Research progress of corneal characteristics and changes in primary angle-closure glaucoma (Review)

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Received September 19, 2024; Accepted January 10, 2025

DOI: 10.3892/br.2025.1937

Abstract. The cornea plays a crucial role in the refractive system of the eyeball, and its changes can significantly impact the visual quality of patients with glaucoma. In patients with primary angle-closure glaucoma, several corneal alterations occur, including changes in corneal thickness and curvature, modification in corneal epithelial cells and nerves, activation of inflammatory cells, and variations in the number and morphology of stromal and endothelial cells. These morphological and structural changes in the cornea are mainly influenced by acute or chronic elevation of intraocular pressure and treatment. In the present review the corneal morphological changes and regularities associated with primary angle-closure glaucoma are examined.

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1. Introduction

Glaucoma is the leading cause of irreversible blindness worldwide. In 2020, ~79.6 million individuals globally were affected by glaucoma, and this number is projected to exceed 111.8 million by 2040 (1). In China, the incidence of primary angle-closure glaucoma is higher than that of primary open-angle glaucoma (2), and the rate of blindness is also greater (3). Primary angle-closure glaucoma is a complex eye disease that can cause varying degrees of damage to both the anterior and posterior segments of the eye. The cornea, part of the anterior segment, is positioned at the very front of the eyeball. It lacks blood vessels but has the densest innervation. Its refractive properties allow light to be transmitted to the retina, and its transparency is essential for clear vision (4). Therefore, studying the effect of angle-closure glaucoma on the cornea is crucial.

With the continuous development of corneal examination technology, our understanding of corneal morphology and structural changes in angle-closure glaucoma has deepened. Ultrasonic thickness measurement is a common method for measuring corneal thickness, but it is a contact examination. By contrast, anterior segment optical coherence tomography (AS-OCT) is a non-contact detection method that conveniently and quickly provides a new reference for measuring corneal thickness (5). Optical biometry can accurately measure the biological parameters of the eye, such as the eye axis, anterior chamber depth, and corneal curvature (6). Specular microscopy, commonly used to detect corneal endothelium, can qualitatively and quantitatively examine corneal endothelial cells at high magnification, although it cannot visually detect the microscopic structure of the remaining corneal layers (7). The emergence of *in vivo* confocal microscopy (IVCM) offers a non-invasive, sensitive, specific, and reproducible method for corneal examination (8). IVCM is frequently used to measure changes in corneal microstructure, including corneal epithelial cells, nerve, dendritic cells, stromal cells, and endothelial cells (9-12). The high resolution and penetrating power of IVCM provide a significant advantage in evaluating corneal microstructure damage in angle-closure glaucoma (13). The increasing number of detection methods also provides valuable reference indices for observing corneal changes in patients with angle-closure glaucoma.

2. Effect of primary angle-closure glaucoma on corneal thickness

Recent studies have demonstrated that central corneal thickness (CCT) in primary angle-closure glaucoma

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Key words: angle-closure glaucoma, cornea, morphological characteristics, *in vivo* confocal microscopy

primarily undergoes fluctuations due to transient spikes in intraocular pressure (IOP). These fluctuations primarily result from stromal and epithelial edema, leading to increased CCT during episodes of elevated IOP. However, investigations into the impact of historical spikes in IOP and diverse surgical interventions have indicated minimal long-term effects on CCT (14,15). A longitudinal study spanning 5 years, involving 26 patients with angle-closure glaucoma, revealed no significant alteration in CCT following laser therapy or trabeculectomy. Moreover, antecedent episodes of acute intraocular hypertension did not correlate with notable changes in CCT during extended follow-up periods (15). Niu *et al* (16) in their comparison of CCT between healthy individuals and those with a history of acute angle closure, similarly concluded that prior instances of acute intraocular hypertension did not induce substantial CCT variations. Chen *et al* (17) corroborated these findings by demonstrating no significant disparity in CCT among individuals with angle-closure glaucoma, their fellow unaffected eyes, and normal controls. Sugumaran *et al* (18) observed that CCT averaged 525 μm when IOP ranged from 20 to 40 mmHg, increasing to 528 μm when IOP escalated to 41-60 mmHg. This association highlighted CCT thickening with rising IOP. Presently, laser peripheral iridectomy exhibits efficacy in enhancing anterior chamber depth and volume in patients with angle-closure glaucoma, consequently reducing the incidence of acute angle closure. Nonetheless, its impact on CCT remains insignificant (19,20). Prolonged administration of glaucoma medications may trigger corneal extracellular matrix degradation, potentially leading to CCT reduction (15).

3. Effects of primary angle-closure glaucoma on corneal curvature and astigmatism

The relatively flat small cornea serves as one of the anatomical foundations for the sudden onset of angle-closure glaucoma. Often, this type of cornea is accompanied by a lax ciliary band and an anteriorly positioned lens. Additionally, individuals with a flat cornea typically exhibit a thicker lens, collectively contributing to increased crowding within the anterior chamber (21). Simultaneously, a reduced posterior corneal curvature poses a higher risk of angular closure compared with the anterior corneal curvature (22). However, a survey conducted among patients with primary angle closure disease revealed that the majority exhibit corneal astigmatism ranging from 0.25 to 1.25D, similar to individuals of the same age with cataracts. This suggests that under normal IOP, the disease itself exerts minimal influence on corneal curvature. Notably, the prevalent type of astigmatism among patients with angle closure disease is primarily oblique astigmatism, potentially contributing to decreased visual acuity (23). Nevertheless, prior research solely retrospectively observed changes in corneal curvature and corneal astigmatism in angle-closure diseases with normal IOP (22). Further investigations are warranted to elucidate differences in corneal curvature following acute attacks of angle-closure glaucoma and their potential impact on the calculation of ocular biological parameters.

4. Effect of primary angle-closure glaucoma on corneal microstructure

Changes of corneal epithelial cells. Some patients diagnosed with angle-closure glaucoma, particularly those with chronic conditions, necessitate prolonged administrations of anti-glaucoma medication to manage IOP. Notably, ~70% of these medications contain benzalkonium bromide as a preservative to ensure their long-term stability (24,25). However, the presence of preservatives can instigate ocular surface damage, leading to the disruption of microvilli on epithelial cell surfaces and loss of cell integrity. Prolonged use and increased dosage of these medications further diminish epithelial cell vitality and may trigger cell apoptosis (24,26). Valladales-Restrepo *et al* (27) observed that prolonged use of anti-glaucoma medications in patients with angle-closure disease induced ocular surface damage. However, the utilization of composite formulations has been found to mitigate eye discomfort and enhance patient compliance (27). Additionally, Güçlü *et al* (28) investigated the impact of varying drug dosages on corneal epithelial cells in patients with angle-closure glaucoma. Their findings indicated that anti-glaucoma drug application resulted in reduced limbal stem cell count and impaired cell migration, ultimately leading to a decrease in central corneal epithelial thickness (28). In addition to therapeutic medications, the extent of angular closure can also inflict damage on the corneal epithelium. In this study involving patients with angle-closure glaucoma, individuals with a history of drug treatment exceeding 1 week were excluded. Results indicated that with the widening of the angle closure range, there was a progressive reduction in corneal epithelial cell count, potentially culminating in limbal stem cell deficiency in severe cases. This phenomenon primarily stems from diminished nutritional support to peripheral corneal endothelial cells as the angle closure range expands. Consequently, dysfunctional corneal endothelial cells lead to alterations in the corneal limbal microenvironment, characterized by an increase in corneal inflammatory cells and a decrease in limbal stem cell count. Therefore, heightened vigilance for limbal stem cell deficiency is warranted in patients with advanced disease and multi-directional angular closure (29). Moreover, abrupt increases in IOP among patients with angle-closure glaucoma can impact epithelial cells, resulting in cell space widening and epithelial cell swelling. Severe cases may exhibit large vacuoles between epithelial cells. Upon decreasing IOP, these changes in epithelial cells can rapidly revert (13). However, there is a scarcity of studies examining the long-term quantity and morphology of corneal epithelial cells following the onset of intraocular hypertension. Thus, further research is imperative. Consequently, the protracted and extensive utilization of anti-glaucoma medications and the broad range of angular closure may underlie the compromised ocular surface microenvironment in patients with glaucoma. Meanwhile the enduring effects of acute intraocular hypertension on corneal epithelium remain enigmatic (Fig. 1).

Changes of corneal subepithelial nerve. Under normal circumstances, corneal nerves play crucial roles in sensing harmful substances on the corneal surface, triggering eyelid closure and tear production, and facilitating corneal

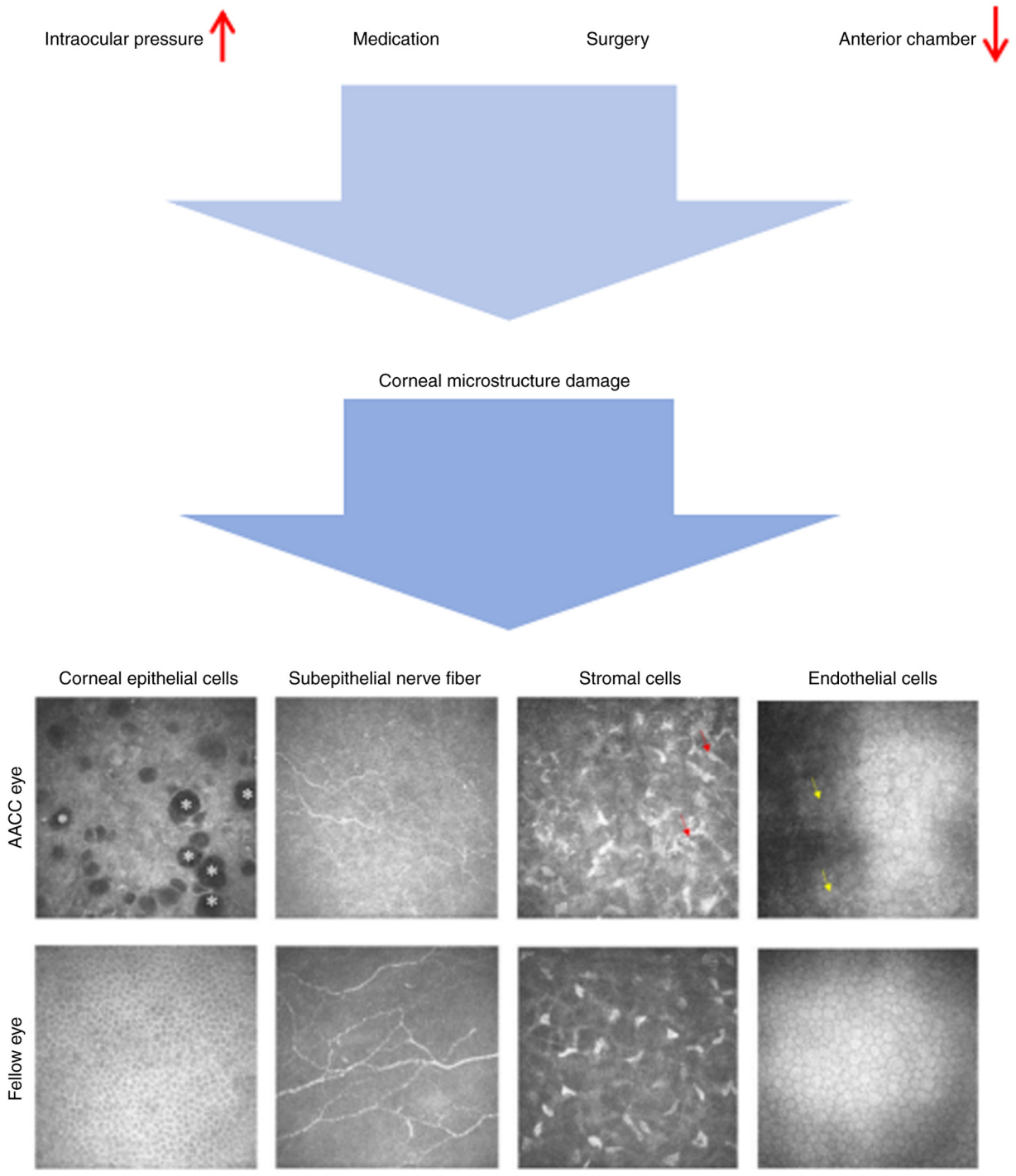

Figure 1. Corneal microstructure injury caused by high intraocular pressure, medication, surgery and a shallow anterior chamber. The four images show epithelial cell swelling, corneal subepithelial nerves, activation of stromal cells, and enlarged endothelial cells. AACC, acute angle-closure crisis. [The images were obtained from Wang *et al* (13). This work is licensed under the Creative Commons Attribution 4.0 International (CC BY 4.0) License: © Wang *et al* 2022].

repair (30). High IOP can directly damage corneal nerves. Research indicates that patients experiencing acute ocular hypertension, such as those with angle-closure glaucoma, show reduced corneal nerve density and length in the affected eye compared with the contralateral eye (13). This reduction is believed to stem from corneal dystrophy induced by diminished blood flow in the corneal limbal vascular network due to elevated ocular pressure (13). Additionally, the neurotoxic effects of anti-glaucoma drugs on the cornea are noteworthy. Clinical investigations have demonstrated that both the drugs themselves and their preservatives can directly harm corneal nerves (31). Rossi *et al* (32) in their examination of patients with angle-closure disease undergoing drug treatment for up to 3 years, observed a significant decrease in corneal nerve density using IVCM. Similarly, Agnifili *et al* (33) reported that an increase in the number of glaucoma medications was associated with a decrease in corneal nerve density, increased tortuosity, and noticeable ocular dryness and discomfort in patients with glaucoma. Injury to the corneal nerve during surgery is a significant concern. Presently, the commonly

used clear corneal incision in cataract phacoemulsification combined with angle separation for treating angle-closure glaucoma results in decreased corneal sensitivity in 38.5% of patients post-surgery, indicating notable damage to corneal nerves (34). Giannaccare *et al* (9) conducted a study involving 30 patients undergoing unilateral cataract surgery. They observed a decrease in the density, length and width of corneal nerve fibers bilaterally 1 month post-surgery compared with preoperative levels, with a relatively smaller and shorter-lasting decrease noted in the contralateral eye. Termed sympathetic change, this phenomenon is primarily attributed to impaired neuroafferent function leading to the local release of pro-inflammatory neuropeptides, thereby causing neurogenic inflammation (9). Agnifili *et al* (35) performed a follow-up study on 38 patients with open-angle glaucoma who had stable IOP control after trabeculectomy for 6 months. They observed a continuous reduction in the number of corneal nerve fibers and high reflex points between nerve fibers in these patients, with the appearance of high reflex points indicative of inflammatory cell deposition. The use of steroid eye drops post-surgery demonstrated efficacy in mitigating corneal inflammation. The reduction in corneal nerve density observed may be attributed to the inhibitory effect of mitomycin on corneal cell proliferation, with most of this effect dissipating within 6 months post-surgery. However, the alterations in corneal nerve parameters, such as the density, length and curvature of nerve fibers, following the cessation of drug effects remain unclear (35). While there is a lack of specific studies on angle-closure glaucoma, it is speculated that similar conclusions can be drawn for patients with this condition. Corneal injury resulting from trabeculectomy may primarily stem from the influence of intraoperative and postoperative medications. In treating patients with absolute angle-closure glaucoma, the extent of nerve damage is contingent upon the degree and duration of cryopreservation. A study involving 18 dogs revealed a decrease in corneal sensitivity across all corneal areas by 10 to 42%, 1 week post-surgery, with six dogs developing corneal ulcers despite avoiding the 3 and 9 o 'clock positions during surgery (36).

Changes of corneal dendritic cells. Normally, dendritic cells are situated between the corneal epithelium and the stromal layer. In the presence of corneal inflammation, there is an upsurge in the activation, quantity and maturity of dendritic cells (37,38). In patients with angle-closure glaucoma, the aqueous humor harbors a plethora of inflammatory factors with their expression escalating alongside IOP. This inflammatory milieu induces a substantial increase in activated dendritic cells within the corneal interlayer. As IOP decreases and the disease enters a remission phase the number of activated dendritic cells may decrease as well (37,39). Mastropasqua *et al* (40) conducted pertinent research on the distribution of augmented dendritic cells in the cornea. They observed a general increase in dendritic cell count in patients with glaucoma receiving two or more relevant medications, particularly concentrated at the corneal limbus compared with the corneal center, a phenomenon associated with dry eye occurrence (40). However, pertinent clinical trials investigating changes in the distribution of corneal dendritic cells during acute ocular hypertension are lacking. In conclusion, during acute angle-closure glaucoma, the pronounced inflammatory response triggers the activation and proliferation of dendritic cells, underscoring the significance of anti-inflammatory therapy alongside IOP reduction.

Changes of corneal stromal cells. Corneal stromal cells are highly active, participating not only in the renewal of the extracellular matrix, but also in ensuring the uniform passage of light through one or more stromal cells. It is crucial for maintaining visual acuity (41). It has been observed that conditions such as diabetes and dry eye reduce stromal cell density and alter their morphology (42,43). However, there is limited research on the impact of angle-closure glaucoma on stromal cells. Activation of the corneal stroma indicates inflammation within corneal tissue. During acute angle-closure glaucoma attacks, the destruction of the blood-aqueous humor barrier leads to the production of numerous inflammatory factors in the aqueous humor, triggering stromal cell activation. This activation is manifested as stromal cell swelling, enhanced reflectivity, and a more interconnected network (13). Pilocarpine nitrate eye drops, a first-line treatment for angle-closure glaucoma, can also induce changes in corneal microstructure. A previous study indicated that concentrations exceeding 0.625 g/l can result in abnormal stromal cell morphology and even apoptosis, with damage progressively worsening over time with prolonged use (44). It is suggested that the morphological changes of corneal stromal cells can be used as one of the indices to evaluate the degree of inflammation in patients.

Effects of primary angle-closure glaucoma on corneal endothelial cells

Effects of high IOP on endothelial cells. Recent studies indicate that regardless of the extent or duration of IOP elevation, there is a decrease in the number of endothelial cells accompanied by an increase in the coefficient of variation. This phenomenon is attributed to endothelial cell dystrophy and pressure imbalances (18,45). The duration of intraocular hypertension is a crucial factor influencing endothelial cell loss. Short-term significant increases in IOP are the primary cause of such loss (46). In an experiment involving rats a rapid increase in eye pressure within 2 h resulted in irregularly shaped endothelial cells and decreased cell count (47). In clinical investigations Li *et al* (48) conducted a comprehensive study on the duration of high IOP leading to severe endothelial cell damage. In this study it was observed that after the onset of acute angle-closure glaucoma, 12.28% of eyes had an endothelial cell density (ECD) <1,000/mm^2, 30.41% had an ECD between 1,000-2,000/mm^2, and 57.31% had an ECD >2,000/mm^2. The variance in ECD was primarily attributed to the duration of intraocular hypertension; durations shorter than 48 h did not significantly affect endothelial cell count or morphology (48). The effects of acute intraocular hypertension on endothelial cells have also been investigated. Tham *et al* (49) noted a significant decrease in the number of endothelial cells in patients with chronic angle-closure glaucoma who had experienced previous episodes of acute intraocular hypertension, with a reduction of ~11.6%. Yeom *et al* (50) conducted measurements revealing that the ECD in eyes following an acute attack of angle-closure glaucoma averaged ~1,818±490 cells/mm^2, whereas the ECD

Table I. Alteration of the cornea in primary angle-closure glaucoma.

A, Corneal macrostructure

Name	Functions	Influencing factor(s)	Mechanism(s)	(Refs.)
Thickness	N/A	IOP	Stromal and epithelial edema	(14,15)
		Medications	Corneal extracellular matrix degradation	(15)
Curvature	N/A	IOP	N/A	(23)

B, Corneal microstructure

Name	Functions	Influencing factor(s)	Mechanism(s)	(Refs.)
Epithelial cells	Barrier	IOP	Cell space widening and epithelial cell swelling	(13)
		Medications	Disruption of microvilli	(24,26)
		Extent of angle closure	Diminished nutritional support	(29)
Subepithelial nerves	Facilitate corneal repair	IOP	Diminished blood flow in the corneal limbal vascular network	(13)
		Medications	Direct injury	(31)
		Surgery	Direct injury and damage brought on by drugs	(9,35)
Dendritic cells	Inflammatory responses	IOP	Inflammatory milieu	(37,39)
Stromal cells	Maintaining visual acuity	IOP	Destruction of the blood-aqueous humor barrier	(13)
Endothelial cells	Barrier	IOP	Endothelial cell dystrophy and pressure imbalances	(18,45)
		Shallow anterior chamber	Cornea iris contact	(51)
		YAG laser	Age-related changes	(57)

IOP, intraocular pressure; N/A, not applicable.

of the contralateral eye averaged 2,675±348 cells/mm^2. The ECD in eyes experiencing an acute increase in IOP was significantly lower compared with the contralateral eye, indicating damage to endothelial cells caused by acute IOP elevation (50). Currently, studies demonstrate that high IOP can lead to increased endothelial cell damage, but there is a lack of research quantifying the extent of damage corresponding to increased IOP levels. Generally, higher IOP levels over short durations can result in further damage to the corneal endothelium.

Influence of the shallow anterior chamber on endothelial cells. The shallow anterior chamber contributes to the reduction in the number of endothelial cells. Verma *et al* (51) investigated 529 patients diagnosed with primary angle-closure glaucoma and noted that even in the absence of acute intraocular hypertension, patients with angle-closure disease exhibited diminished corneal endothelial cell counts, reduced hexagonal cell percentage, and increased coefficient of variation (51). Additionally, the follow-up study of eyes in remission from acute angle-closure glaucoma and normal eyes 3 months post-cataract surgery, by Yeom *et al* (50), revealed that although normal eyes initially displayed higher ECD counts before surgery, there was no significant difference in the percentage decline of ECD between the two groups post-surgery. This suggests that past episodes of acute intraocular hypertension did not exacerbate endothelial cell damage following cataract surgery. The diminished ECD observed in patients with angle-closure glaucoma may be attributed to a history of acute attacks and a shallow anterior chamber (50). This finding was corroborated by Imai *et al* (52).

Effects of YAG laser therapy on endothelial cells. Laser therapy represents a significant treatment modality for patients with primary angle closure glaucoma (53). However, there have been variations in the perceived impact of YAG laser therapy on endothelial cells compared to historical perspectives. Previous research suggested that the energy emitted by YAG laser and the consequent inflammatory response could result in increased heterogeneity, elevated coefficient of variation, and decreased cell density of corneal endothelial cells (54,55). Nevertheless, a previous study indicated no substantial disparity in the number and morphology of ECD in treated eyes compared with contralateral eyes within a 72-month period (56). Ono *et al* (57) conducted a 7-year follow-up study on patients post-YAG treatment and observed that the annual reduction rate of ECD in treated patients mirrored that of healthy individuals of similar age suggesting that age-related changes may predominantly contribute to ECD reduction, with laser treatment posing no significant harm to endothelial cells (57). In essence, YAG laser treatment does not induce severe damage to the cornea.

5. Conclusion

In summary, glaucoma represents an irreversible and sight-threatening ocular disease. Early detection and effective control of IOP stand as paramount steps in preventing further optic nerve damage. Nevertheless, with ongoing research in glaucoma, treatment strategies continue to evolve, aiming not only to alleviate patient discomfort but also to enhance long-term quality of life. During acute attacks of angle-closure glaucoma, patients often experience corneal edema, exacerbated by delayed repair during and after surgery, prolonged wound healing, and the extended use of anti-glaucoma medications (Table I). These factors increase susceptibility to symptoms such as eye redness, dryness and discomfort, significantly impacting the lives of patients. Therefore, alongside IOP reduction, attention must also be directed towards monitoring corneal structural changes. Unlike the past reliance solely on corneal endoscopy for assessing corneal endothelial cell changes, confocal microscopy offers a precise means to identify corneal microstructure damage. This provides an objective framework for understanding the underlying causes of sustained visual impairment and facilitates early detection of ocular surface damage severity. While confocal microscopy yields valuable insights into corneal microstructural changes, further investigation utilizing long-term, large-scale samples is necessary to elucidate the effects of high IOP on corneal parameters and the long-term alterations in angle-closure glaucoma.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Projects of Medical Science Research of Health Commission of Hebei Province, China (grant no. 20220830).

Availability of data and materials

Not applicable.

Authors' contributions

YW wrote and subsequently revised the article. LY and YQ collected related articles. FF proposed the writing directions and reviewed articles. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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