Advances in Ophthalmology Practice and Research 4 (2024) 194–201

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research

Review

Research progress on the impact of cataract surgery on corneal endothelial cells

Chen Yang[a], Qi An[a], Han Zhou[b], Hongyan Ge[a,*]

[a] Department of Ophthalmology, The First Affiliated Hospital of Harbin Medical University, Harbin, China
[b] Department of Cardiology, The First Affiliated Hospital of Harbin Medical University, Harbin, China

ARTICLE INFO

Keywords:
Cataract
Corneal endothelial cells
Surgical treatment

ABSTRACT

Background: Cataracts are a common eye disease and a major cause of blindness in China and worldwide. In China, the incidence of cataracts among people over 60 years old is as high as 80%. Surgery is the primary treatment for various types of cataracts, but such invasive procedures can affect corneal endothelial cells to some extent.
Content: Cataract surgery can damage corneal endothelial cells, leading to complications such as corneal edema in mild cases. Severe damage can result in endothelial decompensation, necessitating secondary corneal endothelial transplantation. Preoperative thorough assessment of endothelial status, intraoperative endothelial protection measures, and postoperative active use of medications to prevent further damage to endothelial cells can reduce endothelial cell loss. Factors influencing endothelial cell status include whether the patient has related systemic diseases or ocular conditions, the hardness of the nucleus, the choice of surgical incision, the method of nuclear fragmentation, the type of viscoelastic agent used, the orientation of the phacoemulsification needle bevel, the duration and energy of ultrasound use, the choice of fluid control system, the use of protective auxiliary instruments, the application of intraocular lens scaffold technology, femtosecond laser assistance, and the use of certain medications.
Conclusions: Actively regulating the factors affecting corneal endothelial cells to reduce damage related to cataract surgery is crucial. This paper reviews the existing literature on various factors affecting corneal endothelial cells during cataract surgery and explores future developments and research directions.

1. Introduction

Cataract is a common blinding eye disease worldwide. In 2010, there were 10.8 million people blind due to cataracts, and with the aging global population and increasing life expectancy, this number is projected to rise to 40 million by 2025.[1] Cataracts are degenerative changes characterized by reduced transparency or color changes in the lens, leading to decreased optical clarity. The pathogenesis of cataracts is influenced by a variety of complex internal and external factors such as aging, metabolic disorders, genetics, trauma, toxicity, radiation, local nutritional deficiencies, and certain systemic metabolic or immune diseases. These factors can cause lens opacity, preventing light from passing through the cloudy lens to form an image on the retina, resulting in clinical symptoms such as decreased vision, visual field defects, and reduced contrast sensitivity, which affect the patient's daily life, work, and study.[2] (see Fig. 1)

The most common cataract surgery is phacoemulsification. Studies have shown that this procedure can damage the corneal endothelium, mainly evidenced by a postoperative decrease in endothelial cell count, an increase in average cell area, and an increase in central corneal thickness.[3] The corneal endothelium is located in the innermost layer of the cornea's five-layer structure and consists of a single layer of hexagonal epithelial cells.[4] It maintains corneal hydration and transparency. However, damaged corneal endothelial cells are difficult to regenerate and can only be replaced by the enlargement and migration of adjacent cells. When endothelial cell damage exceeds a certain limit and there are not enough endothelial cells to compensate for the deficit, it leads to decompensation, resulting in vision loss or even blindness. At this stage, the only treatment option is corneal endothelial transplantation.[5]

Therefore, protecting corneal endothelial cells is crucial. Many factors can lead to damage and reduction of corneal endothelial cells, especially post-cataract surgery, where this reduction is more pronounced. Thus, controlling and preventing these adverse factors is particularly important. We have summarized these adverse factors and the potential

* Corresponding author.
E-mail address: gehongyan@hrbmu.edu.cn (H. Ge).

https://doi.org/10.1016/j.aopr.2024.08.002
Received 14 March 2024; Received in revised form 17 July 2024; Accepted 6 August 2024
Available online 8 August 2024

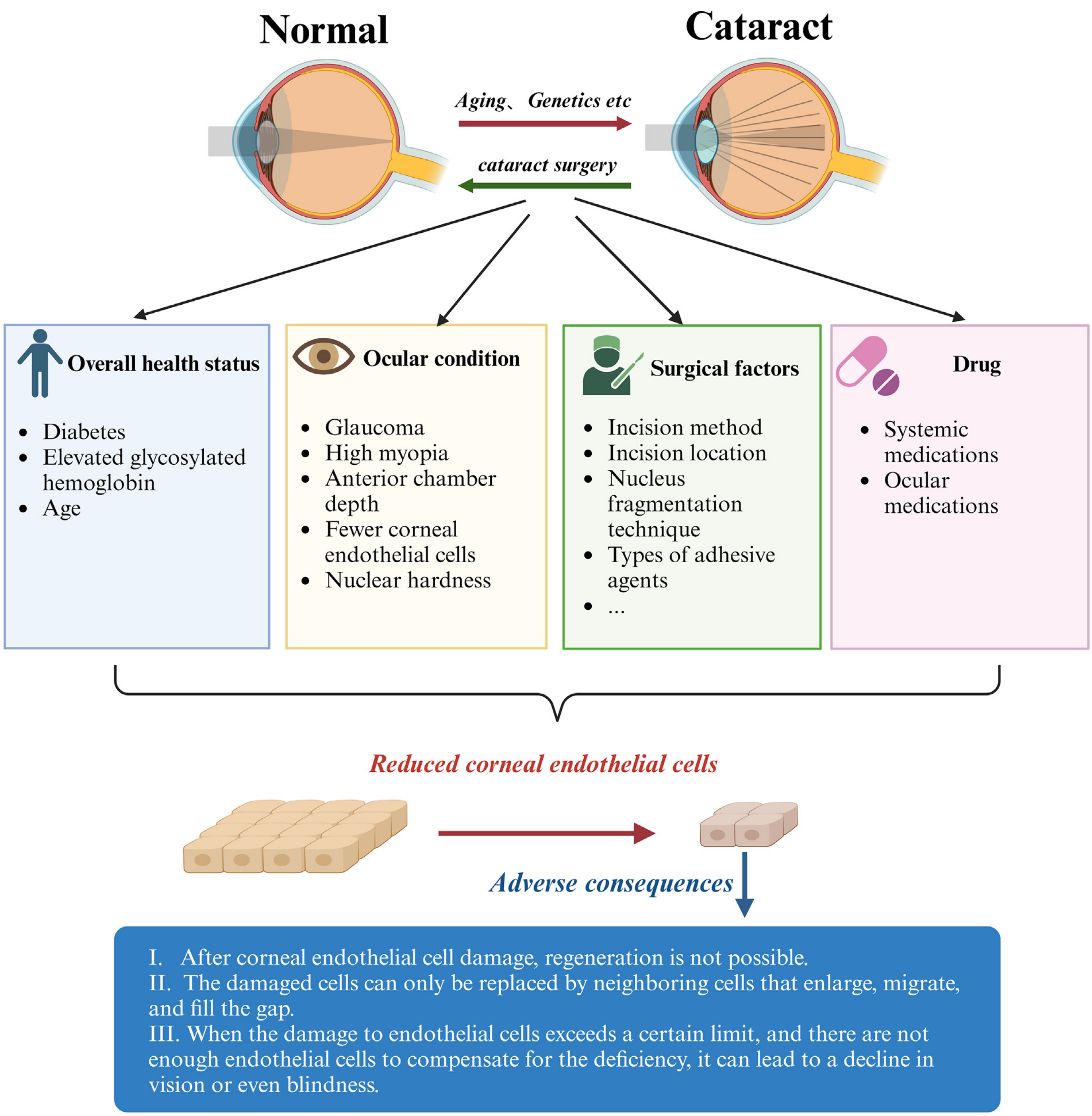

Fig. 1. Factors leading to corneal endothelial cell loss during cataract surgery.

damage caused by the surgery itself to the corneal endothelium, providing insights and new perspectives for protecting the corneal endothelium after cataract surgery. We will discuss and summarize from the aspects of the patient's overall health, local eye condition, cataract surgery, and medication use.

2. Patient's overall systemic condition

2.1. Diabetes and elevated glycated hemoglobin

Multiple studies have found that the hyperglycemic state in diabetic patients causes metabolic stress, leading to corneal morphological abnormalities, higher rates of corneal endothelial cell loss, and reduced cell density.[5,6] The mechanisms by which diabetes affects corneal endothelial cells are not fully agreed upon, but research suggests several key points:

- The primary pump of corneal endothelial cells is Na+/K + -ATPase, which actively pumps fluid from the stroma into the aqueous humor to maintain corneal transparency. Persistent hyperglycemia in diabetes leads to decreased Na+/K + -ATPase activity, resulting in changes in the morphology and permeability of corneal endothelial cells.[7]
- The hyperglycemic state in diabetic patients increases the activity of aldose reductase, causing sorbitol accumulation in corneal endothelial cells. This hyperosmotic condition leads to endothelial cell swelling.[8]
- Diabetic patients exhibit a slower Krebs cycle in the cornea, resulting in reduced ATP production.[9]
- The glucose concentration in the aqueous humor of diabetic patients may often be elevated, leading to metabolic acidosis in the corneal stroma and a decrease in repair capability.[9]
- In diabetic patients, intraoperative pupil constriction is more common than in non-diabetic patients, necessitating phacoemulsification closer to the cornea.[10]
- Diabetic patients have a lower density of the sub-basal nerve plexus compared to non-diabetic patients, and cataract surgery further

reduces this density, making diabetic patients more susceptible to diabetic keratopathy.[11]

Additionally, studies have shown significant differences in corneal endothelial cell loss between diabetic and non-diabetic populations following phacoemulsification cataract surgery, with diabetic patients experiencing greater endothelial cell loss.[12] Therefore, proper blood glucose control is beneficial for protecting corneal endothelial cells.

2.2. Age

Singh R et al.[13] found that increasing age is an independent risk factor for significant reduction in corneal endothelial cell (EC) count following phacoemulsification. Both domestic and international studies have shown that cell density decreases with age, while cell area and polymorphism increase with age.[14] At birth, normal corneal EC density ranges from 4000 to 5000 cells/mm^2. With increasing age, corneal EC density declines at a rate of 0.3%–0.6% per year, with normal adult eyes approximating 2000–3000 cells/mm^2.[14]

Age is an unavoidable factor leading to a decrease in corneal endothelial cell count. Cataract patients are often elderly, and studies have shown that the degree of endothelial cell density reduction after cataract surgery increases with age.[15] Therefore, it is beneficial to opt for surgical treatment as early as possible when there are indications for cataract surgery.

3. The patient's ocular condition

3.1. Glaucoma

Studies by Chen MJ et al.[16] and Ianchulev T et al.[17] have shown that both open-angle glaucoma and angle-closure glaucoma result in varying degrees of corneal endothelial cell loss. The most significant differences in changes of average, maximum, and minimum cell areas are observed in acute angle-closure glaucoma. This indicates that the short-term, severe intraocular pressure (IOP) spikes during acute glaucoma attacks cause more significant damage to the corneal endothelium compared to the long-term, gradual, and sustained IOP elevation seen in open-angle glaucoma and chronic angle-closure glaucoma. The studies also mention that an acute glaucoma attack can result in up to a 33% loss of corneal endothelial cells, with losses as high as 91%. Furthermore, phacoemulsification in patients with cataracts combined with primary open-angle glaucoma leads to greater endothelial cell loss compared to patients with only cataracts.[17]

Therefore, due to the high IOP, glaucoma patients already have a reduced corneal endothelial cell reserve compared to normal individuals. Cataract surgery inevitably affects the corneal endothelium to some extent, and glaucoma patients have lower tolerance to cataract surgery, ultimately resulting in a decrease in corneal endothelial cells postoperatively.

3.2. High myopia

Research by Patel V et al. indicates that patients with high myopia experience more severe corneal endothelial cell loss after intraocular lens implantation compared to non-myopic patients.[18] Coullet J et al.'s study[19] shows that due to the high sensitivity of corneal endothelial cells to damage in patients with high myopia, their postoperative recovery period is longer than that of non-high myopic patients.

Currently, there is limited research on the impact of cataract surgery on corneal endothelial cells in patients with high myopia. More data collection and studies are needed to explore the effects and mechanisms of high myopia on corneal endothelial cells.

3.3. Anterior chamber depth and axial length of the eye

Research by Hwang HB et al.[20] found that patients with an anterior chamber depth (ACD) of 1.5 mm $<$ ACD $\leq$2.5 mm experienced more corneal endothelial cell loss after phacoemulsification cataract surgery compared to those with an ACD of 3.5 mm $<$ ACD $\leq$4.5 mm. This finding is consistent with Khalid M et al.,[21] who suggested that a shallower anterior chamber depth reduces the operational space and distance for the surgeon, leading to greater endothelial cell loss. Khalid M et al. also indicated that a shorter axial length is a risk factor for postoperative corneal endothelial cell loss.

Shallow anterior chamber and short axial length can serve as warning indicators for surgeons, emphasizing the need for meticulous intraoperative techniques to protect the corneal endothelium in these patients. Conversely, Reuschel A et al.[22] argued that there is no significant correlation between anterior chamber depth or axial length and postoperative corneal endothelial cell loss. However, there are no stratified controlled studies comparing corneal endothelial cell loss based on different anterior chamber depths and axial lengths. The impact of these two conditions on corneal endothelial cells requires further investigation.

3.4. Nuclear hardness

During phacoemulsification cataract surgery, removing a hard nucleus requires more ultrasound energy and time compared to a soft nucleus, thereby increasing the risk of surgery-induced trauma, particularly corneal endothelial dysfunction. The study by Singh R et al.[13] confirmed that higher nucleus hardness results in greater postoperative corneal endothelial cell loss. Clinically, it is not uncommon to encounter cataract patients with corneal endothelial cell counts $<$1000 cells/mm^2 and lens nucleus grade $\geq$ IV. These patients experience greater endothelial cell loss and a higher rate of functional decompensation after phacoemulsification.[23]

The increased postoperative corneal endothelial cell loss associated with higher nucleus hardness may be related to the greater energy required during surgery, prolonged ultrasound time, increased mechanical damage to the corneal endothelium from nuclear fragments, and the impact of perfusion fluid on endothelial cells. The use of femtosecond laser-assisted phacoemulsification can significantly reduce corneal endothelial cell loss caused by high nucleus hardness.[24]

Additionally, some patients, particularly the elderly, may delay seeking medical attention for cataracts, which can result in the development of extremely hard nuclei. In severe cases, this can lead to acute angle-closure glaucoma during the hypermature phase, lens protein-induced uveitis, phacolytic glaucoma, or lens dislocation during the intumescent phase. This underscores the importance of promoting cataract awareness and increasing public knowledge and attention to the disease.

3.5. Other ocular diseases

Current research indicates that ocular diseases affecting corneal endothelial cell count include:

- Primary corneal diseases: Fuchs' endothelial dystrophy, Peters' anomaly, ICE syndrome, keratoconus, etc.[25];
- Inflammatory factors: anterior uveitis, endothelial keratitis, etc.[26,27];
- Other ocular diseases: pterygium, dry eye, and pseudoexfoliation syndrome, etc.[28,29]

The presence of these ocular diseases, which inherently affect corneal endothelial cell count, can further impact cataract surgery, potentially leading to a further reduction in endothelial cells postoperatively and creating a vicious cycle. Currently, surgery is the only treatment for cataracts. For cataract patients with an endothelial cell density <1500 cells/mm^2, it is crucial to pay close attention to all possible causes of endothelial cell damage before, during, and after surgery.[30] Actively treating primary diseases and minimizing the impact of ocular diseases affecting endothelial cells is essential to reduce damage to the lowest possible level.

4. Surgical factors

4.1. Incision method and incision location

4.1.1. Incision size

A randomized controlled trial evaluated four different incision sizes for phacoemulsification: ≤1.5 mm, 1.8 mm, 2.2 mm, and approximately 3.0 mm. The results showed no significant differences in endothelial cell loss and central corneal thickness among the different incision sizes.[31] A study based on Kenyan cataract patients indicated that those who underwent small incision cataract surgery had better postoperative visual recovery,[32] possibly due to the protective effect of smaller incisions on endothelial cells. Similarly, research by Hepokur M et al.[33] found that although the 2.2 mm incision group experienced slightly less endothelial cell loss than the 2.8 mm incision group, the difference was not significant. Moreover, the 2.2 mm incision caused faster and more intense fluid jets and did not cool the ultrasound tip as effectively. The study suggested that the choice of incision size should be based on the surgeon's preference and the patient's needs.

However, other studies have shown that for phacoemulsification with the same phaco tip, a 1.8 mm micro-incision results in faster visual recovery, more stable astigmatism, and better intraocular lens (IOL) positioning compared to traditional incisions,[34] making micro-incisions more beneficial for patients. Additionally, adjusting the size of the internal and external incisions, such as creating a trapezoidal incision with a 2.2 mm external and 3.0 mm internal size, can reduce friction from surgical instruments and lower the risk of Descemet membrane detachment.[35] Since the transition zone near the corneal limbus is considered the location of corneal endothelial progenitor cells,[36] choosing a modified incision to protect the Descemet membrane is beneficial for the corneal endothelial cells.

4.1.2. Bimanual incision or single incision

Research by Jiang Y et al. indicated that for cataract surgery patients with low corneal density, choosing a double incision results in less corneal endothelial cell loss compared to a single incision.[23] This could be because the double incision provides additional working channels, avoiding repeated trauma to the same incision during surgery and allowing the dispersal of phacoemulsification energy, thereby reducing damage to the corneal endothelial cells.

Studies have shown that double-incision phacoemulsification cataract extraction combined with intraocular lens implantation and external trabeculectomy is effective for cataract patients with low endothelial cell density and high sensitivity, especially those with coexisting glaucoma. The double incisions can separate the trabeculectomy and phacoemulsification incisions, minimizing instrument and energy-induced irritation to the conjunctiva and sclera, thereby protecting the corneal endothelial cells and reducing postoperative complications. This approach is considered safe and effective for patients with both glaucoma and cataracts.[37]

Additionally, during small incision cataract surgery, inserting the intraocular lens injector through a pre-cut corneal incision can sometimes result in uncontrollable tearing of corneal tissue, causing unnecessary damage to the corneal endothelial cells. A study examining three classic incision shapes—straight, V-shaped, and frown-shaped—found that for straight incisions, an angle of 170° was optimal, while for frown-shaped incisions, a central angle of 6° was best. Both V-shaped and frown-shaped incisions can accommodate larger injectors than straight incisions, potentially reducing the endothelial damage caused by the instruments themselves.[38] Therefore, choosing the appropriate number and shape of incisions is crucial for protecting corneal endothelial cells.

4.1.3. Clear corneal incision、scleral tunnel incision or limbal incision

Research has shown that patients undergoing phacoemulsification with clear corneal incisions are more prone to postoperative intraocular inflammation compared to those with scleral tunnel incisions or limbal incisions, which may lead to greater postoperative corneal endothelial cell loss and longer visual recovery times.[39] Yi Q's study indicated that limbal incisions have advantages in terms of postoperative corneal edema and recurrent retinal detachment, helping to protect corneal endothelial cells and maintain their density.[40]

From an anatomical perspective, clear corneal incisions directly cut through the five layers of the cornea, causing the most damage to the corneal endothelium. Scleral incisions disrupt the conjunctiva and superficial scleral capillary network, potentially leading to postoperative complications such as conjunctival hyperemia. Limbal incisions cause damage to both the cornea and sclera but are less damaging compared to purely corneal or scleral incisions. Additionally, studies have shown that for pediatric cataracts, using long scleral tunnel incisions results in less corneal endothelial damage and better prognoses.[41]

In conclusion, the most suitable incision location should be chosen based on the patient's ocular condition and the surgeon's technique.

4.1.4. Steep meridian clear corneal incision compared to other incisions

Research by Song W[42] indicated that incisions at the steepest meridian of the cornea result in higher postoperative corneal endothelial cell counts compared to clear corneal incisions at other locations and superotemporal limbal incisions. This may be because these locations are closer to the central surgical zone, which can disrupt the anterior chamber and lead to greater endothelial cell loss. Additionally, performing clear corneal incisions for phacoemulsification at the steep meridian can have a significant rotational effect on overall corneal astigmatism and reduce astigmatism along the meridian,[42] which is beneficial for postoperative visual recovery. Therefore, preoperative corneal curvature assessment is essential.

It is important to choose the appropriate incision location—whether temporal, superior, or at the steep meridian—based on the patient's ocular conditions and intraoperative circumstances, especially if other ocular diseases are present.

4.2. Nuclear fragmentation methods (non-phacoemulsification and phacoemulsification)

Research by Pershing S et al.[43] indicated that the postoperative reduction in corneal endothelial cells is less in the small-incision extracapsular cataract extraction (SICS) group compared to the phacoemulsification group. Similarly, Singh R et al.[14] found that corneal endothelial cell loss is significantly greater with phacoemulsification (12 ± 8.2%) compared to manual small-incision cataract surgery (MSICS) (7.1 ± 5.2%), a difference that is statistically significant. During phacoemulsification, the ultrasound energy and duration inevitably cause damage to the corneal endothelium.

In contrast, non-phacoemulsification techniques maintain good anterior chamber stability and are not affected by heat, ultrasonic radiation, or vibrations. Additionally, the use of viscoelastic substances during the delivery of the lens nucleus can prevent direct contact with the inner corneal surface, thereby reducing mechanical damage to the corneal endothelial cells.

4.3. Types of adhesives

Research by Modi S et al.[44] indicated that patients using DisCoVisc viscoelastic agent had a lower corneal endothelial cell loss rate three months postoperatively compared to those using sodium hyaluronate viscoelastic agent. This suggests that DisCoVisc provides better protection for corneal endothelial cells. DisCoVisc is a new viscous-dispersive viscoelastic agent composed primarily of 1.6% sodium hyaluronate and 4% chondroitin sulfate. As the first viscous-dispersive viscoelastic agent, it has stronger adhesiveness, lower surface tension, greater adhesion and retention capabilities, and a superior ability to scavenge free radicals compared to pure sodium hyaluronate viscoelastic agents. These properties contribute to better protection of corneal endothelial cells.

4.4. Ultrasound emulsification needle angled downward

Research by Joo C et al.[45] showed that the Phaco drill phacoemulsification tip, which does not directly face the corneal endothelial cells, and its higher phacoemulsification efficiency, contribute to reduced phacoemulsification time and required energy, thereby minimizing damage to the corneal endothelial cells. However, for inexperienced beginners, the Phaco drill can pose a challenge due to the downward orientation of the tip, making it difficult to accurately judge the phacoemulsification location and increasing the risk of posterior capsule rupture. It requires repeated practice to master the technique.

Moreover, Mizuguchi T et al.[46] found that triamcinolone can assist in visualizing the posterior surface of the lens. When used in the appropriate dosage and with the excess drug aspirated, it does not significantly affect corneal endothelial cells.

4.5. Ultrasound emulsification energy and ultrasonic time

It is widely accepted that higher phacoemulsification energy and longer ultrasound time result in greater damage to corneal endothelial cells. Research by Martínez M et al.[47] demonstrated that higher energy mainly causes damage to adjacent ocular tissues through thermal effects, leading to decreased corneal endothelial function, incision burns and edema, and increased vascular permeability in the iris tissue, all of which contribute to poor postoperative visual recovery. However, excessively reducing energy can prolong the phacoemulsification time, which may be counterproductive. Therefore, selecting the appropriate energy level during surgery is crucial. The specific method to accurately determine the suitable phacoemulsification energy based on each patient's lens hardness or other systemic conditions has not yet been standardized and requires further investigation.

Current studies[48] have found that cold phacoemulsification, or intermittent emulsification, can reduce energy consumption and effectively prevent temperature-induced corneal endothelial damage, thereby improving surgical quality. Yang WJ et al.[49] found that the torsional burst mode in phacoemulsification can reduce the average ultrasound time and total ultrasound energy, minimizing endothelial cell damage. Gigliola S et al.[50] proposed a technique involving a 45-degree inclined single-hand rotational phacoemulsification (where the operator uses lower ultrasound energy, maintains a 45-degree inclination of the tip towards the center of the lens, keeps the phacoemulsification tip at the lens edge, and ensures nucleus rotation), which can reduce effective ultrasound time and energy.

4.6. Active fluid flow control system or gravity fluid flow control system

Research by Nicoli C et al.[51] demonstrated that an active fluidics control system can effectively prevent surges following phacoemulsification tip occlusions, resulting in more stable anterior chamber pressure. We hypothesize that in such cases, there is less intraoperative loss of corneal endothelial cells. Liu Y et al.[52] also validated through Yang that the Centurion active fluidics control system causes less damage to corneal endothelial cells, making it particularly suitable for patients who already have a low number of endothelial cells.

4.7. Femtosecond laser-assisted

With technological advancements, femtosecond laser technology has been applied in cataract surgery. Research by Roberts H[53] showed that three months postoperatively, the corneal endothelial cell count in the femtosecond laser-assisted group was superior to that in the non-femtosecond laser group. Femtosecond laser-assisted cataract surgery can significantly reduce the effective ultrasound time, overall surgery time, and average ultrasound energy required for patients with hard nuclei. The precision and accuracy of femtosecond laser in creating corneal incisions, capsulotomies, and lens fragmentation surpass traditional manual techniques.

However, recent international studies, such as those by Dzhaber D et al.[54] and Narayan A et al.,[55] have generally found no significant differences between femtosecond laser-assisted phacoemulsification and conventional phacoemulsification. An early study by Abell RG et al.[56] indicated that endothelial cell loss was reduced by 36.1% in the femtosecond laser-assisted group.

To account for population differences and the impact of varying surgical techniques, the discrepancies between domestic and international research results suggest that future clinical studies should focus on controlling variables more rigorously. It is essential to select populations treated by a single surgeon or by surgeons with similar techniques and to engage in multicenter collaborations to increase sample size and diversity. This approach will enhance the reliability and evidence level of the data.

5. Drugs and irrigation solutions

5.1. Drugs

Postoperative use of corticosteroid eye drops can activate the remaining endothelial cells, protect corneal endothelial cell function, and improve inflammation and edema, especially in patients with Fuchs' endothelial dystrophy who already have a low number of endothelial cells.[57] Research by Sali F et al.[58] indicated that postoperative anterior chamber injection of triamcinolone causes less damage to corneal endothelial cells compared to subconjunctival injection of dexamethasone.

Wen Y et al.[59] found that postoperative use of sodium hyaluronate eye drops combined with recombinant human epidermal growth factor eye drops effectively reduces inflammation and repairs corneal cells. Patients using the combination therapy had higher postoperative corneal endothelial cell counts than those using only sodium hyaluronate eye drops.

Research by Fujimoto H et al.[60] demonstrated that glaucoma patients using Rho kinase inhibitor eye drops postoperatively to lower intraocular pressure can promote the migration of relatively healthy corneal endothelial cells to repair damaged areas, helping to maintain corneal endothelial function in patients with low endothelial cell density who undergo cataract surgery.

Antibiotics such as norfloxacin and moxifloxacin hydrochloride are commonly used ocular antibiotics. They can cause ocular damage and may have a time- and dose-dependent cytotoxic effect on human corneal endothelial cells, leading to corneal damage. Therefore, it is necessary to choose the appropriate dosage and duration of antibiotic use to achieve therapeutic efficacy while minimizing damage to corneal endothelial cells.[61,62]

Some studies have also found that preoperative mannitolization can effectively reduce postoperative corneal endothelial cell loss.[63]

5.2. Irrigation solutions

The corneal endothelial fluid pump acts as a barrier, protecting corneal endothelial cells and maintaining their transparency.[64] During intraocular surgery, the choice of irrigating solution plays a crucial role. Selecting an appropriate irrigating solution can effectively reduce corneal endothelial cell loss.[65] The solution should closely mimic the composition of aqueous humor, be stable, and possess antioxidant properties.[66] Currently, three commonly used intraocular irrigating solutions are Lactated Ringer's solution, Balanced Salt Solution (BSS), and Balanced Salt Solution Plus (BSS Plus).[66] Among these, Lactated Ringer's solution has been shown to result in less endothelial cell loss after phacoemulsification than BSS, comparable to BSS Plus.

Additionally, research simulating the irrigation process during phacoemulsification found that BSS at 4 °C provides better protection against thermal damage to corneal endothelial cells compared to room temperature BSS, indicating that temperature is a significant factor influencing the impact of the irrigating solution on corneal cells.[67] Furthermore, the extent of corneal damage during phacoemulsification depends on several factors, including the pH, osmolality, composition of the irrigating solution, duration of the procedure, volume of irrigation, intraocular maneuvers, turbulence of the fluid and lens fragments, and the production of free radicals.[68]

An important finding is that using BSS as a solvent to prepare 0.025% povidone-iodine or 0.0025% polyvinyl alcohol-iodine for ocular surface irrigation can minimize anterior chamber bacterial contamination, significantly preventing corneal endothelial cell loss due to anterior chamber contamination.[69] In conclusion, choosing the appropriate irrigating solution based on the individual patient's ocular condition can effectively protect corneal endothelial cells.

6. Reducing corneal endothelial cell loss

In the above paragraphs, we discussed several factors that may lead to a reduction in corneal endothelial cells after phacoemulsification, analyzing them from the perspectives of the patient's overall health, ocular condition, surgical techniques, and medication use. For diabetic and elderly patients, phacoemulsification poses a significantly higher risk to corneal endothelial cells compared to the general population, making blood sugar control crucial. However, there are still no effective methods to mitigate age-related factors, highlighting the necessity of research focused on protecting the corneal endothelial cells in elderly individuals.

For patients with pre-existing ocular diseases such as glaucoma and high myopia, the tolerance of corneal cells is diminished. Therefore, actively managing and preventing these conditions is also essential. Some diseases, aside from those mentioned, inherently lead to a reduction in corneal endothelial cells, such as hypertension, inflammation, renal failure, Fuchs' endothelial dystrophy, and trauma. Actively controlling these primary diseases is equally important.

Regarding surgical procedures, choosing appropriate incision size and location, nucleofractis technique, type of viscoelastic agent, phacoemulsification needle insertion method, and managing time and energy can effectively minimize unnecessary intraoperative corneal endothelial cell loss, thereby improving patient outcomes and quality of life. Additionally, certain ocular medications can protect corneal endothelial cells, such as corticosteroids, sodium hyaluronate, Rho kinase inhibitor eye drops, and preoperative mannitolization, which can reduce endothelial cell loss within certain limits. However, it is important to note that excessive use of antibiotics can adversely affect corneal endothelial cells, necessitating careful adjustment of usage and dosage based on patient needs.

Furthermore, selecting an appropriate intraocular irrigating solution based on the individual patient's condition is equally important for minimizing corneal endothelial cell loss.

7. Current technologies and outlook

Regarding the treatment of various types of cataracts, the efficacy of medications remains uncertain, and surgery continues to be the primary treatment method. The main surgical procedures include phacoemulsification cataract extraction, small-incision cataract surgery, and femtosecond laser-assisted cataract surgery.[70] Cataract surgery is constantly evolving, with innovative approaches such as the femtosecond laser anterior lamellar protection method currently under investigation. Additionally, there are proposals to use hydrogen-enriched irrigation solutions to reduce oxidative stress and thereby protect corneal endothelial cells.

The potential for corneal endothelial cell regeneration remains a controversial issue. However, various approaches based on the possibility of regeneration, including surgical techniques, medications, gene therapy, and cell therapy to promote regeneration, have shown some promising progress. Methods utilizing cultured human corneal endothelial cells are also undergoing clinical trials. Many clinical trials aimed at promoting corneal endothelial cell regeneration will require extensive research to overcome existing challenges and validate their effectiveness through more case studies.

Study approval

Not Applicable.

Author contributions

Chen Yang: Data curation, Project administration, Resources, Writing – original draft. Han Zhou: Formal analysis, Validation, Writing – original draft. Qi An: Formal analysis, Validation, Writing – original draft. Hongyan Ge: Project administration, Supervision. All authors reviewed the results and approved the final version of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors express gratitude to the First Affiliated Hospital of Harbin Medical University and everyone who assisted in the preparation of this article.

References

1. Fang R, Yu YF, Li EJ, et al. Global, regional, national burden and gender disparity of cataract: findings from the global burden of disease study 2019. *BMC Publ Health*. 2022;22(1):2068. https://doi.org/10.1186/s12889-022-14491-0.
2. Boyers LN, Karimkhani C, Hilton J, Richheimer W, Dellavalle RP. Global burden of eye and vision disease as reflected in the Cochrane Database of Systematic Reviews. *JAMA Ophthalmol*. 2015;133(1):25–31. https://doi.org/10.1001/jamaophthalmol.2014.3527.
3. Liu Y, Sun H, Guo P, et al. Characterization and prospective of human corneal endothelial progenitors. *Int J Med Sci*. 2017;14(8):705–710. https://doi.org/10.7150/ijms.19018.
4. Goldstein AS, Janson BJ, Skeie JM, Ling JJ, Greiner MA. The effects of diabetes mellitus on the corneal endothelium: a review. *Surv Ophthalmol*. 2020;65(4):438–450. https://doi.org/10.1016/j.survophthal.2019.12.009.
5. Bamdad S, Bolkheir A, Sedaghat MR, Motamed M. Changes in corneal thickness and corneal endothelial cell density after phacoemulsification cataract surgery: a double-blind randomized trial. *Electron Physician*. 2018;10(4):6616–6623. https://doi.org/10.19082/6616.
6. Grzybowski A, Kanclerz P, Huerva V, Ascaso FJ, Tuuminen R. Diabetes and phacoemulsification cataract surgery: difficulties, risks and potential complications. *J Clin Med*. 2019;8(5). https://doi.org/10.3390/jcm8050716.
7. El-Agamy A, Alsubaie S. Corneal endothelium and central corneal thickness changes in type 2 diabetes mellitus. *Clin Ophthalmol*. 2017;11:481–486. https://doi.org/10.2147/OPTH.S126217. From NLM PubMed-not-MEDLINE.
8. Chowdhury B, Bhadra S, Mittal P, Shyam K. Corneal endothelial morphology and central corneal thickness in type 2 diabetes mellitus patients. *Indian J Ophthalmol*. 2021;69(7):1718–1724. https://doi.org/10.4103/ijo.IJO_3120_20.

9. Lee JS, Lee JE, Choi HY, Oum BS, Cho BM. Corneal endothelial cell change after phacoemulsification relative to the severity of diabetic retinopathy. *J Cataract Refract Surg*. 2005;31(4):742–749. https://doi.org/10.1016/j.jcrs.2004.09.035.
10. Hugod M, Storr-Paulsen A, Norregaard JC, Nicolini J, Larsen AB, Thulesen J. Corneal endothelial cell changes associated with cataract surgery in patients with type 2 diabetes mellitus. *Cornea*. 2011;30(7):749–753. https://doi.org/10.1097/ICO.0b013e31820142d9.
11. Papadakou P, Chatziralli I, Papathanassiou M, et al. The effect of diabetes mellitus on corneal endothelial cells and central corneal thickness: a case-control study. *Ophthalmic Res*. 2020;63(6):550–554. https://doi.org/10.1159/000507197.
12. Ciorba AL, Roiu G, Abdelhamid AM, Saber S, Cavalu S. Evaluation of the corneal endothelium following cataract surgery in diabetic and non-diabetic patients. *Diagnostics*. 2023;13(6). https://doi.org/10.3390/diagnostics13061115.
13. Singh R, Sharma AK, Katiyar V, Kumar G, Gupta SK. Corneal endothelial changes following cataract surgery in hard nuclear cataract: randomized trial comparing phacoemulsification to manual small-incision cataract surgery. *Indian J Ophthalmol*. 2022;70(11):3904–3909. https://doi.org/10.4103/ijo.IJO_1304_22.
14. Singh M, Mishra D, Sinha BP, Anand A, Singhal S. Corneal endothelial protection during manual small-incision cataract surgery: a narrative review. *Indian J Ophthalmol*. 2022;70(11):3791–3796. https://doi.org/10.4103/ijo.IJO_1048_22.
15. Inoue K, Tokuda Y, Inoue Y, Amano S, Oshika T, Inoue J. Corneal endothelial cell morphology in patients undergoing cataract surgery. *Cornea*. 2002;21(4):360–363. https://doi.org/10.1097/00003226-200205000-00006.
16. Chen MJ, Liu CJ, Cheng CY, Lee SM. Corneal status in primary angle-closure glaucoma with a history of acute attack. *J Glaucoma*. 2012;21(1):12–16. https://doi.org/10.1097/IJG.0b013e3181fc800a.
17. Ianchulev T, Lane S, Masis M, et al. Corneal endothelial cell density and morphology after phacoemulsification in patients with primary open-angle glaucoma and cataracts: 2-year results of a randomized multicenter trial. *Cornea*. 2019;38(3):325–331. https://doi.org/10.1097/ICO.0000000000001826.
18. Patel V, Muhtaseb M. Endothelial cell loss after pIOL implantation for high myopia. *J Cataract Refract Surg*. 2008;34(9):1424–1425. https://doi.org/10.1016/j.jcrs.2008.05.037.
19. Coullet J, Mahieu L, Malecaze F, et al. Severe endothelial cell loss following uneventful angle-supported phakic intraocular lens implantation for high myopia. *J Cataract Refract Surg*. 2007;33(8):1477–1481. https://doi.org/10.1016/j.jcrs.2007.03.061.
20. Hwang HB, Lyu B, Yim HB, Lee NY. Endothelial cell loss after phacoemulsification according to different anterior chamber depths. *J Ophthalmol*. 2015;2015:210716. https://doi.org/10.1155/2015/210716. From NLM PubMed-not-MEDLINE.
21. Khalid M, Ameen SS, Ayub N, Mehboob MA. Effects of anterior chamber depth and axial length on corneal endothelial cell density after phacoemulsification. *Pakistan J Med Sci*. 2019;35(1):200–204. https://doi.org/10.12669/pjms.35.1.92.
22. Reuschel A, Bogatsch H, Oertel N, Wiedemann R. Influence of anterior chamber depth, anterior chamber volume, axial length, and lens density on postoperative endothelial cell loss. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(5):745–752. https://doi.org/10.1007/s00417-015-2934-1.
23. Jiang Y, Shi WY, Li FJ, Wang T. [Efficacy of double-incision extracapsular cataract extraction in the treatment of hard-nucleus cataract with low corneal endothelial cell density]. *Zhonghua Yan Ke Za Zhi*. 2020;56(2):126–130. https://doi.org/10.3760/cma.j.issn.0412-4081.2020.02.008.
24. Yang XW, Gao Y, Jiang YQ, Zhou YJ. [Effect of femtosecond laser-assisted phacoemulsification on corneal endothelium and prognosis of diabetic patients with cataract with different nuclear hardness]. *Zhonghua Yan Ke Za Zhi*. 2024;60(6):511–517. https://doi.org/10.3760/cma.j.cn112142-20231223-00305.
25. Bourne WM. Biology of the corneal endothelium in health and disease. *Eye*. 2003;17(8):912–918. https://doi.org/10.1038/sj.eye.6700559.
26. Frifelt LEW, Subhi Y, Holm LM, Singh A. Impact of tobacco use on corneal thickness and endothelial health: a systematic review with meta-analyses. *Acta Ophthalmol*. 2022;100(1):26–34. https://doi.org/10.1111/aos.14897.
27. Sousa DC, Leal I, Faria MY, Pinto LA. A rare manifestation of uveitis-glaucoma-hyphema syndrome. *J Curr Glaucoma Pract*. 2016;10(2):76–78. https://doi.org/10.5005/jp-journals-10008-1205.
28. Vaiciuliene R, Rylskyte N, Baguzyte G, Jasinskas V. Risk factors for fluctuations in corneal endothelial cell density. Review *Exp Ther Med*. 2022;23(2):129. https://doi.org/10.3892/etm.2021.11052.
29. Ostern AE, Sandvik GF, Drolsum L. Late in-the-bag intraocular lens dislocation in eyes with pseudoexfoliation syndrome. *Acta Ophthalmol*. 2014;92(2):184–191. https://doi.org/10.1111/aos.12024.
30. Rosado-Adames N, Afshari NA. The changing fate of the corneal endothelium in cataract surgery. *Curr Opin Ophthalmol*. 2012;23(1):3–6. https://doi.org/10.1097/ICU.0b013e32834e4b5f.
31. Jin C, Chen X, Law A, et al. Different-sized incisions for phacoemulsification in age-related cataract. *Cochrane Database Syst Rev*. 2017;9(9):CD010510. https://doi.org/10.1002/14651858.CD010510.pub2.
32. Rono JK, Nirghin U. Visual outcome after small incision cataract surgery of patients in a Kenyan Hospital Contributors. *Afr Health Sci*. 2023;23(2):469–477. https://doi.org/10.4314/ahs.v23i2.54.
33. Hepokur M, Kizilay EB, Durmus E, Aykut V, Esen F, Oguz H. The influence of corneal incision size on endothelial cell loss and surgically induced astigmatism following phacoemulsification cataract surgery. *North Clin Istanb*. 2022;9(4):385–390. https://doi.org/10.14744/nci.2021.81084.
34. Song E, Li X, Bi MC, et al. A comparison of surgical efficacy between a 1.8-mm microincision and 3.2-mm and 5.5-mm incisions for phacoemulsification. *Int J Ophthalmol*. 2018;11(3):516–519. https://doi.org/10.18240/ijo.2018.03.25.
35. Dai Y, Liu Z, Wang W, et al. Incidence of incision-related Descemet membrane detachment using phacoemulsification with trapezoid vs conventional 2.2-mm clear corneal incision: a randomized clinical trial. *JAMA Ophthalmol*. 2021;139(11):1228–1234. https://doi.org/10.1001/jamaophthalmol.2021.4148.
36. Cheong N, Chui SW, Poon SHL, Wong HL, Shih KC, Chan YK. Emerging treatments for corneal endothelium decompensation - a systematic review. *Graefes Arch Clin Exp Ophthalmol*. 2024;262(2):381–393. https://doi.org/10.1007/s00417-023-06129-7.
37. Honjo M, Tanihara H, Negi A, et al. Trabeculotomy ab externo, cataract extraction, and intraocular lens implantation: preliminary report. *J Cataract Refract Surg*. 1996;22(5):601–606. https://doi.org/10.1016/s0886-3350(96)80017-4.
38. Han Y, Qi N. Numerical study of critical straight, frown, and chevron incisions in small incision cataract surgery. *Front Bioeng Biotechnol*. 2023;11:1283293. https://doi.org/10.3389/fbioe.2023.1283293. From NLM PubMed-not-MEDLINE.
39. Al Mahmood AM, Al-Swailem SA, Behrens A. Clear corneal incision in cataract surgery. *Middle East Afr J Ophthalmol*. 2014;21(1):25–31. https://doi.org/10.4103/0974-9233.124084.
40. Yi QY, Huang J, Chen N, et al. Managing dislocated hard lens nuclei: 23-gauge vitrectomy and lens extraction via a corneoscleral limbal incision versus 23-gauge vitrectomy and phacofragmentation. *J Cataract Refract Surg*. 2019;45(4):451–456. https://doi.org/10.1016/j.jcrs.2018.10.042.
41. Abdullah OO, Oksuz H. A simplified sclerocorneal tunnel approach in performing pediatric cataract surgery. *Oman J Ophthalmol*. 2024;17(1):91–95. https://doi.org/10.4103/ojo.ojo_321_22.
42. Song W, Chen X, Wang W. Effect of steep meridian clear corneal incisions in phacoemulsification. *Eur J Ophthalmol*. 2015;25(5):422–425. https://doi.org/10.5301/ejo.5000575.
43. Pershing S, Kumar A. Phacoemulsification versus extracapsular cataract extraction: where do we stand? *Curr Opin Ophthalmol*. 2011;22(1):37–42. https://doi.org/10.1097/ICU.0b013e3283414fb3.
44. Modi SS, Davison JA, Walters T. Safety, efficacy, and intraoperative characteristics of DisCoVisc and Healon ophthalmic viscosurgical devices for cataract surgery. *Clin Ophthalmol*. 2011;5:1381–1389. https://doi.org/10.2147/OPTH.S22243. From NLM PubMed-not-MEDLINE.
45. Joo CK, Kim YH. Phacoemulsification with a bevel-down phaco tip: phaco-drill. *J Cataract Refract Surg*. 1997;23(8):1149–1152. https://doi.org/10.1016/s0886-3350(97)80307-0.
46. Mizuguchi T, Horiguchi M, Tanikawa A. Visualization of the posterior surface of the lens nucleus with triamcinolone acetonide in phacoemulsification. *Eur J Ophthalmol*. 2021;31(6):2977–2980. https://doi.org/10.1177/1120672120977356.
47. Benitez Martinez M, Baeza Moyano D, Gonzalez-Lezcano, Phacoemulsification RA. Proposals for improvement in its application. *Healthcare (Basel)*. 2021;9(11). https://doi.org/10.3390/healthcare9111603.
48. Choi JY, Cho CS, Han YK. Application of thermoreversible hydrogel (poloxamer 407) to protect the corneal endothelium during phacoemulsification in porcine and rabbit eyes. *J Cataract Refract Surg*. 2018;44(10):1254–1260. https://doi.org/10.1016/j.jcrs.2018.04.043.
49. Yang WJ, Wang XH, Zhao F, Mei ZM, Li S, Xiang Y. Torsional and burst mode phacoemulsification for patients with hard nuclear cataract: a randomized control study. *Medicine (Baltim)*. 2019;98(22):e15870. https://doi.org/10.1097/MD.0000000000015870.
50. Gigliola S, Sborgia G, Niro A, et al. One-handed rotational phacoemulsification technique. *Clin Ophthalmol*. 2021;15:431–435. https://doi.org/10.2147/OPTH.S281857. From NLM PubMed-not-MEDLINE.
51. Nicoli CM, Dimalanta R, Miller KM. Experimental anterior chamber maintenance in active versus passive phacoemulsification fluidics systems. *J Cataract Refract Surg*. 2016;42(1):157–162. https://doi.org/10.1016/j.jcrs.2015.08.017.
52. Liu Y, Hong J, Chen X. Comparisons of the clinical outcomes of Centurion((R)) active fluidics system with a low IOP setting and gravity fluidics system with a normal IOP setting for cataract patients with low corneal endothelial cell density. *Front Med*. 2023;10:1294808. https://doi.org/10.3389/fmed.2023.1294808. From NLM PubMed-not-MEDLINE.
53. Roberts HW, Day AC, O'Brart DP. Femtosecond laser-assisted cataract surgery: a review. *Eur J Ophthalmol*. 2020;30(3):417–429. https://doi.org/10.1177/1120672119893291.
54. Dzhaber D, Mustafa O, Alsaleh F, Mihailovic A, Daoud YJ. Comparison of changes in corneal endothelial cell density and central corneal thickness between conventional and femtosecond laser-assisted cataract surgery: a randomised, controlled clinical trial. *Br J Ophthalmol*. 2020;104(2):225–229. https://doi.org/10.1136/bjophthalmol-2018-313723.
55. Narayan A, Evans JR, O'Brart D, Bunce C, Gore DM, Day AC. Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. *Cochrane Database Syst Rev*. 2023;6(6):CD010735. https://doi.org/10.1002/14651858.CD010735.pub3.
56. Abell RG, Kerr NM, Vote BJ. Toward zero effective phacoemulsification time using femtosecond laser pretreatment. *Ophthalmology*. 2013;120(5):942–948. https://doi.org/10.1016/j.ophtha.2012.11.045.
57. Chikamoto N, Takahashi N, Wakuta M, Fujitsu Y, Nishida T. Recovery of corneal thickness promoted by glucocorticoid administration after phacoemulsification in eyes affected by Fuchs' dystrophy. *Jpn J Ophthalmol*. 2008;52(4):336–339. https://doi.org/10.1007/s10384-008-0534-x.
58. Sali F, Aykut V, Kunbaz A, et al. Endothelial loss following postoperative intracameral triamcinolone acetonide and subconjunctival dexamethasone injections. *Cutan Ocul Toxicol*. 2023;42(4):237–242. https://doi.org/10.1080/15569527.2023.2239897.

59. Wen Y, Zhang X, Chen M, Han D. Sodium hyaluronate in the treatment of dry eye after cataract surgery: a meta-analysis. *Ann Palliat Med*. 2020;9(3):927–939. https://doi.org/10.21037/apm-20-695.
60. Fujimoto H, Setoguchi Y, Kiryu J. The ROCK inhibitor ripasudil shows an endothelial protective effect in patients with low corneal endothelial cell density after cataract surgery. *Transl Vis Sci Technol*. 2021;10(4):18. https://doi.org/10.1167/tvst.10.4.18.
61. Fan TJ, Wu SX, Jiang GJ. Apoptotic effects of norfloxacin on corneal endothelial cells. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2020;393(1):77–88. https://doi.org/10.1007/s00210-019-01711-5.
62. Park JH, Kim M, Chuck RS, Park CY. Evaluation of moxifloxacin-induced cytotoxicity on human corneal endothelial cells. *Sci Rep*. 2021;11(1):6250. https://doi.org/10.1038/s41598-021-85834-x.
63. Hwang HS, Ahn YS, Cho YK. Preoperative mannitolization can decrease corneal endothelial cell damage after cataract surgery. *Curr Eye Res*. 2016;41(9):1161–1165. https://doi.org/10.3109/02713683.2015.1101138.
64. Mishima S. Clinical investigations on the corneal endothelium. *Ophthalmology*. 1982;89(6):525–530. https://doi.org/10.1016/s0161-6420(82)34755-7.
65. Peyman GA. Intraocular irrigating solutions. *Ophthalmology*. 1995;102(10):1413–1414. https://doi.org/10.1016/s0161-6420(95)38040-2.
66. Rubowitz A, Assia EI, Rosner M, Topaz M. Antioxidant protection against corneal damage by free radicals during phacoemulsification. *Invest Ophthalmol Vis Sci*. 2003;44(5):1866–1870. https://doi.org/10.1167/iovs.02-0892.
67. Uthaisang-Tanechpongtamb W, Limtrakarn W, Reepolmaha S. The effect of temperature of eye irrigation solution to reduce corneal endothelial cell loss during phacoemulsification: an in vitro model study. *J Med Assoc Thai*. 2012;95(Suppl 12):S83–S89. From NLM Medline.
68. Nayak BK, Jain EK. Comparison of corneal endothelial cell loss during phacoemulsification using continuous anterior chamber infusion versus those using ophthalmic viscosurgical device: randomized controlled trial. *Indian J Ophthalmol*. 2009;57(2):99–103. https://doi.org/10.4103/0301-4738.45500.
69. Shimada H, Arai S, Nakashizuka H, Hattori T, Yuzawa M. Reduced anterior chamber contamination by frequent surface irrigation with diluted iodine solutions during cataract surgery. *Acta Ophthalmol*. 2017;95(5):e373–e378. https://doi.org/10.1111/aos.13390.
70. Cicinelli MV, Buchan JC, Nicholson M, Varadaraj V, Khanna RC. Cataracts. *Lancet*. 2023;401(10374):377–389. https://doi.org/10.1016/S0140-6736(22)01839-6.