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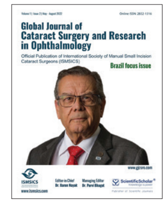

Review Article

Essentials of the corneal endothelium for the cataract surgeon

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ABSTRACT

The human eye is an optical system with two lenses in parallel, with complementary functions essential to vision: the cornea and the lens. There is an intimate relationship between these two structures, especially during cataract surgery when there is inevitably corneal endothelium injury at different severity levels. Every cataract surgeon should be aware of the functioning of the fragile corneal tissue, especially its noblest layer and responsible for corneal transparency: the endothelium. It is of paramount importance to be able to identify the different endothelial pathologies and local conditions associated with greater tissue damage before cataract surgery, as well as to proceed individually in the pre-operative evaluation, during surgery (choice of supplies, technologies and techniques) and prescription of medications or need for additional procedures in the post-operative period. There are several conditions peculiar to cataract surgery and others to the corneal endothelium itself that are described and discussed, as well as information about the physiology, diagnosis and clinical and surgical treatment of diseases that affect it.

Keywords: Corneal endothelium, Cataract, Fuchs dystrophy, Corneal oedema, Bullous Keratopathy

INTRODUCTION

The corneal endothelium is responsible for maintaining the transparency and deturgescence of the cornea (maintains a tissue water content of approximately 78%) by an active mechanism of movement of ions and fluids, besides serving as a selective barrier.[1,2] This singular layer (the only tissue that can be analysed *in vivo* repeatedly without prejudice to its functioning), occupies the posterior surface of the cornea and is composed of cells that are mostly hexagonal and firmly adhered to each other by tight junctions, have large amounts of Sodium/Potassium pumps (Na +/K + ATPases) in their membranes/side walls[3,4] and remain attached to the Descemet's membrane which acts as basement membrane.[5] During the corneal developmental stage, endothelial cells secrete type VIII collagen, an important component of Descemet's membrane which can also be produced on injury or in culture conditions.[2,6]

The corneal endothelium 'rests' on a special membrane (which is secreted by its own cells): the Descemet's membrane. The endothelial cells begin to secrete the Descemet's membrane at the 8th week of gestation,[7,8] and the 3 μm secreted before birth demonstrate a more organised and united aspect than the secreted one throughout life (which present an amorphous aspect). Descemet can accumulate up to 10 μm thick over the years.[9]

The endothelial cells present their highest number at birth, reaching values around 4000 cells/mm^2; however, densities >6000 cells/mm^2 have been described.[10-12] In this phase, the endothelium is approximately 10 μm thick and already occupies the entire face of the posterior surface of the cornea, merging with the trabeculate cells at the periphery, underneath the limbus. The region where the two cell types meet can be seen as a grey line, also known as the Schwalbe line (a gonioscopic reference point that defines the end of the Descemet's membrane and the beginning of the trabecular meshwork).[13,14]

Over the years, the endothelial cells undergo a continuous process of change: their thickness progressively decreases, resulting in cell 'flattening' which will stabilise around 4–6 μm in adulthood. There is a concomitant decrease in the percentage of hexagonal cells and cell density during the individual's life at rates that vary widely. Between birth and 14 years of age, the endothelial loss rate is approximately 3% per year – mainly due to growth in the corneal tissue area and not to death/cell loss – and from 14 years of age onwards, it starts to present an average loss rate of 0.6% per year.[10]

In adulthood, the corneal endothelium has approximately 400,000–500,000 cells in its totality, which is equivalent to an average central cell density of approximately 3000 cells/mm^2,

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with 75% of them presenting a hexagonal shape.[15-17] At 85 years of age, the corneal endothelium has an average count of 2000 cells/mm^2 and a percentage of hexagonal cells of approximately 60% [Table 1]. The distribution of endothelial cells on the posterior surface of the cornea is not homogeneous: the paracentral area has density 5% and the peripheral area is up to 10% larger than the central area. For the maintenance of corneal transparency, it is estimated that the minimum central cell density should be approximately 500 cells/mm².[16,18,19]

Endothelial cells are 'frozen' in the G1 phase of the cell cycle interphase, being typically unable to regenerate or undergo mitosis, without stimulation, *in vivo*.[20-22] However, some may maintain regenerative capacity under specific stimuli and substances (subject to be explored later). In any case, healthy corneas have a significant numerical 'reserve': we have a larger cell quantity than necessary to maintain transparency throughout life.[23]

The process of healing/repairing the layer with replacement of dead/degenerate cells is done through changes in shape (increase in size) and centripetal migration of neighbouring cells to 'occupy the space' left. This process is completed in three steps, which can take weeks: (1) migration of adjacent cells to 'cover' the empty space, leading to an incomplete barrier with reduced number of active pumps (Na +/K + ATPases) and incomplete tight junctions; (2) progressive increase in the number and quality of tight junctions and active pumps, with the endothelial mosaic presenting irregular polygons – at this stage usually the tissue recovers its thickness and transparency; and (3) remodelling of the mosaic, with the cells exhibiting better distribution and greater hexagonal regularity.[24] The result of the process is an increase in the cell area (polymegatism), loss of its hexagonal shape (pleomorphism) and decrease in the overall cell density and locally/by area (per mm², for example). It is important to remember that cells that migrate to 'cover' the empty space need to produce new Descemet's membrane on site.[25,26]

The corneal endothelium occupies the anterior limit of the anterior chamber, being vulnerable to various sources of injury such as trauma (surgical or not), toxic substances, pH changes (tolerance between 6.8 and 8.2), osmolarity (tolerance between 250 and 350 mOsmoles) or metabolic (e.g., hypoxia and hyperglycaemia).

Table 1: The cellular density and morphology of the endothelial layer of the cornea undergo transformations throughout the period of life.

Age range	Average central cell density	Average cell area
Newborn	3000 célls/mm²	18–20 µm
Adult	2500 célls/mm²	25–30 µm
Senior age	2000 célls/mm²	40 µm or more

Blindness by corneal pathologies occupies the fourth position in the world, behind cataracts, glaucoma and macular degeneration. Among the causes of low vision of corneal origin, keratopathy is still the most frequent in the world, occurring mainly due to intraocular surgeries (in this group, cataract surgery is the main cause) and dystrophy (among these stands out fuchs dystrophy, which affects approximately 4% of the population over 40 years of age in the northern hemisphere).[27-30]

ENDOTHELIUM AND CATARACT SURGERY

The manoeuvres and steps/steps of cataract surgery are performed near the endothelium and lead to an inevitable loss/decrease in the number of cells in the central region that can range from 4% to 25% (depending on various factors such as nucleus hardness, anterior chamber depth, technique used, equipment technology and viscoelastic available, skill of the surgeon and length of surgery) by various mechanisms (often acting together):[10,23]

- Direct trauma by incision, inadvertent touch of instruments, pieces of the lens or intraocular lens (IOL)
- Ultrasonic energy (directly or indirectly through cavitation bubbles, free radical generation and temperature increase)
- Irrigation and viscoelastic solutions (composition, turbulence, volume, preservatives, pH, osmolarity and residual toxic substances).

In addition to the acute loss observed in the immediate post-operative period, caused by the factors mentioned above, the annual endothelial loss rate increases from 0.6%[31] to up to 2.5% for at least 10 years after surgery by mechanisms not yet fully understood.[32]

In recent years, it has been possible to observe an important advance in the techniques and materials used in cataract surgery, making surgery less invasive and traumatic, thus allowing a smaller endothelial injury and faster visual rehabilitation. The intensity of endothelial cell loss in this scenario depends on several intraoperative factors, such as anterior chamber depth, crystalline nucleus hardness, type of viscoelastic used, ultrasonic energy used, among other factors related to available technology and surgeon's dexterity.[33-38]

SURGICAL TECHNIQUE − FEMTOSECOND LASER

Once the femtosecond laser gained space in the ophthalmic market, one of the main benefits pointed out by this new technology would be a reduction in the ultrasound energy (US) used during this procedure and a consequent reduction in the loss of endothelial cells due to automated fragmentation of the lens nucleus.

What we observe today in the literature is a difficulty in carrying out a study with a sufficient sample size and consequently, with adequate statistical power, capable of proving the real benefit of the femtosecond laser in terms of endothelial preservation.[37,38] For this purpose, a prospective and randomised study randomised controlled trial would be needed, isolating only one variable: femtosecond laser versus manual phacoemulsification, from a diverse number of unknown covariates. Among them we can mention patient age, pre-operative endothelial count, anterior chamber depth, pupil diameter, nucleus density, type of incision, type and amount of viscoelastic used, irrigation volume, phacoemulsification device and parameters, fracture techniques, surgeon experience and among others. Probably the ideal design for this study would be a prospective, randomised, double-blind, in which the contralateral eye of the same patient was used as a control group, that is, one eye would be submitted to femtosecond laser phacoemulsification and the other to manual phacoemulsification. In addition to all these details, the study should have an adequate sample size to be able to answer this question.

What we observe in the literature is a huge amount of retrospective, observational or even prospective studies, but with small samples, which do not present a design capable of adequately answering questions like this one.[37,38] A study that tried to get closer to that ideal design was that of Murch-Edlmayr and partners.[39] In this prospective and randomised study, the authors performed an intra-individual comparison, using the contralateral eye as a control. Only 50 patients were included and the only variable that differed between the groups was the use or not of the femtosecond laser. At the end of 1 week, 1 month and 3 months of follow-up, no differences were found between endothelial counts and pachymetry between the studied groups.

As a negative point, we can mention the sample size, which would hardly be able to show differences between the groups.

Among the most important works involving this topic, we can mention the meta-analysis study carried out in Canada by Popovic and collaborators published in the journal *Ophthalmology* in October 2016[38] This is a meta-analysis, which, despite being considered the ideal form of study to evaluate a certain controversial topic, presented an inadequate quality since 22 observational studies were included, which generates a considerable number of research bias. As a result, the authors found a statistically significant difference in favour of the femtosecond laser regarding the preservation of endothelial cells. However, the mean difference found between the groups (55.43 cells/mm^2) was not considered clinically significant. Another study worth mentioning is the one by Manning and collaborators, published in December 2017.[40] This is the largest prospective, multicentre study comparing cataract surgery with and without femtosecond laser, involving the largest cataract surgery centres in Europe. In this study, in which there was no financial interest involved, the group of pins patients undergoing cataract surgery with femtosecond laser had a higher percentage of post-operative corneal oedema when compared to the control group without laser (0.5% vs. 0.1%, $P = 0.002$).

As the literature has not yet been able to show adequate and robust evidence of the benefit of femtosecond laser regarding the preservation of endothelial cells after cataract surgery in normal corneas, some authors have tried to verify its benefit in eyes with Fuchs Endothelial Dystrophy (FED).[41-43] Zhu *et al.*,[43] in 2018, in a retrospective study, selected 207 eyes with FED. At the end of 3 months after cataract surgery, endothelial losses were compared between the groups undergoing cataract surgery with femtosecond laser versus manual phacoemulsification and no differences were found between the two studied groups. In the same year, 2018, Fan and collaborators[42] carried out a prospective study involving only 31 eyes with FED with the same goal, to compare endothelial loss between groups undergoing cataract surgery with laser (15 eyes) and without femtosecond laser (16 eyes). At the end of 1, 3, 6 and 12 months, endothelial cell loss was greater in the manual group when compared to the femtosecond laser group ($P < 0.05$). As noted above, the studies showed contradictory results, one being favourable to the femtosecond laser and the other with no difference in terms of its use.

Another group of patients who apparently benefit from the use of femtosecond laser in cataract surgery is patients with advanced nuclear cataract (nuclear density grade 4). In a prospective, non-randomised study performed by Chen *et al.*[44] in 2017 involving a small sample of 95 eyes, comparing the use of femtosecond laser to conventional surgery in a patient with advanced cataract, the group undergoing cataract surgery with a femtosecond laser was associated with significantly less endothelial damage ($P < 0.001$).

To summarise, the literature cannot prove with adequate studies that the use of femtosecond laser would have a benefit in the preservation of endothelial cells when compared to conventional manual phacoemulsification in eyes with normal corneas.

SURGICAL TECHNIQUE - FRACTURE OF THE LENS NUCLEUS

In the early 1990s, the nuclear fracture technique known as divide-and-conquer was described. Later, new techniques emerged with the objective of reducing the ultrasound time and, consequently, the endothelial loss.[45,46] In recent years, different authors have tried to compare the most diverse techniques used in phacoemulsification surgery to find one that was superior to other techniques regarding to safety for the corneal endothelium. Pirazzoli *et al*.,[47] in 1996, in a prospective study involving 100 patients, compared the divide-and-conquer technique with the phaco-chop technique and at the end of 8 weeks of follow-up, no significant differences were observed between the groups in terms of loss endothelial. In 2000, Vajpayee *et al*.[48] compared phaco-chop versus stop-and-chop techniques and found no differences in endothelial loss at the end of 12 weeks of follow-up. In 2006, Pereira *et al*.[49] compared stop-and-chop versus pre-slice/pre-fracture techniques and found no differences in endothelial loss at the end of 3 months of follow-up. In 2008, Storr-Paulsen *et al*.[50] compared divide-and-conquer versus phaco-chop techniques and also found no differences in endothelial loss at the end of 3 months and 12 months of follow-up.

Only in 2013, Park *et al*.,[51] when stratifying their patients according to the density of the lens nucleus, were able to find less endothelial loss in patients undergoing the stop-and-chop technique compared to the divide-and-conquer technique. This difference was significant at the end of 2 months of follow-up only in nuclei with a density of 4+ ($P < 0.05$). Despite being a prospective study, its sample was very small, with only 15 eyes in each group.

To summarise, the literature can prove with adequate studies that the use of pre-fracture or phaco-chop techniques implies a lower use of intraoperative ultrasonic energy; however, this lower ultrasound energy would have little benefit in preserving endothelial cells when compared to conventional techniques such as divide-and-conquer and stop-and-chop in eyes with normal corneas. What is observed is a probable benefit, which deserves further studies to prove it, in patients with advanced nuclear cataract (Grade 4). As with femtosecond laser, it is suggested that the use of pre-fracture techniques, with or without laser, in eyes with advanced cataract, would have the benefit of less endothelial loss.

To master the different nuclear disassembly/breaking techniques, the surgeon must master and feel comfortable in the most diverse scenarios. It is not recommended that the surgeon uses a new technique that he does not have complete mastery of when performing surgeries in complex cases, as the percentage of complications in the learning curve is higher.[52-54] Furthermore, the loss of endothelial cells depends not only on the technique of breaking/dismantling the nucleus used but also on the viscoelastics used, irrigation solutions, etc., – which will be discussed below.

SURGICAL TECHNIQUE – BEVEL POSITION

Recently, some authors started to investigate the effect that the position of the opening of the bevel of the phacoemulsification tip would have on the corneal endothelium.[55-57] We have the technique considered 'conventional' or 'traditional', in which the opening of the bevel is directed toward the endothelium and the opposite or reverse technique, in which the opening of the bevel is directed towards the nucleus. Two *in vivo* studies are worth mentioning. Raskin *et al*.,[57] in 2010, performed a prospective, randomised and unmasked study involving 50 eyes of 25 patients. In one eye, the phaco-chop technique was used with the tip in the traditional position and in the contralateral eye, the same technique, but with the tip in reversed position. At the end of 1 month, 2 months and 6 months, significant differences were observed regarding endothelial loss in favour of the tip in reversed position ($P < 0.05$). Faramarzi *et al*.,[55] in 2011, found completely opposite results. In a prospective, randomised and masked study involving 60 eyes of 30 patients, the authors compared different tip (bevel) positions during cataract surgery. At the end of 3 months of follow-up, endothelial loss was significantly higher in eyes operated with the tip in a reversed position (bevel down) when compared to the traditional position ($P = 0.016$).

Finally, in 2002, Frohn *et al*.[56] carried out a laboratory study with an artificial model of the eye to investigate the propagation of ultrasonic waves that reach the cornea at different positions of the tip (bevel). The sensor used to measure the propagation and amplitude of the ultrasonic waves that reached the cornea did not find a statistically significant difference between the two positions of tips used ($P = 0.78$).

To summarise, once again we find a controversial subject. What is observed are only two articles, totalling 50 patients, with completely opposite results on the same outcome, which implies the need for further studies to prove that a particular bevel position is superior to another. The only laboratory study performed on this topic was not able to identify differences between tip positions and the energy released towards the corneal endothelium.

VISCOELASTIC SUBSTANCES (VESS)

VESs are used for stabilisation of the anterior chamber during cataract surgery and have become essential for protection and greater safety of ocular structures, especially the corneal endothelium. They provide protection by a physical barrier effect and against free radicals (sodium hyaluronate is a great 'scavenger' of free radicals).[58,59] VESs are commonly divided into two categories – dispersive and cohesive. In this case, increasing its dispersive component, or reducing its cohesive component, implies greater protection of the intraocular tissue through the formation of a better quality layer or coating;[60-64] however, it increases the difficulty in its complete removal at the end of the procedure.[65,66] The VESs can also be classified according to their viscosity; in this case, their viscosity is directly related to their ability to create space and maintain anterior chamber depth during surgery.[67-72]

In 2011, van den Bruel *et al.*[73] published a meta-analysis study precisely to evaluate and compare different VESs in terms of their ability to protect the endothelium during cataract surgery. This review study included 21 randomised clinical trial articles totalling 1769 patients, the primary outcome being the endothelial cell density observed at the end of 3 months of cataract surgery in patients with a pre-operative mean of 2385 cells/mm^2. Through a combined comparison analysis, the authors found, among the different viscoelastic substances studied that the viscoadaptive substances had the best protective effect for the corneal endothelium, followed by the use through the soft-shell technique of a combination of dispersive and a cohesive VES. According to the authors, the VESs with the least protective effect on the endothelium would be the low viscosity dispersive viscoelastics. As with any other research, readers should be aware of some negative points presented in the meta-analysis arising from the methodology used, mainly related to the large number of VESs available on the market, which makes it very unlikely to compare them all. Although the studies point out statistically significant differences between the different VESs, the same cannot be said about the clinical difference since all of them had endothelial losses below 100 cells/mm^2.

IRRIGATION SOLUTIONS

The irrigation solutions initially used in cataract surgery were 0.9% sodium chloride solutions (saline), Ringer's solution and Plasma-Lyte 148. Later, in 1960, solutions with more similar composition, osmolarity and pH to aqueous humour were developed and named balanced saline solution (BSS). After a little over a decade, in 1973, a new irrigation solution known as BSS Plus was introduced. This new solution, developed after studies carried out by Edelhauser *et al.*,[74] had some components added to its structure, such as glucose, glutathione and bicarbonate, which made it healthier and less harmful to the corneal endothelium.

As observed in the literature, the different irrigation solutions developed over the years for use in cataract surgery aim to reduce the production of free radicals that attack the corneal tissue through their antioxidant properties. Despite being more expensive and having a better composition, Nayak and Shukla,[75] in a randomised clinical trial published in 2012, were unable to find a statistically significant superiority of BSS Plus (Alcon, USA) when compared to Ringer Lactate in the preservation of endothelial cells. The mean endothelial loss in the group of patients who received the BSS Plus was 5.03% compared to a loss of 8.35% in the group that used Ringer Lactate at the end of 6 months of follow-up (P = 0.483). However, in another randomised clinical trial, Lucena *et al.*,[76] when comparing BSS Plus to Ringer Lactate, identified a statistically significant correlation between an increase in endothelial cell loss with increasing irrigation volume and phacoemulsification surgery time when using Ringer Lactate at the end of 2 months of cataract surgery and this correlation was not observed when the BSS Plus was used.

DIABETES MELLITUS

There are currently questions in the literature about which personal characteristics of patients would have an impact on the greater or lesser change in endothelial density during cataract surgery. Some of these conditions deserve to be addressed.

The presence of diabetes mellitus has been suggested as a possible risk factor related to greater endothelial loss during cataract surgery.[77-79] Hyperglycaemia situations are related to toxic effects on almost every cell in the human body. In individuals with diabetes, ×4 higher concentrations of glucose have already been isolated in the tear film. In addition, the literature shows that diabetic patients present corneal cell dysfunctions responsible for the appearance of persistent epithelial defects, erosions, ulcers and oedema, probably related to diabetic neuropathy.[77]

Recently, studies have been performed trying to compare endothelial loss after cataract surgery between diabetic patients and a control group. Hugod *et al.*,[78] in 2011, published a prospective study, involving 60 patients, 30 diabetics, and 30 patients as controls and after 3 months of cataract surgery, they observed a statistically significant reduction in the mean density of endothelial cells between the groups, with a loss of 154 cells/mm^2 (6.2%) in the diabetes group and 42 cells/mm^2 (1.4%) in the control group (P = 0.04). Mathew *et al.*,[79] also in 2011, performed a prospective cohort study comparing 158 eyes of diabetic patients with 165 eyes of normal patients (control). At the end of 3 months of follow-up, the authors observed an endothelial loss of 19.24% in the diabetic group versus 16.58% in the control group ($P < 0.05$).

To summarise, despite a limited number of studies comparing endothelial loss in diabetic patients to non-diabetic patients, the corneal endothelium in patients with diabetes mellitus appears to be under greater metabolic stress leading to greater loss after cataract surgery.

FED

FED is caused by a complex combination of genetic (preponderant) and environmental factors, presenting an autosomal dominant inheritance with incomplete penetrance. It is a bilateral pathology, often asymmetric, with a typically slow evolution.[80] It has an average prevalence of 4% (ranging regionally from 3.8 to up to 11%) in individuals over 40 years of age in the United States, being the main indication for corneal transplantation in that country. There is a greater involvement of severe forms in women than in men in a proportion that varies between 2.5 and 3.1.[27-30,80,81]

The essential feature of this dystrophy is the presence of Guttae/Guttata: focal extracellular matrix nodules deposited on Descemet's membrane, which represents outgrowths produced by endothelial cells.[82,83] These deposits are found mainly in the central region and over the years (usually decades), there may be coalescence of the same with involvement of the periphery of the tissue associated with a thickening of Descemet.[84,85] Accelerated loss of endothelial cells is a characteristic of this pathology (associated with an apoptotic process), in addition to a decrease in pumps Na-K ATPases over the years lead to stromal oedema and tissue opacity that lead, to varying degrees, to decreased vision.[86-90]

Deterioration in the quality of vision and a lower sensitivity to contrast are also characteristics of this pathology, especially in cases, where the Guttae become confluent in the central area/visual axis, due to the dispersion and deviation of light when it passes through the affected site – in addition to an increased corneal high-order optical aberrations.[91-94] Colour vision is typically unaffected (this is a function of retinal photoreceptor cells).[95]

Hayashi *et al.*,[96] in a 2011 case–control study, compared the percentage of endothelial loss at 1 month and 3 months after cataract surgery between eyes with a previous low endothelial count (between 500 and 1000 cells/mm^2) and eyes from a group control (100 eyes in total). What the authors observed is that at the end of this follow-up period, the endothelial loss in the low cell count group was 5.1% compared to 4.2% in the control group, with no significant difference between the groups ($P > 0.147$).

Due to the reduced number of articles on these topics, it is difficult to reach more assertive conclusions. As the literature seems to point out, the percentage of endothelial cell loss in eyes with a low previous count, as in Fuchs' Endothelial Dystrophy, would be comparable to that in eyes with normal cell numbers. However, as these eyes already have a reduced amount, this loss can be the 'trigger' for an irreversible corneal decompensation/oedema requiring a transplant.

The pre-operative evaluation of these cases must be individualised. Specular microscopy alone cannot predict the outcome of surgery, the need for a future transplant, or the health or functioning of unaffected cells as many other factors may play a role in corneal endothelial loss and dysfunction. The assessment of endothelial function can be indirectly measured by thickness/pachymetry[97-99] and corneal densitometry.[94,97,100-102] In this context, the pachymetric map provides us with valuable information (much more than an isolated central measurement since depending on the population studied, healthy corneas can vary from 415 to 625 μ).[103-105] The thinnest point of healthy corneas is found within the central 3mm of tissue – which does not occur in cases with endothelial disease.[106,107] In corneas with more severe involvement, there is also an important diurnal fluctuation of values, with morning values invariably higher than those in the afternoon.[108,109] A choice of technique (extracapsular with greater endothelial loss than phacoemulsification depending on the scenario), substances and supplies used, procedure duration, type of IOLs (anterior chamber IOLs should be avoided) and surgeon's experience have a direct influence on the final outcome.

PSEUDOEXFOLIATION

The presentation of pseudoexfoliation is variable and heterogeneous, with great challenges for cataract surgery in more advanced cases. First described by Lindberg in 1917, ocular pseudoexfoliation syndrome (PXF) is an extracellular matrix disorder characterised by the gradual and abnormal production, with consequent accumulation and deposition, of fibrillar/exfoliative material in the anterior segment of the eye.[35,83] Observed worldwide and in virtually all populations and ethnicities, PXF is the most common identifiable secondary cause of open-angle glaucoma and is associated with a higher and earlier incidence of nuclear cataract (as a consequence of chronic hypoxia secondary to aqueous humour).[35,83] The prevalence of this condition increases with age, being more common in Nordic and Eastern European countries.

The diagnosis is usually made by a thorough clinical (biomicroscopic) examination, where deposits of fibrillar, white, as 'cigarette ash' material are noted throughout the anterior segment of the eye – particularly in the lens, pupillary border, corneal endothelium, angle, processes ciliary and zonules. The loss of iris pigmentation, mainly in the pupillary margin and midperiphery, often leads to the finding of transillumination of the iris. The possible clinical findings are summarised in [Table 2]. It is a bilateral pathology, not infrequently presenting itself in a markedly asymmetrical manner.

In a study published in 2013 involving patients with PXF, Hayashi *et al.*[110] investigated the pattern of endothelial loss at the end of 3 months of follow-up after cataract surgery and compared it with normal patients. In this prospective, comparative and non-randomised study, the authors evaluated 36 eyes in each group and at the end of the 3-month follow-up period, the PXF group showed an endothelial loss of 9.0% versus 3.4% in the control group ($P = 0.021$). In the study inclusion criteria, patients with PXF had pseudoexfoliative material in the anterior segment of the eyeball and good mydriasis and had no other comorbidity. All surgeries were performed without complications. The study showed that the simple fact that the patient had PXF implied a greater loss of endothelial

Table 2: Clinical findings in patients with pseudoexfoliation syndrome.

Tissue involved	Possible clinical findings
Iris	• Peripupillary/pigmentary atrophy (transillumination) • Restricted/irregular mydriasis • Intrastromal haemorrhages
Trabecular meshwork/Anterior chamber	• Pigment deposition • Increased and persistent 'flare' (pseudouveitis due to breakdown of the blood-aqueous barrier)
Intraocular pressure	• Interocular asymmetry/peak pressure after mydriasis
Cornea	• Deposition of pseudoexfoliative material and pigment on the endothelium • Descemet's thickening, with irregular outgrowths (different from Guttata)
Crystalline and zonules	• Deposition of amorphous fibrillar material in the anterior capsule and zonules • Phacodonesis/Lens subluxation

cells when compared to individuals with normal eyes. Prospective, randomised and masked studies are needed to confirm these findings.

CATARACT IN EYES UNDERGOING CORNEAL TRANSPLANT

Recently, a very interesting study was carried out in an attempt to assess the percentage of endothelial loss after cataract surgery using the phacoemulsification technique in eyes previously submitted to corneal transplant surgery. Acar *et al*.,[111] in 2011 in a prospective, non-randomised study, compared three groups of eyes: Group 1 included patients who had previously undergone penetrating corneal transplantation (*n* = 16 eyes), Group 2 who had previously undergone deep anterior lamellar transplantation (DALK, *n* = 20 eyes) and Group 3 formed by eyes without previous surgery (control, *n* = 20 eyes). At the end of 12 months of follow-up after cataract surgery, the total percentage of endothelial loss in Group 1 (penetrating transplantation) was 43.99%, in Group 2 (DALK), it was 11.22% and in the control group of 12.39%. In a very similar way, Kim and collaborators,[112] in 2010, reported an endothelial loss of 58.1% in eyes previously submitted to corneal transplantation versus 14.98% in normal eyes at the end of 24 months of post-operative follow-up.

To summarise, the literature today points to a significantly greater loss of endothelial cells in eyes previously submitted to penetrating corneal transplant surgery when compared to normal eyes. Again, prospective, randomised and masked studies are needed to confirm these findings.

CORNEAL OEDEMA AND ENDOTHELIUM RECOVERY AFTER CATARACT SURGERY

I. Aetiopathogenesis

The main aetiologies and risk factors for corneal oedema/decompensation after cataract surgery are listed below:

1. Pre-operative
    - Endothelial dystrophies (Congenital hereditary endothelial dystrophy [CHED], fuchs and posterior polymorph)
    - Iridocorneoendothelial syndrome (ICE)
    - Pseudoexfoliation
    - Hard nucleus
    - Chronic Uveitis
    - Chronic angle closure (narrow angle glaucoma/shallow anterior chamber)
    - Corneal trauma with endothelial involvement
2. Intraoperative
    - Direct trauma (instrumental and nuclear fragments)
    - Toxicity of irrigation solutions
    - Intracameral drug toxicity
    - Ultrasound/free radicals
    - Descemet's membrane detachment (DMD)
    - Contact with other eye tissues
    - Factors related to IOL
3. Post-operative
    - Vitreous in the anterior chamber
    - Endophthalmitis
    - IOL-related problems (instability/decentration, subluxation and retention/mobilisation of fragments)
    - Toxic anterior segment syndrome (TASS)
    - Increased intraocular pressure (IOP) (Glaucoma and corticosteroid sensitivity)
    - Retention of lens fragments
    - Brown-McLean syndrome
    - Chronic inflammation
    - Epithelial growth (ingrowth or downgrowth)
    - Leakage from the incision (Seidel)/Hypotony/shallow anterior chamber.

Each of these aetiologies requires a specific strategy to aid in oedema resolution. For treatment purposes, it is best to classify the type of oedema into the categories listed in [Table 3] below:

CLINICAL MANIFESTATIONS

Signs and symptoms: The main symptom secondary to post-phacectomy oedema is a low visual acuity in the immediate post-operative period, below that expected by the pre-operative evaluation. In addition, pain, photophobia, tearing and congestion may be associated with corneal oedema and inflammation, to varying degrees. A detailed examination is necessary to characterise the extent and severity of the case, in addition to indicating

Table 3: Types of corneal oedema and post phakectomy – management.

Beginning	Description	Aetiology	Examples	Management
Immediate	Oedema present from the first day of surgery	Endothelial trauma with loss of function	Ultrasound Excess long surgery IOP increase	Clinical management, if not improved – endothelial transplantation
		Structural injuries	Descemet's Membrane Detachment Endothelium or Descemet rupture/tears	Clinical management with specific repair surgery (e.g., C3F8 injection)
Late	Oedema appears after a period of corneal transparency	Cell loss with endothelial failure	Aphakic bullous keratopathy Bullous pseudophakic keratopathy	Endothelial transplantation or symptomatic treatment in cases poor visual prognosis

the possible causes for the oedema. The incidence of discrete Descemet's detachments (DMD) in uncomplicated surgery is approximately 47%.[113,114] In cases where oedema still allows visualisation of the anterior segment, careful biomicroscopic examination may reveal DMD, lens fragments or problems with IOL. The presence of a capsular tear, vitreous in the anterior chamber and/or multiple sutures may also suggest a complicated surgery.

Differential diagnosis

TASS can result in endothelium failure that leads to limbus-to-limbus oedema, fibrinous reaction in the anterior chamber, iris atrophy and trabecular damage.[115] A picture of herpetic endothelitis should be considered in the presence of signs such as keratic precipitates, loss of corneal sensitivity, presence of corneal opacities, sectoral atrophy of the iris and history of the previous episodes of herpetic keratouveitis.

COMPLEMENTARY EXAMINATIONS

- Pachymetry/pachymetric map
- Specular microscopy
- Anterior segment tomography
- Confocal microscopy.

CLINICAL MANAGEMENT

Hyperosmotics

Initial treatment includes the use of hyperosmotic agents such as dimethylpolysiloxane or sodium chloride eye drops (5%) or gel (6%). These drugs create an osmotic gradient in the tear film that drains water from the swollen cornea. There is no consensus regarding the best efficacy according to the formulation (gel vs. solution), but prescribing at night, before bed, significantly improves morning discomfort. In some cases, hyperosmotic agents are ineffective in reducing stromal oedema and may even lead to ocular surface irritation. However, the treatment with hypertonic solutions can lead to oedema resolution in up to 1/3 of cases, especially in the early cases.[119] Occasionally, the treatment may need to be continued for 2–3 months. A corneal thickness between 613–694 μm (in the central area) and 633–728 μm (in the peripheral area) has been shown to be a reliable indicator for better prognosis/response to hyperosmotics.[19] On the other hand, more advanced cases with corneal thickness above these values and epithelial oedema did not show clinical improvement with treatment. Even so, the use of hyperosmotics can be indicated in these cases, because it promotes a symptomatic improvement in any case of oedema. It is important to emphasise that drug therapy does not interfere with the underlying cause for the oedema that must be identified and treated

Therapeutic contact lenses (TCL)

TCL, especially long-wear hydrophilic ones, is useful in controlling pain associated with epithelial blistering. A thin contact lens with a high hydration content is more suitable in these cases since the permeability to oxygen is greater.[116] The use of LCTs creates a protective layer that prevents the bubbles from bursting during blinking, providing more comfort and decreasing irritative symptoms.[117,118] The association between LCTs and hyperosmolar solutions can be beneficial, creating a hypertonic reservoir that promotes continuous corneal deturgescence for a longer period.[117-119] Prolonged use of LCTs is not recommended due to the potential risk of infection (especially in cases of ruptured blisters)[120,121] and it is prudent to combine the use of broad-spectrum topical antibiotics during their continued use.[118,122]

IOP

Increased IOP causes metabolic stress and possibly direct damage to the endothelium and is also an important cause of corneal oedema. The severity of the endothelial damage is proportional to the duration and intensity of the pressure increase and it must be treated promptly.[123] The management of transient ocular hypertension after cataract surgery is performed with topical use of hypotensive drugs., All classes of ocular hypotensive drugs can be useful in controlling IOP; however, in the presence of oedema, carbonic anhydrase inhibitors should be avoided.

Few studies have investigated the actual effect of dorzolamide, brinzolamide and acetazolamide eye drops in inhibiting endothelial cell carbonic anhydrase pumps and the results are contradictory. In theory, the action of these drugs can lead to a decrease in the flow of fluid from the stroma towards the aqueous humour, precipitating or worsening the oedema.[124] However, in some clinical trials, the use of oral and topical carbonic anhydrase inhibitors was effective and safe in the prevention and post-operative control of IOP.[125] Several studies have shown that the use of these drugs did not change corneal thickness or worsen recovery from oedema after phacoemulsification.[126-129] On the other hand, there is evidence that preservatives present in hypotensive eye drops, such as benzalkonium chloride, have deleterious and toxic effects on endothelial cells.[130] In addition, there are several case reports demonstrating reversible[131] and irreversible[132] endothelial decompensation with the use of these drugs both in healthy patients and in those with endothelial dysfunction.[133,134] In view of the above, the control of IOP is of paramount importance and the prescription of carbonic anhydrase inhibitors should be avoided whenever possible.

Inflammation

Inflammation associated with corneal oedema should be promptly treated with topical corticosteroids. In addition to ocular inflammatory control, there is an increase in the number of Na +/K + ATPases associated with a better performance of the pump function of endothelial cells. Adverse effects associated with prolonged use of corticosteroids at high frequency, such as an increase in IOP, can further delay the resolution of the oedema. Therefore, the dosage of this drug must be considered individually and is subject to careful and periodic evaluation of the situation.[135]

SURGICAL MANAGEMENT

Lens remnants

remnant lens fragments can cause corneal oedema due to direct mechanical trauma to the endothelium[136] or secondary to inflammation triggered by lens epithelial cells.[137] Oedema may have an early onset when the fragments are in the anterior chamber in the immediate/early post-operative period, or appear late (8–24 years) in cases, where a fragment that was lodged in the posterior chamber migrates to the anterior chamber.[138-140] Risk factors associated with lens fragment retention include a longer axial diameter, more curved corneas, myopia, opaque arc senile, clear iris, dense fragments and a small pupil.[141] Diagnosis is usually made by biomicroscopic examination, but in 10–37% of cases, it is necessary to complement the examination with gonioscopy[141] since these fragments can be of tiny size and lodge in the inferior angle due to gravity. The length of time the retained fragment remains in the anterior chamber is directly associated with a higher incidence of corneal complications and cystoid macular oedema.[141,142] In addition, there are reports of progressive endothelial loss progressing to bullous keratopathy. The presence of cortical fragments can be resolved, in selected cases, with a course of corticosteroids. However, the differentiation between cortical and nuclear fragments is very difficult; therefore, removal of retained fragments is indicated at the time of diagnosis.[141]

IOL-related problems

Some situations related to IOL implantation are potential risk factors for endothelial decompensation from direct damage. Among them, we can highlight IOL decentration and instability, presence of free IOL fragments in the anterior chamber, ectopic posterior chamber lenses (implanted in the anterior chamber) and unstable anterior chamber lenses. The IOLs can suffer damage with fragment release during manipulation for the primary implant (manual or with injector) or during the explant manoeuvre for IOL replacement. It is common for oedema to appear initially in the inferior region of the cornea, due to the effect of gravity on the damaged IOL or the free fragment. Oedema can rapidly progress to corneal decompensation (failure has been reported less than 1 month after surgery), so damaged IOLs that incur oedema should be explanted immediately.[143] The technique for explanting will depend on the IOL material and of instruments available to the surgeon (conventional or micro-instruments). IOL removal must be performed meticulously to avoid complications such as posterior capsule rupture, hyphema, iridodialysis and total extraction of the IOL-capsular bag complex.

DMD

The approach to DMD in the immediate post-operative period will depend on the extent, height (distance from the stroma), duration and location of the DMD in relation to the pupil centre (zone 1, within 5 mm of the centre; zone 2, 5–8 mm of the centre and zone 3, ≥8 mm of the centre) – also called the height, extension, length and pupil-based strategy.[144]

- DMD ≤1 mm in length, ≤ 100 μm in height in any zone (planar DMD) ◊ observation or clinical management (spontaneous adhesion is common in these cases)

- DMD 1–2 mm in length, 100–300 µm in height, in zones 2 or 3 ◊ clinical management
- DMD >2 mm in length, >300 µm in height, in zone 3 ◊ clinical management
- DMD >2 mm in length, >300 µm in height, in zones 1 or 2 ◊ descemetopexy with air injection, C3F8 (12–14%) or SF6 (15–20%).
- refractory DMD3
  - Upper ½ of the cornea ◊ Descemetopexy with air
  - Free edges in the upper ½ of the cornea ◊ descemetopexy with C3F8 (12–14%) or SF6 (15–20%).
- Planar or free edges on the lower ½ of the cornea ◊ Descemetopexy with C3F8 (12–14%) or SF6 (15–20%).

PHACO + ENDOTHELIAL TRANSPLANTATION

As previously described, FED affects approximately 4% of the American population over 40 years of age, in different severities.[81] Data show that more than 35,000 endothelial transplants were performed in the year 2018 in the USA, alone or in association with cataract surgery.[145]

Cataract surgery in patients with FED should be evaluated individually,[146] according to the degree of cataract (we suggest LOCS III, using the slit lamp) for the most appropriate study, both for the severity of the endothelial dysfunction and for the indication of the most appropriate treatment: (1) specular microscopy; (2) confocal microscopy; (3) pachymetry (preferably pachymetric map); (4) ecobiometrics; (5) topography; (6) cornea tomography and (7) aberrometry.

Both corneal (endothelial health) and lens (cataract stage) aspects should be considered when choosing the type of surgery to be performed and for pre-operative guidance to the patient and family.[101] In the current literature, there is great controversy about the predictive factors of endothelial decompensation in patients with FED.[102] A confounding factor is the large pachymetric variation during the day in patients with FED. The indication for endothelial transplantation in patients with FED can be made when there is low vision associated with guttata, stromal oedema and, in the presence of cataract, its extraction can be performed before, in combination or after transplantation.[147-150]The preferred surgical techniques for endothelial transplantation at the moment are Descemet Stripping Automatic Endothelial Keratoplasty (DSAEK)[151] and DMEK (Descemet Membrane [EK]).[152] In cases where the donor cornea is very young or has micro-adhesions in the preparation, the use of the pre-Descemet's endothelial keratoplasty (PDEK)[153] technique PDEK is recommended, in which pneumodissection separates the most posterior layer of the stroma (Dua layer), Descemet and endothelium, facilitating positioning of the endothelial lamella.

COMBINED OR SEQUENTIAL SURGERY

There is a great debate in the literature about the best chronological sequence of procedures in cases of FED and cataract. However, some advantages of triple (one-stage) surgery over two-stage surgery, in cases of cancer, may include: [147,154]

- Decreased incidence of endothelial decompensation after cataract extraction (where the endothelium is maintained) in cases of FED with low cell counts
- Lower operative cost, both for the patient (eye drops, returns, etc.) and for the surgeon (hospital supplies, etc.)
- Faster visual rehabilitation.

Biometrics and IOL

In irregular corneas with significant FED oedema, keratometry and/or biometry of the contralateral eye can be used.

When the corneal transplant technique of choice is DSAEK associated with cataract surgery, an average induction of +1.27 dioptres of hyperopia should be expected as a consequence of changes in corneal power.[155-159] Aware of the hyperopic shift the surgeon should discount this value when choosing the IOL, avoiding greater refractive errors in the post-operative period.[160]

For DMEK and PDEK, the calculation can be based on flat refraction or discrete myopia (between −0.50 and −0.75 D) as this type of transplant aims to replace the diseased Descemet membrane and endothelium complex with another of similar thickness.[161]

As for the material of the IOLs used in corneal transplants, there are descriptions of opacifications of hydrophilic IOLs, including those with a hydrophobic cap, due to the need to inject air or gas into the anterior chamber for positioning the graft.[162,163] We recommend the use of IOLs hydrophobic in patients with low endothelial counts or with FED, predicting that, if endothelial transplantation is necessary, this unpleasant complication, which requires IOL explantation, will not occur, increasing surgical complexity.

In cases of combined DMEK and Cataract surgeries, toric IOLs can be used with debatable predictability.[164,165]

PRE-, INTRA- AND POST-OPERATIVE CONSIDERATIONS AND RESULTS

The pre-operative evaluation is a very important factor for a successful surgery. Anaesthetic preparation, patient positioning in the operating room and IOP control before the start of surgery are relevant factors. Intravenously administered 20% mannitol or oral acetazolamide are options available and used by many surgeons. One of the most important factors for the success of corneal transplantation is the meticulous aspiration of viscoelastic, when used in combined surgery. It is one of the main factors responsible for button detachment in endothelial transplants and is also associated with increased IOP in the post-operative period.[154] Another factor that can increase IOP is pupillary block and its prevention requires inferior iridotomy to avoid the migration of the air bubble posterior to the iris. This iridotomy can be performed with Nd: Yag Laser preoperatively or during surgery.[166]

The literature shows that triple surgery with endothelial transplantation does not present an increased surgical risk compared to two-stage surgery, with similar rates of primary endothelial failure, rebubble (re-injection of air into the anterior chamber), IOP control, endothelial loss and final visual acuity.[147,154]

For many decades, the only transplantation option for visually debilitating corneal oedema consisted of penetrating keratoplasty (PK). In 2012, EK surpassed PK as the treatment of choice for endothelial disease and selective keratoplasty became the mainstay of surgical treatment for corneal endothelial diseases.[27-30] PK carries significant intraoperative risks associated with 'open sky' as well as post-operative risks of graft rejection, wound dehiscence, post-operative astigmatism and prolonged visual rehabilitation.[27-30]

NEW MODALITIES FOR THE TREATMENT OF FED

Descemetorhexis Without Endothelial Keratoplasty (DWEK) (also called Descemet Stripping Only - DSO) is an innovative technique described for the treatment of FED, without the need for a donor cornea and, therefore, without the risk of rejection.[167,168]

The selection of the patient must be judicious so that it presents a good result, as not all patients with FED are able to perform this technique. The ideal candidate is one that has a low endothelial count and guttata confined to 4.0–4.5 mm (representing about 10% of the total surface area of the endothelium of a cornea with an average diameter of 12 mm) central to the cornea and who have a healthy periphery, with adequate endothelial count. The patient may be phakic or pseudophakic.[167,168] Repopulation of endothelial cells from the periphery to the centre slowly covers the injured area, with central corneal clearing within 6 months in normal cases. Borkar *et al*. separated the patients into groups according to the time of corneal whitening submitted to DWEK/DSO. They are: fast responders (repopulation within 1 month), normal (repopulation within 3 months), slow responders (repopulation after 3 months) and non-responders (repopulation is never achieved, requiring corneal transplantation).[167]

Rho-kinase inhibitor (ROCK), an enzyme that plays a role in the regulation of contractile tone of muscle tissues, exhibits great potential in corneal endothelial healing, described by Kinoshita et al. researchers to study new possibilities for the treatment of Endothelial Dystrophy of Fuchs.[169,170] Ripasudil (Glanatec 0.4% ophthalmic solution, Kowa Co Ltd., Nagoya, Japan) is a topical and selective inhibitor of ROCK, commercially available in Japan for the treatment of glaucoma and ocular hypertension. No changes in endothelial cell morphology were noted in Phase I human clinical trials. Its use for accelerating endothelial healing is currently off-label. Its association with DWEK is capable of accelerating the migration process of endothelial cells, with corneal transparency more quickly.[168]

Other techniques still under development today involve Descemet's acellular membrane transplantation (without endothelium) described by Soh and Mehta in 2018;[171] the creation of different methods and substrates for the cultivation and migration of endothelial cells in vitro for later implantation of the cultured cells; implantation of reprogrammed stem cells by Oie *et al*.,[91] following the technique described by Shinya Yamanaka (Nobel Prize, 2012)[172] and among other techniques to come.

CONCLUSION

The corneal endothelium suffers a physiological loss of the number of cells throughout life, which is more pronounced in certain pathologies and conditions. All intraocular surgery accelerates this loss, besides causing a direct and relevant acute injury. Cataract surgery is the most commonly performed procedure and is directly related to local changes and specific risks. There are technologies, techniques and substances that can change this situation and every surgeon should have knowledge about them, besides being able to identify and guide preoperatively the cases with higher risk and have the ability to manage each patient individually for the best visual recovery.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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