ABSTRACT

Purpose: To provide a comprehensive overview of ectasia development following laser-assisted in situ keratomileusis (LASIK).

Materials and methods: Literature review of relevant studies dealing with corneal ectasia associated with refractive surgery, keratoconus (KC), and cross-linking.

Results: Post Laser-assisted (PLE) involves histopathologic, clinical, and topographic characteristics similar to KC. Several risk screening indices were developed to enhance the detection of KC suspect and mild KC cases prior to the laser procedure. A grading system of PLE was developed, based on risk factors for the severity of ectasia, primarily measured by visual loss. The aims of the treatment are halting ectasia progression and restoring visual acuity.

Conclusion: Familiarity with the highly sensitive and specific indices for ectasia screening, in addition to procedure parameters that increase the likelihood of ectasia development following the refractive procedure, is essential for minimizing the risk of PLE. However, when ectasia develops, early recognition and proper management are essential to prevent progression and improve visual rehabilitation.

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INTRODUCTION

Corneal refractive surgery is one of the most performed surgeries in ophthalmology. Laser-assisted in situ keratomileusis is the most practiced and performed procedure. Iatrogenic corneal ectasia, though a “rare” complication after corneal laser refractive surgery (CLRS), is one of the most feared situations that can occur after uneventful CLRS. Post-LASIK ectasia consists of progressive corneal steepening with stromal thinning due to a reduction in biomechanical stability of the cornea.1

This review outlines the incidence, risk factors, pathogenesis and histopathology, diagnosis, treatment approaches, and prevention of PLE.

INCIDENCE

Post-LASIK ectasia may occur as early as 1 week following the operation; however, several reported cases show development of PLE as late as 10 years after surgery.2 An incidence rate of 0.04 to almost 2.8% has been reported.3 However, PLE is underreported and the actual number of cases is not known. This could be due to the fact that CLRS is performed mainly in private medical centers and this contributes to the underreporting of complications. Consequently, many of those cases are seen in courts but not in the literature.

Ectasia is most common following LASIK; however, it has been reported following photorefractive keratectomy (PRK).4-6

RISK FACTORS

Recognizing risk factors of ectasia development prior to refractive surgeries is crucial. Randleman et al7 reviewed cases of corneal PLE and did not identify any patients who developed ectasia without recognizable preoperative risk factors.

Risk factors for iatrogenic ectasia development following refractive surgery were evaluated in various studies. In a recently published review, Giri and Azar8 report several risk factors identified in previous studies that include: Forme fruste KC, genetic predisposition to KC, low residual stromal bed (RSB) thickness (due to high myopia, thin preoperative cornea, or thick LASIK flap), irregular corneal topography, eye rubbing, young age, and pregnancy.

According to Santhiago et al,9 abnormal corneal topography remains the most important identifiable risk factor for ectasia. Information derived from tomography, such as pachymetric and epithelial maps as well as computational strategies, is additional and relevant in the detection of KC. Analysis of alterable biomechanical properties, such as the amount of tissue altered by surgery and the remaining load-bearing tissue, is also essential. According to the authors, in eyes with normal preoperative placido disk-based topography, a high value of percentage of tissue altered (PTA), especially 40%, is a relevant factor in the development of PLE. However, Saad et al10
evaluated the role of PTA in PLE development, among eyes with normal topographies prior to the operation. They included 593 eyes; a flap with PTA of 40% or more was performed in about 20%. No eye developed ectasia over a mean follow-up period of 30 months. Therefore, the authors concluded that PTA did not predict PLE, in eyes with normal preoperative topography. With regard to RSB, there are some inconsistencies in determining the cutoff value to avoid ectasia after LASIK. Seiler et al proposed the cutoff value of 250 μm, though this value is questionable in some areas. Low preoperative corneal thickness alone has been found to be a weak predictor of ectasia; nevertheless, the authors state that central corneal thickness (CCT) values <480 μm should still be seen with caution, due to the prevalence of KC in this group. The isolated prevalence of a high myopia within the high-risk range (higher than 8D) in eyes with normal topography is significantly low. When truly associated with the disease, high myopia commonly presents together with clear signs of topographic or tomographic abnormalities. Though controversial, age is another important source of information about a patient’s intrinsic biomechanical properties, when corneal topography is normal. Eyes that develop ectasia tend to be younger than those of controls. This observation can be partially explained by the fact that younger corneas theoretically present lower corneal cohesive tensile strength, which can shift over time, and considering KC is a progressive disease, simply because young patients may have not yet developed the first detectable topographic signs. The authors consider history of eye rubbing and chronic trauma as potential risk factors for the progression of ectasia, although no studies scientifically validate the relationship between them. Unstable and suboptimal refractions with <20/20 best spectacle-corrected visual acuity and a family history of KC may also be warning signs of undetectable ectatic disorders, increasing the risk of corneal ectasia; nevertheless, the authors state that central corneal thickness alone has been found to be a weak predictor of ectasia after refractive surgery, and therefore should be given consideration, especially in borderline candidates. Interestingly, PLE associated with floppy eyelid syndrome as a single risk factor was also reported.

New topographic and tomographic corneal indices have emerged as key parameters for improving the sensitivity of subclinical KC detection prior to the refractive procedure. Referring to a review published by Smadja, different indices based on placido topography, Scheimpflug imaging, slit scanning, and pachymetry may assist in the diagnosis of early ectatic disorders. Based on placido topography, Rabinowitz and Rasheed developed the “I-S ratio,” while a cutoff value of 0.8D is considered KC suspect. Later, Maeda et al have developed the KC prediction index to help differentiating KC from other irregular patterns. The KISA% index proposed by Rabinowitz and Rasheed is more sensitive and specific in diagnosing KC than the previous indices. A novel topographic curvature pattern called the “vertical D” was proposed by Abad et al, which reflects horizontal asymmetry and was found only in eyes suspected for KC based on other parameters like pachymetry and posterior elevation. Based on Scheimpflug-fluc and slit scanning technology, Schlegel et al have reported significant greater posterior astigmatism, posterior elevation, and a more prolate posterior surface in suspect keratoconic eyes compared with normal eyes with the Orbscan IIz system (Bausch and Lomb). This finding was later supported by Pentacam (Oculus) and Galilei system (Ziemen Inc.).

Randleman et al developed a risk factor stratification scale, the Ectasia Risk Score System (ERSS), based on evidence review of a large series of LASIK ectasia cases. The ERSS is a quantitative method used to identify eyes at risk for developing ectasia after LASIK by evaluating multiple risk factors simultaneously, with a specificity of 91% and a sensitivity of 96% in their published series. Risk factors included in this system are: Abnormal corneal topography, low RSB, young age, low pre-op pachymetry, and high myopia. Despite being a helpful tool in the screening strategy, its utility is controversial because over the past decade diagnostic methods of screening for preoperative ectasia have changed and corneal tomography has emerged and have almost totally replaced the placido disk-based “topography,” which only measures anterior corneal curvatures.

Ambrósio and Belin proposed a dual-screening approach for ectasia risk prior to refractive surgery, considering that ectasia occurs as a result of a combined preoperative patient susceptibility and the impact of the procedure on the cornea. Advanced corneal analysis, using corneal tomography, epithelial mapping by optical coherence tomography, and the corneal biomechanical properties assessed by the ocular response analyzer, further enhances the accuracy of mild ectasia detection. Laser procedures carry different biomechanical effects, due to different flap cut parameters. Combining the impact from the procedure with an advanced corneal analysis may considerably improve the detection of high risk cases and minimize PLE development.

PATHOGENESIS

A retrospective study conducted by Pahuja et al suggests an ongoing inflammatory response in PLE corneas. Their study included 12 eyes of PLE subjects (based on corneal topography) and 14 post-LASIK control eyes. Data obtained concerning both groups included: Ocular surface disease index (OSDI) scores (based on questionnaires), corneal dendritic cell density (DCD), and sub-basal
nerve plexus morphology using in vivo confocal microscopy. Moreover, inflammatory cytokines/chemokines in the tears were quantified using flow cytometry-based cytometric bead array. The study results demonstrate a statistically significant positive correlation between OSDI score and total corneal DCD in PLE patients. In addition, a significant difference in the cytokine profile was found between normal and ectatic corneas, as the fold difference of chemokine legend/monocyte chemotactic protein-1 was significantly higher in the latter group. Both evidences may propose an inflammatory process as the mechanism underlies the ectatic changes that occur following LASIK.

HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY

Referring to the study of Dawson et al., inspection of PLE corneas by light microscopy and hematoxylin–eosin staining demonstrated RSB thinning, hypocellular stromal scar, larger than normal artifactaceous interlamellar cleft in RSB, and fewer areas of Bowman’s layer disruption than KC. Furthermore, transmission electron microscopy showed thinning of the collagen lamellae and loss of lamellar number in the RSB and decreased interfibril distance. Immunohistochemical evaluation of PLE revealed abnormal epithelial basement membrane (EBM) structure similar to KC and bullous keratopathy and increase in certain proteinases indicating lysis and remodeling of EBM.

In a prospective comparative case series, Kymionis et al. investigated corneal tissue alterations after corneal collagen cross-linking in patients with post-LASIK keratectasia (five eyes) and KC (five eyes). Three normal/healthy and three post-LASIK without ectasia corneas were also examined as controls. Confocal microscopic analysis of PLE showed unevenly distributed highly reflective collagen scars with reduced keratocyte density and background transparency at the anterior stroma compared with normal post-LASIK eyes.

DIAGNOSIS

Clinical diagnosis of corneal ectasia is made by progressive central or inferior corneal steepening, increased myopia and/or astigmatism, and decreased uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA). Various topographic patterns of keratectasia following LASIK were reported. Eissa has published a retrospective case series of 44 PLE eyes, among them 29 eyes (65.90%) presented early with crab-claw/pellucid-like pattern, 6 eyes (13.63%) first presented with asymmetric bow tie with inferior steepening. Isolated inferior steep cone was the pattern in 6 eyes (13.63%), whereas 3 eyes (6.81%) presented early with superior steepness.

CHARACTERISTICS OF PLE

Padmanabhan et al. reported the refractive, topographic, tomographic, and aberrometric characteristics of PLE and compared those characteristics with normal post-LASIK controls. Their study results show that eyes with PLE had significantly higher myopia with astigmatism and a lower CDVA than control eyes. Mean topographic toricity, mean keratometry at the steepest point, mean highest posterior elevation, and mean coma were significantly higher than corresponding values in the control group (p < 0.001 in all). Spherical aberration was more negative and the change in asphericity indicated significantly greater prolate shape of the cornea in eyes with PLE compared with controls. Likewise, Twa et al. compared the characteristics of 86 PLE eyes with 103 eyes of successful post-LASIK patients. According to their results, residual myopia in the ectasia group was significantly greater than the comparison group. Eyes with ectasia had a statistically significant increased corneal toricity with increased oblique astigmatism and a loss of two lines of CDVA relative to eyes in the comparison group; 35% of reported cases resulted in subsequent corneal transplantation.

GRADING OF ECTASIA

A study of KC cases proposed a grading system for ectasia based on visual limitation. This multicenter, retrospective study was published by Alió et al. and comprised 776 keratoconic eyes. The grading system incorporated between-group differences in the most important clinical parameters, such as mean keratometry, internal astigmatism, corneal higher-order aberrations (HOAs), and biomechanical measurements. Correlations between clinical data and a linear multiple regression analysis for characterizing the relationship between visual limitation and objective clinical data were performed. The mean keratometry (K) correlated significantly with CDVA, internal astigmatism, corneal asphericity, and several corneal HOA coefficients. Significant correlations were found between some corneal aberrometric parameters and CDVA. There were significant differences in mean K, internal astigmatism, and corneal HOAs between four groups differentiated by visual limitation. Based on the evaluated data, the severity of the disease was classified.

Following the development of the visual function-based grading of KC by Alió et al., Brenner et al. used the same grading method to evaluate and characterize the main clinical features of PLE, propose a grading system based on visual limitation, and identify predictive factors.
related to the degree of visual loss. Instead of inspecting preoperative risk factors, the authors focused on the risk factors for the severity of PLE, primarily measured by visual loss. Ninety-six PLE eyes were enrolled and the main outcomes, namely, CDVA, CDVA loss, spherical equivalent (SE), and corneal bulge (delta K) were correlated with the RSB, ablation depth, ablation ratio (ablation depth: pachymetry), corneal depth (flap + ablation depth), and corneal ratio (corneal depth: pachymetry) to characterize their role in the severity of the disease. The results show that the ablation ratio had the strongest correlation with PLE CDVA; the corneal ratio had the strongest correlation with the PLE SE and delta K; and the ablation ratio was the main predictive factor for PLE CDVA loss. Therefore, a high amount of tissue removed by the refractive procedure, rather than the amount of tissue left RSB, was associated with greater corneal biomechanical destabilization, increased corneal steepening, and a worse prognosis.

KERATECTASIA FOLLOWING PRK

Compared with LASIK, ectasia is much less common after PRK. In a large series, the incidence of PLE approached 96%, while only 4% of the cases developed after PRK. Hodge et al reported a case of ectasia developing in a PLE of a patient who underwent LASIK in one eye and PRK in the other eye. Neither eye had risk factors for keratectasia prior to surgeries. Shalchi et al followed 47 post-PRK eyes prospectively, with no evidence of ectasia 18 years following the surgery. In a retrospective case series, Naderi et al evaluated the long-term safety and efficacy of PRK in 74 eyes with myopia and thin corneas (CCT < 500). After the surgery, there was no evidence of corneal ectasia on any of the Orbscan topography images 4 years following the surgery.

Different studies attempted to identify risk factors of such a complication. According to a study by Sorkin et al, the identified significant risk factors for ectasia development after PRK using the ERSS included preoperative corneal topographic abnormalities and thin corneas. Those factors overlap with risk factors known for ectasia development after LASIK; however, the incidence rates are much lower, most probably due to the development of different biomechanical changes following both procedures. The LASIK flap itself is functionally decoupled from the cornea, thus providing minimal tensile strength and in certain patients, where predisposing preoperative factors exist, this results in significant loss of biomechanical integrity.

TREATMENT

The treatment approach is similar to KC, and depends to a large extent on the ectasia severity. However, it is worth noting that the PLE patients’ expectations differ from those of KC patients. The former chose LASIK specifically to obtain excellent vision without correction and loss of visual acuity can be quite frightening for them, as well as deeply frustrating.

The goals of ectasia management are: halting ectasia progression and restoring visual acuity.

Contact Lenses

First line is contact lenses (CLs, a primary tool for improving visual acuity. Soft CLs are suitable for the mild cases. However, as the ectasia progresses, the optically smooth surface from a rigid gas-permeable (GP) lens is necessary to ameliorate the irregular corneal surface of the ectatic eye and provide clearer vision. Not surprisingly, patients who require CLs after LASIK due to postsurgical ectasia are often unsatisfied, since they chose to have LASIK surgery to eliminate their need for glasses and CLs. Piggyback CLs can improve vision in moderate ectasia cases, but can be inconvenient for patients because of their need to clean and care for both soft and GP CLs. Likewise, hybrid CLs may also improve the comfort; however, their variable clinical performance, high giant papillary conjunctivitis rates, and breakage at the GP and soft lens junction may limit their use. Mini-scleral, semi-scleral, and scleral lenses are generally reserved for moderate to advanced stages of ectasia as well as those patients who find traditional GPs uncomfortable and for patients with moderate to severe dry eyes.

Cross-linking

Corneal collagen cross-linking (CXL), either epi-on or epi-off, is a promising treatment to actually delay and potentially halt the progression of many ectasias, including KC, pellucid marginal degeneration, and PLEs by strengthening the collagen lamellae of the cornea. In a retrospective case series study, Yildirim et al reported the long-term outcomes of CXL in 20 PLE eyes of 14 patients. The mean follow-up was 42 ± 7 months (36–60 months). At the last follow-up visit, the UDVA and CDVA improved significantly. No eye lost one or more Snellen lines of UDVA or CDVA. The mean cylindrical refraction decreased significantly, although the mean spherical refraction was not significantly different. The maximum K value decreased from 46.0 ± 4.4 diopters (D) at baseline to 45.6 ± 3.8D at the last visit (p = 0.013). By the last visit, the maximum K value decreased (≥1.0D) in five eyes and remained stable in 15 eyes. Therefore, CXL yielded stability, and improvement in visual acuity, cylindrical refraction, and maximum K values occurred in some cases. Tong et al outlined the results of CXL in a recently published retrospective review of
refloated and adjusted back into position and an accel-and any excess riboflavin is removed. The flap is then stromal bed for 3 minutes. The stromal bed is then dried, soaked with 0.25% riboflavin solution is placed on the pachymetry performed on the stromal bed. A sponge lifting the existing LASIK flap, followed by ultrasound erated UV light exposure is performed (18 mW/cm² for by Wallerstein et al.47 The under-flap technique involves stromal bed CXL (ufCXL) for early PLE, were published the outcomes of a novel technique, namely, under-flap UDV A improved 4.5 logMAR letters as well. Furthermore, the minimum angle of resolution (logMAR) letters. The CDV A improved by an average of 5.0 logarithm of the under-flap CXL (ufCXL) for early PLE, were published the outcomes of a novel technique, namely, under-flap with single-segment implantation; nonetheless, the level of visual acuity in the single-segment group was significantly better than that in the double-segment group. Combined Surgery: ICRS and CXL

The ICRS can be used in combination with collagen cross-linking either prior to the cross-linking or 3 months prior to the cross-linking. While CXL halts the disease
progression, the stromal pathology is not altered by ICRS, rather the insertion of corneal rings lead to flattening that finally modify the corneal curvature. This improves both the refractive error and decreases the possibility of continued progression of the ectasia.

Barbara et al reported the outcomes of sequential CXL followed by ICRS implantation in a rare case of corneal ectasia developing in one eye of a young patient, after PRK that was performed in his both eyes. Prior to CXL, UDVA in the LE was finger counting at 2 m, improving to CDVA 20/40 with −1.50 −1.25 × 150°. Following CXL and ICRS, UDVA improved to 20/80, refraction was plano −3.0 × 110 and CDVA approached 20/30.

Yeung et al evaluated the efficacy of single or paired ICRS combined with ultraviolet-A and riboflavin CXL in patients with KC. Overall, 85 eyes were included in the study (paired ICRS: 47 eyes; single ICRS: 38 eyes). At 1 year, UDVA and mean cylinder improved significantly in both groups, whereas CDVA remained stable. No significant difference in total HOAs. Single ICRS implantation and paired ICRS implantation with CXL were equivalent in all refractive parameters. The authors conclude that implantation of single or paired ICRS combined with same day CXL is safe and effective in patients with KC.

In a noncomparative case series, Kılıç et al evaluated the effectiveness of riboflavin injection into the cornea, through the ring segment channel, in combined surgeries, ICRS and transepithelial CXL. This strategy proved to be effective as UDVA, CDVA, mean manifest spherical refraction, mean manifest cylinder, and keratometry demonstrated statistically significant improvement during the follow-up period. Yet, comparative studies are warranted in order to evaluate the outcomes against epi-off CXL with riboflavin injection.

In an observational study published by Ferenczy et al, ICRS outcomes were compared with the combined CXL and ICRS. Overall, 32 eyes with KC were included, among them 10 eyes underwent CXL following ICRS implantation. Both groups achieved significant improvement in terms of CDVA, spherical and cylindrical errors, mean keratometry values, and SE values, postoperatively.

### Phakic Intraocular Lens

Phakic IOLs fall into two broad varieties: Anterior chamber (ACIOL) and posterior chamber IOLs. The ACIOLs can be further divided into angle-supported ACIOLs originally introduced by Baikoff and Joly, and iris-fixated lens, introduced by Fechner and Worst and posterior chamber sulcus-fixated lens introduced by Fyodorov. In progressive KC treated with implantation of ICRS or CXL, implantation of a phakic IOL is possible to correct residual refractive error. A case of keratectasia 11 years after LASIK, published by Zhang et al., was successfully treated with CXL followed by phakic toric implantable collamer lens with significant improvement in UDVA. Cakir and Utine outlined the outcomes of combined sequential implantation of ICRS and ACIOL, iris-fixated, phakic IOLs in 10 keratectasia eyes, one eye with iatrogenic corneal ectasia. Their results show significant visual and refractive improvements following ICRS implantation and further significant improvement following the phakic IOL implantation. Moshirfar et al reported the results of simultaneous sequential implantation of ICRS followed by Verisyse phakic IOL (AMO, Santa Ana, CA), in eyes with keratectasia, among them 5 PLE eyes demonstrated similar results in terms of mean UDVA.

### Keratoplasty

Penetrating keratoplasty (PKP) and deep anterior lamellar keratoplasty (DALK) are the last resort for visual rehabilitation in patients with PLE. Penetrating keratoplasty is a commonly performed surgical procedure for ectatic corneas, but is associated with complications including graft rejection, induced astigmatism, complications of intraocular surgery, such as glaucoma, cataract formation, retinal detachment, cystoid macular edema, endophthalmitis, and expulsive hemorrhage. Alternatively, lamellar keratoplasty (LKP) avoids the complications associated with “open sky” operation. However, perforation of the Descemet membrane during surgery is a common intraoperative complication of LKP. Besides, postoperative complications, namely, double (pseudo) anterior chamber, corneal stromal graft rejection, interface haze, graft dehiscence as a result of early suture removal, pupillary block due to air/gas in the anterior chamber and suture-related complications, still exist. Though several studies had outlined the outcomes of PKP in KC patients, the data in PLE is scarce.

McAllum et al reported the outcomes of DALK in two PLE eyes ending up with UDVA 20/60+ and 20/40– in their operated eyes, improving to 20/40+ and 20/30- with minimal refractive corrections. Similarly, Villarrubia et al published the results of DALK in 5 PLE eyes. The mean CDVA changed from 0.16 dioptr (D) ± 0.05 (SD) (0.10–0.25 D) before DALK to 0.68 ± 0.19 D (0.5–1.0 D) after DALK.
CONCLUSION

Ectasia development following refractive surgery is more common following LASIK compared with PRK. The important risk factors include: Abnormal corneal topography, low pachymetry, higher PTA, and younger age. Several indices were developed to further enhance the detection of suspicious corneas prior to the laser treatment procedure. An inflammatory response was suggested as the pathogenesis of PLE. The diagnosis is made based on clinical and topographic findings compatible with corneal ectasia. Several ectasia grading systems were developed to classify the severity of the disease. The management of PLE aims to halt the progression of the disease and promote the visual rehabilitation. The treatment comprises CXL for progressive cases combined with CLs or ICSR depending on the ectasia severity. Though the treatment approach is similar to KC, managing PLE patients is more complex owing to the fact that those patients chose to undergo LASIK for the sake of glasses independency. A comprehensive presurgical assessment and a patient guidance of proper postsurgical behavior are highly essential for avoiding the feared PLE development.

REFERENCES


