Title

Laser Refractive Surgery in Corneal Dystrophies: A Systematic Review

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Abstract

Twenty-eight case reports and case series published between 2000 and 2019 concerning laser refractive surgery in patients with corneal dystrophies, resulting in 173 eyes from 94 patients, were included in this systematic review. Best results were achieved in posterior corneal polymorphous and Cogan dystrophy. Unfavorable results were found in Avellino dystrophy and Fuchs endothelial corneal dystrophy (FECD). PRK was not indicated in Meesman and Avellino dystrophy. LASIK was indicated in PPCD but not in FECD, Avellino, or Cogan dystrophy. SMILE technique and other dystrophies such as Lattice, Fleck, Lisch or François did not achieve enough scientific evidence to report any recommendation.

Keywords: laser refractive surgery; PRK; LASIK; SMILE; corneal dystrophies

Introduction

A corneal dystrophy is a bilateral, symmetric , genetic, progressive, and hereditary corneal disorder unrelated to environmental or systemic factors, although there are some exceptions.[1] According to the International Committee for the classification of Corneal Dystrophies (IC3D), there are twenty-two types of dystrophies;[2] classified anatomically depending on the main affected corneal layer and their association to gene mutations.[1] The most common and significant anterior corneal dystrophies include epithelial basement membrane (EBMD),[3] Meesmann corneal Dystrophy (MECD),[4] Lisch epithelial corneal Dystrophy (LECD),[5] Reis-Bücklers corneal dystrophy (RBCD),[6] and Thiel-Behnke corneal dystrophy (TBCD).[7] The main stromal dystrophies are granular corneal dystrophy type I (GCD-I), lattice corneal dystrophy (LCD),[8] granular corneal dystrophy type II (GCD-II) also known as Avellino corneal dystrophy,[9] macular corneal dystrophy (MCD),[10] Schnyder corneal dystrophy (SCD),[11] fleck corneal dystrophy (FCD),[12] and central cloudy dystrophy of François (CCDF).[13] Most common posterior dystrophies are Fuchs endothelial corneal dystrophy (FECD),[14] posterior polymorphous corneal dystrophy (PPCD)[15] and congenital hereditary endothelial dystrophy (CHED).[16] The recent update in 2015 by the same group suggested a new anatomical classification, presumably with a better precision according to whether or not dystrophies are positive for the TGFBI gene, as multiple corneal layers can be affected instead of being limited to a single one in these group.[1] TGFBI gene is expressed by both corneal epithelial cells and keratocytes.[17] Therefore, the current classification divides dystrophies into epithelial and subepithelial dystrophies, epithelial-stromal TGFBI dystrophies, stromal dystrophies, and endothelial dystrophies.[1,17] Tools such as histopathology,[18] optical coherence tomography (OCT)[19], gene testing[20] or confocal microscopy[21] may help in the diagnosis. It is estimated that corneal dystrophies affects 0.09% of the USA population, being 60% of endothelial origin, and its treatment is very varied; from simple monitoring to phototherapeutic keratectomy (PTK) and lamellar or penetrating keratoplasty.[22,23]

Regarding laser refractive surgery, laser-assisted in-situ keratomileusis (LASIK),[24,25] laser-assisted sub-epithelial keratomileusis (LASEK),[26] photorefractive keratectomy (PRK)[27] and Small-incision lenticule extraction (SMILE)[28,29] have proven efficacy and safety for the treatment of refraction errors. However, when the patient also presents corneal dystrophy, it is not always compatible with the classic refractive treatment priorly mentioned.[23] According to the food and drug administration (FDA), LASIK treatment is relatively contraindicated when there are visually significant corneal stromal or endothelial dystrophies. In 1995, PTK treatment was approved for the treatment of corneal opacities in anterior corneal

dystrophies.[23] This treatment seems to be safe for corneal opacifications due to dystrophy, but there is no standardized ablation depth protocol. Some authors recommend the use of intraoperative OCT for corneal opacity thickness measurements.[30]

The aim of this systematic review is to report outcomes of laser corneal refractive surgery, disregarding therapeutic procedures, in corneal dystrophies in the available in scientific literature.

Methods:

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[31,32] statement recommendations. We used Pubmed and Web of Science as databases from January 1988 to April 29, 2020. Data search strategy with Boolean operators were: (corneal dystrophies OR epithelial basement membrane OR Meesmann OR Lisch epithelial OR Reis-Bücklers OR Bowman Layer Type I OR Thiel-Behnke dystrophies OR Bowman Layer Type II OR granular OR lattice OR Biber-Haab-Dimmer OR Avellino OR corneal macular dystrophies OR Schnyder OR fleck dystrophies OR central cloudy dystrophy of Francois OR Fuchs endothelial corneal dystrophy OR posterior polymorphous dystrophy OR Groenouw OR TGFBI OR congenital hereditary endothelial dystrophy) AND (photorefractive keratectomy OR laser in-situ keratomileusis OR laser-assisted sub-epithelial keratomileusis OR PRK OR LASIK OR LASEK OR SMILE OR Small incision lenticule extraction) NOT phototherapeutic NOT ectasia. PTK studies were excluded as our aim is to analyze only whether refractive surgery is recommended in corneal dystrophies. The achieved articles (226) were assessed by one author who selected them according to inclusion and exclusion criteria. The data collection was yielded by two unbiased authors who then verified for duplicates. The inclusion criteria were human studies; full-length original article, case series or case reports, retrospective or prospective studies with any subjects, any duration, and any results. Corneal dystrophy must be known prior to laser refractive surgery. The exclusion criteria were non-English publication, unindexed journals, therapeutic or phototherapeutics treatment for corneal dystrophies. Data from each study was summarized in tables designed by the authors.

The following information was obtained from each of the articles: (1) author and date of publication (year), (2) study design, (3) mean follow-up of all patients in the whole procedure (expressed in months), (4) number of patients, (5) number of eyes involved, (6) mean age of the patients (expressed in years), (7)

patients' gender (female / male), (8) reported corneal dystrophy, (9) classic laser refractive surgery procedure. Regarding results of the studies; (10) previous best spectacle corrected visual acuity (BSCVA) expressed in Snellen scale, (11) previous refractive refraction prior to refractive surgery [expressed in diopters (DP) and spherical equivalent (SE)], (12) postsurgical uncorrected visual acuity (UDVA, expressed in Snellen scale), (13) refractive treatment after refraction (expressed in DP and SE), (14) corneal dystrophy recurrence time after refractive laser procedure (expressed in months), (15) corneal findings on slit-lamp, (16) complementary diagnostic test (such specular microscopy or confocal microscopy), (17) visual symptoms reported, (18) topical or surgery treatment after recurrence and finally (19) authors opinion expressed by commenting in favor or against refractive surgery in each particular corneal dystrophy.

To avoid the risk of bias, two reliable authors created a synopsis table (Table 1) based on the Quality Assessment Tool for Case Series Studies from the National Heart, Lung, and Blood Institute.[33] When disagreements occurred among the two assessors, a third non-blinded assessor decided the matter. The questions included in this tool were as follows: (Q1): Is the study oriented to a clear question?; (Q2): Were all the patients results taken into account?; (Q3): Was the follow-up complete?; (Q4): Were the same conditions used in surgical treatment?; (Q5): Was the intervention clearly described?; (Q6): Was the duration of follow-up adequate?; (Q7): Were the results described correctly? This assessment did not determine the exclusion of any study. Articles with a high-level risk of bias had a lower weight for data synthesis.

Results

Study selection process of this systematic review was presented with a flowchart diagram (Figure 1), resulting in 28 studies[34–61] published between 2000 and 2019. Studies were case reports or series of cases. Cases follow-up, expressed in months, ranged from 6.5 months[34] to 108 months[44]. Mean follow-up within all reported studies was 23.9 months. We studied 173 eyes from 94 patients. Patients mean age was 38.50 years old. Gender distribution was 51 females (54.2%) and 39 males (41.5%). Regarding corneal dystrophy distribution: 12 studies[37–39,41–46,52,56,61] reported GCDII, also called Avellino dystrophy or granular-lattice corneal dystrophy; four studies[34,40,53,57] described EBMD, also called Cogan corneal dystrophy; three studies[35,55,59] reported FECD; three series of cases[47,49,58] described PPCD; one case

series[54] reported LCDI; two case reports[50,51] described MECD; and finally, only a single study of the following dystrophies were included: LECD[48], FCD[36] and CCDF.[60] Regarding laser refractive surgery procedures: LASIK procedure was performed in 19[34–39,41,42,46,52–61] of all 28 studies. PRK o LASEK refractive surgery were carried out in nine [40,43–45,47,48,50,51,61], and finally only a single case report[49] described SMILE in a corneal dystrophy. Detailed studies' characteristics were presented in Table 2.

Evaluation of visual and refractive signs and symptoms were presented in Table 3. In summary, mean BCVA was 20 / 37 ± 58.94, mean previous SE refraction was -4.68 ± 3.26 DP. Mean UDVA was 20 / 51 ± 59.45 and postoperative SE refraction -0.82 ± 1.32 DP. Mean recurrence time was 27.7 ± 37.50 months. Best visual and refractive results was achieved in PPCD with an UDVA of 20/19.1 ± 3.11 and postoperative refraction of -0.12 ± 0.15 DP. Secondly, with similar results to PPCD, EBMD achieved a mean UDVA of 20 / 20.3 ± 3.68 and -0.53 ± 0.75 DP postoperative refraction. Worse findings were found in GCDII with a mean UDVA of 20 / 67.5 ± 63.63 and postoperative refraction of -0.95 ± 1.19 DP. Finally, FECD showed the worst results with a mean UDVA of 20 / 97.3 ± 82.49 and postoperative refraction of -1.73 ± 2.50 D. LCDI, LCD, FCD, CCDF and MCD were not included in this analysis due the lack of sufficient reported cases. This data was described in Table 3. Regarding the authors' conclusion on whether to perform laser refractive surgery in corneal dystrophy or not: PRK was indicated for MCD and not for GCDII. LASIK was indicated for PPCD and not for FECD, GCDII, or EBMD. SMILE technique and other dystrophies such as LCDI, FCD, LCD or CCDF did not achieve enough scientific evidence to declare a recommendation. Since only a case report was available, FCD, LCD and CCDF achieved acceptable results with laser refractive surgery, however it is not recommended in LCDI as it shares similar characteristics to GCDII.

Risk of bias assessment was classified into three evidence-level groups. Studies with yeses from zero to three: Rezende et al.,[57] Zaidi and MacLeod,[60] Banning et al.,[61] Roh et al.,[37] Banning et al.,[36] Aldave et al.,[38] Chiu,[39] Kim et al.,[42] Chao-Shern et al.,[52] and Nithianandan et al.[54] Studies with yeses from four to five: Dastgheib et al.,[34] Vroman et al.,[35] Wan et al.,[46] Dastjerdi and Sugar,[55] Lee et al.,[43] Moshirfar et al.,[59] Park et al.,[44] Ha et al.,[45] Bower et al.,[47] and Wessel et al.[48] Finally studies with yeses from six to seven: Jun et al.,[56] Moshirfar et al.,[58] Kymionis et al.,[40] Kim et al.,[41] Park et al.,[49] Greiner et al.,[51] Ghanem et al.,[50] and Chuckpaiwong et al.[53]

Discussion

Epithelial and subepithelial dystrophies

Epithelial basement membrane dystrophy

Former named as map-dot-fingerprint dystrophy, Cogan microcystic dystrophy or anterior basement membrane dystrophy, is the most common corneal dystrophy, affecting 5-18% of the population.[62,63] Typically slit lamp findings resembled geographic maps, lines, dots, and fingerprints of thickened, round, or linear hazy epithelium. It is associated to painful recurrent corneal erosions (RCE) that typically occur from minor trauma characteristically with sharps objects.[1,23,63] Vision could be affected due to irregular astigmatism.[1] EBMD may have poor adherent corneal epithelium and is predisposed to epithelial sloughing during the microkeratome pass of LASIK.[23,62] Dastgheib et al.[62] found epithelial sloughing during LASIK surgery in 13 of 16 eyes with EBMD; in eight eyes, epithelial growth beneath the flap was observed, and flap melting occurred in four eyes. Posteriorly, and in the same line, Rezende et al.[57] reported epithelial ingrowth and irregular astigmatism in 25,7% and 45,7% of the patients, respectively.[64] Recently, Chuckpaiwong et al.[53] reported corneal epithelial sloughing and diffuse lamellar keratitis (DLK) in both eyes in a patient after wavefront-guided Femto-LASIK (FS-200 Wavelight femtosecond laser and the EX-500 excimer laser- Alcon, Fort Worth, Tex.), surprisingly nine months post-surgery. The author hypothesized[53] that less severe iatrogenic epithelial injury secondary to the advanced femtosecond laser technology could be one of the factors that may explain why this patient suffered corneal erosion nine months after the surgery, and not immediately after the intervention, as it is reported in the previous research priorly mentioned.[63,65]

PRK may be a safer alternative than LASIK for refractive error correction in patients with EBMD as it may have a therapeutic effect due to the elimination of the abnormal epithelium.[23] Kymionis et al.[40] reported successful outcomes after 12 months of follow-up in a single case of EBMD that was treated with classic PRK in both eyes.[66]. In a recent retrospective study by Diez-Feijóo et al.[67], 116 eyes with recurrent corneal erosion (RCE) were evaluated. Results showed that PRK was attributed as the main cause, representing 20 eyes (17.1%), and LASIK in nine eyes (7.7%).[67] Similarly, Ti and Tan[65] reported

the development of RCE syndrome in eight eyes of six patients after LASIK, one of them being an undiagnosed EMBD prior to surgery. Similar findings were reported by Perez-Santoja et al.[63], observing the occurrence of large intraoperative epithelium sloughing during LASIK. The authors[63] suggested that this finding could be a first diagnostic sign for subclinical EBMD. Therefore, clinicians must carefully examine any patient with suspicion of EBMD, and most of the authors recommend not perform refractive surgery if EBMD is present. Finally, as to 10% of EBMD patients could have a mutation in the TGFBI / BIGH3 gene,[68] testing for TGFB1 mutations should be recommended in patients with EBMD, especially if planning for refractive surgery.[1,53]

Lisch cornea dystrophy

Former named as Band-shaped and whorled microcystic dystrophy of the corneal epithelium and with X-chromosomal dominant inheritance is characterized by band-shaped and grayish lesions in whorled, radial or feathery patterns.[1] Patients remain usually asymptomatic, being sometimes visual acuity affected if the opacities reaches the pupillary axis.[17] Only a single case report on refractive surgery in LCD has been published. Wessel et al.[69] performed a bilateral PRK with Mitomycin C (MMC) and followed the patient for 13 months. Although the recurrence was first observed in the first four weeks; during the follow-up, the lesions gradually decreased, turning into a faint linear opacity that covered just about a tenth of the surface area of the initial injury, and observing a 20/15 VA at last follow-up.[69] These results only represent a single case of two eyes, being the only ones described in the literature and therefore being difficult to find a strong evidence. However, according to these results, PRK could be a good option for refractive correction in LCD patients.

Meesmann corneal dystrophy

Former alternative named as Juvenile hereditary epithelial dystrophy[1] and with AD inheritance and due to a mutation in keratin 3 and keratin 12 genes [17] is characterized by multiple, tiny intraepithelial vesicles extend to the limbus and being more numerous in the interpalpebral area. Patients are typically asymptomatic although some patients complain of glare and light sensitivity and even painful RCE had been decribed.[1,17] Greiner et al.[51] and Ghanem et al.[50] performed bilateral PRK each in a single patient,

with 20% alcohol assisted mechanical de-epithelization and with 0.02% MMC only in Ghanem's patient. A complete recurrence of the dystrophy was observed in both patients approximately one-year post-surgery. Regarding VA, Greiner et al.[51] reported 20 / 20 whereas Ghanem et al.[50] reported 20 / 45 after re-PRK enhancement in one-year follow-up. These results represent the outcomes of only four eyes, being difficult to prove a strong evidence. According to these results, PRK should not be a good option for refractive correction in MCD patients.

Epithelial-stromal and stromal dystrophies TGFBI

The molecular functions of the beta-induced transforming growth factor (TGFBI) in vivo are not completely understood, although it has been suggested that it could act as a cell adhesion molecule and as a bifunctional linker protein interconnecting different matrix molecules to each other and to cells.[17] TGFBI gene encodes keratoepithelin protein, which is secreted by the corneal epithelium. The mutated keratoepithelin proteins penetrate the Bowman's layer and the stroma where they bind forming insoluble deposits. It seems that mutations in this gene are the ones that cause certain corneal dystrophies that characteristically associate RCE hence related to a poorer prognosis when laser refractive surgery is carried out in these patients.[23,70]

Lattice Corneal Dystrophy, type 1 (Classic) (LCDI) and Variants

Former named as Biber-Haab-Dimmer dystrophy is clinically characterized by a refractile branching lines and subepithelial, whitish, ovoid dots in the first stages. These lines start centrally and more superficially in first decade of life, and spread centrifugally and deeper later, preserver the peripheral stroma, Descemet membrane and the endothelium. In the last stages is associated with a diffuse subepithelial central and paracentral ground-glass corneal haze along with the lattice lines in the central and paracentral cornea, that diminish the visual acuity.[1,17] LCDI is used to be associated to RCE.[1,17] Typically presents amyloid deposits, that characteristically stain rose or orange with Congo red and display birefringence under polarized light.[1]

Only a single paper has been published regarding refractive surgery in LCDI. Nithianandan et al.[71] recently published one family (mother and son) with LCDI, both of them with a mutation in exon 14 of

the TGFBI gene. LCDI was discovered after LASIK and tree branch trauma, respectively. This case report lacks specific information of the surgical procedure and the follow-up was inadequate. Moreover, due to the central lattice-like changes at the LASIK flap with an impairment of visual acuity reported by the author,[71] it seems reasonable to assume that laser refractive surgery is not recommended in patients with LCDI.

Granular corneal dystrophy type II:

Former named as Avellino corneal dystrophy, or combined granular-lattice corneal dystrophy is an AD dystrophy also arising from a mutation in the TGFBI gene on chromosome 5q31.[1,23,72] The disease-causing mutation is a heterozygous substitution, Arg124His in TGFBI.[17] Characteristically, GCD-II have clinical (crumb-like granular opacities and small spokes[1] or stellate elements[17]) and histologic (hyaline and amyloid deposits which stains with Masson trichrome and / or Congo red) of both granular and lattice corneal dystrophy.[1,17,23] Patients generally experience episodes of painful RCE.[1,17] Vision decreases with age as the central visual axis becomes affected and due to scarring and irregular astigmatism.[1]

Regarding refractive surgery, Wan et al.[46] reported the first case of LASIK in a 23-year old female patient with GCD-II and an exacerbation of the disease one year after the surgery.[73] Since this case, several reports had been published and, as a matter of fact, GCD-II is the most reported corneal dystrophy after laser refractive surgery.[74–80] Two years later, Jun et al.[74] reported similar results in 11 GCD-II eyes that experienced an exacerbation of the opacities, causing visual impairment. They suggested that surgical elimination of the opacities does not prevent a recurrence of the latter and the use of MMC could help to solve this issue. Nevertheless, reporting a single patient followed-up for scarcely 6 months, there is insufficient evidence to support the use of MMC. Roh et al. [76] interestingly pointed out in their research of 3 patients with GCD-II using scanning electron microscopy, how abnormal granular clusters deposit in the LASIK flap and interface. Hypothesizing that LASIK surgery exacerbated these deposits, they demonstrated that deposits observed in LASIK flaps of GCD-II corneas were not found in the paired control corneas.[76] Banning et al.[61] described the first case of post-LASIK recurrence of GCD-II in North America.[81] Kim et al.,[42] studied stromal deposits in the LASIK flap of their patients, finding that these displayed bright red colour staining with Masson trichrome; however, negative staining was observed with Congo red. These authors suggested that hyaline was the main component of the TGFBIp deposits rather than amyloid.[77] Interestingly, Awwad et al.[82] described the histopathological characteristics of the

Aldave[38] patient's left cornea. The authors found that the cornea stained deep red with Masson's trichrome and positively, although weakly, with Congo red too, though showed no apple-green birefringence in light cross-polarization. They suggested that this could be due to the production of amyloid-forming keratoepithelin configurations.[82]

Kim et al.[83] compared 10 eyes from five patients with heterozygous GCD-II. Three patients underwent bilateral LASIK and two patients bilateral PRK. Although a recurrence of the underlying disease was observed in all the patients, curiously, fewer deposits were observed in patients operated with surface ablation surgery compared to the abundant whitish and coalescing deposits at the post LASIK corneal interface. Surprisingly, in a case of LASIK with an incomplete bilateral flap, they observed abundant opacities in both corneas along the interface of the LASIK flap whilst a minimal increase of stromal opacities was noted where no LASIK flap was present. In the same line as the case reported by Park et al.,[44] who described the recurrence of corneal deposits in GCD-II 9 years post-PRK. Lee et al.[43] also published exacerbations of the whitish opacities, manifesting them in the form of a diffuse and confluent pattern, and resulting in a decrease in VA in 15 eyes of eight patients with GCD-II after laser-assisted subepithelial keratomileusis (LASEK). Intraoperative MMC appears to have no benefit in controlling exacerbations in patients with GCD-II.[43] This was subsequently confirmed in a 3-year follow-up study by Ha et al.[45] who compared 10 eyes, in which MMC was used, and other 10 eyes in which it was not. The author did not observe any benefit in the prevention of recurrence of opacities in any patients who underwent surface refractive ablation surgery. The latest published article as far as we know concerning refractive surgery in GCD-II is the case reported by Chao et al.[52], who presented a 29-year-old Chinese GCD-II male patient with a recurrence of opacities and VA deterioration 10 years after LASIK surgery. The authors denote the importance of ruling out mutations in any asymptomatic refractive surgery candidates with a positive family history to avoid future complications.

Surgeons should be cautious with the potential rapid TGFBI opacity deposition in the stromal interface following any form of lamellar corneal surgery in these patients, since accelerated deposition would be expected in TGFBI dystrophies.[75] Although most publications only report a single case or series of cases, most of the authors agree with the early recurrence of these deposits, that moreover appear to be deposited more aggressively, confluently and with a large visual impairment due to the injury of the central cornea. This damage originates an accelerated opacification[1] that has required a penetrating or

lamellar keratoplasty for visual correction in many occasions. Therefore, there seems to be enough evidence to suggest the contraindication of laser refractive surgery, especially LASIK, in patients with GCD-II.

Stromal dystrophies

Fleck Corneal Dystrophy

Formerly known as François-Neetens speckled (mouchetée) corneal dystrophy, FCD has an AD inheritance. Clinically, FCD is asymptomatic and characterized by small, translucent opacities scattered throughout the whole corneal stroma without a defined pattern that may extend to the limbus.[1,23,84] Regarding refractive surgery in FCD, just a single case report has been published. Banning et al.[85] reported myopic LASIK outcomes in a 48-year-old with FCD. Six years after surgery, the patient had a slight amount of myopic regression, but maintained BSCVA of 20 / 25 in both eyes being 20 / 20 in both eyes with rigid gas-permeable contact lens fitting as a consequence of eight corneal incision scars from a previous radial keratotomy. Therefore, as only one case has been reported added to the past medical history of radial keratotomy surgery, it is difficult to establish strong evidence. Based on this case solely and to the asymptomatic course of this dystrophy, it appears that laser refractive surgery may not cause visually significant exacerbation of FCD.

Central Cloudy Corneal Dystrophy of Francois

CCDF has no known genetic locus, and in just few reports AD have been described as inheritance.[16,23] Being mostly asymptomatic, slit-lamp exam reveals central polygonal or rounded stromal opacities characteristic in a mosaic pattern and it is difficult or inclusive may be phenotypically indistinguishable from posterior crocodile shagreen degeneration.[16,17] There is only one case report of refractive surgery, specifically LASIK, in CCDF published in the literature. At 5 years' follow-up, the patient had no progression of corneal opacities in either eye and VA remained 20 / 20. Once again, as it is a single case, it is hard to obtain evidence. Based on the outcomes, the excellent refractive result, the great stability over

time and the asymptomatic course of this dystrophy seem to imply that laser refractive surgery could be a viable option in these patients.

Endothelial dystrophies

Fuchs Endothelial Corneal Dystrophy (FECD)

FECD is characterized by an enhanced loss of endothelial cells disabling its pump mechanism hence developing corneal edema and visual impairment.[86] Early- first decade- and late- fourth decade- onset have been described. Female predominance with a 2.5:1 in both onsets has been described.[16] Slit-lamp examination reveals Descemet membrane excrescences *(guttata)* that can be directly observed in confocal microscopy as focal thickening of Descemet membrane as well as increased endothelial cell size variability (polymegathism) and shape variation (pleomorphism).[1,87]

Healthy endothelium has reported to positively tolerate PRK[35] as well as LASIK surgery[35,59] proving no significant endothelial cell changes throughout a long follow-up. Nevertheless, these results do not apply for dysfunctional endothelium, particularly, LASIK surgery. We found no cases reported in the literature describing PRK in patients with FECD. Vroman et al.[87] reported a single patient with bilateral FECD in both eyes and corneal edema in the left eye that underwent hyperopic LASIK surgery developing persistent corneal edema in both eyes since day-one postoperative. Seven months after the surgery, UDVA was 20/40 in the right eye and 20/100 in the left eye, requiring penetrating keratoplasty in the latter after 14 months. Dastjerdi et al.[88] reported a single patient with a central corneal thickness (CCT) of 587µm in the right eye and 549µm in the left eye. Slit-lamp examination proved guttata in both eyes. One-day postoperative, the patient suffered from corneal stromal edema and confluent guttata 4+. Moshirfar et al.[89] reported a retrospective case series with 1-year outcomes of seven eyes with corneal guttata undergoing LASIK. A loss of two lines in BCSVA was observed in six out of seven eyes, as well as a 12,4% decrease in ECD, increase in CCT and myopic shift.

Several mechanisms describing endothelial damage due to laser treatment have been postulated, such as mechanical trauma due to shock waves, duration of intraocular pressure changes during LASIK and stromal bed irrigation.[59,90,91] Single cases reporting FECD decompensation after LASIK may be biased as the increase in IOP due to the microkeratome itself may be responsible for this event.[87] Femto-LASIK

procedure in these patients would balance this issue. Although CCT may be in normal ranges preoperatively, this value may signify corneal edema in thinner corneas.[88] ECD rate loss in FECD not undergoing surgery is unknown, therefore hindering the interpretation of ECD loss after LASIK surgery.[89] According to these cases, reported unfavorable outcomes of LASIK in FECD patients seem to imply to restrain from this procedure in these patients, especially with evident corneal edema, or family history of FECD.

Posterior Polymorphous Corneal Dystrophy (PPCD)

PPCD is an AD endothelial dystrophy, usually with a stable course.[1] Research suggests that the pathogenesis arises from endothelial cell metaplasia into epithelial-like or fibroblast-like cells.[47,92] Slit-lamp examination shows geographic gray opacities, vesicular lesions, and band-like lesions (railroad tracks) in Descemet membrane and endothelium.[16] Endothelial decompensation is rare as the clinical course is usually benign.[16] However, diffuse PPCD affects the entire posterior corneal surface causing edema and visual loss.[47,93]

Regarding refractive surgery, Moshirfar et al.[94] reported visual acuity, ECD and pachymetry outcomes in 4 eyes with vesicular PPCD undergoing LASIK. All eyes showed an equal or better BSCVA than 20/20 after one-year follow-up, despite a near-normal mean ECD loss of 2,3%. Bower et al.[95] reported PRK outcomes in 14 eyes with vesicular and band-like subtypes. All treated eyes had an equal or better UDVA than preoperative CDVA, no corneal decompensation was reported, and ECD, polymegathism and pleomorphism was unchanged from preoperative baseline. Park et al.[96] described positive and safe results of SMILE procedure in a patient with band-like PPCD and low ECD count (1745 cells / mm^2) in one eye. One-year postoperative, UDVA was 20/20 in both eyes and ECD count was 1859 cells / mm^2 after surgery.

Despite the cases that report corneal decompensation in diseased endothelium, such as FED, the amount of healthy endothelium required to tolerate LASIK surgery is unknown.[94] Risk of LASIK in PPCD is unclear, as decreased VA may result if posterior corneal topographic changes occur.[94,97] Moreover, studies show good results in mild forms of PPCD, vesicular or band-like,[47,49,58] and not in diffuse forms or associated with iris abnormalities or glaucoma. Overall, reported outcomes tend to favor both PRK and LASIK in mild forms of PPMD.

Strengths and limitations

To the best of our knowledge, this is the first systematic review that describes refractive surgery outcomes in corneal dystrophies. We focus only on refractive surgery and do not include PTK results. Moreover, we add to available scientific literature refractive outcomes in LCDI, MCD, and LCD, new cases of GCDII and describe cases reporting Femto-LASIK and SMILE procedures. The main limitation of our review is that all studies included are case reports or series of cases, many of them having a retrospective design and short-term follow-up periods. No randomized clinical trials were included as there is yet none in the available literature.

In conclusion, this systematic review demonstrated that PRK was not indicated for Meesman corneal dystrophy and Granular corneal dystrophy type II. LASIK was indicated for posterior polymorphous corneal dystrophy and not for Fuchs endothelial corneal dystrophy, granular corneal dystrophy type II, or epithelial basement membrane dystrophy. SMILE technique and other dystrophies such as Lattice-I, Fleck, Lisch or central cloudy dystrophy of François did not achieve enough scientific evidence to report a recommendation.

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Figure Legends

Figure 1 – Flow chart diagram