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REVIEW ARTICLE

Fuchs endothelial corneal dystrophy and corneal endothelial diseases: East meets West

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Abstract

Fuchs endothelial corneal dystrophy (FECD) is amongst one of the most common indications for endothelial keratoplasty worldwide. Despite being originally described among Caucasians, it is now known to be prevalent among a large number of populations, including Asians. While the FECD phenotype is classically described as that of central guttate and pigment deposits associated with corneal endothelial dysfunction, there are subtle yet important differences in how FECD and its phenocopies may present in Caucasians vs Asians. Such differences are paralled by genotypic variations and disease management preferences which appear to be geographically and ethnically delineated. This article provides a succinct review of such differences, with a focus on diagnostic and management issues which may be encountered by ophthalmologists practicing in the different geographic regions, when evaluating a patient with FECD.

Introduction

Fuchs endothelial corneal dystrophy (FECD) is a common corneal endothelial dystrophy, characterized clinically by centrally distributed Descemet membrane (DM) guttae and corneal endothelial dysfunction (Fig. 1) [1, 2]. It is a genetically heterogeneous disease attributable to a spectrum of genotypes such as the CTG trinucleotide repeat expansion in chromosome 18, single nucleotide polymorphisms within the TCF4 gene, and mutations in the SLC4A11 gene [3]. While endothelial keratoplasty (EK) is the current gold standard for management of the condition in its advanced stages, significant progress has been made in the development of novel therapeutic modalities such as cell-free descemet membrane transplantation [4, 5] and cell-injection therapy [6]. Discovery of the relatively high prevalence of the CTG trinucleotide repeat expansion sequence in FECD, in tandem with recent advances in gene editing techniques such as the CRISPR-Cas9 endonuclease platform [7, 8], implies that gene therapy may possibly benefit FECD patients as well [9–11]. This review focusses on the comparative differences in FECD phenotypes and genotypes between Asian and Caucasian populations, highlights differences in current management algorithms, and explores the potential for application of novel therapeutic modalities across these populations.

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Prevalence

Among Caucasians, corneal guttae may be found in 11% of females and 7% of male participants in the Icelandic Reykjavik Eye Study [12], and the overall prevalence of FECD has been estimated to be ~21.6% from a small population residing on Tangier Island [13], in the United States of America. In Asia, a Japanese study [14] detected corneal guttae at a frequency of only 5.8% and 2.4% in female and male participants, respectively. While a slightly higher prevalence of the disease was found in a Singaporean-Chinese population (8.5% and 4.4% for females and males, respectively) [15], it is apparent that FECD is more frequent in

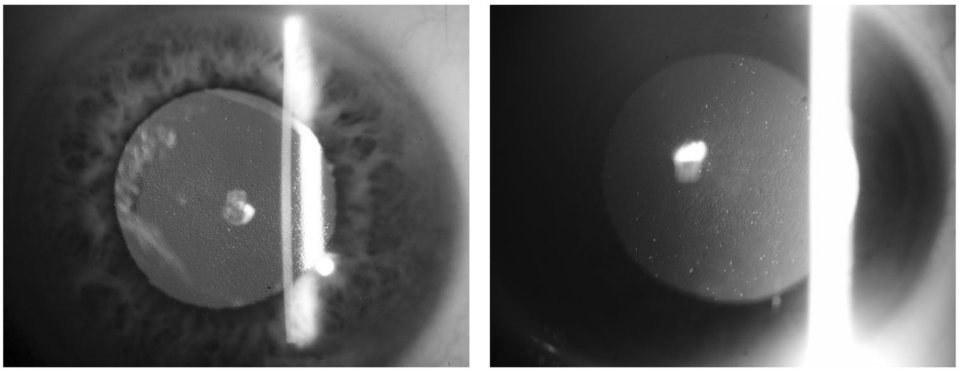

Fig. 1 Retroilluminated anterior segment image of Fuchs endothelial corneal dystrophy. Left—Caucasian patient; Right—Asian patient

Table 1 Prevalence of Fuchs endothelial dystrophy in Western vs Eastern populations

Origin	Year	Author	*N* (eyes)	Age (years)	Prevalence (%)			Ratio F:M
					Overall	Females	Males	
America								
USA	1933	Goar et al. [180]	800	>21	6.62	9.07	3.62	2.5:1
	1967	Lorenzetti et al. [181]	1348	>40	3.9	4	3.8	1.05:1
Europe								
Iceland (Reykjavik)	2006	Zoega et al. [12]	1548	>55	9.2	11	7	1.6:1
Asia								
Chinese Singaporean	2002	Kitagawa et al. [15]	920	>50	6.7	8.5	4.4	2:1
Japan	1996	Nagaki et al. [182]	211	56–76	3.3	3.3	–	–
Japan (Ishikawa Prefecture)	2002	Kitagawa et al. [15]	598	>50	3.7	5.5	1.5	3.7:1
Japan (Southwestern Island)	2011	Higa et al. [14]	7524	>40	4.1	5.8	2.4	2.4:1

Caucasians compared with Asians. In addition, regardless of geographical distribution, females appear to be at greater risk of harboring the disease (Table 1). While this leads to the hypothesis that the pathogenesis of FECD may possibly be subject to the influence of sex hormones, it is counter-intuitive to previous work which has established the beneficial effects of estrogen against cellular senescence [16–19].

Geographical and ethnic differences in FECD prevalence may, in part, be related to genetic variations (read under section 'Genetics'). There is also strong evidence implicating oxidative stress in the pathogenesis of FECD [20–22], which suggests that epigenetic influences such as geographical variations in UV exposure [23] may possibly affect FECD prevalence. Equatorial Asian countries, such as Singapore, are exposed to much higher levels of solar UV radiation compared with Caucasian populations, such as the Nordic countries located along higher latitudes [24], and may thus be expected to be at greater risk of UV-induced corneal endothelial cell oxidative stress/damage. However, Nordic populations are exposed to unique ecological and behavioral risk factors which may increase the risk of ocular UV damage, including: (a) increased levels of snow-reflected solar UV radiation [25], (b) prolonged, full-day UV exposure as a result of the polar day (also known as 'midnight sun') phenomenon during summer months [26], (c) low solar elevation angle during winter months which contributes to persistent and excessive glare [27], (d) progressive ozone layer depletion leading to increased penetrance of solar UV rays [28, 29], and (e) popularity of indoor sunbed usage due to compensate for the lack of exposure to natural sunlight [30–34].

Phenotype and phenocopies

FECD is characterized by the hallmark features of DM guttae and pigment deposition, endothelial cell pleomorphism and polymegathism, and corneal edema as a result of corneal endothelial dysfunction [1, 2]. The presence of such features allows the clinician to make an unequivocal diagnosis of FECD. However, these changes may be subtle in the early stages of FECD, during which time it may be confused with other disease phenocopies.

Posterior polymorphous corneal dystrophy

Posterior polymorphous corneal dystrophy (PPCD) is a relatively rare, autosomal dominant disease. It is clinically

characterized by a corneal endothelial dystrophy which manifests as vesicles and opacities on the posterior corneal surface [35], and ectatic changes [36] resulting in abnormally steep corneal curvatures. Systemic associations include Alport syndrome and abdominal hernias [37–39]. The endothelial dystrophy in PPCD occurs secondary to an upregulation of endothelial–mesenchymal transition (EMT), which results in corneal endothelial cells exhibiting a more fibroblastic and epithelial-like phenotype [40]. In chronic and progressive disease, endothelial failure may be accompanied by features akin to iridocorneal endothelial (ICE) syndrome, such as peripheral iridocorneal adhesions, iris distortions and secondary glaucoma [40, 41]. PPCD is a genetically heterogeneous disease which may be classified into three subtypes, namely: (i) PPCD1 associated with VSX1 mutations in chromosome 20 [42, 43]; (ii) PPCD2 associated with COL8A2 mutations in chromosome 1 [44], and (iii) PPCD3 associated with ZEB1 mutations in chromosome 10, which is the most common subtype among all [38, 45]. The implication of ZEB1 mutations and its effect on upregulation of EMT in the pathogenesis of PPCD is of interest in this review, considering that the pathogenesis of FECD may involve a similar pathway. ZEB1 expression has been shown to be upregulated in FECD patients, which leads to overproduction of extracellular matrix proteins and guttae deposition [46]. TCF4 mutations, which are now known to be strongly associated with the FECD phenotype [47–49], directly affects the activity of transcription factor E2-2, which in turn regulates ZEB1 [50]. The overlapping pathogenetic pathways of these two diseases are paralleled by their relatively similar clinical presentations. In particular, the Descemet membrane (DM) vesicles and thickenings seen in PPCD may be misclassified as FECD, especially in Caucasian populations such as in the Czech Republic, which has the highest reported worldwide prevalence of PPCD (1 in 100,000 inhabitants) [51]. In contrast, PPCD is a rare disease in Asia, which represents only an insignificant minority of cases requiring keratoplasty [52].

Viral endotheliitis

While the majority of anterior uveitis cases are idiopathic, a small proportion may be attributable to viral etiologies, such as cytomegalovirus (CMV), herpes simplex virus (HSV), and rubella virus infections [53]. Regardless of the exact etiological agent, viral anterior uveitis present with a spectrum of overlapping features such as anterior segment inflammation, keratic precipitates (KPs), ocular hypertension, and various patterns of iris atrophy [54]. In particular, CMV anterior uveitis manifests as either acute and relapsing bouts of hypertensive anterior uveitis akin to Posner-Schlossman syndrome (PSS), or chronic hypertensive anterior uveitis as in the case of Fuchs heterochromic iridocyclitis (FHIC) [55]. Both presentations can be associated with a viral endotheliitis [55] which, in the presence of pigmented KPs and endothelial cell loss/dysfunction (Fig. 2), may be mistaken for asymmetrical FECD. In a patient who has previously undergone keratoplasty, CMV endotheliitis with endothelial cell loss and a low-grade anterior chamber inflammatory reaction may also be easily mistaken as acute graft rejection [56].

The diagnostic challenge of differentiating CMV anterior uveitis from the abovementioned non-infectious etiologies is particularly problematic in Asian patients, in whom the disease has been much more commonly reported compared with Caucasians [54, 55, 57–59]. This may be related to the higher seroprevalence of CMV in Asia [60]. CMV seropositivity rates are in the range of 70–90% within Asian countries, including Japan [61] and India [62–64], with lower rates of 50–70% in Western countries, including North America [65] and Europe [66]. Herpes simplex virus appears to be a much more important etiological agent of ocular infections in Caucasians populations, with an incidence of 20.7 per 100,000 patients per year in the United States of America [67]. While there is a paucity of published data regarding the incidence of herpetic keratitis in Asia it is, in our experience as an Asian tertiary eye-care institution, a much less common disease than would be expected in the West.

Imaging modalities such as specular microscopy and confocal microscopy may assist in the evaluation of DM guttae and hyper-reflective endothelial round bodies [68] found in FECD and CMV endotheliitis, respectively. In addition, an aqueous tap in association with either CMV antibody titer assessment (i.e., Goldmann–Witmer coefficient, GWc) or polymerase chain reaction (PCR) should be performed for all patients with anterior uveitis in whom a viral etiology cannot be confidently excluded [69]. In the presence of an active viral anterior uveitis, the treatment of choice should be that of a loading followed by chronic maintenance regime of antivirals [70]. Patients with either a combined diagnosis of FECD and CMV endotheliitis, or those with CMV endotheliitis which has progressed to end-stage endothelial decompensation, should also be adequately treated with antivirals for at least 6 months prior to consideration of keratoplasty, in order to reduce the subsequent risks of graft failure [47, 56, 71]. Specifically for CMV endotheliitis, antiviral therapeutic agents include systemic ganciclovir/valganciclovir [48] and/or topical ganiclovir ointment [49]. While there are currently no standardized guidelines for the treatment of CMV endotheliitis [72], most of such patients seen at our center are commonly treated with a combination of both systemic and topical antiviral agents, which in our opinion is a more effective approach than systemic or topical antiviral

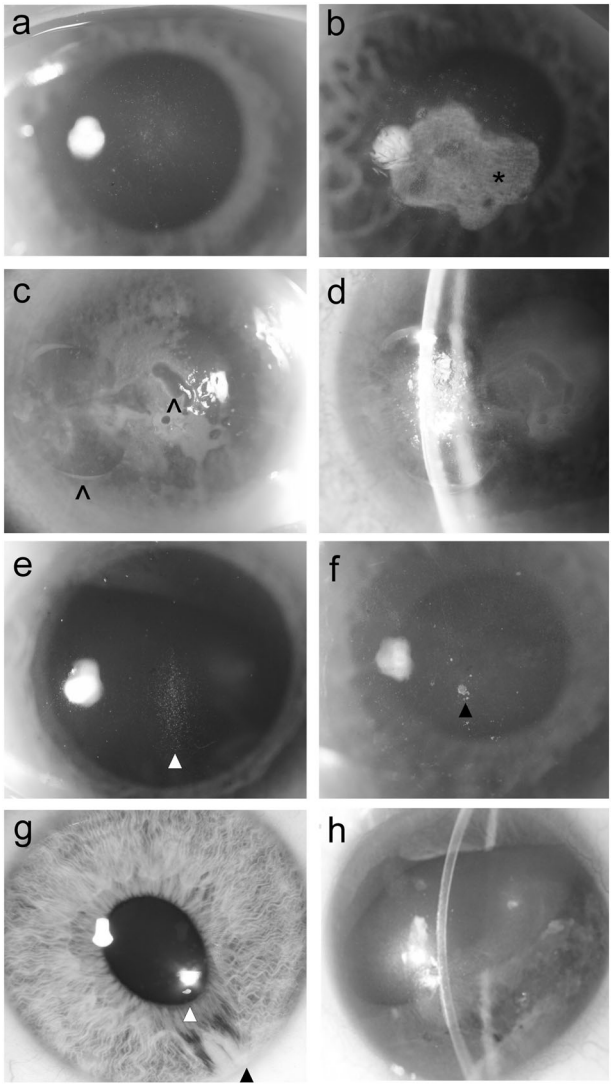

Fig. 2 Anterior segment photographs. **a** Fuchs endothelial corneal dystrophy (FECD) in an Asian eye. **b** FECD with stromal scarring (scar indicated by *). **c** FECD complicated by bullous keratopathy (epithelial bullae indicated by ^). **d** Slit-beam demonstrating concommitant shallow anterior chamber and a brunescent cataract in the same eye. **e** Krukenberg's spindle in an Asian eye with pigment dispersion syndrome (white arrowhead). **f** CMV endotheliitis with endothelial pigment deposits and a 'coin-lesion'/nummular keratic precipitate (black arrowhead). **g** ICE syndrome in a Caucasian patient with corectopia (white arrowhead) and peripheral anterior synechiae at the 5 o'clock position (black arrowhead). **h** ICE syndrome in an Asian patient of the essential iris atrophy subtype

monotherapy. This practice is also in keeping with the findings of the Japan Corneal Endotheliitis Study Group published in 2014 [73]. While intravitreal ganciclovir injection has previously been demonstrated to be effective for the treatment of CMV endotheliitis in a single case report it is, to the best of our knowledge, not a commonly practised approach; similarly, despite the theoretical possibility of intracameral ganciclovir being beneficial in optimizing corneal endothelial drug bioavailability, this approach has not yet been clinically evaluated.

Pigment dispersion

In pigment dispersion syndrome (PDS), reverse pupillary block results in a concave configuration of the mid-peripheral iris and chafing of the posterior iris pigment epithelium (PPE) against the lens zonules [74]. Chronic mechanical trauma of the PPE results in characteristic mid-peripheral iris trans-illumination-defects (TIDs) in association with intraocular deposition of pigments such as in the angle of the anterior chamber (AC), lens capsule and corneal endothelium [75]. In particular, pigment deposited on the corneal endothelium may assume the characteristic configuration of a vertically oriented Krukenberg's spindle (KS) located at the center of the cornea (Fig. 2) [76].

While iris TIDs are often readily visible in Caucasian patients with light-colored irides [75], such a change is rarely observed among Asian patients [77], in whom the iris stroma is significantly thicker and more heavily pigmented. In such cases, the centrally located KS may be mistaken for central pigment deposition analogous to that seen in FECD. The diagnosis of PDS would be missed in the absence of a careful gonioscopic examination and if the clinician fails to look out for other associated features of PDS such as glaucomatous optic disc changes.

ICE syndrome

In the ICE syndrome, corneal endothelial cells undergo EMT to assume fibroblastic characteristics. These cells migrate across the corneal endothelium, angle of the AC and onto the anterior iris surface to result in characteristic pathological changes such as a 'beaten bronze' appearance in Chandler syndrome, pseudopolycoria in essential iris atrophy and numerous iris nevi-like lesions in Cogan-Reese syndrome [78]. In particular, corneal endothelial changes encountered in Chandler syndrome may mimic the clinical appearance of corneal endothelial guttae associated with FECD, and it may be difficult to differentiate these disease entities especially when the other associated features of ICE syndrome such as iris atrophy and peripheral anterior synechiae (Fig. 2) are not obvious. The higher prevalence of Chandler syndrome among Caucasians [79] compared with Asians, in whom Cogan-Reese syndrome [80] and essential iris atrophy [81] were found to be more common, may lead to difficulties in differentiating Caucasians with ICE syndrome, especially those with the Chandler syndrome subtype, from those with FECD, at an early stage. Specular or confocal microscopy would be a useful adjunct in these cases, as ICE syndrome gives rise to the characteristics appearance of dark-light inversion of corneal endothelial

cells [82], while FECD is not associated with such changes. While patients affected by ICE/Chandler syndrome are at risk of eventually developing bullous keratopathy just like in FECD, ICE syndrome is usually unilateral [83–86], and it has a worse visual prognosis which often involves a more complex long-term management plan, in view of its significant associations with glaucoma and the greater risk of disease recurrence even after keratoplasty [87, 88].

Drug-induced endotheliitis

For patients with chronic viral uveitis and endotheliitis, the use of ocular immunosuppressants, such as topical cyclosporine [89], topical prostaglandin analogs [90], and sustained-release intravitreal steroid implants [91], may trigger viral reactivation and recurrent endotheliitis. Amantadine—a medication used to treat Parkinson's disease—has also been associated with a dose-dependent decline in corneal endothelial cell density, pleomorphism, polymegathism, and endothelial decompensation over time [92, 93], in a fashion similar to FECD.

Genetics

FECD is a genetically heterogeneous disease. Mutations in a large number genes including but not limited to FCD1/2/3/4 [94–97], COL8A2 [44], SLC4A11 [98], ZEB1 [99], KANK4, LAMC1, and ATP1B1 [100] have been found in association with FECD. These genetic mutations are generally associated with a relatively conserved set of phenotypic features as would be expected in typical FECD, with the exception of COL8A2 mutations which result in early onset FECD; in this group of patients, corneal endothelial dysfunction has been observed as early as in the 2nd decade of life [44, 101]. In addition, FECD has also been characterized as a trinucleotide repeat (TNR) disease [102], in which an expanded CTG repeat sequence in the TCF4 gene located on chromosome 18.1 (CTG 18.1 genotype) causes the disease phenotype by interference of mRNA splicing [103]. Among these wide spectrum of genetic changes, the CTG 18.1 genotype is the most important identified thus far, as it is associated with the FECD phenotype at a much higher frequency compared with each of the other genotypes. For example, the prevalence of ZEB1 and SLC4A11 mutations were found to be approximately 2% and 5%, respectively [99, 104]. In contrast, the CTG 18.1 was much more prevalent in FECD patients, albeit at a greater frequency among Caucasians compared with Asian populations. Within Asian populations, the CTG 18.1 genotype was found in 43.9% of Chinese patients by Xing et al. [105], 26% of Japanese patients by Nakano et al. [106], and 17.3–34% of Indian patients by Rao et al. [107] and Nanda et al. [108], respectively. In contrast, the prevalence of the CTG 18.1 allele within a North-American Caucasian population was much higher, in the range of 62.1–73.3% [102, 109–111]. A similarly higher prevalence was noted in other Caucasian populations, such as 51% of Australian patients in the study by Kuot et al. [112] and 79% of German patients in the study by Luther et al. [113].

Management

FECD is a progressive disease associated with visual symptoms ranging from transient blurring of vision upon awakening, during the early stages of the disease, to a debilitating loss of central visual acuity when the cornea endothelium eventually decompensates [1]. Management of FECD progresses in a stepwise fashion, ranging from watchful management or topical hypertonic saline ointment in its early stages, to endothelial keratoplasty (EK) or penetrating (PK) for more advanced disease [3].

Indicators such as corneal pachymetry, specular or confocal microscopy findings and central visual acuity are useful adjuncts in guiding the clinician's assessment of disease severity. In addition, the clinician would have to take into consideration the presence of other ophthalmic comorbidities and risk factors in one assessment of a patient's requirement and suitability to undergo surgical intervention. In Asia, the relatively higher prevalence of angle closure compared with Caucasians [114], especially in elderly females [115] who are also at greatest risk of FECD, results in a relatively common scenario wherein an elderly patient presents with the triple combination of (i) shallow anterior chamber, (ii) FECD, and (iii) cataracts (Fig. 3). Phacoemulsification surgery under such circumstances is associated with significantly greater risks of corneal endothelial decompensation. In addition, corneal endothelial reserves in such patients may have been further attenuated by earlier attacks of acute primary angle closure, chronic primary angle closure glaucoma with poorly controlled intraocular pressure or laser peripheral iridotomy (LPI) induced bullous keratopathy (BK) [116, 117]. The latter may be especially problematic among Asian patients [118] with relatively thicker irides who may require a large number of additional high-fluence argon-laser shots to achieve patency during LPI. Preoperatively, it may be worthwhile to counsel these patients on their risk of corneal endothelial decompensation following phacoemulsification, for which surgical options would include either a combined phacoemulsification + EK, or a staged phacoemulsification followed by EK as a separate procedure subsequently. In a phakic patient with concomitant narrow anterior chamber angles and FECD for whom LPI is being considered, it would be judicious for the clinician to lower the visual acuity threshold for considering

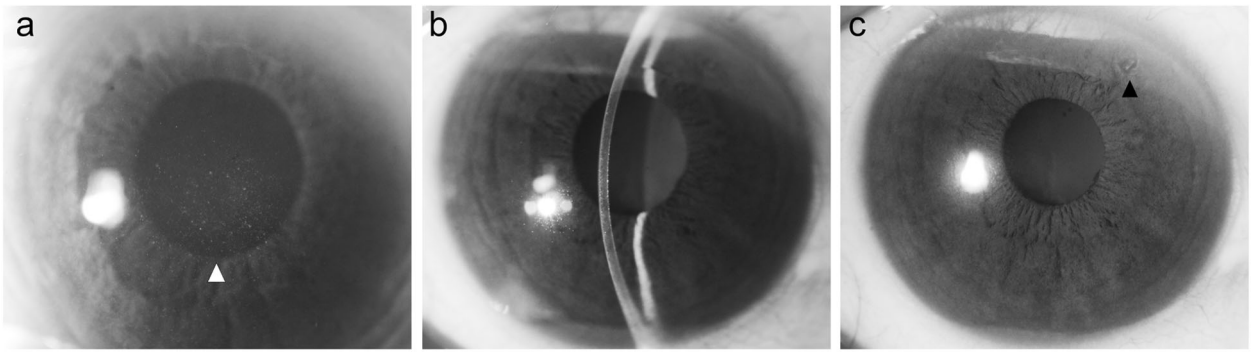

Fig. 3 Anterior segment photographs of a phakic Asian eye with the concommitant diagnoses of **a** Fuchs endothelial corneal dystrophy (white arrowhead indicating endothelial pigments and guttata) and **b** primary angle closure suspect with shallow anterior chamber, for which **c** laser peripheral iridotomy (black arrowhead) has been performed

cataract extraction, and to defer LPI in favor of early phacoemulsification in order to lower the risks of subsequent post-operative corneal endothelial decompensation. In addition, for patients in whom the corneal endothelium is already noted to be compromised preoperatively, it would be advantageous to consider combined phacoemulsification + EK rather than phacoemulsification alone followed by EK only upon the development of BK, as the former is associated with significantly better post-operative visual outcomes [119]. Having said that, it should be qualified that it may not be straightforward to accurately predict preoperatively, the risk of an FECD patient decompensating following phacoemulsification alone. While more severe FECD is correlated to a higher post-phacoemulsification risk of corneal decompensation, such an outcome may occur in FECD patients with milder disease as well.

Besides disease severity, the decision to undergo keratoplasty also depends on a wide spectrum of other non-medical factors such as a patient's lifestyle and visual requirements, access to medical care and surgical expertise, and other psycho-social-economic ideas, concerns and expectations regarding corneal transplantation. In western nations such as the United States of America (USA) and Europe where FECD patients have relatively easy access to high quality medical care, there is increasingly a shift toward early surgical intervention [120]. Keratoplasty used to be offered only to patients with advanced disease who suffer from impaired central visual acuity or corneal edema. Improvements in surgical techniques over the past decade, notably developments in the field of endothelial keratoplasty (EK), have generally led to a favorable tilt in the risk-benefit ratio when considering the merits of keratoplasty for FECD [121–124]. This, coupled with increased awareness of the disease and its treatment options, has resulted in a trend wherein patients are increasingly keen to consider keratoplasty as the definitive therapeutic modality even in early stages of the disease, during which time the only visual symptoms may be those of increased higher-order-aberrations such as glare and halos, or decreased contrast sensitivity [125–127].

EK is generally perceived to be a safe and effective procedure [121–124], and is in fact the procedure of choice for treatment of FECD at most tertiary eye hospitals [128–133]. However, there are exceptions to the norm, such as a large registry study in Australia which indicated poorer survival and visual outcomes for EK compared with PK, regardless of surgeon experience [134]. While such results are in contrast to most other reports [121–124], they are derived from real-world data evaluating outcomes from multiple surgeons and institutions, as opposed to the other studies which typically described the surgical outcomes from a single or small group of surgeons [121–124]. The choice between EK or PK is less dependent on specific geographical distributions (i.e., Western vs Asian countries), than it is on a panel of multiple factors including institutional or surgeon preferences, availability of EK surgical expertise, economic feasibility considerations related to the costs incurred for the establishment of EK tissue preparation facilities, and stage of presentation (e.g., presentation at the stage of BK and stromal scarring would be a contraindication to EK).

All over the world, there are institutions in which PK is still preferred over EK for the treatment of endothelial diseases. For example, in a 2015 survey of keratoplasty trends in China, it was found that only 5% of corneal surgeons have ever received training in or performed EK, in contrast to 88% of surgeons who were adept in PK [135]. A review of keratoplasties performed in Vietnam from 2002 to 2013 showed that EK accounted for only 2% of total keratoplasty load over the decade [136]. While the average rate of EK in Iran from 2006 to 2013 was similarly low at 7.5%, there has been a significant shift toward EK in recent times, as evidenced by an increase in EK load from 0% in 2006 to 14.9% in 2013 (Iran National Registry Data) [137]. In New

Zealand, a survey of corneal transplantation practices from 1999 to 2009 indicated that EK accounted for <3% of all keratoplasties [138], which mirrored the extremely low local rates of lamellar keratoplasty observed over the preceding decade [139]. While there have been reports of endothelial keratoplasty from South Korea [123, 140–143], the majority of all procedures performed are still PKs, with lamellar keratoplasties accounting only for 2.7% of all cases nationwide (collective data from 25 hospitals in South Korea) [144]. In Japan, a cross-sectional national survey of surgical management trends for bullous keratopathy in 2007 found that an overwhelming majority (97.7%) of all patients were managed with PK [145]. Nonetheless, it must once again be emphasized that such rates may differ significantly depending on the availability of surgical expertise, even within the same country—for example, the number of EKs performed at Kanazawa University Hospital in Japan has doubled from 2007 to 2016, with most cases being that of Descemet stripping automated endothelial keratoplasty (DSAEK) [146]. An audit report by the Eye Bank Association of America in 2016 found that PK was generally still the most common keratoplasty procedure performed in international centers using US donor tissue (74.4%), with EK accounting for only 14.9% of all cases [147].

In other institutions such as the University of Toronto in Canada, a contrasting trend has been observed. Over the decade from 2002 to 2012, EKs accounted for 29.5% of all keratoplasties performed, with the increasing popularity of EK accompanied by a commensurate decrease in frequency of PK by 61.8% [148]. In 2016, up to 93.1% of all FECD patients in USA who required keratoplasty were treated with EK, with only 6.9% of patients receiving penetrating keratoplasty (PK) for various reasons such as late presentation and postural difficulties [147]. This has contributed to EK being the most common keratoplasty procedure performed with preserved corneal tissue in USA (44% of total surgical load), in contrast to PK which accounted for only 38% [147]. In France, EK surpassed PK as the most commonly employed technique for the management of FECD in 2013, with EK being performed in up to 70% of FECD cases undergoing keratoplasty in 2015 [131]. The trend toward EK has been even more marked in Italy, in which EK accounted for more than 62% of all procedures performed for patients with BK [149]. EK surpassed PK as the preferred surgical technique for management of BK in Italy in 2008 [149], at about the same time as EK was noted to overtake PK as the procedure of choice for management of FECD in Scotland [150]. The popularity of EK is also rapidly rising in Germany, accounting for 57% of all keratoplasties performed in 2016 in contrast to only 1.4% in 2006 [151]. While it may appear that the preference for EK exists only in Western nations, it should be noted that such a trend has also been observed in Asian nations such as Singapore [152]. At the Singapore National Eye Centre (SNEC), EK overtook PK as the surgical technique of choice for the mangement of FECD in 2009, with PK reserved only for the infrequent patient with neglected, end-stage disease complicated by stromal scarring. In 2017, 59.9% ($n = 340$) of all keratoplasties performed at SNEC were EKs, in contrast to PK which accounted for only 15% of the total caseload. In Eastern India (Prova Eye Bank, Disha Eye Hospitals, Barrackpore, India), an approximately equal number of EKs and PKs were performed in 2015 [153]. A similar trend has been observed at a tertiary eye-care institution in Southern India (Ramayamma International Eye Bank, L. V. Prasad Eye Institute, Hyderabad, India)—while in 2007 only 17% of FECD patients were treated by EK in contrast to PK for the remaining 83%, this trend had reversed by 2011, with 80% of FECD patients being treated by EK instead of PK [154].

Endothelial keratoplasty—surgical techniques

DSAEK and Descemet membrane endothelial keratoplasty (DMEK) are the most common methods of performing EK. While the absence of a donor stroma in DMEK allows a more precise post-operative anatomical configuration which is associated with less refractive change [155–157] and rejection risk [158], DMEK is a more technically challenging procedure than DSAEK due to the difficulties which may be encountered during preparation, insertion and unscrolling of the delicate single-cellular endothelial layer. Both DSAEK and DMEK are widely practised, with the choice of surgical technique dependent on the availability of surgical expertise, access to donor tissue and casemix. For example, while DSAEK used to be the more popular technique accounting for most EK procedures performed at a University Eye Hospital in Germany in 2008, by 2015 the trend has reversed such that DMEK now represents the technique of choice for patients who require EK [129]. At the Singapore National Eye Centre, 58% of all keratoplasty procedures performed in 2018 were endothelial keratoplasty, out of which 50% were DSAEK and 50% were DMEK. For DMEK, the graft is prepared and folded in such a manner as to create an ‘endothelial-in’ graft configuration, followed by insertion via a pull-through technique using a donor-mat device [159]. The endo-in, donor-mat approach is preferred at our center because it facilitates graft insertion and positioning. This is a particularly important advantage for late-presenting FECD cases associated with bullous keratopathy and poor view of the anterior chamber, which are commonly encountered in our practice. While there is scant data available regarding the relative popularities of DMEK vs DSAEK in Asia, we postulate that DSAEK is

likely to be more commonly practised. The relative paucity of eye-bank facilities in Asia equipped to prepare pre-stripped DMEK graft tissue likely precludes DMEK in many institutions. In addition, DSAEK is a relatively easier procedure than DMEK, especially in late-presenting patients with bullous keratopathy, which as mentioned earlier is relatively prevalent in Asia. In fact, when considering the technical difficulties associated with performing even DSAEK in such decompensated eyes, coupled with fears of inadvertent donor tissue wastage and the scarcity of cadaveric donor corneas in Asia, it is not surprising that PK remains a highly popular technique in Asia for the management of patients with FECD.

In view of a worldwide shortage in cadaveric donor grafts, there have been efforts to maximize the therapeutic yield of cadaveric donor grafts. Descemet membrane transplantation (DMT), which involves the transplantation of acellular DM devoid of corneal endothelial cells, represents one such approach which will be discussed in detail in the in next section. In addition, Melles et al. have also successfully demonstrated the efficacy of hemi- and quarter-DMEK [160, 161], i.e., the transplantation of semicircular or quadratic endothelial graft segments instead of a standard, circular endothelial graft, which allows between 2 and 4 patients to benefit from a single cadaveric donor graft.

Timing of surgery

There have been reports of mean pre-operative best-corrected-visual-acuity being in the range of 6/12 or better, among patients undergoing DMEK in USA [120]. This contrasts with other reports wherein the majority of patients listed for keratoplasty have pre-operative visual acuities of worse than 6/24 [162, 163]. In fact, from an Asian perspective, we continue to encounter a significant proportion of patients who either present late or accept surgical intervention only in advanced stages of the disease, such as when BK (Fig. 2) leads to intractable pain and when chronic stromal edema and scarring leads to a significant loss of central visual acuity [164]. Cultural prejudices against cadaveric tissue transplantation may favor the adoption of conservative management options among elderly patients in lieu of the relatively more onerous alternative of surgical transplantation. In our experience as one of the major regional referral centers for keratoplasty in Asia, the lack of access to donor cornea tissue and paucity of surgical expertise in keratoplasty among healthcare institutions offering primary eye-care services leads to yet another unfortunate but often encountered scenario: patients suffering from moderate FECD and cataracts who have undergone phacoemulsification by a general ophthalmologist, present to our clinics only when FECD has progressed to an advanced stage or even BK, as a result of either their misconceptions or the primary physician's failure to adequately counsel regarding the option of further surgical interventions to address their endothelial dystrophy. Regardless of the cause of late presentation, such a scenario is undesirable, as it is known that patients with advanced disease and BK tend to have poorer post-operative outcomes [119, 163]. On the contrary, early surgical intervention appears to be strongly correlated with improved visual outcomes, with up to 67% among all patients undergoing DMEK, with a mean pre-operative visual acuity of 6/12, being able to achieve visual acuity of at least 6/7.5 post-operatively [120, 165].

Future therapeutic modalities

While EK is the current standard-of-care for advanced FECD, significant progress has been made over the past decade to develop novel, alternative therapeutics for FECD. These alternative therapeutics can be broadly divided as (i) Cell-free corneal transplantation, (ii) Pharmacological adjuncts, (iii) Cell-injection therapy, (iv) Tissue-engineered EK (TE-EK), and (v) Gene therapy. Current surgical management options and experimental therapeutic appproaches for FECD are summarized in Fig. 4.

In FECD, diseased corneal endothelial cells and DM guttae are located centrally, with relative sparing of the corneal peripheries. It has been shown in an ex vivo cadaveric human corneal organ culture study that upon removal of central corneal endothelial cells, peripheral endothelial cells may rapidly repopulate the central cornea, especially in subjects younger than 50–60 years of age [166]. In vivo rabbit studies have further demonstrated that central endothelial recovery may occur even after stripping of the central DM, provided the DM defect was replaced by an acellular DM graft [4]. In contrast, Descemet membrane stripping alone, without transplantation of a basement membrane to replace the DM defect (i.e., Descemet stripping without endothelial keratoplasty, DWEK [167]), led to highly unpredictable endothelial recovery responses in adults [3], and are likely to be successful only in young patients who retain excellent functional endothelial reserves [168]. Subsequent to these findings, a phase 1 clinical trial found that transplantation of a cell-free corneal graft, or DMT, following stripping of a central disc of diseased DM in a patient suffering from FECD, resulted in prompt recovery of the central corneal endothelium [5]. While this approach remains to be validated in more patients, it represents an improvement from the status quo of EK, as it holds the potential for greatly increasing the number of FECD patients who can benefit from low cell-count endothelial grafts which would otherwise have been discarded. When

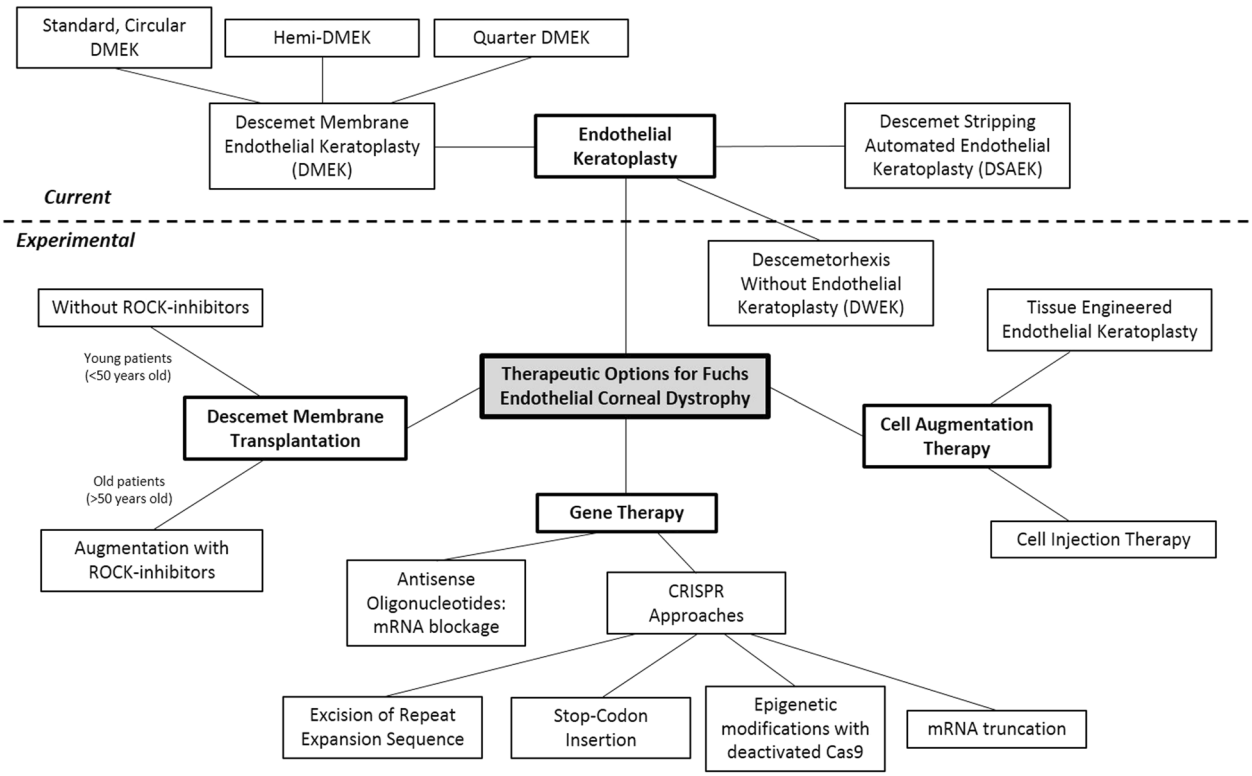

Fig. 4 Current and experimental therapeutic options for the management of Fuchs endothelial corneal dystrophy

considered against the aforementioned differences in management choices between Asians and Caucasians, it appears that the latter group of patients, who are more likely to present and accept surgical intervention at an earlier stage of the disease, would be better poised to benefit from DMT, which is known to work better in younger patients [166].

Rho-associated protein kinase inhibitors (ROCK inhibitors) belong to a relatively novel class of ophthalmic pharmacological agents, with a single formulation (Ripasudil Hydrochloride 0.4% topical eyedrop) having recently been approved in Japan for the treatment of glaucoma, in 2014 [169]. In recent years, ROCK inhibitors have also been shown to be potent stimulants of corneal endothelial cell migration, at least within an in vitro cell culture environment [166, 170]. Accordingly, in 2018, a phase IIa clinical trial was initiated by Kruse et al. in Germany to evaluate the potential efficacy of ROCK inhibitors for the treatment of FECD (clinicaltrials.gov, NCT03575130). In the setting of DMT and amongst Asian patients who tend to present later with more advanced FECD, a combination strategy of DMT in association with topical ROCK inhibitors to promote corneal endothelial recovery may be possibly enhance endothelial recovery following central DM stripping [171]. Alternatively, cell-augmentation following central DM stripping, in the form of either cell-injection therapy [172] or transplantation of a TE-EK, may also be efficacious in such patients who present later. In a recent phase 1 clinical trial, cell therapy via intracameral injection of cultured corneal endothelial cells and Rho-associated protein kinase inhibitor was shown to be effective in restoring corneal transparency and re-establishing a corneal endothelial monolayer among patients suffering from BK [6].

Following the discovery of the association between the CTG 18.1 genotype and FECD, it has been proposed that FECD may be amenable to treatment via gene therapy [3]. Multiple techniques have been suggested, including the use of antisense oligonucleotides to target sense-expanded CUG repeat transcripts and inhibiting misplacing events [173]. In recent years, it has also been found that the prokaryotic CRISPR-Cas9 endonuclease platform may be reprogrammed with appropriately designed guide-RNAs to perform site-specific gene editing in eukaryotic cells [7, 8]. There is great potential in further exploration of CRISPR-Cas9's ability to treat FECD via in vivo gene editing approaches [7, 8, 174–176] such as induction of insertion or deletion (indel) mutations via non-homologous-end-joining, truncation of the CTG repeat expansion sequence, insertion of a stop-codon at a location proximal to the promoter sequence [177], CRISPR-induced epigenetic modifications of gene expression and truncation of the deleterious RNA transcripts [178, 179]. Corneal endothelial cells are relatively accessible in vivo and thus may be easier to transfect

with viral vectors, via intracameral injection, compared with cells from other deep visceral organs. In addition, any phenotypic alterations to the cornea secondary to successful knock-out of the CTG 18.1 genotype may be easily observed as corneal endothelial cell morphological changes on specular microscopy, and functionally as a reversal of corneal edema, all of which provides direct evidence of treatment efficacy. In consideration of the greater prevalence of the CTG 18.1 genotype in Caucasians [102, 109–111] compared with Asians [105], gene editing strategies targeting the CTG 18.1 genotype may be comparatively more successful in Caucasians. An additional factor to take into consideration when evaluating the practicality of gene editing for FECD pertains to the timing of disease detection and treatment. While gene editing may possibly prevent further worsening of the FECD phenotype, it is unlikely that gene editing would be successful in removing the collagenous deposits on the DM (i.e., guttata) once formed. As such, the success of a gene editing approach is premised on the ability to diagnose FECD at an earlier stage (i.e., before significant guttae develop), and on patient attitudes toward accepting treatment while asymptomatic—the discussion of which is beyond the scope of this review.

Conclusion

While FECD was first described among Caucasian patients, it is now known to affect multiple ethnic groups across various geographical borders. The spectrum of phenotypic and genotypic differences among these different populations is paralleled by variations in patient and physician attitudes toward treatment, including keratoplasty. Even when considering novel therapeutic approaches, differences in stage of presentation and prevalence of CTG repeats between Caucasian and Asian populations would most likely be important in guiding the therapeutic modality of choice.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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