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Expression of cytokines in the aqueous humor of cataract patients with pathologic myopia and simple high myopia

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Purpose: To explore the role of cytokines during the progression process of cataract patients with pathologic myopia (PMC) and simple high myopia (SHMC).

Methods: A total of 63 cataract patients who underwent cataract surgery were classified into a PMC group (22 eyes), an SHMC group (21 eyes), and an age-related cataract (ARC) group (20 eyes), based on axial length (AL) and International Myopia Institute (IMI)'s classification. Aqueous humor samples were extracted before surgery. Cytometric bead array (CBA) was employed to measure the level of interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), transforming growth factor-β1 (TGF-β1), basic fibroblast growth factor (bFGF), interleukin-10 (IL-10), interleukin-17a (IL-17a), interleukin-1β (IL-1β), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor -α (TNF-α), intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM). Additionally, the correlations between cytokines and the AL or myopic maculopathy categories were examined.

Results: VEGF, IL-6, MCP-1, ICAM, and VCAM (all $p<0.001$), TGF-β1 ($p=0.018$), and IL-8 ($p=0.008$) were statistically different among the three groups. In parallel, the levels of VCAM ($r=0.718$), MCP-1 ($r=0.591$), ICAM ($r=0.584$), IL-8 ($r=0.435$), IL-6 ($r=0.396$), and TNF-α ($r=0.280$) were positively associated with myopic maculopathy, while VEGF ($r=-0.542$), TGF-β1 ($r=-0.381$), and IL-17a ($r=-0.284$) were correlated inversely with myopic maculopathy (all $p<0.05$). Furthermore, a significant positive correlation was observed between AL and levels of VCAM ($r=0.726$), MCP-1 ($r=0.644$), ICAM ($r=0.573$), IL-6 ($r=0.386$), and IL-8($r=0.376$). VEGF ($r=-0.610$), TGF-β1 ($r=-0.361$), and IL-17a ($r=-0.319$) were inversely associated with AL (all $p<0.05$). Further analysis using multiple regression indicated that, after adjusting for confounding factors, lower VEGF and higher VCAM were significantly associated with AL. However, the limitations of this study were reflected in the inability to determine whether the changes in cytokines were the consequences or causes of the formation of high myopia.

Conclusions: The pathogeneses of PMC and SHMC may differ, and there are significant changes associated with inflammation and the immune response in eyes with PMC.

Pathologic myopia (PM) is recognized as a major reason for visual impairment worldwide, affecting up to 8% of the population, with regional specificity [1-3]. The hallmark of PM is that when the axial length (AL) exceeds 29.50 mm, the fundus commonly presents with degenerative diseases, including choroidal atrophy and macular atrophy [4]. In contrast to PM, simple high myopia (SHM) is characterized by a refractive diopter exceeding −6.00D or AL≥26.00 mm, without retinal degenerative lesions. PM and SHM are distinct categories of eye diseases. While SHM can progress into PM due to progressive elongation of the AL, not all cases of PM are associated with SHM. Variances in the ocular microenvironment and aqueous humor metabolism are responsible for the differences between PM and SHM [5-7]. Previous research has revealed a synergistic interplay between hypoxia, inflammation, and the immune response in the pathogenesis of high myopia [8,9]. The oxidative reaction, inflammatory response, and immune cascade are heightened in eyes with high myopia, resulting in increased susceptibility to lens damage and cataract development. Patients with high myopia are at a higher risk of developing early-onset cataracts and experiencing increased surgical complications, including posterior cataracts and capsular constriction syndrome. Cytokine expression in the aqueous humor has been found to vary among cataract patients with various types of high myopia [10]. However, previous studies have grouped PM and SHM, failing to demonstrate the distinct characteristics of PM. In this study, patients with PM and SHM were divided into separate groups, and the cytokines in the aqueous humor collected from pathologic myopic cataracts (PMC), simple high myopic

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cataracts (SHMC), and age-related cataracts (ARC) were detected with cytometric bead array (CBA). This study aimed to identify the role of cytokines in the pathogenesis of high myopic cataracts, especially in cases with progressive elongation of the ocular globe and retinal atrophy.

METHODS

Ethical approval: This is a prospective study. In total, 63 cases of HMC and ARC were collected. HMC patients were classified into a pathological myopia group (PMC group) and a simple myopia group (SHMC group), with ARC patients as the control group (ARC group). Aqueous humor samples were extracted from these patients, all of whom underwent phacoemulsification combined with intraocular lens implantation at the first Affiliated Hospital of Bengbu Medical University. CBA was used to detect the expression level of cytokines in the aqueous humor of the three groups.

This work was approved by the Institutional Review Board of the Affiliated Hospital of Bengbu Medical University (Approval Number: 2023YJS028) and was performed in compliance with the principles set forth in the Declaration of Helsinki. All patients were informed of and offered their consent for the procedure.

Inclusion criteria: In this study, 63 patients presented to the first Affiliated Hospital of Bengbu Medical University from October 2020 to February 2022. Based on AL and International Myopia Institute (IMI)'s classification [11], the patients were assigned to the PMC group (22 eyes), SHMC group (21eyes), and ARC group (20 eyes), and aqueous humor was extracted from the eyes of all screened patients. Subsequently, data detection was completed with CBA.

The inclusion criteria were as follows: (1) For ARC patients, the AL was 22.00–24.00 mm, without ametropia or any fundus disease. (2) For SHMC patients, the AL at 26.00–29.50 mm, with a diopter exceeding −6.00 D and exhibiting no myopic retinopathy (C0) or tessellated fundus (C1). (3) For PMC patients, the AL≥29.50 mm and the diopter was greater than −6.00 D. The myopic maculopathy categories of the eyes included diffuse choroidal atrophy (C2), patchy choroidal atrophy (C3), and macular atrophy (C4). (4) All patients were without any macular disease other than myopic maculopathy, and they were not using non-steroidal anti-inflammatory eye drops before surgery.

Exclusion criteria: The exclusion criteria were as follows: (1) Patients who had undergone any previous intraocular surgery or trauma or who had any known eye disease, including uveitis, glaucoma, and myopic choroidal neovascularization, were excluded. Patients with systemic and metabolic diseases, including rheumatic disorders, diabetes, or cerebral infarction, were excluded, as were patients using steroids. (2) Patients who experienced complications during the surgical procedure, such as anterior chamber bleeding, irregular tearing of the anterior capsule membrane of the lens, rupture of the posterior capsule membrane, rupture of the suspensory ligament, and vitreous prolapse were also excluded.

Examination: The eyes of each patient were comprehensively assessed, including visual acuity tests, objective refraction (Topcon, Tokyo, Japan), slit lamp exams (66 Vision Tech, Suzhou, China), anterior ophthalmoscope exams (Volk Optical Inc., OH), and ultra-wide-angle fundus photography (Carl Zeiss AG, Baden-Wurttemberg, Germany). The AL was measured using IOL Master 700 (Carl Zeiss AG).

Aqueous humor collection: After conjunctival topical anesthesia was administered three times, the eyelids and surrounding skin were disinfected. The conjunctival sac was soaked with povidone iodine and then rinsed fully with normal saline. Samples of aqueous humor (100 µl) were drawn slowly from the anterior chamber using a 30 G needle at a distance of 1 mm inside the corneal limbus at 3 o'clock before cataract surgery. In addition, the samples were placed in an Eppendorf (EP) tube at −80 °C for cryopreservation.

Cytokine analysis: A CBA flex set with commercially available cytokine flex set kits (BD Biosciences, San Jose, CA) was employed to assess the levels of VEGF, TGF-β1, bFGF, IL-6, MCP-1, IL-17a, IL-1β, IL-10, TNF-α, IL-8, ICAM, and VCAM in the samples. The test was performed following the guidelines of the manufacturer. This technology uses multiple-microsphere-based immunoassays by applying flow cytometry resolution to the spectral measurements of microspheres coupled to capture molecules and applying reporter fluorescent dyes binding to detect antibodies.

Statistical analysis: IBM SPSS Statistics, version 26.0 software (SPSS Inc., Chicago, IL) was adopted for the statistical analysis. A one-way ANOVA followed by Tukey's test was used to compare the levels of cytokines. As three different comparisons were made (k=3), Bonferroni correction was adopted for pairwise comparisons (p=0.0167). A Chi-square test was applied to assess the differences in categorical data between the groups. Pearson's or Spearman's correlations were used to examine the relationships between cytokines and AL or the myopic maculopathy category. Additionally, multiple regression using the level of cytokines in the aqueous humor was performed to predict the possibility of a shift toward PM. A p value of <0.05 was considered to indicate a statistically significant difference.

Table 1. The specific features of ARC, SHMC and PMC patients (mean ±SD).

Factors	ARC	SHMC	PMC	P value
Number	20	21	22	
Age (years)	61.85±7.93	63.04±5.38	62.09±6.92	0.836
IOP (mmHg)	15.38±2.45	15.60±2.22	15.58±2.55	0.949
Gender				0.698
Male	8(40%)	8(38%)	11(50%)	
Female	12(60%)	13(62%)	11(50%)	
AL (mm)	23.48±0.75	27.52±1.07	31.52±0.82	<0.001
Myopic maculopathy category				<0.001
C0	20(100%)	0(0%)	0(0%)	
C1	0(0%)	21(100%)	0(0%)	
C2	0(0%)	0(0%)	5(22.73%)	
C3	0(0%)	0(0%)	6(27.27%)	
C4	0(0%)	0(0%)	11(50%)	

P is the comparison between three groups. SD is standard deviation.

RESULTS

In this study, we obtained 63 aqueous samples from 63 patients who were receiving phacoemulsification combined with intraocular lens implantation. Among the 63 samples, 20 were ARC, 21 were SHMC, and 22 were PMC. The age distribution (F=0.180, p>0.05), gender (χ 2=0.71, p>0.05), and intraocular pressure (IOP; F=0.052, p>0.05) showed no significant difference among the three groups. AL, as measured by IOL Master 700, was longer in the PMC group than in the ARC and SHMC groups, with a significance of 0.001. Moreover, the distribution of myopic maculopathy showed significant differences among the groups (p<0.001). The characteristics of the study subjects, AL, and myopic maculopathy category are presented in Table 1.

Levels of cytokines in the aqueous humor: In this study, 12 cytokines were detected. One of these cytokines, bFGF, was 0.00 pg/ml (>90%) with a low detection rate and was thus excluded from the statistical analysis. The results for the other cytokines are presented in Table 2. The levels of IL-6, ICAM, MCP-1, and IL-8 were significantly elevated in the aqueous humor of the PMC group compared to the SHMC and ARC groups. Moreover, significantly increased VCAM values were observed in PMC and SHMC patients. In contrast, VEGF levels in the aqueous humor were lower in PMC eyes than in SHM eyes. In addition, TGF-β1 expression was significantly reduced in the aqueous humor of patients in the PMC group compared to the SHMC and ARC groups. Nevertheless, there were no notable variances observed between the three groups in terms of IL-1β, TNF-α, IL-17a, and IL-10.

Association between myopic maculopathy and cytokines in the aqueous humor: The levels of MCP-1, VCAM, IL-6, ICAM, IL-8, and TNF-α were positively related to the severity of the myopic maculopathy category (Figure 1A–F). VEGF, TGF-β1, and IL-17a were correlated inversely with the myopic maculopathy category (Figure 1G–I), while no significant differences were found in IL-10 or IL-1β according to the myopic maculopathy category (Figure 1J–K).

Association between AL and cytokines in the aqueous humor: A significant positive association was found between AL and levels of VCAM, IL-6, ICAM, IL-8, or MCP-1 in the aqueous humor (Figure 2A–E). VEGF, TGF-β1, and IL-17a were inversely associated with AL (Figure 2F–H), while no significant relationship was observed between AL and IL-1β, TNF-α, or IL-10 (Figure 2I–K).

Furthermore, multiple regression indicated that after adjusting for confounding factors, AL was inversely related to VEGF (β=-0.110, p<0.001) and positively related to VCAM (β=0.002, p<0.001) in aqueous humor. Both VEGF and VCAM may be key factors influencing AL (Table 3).

DISCUSSION

Previous studies have demonstrated that the expression of cytokines in the aqueous humor of eyes with high myopic cataracts (HMC) was altered, but such studies did not distinguish between different types of myopia [10]. In the present study, high myopia was categorized into PM and SHM, and the changes in cytokines in the aqueous humor were examined for both types of myopia. The results revealed a greater upregulation of five factors (IL-8, IL-6, MCP-1, VCAM, and

Table 2. Levels of cytokines in cataract patients with different types of high myopia and ARC patients (mean ±SD).

Cytokine (pg/ml)	ARC	SHMC	PMC	P_1 value	P_2 value	P_3 value
VEGF	18.85±11.44	11.24±7.99	4.47±6.51	0.023	<0.001	0.043
TGF-β1	16.04±13.26	15.47±11.61	6.35±11.47	1.000	0.036	0.049
IL-6	12.64±11.07	12.90±9.86	28.92±16.50	1.000	<0.001	<0.001
IL-8	1.95±2.77	2.14±1.62	4.26±3.09	1.000	0.015	0.028
IL-10	1.21±0.76	1.17±0.60	1.01±0.75	1.000	1.000	1.000
IL-17a	3.84±1.38	3.29±1.56	2.75±1.43	0.710	0.060	0.705
IL-1β	1.32±1.02	1.38±0.80	1.42±0.70	1.000	1.000	1.000
TNF-α	2.70±2.28	1.93±1.81	3.30±1.41	0.572	0.890	0.056
MCP-1	234.95±129.91	256.23±132.65	593.40±208.29	1.000	<0.001	<0.001
ICAM	30.19±18.11	34.63±23.21	83.61±38.03	1.000	<0.001	<0.001
VCAM	178.52±237.03	382.72±384.60	1225.83±584.74	0.047	<0.001	<0.001
bFGF	0.00	0.00	0.00	-	-	-

P_1 is the comparison between SHMC group and ARC group, P_2 is the comparison between PMC group and ARC group, P_3 is the comparison between PMC group and SHMC group.

ICAM) in the PMC group compared with the ARC or SHMC groups. In addition, two factors (VEGF and TGF-β1) were downregulated in the PMC group compared with the ARC or SHMC groups. Furthermore, compared with the ARC samples, VCAM expression increased and VEGF decreased in the SHMC group. This trend is consistent with Zhu et al.'s research findings on cytokines in the anterior chamber of eyes with HMC [12]. The disparities between these two groups suggest that PM differs from SHM due to an abnormal intraocular microenvironment caused by axial elongation and fundus atrophy.

IL-6 is considered to be an inflammatory trigger factor correlated with high myopia. By upregulating matrix metalloproteinase-2 (MMP-2), IL-6 induces degradation of the scleral extracellular matrix and scleral remodeling, causing elongation of the AL [13,14]. Yuan et al. [15] believed that when the AL of myopic eyes ranged from 22.0 to 36.00 mm, IL-6 increased by 1.85pg/ml for every 1 mm increase in the AL. It was demonstrated in the present study that the axial elongation and IL-6 expression were elevated to a greater extent in the PMC group than in the SHMC group. Additionally, the average IL-6 value was more elevated in the SHMC group than in the ARC group, although this disparity did not attain statistical significance. The cytokines IL-8 and MCP-1, which are implicated in the inflammatory response [16,17], exhibited similar changes to IL-6 across all three groups. Zhu et al. [12] found an increase in MCP-1 expression in HMC, suggesting a potential association between MCP-1 and the onset of complications related to inflammation. In addition, a proinflammatory status was found in retinitis pigmentosa (RP)–complicated cataracts, uveitis-related cataracts, and congenital cataracts [18-20]. Studies have suggested that the inflammatory response is involved in developing posterior subcapsular cataracts in eyes with RP and that a severe inflammatory response can cause the early onset of cataracts [21,22], conforming to the age-related onset characteristics of HMC. The expression levels of MCP-1, IL-8, and IL-6 in the three groups demonstrated that the intraocular microenvironment status of patients with SHMC closely resembled that observed in ARC patients. SHMC was distinct from PMC in that the level of intraocular inflammation was more obvious in PMC patients than in SHMC patients. Multiple mechanisms contribute to the development of high myopia, involving not only inflammatory stimuli but also various types of cytokine interactions [23]. While IL-6 and TGF-β1 are beneficial for the expression of VEGF, VEGF also facilitates increased vascular permeability and triggers and contributes to an inflammatory response. Some studies have considered the retina as a component of the nervous system, with VEGF serving as a neuroprotective factor, the concentration of which decreases in high myopia eyes [24]. A downregulation of VEGF expression was observed in both the PMC and SHMC groups in the present study. Furthermore, the PMC group exhibited a further decrease compared with the SHMC group. In addition, the myopic maculopathy category was negatively related to expression levels of VEGF in aqueous humor. In SHMC patients, the retina exhibited mild degeneration, which manifested primarily as fundus tessellation. In contrast, PMC patients commonly presented with diffuse or patchy retinal atrophy, including macular

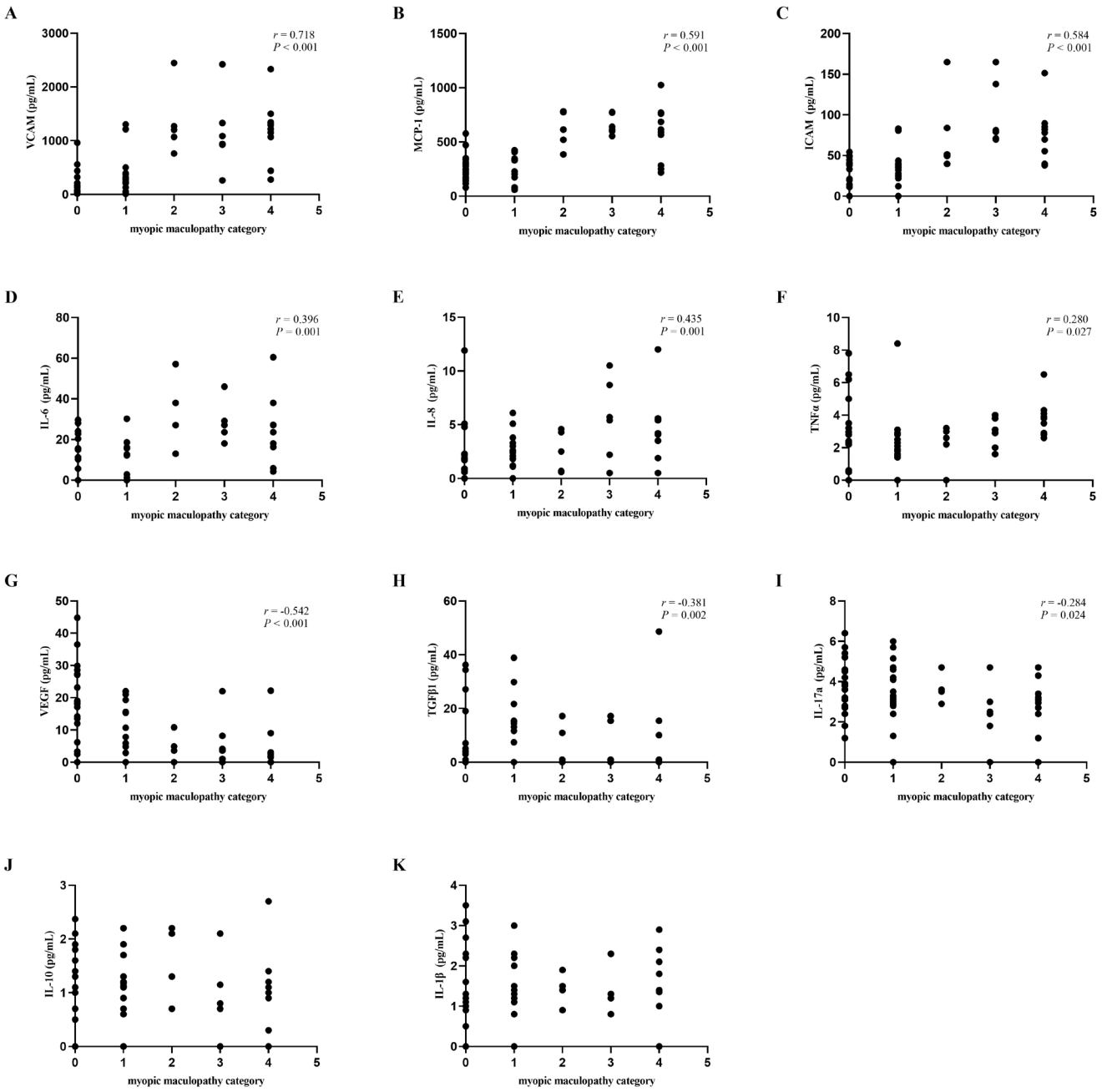

Figure 1. Correlation between cytokine levels in aqueous humor and myopic maculopathy categories. **A-F**: A positive correlation was shown between myopic maculopathy categories and levels of VCAM (r=0.718, p<0.001), MCP-1(r=0.591, p<0.001), ICAM (r=0.584, p<0.001), IL-6(r=0.396, p=0.001), IL-8(r=0.435, p=0.001), and TNF-α (r=0.280, p=0.027). (G-I) An inverse correlation was observed between VEGF (r=-0.542, p<0.001), TGF-β1(r=-0.381, p=0.002), and IL-17a (r=-0.284, p=0.024) and myopic maculopathy categories. **J**-**K**: No correlation was found between IL-1β and IL-10 and myopic maculopathy categories (p>0.05).

atrophy. The variation in VEGF levels may be consistent with the extent of retinal atrophy and degeneration in myopic eyes. However, there is still no consensus on the mechanism behind the downregulation of VEGF expression in myopic eyes. Some researchers have suggested that in myopic eyes, choroidal thinning and reduced blood flow may cause neurodegenerative changes in the retina, resulting in decreased VEGF production [25]. While some studies have revealed no correlation between VEGF concentration and choroidal thickness, our study is consistent with others showing a negative

Table 3. Multiple regression analysis of possible influencing cytokines and AL.

Factors	β ± SEM	P value	95%CI	
VEGF	−0.110±0.028	<0.001	−0.165	−0.055
VCAM	0.002±0.001	<0.001	0.001	0.003
TGFβ1	−0.017±0.022	0.435	−0.061	0.027
IL6	0.014±0.020	0.496	−0.027	0.054
IL17a	−0.139±0.199	0.487	−0.537	0.259
MCP1	0.002±0.002	0.258	−0.001	0.005
ICAM	0.015±0.009	0.101	−0.003	0.033
IL8	0.066±0.106	0.536	−0.147	0.279

β is coefficient. SEM is standard error.

association between VEGF and AL [15,26]. This study revealed that with an increase in AL, the severity of atrophic lesions in the fundus also tends to increase, and there is a more pronounced downward trend in VEGF levels. This may be caused by extensive degenerative changes that occur in the retina during the axial elongation of myopic eyes, contributing to decreased VEGF production and the weakening of its protective effect on the retina, thereby exacerbating degenerative changes in the fundus.

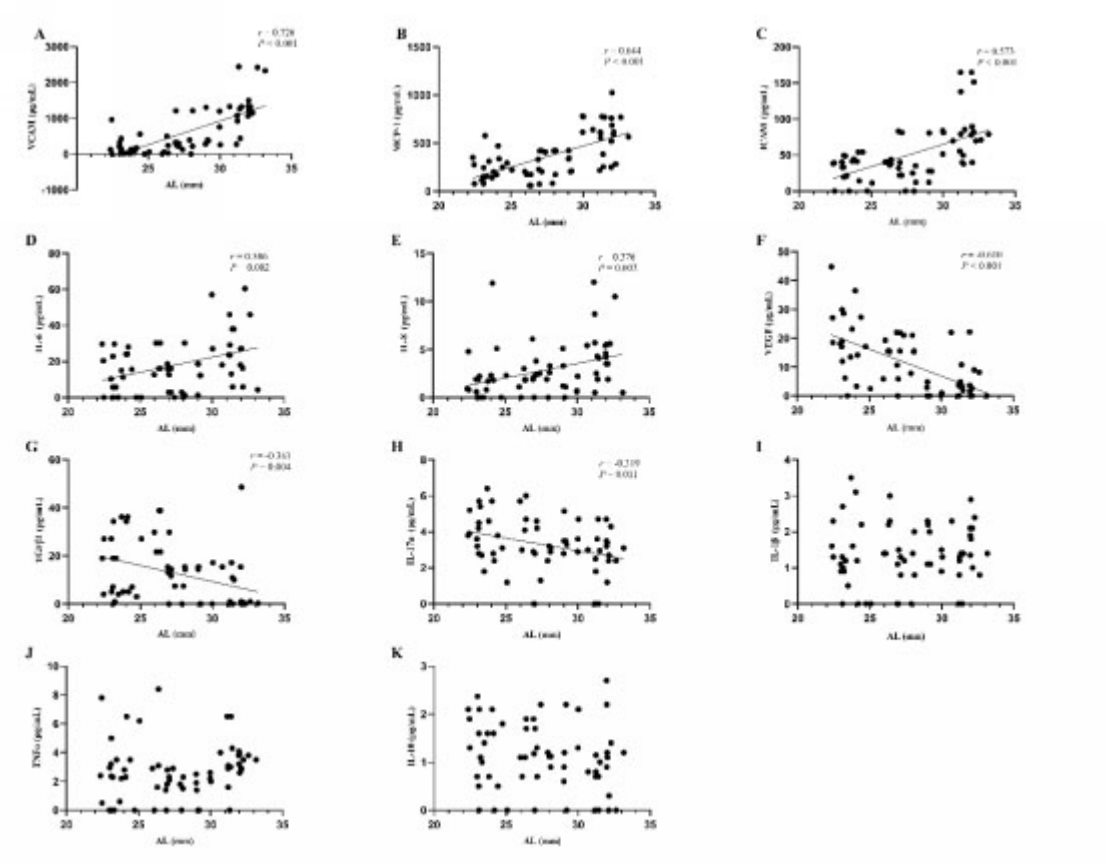

Figure 2. Relationships between levels of cytokines in the aqueous humor and AL. **A**-**E**: A positive relationship was found between AL and levels of VCAM (*r*=0.726, p<0.001), MCP-1(*r*=0.644, p<0.001), ICAM (*r*=0.573, p<0.001), IL-6(*r*=0.386, p=0.002), and IL-8(*r*=0.376, p=0.002). **F**-**H**: An inverse relationship was found between VEGF (*r*=-0.610, p<0.001), TGF-β1(*r*=-0.361, p=0.004), IL-17a (*r*=-0.319, p=0.011), and AL. **I**-**K**: No correlation was found between IL-1β, TNF-α, and IL-10 and AL (p>0.05).

TGF-β contains three subtypes, which are implicated in the regulation of cell growth and differentiation, immune regulation, tissue repair and fibroplasia [27,28]. Jobling et al. [29] established a model of myopic tree shrews with form deprivation, finding that three subtypes of TGF-β were negatively correlated with AL in the sclera. Li et al. [30] indicated a significant reduction in TGF-β1 in sclera tissue in a guinea pig model of form-deprivation myopia. In the present study, TGF-β1 was negatively correlated with AL, which is consistent with the findings of Li et al. However, Hsiao [31] reported an upregulation of TGF-β1 expression in the aqueous humor of myopic patients with longer AL. This discrepancy may be due to the selection of myopic patients undergoing ICL implantation, as they were younger and had transparent lenses.

VCAM and ICAM, both members of the immunoglobulin superfamily, have been found to be closely related to various immune diseases, including thyroid-associated ophthalmopathy and rheumatoid arthritis [32]. Using RNA-seq techniques, Zeng et al. indicated that differential genes in the retina of form-deprivation myopia are implicated in immune, inflammatory, and tyrosine metabolism-related pathways, shedding light on the potential mechanism of retinal degeneration in developing myopia [33]. VCAM plays an important role in leukocyte recruitment in the inflammatory response [34]. ICAM is engaged in inflammatory cell adhesion, migration, infiltration, and cell signal transduction, and its expression is increased in some immune-related eye diseases, such as uveitis and allergic conjunctivitis [35,36]. Mimura et al. [37] suggested that ICAM is correlated with inflammation in their study of retinal degenerative diseases, including age-related macular degeneration. By comparing the variations in VCAM and ICAM in the different groups, we observed that immune factors might contribute to the pathological changes found in high myopia, which could further exacerbate the intraocular inflammation state. Therefore, it is hypothesized that the interaction between adhesion molecules may cause mechanisms of retinal degeneration through the immune response and inflammation.

Our findings revealed a significant association between cytokine levels and both the severity of grades of maculopathy and the AL. The potential value of cytokine levels lies in predicting the possibility that SHM will shift toward PM. The limitations of this study are reflected in the inability to determine whether the changes in cytokines were a cause or a consequence of abnormal axial elongation and degenerative fundus changes during the formation of high myopia. Previously, data indicated that subclinical inflammation of the retina and choroid could result in axial elongation and the progression of myopia [38]. Researchers have also noted that changes in cytokines occur before atrophic retinal lesions [15]. The relationship between cytokines and the development of high myopia requires further prospective cohort research for confirmation.

Conclusion: In conclusion, the expression levels of inflammatory cytokines, including MCP-1, IL-8, and IL-6, and immune-related factors, including ICAM and VCAM, are increased in the aqueous humor of patients undergoing HMC, while the concentrations of VEGF and TGF-β1 are decreased, suggesting a mild pre-inflammatory state in high myopia. More significant changes related to inflammation and the immune response were found with PM than with SHM. Different pathogeneses may exist for PMC and SHMC, and they require further investigation. Inhibiting the expression levels of proinflammatory cytokines and immune-related factors in the aqueous humor may have some value for the treatment of patients with PM and SHM.

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