Journal of Ophthalmology

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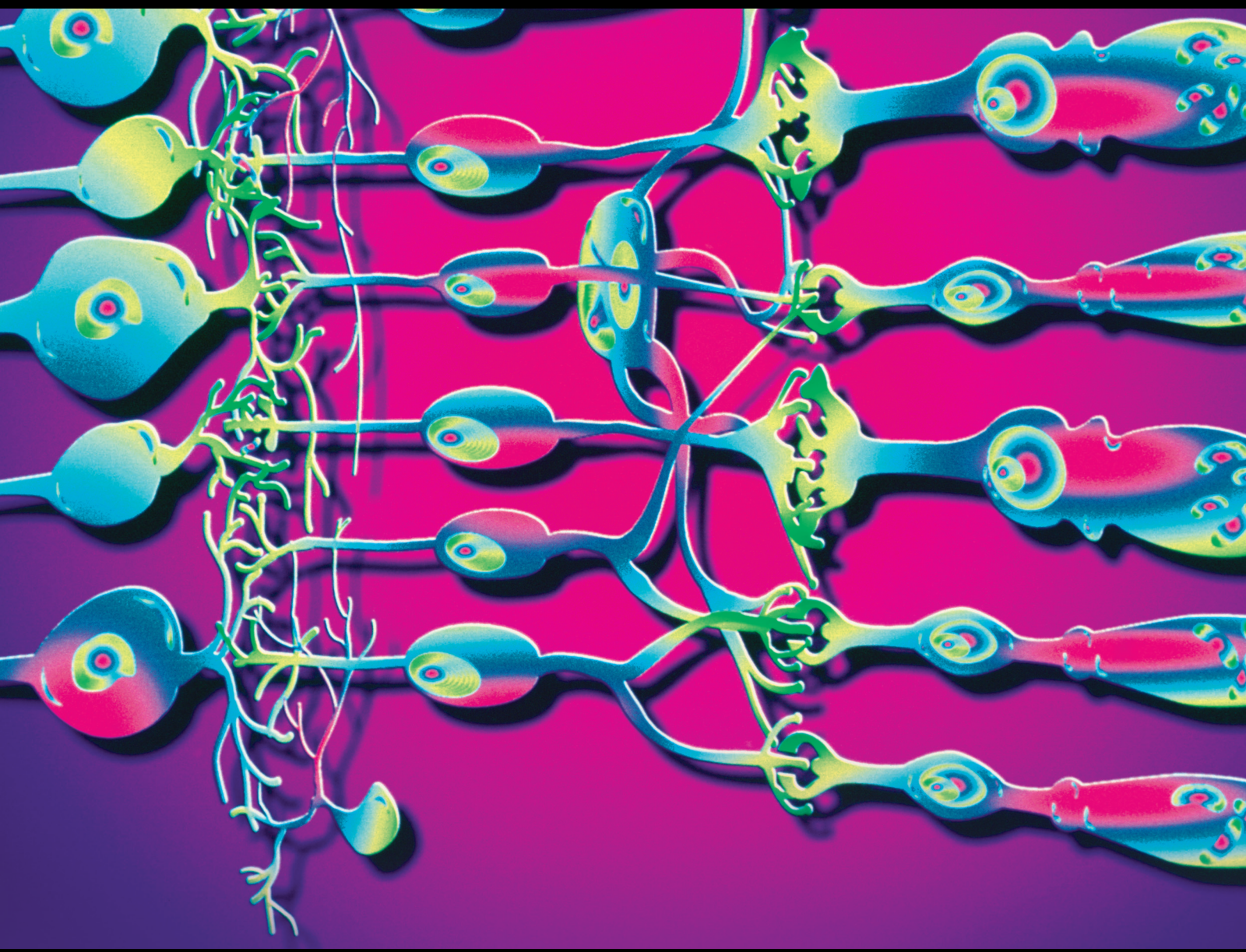

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Review Article

Corneal Endothelial Cell Loss in Glaucoma and Glaucoma Surgery and the Utility of Management with Descemet Membrane Endothelial Keratoplasty (DMEK)

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The corneal endothelium has a crucial role in maintaining a clear and healthy cornea. Corneal endothelial cell loss occurs naturally with age; however, a diagnosis of glaucoma and surgical intervention for glaucoma can exacerbate a decline in cell number and impairment in morphology. In glaucoma, the mechanisms for this are not well understood and this accelerated cell loss can result in corneal decompensation. Given the high prevalence of glaucoma worldwide, this review aims to explore the abnormalities observed in the corneal endothelium in differing glaucoma phenotypes and glaucoma therapies (medical or surgical including with new generation microinvasive glaucoma surgeries). Descemet membrane endothelial keratoplasty (DMEK) is increasingly being used to manage corneal endothelial failure for glaucoma patients and we aim to review the recent literature evaluating the use of this technique in this clinical scenario.

1. Introduction

Glaucoma is a group of conditions with varying pathophysiological processes, which cause progressive optic neuropathy associated with characteristic structural damage to the optic nerve and associated visual field loss [1]. The condition can be caused by various pathophysiological processes. Worldwide, glaucoma is the leading cause of irreversible blindness worldwide with a global prevalence of 3.54% in people aged 40–80 years with the highest prevalence being in Africa [2].

Corneal endothelial abnormalities, including a reduction in cell count and morphology, have been detected in glaucoma patients [3]. The corneal endothelium is a monolayer of hexagonal cells, which plays a critical role in regulating corneal hydration and thus transparency [4]. The cells are highly interdigitated and possess apical junctional complexes that, together with abundant cytoplasmic organelles, including mitochondria, are indicative of their crucial role in active fluid transport [5]. The abnormal endothelial changes observed in glaucoma are due to multiple influences including the intraocular pressure (IOP), aqueous humour abnormalities, medication use, and surgical interventions [3]. This review article aims to describe the endothelial changes seen in glaucoma and the role Descemet membrane endothelial keratoplasty (DMEK) has in managing corneal endothelial cell loss in glaucoma patients.

In preparing this article, electronic database searches were performed for English publications using the following search terms; glaucoma (including different types of glaucoma), glaucoma surgery (including different types of

glaucoma surgery), glaucoma medication (including different types of glaucoma topical therapy), corneal endothelium, and Descemet membrane endothelial keratoplasty (DMEK). The databases analysed included Medline, Embase, ClinicalTrials.gov, and PubMed. From the searches, all articles pertaining to the relevant topic were included in this review.

1.1. Assessment of the Corneal Endothelium. Slit-lamp biomicroscopy can detect macroscopic changes in the corneal endothelium and corneal endothelial diseases, such as Fuchs endothelial corneal dystrophy (FECD). Precise examination of corneal endothelial cell density (ECD) or cell count can be evaluated using, most commonly, specular microscopy or *in vivo* confocal microscopy (see Figure 1). Endothelial density is defined as the number of cells present in a 1 mm^2 area.

1.2. Endothelium and Ageing. As mentioned, the corneal endothelium is a monolayer of hexagonal cells which maintain homeostasis of corneal hydration and transparency [4]. It sits upon a collagen basement membrane called Descemet's membrane. At birth, the Descemet's membrane is 3 μm thick, but this increases with age to an average of 13 μm at 70 years of age.

Corneal transparency is maintained by the active transport of ions across Na^+/K^+ ATPase pumps [6]. These pumps continually function to preserve the clarity of the cornea even if the IOP within the anterior chamber rises [7]. The integrity of the corneal endothelial monolayer is critical in maintaining this physiological function. The average corneal ECD during adulthood is 2500 cell/mm^2, but natural ageing results in both the deterioration in number and morphology of these cells, including cell size and pleomorphism (loss of hexagonal shape) [8–10]. The rate of cell loss is constant throughout life at a rate of approximately 0.6% per year after the age of 18 [11]. This cell loss increases the permeability of the endothelial barrier and reduces its ability to pump fluid out of the corneal stroma and maintain corneal transparency [12]. Corneal endothelial cells show limited replicative ability *in vivo* [13].

Additionally, the ability of the Na^+/K^+ ATPase pumps deteriorates with age, decreasing from 32 μamps.cm^{-2} in people aged 60 years old to 22 μamps.cm^{-2} in those aged 90 (natural variation is ±6 μamps.cm^{-2}) [14]. These age-related changes are well documented in the literature. Studies have reported that as the morphology of the corneal endothelial monolayer alters with age, it loses its barrier permeability as a result of a lower resistance at the intracellular junctions of the apical cell membranes [15]. Carlson et al. [16] reported in a study of corneas aged 5–79 years old that the number of hexagonal cells significantly decreased with age, but the number of pentagonal and heptagonal cells increased simultaneously [16]. In addition, they observed a 23% increase in endothelial permeability to fluorescein with age but found no differences in corneal thickness or pump rate. The flow rate of aqueous also remained stable. The authors concluded that as the cell morphology altered with age, the cell barrier became more permeable [16].

Age-related loss and changes of the corneal endothelium usually do not have much clinical relevance unless further cell loss is encountered in diseases such as FECD or surgical intervention. In these cases, the cell loss eventually overwhelms the ability for the corneal endothelium to maintain homeostasis leading to irreversible corneal oedema and blindness [12].

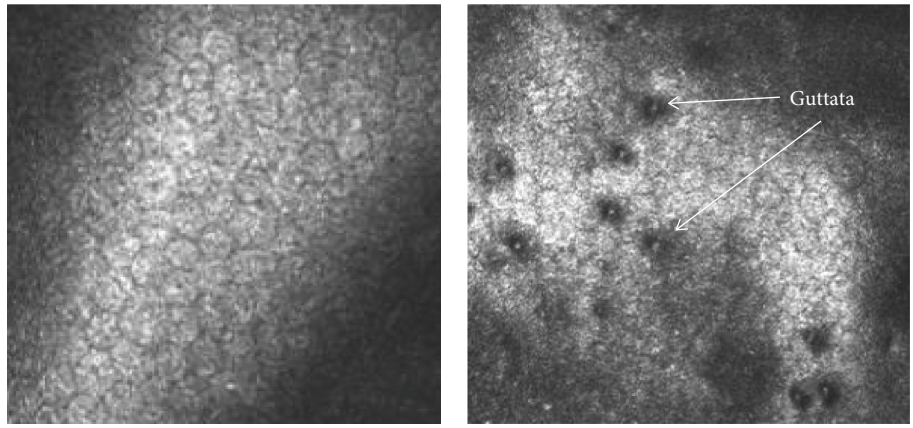
1.3. Influence of the Aqueous Humour on Corneal Endothelial Cells. The biological mechanisms responsible for the gradual loss of corneal endothelial cells are likely multifactorial including environmental, hormonal, and immune responses which may be responsible for cell migration, senescence, and apoptosis/necrosis of cells within the anterior segment during normal ageing [17]. As mentioned, corneal endothelial cells display limited proliferative capacity, although this is lower in older donors compared to younger ones [18]. A study on donor corneas also demonstrated that the length of the G1 phase of the cell cycle in corneal endothelial cells is longer in older donors (50 years) compared to younger donors (30 years) [13]. Transforming growth factor beta (TGF-β) may be partly responsible for this as it reportedly inhibits degradation of the G1-phase inhibitor, p27kip1, thus preventing the cells from entering into S-phase [19].

The anterior chamber and aqueous humour have immunosuppressive effects that permit inflammatory mediators and cells to circulate within the eye [20]. TGF-β2 [21] and α-melanocyte-stimulating hormone [22] are the dominant immunosuppressive molecules within the aqueous humour. Transforming growth factor (TGF)-β2 is known to be present within aqueous humour in normal eyes, which is in direct contact with the corneal endothelium [23]. Trivedi et al. demonstrated that significantly more TGF-β2 is present in the aqueous of older eyes without glaucoma [24].

Additional levels of inflammatory cytokines within the aqueous humour such as tumour necrosis factor (TNF), interleukin-1, and interferons (IFNs) are known to increase with age [25]. *In vitro,* they have been shown to induce apoptosis in corneal endothelial cells [25]. Intraocular surgery, such as cataract surgery, which is usually performed on older patients, has also been shown to increase cytokine levels associated with inflammation and apoptosis including interleukins, TNF-α, IFN-γ, TGF-β, and monocyte chemoattractant protein-1 (MCP-1) [26, 27]. Cataract surgery can also lead to long-term alterations of the intraocular microenvironment in normal, glaucomatous [28], and FECD eyes [29].

2. Changes in the Corneal Endothelium Parameters in Glaucoma

Research has shown that TGF-β plays a crucial role in the aetiology of glaucoma, with significantly elevated levels identified in the anterior chamber of glaucomatous eyes [30]. TGF-β is a key mediator of fibrosis in all organs [31], through the excess production of extracellular matrix proteins including collagens and fibronectin [32, 33]. In addition, fibroblasts transform into highly contractile



(a) (b)

Figure 1: Confocal microscopy of corneal endothelial cells. (a) Normal endothelial cells with a regular hexagonal shape. (b) Fuchs endothelial corneal dystrophy shows a loss of defined hexagonal shape, increased cell size, and the formation of guttata (as labelled).

myofibroblasts, as demonstrated by the expression of alpha smooth muscle actin (α-SMA) [34–36] or mesenchymal transformation in endothelial cells [37]. Collectively, these changes result in cellular and molecular changes in the trabecular meshwork causing a reduction of outflow facility and hence raised IOP [38].

A reduction in the endothelial cell count has been demonstrated in different types of glaucoma. Three hypotheses have been formulated for this: damage from direct compression of the corneal endothelium because of higher IOP; alteration of both the corneal endothelial cell layer and the trabecular meshwork in patients with glaucoma (e.g., due to TGF-β); and glaucoma medication toxicity [39]. The relevance of endothelial cell loss in glaucoma is important to consider if patients are to undergo intraocular surgery.

Interestingly, in 1997, Gagnon et al. reported that despite the reduction in cell numbers, the morphology of corneal endothelial cells (including the percentage of hexagonal cells and coefficient of variation in cell area) did not differ significantly when different types of glaucoma patients were compared to controls [39]. Whilst increased intraocular pressure had been associated with deceased corneal endothelial cell density, no significant correlation between cell density and duration of the glaucoma has been identified [39, 40]. Table 1 provides a summary of corneal endothelial density changes in different forms of glaucoma.

2.1. Angle Closure Glaucoma. Angle closure glaucoma is caused by obstruction of the trabecular meshwork by iris tissue, which prevents the drainage of aqueous humour and therefore a rise in IOP in the eye, which often results in optic nerve damage [41]. Corneal endothelial cell loss has been frequently reported after acute angle closure glaucoma (AACG) [42–48] and chronic angle closure glaucoma (CACG) [46, 49]. Multivariate analysis for AACG found that duration of the acute attack was the only factor independently associated with reduced corneal ECD ($p < 0.001$) [47]. As demonstrated in a study which analysed AACG patients into two groups, an AACG attack was less than 72 hour durations or more than 72 hours duration [46]. Mean endothelial cell count in eyes which had a shorter duration (<72h) was 2016 ± 306 cells/mm^2 compared to 759 ± 94 cells/mm^2 in those who had AACG for more than 72 hours ($p < 0.001$) [46]. Two more recent studies which evaluated the cell count and morphological characteristics of corneal endothelial cells revealed no clinically significant differences across the angle closure disease spectrum (primary angle closure suspect, primary angle closure glaucoma, and previous acute angle closure glaucoma) [50, 51].

2.2. Open Angle Glaucoma. High tension primary open angle glaucoma (HTG) patients have a raised IOP despite an anatomically unoccluded angle, which results in optic nerve damage. In normal tension glaucoma (NTG), patients demonstrate optic nerve damage despite having a normal intraocular pressure and an open angle. Research demonstrates that there is a reduction in corneal endothelial cell density in HTG; however, the limited analyses of these changes when compared to NTG present conflicting findings [40, 48, 52]. One group found comparable cell counts between NTG and HTG patients: $2{,}343 \pm 394$ and $2{,}326 \pm 231$ cells/mm^2, respectively [48]. Whilst others have reported significantly lower endothelial cell counts in NTG versus HTG patients ($2{,}380.0 \pm 315.4$ vs. $2{,}530.0 \pm 320.4$ cells/mm^2, $p = 0.04$), that is 6.3% less in NTG(54). Lee et al. postulated that in NTG a hypoperfusion mechanism accounted for both progressive optic neuropathy and endothelial cell density reduction [52].

Cho et al. found that the patients with HTG had a significantly lower endothelial cell density than controls ($p < 0.001$), but NTG patients had a similar cell density compared to controls [40]. The benefit of the Cho et al.'s study was that patients had no previous history of treatment with glaucoma medications. Analysis of 18,665 donor corneas received at the Lion's Eye Institute demonstrated that a past ocular history of glaucoma (in 2.7%) did not significantly affect endothelial cell density ($p = 0.094$), although the type of glaucoma was not specified [53].

Table 1: Corneal endothelial densities in different forms of glaucoma.

	Control mean (cells/mm^2)	Control SD (cells/mm^2)	No. controls	Cases mean (cells/mm^2)	Cases SD (cells/mm^2)	No. of cases	P value
Ocular Hypertension							
Baratz et al., 2006 [70]	2415	300	21	2331	239	26	0.6
Chawla et al., 2021 [71]	2509.1	298.5	91	2559.8	268.2	8	0.588
All forms of glaucoma							
Gagnon et al., 1997 [39]	2560	306	52	2154	419	102	<0.0001
Novak Stroligo et al., 2010 [68]	2528	306	100	2148	317	100	<0.0001
Acute PACG							
Setala et al., 1979 [43]	2392	346	25	2161	633	25	N/A
Bigar et al., 1982 [44]	2243	N/A	20	1534	N/A	20	0.002
Malaise-Stals et al., 1984 [45]	2398	380	174	1640	N/A	44	N/A
Chen et al., 2012 [47]	2559	50	50	2271	80	40	0.002
Sihota et al., 2003 [46]	2461	321	30	1597	653	30	<0.001
Verma et al., 2018 [50]	N/A	N/A	N/A	2504.0	558.1	74	N/A
Subacute ACG							
Sihota et al., 2003 [46]	2461	321	30	2396	271	30	<0.001
PACG-unspecified							
Gagnon et al., 1997 [39]	2560	306	52	2000	585	30	<0.0001
PACS							
Varadaraj et al., 2017 [51]	N/A	N/A	N/A	2676.8	270.0	466	N/A
Verma et al., 2018 [50]	N/A	N/A	N/A	2582.0	472.8	51	N/A
CACG							
Tham et al., 2006 [49]	N/A	N/A	N/A	2271.7	312.9	39	N/A
Chen et al., 2012 [47]	2559	50	50	2379	50	44	0.316
Sihota et al., 2003 [46]	2461	321	30	2229	655	30	<0.001
Varadaraj et al., 2017 [51]	N/A	N/A	N/A	2681.2	275.7	127	N/A
Verma et al., 2018 [50]	N/A	N/A	N/A	2523.8	406.8	234	N/A
Chawla et al., 2021 [71]	2509.1	298.5	91	2378.2	677.9	13	0.588
ACG Unspecified							
Novak Stroligo et al., 2010 [68]	2528	306	100	2113	243	24	N/A
NTG							
Lee et al., 2015 [52]	N/A	N/A	N/A	2380	315.4	30	N/A
Cho et al., 2009 [40]	2723.6	300.6	91	2696.7	303.9	87	1
Chawla et al., 2021 [71]	2509.1	298.5	91	2420.6	515.7	19	0.588
HTG							
Gagnon et al., 1997 [39]	2560	306	52	2226	311	55	<0.0001
Cho et al., 2009 [40]	2723.6	300.6	91	2370.5	392.3	49	<0.001
Lee et al., 2015 [52]	N/A	N/A	N/A	2530	320.4	28	N/A
Yu et al., 2019 [72]	2959	236	60	2757	262	60	<0.001
Chawla et al., 2021 [71]	2509.1	298.5	91	2517.9	245.3	39	0.588
ACG Unspecified							
Knorr et al., 1991 [59]	2302	394	4432	1812	297	123	<0.001
Seitz et al., 1995 [60]	2372	276	33	2214	251	16	N/A
Inoue et al., 2003 [61]	2362	327	30	2337	407	19	N/A
Wali et al., 2009 [62]	2460	N/A	N/A	2483	511.2	78	N/A
Zheng et al., 2011 [63]	2738.7	233.3	27	2240.7	236.6	27	<0.0001
Wang et al., 2012 [64]	2562	18	20	2505	284	7	N/A
XFS and senile cataract							
Quiroga et al., 2010 [65]	2482	N/A	356	2315	N/A	61	0.002
Tomaszewski et al., 2014 [66]	2503	262	84	2297	359	68	0.0008
Bozkurt et al., 2015 [67]	2363	229.3	51	2299.5	213.9	33	0.48

Table 1: Continued.

	Control mean (cells/mm^2)	Control SD (cells/mm^2)	No. controls	Cases mean (cells/mm^2)	Cases SD (cells/mm^2)	No. of cases	P value
PXG and senile cataract							
Tomaszewski et al., 2014 [66]	2503	262	84	2241	363	65	0.000005
Bozkurt et al., 2015 [67]	2363	229.3	51	2199.5	176.8	19	0.02
PXG							
Knorr et al., 1991 [59]	2302	394	4432	1482	267	59	<0.001
Seitz et al., 1995 [60]	2372	276	33	2014	254	69	N/A
Inoue et al., 2003 [61]	2362	327	30	2332	336	7	N/A
Wali et al., 2009 [62]	2460	N/A	N/A	2438	503.4	48	N/A
Novak Stroligo et al., 2010 [68]	2528	306	100	2024	254	16	<0.0001
Wang et al., 2012 [64]	2562	18	20	2186	2	13	N/A
Chawla et al., 2021 [71]	2509.1	298.5	91	2392.2	258.4	12	0.588
Juvenile Open Angle Glaucoma							
Urban et al., 2015 [73]	2955.5	N/A	33	2639.5	N/A	66	<0.0001
Congenital glaucoma							
Guigou et al., 2008 [74]	3470	357	401	2922	553	69	<0.001
Congenital and secondary juvenile glaucoma							
Wenzel et al., 1989 [75]	N/A	N/A	N/A	2780	N/A	20	N/A

SD, standard deviation; PACG, primary angle closure glaucoma; PACS, primary angle closure suspect; CACG, chronic angle closure glaucoma; NTG, normal tension glaucoma; XFS, pseudoexfoliation syndrome; PXG, pseudoexfoliation glaucoma; HTG, high tension primary open angle glaucoma.

2.3. Pseudoexfoliative Glaucoma. Pseudoexfoliative glaucoma (XFG) is the most common cause of open angle glaucoma worldwide [54, 55]. It is characterized by deposition of pathological greyish-white extracellular fibrillar protein components (PEX material) in multiple ocular tissues which is comprised of constituents of the basement membrane and elastic fibre components [56]. Deposition of this PEX material in the trabecular meshwork obstructs aqueous outflow and almost 50% of pseudoexfoliation syndrome (XFS) patients will ultimately develop XFG in their lifetime [57]. Electron microscopy has revealed large clumps of pseudoexfoliation material adhering to the corneal endothelium and this becomes incorporated into the posterior Descemet's membrane [58]; these may lead to early corneal endothelial decompensation. Patients with XFS and/or XFG have been consistently found in multiple studies to have lower corneal endothelial cell density than controls [59–68]. However, multiple groups have demonstrated that there is no significant difference between the endothelial cell density between patients with XFS alone compared to XFG [66].

Comparison of cell densities in all cell layers of the cornea have been found to be significantly lower in XFS eyes compared to age matched controls [63]. A Japanese study found a higher degree of pleomorphism and polymegathism in PEX eyes compared to control eyes, with the coefficient of variation of the cell area being significantly higher and the percentage of hexagonal cells was significantly lower in XFS [63]. Miyake et al. also demonstrated similar findings [69]; however, this was in contrast to another Japanese population [61] and in other regional studies in which there was no significant difference found in these coefficients of variation of cell size and frequency of hexagonality between XFS and control cataract patients: Paraguay population [65], Turkish population [67], and Chinese population [64]

3. Glaucoma Medications and Corneal Endothelium

Kwon et al. analysed the effect of topical medications used to treat glaucoma on the corneal endothelium in 134 donor corneas at the Lion's Eye Institute. No statistically significant reduction of ECD in patients on glaucoma medication was found. The mean ECD for donors not on glaucoma medication and pooled donors on glaucoma medication was 2561 ± 348 and 2516 ± 320 cells/mm^2, respectively ($p = 0.42$) [76]. Analysis of ECD in patients on the ocular hypertensive treatment study (OHTS) demonstrated there was no statistically significant difference between those who had been observed for six years ($n = 21$) compared to those treated with any topical medications ($n = 26$) -2415 ± 300 compared to 2331 ± 239 cells/mm^2, respectively ($p = 0.6$) [70]. There was no significant difference in the percentage of hexagonal cells between the two groups at six years either ($p = 1.0$). Other human studies have also not found a deleterious effect of topical glaucoma medications on ECD [77–79].

Gagnon et al. demonstrated that patients on three or four glaucoma medications had lower cell counts that patients receiving one or two medications [39]. This may be due to a correlation between disease severity and/or medication toxicity. Combined topical agents available for glaucoma treatment have also been analysed [73, 80, 81]. Two studies analysing the effects of latanoprost [80], brinzolamide/latanoprost [80, 81], and latanoprost/timolol [81] for shorter periods of two-three months also demonstrated no significant effect on corneal ECD.

Urban et al. analysed the difference in endothelial cell count in patients with juvenile open angle glaucoma treated with carbonic anhydrase inhibitor, prostaglandin analogue, beta blocker, and carbonic anhydrase inhibitor (CAI)/beta blocker combination. [73] They found no statistical difference in endothelial cell count between these four groups. Ayaki et al. exposed human cultured corneal endothelial cells to different glaucoma medications preserved and nonpreserved. They reported that cell viability in the presence of a commonly used preservative in eye drops (benzalkonium chloride) was markedly lower, especially with higher concentrations and longer exposure [82].

There has been concern over the use of carbonic anhydrase inhibitors and potential deleterious effects on the cornea. The corneal endothelium function relies on a bicarbonate pump to reduce corneal resurgence, for which carbonic anhydrase is a catalyst. However, central ECD cannot directly relate to endothelial function because of the significant functional reserve of this cell layer. No conclusive findings have been observed between carbonic anhydrase inhibitor use and corneal ECD loss [78, 79, 83].

Recently, there has been increasing interest in the use of Rho kinase inhibitors for glaucoma therapy due to the effects on the cytoskeleton of TM cells and Schlemm's canal cells which result in changes of cell morphology and permeability [84]. Netarsudil is the first Rho kinase inhibitor approved for glaucoma therapy in the US. Data from subjects who had 3 months of therapy with either netarsudil 0.02%/latanoprost 0.005% fixed combination ($n = 126$), netarsudil 0.02% ($n = 143$) only, or latanoprost 0.005% ($n = 146$) only compared to baseline found to have no significant difference or effect on ECD or morphology [85]. A significant decrease was observed in the central corneal thickness (CCT) in the fixed combination group (−6.4 μm) compared to the two individual component groups (latanoprost (−1.2 μm) or netarsudil (−3.3 μm)), which may indicate that the potential effects of each drug on CCT are additive, although the magnitude of the observed effects is likely of negligible clinical significance [85].

A summary of changes observed in studies evaluating the effect of topical medications on corneal endothelial density is shown in Table 2. In conclusion, the active ingredients in topical ocular medications have little effect on the corneal endothelium [12]; however, the preservatives used within the medication can potentially affect corneal endothelial physiology [82].

4. Corneal Endothelium and Glaucoma Surgery

Endothelial cell damage and reducing ECD have been observed in most anterior segment procedures, including various types of glaucoma surgery [89]. Firstly, all implants within the anterior chamber can result in progressive endothelial cell loss [90] including glaucoma drainage devices, although the mechanism is unknown. Secondly, endothelial damage can be caused by a shallow or flat anterior chamber which occurs frequently after trabeculectomy or other filtering glaucoma surgeries [91]. Thirdly, the microinvasive glaucoma surgeries (MIGS) may cause damage related to their close proximity to the endothelium.

5. Glaucoma Drainage Devices (GDDs)

Numerous studies have evaluated endothelial cell loss after the implantation of tube drainage devices; however, varying methodologies used to quantify ECD, combination surgeries, and differing postoperative management strategies make it difficult to directly compare these studies.

5.1. Ahmed Valve. Statistically significant endothelial cell loss occurs following Ahmed valve implantation [90, 92–97]. Central corneal endothelial cell loss is reported to be between 7.6% and 11.5% ($p < 0.05$) at six months [90, 93, 94, 97], between 10.5% and 15.3% ($p < 0.05$) at 12 months [90, 93, 94] and one study reports 15.4% ($p < 0.05$) at 24 months [94]. A five-year retrospective case series reported that the cumulative risk of corneal decompensation following Ahmed valve insertion is 3.3% [92]. The same study demonstrated accelerated corneal endothelial cell density loss in eyes that had an Ahmed valve compared to fellow glaucomatous eyes which were medically managed (decrease of 7.0%/year and 0.1%/year, respectively; $p < 0.001$) [92]. However, the rate of loss decreased over time and was no longer statistically significant after two years compared to the controls [92].

Although the exact mechanism causing corneal endothelial cell loss after tube surgery is unknown, it is likely to be multifactorial. For example, changes in the circulation patterns of aqueous humour due to the glaucoma tube have been shown to adversely affect the endothelial cell viability [98–102]. In addition, the glaucoma drainage device itself may induce a breach in the blood-aqueous barrier, either by intermittent tube-uveal touch and/or chronic trauma from intermittent tube-corneal touch caused by heavily rubbing the eye or forcefully blinking, resulting in an increase of influx of oxidative, apoptotic, and inflammatory proteins, potentially causing corneal endothelial damage [98, 101, 103, 104].

A two-year prospective study of 41 eyes evaluated corneal ECD in various locations of the cornea before and after Ahmed valve insertion [94]. After 24 months, the greatest loss was seen in the supratemporal area (22.6%), closest to the site of the tube, whereas the central cornea showed the smallest decrease (15.4%) [94]. A one-year study of 30 eyes reported similar results [90]. Another study of 33 eyes with superotemporally placed Ahmed valves used the difference between supratemporal and inferonasal ECD as an estimate of the change in total ECD [95]. Distance from the tip of the tube to the cornea was significantly associated with fewer endothelial cells superotemporally compared with inferotemporally. Each millimetre that the tube was closer to the endothelial surface was associated with 353.1 fewer endothelial cells superotemporally ($p = 0.02$) [95]. No significant change in the cell morphology has been reported, except one study that documents an increase in the polymegathism and pleomorphism of corneal endothelial cells in the early postoperative period, but these returned to baseline after six months [90, 94, 105]. In addition, a comparison of sulcus sited Ahmed valve compared to anterior chamber sited

Table 2: Effect of topical medication on corneal endothelial cell density (CECD).

	% mean cell CECD change at 1 year to baseline (SD)	Number of patients	Citation
Prostaglandin analogues			
Latanoprost	0.3 (2.2)	127	[86]
	−2.3	18	[87]
	−3.2 (6 months)	54	[88]
	−0.04 (3 months)	146	[85]
Carbonic anhydrase inhibitor			
Dorzolamide	No significant difference		[79]
	0.2	7	[78]
	−3.6 (5.0)	148	[83]
Beta blocker			
Timolol	−4.5 (4.2)	72	[83]
	0.1 (1.8)	126	[86]
Betoxalol	−4.2 (3.6)	78	[83]
Rho Kinase Inhibitor			
Netarsudil 0.02%	0.6 (3 months)	143	[85]
Combined therapy			
Latanoprost-timolol	0 (2.5)	126	[86]
Latanoprost-brinzolamide	−0.6	16	[87]
Netarsudil 0.02%/latanoprost	0.6 (3 months)	126	[85]

valves demonstrated that the mean monthly central endothelial cell loss was significantly higher in tubes sited in the anterior chamber [106, 107]. There was also a significant increase in endothelial cell size in anterior chamber tubes compared to those placed in the sulcus [107]. Furthermore, increasing age of the patient and tube location in the anterior chamber were significantly associated with faster endothelial cell loss [106]. These findings support the theory that tubes closer to the cornea potentially result in increased endothelial cell loss.

When compared to trabeculectomy, Ahmed valves have demonstrated significantly higher endothelial cell loss [93, 96]. In a prospective study of 40 eyes that had Ahmed valves inserted compared with 28 eyes that underwent trabeculectomy, mean central corneal endothelial cell density decreased by 9.4% at 6 months and 12.3% at 12 months compared with baseline values (both, $p < 0.001$) in the Ahmed valve group [93]. Whist the decrease was less marked in the trabeculectomy group, there was a 1.9% loss at 6 months and 3.2% loss at 12 months ($p = 0.027$ and $p = 0.015$, respectively) [93]. In the Ahmed valve group, there was a significant decrease in the corneal ECD between baseline to 6 months and between 6 and 12 months ($p < 0.001$ and $p = 0.005$, respectively). However, in the trabeculectomy group, a significant decrease was observed only between baseline to 6 months ($p = 0.027$) [93]. This study demonstrated that the corneal endothelial cell loss was not only greater in the Ahmed valve group but also persisted for longer. Another study involving 18 patients reported similar findings that corneal endothelial cell loss was statistically significant and higher in the Ahmed group compared to the trabeculectomy group ($p > 0.001$) [96].

5.2. Molteno Implant. A cohort study directly comparing Ahmed valves in 29 eyes with Molteno implants in 28 eyes demonstrated no significant difference in central corneal endothelial cell loss (11.52% and 12.37%, respectively) after 24 months [108]. They also noted minor increases in central corneal endothelial cell area for both implants. These findings suggest that the type of implant may not matter, rather the presence of a silicone tube in the anterior chamber.

5.3. Baerveldt Glaucoma Drainage Device. Two prospective studies have evaluated the effect of the Baerveldt (BV) glaucoma drainage device on the corneal endothelium [109, 110]. The first study found that after 36 months, central and peripheral corneal ECD had decreased by 4.54% per year and 6.75% per year, respectively ($p < 0.001$) [109]. Moreover, corneal endothelial cell loss was related to the distance from the tube, with patients with a shorter tube-corneal (TC) distance experiencing an annual loss of 6.20% in the central cornea and 7.25% in the quadrant closest to the BV compared to those with longer TC distances who had an annual loss of 4.11% in the central cornea and 5.77% in the quadrant closest to the BV ($p < 0.001$) [109].

A second recent study of 64 eyes found that the mean percentage central ECD and peripheral ECD loses at five years were 36.8% and 50.1%, respectively [110]. Tube insertion in the vicinity of, or anterior, to Schwalbe's line as well as a shorter tube length were significantly associated with endothelial cell loss over time [110]. This suggests significant corneal endothelial cell loss with Baerveldt glaucoma drainage devices, particularly in the quadrant closest to the valve.

6. Trabeculectomy

Surgical trauma produced by trabeculectomy and the adjuvant use of mitomycin C (MMC) reduces ECD. Indeed MMC has been found in the aqueous humour after trabeculectomy [111], the presence of which could inhibit periodic repair of DNA as human corneal endothelium is

primarily a nonreplicative tissue [112]. Additionally, short-term exposure of human corneal endothelial cells to MMC has shown the formation and interaction of free radicals that cause corneal swelling and disruption of intracellular endothelial organelles [113].

A number of studies showed that ECD loss after trabeculectomy with MMC was 1.9% to 18% [105, 114–121]. However, the results were derived from a relatively small number of cases with short postoperative follow-up periods (i.e., most were 12 months). A study with a longer follow-up of 24 months found the mean ECD decrease was 9.3%, but subgroup analysis demonstrated this was higher in XFG (18.2%) and uveitic glaucoma (20.6%) compared to 1.8% in POAG [122]. Two prospective randomised clinical studies on humans demonstrated endothelial cell damage at 3 and 12 months after MMC trabeculectomy [114, 115], but a subsequent study confirmed significant cell loss occurs during or immediately after MMC-augmented trabeculectomy [123]. Additionally, the active endothelial adaptations observed with no change in ECD between 3 and 12 months suggests that MMC has no prolonged toxic effect on the corneal endothelium. The grade of iridocorneal touch after an overdraining trabeculectomy is also correlated with an increased reduction in ECD [91].

Use of an anterior chamber maintainer or an injection of viscoelastic into the anterior chamber during trabeculectomy might provide more protection for the corneal endothelial cells [120, 124].

7. Deep Sclerectomy

There is presently only one published study evaluating the changes in ECD after deep sclerectomy (DS) and trabeculectomy [116]. The authors reported a significant reduction in cell loss between sclerectomy and trabeculectomy, 2.6% vs. 7% in central cornea, and 3.3% vs. 10.6% in upper cornea, respectively. They hypothesized the reason for this difference is because DS is less invasive than trabeculectomy as it does not penetrate the anterior chamber. When either DS or trabeculectomy was combined with cataract surgery, the difference was not statistically significant [116]. It is important to remark that this study compared DS with trabeculectomy without the use of antimetabolites.

8. Microinvasive Glaucoma Surgeries (MIGS)

In the last 10 years, microinvasive glaucoma surgeries (MIGS) have been increasingly used as an approach for treating glaucoma. MIGS can be divided into three main groups: Schlemm's canal MIGS, suprachoroidal MIGS, and subconjunctival MIGS.

8.1. Schlemm's Canal MIGS. The iStent (Glaukos Corp., San Clemente, CA, USA) has shown a moderate effect in controlling IOP [125, 126]. In a series of 10 Japanese eyes with OAG undergoing standalone implantation of 2 first-generation iStents, no change in ECD was observed through 6 months of follow-up [127]. An evolution of the iStent, the iStent Inject, has been developed to increase the efficacy of this device [128]. The iStent Inject's pivotal trial evaluated ECD and found a 13.1% reduction at 24 months postoperatively in the iStent-phaco group compared to a 12.3% reduction in eyes going phacoemulsification only [128]. The majority of the reduction in the ECD occurred within the first 3 months [128]. Similarly, a further study found a reduction of 9.0% ($n = 21$) at a mean follow-up of 18.2 months, as well as a significant reduction in the percentage of hexagonal cells [128].

In a prospective, uncontrolled case series of 20 eyes undergoing combined iStent-phaco, mean ECD decreased from 2290 to 1987 cells/mm^2 (13.2% decrease) at 12 months [129]. Evaluation of 12-month data after the implantation of 2 iStent Inject devices combined with phacoemulsification ($n = 54$) found a 14.6% reduction in the endothelial cell count from baseline (2417 ± 417 cells/mm^2 at baseline to 2065 ± 536 cells/mm^2 at 12 months, $p = 0.001$) which was comparable to patients undergoing phaco alone (-14.4%) [130].

Ivantis, Inc., (Irvine, CA, USA) developed a new device in 2014 called the Hydrus Microstent [131]. A retrospective nonrandomised clinical study comparing the endothelial changes after a Hydrus (Hydrus, Ivantis, Irvine, CA) MIGS implant combined with cataract surgery ($n = 37$) versus cataract surgery alone ($n = 25$) did not show any difference in endothelial parameters 6 months [132]. The HORIZON study found that the ECD reduced from 2417 ± 390 cells/mm^2 at baseline to 2056 ± 483 cells/mm^2 at 3 years in the combined phacoemulsification and Hydrus ($n = 369$) group compared to a reduction from 2426 ± 371 cells/mm^2 at baseline to 2167 ± 440 cells/mm^2 at 3 years in the phaco alone group ($n = 187$) [133]. This reduction was initially related to the surgical procedure and the addition of the Microstent induced an incremental nonsignificant loss in mean central cell count of 2% (approximately 75 cells/mm^2) [133]. This finding may be related to the additional surgical manipulation with insertion and removal of additional cohesive viscoelastic when placing the device. Sequential visit-to-visit changes in endothelial cell counts were consistent between the study groups and this was not statistically significant [133]. After the initial loss in cell count related to the surgery, no difference was found in the year-to-year change in the proportion of eyes with 30% endothelial cell loss between groups [133].

8.2. Suprachoroidal MIGS. Suprachoroidal MIGS target the uveoscleral pathway to reduce the IOP. Cypass (Alcon, Ft. Worth, TX, USA) [134], a suprachoroidal MIGS was unfortunately recalled in 2018 as the 5-year data demonstrated high rates of endothelial cell loss (3% per year in the Cypass group compared to 1% control phaco alone) that were deemed to compromise its safety [135]. At month 60, the mean percent of changes in ECD was −20.4% (95% CI, −23.5% to −17.5%) in the phaco and Cypass group ($n = 282$)

Table 3: A table to show the previous studies performed evaluating the clinical outcomes of DMEK after glaucoma surgery.

Paper	Number of patients	Previous glaucoma surgery	Length of follow-up	VA improvement	Rate of ECD loss postop	Primary graft failure	Rebubbling rates	Secondary graft failure	Postoperative IOP
Alshaker et al., 2021 [160]	$N = 48$ DMEK, $N = 41$ DSAEK	62.5% tube, 37.5% trab only, 61.0% tube, 39.0% trab only	30.0 ± 15.5 months, 33.9 ± 22.5 months	Postoperative BCVA was significantly better in DMEK group at 24 months ($p = 0.047$)	57%, 50% ($p = 0.886$) at 36 months	14.6%, 14.6% ($p = 1.0$)	25.0%, 19.5% ($P = 0.615$	20.8%, 19.5% ($p = 1.0$)	14.6%, 17.1% (IOP: 25–45 mmHg) ($P = 0.768$)
Fili et al., 2021 [161]	$N = 16$ DMEK, $N = 9$ DSAEK, $N = 15$ PK	68.8% trab, 43.8% tube, 100.0% trab, 22.2% tube, 80.0% trab, 40% tube,	24 months	Final BCVA at 24 months 0.34 ± 0.29 0.17 ± 0.18 0.06 ± 0.07	50.7%, 48.9%, 42.7% at 12 months ($P < 0.45$)	6.25%, 11.11%, 0	N/A	12.5%, 33.33%, 13.33%	6.25%, 11.11%, 0
Bonnet et al., 2020 [158]	$N = 11$ medically treated GL, $N = 38$ surgically treated Gl, $N = 41$ no GL	55.3% previous trab, 68.4% previous tube	38.4 ± 11.2 months	Achieved BCVA of ≥20/20, 46%, 8%, 49% **($p < 0.01$)**	47.6%, 63.8%, 44.0% **($p < 0.05$)**	0%, 0%, 0%	18.2%, 15.8%, 19.5% ($p = 0.93$)	0%, 41.6%, 2.4% **($p < 0.05$)**	54.5%, 26.3%, 34.1% (IOP >24 mm Hg or >8 increase) ($p = 0.21$)
Sorkin et al., 2020 [162]	$N = 51$ surgically treated Gl, $N = 43$ controls	49.0% previous tube, 13.7% trab and tube, 37.3% previous trab	37.9 ± 15.2 months, 33.8 ± 13.5 months	Mean BCVA improved from 1.82 ± 0.88 logMAR preop to 1.06 ± 0.87 at 6 months (no comparison to controls)	74%, 52% at 48 months **($P = 0.004$)**	15.7%, 11.6% $P = 0.766$	23.5%, 30.2% $P = 0.491$	47.1%, 0% **$P < 0.001$**	7.8% (control group not reported)

Table 3: Continued.

Paper	Number of patients	Previous glaucoma surgery	Length of follow-up	VA improvement	Rate of ECD loss postop	Primary graft failure	Rebubbling rates	Secondary graft failure	Postoperative IOP
Boutin et al., 2020 [163]	$N = 27$	44.4% prior tube, 33.3% prior trab, 14.8% trab and tube, 3.7% trab and gold Microshunt, 3.7% prior tube and hydrus	14.6 ± 6.1 months	Mean BCVA improved from 1.34 ± 0.65 logMAR preop to 0.50 ± 0.33 at 1 year	50.4% at one year **(P = 0.001)**	3.7%	18.5%	10.3%	3.7%
Lin et al., 2019 [164]	$N = 46$ DMEK $N = 46$ DSEK	48% prior trab, 78% prior tube, 50% prior trab, 74% prior tube	12 months	Improved by -0.89 logMAR, -0.62 logMAR **(p = 0.005)**	N/A N/A	2% 2% ($p = 0.65$)	22% 9% ($p = 0.14$)	0% 17% **(p = 0.006)**	30% IOP elevation, 36% IOP elevation (increase >8 mmHg) ($p = 0.66$)
Birbal et al., 2018 [153]	$N = 23$	65% trabeculectomy, 100% tubes (85% 1 tube, 15% 2 tubes)	19 ± 17 months	BCVA improved by ≥ 2 Snellen lines in 73%	71%	8.7%	21.7%	8.7%	9% (IOP >24 mmHg or >10 mmHg increase)
Aravena et al., 2017 [165]	$N = 14$ medically treated GL, $N = 34$ surgically treated Gl, $N = 60$ no GL	52.9% tube only, 14.7% trab and tube, 32.3% trab only	9.7 ± 7.3 months	Achieved BCVA of ≥20/25, 71.4%, 32.4%, 62.6% **P < 0.0001**	$29.9 \pm 12.0\%$, $44.6 \pm 17.8\%$, $32.7 \pm 11.3\%$, **P = 0.001**	0, 0, 1.7% $P = 1.0$	21.4%, 23.5%, 23.3%	0, 0, 0	50.0%, 14.7%, 23.3% **(p = 0.001)**

N: number; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet striping automated endothelial keratoplasty; BCVA: best corrected visual acuity; ECD: endothelial cell density; IOP: intraocular pressure; GL: glaucoma.

and −10.1% (95% CI, −13.9% to −6.3%) in the control group ($n = 67$) [135]. In addition, 9 adverse events were possibly related to ECD loss, including 3 eyes with transient focal corneal oedema and 4 eyes that required Cypass trimming due to protrusion. The prominent position of the device within the anterior chamber was deemed to be the reason for the changes observed and in some instances the Cypass stent has been explanted due to corneal decompensation [136].

8.3. Subconjunctival MIGS. Subconjunctival MIGS include the XEN subconjunctival implant gel stent (Aquesys, Aliso Viejo, CA, USA/Allergan, Irvine, CA, USA). One study evaluated standalone phacoemulsification ($n = 15$) and found a mean reduction of ECD by 14.5% at 24 months compared to a mean reduction of 14.3% at 24 months in the combined phaco/XEN surgery ($n = 17$). The difference in percentage reduction of ECD between the 2 groups was not significant ($p = 0.226$) [137]. A further study compared trabeculectomy ($n = 31$) to XEN gel stents ($n = 49$) and found a significantly higher rate of cell loss at 3 months in the trabeculectomy group (-10%) than the XEN gel stent group (-2.1%) when compared to baseline [138].

In recent years, the Preserflo (formerly InnFocus) (Santen Co., Japan), which creates a bleb by the insertion of an 8.5 mm polymeric in anterior chamber via a scleral pocket, has come to the market. Results showed no significant difference at 6 months between endothelial cell loss in 26 eyes with Preserflo (gain of 2.7%) compared to 26 after trabeculectomy (loss of 3.2%) [139]. Both procedures significantly changed the coefficient of variation but had no significant changes on percentage of hexagonal cells. The endothelial cell count was evaluated at one year as part of a 2 year prospective randomised multicentre study of the Microshunt ($n = 395$) versus trabeculectomy ($n = 132$) [140]. Endothelial cell loss was similar in both groups at year 1 (05.2% after Microshunt implantation and -6.9% after trabeculectomy). One patient in the Microshunt group experienced endothelial cell loss of 9.4% between 6 months and 1 year, which was presumed to be due to the proximity of the device to the cornea [140].

The Ex-Press mini glaucoma shunt (Alcon Laboratories, Fort Worth, TX) is a further subconjunctival Microshunt. Studies have compared the Ex-Press shunt with trabeculectomy and Ahmed valves [105, 119]. In a 3-month prospective study, no significant reduction in corneal ECD occurred in the Ex-Press group (1.3%, $p > 0.05$) [105]. Unlike the trabeculectomy group which had a significant decrease of 3.5% at 1 month ($p = 0.012$) and 4.2% at 3 months ($p = 0.007$), and the Ahmed valve group, where a significant decrease of 3.5% was seen after 3 months ($p = 0.04$) [105], a further group found reduction of endothelial cell count after Ex-Press implantation by 3.5%, but no significant difference between trabeculectomy and the Ex-Press shunt [119]. Other groups, however, have demonstrated cases of corneal decompensation after the Ex-Press stent and significant reductions of endothelial cell count (4% at 24 months from baseline), which may have been due to intermittent endothelial contact [141, 142]. In addition, the endothelial cell loss has been observed to be significantly higher in the superior cornea, which is close to the shunt site (-17.6%) compared to the inferior cornea (-11.7%) [143].

Alternative MIGS interventions include Ab interno-trabeculotomy with the Trabectome device (NeoMedix, Tustin, CA, USA) which has been shown to have minimal effects on corneal endothelial cells at 6 months and up to 36 months postoperatively [144, 145]. A goniotomy with the Kahook Dual Blade (KDB, New World Medical, Rancho Cucamonga, CA) has been shown to reduce the endothelial cell density by only 3.4% at a mean follow-up of 18.2 months after procedure ($n = 21$) with no significant effect on other morphological parameters [146]. Furthermore, the Excimer Laser Trabeculotomy (ELT, Glautec AG, Nurnberg, Germany) [147], the Fugo Blade (MediSurg Research and Management Corp., Norristown, PA, USA) [98, 148], the Ab interno-canaloplasty (ABIC) [99, 100], and the gonioscopy-assisted transluminal trabeculotomy (GATT) [101] could potentially have an impact on the endothelial cell count. No studies are presently available in the literature in regard to these.

9. Descemet Membrane Endothelial Keratoplasty (DMEK) Use in the Management of Glaucoma-Related Endothelial Cell Loss

Corneal endothelial cell loss can subsequently result in corneal decompensation, and this continues to be a common comorbidity after glaucoma surgery [102]. The introduction of Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) has replaced the use of penetrating keratoplasty (PK) as the standard of care for endothelial disorders [103]. In the presence of glaucoma drainage devices, higher rates of corneal graft failure and increased ECD loss are observed after penetrating keratoplasty and DSAEK; as suggested earlier, the reasons for this are multifactorial [104, 149–153].

DMEK surgery is increasingly used as a method of treating corneal endothelial dysfunction and shows reduced rejection rates and faster visual recovery when compared to DSAEK [154–156]. A key benefit is that the rapid visual recovery and reduction in corneal oedema allows for early visual field testing or optic nerve examination to decide on further glaucoma management [157]. Another advantage of DMEK is that the taper of topical corticosteroids postoperatively is quicker than that after PK and DSEK. The quicker taper potentially lowers the risk of IOP elevation, resulting from the steroid response [158]. The steroid IOP response rates after DMEK and DSAEK have been shown to be 15% and 17%, respectively ($p = 0.768$) [159, 160]. These are not any higher than expected for any patient on long-term steroidal treatment [159, 160].

Performing a DMEK surgical procedure is, however, more challenging in eyes with previous glaucoma surgery. For example, the presence of corneal oedema, a tube shunt, anterior synechiae, previous trabeculectomy, or an abnormal

anterior segment can make the surgery more difficult [157]. Studies have been performed to evaluate the outcomes and complications of DMEK surgery after glaucoma surgery, as summarized in Table 3.

10. Conclusions

In summary, we have outlined the endothelial cell changes which occur due to glaucoma itself, as well as those which occur as a result of its medical and surgical management, including new generation MIGS devices. We have explored the use of DMEK for the management of corneal endothelial failure and the recent literature illustrating the results including complications after performing DMEK for postglaucoma endothelial loss. Additional studies are required to investigate the cause of the accelerated endothelial cell loss in glaucoma patients undergoing DMEK surgery and assessment of glaucoma progression related to DMEK surgery.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Corneal Subbasal Plexus in Eyes with Fuchs' Endothelial Corneal Dystrophy after Two Different Endothelial Surgeries

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Purpose. To evaluate the morphological features and density of corneal subbasal plexus (SBP) using in vivo corneal confocal microscopy (IVCCM) in patients affected by Fuchs' endothelial corneal dystrophy (FECD) six months after Descemet membrane endothelial keratoplasty (DMEK) and Descemet-stripping automated endothelial keratoplasty (DSAEK). *Methods*. We included patients affected by FECD, requiring corneal endothelial surgery due to corneal oedema occurred from 3 to 6 months. 7 eyes underwent DMEK and 7 eyes DSAEK. All patients performed IVCCM preoperative and in six months postoperative. We analyzed SBP parameters, using CS4 Nerves Tracking Tool, and we studied the differences between the two endothelial keratoplasties. *Results*. Comparing the eyes treated with DMEK with those treated with DSAEK, preoperative corneal thickness, corrected distance visual acuity (CDVA), and age were similar in both groups. SBP was not detectable at preoperative IVCCM in any eye. Postoperatively, the nerve fibers length, the nerve fibers density, the tortuosity, and the number of fibers and of branching did not differ in the eyes that underwent DMEK compared to DSAEK. The corneal beadings density was higher after DMEK than DSAEK, and this difference was statistically significant ($P = 0.004$). The type of endothelial keratoplasty was not associated with the presence or absence of postoperative corneal SBP (Pearson' chi-square, 0.755). *Conclusions*. Postoperative corneal reinnervation should be easily and noninvasively studied using IVCCM. Morphological postoperative features of SBP did not differ between two different types of endothelial keratoplasty, DMEK and DSAEK, despite the different sizes of the corneal incision. The lower beading density in the DSAEK group should be the consequence of a different distribution of mitochondria along the nerve fibers, as expression of a supposed higher metabolic distress in the DSAEK group.

1. Background

Fuchs' endothelial corneal dystrophy (FECD) is a bilateral posterior corneal disease characterized by the loss of corneal endothelial cells and the development of posterior focal guttae, which are caused by Descemet membrane (DM) outgrowth [1]. Disruption of corneal endothelial pump-leak function can lead to corneal oedema and reduce visual acuity [2]. The FECD represents one of the most common indications for corneal transplantation worldwide [3, 4], and over the last two decades, significant surgical developments have been made for endothelial diseases. In particular, the full-thickness penetrating keratoplasty (PK) has been replaced by the posterior lamellar transplantation techniques: Descemet-stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) [5, 6]. In the first technique, DSAEK, healthy donor endothelium with DM, and a variable thickness of posterior stroma is used to replace the diseased host endothelium [7]. Unlike the DSAEK, DMEK consists of the selective transplant of DM and endothelium [8–10].

The posterior lamellar techniques have several advantages compared with PK as lower incidence of intraoperative and postoperative complications, including rejection rates.

Furthermore, regarding corneal innervation, endothelial keratoplasty is expected to have the ability to preserve fibers, while PK chopped off nerves both of the donor and of the host cornea [11–13].

The posterior lamellar surgeries also differ from each other in corneal incision size (4.1 mm and 2.8–3.0 in the DSAEK and DMEK, respectively) [7, 9], and this factor should influence the preservation and postoperative recovery of corneal nerves.

A rapid, noninvasive, high-resolution, and real-time imaging technique that can provide images of corneal fiber nerves is represented by in vivo corneal confocal microscopy (IVCCM) [14]. This examination allows, in particular, the analysis of the subbasal nerve plexus (SBP), placed between Bowman's layer and the basal epithelium in a radial distribution [15, 16]. Thus, IVCCM has demonstrated to be an important tool for studying the SBP after different corneal surgeries, as PK [12], laser assisted in situ keratomileusis (LASIK) [17], and DMEK [11].

Currently, in literature, there is any study comparing the SBP features between these two endothelial keratoplasties, DMEK and DSAEK. Consequently, we would investigate whether the choice of the surgical lamellar technique could also influence the corneal innervation in the follow-up of the surgery.

Therefore, the aim of our study is to evaluate the morphological features and density of SBP using IVCCM in patients affected by FECD at six months after DMEK and DSAEK.

2. Methods

2.1. Study Population. We enrolled patients affected by FECD requiring corneal endothelial surgery due to corneal oedema, who referred to the Anterior Segment Unit of IRCCS Fondazione Bietti, Rome, Italy, from November 2017 to May 2019. Patients with previous uneventful cataract surgery, performed more than 6 months before corneal surgery, were enrolled. We included the eyes with corneal oedema occurred for at least 3 and more than 6 months prior to keratoplasty. The onset of corneal oedema was evaluated by slit lamp microscopy at each preoperative visit. One eye for each patient was considered.

Exclusion criteria were as follows.

(1) Presence of any corneal disease, as herpetic keratitis or stromal scar, and/or the history of previous refractive, glaucoma, or retinal surgery

(2) Diagnosis of ocular disease which could influence visual outcome, as maculopathy, optic neuropathy, or amblyopia

(3) History of diseases inducing a peripheral neuropathy (diabetes mellitus, inflammatory diseases, alcohol abuse, vitamin deficiency, malignancy treated with chemotherapy agents, chronic liver or renal failure, central nervous system diseases, entrapment mononeuropathies, and cervical or lumbosacral radiculopathies)

(4) Intra or postoperative complications of corneal endothelial surgery

All patients underwent a complete ophthalmologic examination, such as corrected distance visual acuity (CDVA) (LogMar), slit-lamp biomicroscopy, intraocular pressure measurement using the Goldmann applanation tonometer, and fundus examination using the indirect ophthalmoscope before and 6 months after surgery. Endothelial cell count (ECD), corneal pachymetry, and SBP features were collected using IVCCM (ConfoScan 4; Nidek Technologies) before and after 6 months from surgeries.

All research procedures described in this work adhered to the tenets of the Declaration of Helsinki and were performed for clinical purposes using routine techniques. All recruited subjects gave written informed consent. The informed consent forms include consent for the use of anonymized instrumental results for scientific publications.

2.2. Surgical Procedures. Skilled surgeons (DSL and AP) performed the endothelial keratoplasty of the included patients as previously described [5, 7]. Specifically, the donor tissue was inserted through a corneal incision of 4.1 mm and 2.8–3.0 in the DSAEK and DMEK, respectively. The size of descemetorhexis was approximately 8.5–9.5 mm in both techniques [18].

The postoperative treatment was an association of topical antibiotics and prednisolone acetate 1%, administered 4 times a day, tapering to once daily by 2–6 months after surgery in all cases.

Intracameral air bubble or gas (20% sulfur hexafluoride, SF_6) was used to facilitate tamponade of the graft to the host cornea. If it was necessary, the day after the operation anterior chamber was refilled by air/gas.

2.3. In Vivo Corneal Confocal Microscopy (IVCCM). IVCCM (ConfoScan 4; Nidek Technologies, Gamagori, Japan) of the central cornea was performed in all patients with a z-ring adapter. All examinations were carried out by the same experienced operator (DSL). We applied to the tip of the lens a transparent and sterile gel (dexpanthenol 5%) to eliminate optical interfaces with different refractive indices, to keep constant the refractive index, and to allow a no-contact examination. After autoalignment, a full-thickness scan of the cornea was performed with 72% light intensity and a 6 μm scan step, as previously described [19].

Corneal thickness was obtained measuring the distance between the endothelium and the last clear and the centred frame of epithelial image and ECD, using automated cells analysis of the central or paracentral area of the best image selected for the analysis [20].

2.4. Corneal Subbasal Nerve Plexus Analysis. Two experienced researchers (MG and IA) carefully examined only the images between the basal epithelial layer and Bowman's layer. They were masked to group assignment and cannot relate each image to the performed surgery. They selected the best focused frame of the SBP for each patient

without motion folds and without more than one layer capture. The frames were analyzed using CS4 Nerves Tracking Tool CS4 software v1.3.0, each area was reviewed and any error was manually edited, after automated identification of fibers. Each operator (MG and IA) worked separately. In case of mismatch, a third operator (DG) chose the best option.

The corneal SBP parameters analyzed [21] were as follows.

(1) Nerve fibers length (μm/frame): the total length of all fibers and branches in a frame

(2) Nerve fibers length density (μm/mm^2): the total density of the nerve fibers in mm^2

(3) Number of fibers: the total number of nerve fibers, including main nerves and branches

(4) Number of branching: points where nerve branches arise from the main nerve

(5) Nerve fiber tortuosity using Nidek Nerve index, a unitless measure which represents the degree of twistedness of a curved structure

(6) Beadings: well-defined hyperreflective points along the corneal fiber, which are an agglomerate of mitochondria and glycogen. They consequently represent an expression of oxidative damage, and the study of their characteristics should help to evaluate the metabolic stress of corneal fiber [22]. We explored beadings features through two indices.

(a) Number of beadings: the total number of beadings identified in the main nerves (trunks, long fibers that crossed the borders of the area of analysis)

(b) Beadings density (beadings/mm): the total number of nerve beadings divided by the total length of nerve trunks in millimetres

We excluded patients showing no evidence of SBP in postoperative IVCCM.

2.5. Statistical Analysis. All the analyses were performed using Statistical Package for Social Sciences (SPSS), IBM Corp., Statistics, version 25.0. All results were expressed as the mean ± standard deviations. The normal data distribution was tested by using the one-sample Kolmogorov–Smirnov test. The independent sample *t*-test or the Mann–Whitney test was applied, as appropriate, to compare subbasal plexus parameters changes between DMEK and DSAEK groups. To study the relationship between corneal nerves parameters, the Spearman correlation coefficient was computed. In all analyses, $P < 0.05$ was considered to be statistically significant.

3. Results

Thirty-two eyes of 32 patients, affected by FECD and scheduled for an endothelial keratoplasty, performed IVCCM. Due to the persistence of corneal oedema and the presence of subepithelial haze, SBP was not detectable in a subgroup of patients (10 eyes of the DMEK group and 8 eyes of the DSAEK group), so we decided to exclude them.

Therefore, our study population included 14 eyes; 7 eyes (50% of 14 eyes) underwent DMEK, while the remaining 50% underwent DSAEK. Any patient underwent a postoperative anterior chamber rebubbling. The age was similar between the two groups ($P = 0.55$). Females were 85.71% and 71.43% in the DSAEK and DMEK groups, respectively.

No differences were found in preoperative corneal thickness between groups, 650.75 ± 81.21 and 662.5 ± 64.77 micron, respectively, in case of DMEK and DSAEK. Due to the presence of confluent guttae and diffuse oedema with subepithelial haze, preoperative ECD and preoperative SBP were both not detectable at IVCCM in any eye. Preoperative CDVA was 0.63 ± 0.24 and 0.64 ± 0.25 in case of DMEK and DSAEK, respectively ($P = 0.970$).

We analyzed the characteristics of SBP at IVCCM, using CS4 Nerves Tracking Tool, and we compared the DMEK and DSAEK groups at 6 months after surgery.

None of the postoperative ocular characteristics analyzed differs significantly between DMEK and DSAEK, as given in Table 1. Comparing the SBP parameters, only the corneal beadings density was higher after DMEK than DSAEK, and this difference was statistically significant (Table 2).

We found that, after DMEK, corneal nerve tortuosity of SBP showed a high direct correlation with postoperative thickness ($r = 0.865$; $P = 0.012$), and the same correlation was present between the number of branching and the age of patients ($r = 0.817$; $P = 0.025$).

In the DSAEK group, instead, no correlation was found between corneal nerve parameters and postoperative corneal thickness. Nevertheless, an inverse and high correlation was found between age and two corneal nerve parameters and specifically, the number of fibers ($r = -0.837$; $P = 0.019$) and the number of corneal beadings ($r = -0.793$; $P = 0.033$).

The type of endothelial keratoplasty was not associated to the presence or absence of postoperative corneal SBP (Pearson' chi-square, 0.755).

4. Discussion

This is the first study comparing postoperative corneal innervations in patients affected by FECD who underwent two different techniques of endothelial keratoplasty, DMEK and DSAEK.

Morphological alterations of SBP were already described in FECD. In particular, nerves density, length, and bifurcations should be lower than healthy corneas, even at early stages of disease [23, 24]. As the FECD got worse, the SBP nerves decreased, up to being completely absent in the severe stages [2].

FECD is one of the main corneal disease requiring a posterior keratoplasty, DSAEK and DMEK.

Preoperative and postoperative innervation in the eyes affected by FECD and treated with DMEK was speculated by Bucher et al., reporting a consistent reduction of number and length fibers in the early postoperative. Nevertheless, up to 4 months post-DMEK, a complete recovery of subbasal plexus was shown [11]. Similarly, after Descemet-stripping

Table 1: Postoperative characteristics of study population.

	DMEK ($n = 7$) (mean ± SD)	DSAEK ($n = 7$) (mean ± SD)	P value
Age (years)	66.29 ± 6.1	68.86 ± 9.41	0.55
Postoperative ECD (cell/mm^2)	1571.86 ± 355.44	1716.57 ± 583.71	0.142
Postoperative corneal thickness (μm)	523.71 ± 48.28	583.71 ± 122.65	0.252
Postoperative CDVA (LogMAR)	0.03 ± 0.04	0.05 ± 0.04	0.304

Table 2: Summary of corneal nerves morphological parameters of study population.

Corneal nerves parameters	DMEK ($n = 7$)	DSAEK ($n = 7$)	P value
Nerve fibers length (μm/frame)	487.93 ± 304.16	630.88 ± 408.34	0.472
Nerve fibers length density (μm/mm^2)	5490.51 ± 3422.59	7098.98 ± 4584.93	0.472
Number of fibers (n°)	3.14 ± 1.95	4 ± 2.58	0.497
Number of branching (n°)	0.71 ± 0.76	0.71 ± 1.5	0.43
Number of beadings (n°)	31.43 ± 20.58	30.57 ± 22.44	0.942
Beadings density (beadings/mm)	71.09 ± 8.93	49.62 ± 12.97	0.004*
Nerve fiber tortuosity (n°)	5.12 ± 2.03	4.88 ± 2.87	0.857

*Statistically significant ($P < 0.05$)

endothelial keratoplasty (DSEK), Ahuja et al. described regeneration of the subbasal nerve through 36 months, but with an irregular branching compared to healthy [23].

A small corneal incision at the limbus was necessary in both surgeries, DMEK and DSAEK, as cataract surgery. In literature, SBP alterations, even in uneventful cataract surgery, were already reported [25]. Authors suggested that, in endothelial keratoplasty, at first, the surgical trauma, and in particular, limbar incision and descemetorhexis, induced some fiber transection and a transient reduction of them. Subsequently, due to the release of neurotrophic factors by the graft cells, the nerve fibers could regenerate [9, 23].

Since the size of the corneal incision during DMEK was smaller than during DSAEK (2.8–3.0 versus 4.0 mm), we decided to investigate the postoperative characteristics of SBP after these two different posterior surgeries and to compare them.

We performed preoperative IVCCM and we did not identify any corneal subbasal fiber because of subepithelial haze associated to corneal oedema. However, as our purpose was to compare the postoperative SBP after the two different keratoplasty, we included corneas with similar preoperative characteristics (corneal thickness, age, and CDVA), but sufficiently transparent at 6 months after keratoplasty, and with low subepithelial haze to assess the characteristics of subbasal plexus.

We found that the corneal nerve fibers length, the nerve fibers density, the tortuosity, and the number of fibers and branching did not differ in patients who underwent DMEK compared to DSAEK.

The total nerve length and the number of branching recovery reported by Bucher [11] were higher than our postoperative data in the DMEK group. Unlike Bucher's group, our sample included the eyes without an evident preoperative SBP, due to subepithelial haze and diffuse oedema. We assumed that our corneas belonged to a more severe stage than those described by Bucher and that consequently, our postoperative recovery should require more time.

The most consistent reason for the corneal fiber injury after posterior surgery was, in our opinion, the surgical trauma and specifically, the corneal incision and descemetorhexis. Our results showed that the different sizes of corneal incision between DMEK and DSAEK seemed to not affect the main parameters of the corneal subbasal plexus. We also concluded that the type of endothelial surgery did not influence the presence of subbasal corneal plexus at 6 months postoperative (Pearson' chi-square, 0.755).

Our study group included patients with an average age of over sixty (66.26 ± 6.1 and 68.86 ± 9.41 years in the DMEK and DSAEK groups, respectively). Previously in literature, the lowering of corneal nerve density had been described in association with ageing [26, 27]. Our analysis was not affected by this age-related variability because in the two groups, patients treated with DMEK and those with DSAEK did not show a statistically significant difference. Age was highly related to some postoperative SBP features. In particular, branching was directly correlated to age in the DMEK group, and a negative correlation with the number of fibers was shown in the DSAEK group. Data in literature about relationship between age and corneal nerves parameters alterations were discordant, probably due to different methods applied, and it was beyond the scope of our study.

We examined the metabolic activity of corneal fibers through the analysis of beadings, which are an agglomerate of mitochondria and glycogen along the nerves [28].

We found that the number of corneal beadings was similar between the DMEK and DSAEK groups ($P = 0.942$), but the beading density was lower in the DSAEK group ($P = 0.004$). We described, for the first time, data regarding the corneal beadings after posterior lamellar corneal surgery. We supposed that these alterations should be the consequence of a different distribution of mitochondria along the nerve fibers, as expression of a supposed higher metabolic distress in the DSAEK group. The number of beadings per frame was similar between the two groups, but not the density of beadings along the total length of the trunk, probably due to

the lower average length of the fibers after DMEK than after DSAEK, although not having a statistically significant difference. A preoperative analysis of beadings in patients affected by FECD should be useful to give clinical significance to our result. However, an interesting result of our study was that the beadings density at 6 months after DMEK was similar to the previously described, by our group, in healthy patients (71.09 ± 8.93 in our DMEK group versus 71.37 ± 10.30 in healthy corneas), showing indirectly a good metabolic balance of subbasal plexus at six months after surgery [21]. We concluded that the damage on the corneal fibers was similar between the two surgeries, but that the postoperative metabolic stress was greater in DSAEK than in DMEK. However, the main limitation of our study was the small number of corneas included. It was the first time that corneal beadings were analyzed after posterior keratoplasty, and these results will need to be studied on a larger population.

5. Conclusions

Corneal subbasal plexus did not show morphological postoperative differences between two different types of endothelial keratoplasty, DMEK and DSAEK. In the DSAEK group, we found a lower beading density, which should be the expression of a supposed higher metabolic distress in this group. IVCCM is a useful and noninvasive tool for the speculation of postoperative reinnervation.

Data Availability

The datasets used and analyzed to support the findings of this study are available in Supplementary Materials.

Consent

All recruited subjects gave written informed consent. The informed consent forms include consent for the use of anonymized instrumental results for scientific publications.

Disclosure

The funders had no role in study design, data collection, and analysis decision to publish or preparation of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplementary files include the data used and analyzed to support the findings of this study (Dataset.pdf). (*Supplementary Materials*)

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Review Article

Tips, Tricks, and Guides in Descemet Membrane Endothelial Keratoplasty Learning Curve

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Lamellar keratoplasty is fast becoming the most popular form of corneal transplantation. The adoption of Descemet membrane endothelial keratoplasty (DMEK) in the management of Fuchs endothelial dystrophy and pseudophakic bullous keratopathy is partly responsible for this shift in the paradigm of management of corneal pathology. The learning curve of DMEK, however, has been proven to be much steeper than previous endothelial keratoplasty procedures. To ease the procedure, experts have proposed multiple innovative techniques from tissue preparation to graft unfolding to aid the more novice surgeon. Here, we collate and share tips and tricks from our collective experiences to support the learning curve and outcomes in DMEK for both the novice and more experienced corneal transplant surgeons.

1. Introduction

The most common causes of endothelial failure are Fuchs endothelial dystrophy (FED) and pseudophakic bullous keratopathy (PBK) following intraocular surgery [1]. These remain a common indication for corneal transplantation, and in spite of developments in cataract surgery, we continue to see patients with these conditions warranting corneal transplantation in our clinics [2–4]. In modern times, endothelial keratoplasty (EK) has become the gold standard of care in the management of endothelial dysfunction in otherwise healthy eyes, replacing penetrating keratoplasty (PK) in the management of FED and PBK. EK delivers more predictable refractive outcomes and stronger structural integrity than PK without the protracted need for postoperative suture management [5–7]. Since its introduction by Melles et al. in 2006, Descemet membrane endothelial keratoplasty (DMEK) has increasingly gained in popularity with demonstratable benefits over other forms of EK [8]. DMEK involves only the transplantation of the

Descemet membrane (DM) and endothelium in contrast to Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) where the donor graft includes a variable portion of stroma [9–11]. This may confer the major benefit of DMEK which is a significantly lower risk of immunologic rejection compared to DSAEK [12, 13]. In the United Kingdom, data demonstrates the rising popularity of DMEK, which now represents 38.1% of EK compared to only 18.7% in 2015. Despite this, the difficulty in adopting this new technique means that DMEK remains less popular than DSAEK across the globe. The challenges posed by DMEK to the corneal transplant surgeon include a new method of graft preparation, delivery, unfolding, and increased incidence of postoperative graft detachment [14, 15]. Here we share tips, tricks, and our experience with the aim of making DMEK surgery simpler and safer.

2. Graft Preparation

The first step towards successful DMEK surgery is to master the donor tissue preparation technique [16]. Although many different techniques have been proposed for DMEK graft preparation, there is no consensus as to which is the optimum [17]. The most commonly used techniques include pneumatic dissection [18], stripping methods, and many more [19, 20]. The stripping methods have been the most widely adopted and we suggest starting learning DMEK with these techniques. We currently use 2 standard DMEK graft stripping preparation techniques, depending on our setting. In an eye bank setting, we use a double trephine technique. It involves the use of 2 punches, a mark on the graft, and multiple checks of endothelial cells during the procedure. A DMEK graft prepared in an eye bank setting reduces the surgeon's stress level due to possible failure in tissue preparation before surgery [21]. The second method is used in a theatre setting before the operation. It is quicker and it involves the use of a single trephine. For beginners, we suggest starting using DMEK tissue prepared in an eye bank setting and planning the first surgeries with the use of prestripped tissues [22].

2.1. In the Eye Bank: The Double Trephine Technique. The corneal tissue is washed with sterile phosphate-buffered saline (PBS) to remove traces of storage media [23]. The cornea is then checked for endothelial cell mortality using trypan blue stain (0.025%) and endothelial cell density (ECD) is recorded using a calibrated graticule in the eyepiece of an inverted microscope. Average readings of 5 counts are usually obtained to avoid counting errors. If the tissue shows <5% trypan blue positive cells and >2200 cells/mm^2, then it can be used for transplantation. The tissue is fixed on a vacuum block with the endothelium facing up (Figure 1(a)).

Using a corneal punch blade (9.5 mm), the endothelium is superficially trephined by gentle tapping on the top of the endothelium. Strong tapping or full thickness punches can end with the endothelium margins incarcerated in the corneal stroma increasing the preparation time. The cut margins are visualized using trypan blue stain (Figure 1(b)). The margin distinguishes the border between the central endothelium and the peripheral endothelium. Using sharp acute forceps, the peripheral endothelium is removed, leaving only the central endothelium (Figure 1(c)). To reduce radial tears and peripheral cuts of the tissue, we suggest using a cleavage hook to identify the cleavage plane and separate the periphery of the central endothelium from the stroma (Figure 1(d)).

The separated periphery is then grasped using the sharp acute forceps at the superior end and is peeled towards the inferior end (Figure 1(e)). The entire process may take a few to several minutes depending on the adherence of Descemet membrane (DM) to the underlying stroma. The tissue is peeled leaving approximately 10% of the inferior peripheral hinge. The hinge protects the DMEK tissue from free floating or forming a roll in the media. It is also helpful to allow stamping of the DMEK tissue on the DM side to avoid the tissue being transplanted upside down. Marking the tissue is not mandatory but it will ease DMEK unfolding. A biopsy punch is used to create a small stromal punch (Figure 1(f)) and the peeled DMEK tissue is replaced back on the stroma (Figure 1(g)). The vacuum is released, and the tissue is inverted on the vacuum block with the corneal epithelial side facing up. The punched stromal piece is then removed from the epithelial side. This allows gentian violet dye on the tip of a cleavage hook to be used to mark the letter "F" (with correct orientation) on the DM (Figure 1(h)). The stromal piece is returned and the tissue is inverted back and fixed on the vacuum holder. Although we have used letter "F," other letters like "S" [24] can also be used. Once the tissue is ready, the endothelium is restained using trypan blue (Figure 1(i)) for final quality assurance of the graft in terms of ECD and mortality. The surgeon can then choose the diameter required for the patient and use a second trephine for excision of the graft before the transplant. We have observed minimal mortality and a high success rate using this technique [21]. Slight modifications such as oscillating movements, different points of initiation, and use of peripheral DMEK grafts have allowed us to manage challenging cases with tight adherence, cut/horse-shoe-shaped tears, and postcataract surgery tissues [23].

2.2. In the Operating Theatre: The Single Trephine Technique. This technique involves the use of only 1 trephine [23]. The cornea is centered on a punch base using suction. The vacuum is created with a syringe and the tissue is secured on the base. We start by staining the endothelium with trypan blue 0.06% (Vision Blue®; DORC, Zuidland, Netherlands) for 15–20 seconds. Thereafter, we identify an area in the periphery of the trabecular meshwork (TM) without damage, residual uveal tissue, or previous corneal incisions to start peeling the DM (Figure 2(a); marked in red).

DM is peeled from TM (Figure 2(b)) by gently swiping the DM layer from its periphery towards the center (Figure 2(c)) using a pediatric crescent knife of 2.3 mm, angled bevel up (Alcon Laboratories, Inc., Fort Worth, Texas). During this step, it is important to be careful not to apply too much pressure. If the crescent blade is too deep in

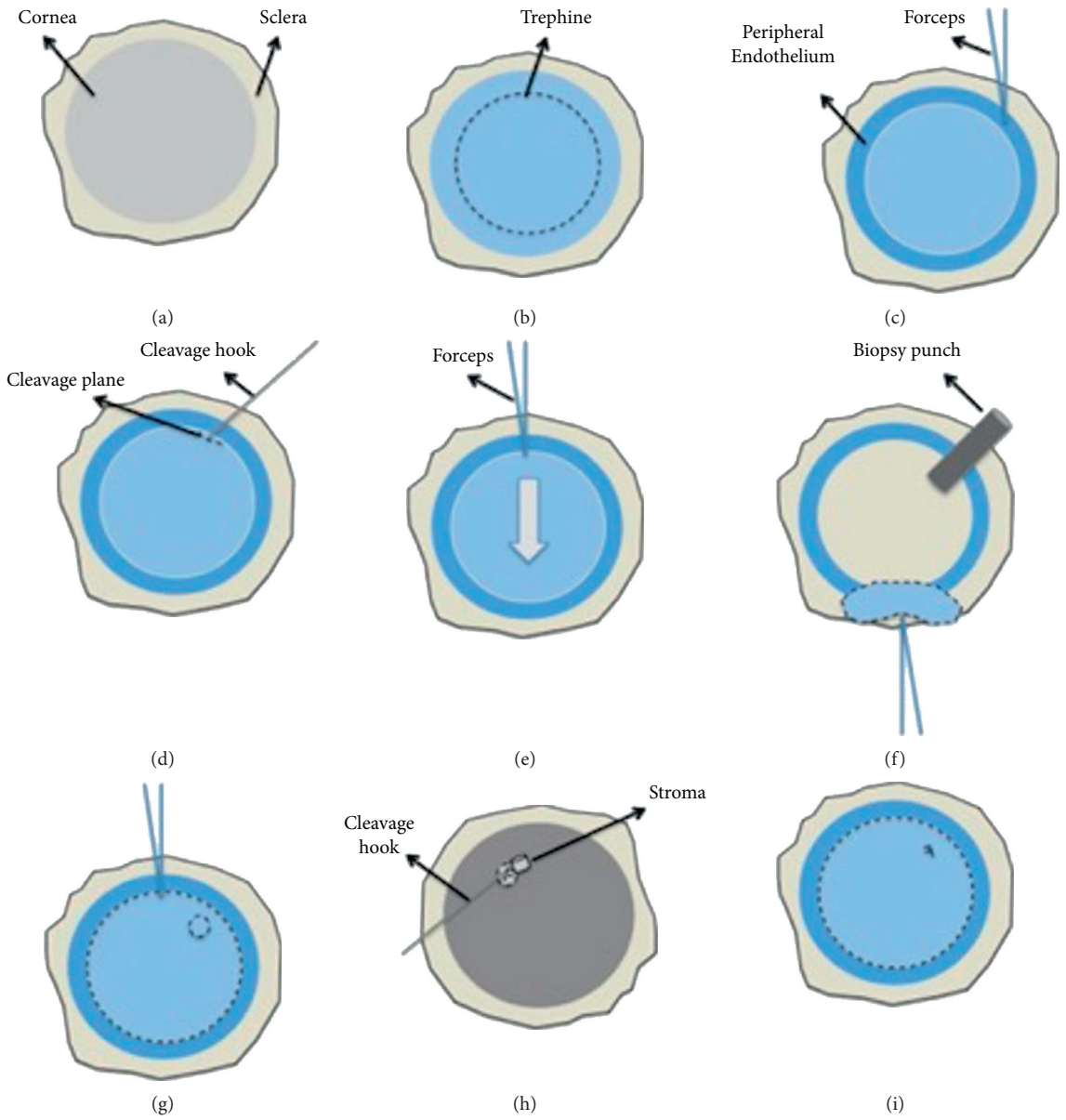


Figure 1: The double trephine technique: (a) healthy corneal tissue; (b) cut margins; (c) peripheral endothelium is removed; (d) separate the periphery of the central endothelium from the stroma; (e) the separated periphery is then grasped using the sharp acute forceps at the superior end and is peeled towards the inferior end; (f) a biopsy punch is used to create a small stromal punch; (g) the peeled DMEK tissue is replaced back on the stroma; (h) the tissue is marked; (i) endothelium is restained using trypan blue.

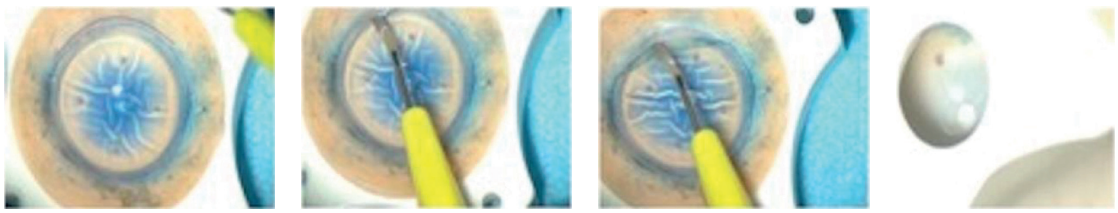


Figure 2: (a) Area selection; (b) beginning of peeling; (c) 100-degree 3 mm endothelium peeling; (d) tissue visualization.

the stroma, it will compromise the stripping by cutting into the stroma. The blade should be used perpendicularly to the cornea and an area of 100 degrees should be peeled for 3 mm towards the center of the cornea (Figure 2(c)). If this crucial step fails, it can be redone in another sector of the cornea leaving in place the managed endothelium.

The successfully peeled endothelium is then replaced back on the corneal stroma. The diameter of the punch is selected as required for the patient. The punch is placed on the graft and, before punching, the stripped and stained endothelium should be visible through the center of the punch (Figure 2(d)). If the trypan blue staining is not visible, the graft should be replaced in a different position or the peeled area should be increased. A donor cornea punch is then used to cut the graft. The size of the graft usually ranges from 8.25 to 9.5 mm in diameter.

Once the graft is cut, the cornea scleral rim is removed and the stripped area should be visible and possible to grasp. The forceps should not be pressed together too strongly. Higher grasping force could break the grasping point leading to a loss of tissue and need for regrasping potentially leading to higher loss of EC. The suction of the punch should be kept on throughout the procedure. If the surgeon has experience in DMEK stripping, a suction-free peeling could be considered. Having a mobile tissue to strip is more difficult to manage but it gives more freedom in the management of tensions and vectorial forces. The stripping is then completed with a longitudinal movement trying to avoid damages and tears [25].

During the peeling, high tension on the graft should be avoided to minimize the risk of ruptures. Sometimes however, stripping movement of the cornea could occur due to tension forces. In this case, additional toothed forceps could aid in keeping the corneal stroma in position. In the first cases, fast peelings are discouraged because they can create tight grafts [26]. Slow peeled grafts have the potential to ease unfolding during the DMEK surgery [26].

Once fully stripped, the tissue is placed on the corneal stroma and drops of preservative medium are placed on top of it. At this point, the patient should be called to theatre to start the surgery.

2.3. Graft Size. Graft diameter can vary as the size of the defective area changes. Corneal endothelial cell density (ECD) is higher in the periphery compared to the central cornea, especially beyond 9.00 mm [27, 28]. Delivering larger grafts could theoretically not only provide a higher number of transplanted cells but also include an area containing cells with high proliferative potential, which could potentially increase graft survival [29–31].

Although the use of a large DMEK graft is desirable in order to deliver more endothelial cells, the size of the graft must be carefully customized by measuring the white-to-white distance in cases that are not straightforward, such as Asian populations, high hyperopic eyes, and narrow anterior chambers, where smaller grafts are preferred. On the contrary, myopic and buphthalmic eyes can benefit from grafts larger than 9.5 mm [32]. In our experience, graft unfolding is more difficult when using DMEK grafts larger than 9 mm. We suggest that inexperienced surgeons who are new to the procedure should undertake their first cases using smaller graft diameters.

3. Preoperative Assessment: Anesthesia and Dilating Drops

We suggest performing DMEK surgery under topical anesthesia (TA) using Minims Proxymetacaine hydrochloride 0.5% w/v eye drop solution (Bausch & Lomb House, Surrey, UK) combined with peribulbar anesthesia (PA) with lidocaine 2% and bupivacaine 0.5% in a 3 : 2 ratio. We routinely use a 24-gauge needle and a trans-eyelid approach: the needle is inserted at a right angle to the skin at the lower orbital margin and advances 1.0–2.0 cm along the orbital floor at the temporal third of the lower eyelid with the eye in the neutral position of gaze, approximately 20 min before the surgery [33].

In cases where PA cannot be used, DMEK surgery can be safely performed under TA [34]. Indeed, the block can be avoided if surgery is brief, preferring TA with intracameral lidocaine [35]. Although levels of subjective pain are lower under PA than under TA, in pseudophakic patients without ocular comorbidities, Rickmann et al. suggest that TA combined with intracameral anesthesia could be considered, since it does not affect functional outcomes [36]. In agreement with them, in our opinion, it is feasible but it could complicate and prolong DMEK surgery for less experienced surgeons. Only experienced surgeons should use it for selected cooperative patients. Oral premedication with 15 mg midazolam or 10 mg diazepam before local anesthesia could be considered in anxious patients [37].

Sub-Tenon's capsule injection of local anesthesia is another method to achieve adequate local anesthesia for anterior segment surgery. Since any bleeding at the surgical site can track through the wounds and lead to fibrin formation in the anterior chamber (AC), the injection should be performed with caution to avoid large episcleral and conjunctival vessels.

Many surgeons perform DMEK with a peripheral iridotomy (PI) either prior to [38] or during the DMEK surgery to prevent air/gas bubble induced pupil block [39, 40]. However, an intraoperative PI is not without risks. Bleeding, glare, photophobia, lens capsule compromise, and vitreous strands through the PI are some of the complications reported to result from a surgical PI [41, 42]. We recommend a PI-less DMEK technique. This approach involves dilating the pupil with drops like tropicamide 1% or atropine 1% 30 minutes before surgery to obtain maximum dilatation. A dilated pupil helps to optimize red reflex, reduce the surface contact between iris and graft, and reduce the risk of pupillary block, and aids the visualization of the endothelium during descemetorhexis (Figure 3(a)). Conversely, we recommend a constricted pupil in selected cases like aphakic and vitrectomized eyes [43].

4. DMEK Surgery

4.1. Incisions. From early on, the DMEK technique has been carried out with small 3.0 mm, superior, 50% scleral depth, limbal, tunneled, self-sealing, sutureless main incision and

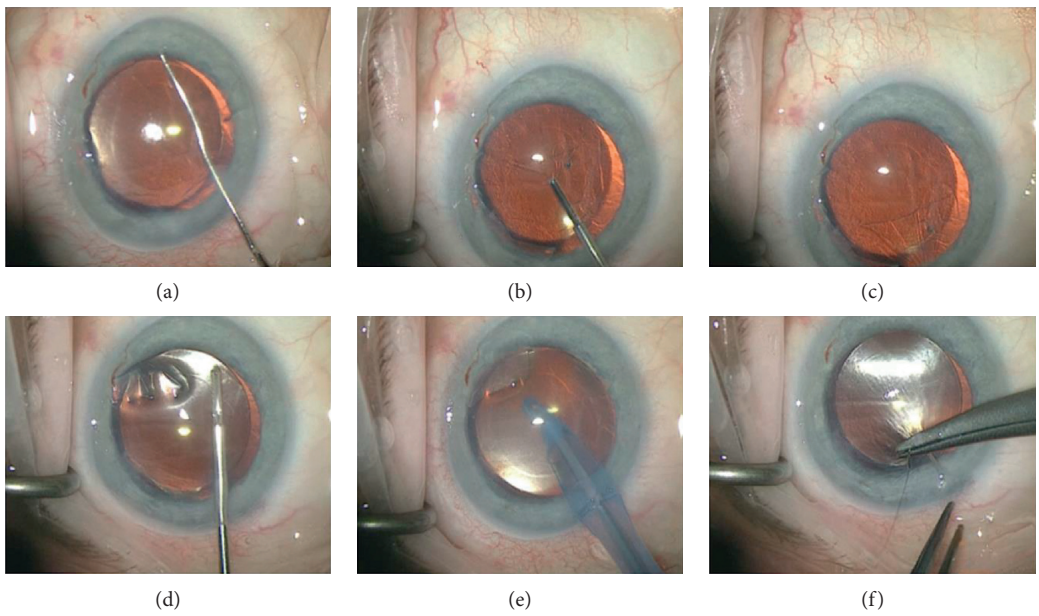


Figure 3: Descemetorhexis: (a) starting point; (b, c) peeling of the recipient Descemet's membrane and endothelium; (d) remnants removal; (e) AC washout; (f) suture.

three auxiliary paracenteses [8]. The technique for the main incision and auxiliary paracentesis has remained unchanged in the subsequent standardization of the technique [33]. Other publications describe the creation of a clear corneal main incision that ranges from 2.2 to 3.2 mm (Figure 4), depending on size and nature of the insertion device for the DMEK graft [39, 44]. We suggest placing the first 2 side ports 80–90° away from the main wound. They should be directed horizontally, so that the reversed Sinskey hook can be inserted avoiding the escape of the air placed in the AC and allowing the BSS to leave when shallowing the chamber. These ports will aid the unfolding process. The third side port should be more perpendicular as it will be useful at the end of the surgery to manage the level of air in the AC. The location and the placement of a suture on the main incision after graft insertion also varies greatly depending on the surgeon [44]. Nevertheless, DMEK can be considered a virtually sutureless procedure, increasing the postoperative refractive stability and decreasing the suture-related complications compared to previous keratoplasty techniques [45, 46].

4.2. Descemetorhexis. Descemetorhexis, the scoring and stripping of Descemet's membrane, is usually performed with a reversed Sinskey hook or a scraper or more rarely with a cystotome in a circular fashion. The usual diameter of descemetorhexis ranges from 8.5 to 9.5, depending on the size of the graft. The descemetorhexis can be performed under air or with the help of ophthalmic viscosurgical devices (OVD) which many will find easier when starting [47, 48]. Descemet's membrane visibility under air is superior, although the technique is technically more challenging due to air escaping during wound manipulation. Unless the AC is very shallow or there is posterior pressure, the need for air reinjection does not preclude the performance of descemetorhexis. If the surgeon needs more air, a continuous air infusion of a posterior vitrectomy device injection can be used by connecting an anterior chamber maintainer to the fluid air exchange system. Using a pars plana infusion can be useful in previously vitrectomized eyes.

Descemetorhexis under OVD has advantages such as a more stable anterior chamber, reduction of flare, and iris fluctuation [49]. If you choose this technique, we suggest performing at least a 180° descemetorhexis followed by the peeling of the recipient Descemet's membrane and endothelium with forceps (GRIESHABER® Asymmetrical Forceps, Alcon, Fort Worth, TX, US) (Figures 3(a)–3(c)). To facilitate the insertion of the forceps in the AC, we suggest bending it 60° in the middle. This is to avoid any contact/damage with the recipient corneal stroma. When required, forceps could aid with the refining and enlarging of the descemetorhexis reducing the donor-recipient overlaps (Figure 4(d)), in order to reduce the requirement for rebubbling.

It is important to completely remove OVD before inserting the graft, as it can interfere with graft adherence (Figure 3(e)). To double check if the AC is free from OVD, it is possible to insert a bubble of air and record its expansion. If OVD remnants are present, the air bubble will not expand in the AC. Additionally, air in the AC prevents swelling of the recipient cornea during the graft staining and loading phase.

At this point, a 10/0 nylon suture may be placed on the main incision. Performing this step before the insertion of the graft will facilitate faster suturing at the end of the surgery, avoiding major complications like expulsion of the graft from the AC or loss of air (Figure 3(f)).

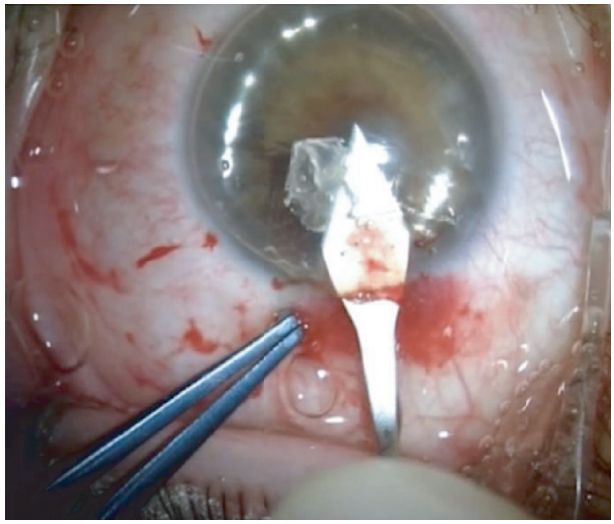


Figure 4: Main incision under air.

4.3. DMEK Graft Staining, Loading, and Insertion. Staining the graft before its insertion into the AC is an important step for a successful and safe surgery. It is important to obtain a thoroughly stained graft, as it will aid with proper visualization during unfolding. The traditional dye used is 0.06% trypan blue (Vision Blue™, D.O.R.C. International) for 1-2 minutes [14], depending on the characteristics of the graft. Tight rolls may take longer to stain. The graft is then placed in a pot with BSS to facilitate the loading process. We suggest using a pot with a low height wall to ease the loading of the graft. To insert the prepared DMEK graft into the AC requires a specialized injector. Ideally, it should facilitate the loading of the graft, cause minimal cell loss/damage to the endothelium, and preserve the AC volume upon insertion. Surgeons may choose from a range of different insertion devices available commercially [50]. In our experience, we found that it was easier to start with glass injectors such as the Geuder glass tube (Geuder AG, Heidelberg, Germany). During the loading of the graft, the injector should be full of BSS and its tip completely submerged under the BSS to avoid air being taken up. If the graft is loaded but air is present in the injector, we suggest trying to remove as much as possible. If air is accidentally injected in the AC, it could complicate the unfolding process and it should be removed. Prior to injection, the graft is key to recheck the orientation (it must look like a "double roll" with the hinge down and the flanges up). When injecting the graft, it is important to have a low AC pressure and flat AC. This is because when injecting the graft, BSS is also being injected and an elevated AC pressure could result in a torpedo reaction that will push the graft back outside the AC.

4.4. DMEK Unfolding and Air Injection. Graft unfolding is the most variable step in DMEK surgery. DMEK graft, when peeled and submerged in BSS, will spontaneously roll outwards, exposing the endothelium. This requires unfolding manipulation once the tissue is injected into the AC. At the end of the surgery, DM should be well attached to the stroma. If DM spontaneously rolls inwards, complete unrolling is required to allow it to roll in the correct manner, before it can be attached using a standard AC air or sulfur hexafluoride (SF6) gas as tamponade [49]. Patient selection is a critical step, as a number of patient factors greatly influence the surgical course. Both very deep and very shallow AC configurations can be a major challenge [51]. Tissue from older donors tends to form wider graft rolls, which consequently require less manipulation during surgery, and where possible they should be considered for complex surgery and recipient eyes with deep AC anatomy [52].

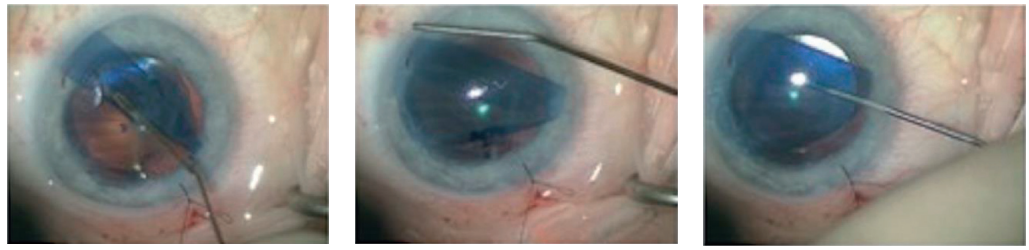
The presence of coexisting ocular pathologies, such as glaucoma tubes, anterior synechiae, iris malformations, and anterior chamber intraocular lenses, increases the risk of intra- and postoperative complications including AC bleeding, bubble dislocation into the vitreous cavity, and graft detachment. When first learning the DMEK procedure, such cases with higher complication risks should be avoided [53, 54]. An AC free from OVD, air, and fibrin remnants is the first prerequisite for a successful and safe unfolding.

The surgeon must take care not to dislocate the DMEK graft in the vitreous chamber [55]. In postvitrectomy eyes, a temporary hydrophilic methacrylate sheet can be useful [56]. Different techniques to unfold DMEK grafts are reported in the literature [57–59]. For beginners, we suggest the tap technique: after the insertion of the graft, a suture to the main wound is closed and bordered. Short taps with 2 cannulas on the corneal surface and delicate bursts of BSS from the side ports help to open the graft and position it in the correct orientation (Figures 5(a)–5(c)). Fluid waves within the AC from the side ports as a result of corneal tapping also help to open the graft. In cases of a very tight scroll, an air bubble injected inside the scroll's lumen using a 30G-cannula may enlarge the scroll and help it to unfold [60].

It is better to keep the AC shallow but not completely flat [61]. For more experienced surgeons and as an approach to reduce the degree of graft manipulation in the AC, the endothelium can be manually tri-folded (taco-fold) endothelium-in way, thus protecting the now inward endothelial cells and leaving the DM exposed. Tri-folded endothelium inward DMEK surgery is associated with similar endothelial cell loss compared to the endothelium-outward technique. Additionally, the mostly spontaneous unfolding of the graft inside the recipient eye reduces time and extent of surgical manipulation [62].

The correct orientation of the graft must be repeatedly verified during surgery and especially before attaching the graft to the posterior corneal stroma. The direct observation of the Moutsouris sign or the F mark is usually quick and helpful [59]. When the orientation is correct, a partly unfolded graft can be completely opened. If the graft is upside down, the anterior chamber can be deepened and a BSS burst between the iris and the graft will invert the graft in the AC.

Caution is advised when adding fluid to the AC during the unfolding process, as increased AC pressure may cause the graft to be flushed out of a corneal incision when entering the AC with an instrument. Even just minimal graft dislocation into a corneal wound will make surgery more



(a) (b) (c)

Figure 5: (a) Tap to unfold DMEK tissue; (b) tap to center the tissue; (c) DMEK orientation checks.

complex and will result in endothelial cell loss in the affected graft areas. We therefore suggest placing a tight suture on the main incision and only then proceed to increasing AC pressure using BSS via the side ports. When the tissue is completely unscrolled and centered, air can be inserted under it to attach the graft to the recipient stroma [39, 63].

After air is injected in the anterior chamber, the centration of the graft can still be gently corrected using forceps (GRIESHABER® Asymmetrical Forceps, Alcon, Fort Worth, TX, US) to pull the graft into the desired position. To increase graft mobility, we suggest performing this procedure with no more than a 50% AC air fill. Despite the fact that this procedure may result in a small loss of endothelial cells, it will improve the centration of the graft. Improved centration again will result in faster corneal clearing and a lesser risk of peripheral graft overlap with recipient endothelium, thus reducing the likelihood of graft detachment [64].

At the end of the surgery, the vertical incision can be used to fill the AC with air, aiming to create a 90% air or gas fill. If available, intraoperative Optical Coherence Tomography (OCT) may facilitate all surgical steps by increasing the visualization of the graft and its orientation [65]. If the graft, despite rigid supine position of the recipient head during the early postoperative hours or days, detaches from the posterior corneal stroma and the detachment involves the pupil area or is seen to progress towards the pupil area, it needs to be reattached [66].

5. Conclusions

Tips and tricks can help surgeons new to DMEK to improve their outcomes and facilitate the uptake of DMEK surgery. A well-prepared DMEK graft and different surgical techniques improve the desired surgical outcome. The tips and tricks described in this article could be beneficial for new and experienced corneal surgeons.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

DB, MR, AT, HL, CB, VR, KG, and RCM contributed to concept and design of the review; DB, MR, CB, BS, and KG drafted the manuscript; DB, MR, MP, AT, HL, CB, CR, BS, VR, and KG critically revised the manuscript; MP, HL, VR, and RCM performed study supervision; and DB, VR, CB, and RCM are guarantors. All authors approved the final version of the manuscript.

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Research Article

Changes in Corneal Parameters after DMEK Surgery: A Swept-Source Imaging Analysis at 12-Month Follow-Up Time

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Purpose. To assess the time course changes in corneal topographic parameters during the one-year follow-up after Descemet membrane endothelial keratoplasty (DMEK) surgery. *Materials and Methods*. Twenty-one patients (24 eyes) who underwent DMEK surgery were evaluated. Best corrected visual acuity (BCVA), endothelial cell count (ECC), central corneal thickness (CCT), mean keratometry (MK), mean astigmatism (MA), astigmatism asymmetry (AA), and higher-order aberration (HOA) were assessed at baseline and 1, 3, 6 and 12 months after the surgery using CASIA2 anterior segment swept-source OCT (Tomey, Japan). *Results*. In patients who underwent DMEK surgery, BCVA improved gradually at the subsequent visits during the 12-month follow-up. A significant reduction in ECC and CCT at the 1st month was noted, which remained stable until the 6th month postoperatively. Anterior and total MK values remained unchanged, whereas changes in posterior keratometry were noticeable until the 6th month after surgery. A significant reduction in the anterior, posterior, and total astigmatism magnitude as well as astigmatism asymmetry was observed during the first 6 months after surgery. A gradual anterior, posterior, and total HOA decrease was documented until the 12th month after surgery. Negative correlations between baseline values of CCT, MK, MA, AA, and HOA and postoperative variations in those parameters at consecutive follow-up time points were observed. Accordingly, negative correlations between baseline CCT and postoperative changes in corneal topographic parameters after surgery were found. *Conclusion*. The stabilization of most corneal topographic parameters takes place within 6 months after the procedure, whereas HOA reduction and BCVA improvement gradually occur during the first year after surgery. Preoperative values of corneal topographic parameters strongly determine their changes detected after DMEK surgery, which may suggest that early therapeutic intervention results in better visual outcomes.

1. Introduction

In the last few years, Fuchs corneal endothelial dystrophy and pseudophakic bullous keratopathy have become the most common indications for corneal transplantation [1]. Less than 25 years ago, the introduction of endothelial keratoplasty (EK) by Melles in 1998 revolutionized corneal transplantation [2] and was a salvation for patients with corneal endothelial disease. The introduction of the Descemet membrane endothelial keratoplasty (DMEK) technique, a selective replacement of the Descemet membrane and its endothelium, has resulted in significant progress in lamellar corneal surgery [3, 4]. Following the first procedures performed in 2006, the popularity of DMEK surgery quickly began to grow. DMEK, next to the other lamellar keratoplasty techniques as Descemet stripping endothelial keratoplasty (DSEK) or Descemet stripping automated endothelial keratoplasty (DSAEK), began to replace the conventional penetrating keratoplasty (PKP) for selective replacement of the diseased posterior layers of the

cornea in patients with endothelial insufficiency [5]. Furthermore, it soon became evident that the near complete restoration of the corneal anatomy with the DMEK technique provided unprecedented visual outcomes and an even lower risk of allograft rejection [5–8]. Moreover, there was no need for expensive and specialized equipment, such as a microkeratome or femtosecond laser, for the preparation of the donor tissue while conducting DMEK surgery [9].

Since the introduction of the DMEK technique, changes in endothelial cell count (ECC), best corrected visual acuity (BCVA), and central corneal thickness (CCT) after surgery have been widely studied [7, 10–13]. There are only a few reports analyzing postoperative corneal aberrations [14–16], keratometry [17–19], and astigmatism changes [20–22]. Regrettably, there are few studies that assess the dynamics of changes in corneal parameters over time in a detailed way.

In the present study, we aimed to assess the time course changes in corneal topographic parameters during a one-year follow-up after DMEK surgery. We also explored the relationship between dynamic variations in corneal curvature, CCT, BCVA, and ECC between individual visits throughout the 12-month postoperative observation time. To the best of our knowledge, this might be the first retrospective study to provide such a broad and precise analysis of dynamic variations in corneal keratometry, astigmatism, astigmatism asymmetry, and HOA values based on anterior segment swept-source optical coherence tomography (SS-OCT) recordings.

2. Materials and Methods

This retrospective case series included 24 eyes after DMEK surgery, which was carried out due to various causes of endothelial decompensation: Fuchs endothelial corneal dystrophy (FECD) or pseudophakic bullous keratopathy (PBK). The patients enrolled in the study were operated on at the First Ophthalmology Clinic in Szczecin in 2018–2020 and then monitored 1, 3, 6, and 12 months after the surgery. All participants underwent a complete ophthalmologic examination, including the following: best corrected distance visual acuity with Snellen charts, slit lamp biomicroscopy, and a detailed fundus examination after pupil mydriasis. Intraocular pressure (IOP) measurement and corneal quality parameters were evaluated with swept-source anterior segment optical coherence tomography (AS-OCT) at each follow-up visit.

2.1. Surgical Technique and Graft Preparation. Donor corneas were obtained with the multiorgan procurement method and in the dissecting room during autopsy. Corneoscleral buttons were stored in Eusol-C medium (Alchimia, Italy) in hypothermic storage at 2–6°C at the West Pomeranian Eye Tissue Bank in Szczecin. The prestorage evaluation of the endothelium was performed by specular microscopy (Konan CellCheck EB-10, Konan Medical, USA). All corneas had an endothelial cell count of at least 2800 cells/mm^2.

Direct preparation of the graft before transplantation took place in the operating theatre. All grafts were stripped and left on their natural support immersed in 0.06% trypan blue dye (Vision blue; D.O.R.C). Then, grafts were trephined by the surgeon to the desired diameter (6.0–8.0 mm) using a Hessburg-Barron donor corneal punch (Barron Precision Instruments, USA).

Each surgery was performed by the same surgeon. All patients underwent prophylactic basal laser iridectomy at 6 o'clock position before endothelial keratoplasty to minimize the risk of postoperative pupillary block. Patients with retinal diseases significantly affecting visual acuity were excluded from the study. All procedures were performed with peribulbar block.

The epithelium of the recipient was marked to guide the subsequent Descemetorhexis and to allow the correct positioning and perfect centring of the transplanted donor flap. The anterior chamber (AC) of the eye was then entered through a clear corneal incision. After the injection of a hyaluronate viscoelastic material, the endothelium and the Descemet membrane were stripped using an inverted Price-Sinskey hook. The stripping diameter was 1 mm wider than the graft diameter. The viscoelastic material was rinsed after stripping. The removed flap was exposed on the anterior surface of the receiver's cornea to verify its integrity.

The surgery was performed following the "no-touch" technique. The trephined DMEK graft was carefully detached from the surrounding Descemet membrane, immersed in sterile balanced salt solution, and aspirated into the transparent glass cartridge (Geuder AG, Germany). The rolled graft was injected into the AC with slow and continuous pressure through the main incision (2.4 mm). The graft was then unfolded and positioned using the tap-tap technique. After ensuring the correct orientation and centration, the graft was pressed against the recipient stroma by injecting SF6 underneath. One nonabsorbable 10-0 suture was applied to the operating port and kept until the first-week follow-up visit.

All patients were instructed to stay in a supine position until the first postoperative flap position control was done. In the case of a pupillary block or ocular hypertension, topical mydriatics were administered, or if this procedure was insufficient, a small quantity of air was released from the AC in the operating theatre. The postoperative treatment consisted of a topical antibiotic given 4 times a day for 1 week and topical preservative-free dexamethasone sodium phosphate 8 times a day for the first month. The topical steroid was tapered down to one drop every other day and then discontinued over a 1-year period.

2.2. Visual Acuity and Endothelial Cell Count Measurements. Visual function was assessed in all participants by evaluating BCVA using a Snellen chart. The result was recorded in the decimal system.

The ECC was measured at each follow-up visit using a specular microscope (EM-4000, Tomey, Japan).

2.3. AS-OCT Measurements. Both corneal thickness and keratometry values were determined using a swept-source anterior segment OCT CASIA2 (Tomey, Japan). During the entire observation period, the CASIA2 was placed in the same room under the same lighting conditions. All measurements were taken by trained operators. Operators gently held patients' eyelids to avoid putting pressure to the globe. The scan was performed using the autoalignment function. The CASIA 2 measurements were obtained with the corneal map mode of the anterior segment module. The images were analyzed by built-in 2D analysis software that automatically calculated the measurements along with the structural outlines and reference lines. The outline tracer was edited where needed.

Central corneal thickness (CCT) (μm), mean keratometry values (D), astigmatism power (D) and axis (°), astigmatism asymmetry (D), and higher-order aberration (HOA) power (D) were recorded and analyzed at assumed time points after surgery using the Fourier analysis 3D/2D function. Measurements were read from both the anterior and posterior surfaces of the cornea, and the total values were taken into account. All parameters were assessed at optical zones (OZs) with 3 and 6 mm diameter. The image quality was assessed during acquisition by the operator. Only well centred measurements with high-quality indexes were included in the study.

2.4. Statistical Analysis. The statistical analysis was conducted using Statistica software. Parametric variables were established by the Shapiro–Wilk test. The Wilcoxon signed-rank test was used to compare the preoperative and postoperative values. The correlations between the baseline variables and the corneal parameters were analyzed with Spearman's rank correlation coefficient (Rs). A p value of less than 0.05 was considered significant.

3. Results

3.1. Baseline Characteristics of the Study and Donor Groups. Twenty-four eyes of 21 patients qualified for DMEK surgery ($n = 24$). No graft failures or rejections were observed. The preoperative characteristics of the patients, as well as donor graft characteristics, are shown in Table 1. The study group consisted of 5 men and 16 women. The mean age of the patients was 66.25 ± 11.23 years. All men and 12 women underwent surgery secondary to FECD. In 4 women, the indication for surgery was PBK. At baseline, the mean values of BCVA and CCT were 0.2 and 680.50 μm, respectively.

3.2. The Influence of DMEK Surgery on BCVA. First, the influence of DMEK surgery on BCVA improvement was evaluated (Figure 1(a)). The median baseline BCVA was 0.2, and it increased gradually at the consecutive follow-up visits (median = 0.5 at the 1st month, median = 0.6 at the 3rd month, median = 0.8 at the 6th month, and median = 1 at the 12th month).

3.3. The Dynamics of Changes in Endothelial Cell Count and Central Corneal Thickness. Next, the dynamics of the changes in endothelial cell count after DMEK surgery were analyzed (Figure 1(b)). A significant decrease of 51,67% in ECC value was noted after 1st month compared to baseline (median = 3045.5 cells/mm^2 at baseline and median = 1472 cells/mm^2 at the 1st month after surgery; $p < 0.001$). No significant changes in ECC values (cells/mm^2) at the 1st, 3rd, and 6th month after surgery were noted. Subsequently, we observed a significant reduction in ECC at the 12th month compared to the values recorded at the 6th month.

Regarding corneal thickness, in comparison with the baseline values (μm) (Figure 1(c)), CCT decreased significantly at the 1st month after the procedure, remaining stable and unchanged from the 1st month until the 6th month postoperatively. Then, we observed a significant increase in CCT at the 12th month compared to the values recorded at the 6th month.

3.4. The Dynamics of Changes in Corneal Topography. Further, we analyzed the dynamics of changes in keratometry recordings after DMEK surgery (Table 2). No significant changes in the magnitude of anterior keratometry values (D) between the follow-up time points were noted. Similarly, we observed no significant changes in total keratometry between time points with only one exception: the values noted at the 1st month postoperatively were lower than those recorded preoperatively exclusively in the 6 mm OZ group. This could suggest that the DMEK procedure might not have an impact on anterior and total keratometry values. Regarding the posterior corneal surface, we observed a significant reduction in keratometry values at the 1st month compared to baseline values. Then, a significant increase in posterior keratometry recordings at the 3rd month compared to the 1st month was noted. Accordingly, the values obtained at the 6th month were higher than those observed at the 3rd month postoperatively. The posterior keratometry recordings stabilized at the 6th month, remaining unchanged until the 12th month after surgery (median = −6.34 D for 3 mm OZ and median = −6.32 D for 6 mm OZ, $p = 0.38$ and $p = 0.26$, respectively).

Afterwards, the influence of the DMEK procedure on astigmatism changes was evaluated (Table 2). We observed a significant reduction in the anterior, posterior, and total astigmatism magnitude at the 12th month follow-up visit postoperatively compared to baseline values (D). Interestingly, no changes in total astigmatism power were detected directly after the procedure at the 1st month after DMEK procedure compared to preoperative values. A subsequent reduction in total astigmatism power was detected only at the 3rd month after the procedure compared to values recorded at the 1st month visit, with subsequent stabilization of astigmatism power from the 3rd month up to the 12th month of follow-up. A similar pattern of astigmatism reduction was observed for the anterior and posterior cornea at the 3 mm and 6 mm OZ. Additionally, we noted a significant decrease in posterior astigmatism power at the 6th month compared to baseline values exclusively in the 6 mm

Table 1: Preoperative characteristics of the patient and donor corneas.

Parameter	Value
Preoperative BCVA (decimal)	0.22 ± 0.15
Preoperative CCT (μm)	680.50 ± 89.6
Recipient age (y)	66.25 ± 11.23
Recipient sex (m/f)	5/16
Donor age (y)	60.08 ± 6.23
Donor sex (m/f)	11/13
Donor graft ECC (cells/mm^2)	3057.83 ± 317.73
Type of cornea donation	19 multiple organ procurements, 5 procurements during the autopsy
Indications for the surgery (FECD/PBK)	19/4

BCVA = best corrected visual acuity (in decimal values); CCT = central corneal thickness; y = years; m = male; f = female; ECC = endothelial cell count; FECD = Fuchs endothelial corneal dystrophy; PBK = pseudophakic bullous keratopathy. Where possible, data are presented as the mean ± standard deviation (SD).

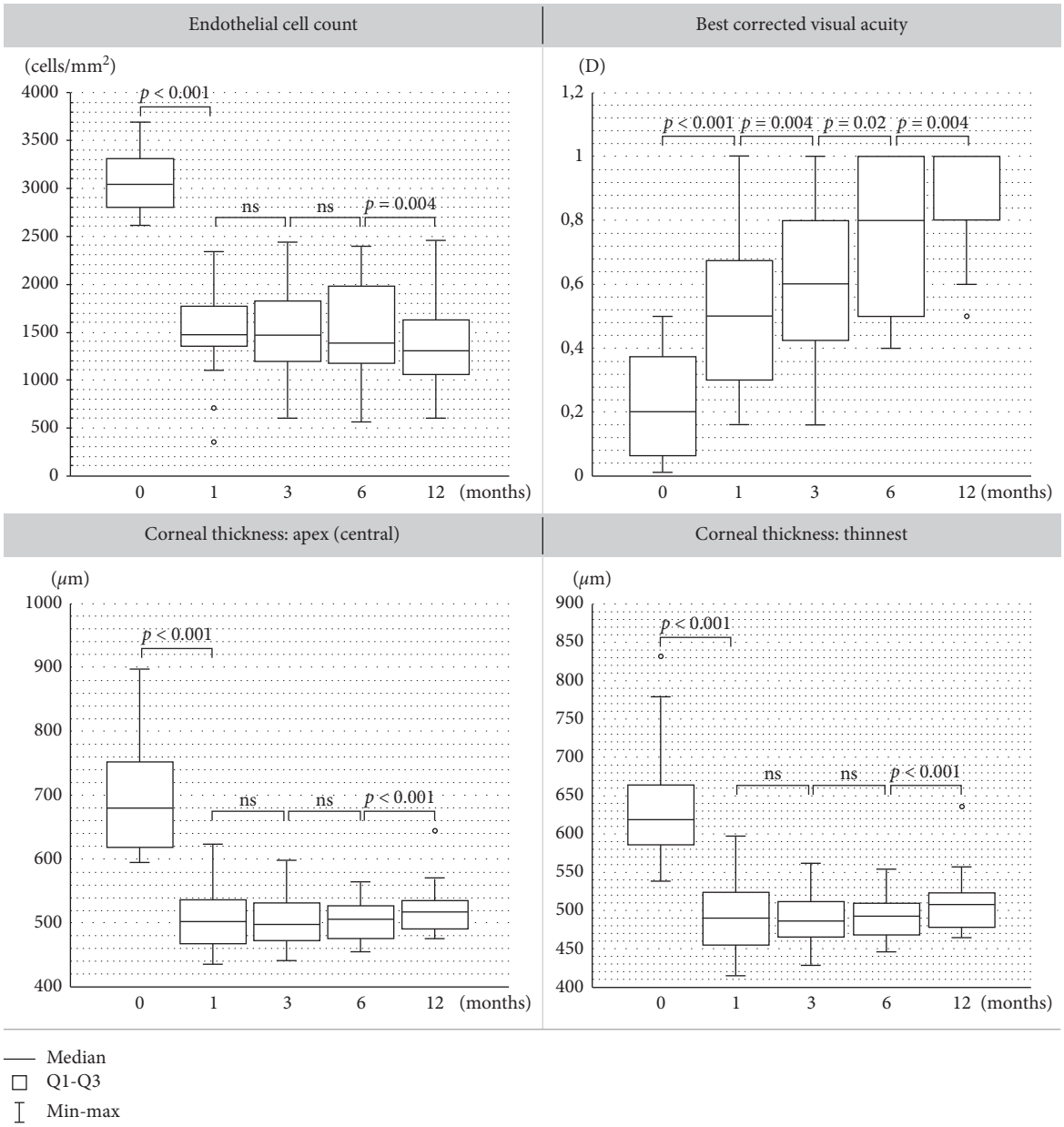

Figure 1: Boxplots showing (a) endothelial cell count (ECC), (b) best corrected visual acuity (BCVA), and corneal thickness ((c) apex-central and (d) thinnest) at baseline and at the 1st, 3rd, 6th, and 12th month after DMEK surgery. ns = not significant.

Table 2: The dynamics of changes in mean keratometry, astigmatism magnitude, astigmatism asymmetry, and higher-order aberration power between the follow-up time points in the different corneal optical zones after Descemet membrane endothelial keratoplasty.

			Baseline median (IQR)	1-month median (IQR)	3-month median (IQR)	6-month median (IQR)	12-month median (IQR)
Mean keratometry (D)	Anterior	3 mm OZ	49.96 (4.96)	48.34 (2.85)	48.11 (2.90)	49.02 (2.68)	49.26 (2.68)
		6 mm OZ	49.39 (3.60)	47.47 (2.33)	47.47 (2.64)	48.72 (2.19)	48.77 (2.48)
	Posterior	3 mm OZ	−6.06 (0.89)	**−6.47 (0.40)**	**−6.37 (0.35)**	**−6.32 (0.41)**	−6.34 (0.31)
		6 mm OZ	−6.01 (0.90)	**−6.51 (0.37)**	**−6.35 (0.40)**	**−6.29 (0.45)**	−6.32 (0.29)
	Total	3 mm OZ	43.88 (4.46)	42.07 (2.18)	41.92 (2.29)	42.76 (2.21)	42.92 (2.31)
		6 mm OZ	43.41 (3.38)	**41.17 (2.08)**	41.46 (2.18)	42.45 (1.93)	42.58 (2.28)
Mean astigmatism (D)	Anterior	3 mm OZ	1.47 (1.01)	1.58 (1.28)	**0.93 (0.83)**	0.92 (0.68)	0.88 (0.90)
		6 mm OZ	1.37 (0.97)	1.38 (1.25)	**0.87 (0.57)**	0.83 (0.84)	0.78 (0.81)
	Posterior	3 mm OZ	0.30 (0.30)	0.28 (0.20)	0.22 (0.13)	**0.19 (0.13)**	0.18 (0.14)
		6 mm OZ	0.26 (0.2)	0.25 (0.14)	**0.21 (0.115)**	**0.18 (0.09)**	0.17 (0.08)
	Total	3 mm OZ	1.31 (1.57)	1.63 (1.15)	**0.89 (0.825)**	0.93 (0.6)	0.835 (0.51)
		6 mm OZ	1.55 (1.08)	1.32 (1.08)	**0.83 (0.58)**	0.89 (0.65)	0.83 (0.755)
Astigmatism asymmetry (D)	Anterior	3 mm OZ	1.11 (1.79)	**1.00 (0.59)**	0.57 (0.44)	**0.50 (0.29)**	0.49 (0.30)
		6 mm OZ	1.50 (2.44)	**1.09 (0.57)**	**0.74 (0.63)**	0.74 (0.41)	0.63 (0.36)
	Posterior	3 mm OZ	0.43 (0.54)	**0.24 (0.23)**	**0.18 (0.09)**	0.15 (0.1)	0.13 (0.09)
		6 mm OZ	0.51 (0.66)	**0.30 (0.18)**	**0.22 (0.10)**	0.18 (0.1)	0.15 (0.11)
	Total	3 mm OZ	1.41 (1.69)	**0.78 (0.66)**	0.62 (0.42)	**0.51 (0.32)**	0.55 (0.39)
		6 mm OZ	1.92 (2.53)	**1.16 (0.76)**	**0.87 (0.60)**	0.74 (0.46)	0.67 (0.44)
Higher-order aberrations (D)	Anterior	3 mm OZ	0.48 (0.98)	0.34 (0.37)	0.28 (0.19)	0.28 (0.15)	**0.22 (0.10)**
		6 mm OZ	0.48 (0.7)	0.44 (0.56)	**0.38 (0.195)**	0.36 (0.22)	**0.31 (0.125)**
	Posterior	3 mm OZ	0.18 (0.16)	**0.09 (0.05)**	0.08 (0.06)	**0.08 (0.06)**	0.07 (0.05)
		6 mm OZ	0.17 (0.14)	**0.11 (0.06)**	**0.085 (0.05)**	0.09 (0.04)	0.09 (0.05)
	Total	3 mm OZ	0.46 (0.85)	**0.37 (0.33)**	**0.27 (0.15)**	0.27 (0.1)	**0.21 (0.08)**
		6 mm OZ	0.53 (0.81)	0.43 (0.55)	**0.37 (0.20)**	0.35 (0.18)	**0.305 (0.095)**

Statistically significant values are shown in bold. p values are calculated for intervals "baseline-1st month," "1st month–3rd month," "3rd month–6th month," and "6th month–12th month."

OZ. Interestingly, the axis of the baseline total astigmatism remained unchanged throughout the whole follow-up period (data not shown).

Next, we evaluated irregular corneal astigmatism with an asymmetry of the astigmatic components (Table 2). We observed a significant reduction in the anterior, posterior, and total astigmatism asymmetry at the 12th month follow-up visit postoperatively compared to baseline values (D). The follow-up analysis of the astigmatism asymmetry dynamics revealed a significant reduction at the examination conducted 1 month after surgery with subsequent stabilization of this parameter after the 6 months of observation.

Accordingly, we found no differences in astigmatism asymmetry (AA) values between the 6-month and 12-month follow-up visits.

To provide a broad-based assessment of corneal topography after DMEK surgery, we analyzed the higher-order corneal aberrations (D) that may influence vision quality and acuity (Table 2). A gradual HOA reduction of the total cornea as well as the anterior HOA after the treatment was observed up to the 12th month after surgery. Regarding posterior HOA, a significant decrease in HOA values was observed at early time points, while the values stabilized at the 6th month and remained unchanged until the 12th month postoperatively. Interestingly, a significant reduction in posterior and total surface HOA was detected directly after the procedure beginning from the 1st month after surgery, while the values of anterior HOA did not decrease until the 3-month follow-up visit.

3.5. The Potential Relationships between Corneal Parameters at Consecutive Time Points after Surgery. In the next step, we evaluated the potential relationships between corneal parameters at consecutive time points after surgery. We detected that preoperative values of corneal parameters strongly determined their changes detected after DMEK surgery. Accordingly, we found negative correlations between baseline values of CCT, keratometry, astigmatism, astigmatism asymmetry, and HOA and postoperative variations in those parameters at consecutive follow-up time points (Table 3). This finding indicates that the thicker the cornea and the higher the values of keratometry, astigmatism, astigmatism asymmetry, and HOA preoperatively, the lower the reduction in those parameters postoperatively.

Importantly, we determined that baseline CCT strongly influences the changes in other corneal topographic parameters after surgery. Table 4 shows the correlations between baseline CCT and the changes in VA, CCT, keratometry, astigmatism, astigmatism asymmetry, and higher-order aberration values after DMEK surgery. We found that preoperative CCT negatively correlated with changes in corneal thickness, astigmatism power, astigmatism asymmetry, and HOA at the following postoperative visits. This result indicates that the thicker the cornea before surgery, the lower the decrease in magnitudes of regular and irregular corneal astigmatism and HOA after DMEK surgery.

4. Discussion

Endothelial corneal transplantation techniques are constantly being improved, and their continuous development contributes to more effective and safer treatment of patients with endothelial damage.

Many previous studies have focused on the variations in visual acuity and corneal topographic parameters in 6- or 12-month observation periods, comparing them to the baseline conditions [7, 13, 23, 24]. Very few studies have also analyzed the dynamics of changes in topographic recordings at individual visits during the observation period [19].

This retrospective study provided such detailed analysis of the relationships between the dynamic status of corneal topographic parameters, corneal thickness, best corrected visual acuity, and endothelial cell count analyzed at several postoperative follow-up points throughout a 1-year observation period.

Our data provided evidence that posterior keratometry recordings decreased just after the operation at the 1st month postoperatively compared to those recorded preoperatively, which indicates a steepening of the posterior corneal curvature. Altogether, the potential explanation is that the recipient endothelium is replaced with an undersized donor graft; thus, the peripheral margin of the stripped area is deprived of endothelial cells, causing marginal thickening that is due to the unsealed endothelial cell barrier at the peripheral corneal area. This consequence occurs with subsequent steeping of the posterior corneal surface. With time, the donor cells migrate and fill the gaps between recipient and donor tissue, thus leading to a resolution of the peripheral oedema and a flattening of the posterior corneal surface. Subsequently, the cornea returns to a physiologically hydrated status. Indeed, we found a significant increase in posterior keratometry values at 3 and 6 months after DMEK surgery, with subsequent stabilization at 6 to 12 months. Van Dijk et al. in their large prospective study on DMEK indicated that a potential cause of posterior keratometry decrease is the specific corneal healing process. In the early phase after DMEK surgery, the cornea shows central thinning while the periphery is still edematous, creating a steepening of the posterior cornea curvature and a flattening of the anterior cornea curvature, which results in a "hyperopic shift." As the transplanted cornea returns to a physiological hydration status, the induced hyperopic shift is again reduced but still detectable in comparison to the preoperative power [6].

In our study posterior keratometry outcomes coincided with a decrease in ECC at the 12-month compared to the 6-month measurements since endothelial cells have limited potential to proliferate. We cannot exclude the possibility that a decrease in ECC results in an increase of CCT at the 12th month postoperatively since we documented an increase in CCT at the 12-month compared to the 6-month values.

Indeed, similar patterns of ECC and CCT changes were documented in previous studies [7, 11, 23–25].

Importantly, Brockmann et al., in their prospective observational study [13], noted that patients with baseline CCT over 625 μm might have a thicker cornea at the 12-month follow-up. This finding is in line with our observation that baseline CCT determines the variations in corneal thickness after surgery since we found a strong negative correlation between baseline and postoperative changes in corneal thickness at subsequent postoperative visits.

Furthermore, we observed that the DMEK procedure did not impact anterior or total keratometry values. This observation is in line with the data of Kwon et al., who documented that total keratometry did not change significantly after the DMEK procedure and that postoperative values were comparable to those in the healthy cohort.

Table 3: The correlations between changes in VA, CCT, keratometry, astigmatism, astigmatism asymmetry, and higher-order aberration and baseline values of those parameters.

Correlation			The change of the selected parameter at 1 month as compared to baseline	The change of the selected parameter at 3 months as compared to baseline	The change of the selected parameter at 6 months as compared to baseline	The change of the selected parameter at 12 months as compared to baseline
Baseline BCVA			−0.11	−0.28	−0.19	**−0.57**
Baseline CCT			**−0.90**	**−0.87**	**−0.91**	**−0.91**
Baseline mean keratometry	Anterior	3 mm OZ	**−0.79**	**−0.84**	**−0.81**	**−0.85**
		6 mm OZ	**−0.72**	**−0.76**	**−0.75**	**−0.78**
	Posterior	3 mm OZ	**−0.86**	**−0.94**	**−0.93**	**−0.92**
		6 mm OZ	**−0.83**	**−0.87**	**−0.89**	**−0.89**
	Total	3 mm OZ	**−0.88**	**−0.89**	**−0.87**	**−0.90**
		6 mm OZ	**−0.86**	**−0.86**	**−0.87**	**−0.86**
Baseline mean astigmatism	Anterior	3 mm OZ	**−0.46**	**−0.84**	**−0.86**	**−0.70**
		6 mm OZ	−0.13	**−0.59**	**−0.65**	**−0.57**
	Posterior	3 mm OZ	**−0.64**	**−0.83**	**−0.83**	**−0.74**
		6 mm OZ	**−0.55**	**−0.83**	**−0.84**	**−0.75**
	Total	3 mm OZ	**−0.52**	**−0.86**	**−0.86**	**−0.78**
		6 mm OZ	−0.40	**−0.76**	**−0.81**	**−0.74**
Baseline astigmatism asymmetry	Anterior	3 mm OZ	−0.12	−0.14	−0.12	−0.16
		6 mm OZ	−0.01	−0.14	+0.05	+0.05
	Posterior	3 mm OZ	**−0.90**	**−0.95**	**−0.92**	**−0.94**
		6 mm OZ	**−0.92**	**−0.93**	**−0.91**	**−0.94**
	Total	3 mm OZ	**−0.91**	**−0.92**	**−0.95**	**−0.91**
		6 mm OZ	**−0.90**	**−0.94**	**−0.96**	**−0.91**
Baseline higher-order aberrations	Anterior	3 mm OZ	**−0.84**	**−0.87**	**−0.88**	**−0.97**
		6 mm OZ	**−0.80**	**−0.92**	**−0.92**	**−0.98**
	Posterior	3 mm OZ	**−0.89**	**−0.93**	**−0.90**	**−0.95**
		6 mm OZ	**−0.85**	**−0.87**	**−0.85**	**−0.89**
	Total	3 mm OZ	**−0.83**	**−0.85**	**−0.93**	**−0.98**
		6 mm OZ	**−0.81**	**−0.94**	**−0.95**	**−0.97**

The correlations were calculated for 4 consecutive time points, i.e., 1, 3, 6, and 12 months postoperatively. Significant values are shown in bold.

Accordingly, the authors found that the anterior corneal surface remained relatively unchanged, whereas the posterior corneal surface displaced forward [19]. On the other hand, Van Dijk et al., in a large prospective study of 217 eyes, evaluated the keratometry outcomes of patients after the DMEK procedure and showed a pre- to postoperative change in the spheric equivalent of $+0.41 \pm 1.06$ D for the whole study group [6]. Similarly, Ham et al., in a study of 50 eyes,

Table 4: The correlations between baseline CCT and the changes in VA, CCT, keratometry, astigmatism, astigmatism asymmetry, and higher-order aberration values obtained in the 3 and 6 mm optical zones after DMEK surgery.

Correlation of baseline CCT and			At baseline	At 1 month	At 3 months	At 6 months	At 12 months
BCVA change			**−0.54**	+0.20	+0.26	+0.20	+0.27
CCT change			1.00	**−0.90**	**−0.87**	**−0.91**	**−0.91**
Mean keratometry change	Anterior	3 mm OZ	+0.04	−0.005	−0.03	−0.01	−0.14
		6 mm OZ	−0.01	−0.07	−0.03	+0.01	−0.06
	Posterior	3 mm OZ	+0.04	−0.13	−0.07	−0.004	−0.05
		6 mm OZ	+0.08	−0.22	−0.12	−0.13	−0.18
	Total	3 mm OZ	+0.05	−0.07	−0.03	+0.02	−0.15
		6 mm OZ	+0.02	−0.09	−0.06	+0.002	−0.09
Mean astigmatism change	Anterior	3 mm OZ	**+0.42**	−0.18	**−0.45**	**−0.50**	**−0.56**
		6 mm OZ	**+0.48**	−0.30	**−0.52**	**−0.57**	**−0.63**
	Posterior	3 mm OZ	**+0.52**	**−0.62**	**−0.54**	**−0.52**	**−0.62**
		6 mm OZ	**+0.48**	**−0.48**	**−0.45**	**−0.44**	**−0.49**
	Total	3 mm OZ	**+0.49**	−0.31	**−0.54**	**−0.55**	**−0.65**
		6 mm OZ	**+0.66**	−0.41	**−0.62**	**−0.65**	**−0.70**
Astigmatism asymmetry change	Anterior	3 mm OZ	**+0.58**	−0.20	−0.29	+0.07	−0.11
		6 mm OZ	**+0.51**	−0.15	−0.31	+0.02	+0.02
	Posterior	3 mm OZ	**+0.58**	−0.36	**−0.51**	**−0.52**	**−0.58**
		6 mm OZ	**+0.62**	**−0.49**	**−0.52**	**−0.56**	**−0.66**
	Total	3 mm OZ	**+0.61**	**−0.58**	**−0.55**	**−0.53**	**−0.60**
		6 mm OZ	**+0.59**	**−0.45**	**−0.53**	**−0.54**	**−0.66**
Higher-order aberrations change	Anterior	3 mm OZ	**+0.44**	−0.33	**−0.44**	**−0.53**	**−0.54**
		6 mm OZ	**+0.48**	−0.31	−0.40	**−0.46**	**−0.54**
	Posterior	3 mm OZ	**+0.73**	**−0.64**	**−0.63**	**−0.57**	**−0.68**
		6 mm OZ	**+0.77**	**−0.77**	**−0.65**	**−0.58**	**−0.71**
	Total	3 mm OZ	**+0.56**	−0.35	**−0.48**	**−0.64**	**−0.61**
		6 mm OZ	**+0.57**	−0.36	**−0.48**	**−0.50**	**−0.60**

Correlations were calculated for 4 consecutive time points, i.e., 1, 3, 6, and 12 months postoperatively. At the zero observation time point, baseline CCT values refer to baseline absolute values of listed parameters. Significant values are shown in bold.

showed a pre- to postoperative hyperopic shift of +0.32 ± 1.01 D at the 6-month follow-up after DMEK surgery [26]. A change in total refractive corneal power was the result of posterior surface MK change, since the anterior corneal curvature in Scheimpflug imaging was stable. Nevertheless, the authors concluded that normal intraocular power nomograms for cataract surgery should be applied before or during DMEK surgery. Dirisamer et al. demonstrated nearly the same behavior of pre- to postoperative refractive changes [27]. On the other hand, the data presented by Alnaweiseh et al. show a significant change in the refractive power of the posterior surface of the cornea and thus a decrease in the total refractive power of approximately 1 D, whereas the anterior cornea remained nearly unchanged [18]. Interestingly, the retrospective cohort study published by Fritz et al. has proven that patients with centrally flatter, oblate posterior corneas (positive posterior Q) are at higher risk of having postoperative hyperopic shift than other patients. Authors suggest that subtracting 0.5 D of planned refraction before conducting triple procedure (combined DMEK and cataract surgery) in those eyes significantly reduce unexpected hyperopia [28]. Accordingly, Diener et al. indicated Q value and R_{PA} parameter, which was calculated as the posterior to anterior corneal curvature radii ratio, as surrogate markers to identify eyes that might be at risk of a greater postoperative hyperopic shift after DMEK [29]. Bearing in mind the above studies, Campbell et al. evaluated the refractive accuracy of different IOL formulas and proposed Haigis formula to reduce the hyperopic error in patients undergoing the triple procedure [30].

Taken together, the observed inconsistences between studies might have been associated with the use of different topography devices, possible differences in operating technique and donor tissue preparation, different conditions of donor graft storage, or differences in the criteria for study group selection. Thus, we suggest that while carrying out such procedures, surgeons should create their own intraocular power nomograms for cataract surgery before or during DMEK surgery based on their definite observations and own experience.

Data on corneal aberrations after DMEK surgery differ between studies and are not consistent. In terms of astigmatism power astigmatism power, we documented a reduction in the total astigmatism power detected exclusively between the 1st and 3rd months after the procedure with subsequent stabilization of astigmatism magnitude. Contrary to our study, the recent report by Gundlach et al. presented the opposite pattern of a decrease in astigmatism from the 3rd to the 12th month postoperatively [31]. However, the authors scheduled only two postoperative examinations, while our study provided a more detailed analysis based on four follow-up time point observations. On the other hand, Guerra et al., in their prospective, consecutive, interventional series of 136 eyes, did not

observe any significant changes between post- and preoperative astigmatism [11]. Accordingly, Shajari et al. concluded that the extent of corneal astigmatism change after the DMEK procedure in patients with Fuchs endothelial dystrophy is not predictable, which might explain the mentioned discrepancies between published data [20]. It is also worth mentioning that the axis of the baseline total astigmatism remained unchanged throughout the whole follow-up time in our study. Hence, it can be concluded that the DMEK procedure did not induce secondary astigmatism itself. Accordingly, when analyzing the asymmetry of astigmatism components, we found that astigmatism asymmetry remained stable 6 months postoperatively. With regard to higher-order aberrations, we documented that corneal HOA underwent a gradual reduction throughout the whole 12-month observation time, suggesting the ongoing process of tissue remodeling from a long-term perspective. This outcome corresponds with the gradational improvement in vision acuity recorded at subsequent visits in our study. It is noteworthy that previous analyses reporting the changes in HOA after the DMEK procedure are inconclusive. Contrary to our data, Duggan et al. reported no differences in HOA values documented at 12 months postoperatively compared to preoperative values for the total and anterior cornea. The only differences the authors found were for the posterior cornea 6 months after DMEK surgery. Likewise, Gundlach et al. [31] did not show differences between pre- and postoperative anterior and posterior HOA values at the 12-month follow-up. On the other hand, the investigation of Hayashil et al. documented a significant decrease in anterior, posterior, and total HOA recordings starting from the 3rd month after surgery. Accordingly, the authors found no changes in HOA values in early postoperative follow-up times up to the 3rd month [32]. The possible explanation for this discrepancy is diverse stages of endothelial decompensation at baseline in various studies strongly interrelated with differential preoperative visual acuity and corneal thickness. This possibility is supported by our observation that baseline CCT influences the changes in corneal topographic parameters after surgery and negatively correlates with the changes in corneal thickness, astigmatism power, astigmatism asymmetry, and HOA at subsequent postoperative visits. These observations are consistent with previous studies, as baseline CCT represents an efficient predictor for relevant outcome parameters after DMEK surgery [13]. Our findings support the view that different preoperative conditions of corneal oedema may result in different corneal curvature and pachymetry changes. Thus, the more "decompensated" corneas preoperatively are expected to present higher values of regular and irregular corneal astigmatism with an asymmetry of the astigmatic components and HOA after surgery.

Importantly, we detected that preoperative values of corneal topographic parameters strongly determined the changes detected after DMEK surgery since we found negative correlations between their baseline values and postoperative variations. This result strongly corroborates the notion that early therapeutic intervention results in better visual outcomes.

In conclusion, the results of our study provide valuable information regarding the dynamics of postoperative changes in corneal parameters after the DMEK procedure. The presented data clearly demonstrate that the stabilization of most corneal topographic parameters (i.e., mean keratometry, mean astigmatism, and asymmetry of astigmatism) takes place within 6 months after the procedure, whereas HOA and BCVA gradually improve during the first year after surgery.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Anna Machalińska and Agnieszka Kuligowska contributed equally to this work.

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Review Article

New Horizons in the Treatment of Corneal Endothelial Dysfunction

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The treatment of corneal endothelial dysfunction has experienced a revolutionary change in the past decades with the emergence of endothelial keratoplasty techniques: descemet stripping automated endothelial keratoplasty (DSAEK) and descemet membrane endothelial keratoplasty (DMEK). Recently, new treatments such as cultivated endothelial cell therapy, Rho-kinase inhibitors (ROCK inhibitors), bioengineered grafts, and gene therapy have been described. These techniques represent new lines of treatment for endothelial dysfunction. Their advantages are to help address the shortage of quality endothelial tissue, decrease the complications associated with tissue rejection, and reduce the burden of postoperative care following transplantation. Although further randomized clinical trials are required to validate these findings and prove the long-term efficacy of the treatments, the positive outcomes in preliminary clinical studies are a stepping stone to a promising future. Our aim is to review the latest available alternatives and advancements to endothelial corneal transplant.

1. Introduction

1.1. The Evolution of Keratoplasty. Corneal endothelium is formed by a single layer of hexagonal cells that preserve corneal transparency by regulating the outflow of aqueous humor (AH) to the stroma through its barrier and pump mechanisms. It is supposed that corneal endothelial cells (CEC) have a limited regenerative capacity *in vivo* as they remain inactive in the G1 phase of the cellular cycle [1]. When there is a loss of CEC, the damage triggers a countervailing migration and an increase in the size (polymegathism) of the adjacent healthy CEC, resulting in a global decrease in endothelial cell density (ECD) in order to restore the single layer of CEC [1].

Fuchs Endothelial Dystrophy (FED) is a bilateral, sporadic, or autosomal dominant or corneal dystrophy that involves a progressive loss of CEC [2, 3]. Pseudophakic bullous keratopathy (PBK) is caused by an accelerated loss of CEC, mainly after cataract surgery though it is also described after other procedures [3]. Both entities are the most common indication for keratoplasty in the USA [3]. Over 100 years, penetrating keratoplasty (PK) has been the only surgical technique for the treatment of corneal diseases. In the past two decades, PK has been gradually replaced by lamellar keratoplasties for the treatment of endothelial disorders [4–6]. Descemet stripping automated endothelial keratoplasty (DSAEK) is an additive surgery as the donor graft includes the DM, endothelium, and a portion of stroma [7]. Descemet membrane endothelial keratoplasty (DMEK) was introduced later as a finer modification of endothelial keratoplasty (EK), and it comprises the transplantation of the DM and endothelium [5, 6]. DMEK has proven to attain better results in best-corrected visual acuity (BCVA) and a faster recovery compared to PK and DSAEK [6, 8–10]. Nevertheless, this technique has reported to have a longer learning curve than DSAEK, and a higher rate of postoperative graft detachment which is usually balanced after the learning curve [10–13]. The use of thinner grafts in DSAEK ($<100\,\mu$m), termed ultrathin DSAEK, shows better BCVA results compared to standard DSAEK, although it has not proven to be superior to DMEK in BCVA results nor in complication rates [13–17].

Recent innovations of DMEK are hemi-DMEK [18] and quarter-DMEK [19]. Hemi-DMEK consists of 12 mm long × 5 mm wide semilunar-shaped grafts, proving an equivalent surface and postoperative ECD of a standard round 8 mm DMEK graft [20]. Quarter-DMEK comprises 6 × 5 mm grafts shaped as a quarter of a circle and has proven an equivalent surface and postoperative ECD to a 6 mm DMEK graft [21] (Figure 1). Although it is not authorized in all countries, the possible advantage of these techniques is to provide higher availability of endothelial donor tissues [21, 22]. Both techniques proved similar postoperative BCVA results, although ECD was lower than a standard DMEK [23–25]. However, BCVA remained stable after three years in hemi-DMEK and after two years in quarter-DMEK procedures [23–25]. Both techniques, especially quarter-DMEK, could be reserved for cases of central FED and patients with different anterior chamber (AC) abnormalities, such as peripheral anterior synechiae or the presence of glaucoma valve implants.

Another technique termed descemet membrane endothelial transfer (DMET) was developed after observing corneal clearance despite subtotal graft detachment in patients operated for DSAEK or DMEK [26, 27]. In this procedure, the DMEK graft is introduced into the AC as a free-floating graft roll attached to the receptor cornea only by the main incision where the graft was introduced [28] (Figure 2). Interestingly, spontaneous clearance despite graft detachment only occurred in patients with FED and not in those with PBK [29]. Peripheral endothelium is relatively conserved in FED; hence, a migratory endothelial response of functioning peripheral cells could occur despite the graft not being completely attached [29]. Nevertheless, the cell regenerative capacity of FED patients might not be enough to guarantee permanent corneal transparency, as corneal decompensation six months after DMET has been reported [29].

2. Alternatives to Tissue Grafting

2.1. Descemetorhexis without Endothelial Keratoplasty (DWEK)/Descemet Stripping Only (DSO). Some FED patients have reported corneal clearance by simply performing descemetorhexis intentionally or unintentionally [30]. The technique was named descemetorhexis without endothelial keratoplasty (DWEK) by Kaufman in 2018 [31] and was also called descemet stripping only (DSO) by Gorovoy [7] (Figure 2). However, the original idea was first described by Paufique in 1955 [32].

This technique is based on the assumption that the remaining peripheral CEC could migrate onto the denuded central stroma [30, 33, 34]. As mentioned priorly, CEC have a limited regenerative capacity *in vivo* [35–37]. Therefore, it is generally believed that endothelial wound healing occurs through cell migration rather than the proliferation of new cells [34]. However, stem cell markers (LGR5) have been identified in the posterior limbus near the trabecular meshwork [35–37], hence suggesting that some endothelial stem cells may be involved in endothelial wound repair [30, 34, 38].

A series of cases by Koenig, Bleyen et al., and Arbelaez et al. [30, 33, 39] described failure or inconclusive results of DSO after an 8 mm, 6–6.5 mm, and 6 mm descemetorhexis, respectively. It was hypothesized that the rough zone could have been somehow linked to the disfunction and/or the damage of endothelial cells due to surgical trauma [32, 39]. Corneal clearance has been reported after performing a smaller descemetorhexis (4 mm) in the following studies: Ioveno et al. [40], in four out of five cases; Borkar et al. [41], in 10 out of 13 eyes; and nine out of 12 in the series of Garcerant et al. [32]. Thus, it seems that DSO achieves better results when descemetorhexis is performed with a smaller size [32, 40, 41].

An increase in the descemetorhexis diameter from 4 to 6 mm requires more than double the surface area for the remaining endothelium to repopulate, whereas an 8 mm descemetorhexis requires a repopulation of four times the

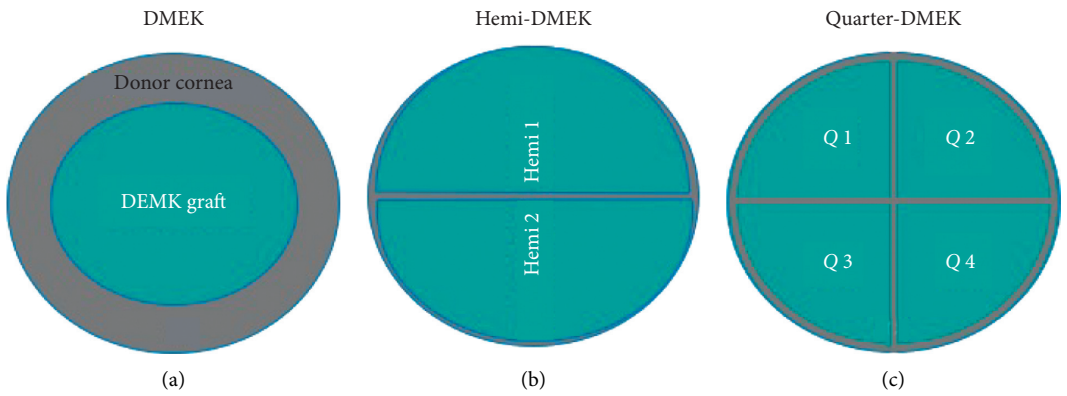


Figure 1: Comparison of graft diameter in DMEK (8.5 to 9.5 mm), hemi-DMEK (11-12 mm × 5-6 mm), and quarter-DMEK (6 mm × 5 mm) (based on the articles by Lam et al. and Müller et al. [19, 28]).

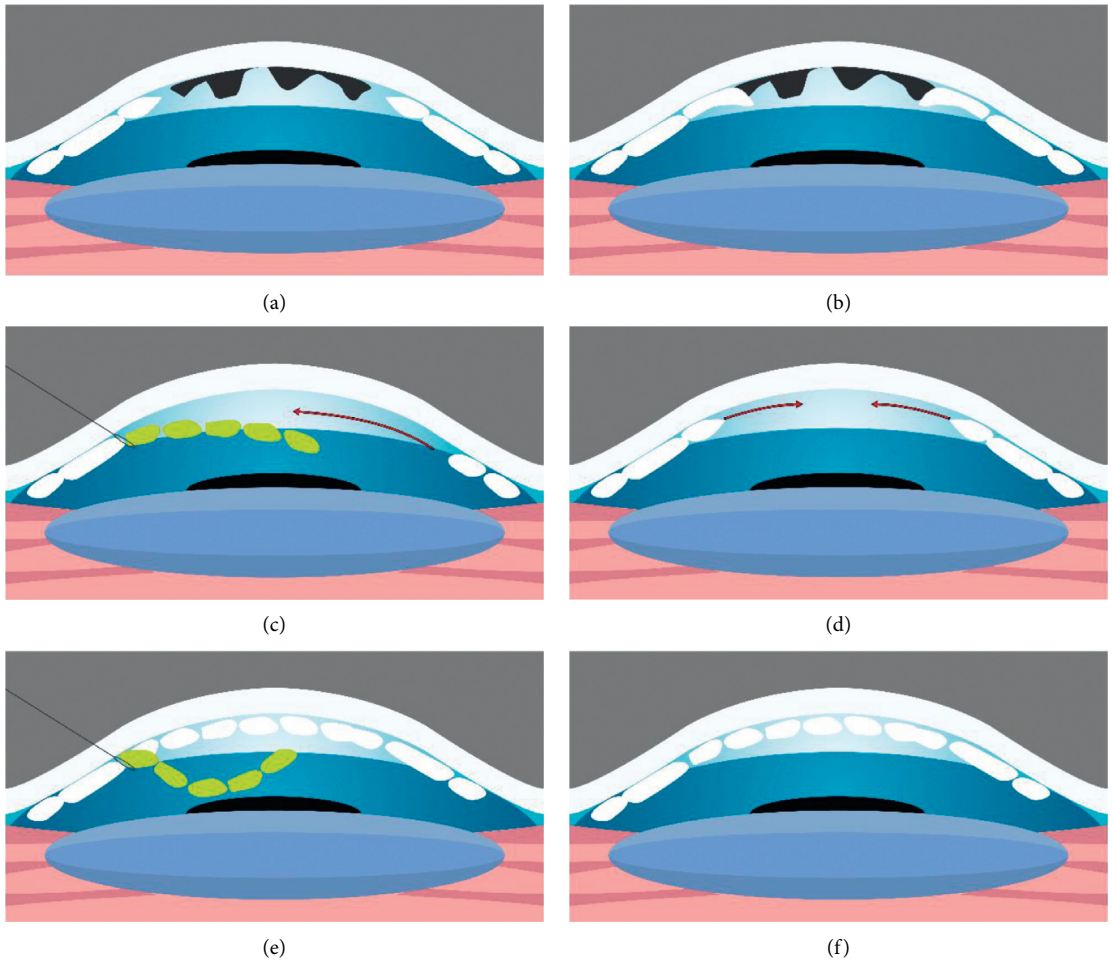


Figure 2: (a, b) Fuchs endothelial dystrophy disease with guttae protruding from the descemet membrane (DM). (a, c, e) The DMET technique. After descemetorhexis, the graft is inserted and fixated to the main corneal incision; the rest of it remains free-floating in the anterior chamber. (d) The DWEK/DSO technique in which a descemetorhexis is performed without further graft implantation. (b, d, f) The DMT technique in which descemetorhexis is performed and a DM graft devoid of endothelial cells is transplanted (based on the articles by Lam et al. and Bruinsma et al. [28, 89]).

area of a 4 mm descemetorhexis [40]. Consequently, DSO would be better reserved for patients with central and nondecompensated FED, with a good peripheral CEC reservoir (over 1,000 cells/mm^2), considering the relatively low postoperative central CEC count described [40–42]. Borkar et al. [41] reported that corneal transparency was achieved in different time periods after undergoing DSO. These periods were as follows: from after one to three months (fast responders), after six months (slow responders), and unsuccessful surgeries that required EK (no responders).

There is some disagreement among ophthalmologists whether a secondary EK performed after an unsuccessful DSO could achieve favorable results. Both Rao et al. and Moloney et al. [43, 44] reported positive outcomes. Therefore, DSO may not hinder the outcome of a secondary EK if necessary [32]. However, some authors, such as Arbelaez et al. [39], suggested that a subsequent DMEK graft may not easily adhere to areas that were stripped off and then repopulated with the endothelium, unless the repopulated endothelial cell layer is removed. Future prospective studies are required to confirm these findings.

Combination of DSO with cataract surgery does not seem to affect the results, hence being a viable option [31, 32, 40–42]. Borkar et al. [41] stated that approximately 75% of eyes that had combined DSO and cataract with IOL placement surgery showed corneal clearance and repopulation of the central endothelial mosaic by confocal microscopy.

However, the results of DSO are inconsistent as some studies have reported the failure of this technique in achieving corneal transparency [40, 45]. It is reasonable to suppose that surgery outcomes may depend on patients' innate features, possibly genetic, that involve CEC migration ability, anterior segment configuration, and surgery-related factors [32]. For instance, Davies et al. [45] stated that achieved corneal transparency time period after DSO in the fellow eye was observed to happen in the similar time period as the first eye, suggesting that patients' innate factors, such as growth factors in the AC, could be involved although they are yet to be defined [32, 45]. It is possible that differences in the number of trinucleotide repeated expansions in FED patients may affect the success or failure of DSO [41]. It is worth mentioning that an *in vitro* analysis of endothelial cell migration by Soh et al. [46] identified that younger ages and intact DM are important factors that may promote cell migration.

Soh et al. [46] found that CEC migrate more efficiently over a denuded but intact DM compared to bare stroma. Similarly, Garcerant et al. [32] described posterior stromal scarring in the edematous zone during the corneal clearance process in slow responders or nonresponders. Therefore, they assumed that surgical trauma of the stroma could induce an unpredictable healing response favoring fibrosis, hence recommending a surgical procedure that avoids stromal contact. They recommend using a peeling technique, to maximize both cell preservation and migration [32], as they observed an increased cell loss in techniques where constant pressure was applied during Descemet's scoring. This theory is supported by Davies et al. [45], who observed that DSO performed with a 360-degree scoring technique resulted in a visually significant stromal scarring, either from the scoring itself or from persistent edema. This group described that all failed cases in healing after DSO shared the 360-degree scoring technique followed by stripping. Nevertheless, all cases that underwent stripping by peeling without scoring cleared successfully [32, 45]. They proposed that manual stripping can result in an irregular DM border that promotes small DM detachments and edema [45]. Macsai and Shiloach [47] recommended attempting a smooth transition edge without any interruptions of subjacent stromal fibers by a slow and steady aspiration using the irrigation/aspiration handpiece connected to the phacoemulsification unit. The DM should be torn in a curvilinear fashion such as the capsulorhexis technique in cataract surgery.

Regarding postoperative visual quality, Garcerant et al. [32] had the following theory explaining irregular astigmatism despite corneal clearance [40]. First, they described central corneal thinning in cases that attained corneal clearance [32, 46]. It is known that any corneal procedure that leads to central corneal thinning may simulate a myopic ablation, and a small or off-centered optic zone may induce higher-order aberrations [32]. It is therefore hypothesized that off-centered descemetorhexis could act as an off-centered optical zone and be the cause of visual disturbances. Thus, it is highly recommended to attempt symmetry and to meticulously center the procedure [32]. Lastly, performing relaxing incisions in DM may possibly have an astigmatic effect [32].

Regarding BCVA, DSO has proven to be successful in some patients: Borkar et al. [41] reported BCVA between −0.12 and 0.00 LogMAR. Davies et al. [45] achieved corneal clearance in 14 (82.4%) eyes, with a corneal edema resolution meantime from 3.14 to 6.17 months. Out of the 14 eyes cleared, 13 eyes achieved a BCVA of 20/25.

Huang et al. [42] compared visual outcomes of 12 DSO with 15 DMEK cases in mild to moderate FED. Although meantime to achieve 20/40 vision was longer for DSO than DMEK cases (2.2 ± 2.8 weeks compared to 7.1 ± 2.7 weeks, respectively), they found no statistical differences in final BCVA with less rate of adverse events in the DSO group. Huang et al. [42] did not provide ECD comparison between the two groups. Therefore, their conclusion [42] of relatively similar results among both DSO and DMEK should be taken cautiously.

As a donor graft is not necessary, the short-term (graft detachment and postoperative elevated intraocular pressure (IOP) due to topical steroid treatment or air bubble placement) and long-term complications (rejection, glaucoma, secondary cataract, potential disease transmission, or infectious keratitis) are reduced. On the other hand, lower postoperative ECD has been reported following this technique [39].

Therefore, despite contradictory outcomes, it may be reasonable to include DSO as a potential technique to treat endothelial disorders, especially for the treatment of central FED. It would be useful in areas with difficult access to donor grafts, in personal circumstances that could force patients to

refuse graft surgery or when side effects of this technique outweigh the benefits. Although longer follow-up studies are needed, a recent retrospective case report of a successful and stable 5-year, bilateral DSO [48] suggested stability in the short term.

2.2. Descemet Membrane Transplantation (DMT). Primary descemetorhexis followed by acellular descemet membrane transplantation (DMT) [49] is a recently introduced technique for FED patients. Although donor tissue is required, no donor CEC are needed for DMT, which majorly increases the donor pool and decreases the risk of rejection. Similar to DSO, it seems to work better with smaller stripped areas that leave peripheral CEC intact (Figure 2).

3. ROCK Inhibitors

RhoA/Rho-kinase (ROCK) intracellular pathway plays a role in actin cytoskeleton regulation and actomyosin contractile forces [50, 51], as well as numerous cellular processes that include cell proliferation (especially cell cycle progression), migration, adhesion, rigidity, morphology, apoptosis, and extracellular matrix reorganization [35, 36, 50–53]. The effect of ROCK pathway signaling seems to be dependent on each type of cell.

ROCK signaling is involved in numerous pathologies such as vascular diseases, cancer, asthma, insulin resistance, renal insufficiency, osteoporosis, neuronal degenerative diseases, and glaucoma [35, 52]. Thus, ROCK inhibitors have been conceived as a therapeutic target for the treatment of several conditions [35, 52].

Regarding glaucoma, ROCK inhibitors alter trabecular meshwork configuration, increasing AH outflow through the trabecular pathway, hence decreasing IOP [43]. Two ROCK inhibitors have been approved for the treatment of ocular hypertension and glaucoma: ripasudil (Glanatec™) and netarsudil (Rhopressa™) [53].

3.1. ROCK Inhibitors and Corneal Endothelium. CEC have proliferative activity *in vitro*, implying that corneal endothelium could proliferate under appropriate conditions [36, 52, 53]. The latest evidence supports that ROCK inhibition stimulates *in vivo* CEC proliferation, as well as cellular migration and apoptosis suppression [35]. Therefore, ROCK signaling modulation could be a potential therapeutic target for the early phase of the corneal endothelial disease [35–37, 52–54].

3.2. Studies in Animals. Okumura et al. [55, 56] reported that ROCK inhibitor Y-27632 increased cellular proliferation *in vitro* of cultivated CEC in primates. Later on, both Koizumi et al. and Okumura et al. [54–56] from the Kinoshita group proved its use in *in vivo* corneal endothelial dysfunction models in rabbits [55, 56] and primates [52]. They demonstrated that topical Y-27632 improved ECD, corneal edema, wound size, and scarring of endothelial wounds. They also confirmed that CEC proliferation in rabbits increased in a dose-dependent pattern after the instillation of Y-27632.

3.3. Studies on Humans. The efficacy of Y-27632 for the treatment of central corneal edema caused by FED has recently been investigated [36, 53, 54]. Koizumi et al. [54] carried out a study observing a stable reduction in central corneal thickness in three out of four eyes after topical Y-27632 application six times a day for one week. Similarly, Okomura et al. [53] found a recovery of corneal transparency in eight patients after being treated with topical Y-27632. These findings suggest that topical Y-27632 could be clinically beneficial for patients with central corneal edema secondary to FED [36, 53].

In both the studies mentioned above [53, 54], there were four cases of diffuse edema related to PBK that did not show a decrease in corneal thickness or any improvement in BCVA, despite the treatment with Y-27632.

Consequently, these findings suggest that topical Y-27632 could be clinically beneficial for patients with central corneal edema caused by FED, with less evidence in PBK [53, 54].

3.4. ROCK Inhibitors Combined with DSO. DSO in combination with topical ROCK inhibitors could improve BCVA results and may obviate or delay EK, therefore optimizing endothelial graft donor availability. Endothelial restoration without donor tissue could reduce higher-order aberrations and dispersion that often reduce BCVA after EK caused by the donor-receptor interface, mainly in DSAEK [47, 57, 58]. Soh et al. [46] found that Y-27632 supplementation may counterbalance the negative effect of older age in CEC migration.

Koizumi et al. [36] were the first to report the resolution of corneal edema caused by FED with the combination of endothelial denudation by transcorneal freezing and topical ROCK inhibitors. Macsai and Shiloach [47] studied the use of ROCK inhibitors in patients with FED with a peripheral corneal reserve >1,000 cells/mm^2 that underwent DSO. In this study, nine patients were treated with ripasudil after DSO and another nine patients only underwent DSO. The use of ripasudil resulted in a faster BCVA recovery, higher central ECD after a year of treatment, and a decrease of peripheral ECD loss. Patients in the control arm showed a reduction in peripheral ECD by 10% after one year of treatment. Interestingly, the treatment arm showed no significant differences in peripheral ECD compared to preoperative values. The fact that the group treated with ripasudil revealed a postoperative ECD equivalent to preoperative ECD supports the concept of peripheral endothelial cell proliferation and/or migration after combining DSO with ripasudil.

DSO combined with ripasudil could imply an economical saving for society, as it does not require donor tissue nor much postoperative care. Moreover, Davies [59] recently observed that netarsudil could be effective in achieving corneal clearance in different cases of endothelial dysfunction that may present in a daily cornea practice, such as

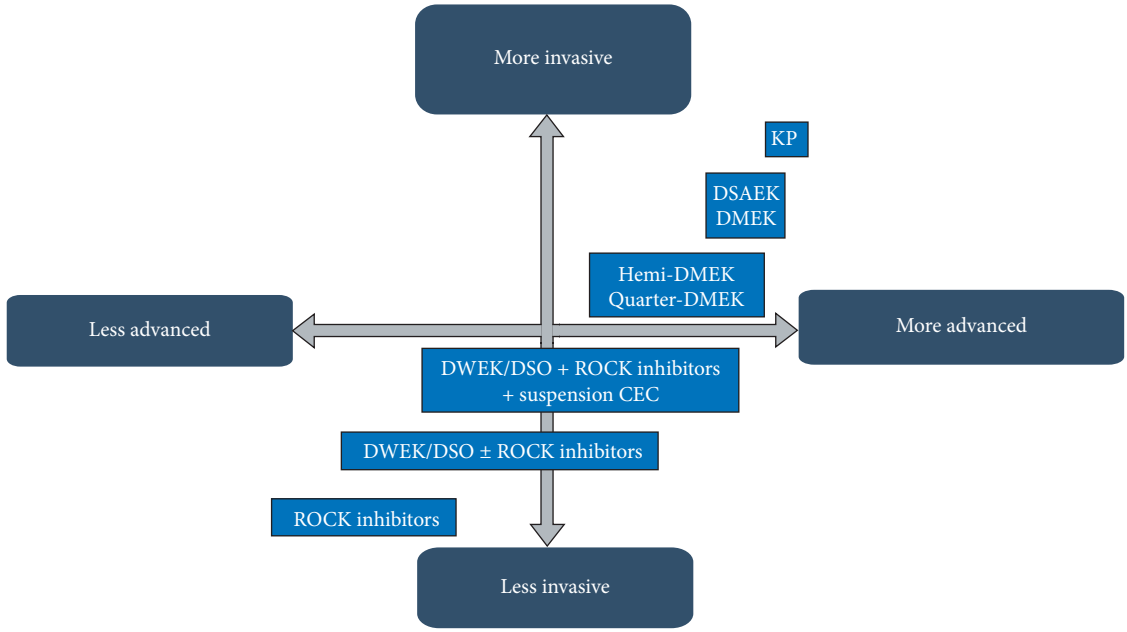


Figure 3: Schematic images of cultivated endothelial corneal cells (CEC) injected in the anterior chamber (AC) therapy. (a) CEC injected with a ROCK inhibitor in the AC; (b) prone position to help in the adherence of the cultivated CEC to the recipient stroma; (c) prone position should be maintained for three hours postoperatively; and (d) regeneration of the corneal endothelium by the injected CEC (based on the article by Okumura et al. [62]).

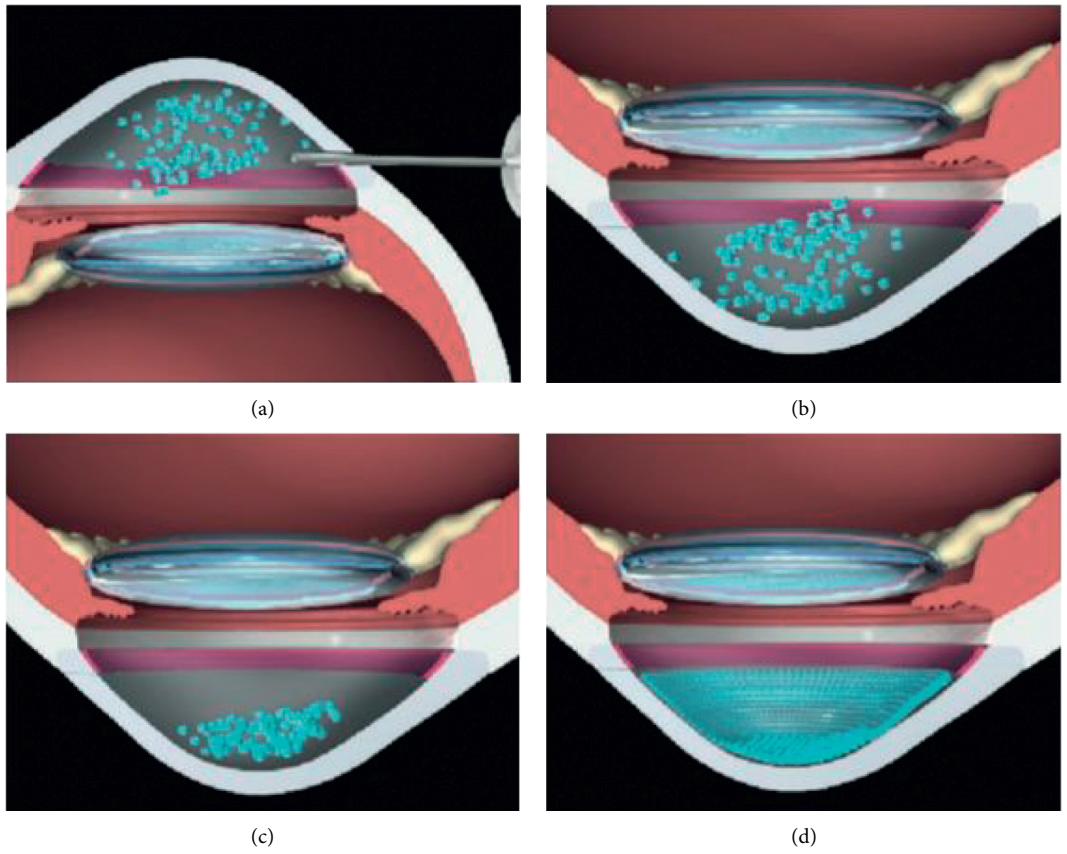
iridocorneal endothelial syndrome, after an early PK graft failure and after a chronic PK graft failure. Likewise, this has recently been verified by Schlötzer-Schrehardt et al. [60] in a large database with an *ex vivo* FECD tissue culture model, where a single dose of ripasudil induced a significant upregulation of genes and proteins related to cell cycle progression, adhesion, and migration of the cellular matrix, as well as increasing the endothelial pump and barrier function up to 72 hours after instillation without inducing adverse phenotypic changes.

3.5. ROCK Inhibitors and Cell Therapy. Tissue engineering has been suggested as a novel therapy that could replace conventional corneal transplantation [61, 62]. There are two possible available strategies to transplant cultivated CEC in receptor corneas: scaffold-based and cell-based [61, 62]. Scaffold-based strategy is based on transplanting cultivated corneal endothelium on a vector plate in a similar procedure to EK [35, 63]. Okumura et al. and Koizumi et al. [53, 63] and other researchers [64–66] have cultivated CEC on specific substrates. Examples of substrates are amniotic membrane [67], DM, human anterior lens capsule [68, 69], and bioengineered matrices composed of compressed collagen [70], gelatin [71, 72], silk-fibroin, and a combination of biopolymers. Subsequently, the resulting CEC sheets have been transplanted in animal models observing corneal clearing. However, these sheets are composed of a fragile single layer of cells and its attachment to the receptor requires a relatively challenging surgical technique [35].

Cell-based strategy is based on injecting cultivated CEC into the AC in the form of cell suspension. Okomura et al. [62] defended that cellular injection has certain advantages. For instance, it is a simple, noninvasive, and easy to prepare procedure. The injected CEC in the AC would not spontaneously attach to the receptor corneal endothelial layer, but ROCK inhibitors are known to improve the adhesion of CEC to a substrate [55]. This led researchers to pioneer animal experiments that proved the safety and efficacy of cultivated CEC injections in combination with ROCK inhibitors [35–37].

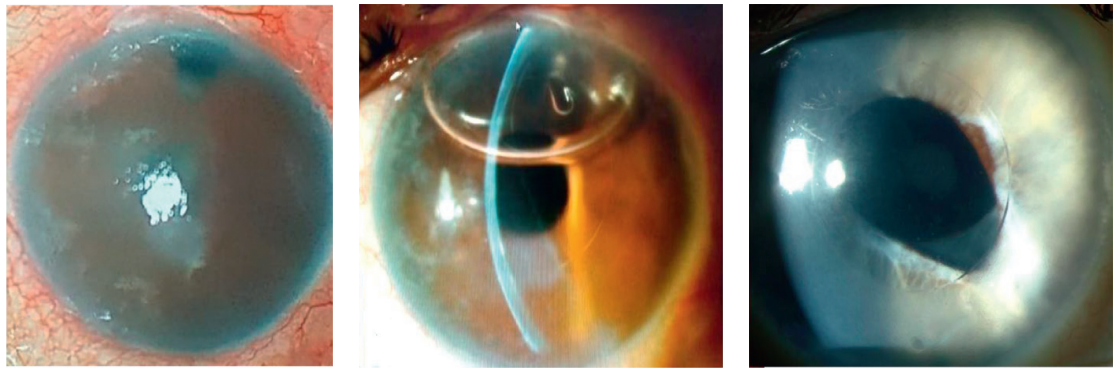
Kinoshita et al. [73] carried out a study on humans with a two-year follow-up. They included 11 patients, seven with FED and the rest with bullous keratopathy (BK) of various causes. A mechanic 8 mm descemetorhexis followed by an injection of cultivated CEC in combination with ROCK inhibitor Y-27632 was performed. After the procedure, the patients rested in a prone position for three hours (Figure 3). After six months, ECD >500 cells/mm^2 was observed in all patients, and 10 out of 11 had an ECD >1,000 cells/mm^2. Regarding visual outcomes, nine out of 11 showed a BCVA equal to or higher than 0.3 LogMAR. Furthermore, 10 out of 11 patients revealed a central corneal thickness <630 μm. Two years after the procedure, all the corneas remained transparent, with an average ECD of 1,534 cells/mm^2, and nine out of 11 patients had a BCVA equal or higher than 0.1 LogMAR.

The authors hypothesized a few concerns, namely, what happened to the CEC that did not attach to the receptor endothelium and whether it could obstruct the trabecular meshwork or lead to iris adhesions. Another concern was that CEC could pass onto the systemic circulation and could potentially cause tumor development. However, according to the



(a) (b) (c) (d)

Figure 4: Future strategies for the treatment of endothelial diseases, from less invasive treatments to more invasive ones (based on the article by Okumura et al. [35]).



(a) (b) (c)

Figure 5: EndoArt® device in the first-in-human trial: (a) corneal edema prior to implantation. (b) The same eye on the first postoperative day. Note the air bubble at the AC that works as a tamponade agent. (c) Another eye several weeks following implantation. The central area corresponding to the implant zone is transparent, whereas the periphery outside the implant borders is edematous.

latest evidence, ROCK inhibitors and cell therapy can effectively be used in both FED and BK patients with optimal results (Figure 4).

Other substances that are currently being investigated for the treatment of endothelial diseases are antioxidants, such as N-acetylcysteine, coenzyme Q-10, sulforaphane [74], RTA-408 [75], and fibroblast growth factors, such as FGF-1 and bioengineered eFGF synthesized by Trefoil™.

4. Gene Therapy

Two types of gene therapy could play an important role in corneal diseases: antisense oligonucleotides (ASO) and prokaryotic clustered regularly interspaced palindromic repeats (CRISPR) [76, 77].

An ASO molecule consists of a small sequence of nucleotide fragments complementary to a specific gene

sequence (messenger RNA, mRNA). In antisense therapy, base pairing between the ASO molecule and mRNA inhibit gene translation hence disabling protein synthesis. The CRISPR are a defense mechanism against virus present in bacteria and archaea. They consist of a palindromic short sequence DNA, originated from the virus that has previously infected these bacteria. These DNA loci are usually associated with Cas genes that code a type of nuclease (enzymes that can split DNA). CRISPR spacers recognize specific sequences and guide Cas nuclease to split and degrade exogenous genic elements [77]. Thus, when a virus attacks a determined bacterium, it interacts with the Cas protein complex bound to the RNA produced by the CRISPR sequence. Then, the viral genetic material gets inactivated, degraded, modified, and integrated in the CRISPR sequence. Ultimately, the defense will be more effective in case of a future contact of the bacteria or its descendants with the affected virus.

The CRISPR/Cas9 system could be used to edit and regulate the genome [78]. A RNA molecule can be designed and inserted in the nucleus, where it recognizes the exact genome location that the Cas9 enzyme must split. Later, a second mechanism allows the split DNA to be repaired, embodying the correct genetic sequence in the exact original site of splitting [78].

Although FED is a heterogenous genetical disease, a major number of patients, especially Caucasians, possess a pathological trinucleotide expansion sequence (typically, cytosine-thymine-guanin (CTG) in the TCF4 gene located in chromosome 18q21) [76, 79]. ASO molecules targeting specific trinucleotide expansion mRNA and CRISPR/Cas9 systems designed to bind to DNA trinucleotide repeated sequences may interrupt these mRNA anomalous repetitions that cause some subtypes of FED, especially in cases of intermediate and short anomalous lengths [76, 80, 81].

Koenig [30] suggested that RNA toxicity contributes to the pathogenesis of FED. Changes in the endothelial barrier function, a known event in the development of FED, were identified as a key biological process influenced by the misplacing events. Moreover, anomalous DNA segments may possibly be directly excised by endonucleases, such as transcription activator-like effector nucleases (TALENS) [82]. These findings support that gene therapy could be effective in treating the genetic defects responsible for some types of FED, therefore changing the phenotype.

Recent studies have managed to administer transcription activators Cas9 molecules in vivo in CEC in rats, stimulating corneal endothelial proliferation and the restoration of normal endothelium after corneal cryotherapy. The latest research suggests that this technique could work on humans by adding additional improvements [83–86].

5. Mechanic Artificial Endothelium

Endothelial dysfunction is manifested by corneal edema caused by endothelial pump malfunction. EndoArt® is a flexible silicon sheet covered with an adhesive substance, that is inserted into the AC and attached to the posterior surface of the cornea by air/gas pneumopexy, similar to a DMEK graft. This silicon sheet prevents the passive inflow of electrolytes and water into the cornea while allowing water evaporation from the corneal surface. Since this is a relatively new concept and device, there are no relevant peer-reviewed studies yet. However, the first experiments in humans after several years of animal studies were recently published in international meetings, showing promising results [87, 88] (Figure 5). This approach may be interesting in patients that cannot undergo EK, as a bridging procedure from diagnosis until EK is available, or even as a substitute to EK altogether. Nevertheless, a prospective, long-term study is needed to verify the promising preliminary results.

6. Conclusion

In the last decades, we have witnessed a true revolution in the treatment of corneal endothelial dysfunction. We have gone from penetrating keratoplasty as a sole therapy for all the corneal diseases, regardless of its origin and localization, to the great advancement that endothelial keratoplasty (EK) has supposed, being descemet stripping automated endothelial keratoplasty (DSAEK) and descemet membrane endothelial keratoplasty (DMEK) its two most exalted examples. The tenacious concept that corneal endothelial cells (CEC) cannot proliferate in vivo has been surpassed in recent years with research findings supporting that peripheral CEC possesses stem cell features. Similarly, many authors have proven that it is technically possible to cultivate and transplant CEC in both animals and humans.

Currently, we are witnessing the development of new techniques and therapies that try to reduce complications derived from EK: descemet stripping only (DSO), ROCK inhibitors, cellular therapy, bioengineered grafts, gene therapy, endothelial regeneration, and artificial endothelial substitutes. These procedures offer a new perspective in the treatment of endothelial dysfunction. Moreover, they contribute to mitigating the scarcity of quality endothelial donor tissue and decreasing the complications derived from the immune rejection of the donor graft, as well as reducing the use of steroid treatment. Although additional randomized prospective peer-reviewed trials are necessary to validate the findings and to confirm the effectiveness and safety of these procedures, the positive results in preliminary clinical studies predict a promising future.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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