Update on the Surgical Management of Fuchs Endothelial Corneal Dystrophy

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ABSTRACT

Fuchs endothelial corneal dystrophy (FECD) is the most common posterior corneal dystrophy and the leading indication for corneal transplantation in the United States. FECD is slowly progressive, and patients develop gradual corneal endothelial decompensation, eventually resulting in failure of the endothelium to maintain corneal deturgescence. Medical management consists of topical hyperosmotic agents to facilitate dehydration of the cornea, but surgical intervention is often required to regain corneal clarity. The surgical management of FECD has evolved over the past two decades as corneal transplantation techniques have allowed for more selective keratoplasty and replacement of only the diseased layers of the cornea. Prior surgical management consisted of penetrating keratoplasty (PK) that carried significant intraoperative risks associated with “open sky” as well as postoperative risks of graft rejection, wound dehiscence, postoperative astigmatism, and prolonged visual rehabilitation. In the past 15 years, endothelial keratoplasty (EK) has become the treatment of choice for endothelial disease, significantly reducing the risks associated with the surgical treatment of FECD. Here we discuss the current surgical management of FECD, including the introduction of Descemet stripping only (DSO), and highlight future investigative efforts.

Keywords: Corneal transplantation; Descemodorhexis; Descemet membrane endothelial keratoplasty; Descemet stripping; Descemet stripping automated endothelial keratoplasty; Fuchs dystrophy

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Key Summary Points

Why carry out this study?
This review summarizes the surgical management of Fuchs endothelial corneal dystrophy (FECD).

What was learned from the study?
The surgical management of FECD has evolved over the past two decades as corneal transplantation techniques have allowed for more selective keratoplasty.
The current preferred surgical management of FECD is endothelial keratoplasty, which carries risks associated with the need for indefinite immunosuppression with topical steroids.

Descemet stripping only (DSO) involves removal of the diseased endothelium and guttae without the placement of any donor graft.

DSO has a very high rate of success, but requires careful patient selection.

INTRODUCTION

Fuchs endothelial corneal dystrophy (FECD), the most common endothelial dystrophy, is the leading indication for corneal transplantation in the United States, accounting for more than one third of the transplants performed in 2019 [1]. In the past decade, corneal transplantation, and specifically the surgical management of FECD, has changed drastically [2]. For many years, the only transplantation option for visually debilitating FECD consisted of penetrating keratoplasty (PK). In 2012, endothelial keratoplasty (EK) surpassed PK as the most commonly performed keratoplasty procedure, and selective keratoplasty became the mainstay of surgical treatment for FECD [1, 3]. While the majority of FECD patients requiring keratoplasty continue to undergo EK, recent findings in the lab and in multiple clinical case series have suggested a role for descemetorhexis without keratoplasty, known as Descemet stripping only (DSO). Here we review the pathogenesis of FECD, compare DSO with EK as treatment options, and highlight future directions for the management of FECD. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

OVERVIEW OF FUCHS ENDOTHELIAL CORNEAL DYSTROPHY

The corneal endothelium is a neural crest-derived monolayer of cells, halted in the G1 phase of the cell cycle and thought to not divide after birth, though in vitro studies have revealed a potential for cell division [4]. The endothelium plays a critical role in corneal homeostasis by maintaining deturgescence, a requirement for corneal transparency. The corneal stroma has a robust capacity to swell [5], which is counteracted by the endothelial cells. As water passively moves into the stroma during the active transport of nutrients, the endothelial cells provide both a passive barrier to excessive aqueous humor influx and maintain an active pump mechanism to transport fluid out of the cornea. Deturgescence requires a sufficient number of endothelial cells, and when the density of corneal endothelial cells drops below about 500 cells/mm², as may occur in FECD, the endothelial pump function fails and the cornea becomes edematous.

At birth, the cornea has the highest density of corneal endothelial cells at about 4000 cells/mm². As the cornea ages, the cell density will decrease to about 2500 cells/mm² in a healthy adult cornea [6]. Because of the limited proliferative potential of the corneal endothelium, cells must migrate to take the place of neighboring cells that are lost due to injury or aging, resulting in decreased cell density, increased variation in cell size, and loss of the typical hexagonal architecture. Despite these changes, normal corneal aging does not typically result in endothelial cell failure leading to edema. However, in diseased states such as in FECD, the number of endothelial cells may drop below the critical density necessary to maintain the endothelial pump function, resulting in a loss of corneal clarity.

The hallmark finding in FECD is the presence of central guttae, excrescences of Descemet membrane (DM), on the posterior cornea. Though guttae may be found in up to 4% of patients, few of them will develop the corneal edema associated with FECD [7]. FECD is slowly
progressive, with clinically apparent guttae usually presenting in the fourth decade of life, and significant reduction in vision requiring intervention often not occurring until decades later. Though visual acuity can remain good even in advanced FECD, glare and diurnal variations in vision may become disabling. The Visual Function and Corneal Health Status instrument (V-FUCHS) is a self-administered questionnaire that can be used in the clinic to effectively measure visual disability in patients with FECD [8]. Guttae may directly degrade vision quality by producing light scatter [9, 10]. In addition to this direct effect on vision, in vitro studies have shown that guttae may create a toxic environment that contributes to endothelial cell loss that may in turn allow for the development of more guttae and promote a cycle of endothelial decompensation [11].

SURGICAL MANAGEMENT FOR FUCHS ENDOTHELIAL CORNEAL DYSTROPHY

Current medical therapy for FECD-related vision loss is limited to decreasing corneal edema with topical hyperosmotic drops and ointment, and often surgical intervention is required to regain corneal clarity. When the only available transplantation option for FECD was PK, the threshold for surgical intervention was high, and patients were followed conservatively until they developed advanced disease. Nearly a century after Zirm performed the first PK in 1905, Melles described a method for transplanting only the posterior layers of the cornea while leaving the host anterior cornea intact [12]. Posterior lamellar keratoplasty (PLK), also termed deep lamellar endothelial keratoplasty (DLEK) [13], involved replacing the host posterior stroma, DM, and endothelium with a donor button through a sclerocorneal incision and has paved the way for modern EK. With EK, the risk of surgical intervention including graft rejection, prolonged visual rehabilitation, infection, and postoperative astigmatism has decreased significantly, and the risk associated with “open sky” is eliminated. Patients are now undergoing transplantation earlier in the disease course, guided by visual symptoms and clinical findings [2].

Descemet Stripping Automated Endothelial Keratoplasty

Descemet stripping automated EK (DSAEK) is the most commonly performed EK in the United States. In DSAEK, a descemetorhexis is performed on the host cornea to remove the diseased endothelium and DM. Typically the descemetorhexis is large (at least 8 mm) but may be smaller depending on surgeon preference. This tissue is then replaced by a donor posterior lamellar button that is approximately 100–200 μm thick and contains endothelium, DM, and a thin layer of stroma. Handling of the transplant graft is facilitated by the attached stromal lamellae, and an air bubble is placed in the anterior chamber to promote graft adherence.

DSAEK, described in its first iteration by Melles et al. in [14] and later modified by Gorovoy [15], represented a major breakthrough in the surgical management of posterior corneal disease. Though graft rejection remains a risk, it is significantly decreased compared to PK [16]. Additionally, visual outcomes are better, though acuity may be limited by the interface between host and donor stroma and posterior corneal higher-order aberrations resulting from graft thickness variations. Visual rehabilitation is quicker than in PK, and there is less risk of postoperative astigmatism. Newer modifications to DSAEK have created thinner grafts. Ultrathin DSAEK (UT-DSAEK) (60–90 μm grafts) and nanothin DSAEK (NT-DSAEK) (grafts 50 μm or thinner) have been shown to have improved visual outcomes with faster visual recovery than standard DSAEK [17–20].

Descemet Membrane Endothelial Keratoplasty

With the development of Descemet membrane endothelial keratoplasty (DMEK) in 2006, Melles et al. again changed the landscape of corneal transplantation [21, 22]. DMEK allows for transplantation of only DM and
endothelium to the host cornea after descemetorhexis, with grafts as thin as 10 μm.

DMEK requires greater surgical skill than DSAEK. Without the adherent stroma, the elastic nature of the tissue causes the graft to fold into a scroll or double scroll, and there is a steep learning curve to developing unfolding techniques. The natural scroll causes the endothelium to face outward, but alternatively the graft may be manipulated to an endothelial-inward trifold configuration [23]. Though this increases the time for graft preparation, it may minimize surgical time and endothelial cell loss. A comparison of grafts inserted in the endothelium-outward scroll or endothelium-inward trifold showed comparable graft failure rates, suggesting that the insertion method ultimately depends on surgeon preference [24].

Other modifications to DMEK include the use of a femtosecond laser to create a more precise descemetorhexis [25], hemi- and quarter-DMEK to increase the availability of donor tissue [26, 27], and eye bank preparation of pre-stripped and preloaded tissue to decrease surgical time. Despite its technical challenges, the number of DMEK procedures has increased each year in the United States, even as the number of DSAEK procedures has decreased [1]. Compared to DSAEK and PK, DMEK has the least risk of graft failure and results in the fastest visual recovery [28, 29].

Descemet Stripping Only

EK has produced favorable outcomes for patients with FECD in the United States; however it is not without risk; and even DMEK carries the possibility of graft rejection if topical corticosteroid immunosuppression is stopped [30–32]. Additionally, there remains a worldwide shortage of donor corneas for transplantation procedures. For these reasons, there is an interest in developing a treatment for FECD that does not require placement of a graft.

The endothelium of patients with FECD may be capable of self-regeneration. Ex vivo studies of human corneal buttons have shown that endothelial cells, even those from older donors, retain the ability to undergo mitosis [6]. Further, peripheral endothelial cells appear to have a higher potential for mitotic activity [6]. Clinically, numerous reports of inadvertent loss of endothelium and DM in patients with FECD have resulted in spontaneous resolution of corneal edema [33–43].

Encouraged by these findings, Borkar et al. published a case series of FECD patients managed with deliberate Descemet stripping only (DSO) [44]. DSO involves creating a small (4–5 mm) descemetorhexis to remove the diseased endothelium and guttae without the placement of any donor graft. In this series of 13 eyes in 11 patients, ten eyes had restoration of corneal clarity and at least 20/20 vision in all eyes without macular pathology. The remaining three patients underwent subsequent uneventful DMEK that resulted in corneal clearing [45].

Review of this and other case series may reveal why DSO is an effective treatment for some, but not all, FECD patients [46, 47]. Advanced disease appears to have a poor prognosis for corneal clearing with DSO. Patients with pachymetry greater than 625 μm had a reduced rate of corneal clearance [44]. The presence of guttae extending into the periphery of the cornea may also reduce the likelihood of successful DSO, as there is an observed trend that a larger descemetorhexis is more likely to have prolonged corneal clearing or fail to clear without subsequent EK. Given that the peripheral endothelial cells need to repopulate the central denuded cornea, there is likely a limit to the area that they are able to cover. Overall, multiple recent case series of DSO with careful patient selection have shown excellent success, with corneal clearing in up to 100% of patients [48–50].

ADVANTAGES OF DESCEMET STRIPPING ONLY

There are many advantages to performing DSO as the primary surgery in the management of FECD. The absence of a donor tissue obviates the need for indefinite immunosuppression with topical steroids to prevent graft rejection. It also provides a possible surgical procedure in regions where there is a shortage of donor
corneas. Unlike DMEK, which is a technically difficult surgery with a steep learning curve, DSO is a relatively simple procedure that utilizes techniques well known to corneal surgeons.

**DISADVANTAGES OF DESCemet STRIPPING ONLY**

The optimal patient for DSO is still unknown. DSO requires a healthy population of peripheral endothelial cells, and is therefore unlikely to be successful in the setting of advanced FECD with peripheral guttae and decreased peripheral endothelial cell density. A peripheral endothelial cell count lower than 1800 cells/mm² has been shown to be associated with a lack of corneal clearance following DSO [51]. DSO is only suited to FECD, where disease starts centrally and is related to endothelial dysfunction, in contrast to other causes for endothelial decompensation, such as pseudophakic bullous keratopathy (PBK) that causes endothelial depletion affecting the entire endothelial layer including the periphery. Because DSO does not replace the endothelium at the time of surgery, there is a longer visual recovery while the endothelium repopulates enough to maintain corneal deturgescence. In contrast, DMEK demonstrates significantly faster corneal clearance and would likely be more appropriate in a patient who cannot tolerate extended periods of decreased vision. Patients need to be counseled that, if the cornea fails to clear after DSO, they may require an EK. As DSO is a newer procedure, long-term follow-up is limited. Recently published 5-year data showed sustained corneal clarity and visual acuity [52]; however, further studies will be needed to determine the long-term viability of the procedure, specifically the risk of late endothelial cell loss and delayed failure.

**FUTURE DIRECTIONS**

Patients fall into three categories after DSO: rapid responders, slow responders, and nonresponders. While case series suggest that lack of peripheral endothelial reserve, the size of the descemetorhexis, and the preoperative pachymetry may be predictive of corneal clearance after DSO, more work is needed to determine the optimal patients for DSO [51].

Recently, the use of topical Rho-associated kinase (ROCK) inhibitors, used in the treatment of glaucoma, has shown promise as an adjunctive therapy to DSO. ROCK inhibitors have been shown to hasten corneal clearance in animal studies, and have been used for the treatment of FECD in conjunction with endothelial removal with a cryoprobe in four patients [53, 54]. The use of a ROCK inhibitor after DSO was able to rescue two slow responders [48], and has been shown to increase cell density and hasten corneal clearance when compared to DSO without ROCK inhibitor therapy [50].

Current randomized, placebo-controlled studies aimed at investigating the use of ROCK inhibitors after DSO are underway. ROCK inhibitors are also being evaluated in the absence of DSO to determine whether there is any potential for corneal clearance with medical therapy alone, though the current understanding of the pathogenesis of FECD suggests that this may have limited utility.

There have been exciting advancements in the use of cultured endothelial cells for corneal disease. In animal studies, cells cultured from a donor corneal endothelium have been shown to self-organize and function normally when injected, in conjunction with a ROCK inhibitor, into the anterior chamber [55]. Recently, intracameral injection of cultured endothelial cells supplemented with a ROCK inhibitor was shown to successfully treat PBK, resulting in sustained corneal clarity and improved visual acuity 2 years after treatment [56]. No allogeneic rejection has been observed.

**CONCLUSIONS**

FECD is the most common endothelial dystrophy and the leading indication for corneal transplantation in the United States. Medical treatment of FECD is limited to topical hyperosmotic agents, and with the excellent risk–benefit profile of modern corneal transplantation, patients often elect to undergo...
surgical intervention when FECD becomes visually debilitating (Table 1).

The current preferred surgical management of FECD is EK, which has shown excellent rates of corneal clearance. Though the rate of graft rejection in EK, particularly in DMEK, is low, there remains a risk of rejection with discontinuation of a topical corticosteroid. DSO is a technically simple and effective means of treating FECD without the need for donor tissue. This low-risk procedure can be performed in combination with cataract surgery. Recent studies have shown increased success of DSO when an adjunctive topical ROCK inhibitor is used. Continued research into the use of ROCK inhibitors following DSO is underway, and determination of the optimal patient characteristics for successful DSO warrants further investigation.

### Table 1 Surgical techniques for the management of Fuchs endothelial corneal dystrophy

| Technique | Advantages | Disadvantages |
|-----------|------------|---------------|
| DSAEK     | Eliminates ‘open sky’ risk compared to PK | Requires indefinite immunosuppression |
|           | Less postoperative astigmatism than PK | Acuity may be limited by host–donor stroma interface and higher-order aberrations |
| DMEK      | Improved visual outcomes | Technically difficult to perform |
|           | Fastest corneal clearance | Graft rejection remains a risk |
| DSO       | No introduction of donor tissue | Requires careful patient selection |
|           | Technically simple to perform | Long-term viability studies are ongoing |

**DSAEK** descemet stripping automated endothelial keratoplasty, **DMEK** descemet membrane endothelial keratoplasty, **DSO** descemet stripping only, **PK** penetrating keratoplasty

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