Rubella virus.

The severity of PCO can be classified as grade 0 to 5 according to the LOCS III grading system, as mentioned above. The number of patients with grade 5 PCO was 0. The scatter plot graph showing the relationship between IL-6 and IL-8 levels and PCO grade was shown in Fig. 2.

Discussion

Fuchs uveitis syndrome, also called Fuchs heterochronic uveitis, is an unilateral chronic recurrent non-granulomatous uveitis syndrome first described in 1906 by Fuchs, and its diagnosis is determined based on clinical manifestations[1]. In this paper, the clinical manifestations and ocular signs of 27 patients were studied in detail. We found our FUS patients were characterized by a mild uveitis with characteristic stellate KPs, iris heterochromia, iris nodule, complicated cataract and vitreous inflammatory reaction. The expression of inflammatory cytokines in the aqueous humor was significantly increased compared to the controls. Immune mediators play a crucial role in specific viral intraocular inflammation. The incidence of complicated cataract in FUS patients is positively correlated with the aqueous humor inflammatory cytokine levels.

The clinical features of FUS have been described in many studies, including blurred vision[13, 14], stellate KP[13, 15, 16], iris heterochromia[14], iris nodules[17], anterior chamber and vitreous opacities[18]. FUS is the most easily misdiagnosed uveitis because a comprehensive understanding of it is lacking, there are hidden incidence and its pathological mechanisms are complex. In the present study, the most common symptoms were blurred vision and floaters. Stellate KPs were noted in 16 eyes (57%). Heterochromia was observed in 21% of affected eyes. Iris nodules were present in 36% of the affected eyes. These results are similar to the above-mentioned studies.

Inflammatory mediators may play an important role in the development of uveitis, such as T helper 1 (TH1) cytokines, T helper 2 (TH2) cytokines, anti- and pro-inflammatory mediators. The TH1 cytokines are

mainly responsible for the immune response against intracellular bacteria and protozoa, including IFN-γ, TNF-α, IL-2, IL-7, IL-8 and IL-12. The TH2 cytokines including IL-4, IL-5, IL-6, IL-10 and IL-13. The Th1 cells mainly mediate cellular immunity, activate macrophages to kill intracellular pathogens (including viruses and bacteria), and play an important role in immune regulation in the induction of organ-specific autoimmune diseases and anti-infective immunity. The Th2 cells are mainly involved in humoral immunity, resisting extracellular pathogens (such as parasites). As indictated in a previous report, Posner–Schlossman Syndrome (PSS) is a common misdiagnosis for FUS, and only on the basis of clinical findings, the confirmed diagnosis of FUS was often delayed (mean delay is 4.6 years)[13]. Recently, with the help of an analysis of levels of cytokine levels in the aqueous humor, Pohlmann D et al. [19] found that PSS patients showed a stronger and more active ocular inflammatory response, than FUS patients, IL-2, IL-4, IL-5, IL-6, IFN-γ and TNF-α were significantly higher in FUS and Posner-Schlossman-Syndrome patients compared to controls. Sijssens et al.[20] found that high IL-10 levels are associated with active infectious uveitis are considered to be important in early stage of infection. High IL-6 levels induce an increase in intraocular inflammation, as seen in idiopathic uveitis and in ocular infection such as toxoplasmosis gondii.

FUS is an unilateral chronic recurrent non-granulomatous uveitis syndrome accounts for 2 ~ 11% of all uveitis. There are also some studies that explore the changes in inflammatory factors in FUS patients. Pohlmann found that IL-2, IL-4, IL-5 and IL-6 were significantly higher in FUS patients compared to controls, but the level of IL-8 and IL-10 were not different. In our study, we tried to detect differences in inflammatory factors, mainly IL-6, IL-8 and IL-10, in FUS patients compared with normal eyes. We detected significantly increased levels of immune mediators (IL-6, IL-8 and IL-10) in FUS patients. High IL-10 levels are mainly associated with active infectious uveitis and are considered to be important in early stages of infection[20]. In FUS patients, increased levels of IL-10 are assumed to imply a distinctively acute inflammation triggered by RV. Our study also found an increase in the level of IL-6, which can stimulate the proliferation, differentiation and function of cells involved in immune responses and play an important role in anti-infective immune response. We also found high IL-8 levels in FUS patients, suggesting that RV induces IL-8 production and increases the gene expression of receptor of IL-8 in fibroblast cell lines. Interleukin-8 is a cytokine secreted by TH1 cells, which mainly mediate the production of immune antibodies related to the organism's local inflammatory reaction and participate in cellular immunity and delayed hypersensitivity inflammation. IL-8 may act as a marker for inflammation in the aqueous humor in FUS. Because IL-6, IL-10 and IL-8 are expressed simultaneously, we suggest that IL-6, IL-10 and IL-8 control the migration and infiltration of monocytes/macrophages during inflammation and contribute to the viral response in FUS.

Cataract is a common complication of chronic or recurrent uveitis and is a sequelae to chronic intraocular inflammation and chronic systemic and/or topical corticosteroid therapy. The expression of pro-inflammatory cytokines in the cataract formation of non-infectious uveitis is gradually understood. Recurrent uveitis attacks may lead to lens permeability, then result in cataract[21]. Cataracts occur in many types of uveitis, such as FUS, juvenile idiopathic arthritis-associated uveitis, Behcet's disease,

Vogt–Koyanagi–Harada syndrome (VKH) and ocular toxoplasmosis. In FUS patients, the incidence of complicated cataract in patients with uveitis is as high as 50%-70%. Cataract occurs in 17–36% of ocular Behcet's disease patients and the most frequent complication is posterior capsular opacification (PCO)[22, 23]. In VKH, cataract is the most common complication, with a prevalence of about 40%.

Previous clinical studies have emphasized that cataract is the most common complications in FUS patients[13, 16, 24]. Tugal-Tutkun et al.[16] found a 56% risk of cataract formation in FUS patients who did not receive steroid treatment over their 8-year follow-up period. Yang et al.[13] found cataract was appeared in 70.7% of their FUS patients. Similarly, cataract was observed in 57.14% of patients in our study. The variations reported in different studies may be related to disease duration and the chronic nature of the disease. The use of hormonal drugs to treat of inflammation also promotes the development of cataract. Current studies have confirmed the high probability of complicated cataract in patients with FUS, and there is a correlation between cataract and intraocular inflammation, but few studies have explored the association between cataract in FUS patients and the high expression of inflammatory cytokines in the aqueous humor. Thus, the relationship between the levels of intraocular cytokines and cataract in FUS is evaluated in this study. In the current study, there was a statistically significant positive correlation between the severity of cataract and IL-6 and IL-8 levels in the aqueous humor. These results confirm that the occurrence of complicated cataract in patients with FUS is positively correlated with the intraocular high expression of inflammatory factors. Studies have found that IL-8 levels are significantly higher in patients with active uveitis, while IL-6 levels rise in chronic uveitis. Cataract in FUS patients are mainly characterized by PCO. This may be because IL-6 can regulate the activity of transforming growth factor-β (TGF-β), epidermal growth factor (EGF), matrix metalloproteinase (MMP-2/-9) and immune cells, thereby playing a role in the formation of PCO. The pro-inflammatory cytokine IL-8 exerts a defence mechanism by regulating the activity of neutrophil cells. However, the persistence of IL-8 in the inflammatory response can cause different degrees of tissue damage. These main that proinflammatory cytokines play an important role in the development of complicated cataract in uveitis by interacting with other cytokines. Further studies are needed to confirm their exact effect on the course of uveitis and complicated cataracts.

The study has also several limitations. First, this study only analysed some inflammatory factors (IL-6, IL-10 and IL-8) in the patients' aqueous humor, but did not analyse and compare the other inflammatory factors; second, the sample sizes and exploratory analysis were still limited. Further study should focus on exploring the progression of other inflammatory factors in the aqueous humor, such as TH1 cytokines, TH2 cytokines, anti- and pro-inflammatory mediators (IL-1RA, MIP-1α), chemokines (IP-10, Eotaxin, MCP-1) and growth factors(G-CSF, PDGF, FGFbasic,VEGF, GM-CSF) during the course of FUS, and their associations with PCO grade.

Conclusions

In conclusion, the present results showed that in the current study the expression of inflammatory factors in the aqueous humor of FUS patients is significantly increased, and further revealed a positive

correlation between the levels of IL-6 and IL-8 levels in the aqueous humor and the PCO grade in FUS, which may help to explain the early formation of cataract in FUS.

Abbreviations

AI
Antibody index (AI)
BCVA
Best-corrected visual acuity
EGF
Epidermal growth factor
FUS
Fuchs uveitis syndrome
IL
Interleukin
IOP
Intraocular pressure
KP
Keratic precipitates
MMP
Matrix metalloproteinase
PCO
Posterior capsular opacification
PSS
Posner–Schlossman Syndrome
RV
Rubella virus
TGF
Transforming growth factor
TH
T helper
VCAM
Vascular cell adhesion molecule
VEGF
Vascular endothelial growth factor
VKH
Vogt–Koyanagi–Harada syndrome

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the local ethics committee of Beijing Chaoyang Hospital and with the 2013 Helsinki declaration. Written informed consent was obtained from each patient before the study.

Consent to publish

Not applicable.

Availability of data and materials

A supplemental material which included the primary data has been uploaded accordingly (see Additional file 1).

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HW and YT. The first draft of the manuscript was written by HW and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

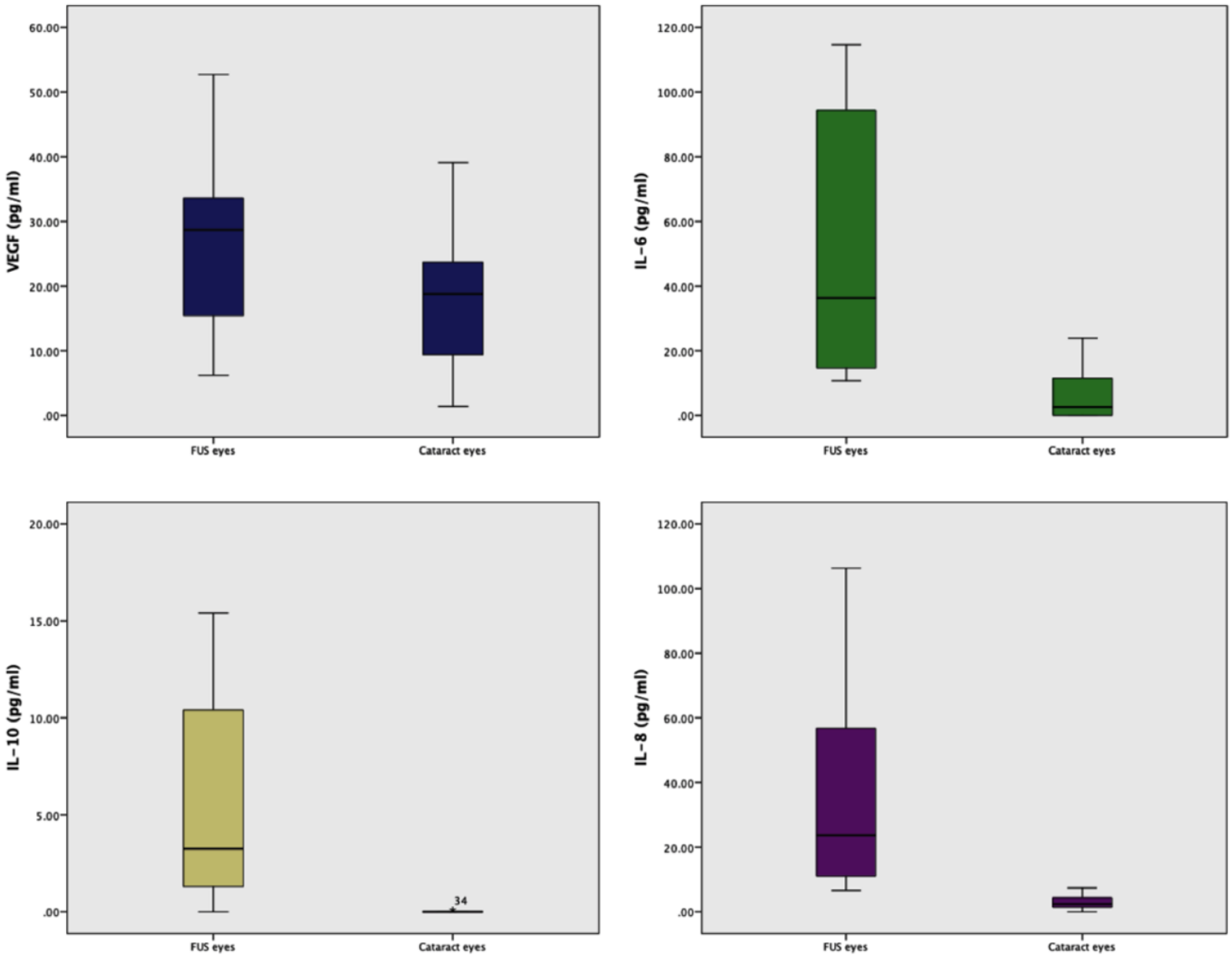

Figure 1

The aqueous humor cytokine levels in FUS eyes and cataract eyes. The FUS eyes had significantly higher VEGF and aqueous humor cytokine levels (IL-6, IL-8 and IL-10) compared with the cataract eyes.

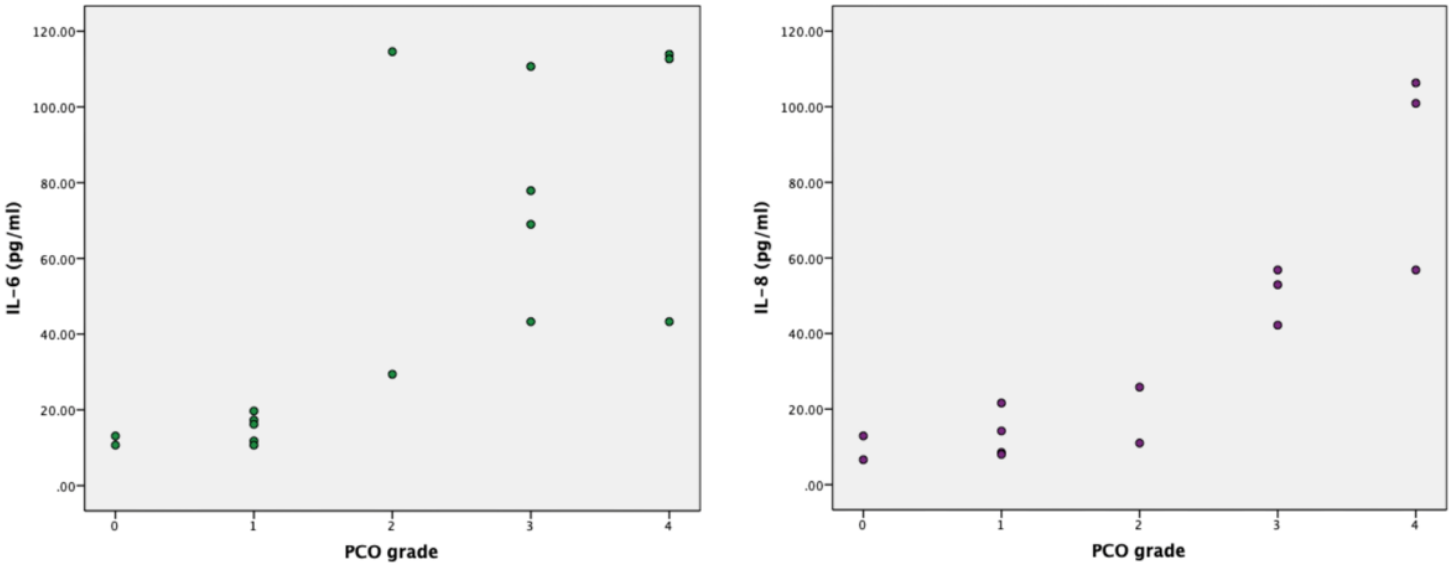

Figure 2

Scatter plot graph showing the relationship between cytokine levels and PCO grade.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Rawdata.xlsx