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Higher TGF-β1, TGF-β2, MMP-2, and TIMP-1 Levels in the Aqueous Humor of Patients with Acute Primary Angle Closure

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Keywords
TGF-β · MMP · TIMP · Acute primary angle closure · Aqueous humor

Abstract

Purpose: To assess the quantitative differences in the levels of members of the transforming growth factor (TGF-β), matrix metalloproteinase (MMP), and tissue inhibitor of MMP (TIMP) families in the aqueous humor (AH) between patients with acute primary angle closure (APAC) and those with cataract only. ***Methods:*** AH samples were collected from 26 patients with APAC and cataract as well as 26 patients with age-related cataract only. Multiplex assays were used to measure the concentrations of TGF-β1, TGF-β2, and TGF-β3; MMP-1, MMP-2, MMP-7, MMP-9, and MMP-10; and TIMP-1 and TIMP-2. ***Results:*** The concentrations of TGF-β1, TGF-β2, MMP-2, ($p < 0.001$), and TIMP-1 were significantly higher (all $p < 0.001$) in AH samples from patients with APAC versus cataract only. Conversely, the AH concentrations of MMP-7 ($p = 0.524$), MMP-9 ($p = 0.103$), MMP-10 ($p = 0.111$), and TIMP-2 ($p = 0.059$) did not significantly differ between the groups. The concentrations of TGF-β3 and MMP-1 were below the respective detection limits in most AH samples. ***Conclusion:*** The AH levels of TGF-β1, TGF-β2, MMP-2, and TIMP-1 were elevated in APAC eyes. Such altered protein levels could induce abnormal deposition of extracellular matrix in the trabecular meshwork, resulting in an increase in aqueous outflow resistance and, thereby, providing a possible explanation of the mechanism of residual glaucoma after cataract surgery.

Introduction

Acute primary angle closure (APAC) is a well-known ophthalmic emergency caused by sudden mechanical blockage of aqueous outflow due to direct contact of the iris root with the trabecular meshwork (TM) with a subsequent rapid increase in intraocular pressure (IOP). Research on the incidence of APAC has shown that individuals of Chinese ethnic origin are prone to be affected by APAC [1]. Most patients are initially treated with medications, and iridotomy is performed as soon as possible. However, after iridotomy, 21–47% of patients still need further treatment to control IOP [2]. For such treatment, lens extraction with or without goniosynechiolysis, which

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can widen the angle, has been proposed for the long-term control of IOP. Although this treatment approach is more effective than iridotomy for IOP control, glaucoma medication is still needed postoperatively [3]. Accordingly, it is likely that the function of the anterior angle is damaged by the excessive IOP during the acute phase, which results in increased aqueous humor outflow resistance.

The sharp rise in the IOP in APAC causes ischemic injury to the ocular tissue within the anterior chamber, which can significantly alter the aqueous humor (AH) composition [4, 5]. The TM is an avascular tissue in the anterior chamber that obtains oxygen and nutrients from the AH. Therefore, alterations in the AH composition likely influence the metabolic homeostasis of the TM, leading to changes in the TM microstructure. Previous studies demonstrated that increased concentrations of transforming growth factor (TGF)-β and altered activity of matrix metalloproteinases (MMPs) and tissue inhibitor of MMPs (TIMPs) in AH are probably associated with abnormal accumulation of extracellular matrix (ECM) in the TM and result in increased aqueous outflow resistance [6, 7]. TGF-β promotes the production of ECM components, whereas the MMPs/TIMPs modulate ECM turnover [6, 8]. Additional research showed that ischemia injury increases the local production of TGF-β, MMP, and TIMP family members [9, 10]. Therefore, we hypothesized that the ischemia injury induced by the acute increase in IOP in APAC alters the expression of TGF-β, MMP, and TIMP family members in the AH, leading to impaired function of the TM, which may contribute to the development of residual glaucoma in APAC patients after lens extraction with goniosynechiolysis. In the present study, we measured the TGF-β, MMP, and TIMP levels in the AH of APAC patients using a multiplex bead immunoassay technique and compared them to the levels measured in the AH of control cataract patients.

Materials and Methods

Patients

This study was performed according to the guidelines of the Declaration of Helsinki and approved by the local Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Participants were recruited prospectively and consecutively in the Ophthalmology Department of the First Affiliated Hospital of the Chongqing Medical University between January 2018 and December 2018. Written informed consent was obtained from all participants.

All recruited APAC patients fulfilled the following inclusion criteria: age >55 years; APAC treatable with topical and systemic antiglaucomatous medications; and coexisting cataract in the affected eye. APAC was defined as (1) the presence of at least 2 of the following symptoms: ocular or periocular pain, headache, blurred vision, and nausea with/without vomiting; (2) the presence of the following signs: conjunctival injection, a mid-dilated unreactive pupil, corneal edema, and shallow anterior chamber; and (3) an IOP >40 mm Hg by Goldmann applanation tonometry.

Cataract patients without glaucoma of similar age were enrolled as a control group and underwent routine phacoemulsification and intraocular lens implantation. The exclusion criteria included a history of previous ocular surgery, evidence of inflammation, fundus pathology, optic nerve disease, or systemic diseases, such as hypertension and diabetes.

A standard protocol was used to initially treat the APAC attack with the following topical and systemic medications in order to lower the IOP: 1% topical pilocarpine 4 times daily; topical β-blocker twice daily and/or brinzolamide, and/or topical α_2-agonists; oral methazolamide at 50 mg twice daily, and 20% intravenous mannitol at 1–2 g/kg every 6 h. Anterior chamber paracentesis was performed in cases in which the IOP still exceeded 35 mm Hg 4 h after the initiation of the aforementioned treatments. A topical steroid (dexamethasone 3 times daily) was prescribed to alleviate the inflammatory reaction in the anterior eye segment. All APAC patients received phacoemulsification and intraocular lens implantation within days after cessation of the APAC attack, as soon as the IOP decreased to <21 mm Hg, and the inflammation had subsided sufficiently for safe intervention. The surgeries were performed by 2 experienced surgeons (H.Y. and Mei Xu).

Sample Collection

AH samples (80–200 μL) were aspirated via limbic paracentesis using a 27-gauge needle at the beginning of the phacoemulsification procedure. The samples were stored at –20 °C for up to 1 month and at –80 °C thereafter until all specimens had been collected for in-parallel analysis.

Quantitation of TGF-β, MMP, and TIMP Concentrations in AH Samples

The TGF-β, MMP, and TIMP concentrations of AH samples were analyzed using a multiplex system (Bio-Plex Magpix Multiplex Reader). With this system, multiple analytes can be detected and quantified in parallel in a single 25-μL sample. In the current study, the concentrations of the following analytes were measured with the commercial multiplex bead immunoassay kit: TGF-β1, TGF-β2, and TGF-β3 (Milliplex Map TGFβ Magnetic Bead 3 Plex Kit, Millipore; working range: 9.8–2,500 pg/mL); MMP-1, MMP-2, MMP-7, MMP-9, and MMP-10 (Milliplex Map Human MMP Magnetic Bead Panel 2, Millipore; working range: 27–20,000; 68–50,000; 548–400,000; 14–10,000; and 27–20,000 pg/mL, respectively); and TIMP-1 and TIMP-2 (Milliplex Map Human TIMP Magnetic Bead Panel 1, Millipore; working range: 20–20,000 and 49–50,000 pg/mL, respectively). AH samples were diluted 1:1 for processing with the MMP kit and at 1:4 for processing with the TIMP kit.

All analytic procedures were performed according to the manufacturer's instructions. Briefly, magnetic microspheres tagged with a fluorescent label were coupled to specific capture antibodies and mixed with samples containing unknown quantities of the proteins. Biotinylated detection antibodies and streptavidin R-phycoerythrin were then added. The mixture was analyzed using the Luminex Magpix system. The 2 lasers of the instrument identified the microsphere type and quantified the amount of bound

antigen. A concentration standard was run in parallel on each test plate for the generation of a standard curve to which the sample values were compared.

Statistical Analysis

If the detection rate of an analyte in any group was ≥85%, the concentration of the analyte is shown as mean ± SD. Differences between groups were evaluated using the Mann-Whitney U test. Data below the limit of detection for each assay were excluded from the mean calculation and Mann-Whitney U test. If the detection rate of an analyte in any group was <85%, Fisher's exact probability test was used to compare the detection rates between groups. Statistical analysis was performed using SPSS version 23.0 (IBM SPSS Statistics, Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

Results

Demographic Data of Study Participants

A total of 26 patients with APAC coexisting with cataract and 26 age-related patients with cataract who fulfilled the inclusion criteria were enrolled in the study. All cataract surgeries were performed uneventfully. The demographic data of all 52 patients are summarized in Table 1. The time interval between the acute attack and surgical treatment for all APAC patients was 3 ± 1 days (Table 2).

TGF-β, MMP, and TIMP Levels in AH Samples from APAC Patients versus Controls

As shown in Table 3, TGF-β1 and TGF-β2 levels were significantly higher in the AH of APAC patients than controls ($p < 0.001$ and $p < 0.001$, respectively). Notably, the TGF-β2 concentration was quite high in the AH of both groups. TGF-β1 could be detected in most samples, but the concentration was far below that of TGF-β2. In most AH samples from both groups, the concentration of TGF-β3 was below the detection limit. Figure 1 shows the TGF-β1 and TGF-β2 concentrations in the AH of individual patients.

Among the detected MMPs and TIPMs, the levels of MMP-2 and TIMP-1 were found significantly elevated in the AH of APAC patients compared with levels in the controls ($p < 0.001$ and $p < 0.001$, respectively). Although the mean concentrations of MMP-7, MMP-9, MMP-10, and TIMP-2 in the AH of APAC patients were higher than those in the AH of controls, the differences were not significant ($p = 0.524$; $p = 0.103$; $p = 0.111$; and $p = 0.059$, respectively). The concentrations of all detected MMPs and TIMPs are presented in Table 4. Notably, MMP-2, TIMP-1, and TIMP-2 were detected at relatively high concentrations, whereas MMP-1 concentrations were quite low and even undetectable in many samples in both groups. Figure 2 depicts the MMP-2 and TIMP-1 concentrations in AH samples of individual patients in both groups.

Table 1. Demographic characteristics of study participants

	APAC group ($n = 26$)	Control group ($n = 26$)
Age (mean ± SD), years,	64±6	66±7
Sex, *n* (%)		
Male	7 (27)	12 (46)
Female	19 (73)	14 (54)

Table 2. The time interval between the acute attack and surgical treatment

Interval between the attack and surgery, days	Patients, *n*
2	4
3	12
4	5
5	4
6	1

Table 3. TGF-β concentrations (means ± SD) in AH samples of APAC and control patients

Analytes	Concentration, pg/mL,		*p* value
	APAC group	control group	
TGF-β1	23/26 (88) 17.90±8.82	25/26 (96) 43.84±19.16	<0.001
TGF-β2	26/26 (100) 2,111.05±890.68	26/26 (100) 3,686.60±1,490.62	<0.001
TGF-β3	6/26 (23)	11/26 (42)	0.237*

Detection rate, *n*/*n* (%), represents the number of samples in which the analyte was detectable divided by the total number of samples. * *p* value calculated by Fisher's exact probability test.

Discussion

In the present study, the concentrations of members of the TGF-β, MMP, and TIMP families in AH were assessed to explore the possible mechanisms of residual glaucoma

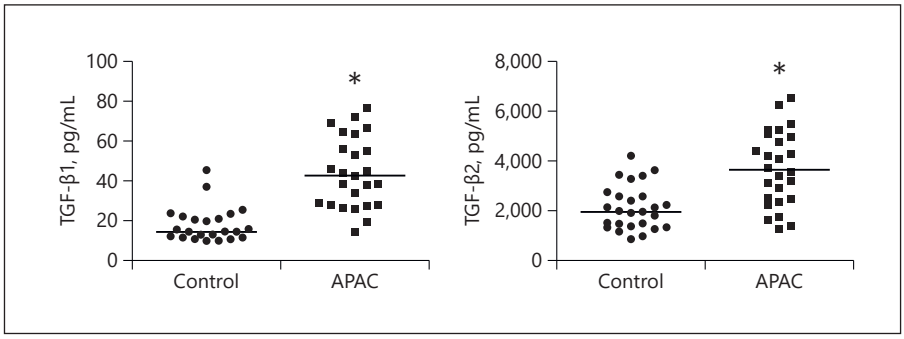

Fig. 1. Concentrations of TGF-β1 and TGF-β2 in AH samples of individual patients within the APAC and the control group (*$p < 0.001$).

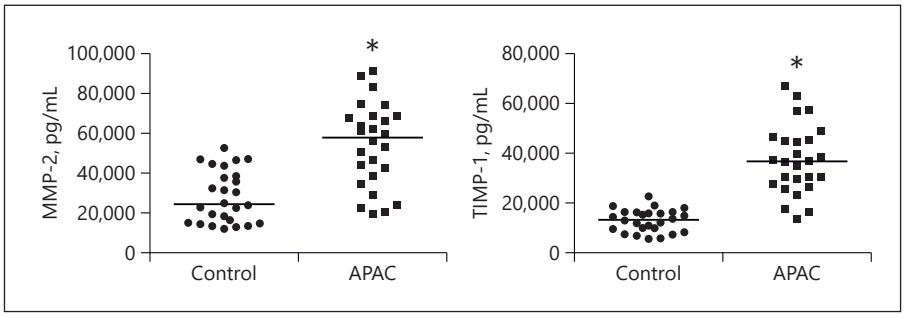

Fig. 2. Concentrations of MMP-2 and TIMP-1 in AH samples of individual patients within the APAC and the control group (*$p < 0.001$).

Table 4. Concentrations of MMPs and TIMPs (means ± SD) in AH samples of APAC and control patients

Analyte	Concentration, pg/mL		*p* value
	APAC group	control group	
MMP-1	5/26 (19)	10/26 (38)	0.22*
MMP-2	26/26 (100) 28,056.37±13,141.52	26/26 (100) 54,207.71±21,051.97	<0.001
MMP-7	22/26 (85) 1,074.18±425.82	24/26 (92) 1,169.37±487.46	0.524
MMP-9	26/26 (100) 87.69±36.48	26/26 (100) 108.10±45.60	0.103
MMP-10	26/26 (100) 97.78±34.89	26/26 (100) 117.89±47.15	0.111
TIMP-1	26/26 (100) 12,876.02±4,556.16	26/26 (100) 37,085.00±13,951.38	<0.001
TIMP-2	26/26 (100) 10,597.14±4,595.75	26/26 (100) 13,512.66±5,610.86	0.059

Detection rate, *n*/*n* (%), represents the number of samples in which the analyte was detectable divided by the total number of samples. * *p* value calculated using Fisher's exact probability test.

in APAC patients after lens extraction with or without goniosynechiolysis. Because the pupillary block is interrupted, and the angle is widened by lens extraction with or without goniosynechiolysis, we considered that the increased IOP in APAC patients may be associated with dysfunction of the TM as in primary open-angle glaucoma (POAG) patients. Research has established that excess ECM synthesis occurs in the TM of POAG eyes, and this is believed to be the cause of the increased resistance to aqueous outflow [11, 12]. Upregulation of TGF-β expression and altered activation of MMPs and TIMPs are well-known factors that influence ECM composition in the TM [13].

In the present study, we found that the levels of TGF-β1 and TGF-β2 were higher in the AH of APAC patients than in our control cataract patients, whereas the expression of TGF-β3 did not significantly differ between the groups. TGF-βs, as pleiotropic factors, are well-established regulators of a variety of biological processes including cell proliferation, differentiation, epithelial-mesenchymal transition, ECM production, and ECM deposition [14]. The TGF-β family consists of 5 subclasses (β1, β2, β3, β4, and β5), and only the first 3 of the 5 isoforms are known to be expressed in mammalian tissue. Several studies have shown significantly elevated levels of TGF-β2 in the AH of POAG patients. For example, in TM cells and tissues, TGF-β2 was found to specifically upregulate

multiple ECM-related genes, which results in excessive production and deposition of ECM proteins, such as collagen and fibronectin [6, 15]. Continuous perfusion of TGF-β2 into pig, monkey, and human anterior segments generated an increase in IOP not seen in anterior segments perfused with a vehicle control [6, 16]. Similar to TGF-β2, TGF-β1 was also reported to be present at an elevated concentration in the AH and even plasma of POAG patients [17, 18]. Moreover, TGF-β1 was shown to upregulate important ECM-related genes more robustly than TGF-β2 in cultured human TM cells [19]. However, TGF-β3, in contrast to TGF-β1 and TGF-β2, maintains appropriate ECM synthesis and promotes regenerative repair, protecting tissues against fibrosis [20]. Among these 3 members of the TGF-β family, TGF-β2 is regarded as the predominant isoform and maintained at a high level in human AH, whereas the amounts of TGF-β1 and TGF-β3 are generally very low, especially that of TGF-β3, which is not frequently detectable [21]. In a previous study in APAC patients, only TGF-β2 was detected and found to be elevated in the AH, which is consistent with our findings [5]. However, expression of TGF-β1 and TGF-β3 has not been detected in the published literature. An acute high IOP causes ischemic damage to both the anterior and posterior ocular segments [22], and previous research showed that acute focal cerebral ischemia increases the expression of all TGF-β isoforms [23]. We considered that the increased amounts of TGF-β1 and TGF-β2 in the AH of APAC patients were produced by local cells of the anterior ocular segments in response to ischemia resulting from the high IOP. A possible reason that we did not detect a significant increase in the TGF-β3 concentration may be that this cytokine is expressed at only very low levels by ocular local cells.

Previous studies showed that ischemia injury induces the expression of MMPs and TIMPs, which were also shown to be involved in the pathogenesis of POAG via the impairment in ECM turnover in the TM [7, 24]. As a large family of endopeptidases that degrade ECM proteins, MMPs are known to mediate ECM turnover, and their activity is regulated in part by specific endogenous inhibitors, TIMPs, which inhibit their proteolytic activity by obstructing their active site in a tight, reversible interaction with a 1:1 stoichiometry [8, 25]. Individual members of the TIMP family exhibit selective affinities for different members of the MMP family. TIMP-1 controls the activity of most MMPs, MMP-1 in particular, whereas TIMP-2 is the major inhibitor of MMP-2 [8]. In the present study, the concentrations of MMP-2 (activated and inactivated) and TIMP-1 in the AH of APAC patients were markedly higher than those in our control cataract patients, implying a more active ECM degradation and remodeling process in APAC eyes. An increased concentration of MMP-2 would shift the ratio of MMP-2 to TIMP-2, causing an imbalance with more enzyme than inhibitor. This could ultimately permit the generation of active enzyme and result in local degradation of most ECM constituents, except for native collagen type I, which is targeted mainly by MMP-1. On the other hand, the increased concentration of TIMP-1 would strongly inhibit MMP-1 activity as well as most other MMPs. Thus, the net effect could be absolute and relative accumulation of collagen type I in the AH-exposed ocular tissue of the APAC eye. This condition has been observed in the iris stroma of the APAC eye, where the total amount of collagen and proportion of type I collagen detected by Sirius red polarization were considerably greater than those seen in normal controls [26]. We postulate that such a pathological process likely occurs in the TM of the APAC-affected eye and results in the abnormal deposition of ECM, which increases aqueous outflow resistance. It is worth noting that the elevated levels of MMP-2 and TIMP-1 in the AH of the APAC eye may be related to increased TGF-β expression, which was shown to promote the production of MMP-2 and TIMP-1 in hepatic stellate cells and gingival fibroblasts [27, 28]. We recognize that a major limitation of this study is that we only measured the concentrations of MMP-1, -2, -7, -9, and -10 and TIMP-1 and TIMP-2, and did not assay MMP activity, which needs to be investigated in a future study. Another limitation is that the majority of APAC patients were on treatment with topical medications, such as the β-blocker timolol and α-agonist brimonidine, which could potentially affect the aqueous MMP and TIMP concentrations.

In conclusion, we found elevated levels of TGF-β1, TGF-β2, MMP-2, and TIMP-1 in the AH of eyes affected by APAC. The increased presence of these proteins likely causes excessive deposition of ECM as well as an abnormal ECM composition, particularly accumulation of collagen type I in the TM, resulting in an increase in aqueous outflow resistance. Such events may explain the occurrence of residual glaucoma in patients who experience APAC after lens extraction with goniosynechiolysis.

Statement of Ethics

This study was approved by the local Ethics Committee of the First Affiliated Hospital of Chongqing Medical University according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.Y.: design of the study; Y.C. conduct of the study: Y.C., Y.Z., and G.L.: collection and management of data; H.Y. and Y.C.: analysis and interpretation of data; H.Y. and Y.C.: preparation, review, or approval of the manuscript. All authors read and approved the final manuscript.

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