

Fuchs Endothelial Dystrophy: Pathogenesis and Management

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Core Messages

- Fuchs endothelial dystrophy (FED) is a progressive disorder of the corneal endothelium with accumulation of focal excrescences called guttae and thickening of Descemet's membrane, leading to stromal edema and loss of vision
- The inheritance of FED is autosomal dominant, with modifiers such as increased prevalence in the elderly and in females
- Corneal endothelial cells are the major "pump" cells of the cornea that allow for stromal clarity
- Descemet's membrane is grossly thickened in FED, with accumulation of abnormal wide-spaced collagen and numerous guttae
- Corneal endothelial cells in end-stage FED are reduced in number and appear attenuated, causing progressive stromal edema
- Symptoms include visual blurring predominantly in the morning with stromal and epithelial edema from relatively low tear film osmolality
- FED can be classified into four stages, from early signs of guttae formation to end-stage subepithelial scarring
- Diagnosis is made by biomicroscopic examination; other modalities, such as corneal pachymetry, confocal microscopy, and specular microscopy can be used in conjunction
- Exact pathogenesis is unknown, but possible factors include endothelial cell apoptosis, sex hormones, inflammation, and aqueous humor flow and composition
- Mutations in collagen VIII, a major component of Descemet's membrane secreted by endothelial cells, have been linked to FED
- Medical management includes topical hypertonic saline, the use of a hairdryer to dehydrate the precorneal tear film, and therapeutic soft contact lenses
- Definitive treatment is surgical in the form of penetrating keratoplasty (PK)
- New surgical modalities such as various forms of endothelial keratoplasty are gaining popularity in the treatment of FED
- DLEK and DSEK avoid the surgical complications of PK, such as wound dehiscence, suture breakage/infection and high postoperative astigmatism
- Future directions in the treatment of FED include gene or cell therapy and continued advances in endothelial keratoplasty

1.1 Introduction

Fuchs endothelial dystrophy (FED) is a primary, progressive disorder of the corneal endothelium that results in corneal edema and loss of vision. The initial stages of FED typically begin in the fifth through seventh decades of life and are characterized by progressive accumulation of focal excrescences, termed “guttae,” and thickening of Descemet’s membrane, a collagen-rich layer secreted by endothelial cells. Eventually, there is loss of endothelial cell density and functionality as the “pump” of the cornea, causing vision-threatening corneal edema. Although corneal guttae are not pathognomonic for FED, the development of stromal edema defines this disorder.

1.2 Historical Perspective

In 1902 Ernst Fuchs initially described the disorder that would later bear his name, and he postulated that this disease of the elderly was related to changes in the posterior cornea that allowed for increased fluid movement from the aqueous into the corneal stroma [11]. He later published a case series of 13 patients with FED in which he suggested pathologic involvement of both the endothelial and epithelial corneal layers [12]. After the introduction of the slit-lamp biomicroscope in 1911, Vogt was the first to report detailed biomicroscopic observations of FED and coined the term “cornea guttata,” in reference to focal excrescences on the endothelial surface, which when confluent, resembled beaten bronze [58]. The natural progression of FED from isolated, asymptomatic guttae to the formation of corneal edema with painful loss of vision was first noted in 1953 [53]. These and other important observations led to the understanding of FED as a primary disease of the corneal endothelium with secondary involvement of the other layers of the cornea.

1.3 Epidemiology and Inheritance

The prevalence of FED is difficult to estimate given its later onset, slow progression, and lack

of symptoms in the early stages. Furthermore, mild guttae can occur in normal individuals in such conditions as aging, ocular trauma, ocular inflammation, and glaucoma. In a large study of 2002 normal individuals, Lorenzetti et al. found scattered central guttae in 0.18% of eyes in those between the ages of 20 and 39, and in 3.9% of eyes in those above 40 years of age [33]. Despite the lack of an accurate estimate of the prevalence of FED, it remains one of the most common indications for corneal transplantation, accounting for up to 29% of cases [1].

Fuchs endothelial dystrophy can be either sporadic or hereditary. In hereditary cases, the inheritance of FED has been demonstrated to be autosomal dominant, with penetrance as high as 100% [10, 35]. In a large study of 228 relatives from 64 pedigrees with FED, Krachmer et al. observed that 38% of first-degree relatives over 40 years of age were affected, suggesting autosomal dominant inheritance with possible genetic or environmental modifiers [30]. Some studies, including Fuchs’ original case series, also report an increased prevalence and severity in female patients [12, 30, 49]. This may reflect a possible recruitment bias or a physiologic effect of sex hormones on corneal endothelial cell function and survival [1, 62]. The incidence of FED has been reported to be similar among white and black patients, and much lower in Japanese individuals [17]. Central corneal guttae have been reported in Japanese individuals and significant vision loss is rare in these patients [29].

Summary for the Clinician

- Corneal guttae can be present in non-affected individuals and are associated with conditions such as aging, inflammation, trauma, and glaucoma
- Fuchs endothelial dystrophy is defined as the accumulation of corneal guttae with stromal edema
- Inheritance of FED is autosomal dominant, but sporadic forms can occur

1.4 Pathology

The corneal endothelium is a neural crest-derived cellular monolayer that utilizes an ATP-dependent pump to maintain physiologic stromal hydration necessary for corneal clarity [13, 61]. Corneal endothelial cells in humans do not normally proliferate in vivo [25, 26]. Corneal endothelial cells are normally lost throughout life at an estimated rate of 0.6% per year, although higher rates of cell loss occur in the settings of trauma (both surgical and nonsurgical) and primary endotheliopathies [3, 7]. Corneal endothelial cell loss is compensated for through flattening and enlargement of remaining cells without cell division in order to maintain a continuous monolayer [61].

The corneal endothelial cells in end-stage FED are reduced in number and appear thinned with attenuated nuclei, as seen by light microscopy (Fig. 1.1) [17]. With scanning electron microscopy, corneal endothelial cells show evidence of degeneration with large vacuoles and swollen organelles with disrupted membranes [17]. Corneal endothelial cells also demonstrate dilated sacs of endoplasmic reticulum filled with a finely granular material along with a marked increase in cytoplasmic filaments and ribosomes, suggesting transformation to a fibroblastic cell type [17, 20, 62].

Normal corneal endothelial cells produce Descemet's membrane, beginning in utero and continuing throughout postnatal life [34]. Histologically and ultrastructurally, Descemet's membrane consists of an anterior "banded" zone subjacent to the corneal stroma and containing 110 nm of banded collagen and a posterior "non-banded" zone that lies anterior to the corneal endothelium [62]. At birth, the thickness of the anterior banded zone is approximately 3 μm , and this varies little throughout life [62]. In contrast, the thickness of the posterior nonbanded zone increases from approximately 3 μm at age 20 to 10 μm at age 80 [9], reflecting the ongoing synthesis and deposition of Descemet's membrane by the corneal endothelium [22].

Normal Descemet's membrane contains collagen IV, collagen VIII, fibronectin, entactin, laminin, and perlecan [31, 32]. The supramolecular structure of Descemet's membrane resembles

stacks of hexagonal lattices arranged parallel to the surface of the membrane [52]. Monoclonal antibody analysis has shown the lattice array of Descemet's membrane to be composed of collagen VIII, a nonfibrillar short chain collagen [50, 52].

The abnormalities of Descemet's membrane are a striking feature of FED. Descemet's membrane is invariably thickened in FED up to 20 μm or greater [62]. Thickened Descemet's membrane also contains numerous focal excrescences (guttae) along its posterior surface (Fig. 1.2a).

Descemet's membrane also differs strikingly from normal on electron microscopy. In addition to a relatively normal anterior banded zone produced in fetal life, the posterior nonbanded zone of Descemet's membrane is attenuated or absent in FED and is replaced by a markedly thickened posterior collagenous layer with an average thickness of 16.6 μm (Fig. 1.3a) [7, 20]. The posterior collagenous layer is characterized by a diffuse, granular banding pattern, focal posterior guttae, and the accumulation of spindle-shaped bundles with 110-nm collagen banding, known as wide-spaced collagen (Fig. 1.3b) [7]. The composition of wide-spaced collagen in the posterior collagenous layer of FED corneas was shown by immunoelectron microscopy to be collagen VIII [31].

Summary for the Clinician

- Corneal endothelium is a monolayer of cells that acts as the major pump to de-turgesce the cornea and ensure clarity
- There is a normal attrition rate of endothelial cells of 0.6% per year; the rate is accelerated in FED
- Normal endothelial cells produce Descemet's membrane, made up of an anterior banded zone and posterior non-banded zone, the latter of which expands with age
- In FED, Descemet's membrane is abnormally thickened, with attenuation or absence of the posterior nonbanded zone and replacement with abnormal collagen, known as wide-spaced collagen

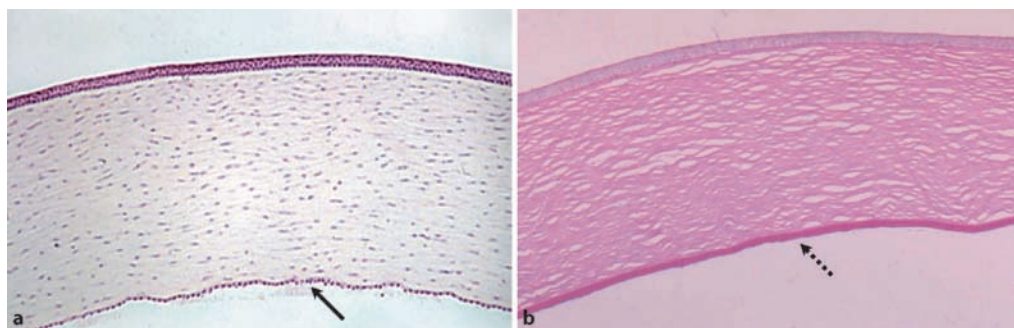


Fig. 1.1 **a** Light microscopy section of a normal human cornea. Note numerous endothelial cell nuclei lining the posterior surface (*arrow*). **b** Light microscopy section of FED cornea. Note the markedly thickened Descemet's membrane and the absence of endothelial cell nuclei on the posterior surface (*dashed arrow*). (Photos courtesy of W. Richard Green, M.D.)

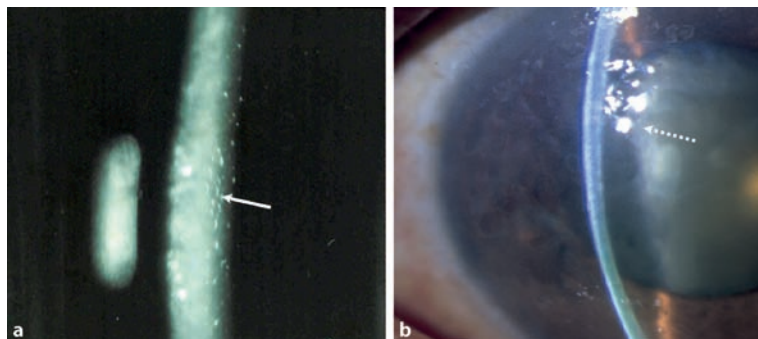


Fig. 1.2 **a** Slit-lamp biomicroscopy of stage I Fuchs endothelial dystrophy (FED; see Table 1.1). Note scattered, punctate, refractile endothelial guttae to the left of the *arrow*. **b** Stage III FED. Note thickening of the cornea, with the irregular surface and epithelial bullae indicated by scattered surface reflection (*dashed arrow*). (Photos courtesy of Walter J. Stark, M.D.)

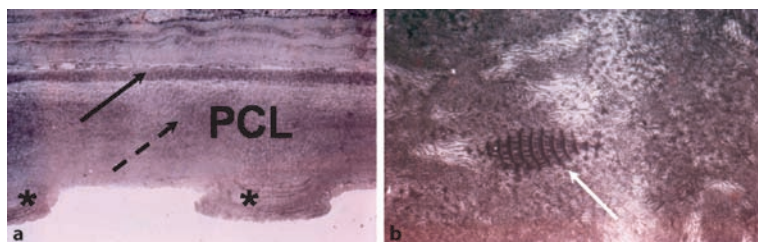


Fig. 1.3 **a** Low power electron micrograph of Descemet's membrane from a FED patient. Note the normal anterior banded zone (*arrow*), the markedly thickened and diffusely banded posterior collagenous zone (PCL; *dashed arrow*), and the focal posterior excrescences (guttae, *asterisks*). **b** High-power electron micrograph of PCL showing a spindle-shaped bundle with 110-nm collagen banding (wide-spaced collagen, *white arrow*). (Photos courtesy of W. Richard Green, M.D.)

1.5 Clinical Findings

The earliest clinical signs of FED include few (<10), central, focal excrescences (guttae) of Descemet's membrane (Fig. 1.2a). Over decades, accumulation of guttae coincides with the normal, gradual attrition of corneal endothelial cells occurring throughout postnatal life. Normal adult central corneal endothelial cell density is approximately 2,500 cells/mm², and a density of approximately 500–1,000 cells/mm² is the minimum threshold for physiologic corneal deturgescence. Once this threshold is crossed, corneal edema occurs, resulting in loss of vision and pain due to formation of epithelial bullae (Fig. 1.2b).

The clinical course of FED can be divided into four stages (Table 1.1) [1]. Stage I is characterized by biomicroscopic evidence of central corneal guttae, with a possibly thickened, grayish Descemet's membrane (Fig. 1.2a). At this stage, the patient is asymptomatic. In stage II disease, the vision may be predominantly blurred in the morning because of decreased tear evaporation, which lowers tear film osmolality when the eyes are closed [36]. Stromal and epithelial edema is notable on biomicroscopy. Stage III and IV disease are characterized by the presence of epithelial bullae, which cause pain upon rupture (Fig. 1.2b). Stage IV is distinguished by the presence of subepithelial scar tissue, resulting in further worsening of visual acuity, but relief from pain.

The diagnosis of FED is made principally on the basis of the biomicroscopic examination. Other modalities that have been used in conjunction with slit-lamp biomicroscopy include corneal pachymetry, confocal microscopy, and noncontact specular microscopy. Corneal pachymetry measures are of limited utility given the wide variation in corneal thickness of normal individuals. The greatest utility of pachymetry is in the consideration of penetrating keratoplasty (PK) in known or suspected FED patients being evaluated for cataract surgery (see Sect. 1.8).

Confocal microscopy and noncontact specular microscopy rely on slightly different methods of light emission and different patterns of light reflection at the interface between Descemet's membrane and corneal endothelial cells. The absence of corneal endothelial cells adjacent to and overlying guttae leads to transmission of light without reflection in these areas. Corneal endothelial cells (Fig. 1.4a) and corneal guttae (Fig. 1.4b) can be easily demonstrated with confocal microscopy. Both confocal and specular microscopy can aid in demonstrating corneal endothelial cell polymorphism and pleomorphism, as well as measuring endothelial cell density. These characteristics have potential clinical and research applications as markers of disease progression.

Confocal microscopy is superior to specular microscopy for evaluating the corneal endothelial layer in the setting of corneal stromal edema [8, 16]. However, the benefits of specular mi-

Table 1.1 Clinical stages of Fuchs endothelial dystrophy^a

Stage	Symptoms	Clinical findings	Visual acuity
Stage I	No symptoms	Few to moderate corneal guttae	Normal (20/20)
Stage II	Mild to moderate loss of vision, no pain	Moderate to numerous corneal guttae, mild corneal edema	Mild to moderate reduction (20/20 to 20/80)
Stage III	Moderate to severe loss of vision and pain	Confluent corneal guttae, moderate to severe corneal edema, epithelial bullae	Moderate to severe reduction (20/100 to 20/400)
Stage IV	Severe loss of vision, reduced pain	Subepithelial scar, fewer epithelial bullae	Severe reduction (20/400 or worse)

^aAdapted from [1].

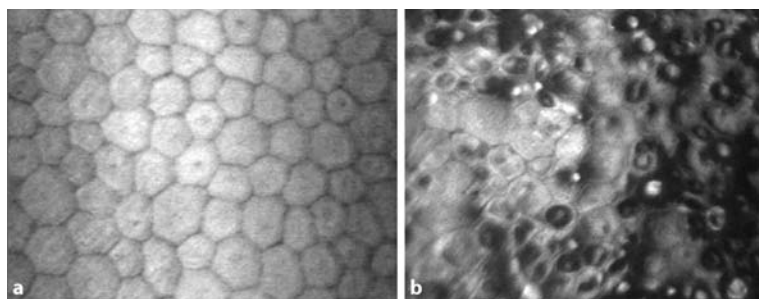


Fig. 1.4 **a** In vivo confocal microscopy image of normal corneal endothelial cells (CECs). Note ordered, hexagonal array of cells. **b** Confocal microscopy image of CECs in FED. Note the numerous excrescences (guttae) of Descemet's membrane as well as the irregular size and shape of the cells

croscopy over confocal microscopy include its relative cost-effectiveness and its ease of use [8]. Neither modality is effective in cases of extreme corneal edema or stromal opacity [16]. In addition, the utility of these auxiliary tests in the diagnosis of FED is primarily in unusual cases, as the diagnosis can usually be made on the basis of slit-lamp biomicroscopy.

Summary for the Clinician

- Diagnosis of FED is primarily made by the appearance of guttae with or without corneal edema on biomicroscopy
- Fuchs endothelial dystrophy can be classified into four stages: (I) presence of subclinical central guttae; (II) presence of stromal and epithelial edema; (III) presence of epithelial bullae; (IV) presence of subepithelial scarring

1.6 Pathophysiology and Genetics

Studies of FED have been predominantly limited to end-stage corneas because milder cases are asymptomatic and therefore less readily available for clinicopathologic correlation. Many of the observations likely reflect complex secondary changes occurring as a result of corneal endothelial cell decompensation. Furthermore, initiating events are largely unexplored, and virtually no

information exists about early cellular and extracellular matrix changes leading to corneal endothelial cell loss.

Using scanning fluorophotometry, Wilson et al. demonstrated a decreased endothelial pump rate in corneas with advanced FED [63]. McCartney et al. demonstrated a decline in the density of ATPase pump sites in the basolateral corneal endothelial cell membranes [39]. Nucleus labeling, transmission electron microscopy, and TUNEL assays were used to demonstrate apoptosis in corneal endothelial cells of advanced stage FED corneas [6]. Serial analysis of gene expression studies of FED corneal endothelial cells demonstrated decreased transcripts related to apoptosis defense and mitochondrial energy production [14]. Whether corneal endothelial cell apoptosis is primary in the pathogenesis of FED or secondary to an abnormality of the basement membrane remains to be elucidated. Other proposed factors with unclear relevance include fibrinogen/fibrin, reduced sulfur content and increased calcium of Descemet's membrane, aqueous humor flow/composition, sex hormones, and inflammation [5].

To date, only mutations in the $\alpha 2$ collagen VIII (COL8A2) gene have been identified as causing FED [4, 15]. Biswas et al. performed genetic linkage analysis of a pedigree with three affected generations and identified an FED locus on chromosome 1p34.2-p32. DNA sequencing revealed a mutation in the COL8A2 gene resulting in a substitution of glutamine with lysine at amino acid 455 (Q455K). This

mutation cosegregated with FED in this pedigree and was absent in 244 ethnically matched control individuals [4]. The COL8A2 gene was sequenced in 115 additional unrelated FED patients, with a total of 8 individuals demonstrating mutations in the COL8A2 gene [4]. Gottsch et al. performed genetic linkage analysis in a large early-onset FED pedigree originally described by Magovern [35] and identified a second point mutation in COL8A2 at amino acid 450, resulting in a substitution of leucine with tryptophan (L450W) [15]. In contrast to common FED, members of this pedigree had an earlier onset of disease with children as young as 3 years of age affected and with distinct features such as a fine, patchy distribution of guttae.

Collagen VIII is a major component of normal Descemet's membrane and forms the abnormally thick posterior collagenous layer in FED corneas. Furthermore, the characteristic aggregates of wide-spaced collagen in Descemet's membrane of FED consist of collagen VIII [31]. Based on the implied functional effects of these mutations, one pathophysiologic hypothesis is that amino acid substitutions reduce the turnover of COL8A2, resulting in the abnormal accumulation of collagen VIII and abnormalities of Descemet's membrane. These abnormalities eventually become incompatible with endothelial cell function and survival, resulting in apoptosis. If this model proves accurate, additional candidate genes for FED could include other protein constituents of Descemet's membrane. To date, however, no published reports have associated mutations in these genes with FED.

Alternatively, the accumulation of collagen VIII in FED may occur as a secondary response to another primary insult to the endothelium. This possibility is consistent with the observation that a posterior collagenous layer of Descemet's membrane, presumably composed of collagen VIII, is present in other hereditary and acquired diseases of the corneal endothelium [23, 31, 38, 48]. Thus, a more complex relationship may exist between corneal endothelial cell dysfunction and abnormal accumulations of collagenous material in Descemet's membrane [15, 31].

Summary for the Clinician

- The pathogenesis of FED is unclear. Possible factors include sex hormones, inflammation, and endothelial cell apoptosis
- Collagen VIII is a major component of Descemet's membrane and is secreted by healthy and pathologic corneal endothelial cells
- Mutations in collagen VIII have been linked to FED

1.7 Differential Diagnosis

The diagnosis of FED is based on clinical findings, mainly slit-lamp biomicroscopy. Distinguishing FED from other entities is important because the diagnosis has implications for treatment and prognosis of both patients and their family members. Other entities that must be differentiated from FED include other posterior dystrophies, including posterior polymorphous dystrophy. In this autosomal dominant condition, groups of small round vesicles are found at the level of the endothelium, interspersed with sheets of gray material within Descemet's membrane [60]. This condition is not generally associated with stromal or epithelial edema or corneal guttae.

Another form of endothelial dystrophy, congenital hereditary endothelial dystrophy, is present at birth or early in postnatal life and is characterized by edema of the entire cornea and severe visual impairment [60]. Hassall-Henle bodies have the same appearance as guttae, but are located only in the peripheral cornea and are not associated with progressive visual loss or corneal edema [23]. Aphakic and pseudophakic bullous keratopathies are caused by endothelial cell dysfunction related to trauma during or after cataract extraction and presuppose a normal corneal endothelium prior to cataract extraction [23]. Inflammatory diseases, such as anterior uveitis or interstitial keratitis, may be mistaken for FED and can be differentiated by resolution of keratic precipitates with proper treatment in the case of anterior uveitis, or on the basis of se-

rologic testing for syphilis in the case of interstitial keratitis [59].

1.8 Management

1.8.1 Medical

Early treatment modalities are not specific for FED, but are commonly applied to all etiologies of corneal epithelial and stromal edema. These approaches involve artificially raising the osmolality of the tear film and include hypertonic saline solutions and ointments, as well as the use of a hairdryer in the morning to dehydrate the precorneal tear film [62]. The use of therapeutic soft contact lenses may help in relieving the pain from recurrent epithelial erosions, while decreasing irregular astigmatism in cases that have progressed to bullous keratopathy [62]. The use of cycloplegics and nonsteroidal anti-inflammatory agents may also aid in diminishing corneal pain from bullous keratopathy. The use of intraocular pressure-lowering medications may reduce corneal edema in patients with elevated or even normal intraocular pressure [1].

1.8.2 Surgical

If conservative management options do not provide adequate clarity of the visual axis or alleviation of discomfort or pain, surgical options may be considered [37]. PK has been regarded as the definitive procedure in patients with corneal decompensation due to FED. In one study of PK in patients with FED, the proportion of patients with visual acuity of 20/40 or better was 50% at 3 months postoperatively, and increased to 80% by 24 months [47]. The authors attribute this improvement over time to corneal healing, suture removal, and fitting of rigid contact lenses. A 10-year follow-up study of 908 patients who underwent PK for FED found a graft survival rate of 97% at 5 years and 90% at 10 years [56]. The most common cause of graft failure in these patients was endothelial rejection, followed by non-immunologic endothelial failure. Uncorrectable irregular astigmatism was another leading cause of poor postoperative visual acuity. Others have

reported graft survival rates of 89% at a mean follow-up of 8.4 years [44], and 81% after 10 years' follow-up [18] in patients with FED.

However, visual function after PK may not be dramatically improved, as one study found 42% of patients who had undergone corneal transplant for FED had visual acuities of worse than 20/200 at an average of 50 months after surgery [42]. The disparity between these results suggests that outcomes may be operator-dependent, and surgeons with more experience tend to have better results [57].

Because many patients with FED and corneal decompensation also have cataracts, attention has turned toward combined versus staged surgical management of the cataract and cornea. It has been suggested that combined procedures in the hands of an experienced surgeon have the same outcome as staged procedures with PK preceding cataract extraction [2]. The American Academy of Ophthalmology suggests that corneal thickness measurements greater than 600 μm portend a poor prognosis following cataract surgery and recommends consideration of combined cataract extraction and PK in these patients [21]. However, in the hands of a skilled surgeon, one study suggests that cataract extraction may be safely performed in patients with corneal thickness measurements up to 640 μm [51].

New posterior lamellar techniques to selectively replace diseased endothelium, as in FED, have been developed and are gaining popularity over traditional PK. In 1998, Melles described "posterior lamellar keratoplasty," or PLK, which consisted of manually dissecting both recipient and donor tissues at 80–90% stromal depth and transplanting the donor posterior lamellar disc through a scleral incision [40]. This technique was later modified and popularized as deep lamellar endothelial keratoplasty (DLEK) by Terry and Ousley [54].

Deep lamellar endothelial keratoplasty has the advantage over PK of being a "sutureless" technique, thereby avoiding the potential infectious and refractive complications associated with sutures. This technique also has the advantage of maintaining the tensile strength of the cornea, which is not possible with PK. The largest disadvantage of DLEK is its technical difficulty, even for highly-experienced anterior segment sur-

geons, and the potential media opacity created by irregularities in the lamellar dissection stage of the procedure. Early results of DLEK are encouraging, with mean best corrected visual acuities of 20/46 and 20/50 and mean average astigmatism of 1.34 and 2.3 D at 6 and 12 months respectively [43, 55].

More recently, Descemet's stripping with endothelial keratoplasty, or DSEK, has been developed, which eliminates the need to perform the recipient lamellar dissection and posterior button excision in DLEK. DSEK replaces the sometimes laborious lamellar dissection of the recipient cornea by simply stripping Descemet's membrane and endothelium, a maneuver first introduced in 2004 by Melles et al. [41]. The folded donor posterior lamellar button is then inserted into the recipient anterior chamber and allowed to unfold adjacent to the bare stromal surface, while maintaining the proper endothelial orientation. An intracameral air bubble is placed to promote

attachment of the disc to the recipient stromal bed, and the patient is maintained in the supine position postoperatively. With attachment of the donor posterior lamellar disc, the donor endothelial cells deturgesce the recipient stroma and epithelium, allowing for a clear cornea (Fig. 1.5). Anterior chamber optical coherence tomography (AC-OCT) can be utilized to demonstrate attachment of the donor posterior disc (Fig. 1.6).

Initially, the donor lamellar button for DSEK was created with manual lamellar dissection. Recently, however, preparation of the donor endothelial button has been simplified by use of an automated microkeratome to cut the corneal button mounted on an artificial chamber. This variation has been termed Descemet's stripping with automated endothelial keratoplasty (DSAEK). However, the terms DSEK and DSAEK have generally become interchangeable, as use of the automated microkeratome for donor button preparation has gained popularity.

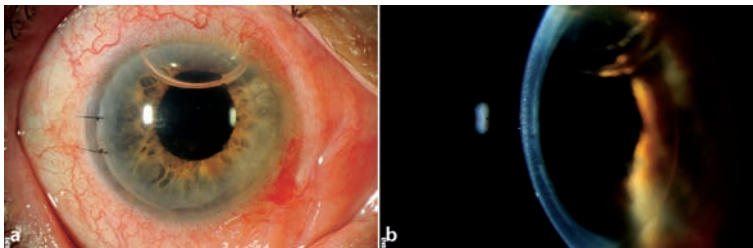


Fig. 1.5 **a** Slit-lamp examination of a cornea after Descemet's stripping with endothelial keratoplasty (DSEK) shows a clear stroma with a remaining air bubble that resolves postoperatively. **b** Slit-lamp beam shows thinning of the recipient stroma with an attached donor posterior disc. (Photos courtesy of William W. Culbertson, M.D.)

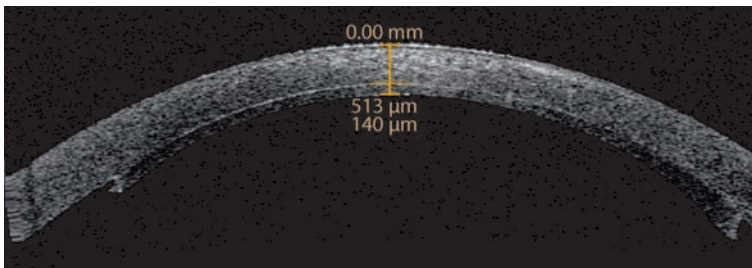


Fig. 1.6 Anterior chamber optical coherence tomography (AC-OCT) image shows a cross-section of a recipient cornea with an attached donor posterior disc. (Image courtesy of William W. Culbertson, M.D.)

The DSEK/DSAEK procedures have largely supplanted DLEK in the surgical treatment of FED. Advantages over DLEK include an easier technique of removing the diseased endothelium, less trauma to the recipient tissue, a more structurally sound recipient stroma, and a smoother corneal interface [43]. In a review of 50 eyes undergoing DSEK, Price et al. [45] showed that at 6 months, 31 eyes (62%) had best corrected visual acuities of $\geq 20/40$ and 38 eyes (76%) had best corrected visual acuities of $\geq 20/50$. At 6 months, the mean manifest cylinder was 1.5 ± 0.94 D and the mean manifest spherical equivalent was 0.15 ± 1.0 D. The most common complication encountered in DSEK is detachment of the lamellar disc, which has been reported in 15–30% of cases in the early postoperative period [46]. This complication, however, can be addressed in the immediate postoperative period by repositioning the button and/or injecting more air into the anterior chamber (called “rebubbling”). Figure 1.7 shows an AC-OCT image of a detached DSEK button (Fig. 1.7a) that was repositioned and rebubbled with subsequent reattachment and progressive resolution of stromal edema (Figs. 1.7b–f).

Summary for the Clinician

- Medical management of FED includes topical hypertonic saline, use of a hair dryer in the morning to dehydrate the precorneal tear film, and therapeutic contact lenses
- For several decades, penetrating keratoplasty (PK) has been the standard surgical treatment for FED
- Preoperative corneal pachymetry in FED patients can be helpful in assessing the risk of corneal decompensation after cataract surgery
- Cataract surgery alone should be considered in FED patients with corneal pachymetry less than 600–640 μm
- Various forms of endothelial keratoplasty are gaining popularity over traditional PK in the treatment of FED

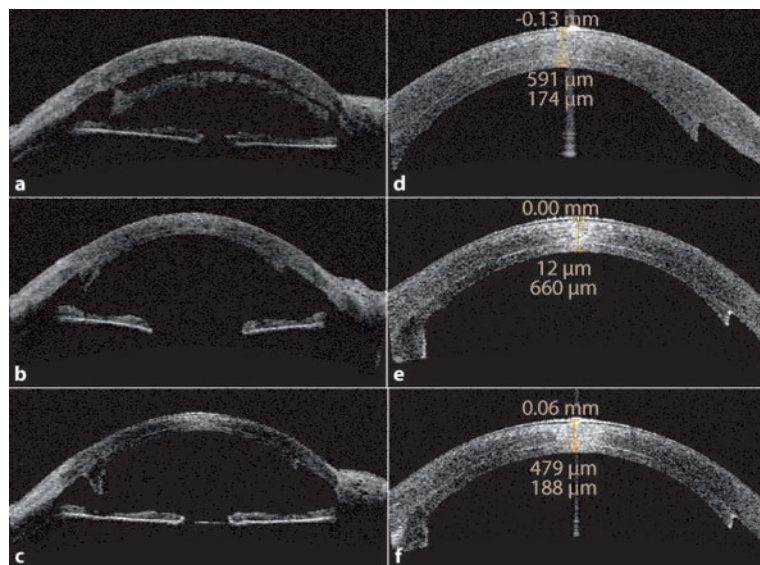


Fig. 1.7 **a** An AC-OCT image of a detached donor posterior disc. **b** Reattachment of the disc to the recipient stromal bed with repositioning and rebubbling within 1 week of the DSEK procedure. **c** The cornea at postoperative month 3. **d–f** Progressive deturgescence of the cornea after DSEK. (Images courtesy of William W. Culbertson, M.D.)

1.9 Future Directions

Future therapies for FED would ideally provide definitive treatment of the diseased endothelium early in the disease course, before vision loss or discomfort occurs. Improvements in endothelial transplantation will likely result in less invasive approaches with reduced complication rates and faster visual recovery. Although endothelial cells do not proliferate in vivo, several groups have demonstrated the proliferative capacity of human corneal endothelial cells in vitro [24]. Recent work demonstrating the ability to culture human corneal endothelial cells on several substrates, such as denuded Descemet's membrane and amniotic membrane [19], indicates promising areas of future research. Additional cell-based approaches could utilize our understanding of the mechanisms of cell cycle arrest in human corneal endothelium to stimulate cell division in vivo [27].

Fuchs endothelial dystrophy also represents an attractive disease for gene therapy-based approaches. Mutations in the COL8A2 gene have already been shown to cause FED, and additional causal mutations in different genes will probably be identified. Genetic modification of corneal endothelial cells has already been accomplished, and FED mutations could theoretically be corrected in corneal endothelial cells as a potential treatment for this disease [28].

1.10 Summary

Fuchs endothelial dystrophy is a primary disease of the corneal endothelium that is characterized by loss of endothelial cells and abnormalities of Descemet's membrane. These changes result in the decreased capacity of the endothelium to dehydrate and maintain the optical clarity of the corneal stroma and epithelium, resulting in pain and decreased visual acuity. Experimental studies on FED suggest endothelial cell apoptosis and abnormal basement membrane physiology as mediators in the pathogenesis of this disease. To date, PK has been largely successful in managing advanced FED. Newer techniques such as DLEK, DSEK, and DSAEK avoid the potential complications of PK and instead provide increased globe integrity, minimal refractive change, and faster

recovery of vision. Future advances, including improvements in endothelial keratoplasty, endothelial cell transplantation/engineering, and gene therapy, represent promising new approaches to the management of this common corneal disorder.

References

1. Adamis AP, Filatov V, Tripathi BJ, et al. (1993) Fuchs' endothelial dystrophy of the cornea. *Surv Ophthalmol* 38:149–168
2. Arentsen JJ, Laibson PR (1978) Penetrating keratoplasty and cataract extraction. Combined vs nonsimultaneous surgery. *Arch Ophthalmol* 96:75–76
3. Bahn CE, Falls HE, Varley GA, et al. (1984) Classification of corneal endothelial disorders based on neural crest origin. *Ophthalmology* 91:558–563
4. Biswas S, Munier FL, Yardley J, et al. (2001) Missense mutations in COL8A2, the gene encoding the alpha2 chain of type VIII collagen, cause two forms of corneal endothelial dystrophy. *Hum Mol Genet* 10:2415–2423
5. Borboli S, Colby K (2005) Mechanisms of disease: Fuchs' endothelial dystrophy. *Ophthalmol Clin North Am* 15:17–25
6. Borderie VM, Baudrimont M, Vallee A, et al. (2000) Corneal endothelial cell apoptosis in patients with Fuchs' dystrophy. *Invest Ophthalmol Vis Sci* 41:2501–2505
7. Bourne WM, Nelson LR, Hodge DO (1997) Central corneal endothelial cell changes over a ten-year period. *Invest Ophthalmol Vis Sci* 38:779–782
8. Chiou AGY, Kaufman SC, Beuerman RW, et al. (1999) Confocal microscopy in corneal guttata and Fuchs' endothelial dystrophy. *Br J Ophthalmol* 3:185–189
9. Cogan, DG, Kuwabara T (1971) Growth and regenerative potential of Descemet's membrane. *Trans Ophthalmol Soc UK* 91:875–894
10. Cross, HE, Maumenee AE, Cantolino SJ (1971) Inheritance of Fuchs' endothelial dystrophy. *Arch Ophthalmol* 85:268–272
11. Fuchs E (1902) On keratitis, being the Bowman lecture. *Trans Ophthalmol Soc UK* 22:15–34
12. Fuchs E (1910) Dystrophia epithelialis corneae. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 76:478–508

13. Geroski DH, Matsuda M, Yee RW, et al. (1985) Pump function of the human corneal endothelium. Effects of age and cornea guttata. *Ophthalmology* 92:759–763
14. Gottsch JD, Bowers AC, Marguiles EH, et al. (2003) Serial analysis of gene expression in the corneal endothelium of Fuchs' dystrophy. *Invest Ophthalmol Vis Sci* 44:594–599
15. Gottsch JD, Sundin OH, Liu SH, et al. (2005) Inheritance of a novel COL8A2 mutation defines a distinct early-onset subtype of Fuchs corneal dystrophy. *Invest Ophthalmol Vis Sci* 46:1934–1939
16. Hara M, Morishige N, Chikama T, et al. (2003) Comparison of confocal biomicroscopy and non-contact specular microscopy for evaluation of the corneal endothelium. *Cornea* 22:512–515
17. Hogan MJ, Wood I, Fine M (1974) Fuchs' endothelial dystrophy of the cornea. 29th Sanford Gifford memorial lecture. *Am J Ophthalmol* 78:363–383
18. Ing JJ, Ing HH, Nelson LR, et al. (1998) Ten-year postoperative results of penetrating keratoplasty. *Ophthalmology* 105:1855–1865
19. Ishino Y, Sano Y, Nakamura T, et al. (2004) Amniotic membrane as a carrier for cultivated human corneal endothelial cell transplantation. *Invest Ophthalmol Vis Sci* 45:800–806
20. Iwamoto T, DeVoe AG (1971) Electron microscopic studies on Fuchs' combined dystrophy. I. Posterior portion of the cornea. *Invest Ophthalmol* 10:9–28
21. Johns KJ, Feder RS, Hamill MB, et al. for the American Academy of Ophthalmology (2003) Basic and Clinical Science Course. Section 11. Lens and cataract. American Academy of Ophthalmology, San Francisco
22. Johnson DH, Bourne WM, Campbell RJ (1982) The ultrastructure of Descemet's membrane. I. Changes with age in normal corneas. *Arch Ophthalmol* 100:1942–1947
23. Johnson DH, Bourne WM, Campbell RJ (1982) The ultrastructure of Descemet's membrane. II. Aphakic bullous keratopathy. *Arch Ophthalmol* 100:1948–1951
24. Joyce NC (2003) Proliferative capacity of the corneal endothelium. *Prog Retin Eye Res* 22:359–389
25. Joyce NC, Meklikr B, Joyce SJ, et al. (1996) Cell cycle protein expression and proliferative status in human corneal cells. *Invest Ophthalmol Vis Sci* 37:645–655
26. Joyce NC, Navon SE, Roy S, et al. (1996) Expression of cell cycle-associated proteins in human and rabbit corneal endothelium in situ. *Invest Ophthalmol Vis Sci* 37:1566–1575
27. Joyce NC, Harris DL, Mello DM (2002) Mechanisms of mitotic inhibition in corneal endothelium: contact inhibition and TGF-beta2. *Invest Ophthalmol Vis Sci* 43:2152–2159
28. Jun AS, Larkin DF (2003) Prospects for gene therapy in corneal disease. *Eye* 17:906–911
29. Kitagawa K, Fujisawa A, Mizuno T, et al. (2001) Twenty-three cases of primary corneal guttata. *Jpn J Ophthalmol* 45:93–98
30. Krachmer JH, Purcell JJ, Young CW, et al. (1978) Corneal endothelial dystrophy. A study of 64 families. *Arch Ophthalmol* 96:2036–2039
31. Levy SG, Moss J, Sawada H, et al. (1996) The composition of wide-spaced collagen in normal and diseased Descemet's membrane. *Curr Eye Res* 15:45–52
32. Ljubimov AV, Burgeson RE, Butkowsky LJ, et al. (1995) Human corneal basement membrane heterogeneity: topographical differences in the expression of type IV collagen and laminin isoforms. *Lab Invest* 72:461–473
33. Lorenzetti DW, Uotila MH, Parikin N, et al. (1967) Central cornea guttata. Incidence in the general population. *Am J Ophthalmol* 64:1155–1158
34. MacCallum DK, Lillie JH, Scaletta LJ, et al. (1982) Bovine corneal endothelium in vitro. Elaboration and organization of a basement membrane. *Exp Cell Res* 139:1–13
35. Magovern M, Beauchamp GR, McTigue JW, et al. (1979) Inheritance of Fuchs' combined dystrophy. *Ophthalmology* 86:1897–1923
36. Mandell RB, Polse KA, Brand RJ, et al. (1989) Corneal hydration control in Fuchs' dystrophy. *Invest Ophthalmol Vis Sci* 30:845–852
37. Matoba AY, Harris DJ, Mark DB, et al. (2000) American Academy of Ophthalmology Preferred Practice Patterns Committee: Corneal Opacification and Ectasia. American Academy of Ophthalmology, San Francisco
38. McCartney AC, Kirkness CM (1988) Comparison between posterior polymorphous dystrophy and congenital hereditary endothelial dystrophy of the cornea. *Eye* 2:63–70
39. McCartney MD, Wood TO, McLaughlin BJ (1989) Moderate Fuchs' endothelial dystrophy ATPase pump site density. *Invest Ophthalmol Vis Sci* 30:1560–1564

40. Melles GRJ, Eggink FAGJ, Lander F, et al. (1998) A surgical technique for posterior lamellar keratoplasty. *Cornea* 17:618–626
41. Melles GRJ, Wijdh RHJ, Nieuwendaal CP (2004) A technique to excise the Descemet membrane from a recipient cornea (descemetorhexis). *Cornea* 23:286–288
42. Olsen T, Ehlers N, Favini E (1984) Long term results of corneal grafting in Fuchs' endothelial dystrophy. *Acta Ophthalmol* 62:445–452
43. Ousley PJ, Terry MA (2005) Stability of vision, topography, and endothelial cell density from 1 year to 2 years after deep lamellar endothelial keratoplasty surgery. *Ophthalmology* 112:50–57
44. Pineres O, Cohen E, Rapuano CJ, et al. (1996) Long-term results after penetrating keratoplasty for Fuchs endothelial dystrophy. *Arch Ophthalmol* 114:15–18
45. Price FW, Price MO (2005) Descemet's stripping with endothelial keratoplasty in 50 eyes: a refractive neutral corneal transplant. *J Refract Surg* 21:339–345
46. Price FW, Price MO (2006) Descemet's stripping with endothelial keratoplasty in 200 eyes: early challenges and techniques to enhance donor adherence. *J Cataract Refract Surg* 32:411–418
47. Price FW, Whitson WE, Marks RG (1991) Progression of visual acuity after penetrating keratoplasty. *Ophthalmology* 98:1177–1185
48. Rodrigues MM, Stulting RD, Waring GO (1986) Clinical, electron microscopic, and immunohistochemical study of the corneal endothelium and Descemet's membrane in the iridocorneal endothelial syndrome. *Am J Ophthalmol* 101:16–27
49. Rosenblum P, Stark WJ, Maumenee JH, et al. (1980) Hereditary Fuchs' dystrophy. *Am J Ophthalmol* 90:455–462
50. Sawada H, Konomi H, Hirokawa K (1990) Characterization of the collagen in the hexagonal lattice of Descemet's membrane: its relation to type VIII collagen. *J Cell Biol* 110:219–227
51. Seitzman GD, Gottsch JD, Stark WJ (2005) Cataract surgery in patients with Fuchs' corneal dystrophy: expanding recommendations for cataract surgery without simultaneous keratoplasty. *Ophthalmology* 112:441–446
52. Shuttleworth CA (1997) Type VIII collagen. *Int J Biochem Cell Biol* 29:1145–1148
53. Stocker FW (1953) The endothelium of the cornea and its clinical implications. *Trans Am Ophthalmol Soc* 51:669–786
54. Terry MA, Ousley PJ (2003) Replacing the endothelium without corneal surface incisions or sutures: the first United States clinical series using the deep lamellar endothelial keratoplasty procedure. *Ophthalmology* 110:755–764
55. Terry MA, Ousley PJ (2005) Deep lamellar endothelial keratoplasty: visual acuity, astigmatism, and endothelial survival in a large prospective series. *Ophthalmology* 112:1541–1549
56. Thompson RW, Price MO, Bowers PJ, et al. (2003) Long-term graft survival after penetrating keratoplasty. *Ophthalmology* 110:1396–1402
57. Vail A, Gore SM, Bradley BA, et al. for the Corneal Transplant Follow-up Study Collaborators (1994) Corneal graft survival and visual outcome. A multicenter study. *Ophthalmology* 101:120–127
58. Vogt A (1921) Weitere Ergebnisse der Spaltlampenmikroskopie des vorderen Bulbusabschnittes. *Graefes Arch Clin Exp Ophthalmol* 106:63–103
59. Waring GO, Font RL, Rodrigues MM, et al. (1976) Alterations of Descemet's membrane in interstitial keratitis. *Am J Ophthalmol* 81:773–785
60. Waring GO, Rodrigues MM, Liabson PR (1978) Corneal dystrophies. II. Endothelial dystrophies. *Surv Ophthalmol* 23:147–168
61. Waring GO, Bourne WM, Edelhauser HF, et al. (1982) The corneal endothelium. Normal and pathologic structure and function. *Ophthalmology* 89:531–590
62. Wilson SE, Bourne WM (1988) Fuchs' dystrophy. *Cornea* 7:2–18
63. Wilson SE, Bourne WM, O'Brien PC, et al. (1988) Endothelial function and aqueous humor flow rate in patients with Fuchs' dystrophy. *Am J Ophthalmol* 106:270–278

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