Impact of corneal refractive surgery on the precorneal tear film

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Corneal refractive surgeries are one of the commonly performed procedures for correction of refractive errors. Tear film abnormality is the most common postoperative complication of corneal refractive surgeries. Consequently, these procedures represent a clinically significant cause of dry eye disease. The mechanisms which lead to dry eye disease include corneal sensory nerve dysfunction, ocular surface desiccation, glandular apoptosis and ocular surface inflammation. Although transient tear film abnormalities occur in almost all patients following surgery, patients with pre-existing dry eye symptoms or dry eye disease are at significant risk of developing more severe or long-term ocular surface disease. As such, careful patient selection and preoperative evaluation is essential to ensuring successful surgical outcomes. This is particularly important with LASIK which has the strongest association with dry eye disease. Appropriate surface lubrication and anti-inflammatory therapy remains the cornerstone treatment. Timely and effective management is important to facilitate visual rehabilitation and reduce the risk of secondary complications. In this review we describe the causes, pathophysiology, risk factors, manifestations, and management of tear film dysfunction and dry eye disease following corneal refractive surgery.

The precorneal tear film is an essential component of ocular surface and consists of lipid, aqueous, and mucin layers. It plays a crucial role in promoting and maintaining the health and vitality of underlying cornea and can be adversely affected by various local and systemic factors, including refractive surgery. The most common manifestation of tear film dysfunction is dry eye disease (DED), which can lead to ocular discomfort, reduced vision, and decreased quality of life.[1-3]

Corneal refractive surgery is an umbrella term that includes laser assisted in–situ keratomileusis (LASIK), surface ablation procedures including photorefractive keratectomy (PRK), laser epithelial keratomileusis (LASEK) & epi-LASEK and small incision lenticule extraction (SMILE). These procedures aim to permanently correct refractive error by reshaping the cornea. DED is a well-recognized complication of corneal refractive surgery, with transient dry eye symptoms affecting almost all patients postoperatively.[4-9] Thus, corneal refractive surgery represents a clinically significant cause of dry eye disease, in particular due to the high prevalence of these procedures in the population.

A literature review was performed within PubMed and MedlinePlus using the following keywords: dry eyes, refractive surgery, tear film, LASIK, LASEK, PRK, SMILE, FLEX, LASIK and dry eyes, LASEK and dry eyes, PRK and dry eyes, SMILE and dry eyes, FLEX and dry eyes, refractive surgery and dry eye, abnormality, derangement, refractive surgery and tear abnormality. One keyword/phrase from each cluster was used, unless repeated. All reports consisting of ≥10 patients, published before October 2019, were screened and evaluated, with relevant studies then included.

Incidence

The incidence and severity of DED and tear film dysfunction following corneal refractive surgery varies greatly according to the procedure performed. LASIK carries the greatest risk with Yu *et al.* reporting 94.8%, 85.4%, and 59.4% of patients experiencing dry eye symptoms on day 1, one week, and one month post-LASIK, respectively.[9-11] However, almost all patients develop some degree of transient DED postoperatively, regardless of the type of procedure performed.[4]

Pathogenesis

Multiple factors contribute to the development of DED following corneal refractive surgery including neurotrophic epitheliopathy, postoperative inflammation, goblet cell damage, preservative induced toxic corneal epitheliopathy, and inadequate tear film resurfacing secondary to alterations in corneal contour [Fig. 1].[12]

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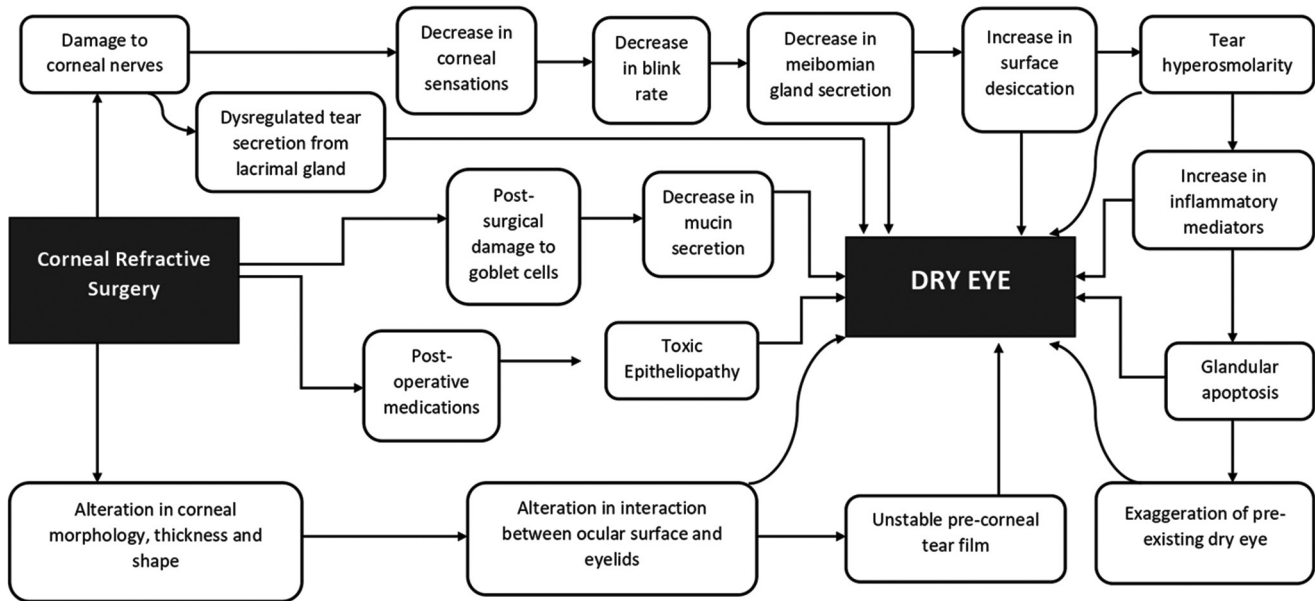
Figure 1: Flow chart depicting etiological factors and their complex relationship leading to development of dry eye disease

Neurotrophic epitheliopathy

Refractive surgeries have a neurotrophic effect on cornea attributable to the cutting of corneal sensory nerves particularly after flap procedures. Surgical transection of the sensory nerve fibers in the sub-basal plexus and stroma, which regulate tear production and composition, further exacerbates postoperative DED. This is caused by reduced corneal sensation which leads to epitheliopathy, tear hyperosmolarity, ocular surface inflammation and glandular apoptosis.[13]

Postoperative inflammation

Postoperative inflammation contributes significantly to the development of DED following corneal refractive surgery. Corneal wound healing occurs via prostaglandin and cytokine mediated pathways, which promote keratocyte apoptosis and the recruitment of inflammatory cells.[14] This incites a cyclical process whereby further proinflammatory mediators, including matrix metalloproteinase-9 (MMP-9) are released, causing further degradation of the ocular surface.[15] MMP-9 is a proteolytic enzyme released by epithelial cells, that is elevated in patients with DED. It acts by destabilizing the tear film and disrupting the barrier function of the cornea.[16] This inflammatory response is further potentiated by the sensory nerves of the cornea, through the release of the neuropeptides, substance P, and calcitonin gene-related peptide (CGRP). Although these substances are thought to act as epithelial trophic factors,[17] they have a proinflammatory effect on the limbal vasculature and destabilize the tear film. Specifically, they promote limbal vasodilation and vessel permeability.[18,19]

Goblet cell damage

Goblet cells contribute to the mucin layer of the tear film through the secretion of glycoproteins. Their function and density are essential for the health of tear film and the underlying cornea. Reduced number or impairment of goblet cells' function eventually results in abnormalities of the mucin layer and hence the corneal tear film. Corneal refractive surgery results in a reduction in goblet cell density, in part due to direct damage inflicted by suction devices used to create LASIK

flaps. This occurs irrespective of whether a microkeratome or femtosecond laser is used.[9,20-22]

Toxic epitheliopathy

Frequent instillation of preservative containing eye drops may induce a toxic effect on the conjunctiva and cornea, promoting DED.[23] The most widely used eye drop preservative, benzalkonium chloride (BAK), dissolves the lipid layer leading to increased tear evaporation and instability. Furthermore, it also causes goblet cell and microvilli destruction and disrupts epithelial tight junctions.

Alterations in corneal contour

Alteration in corneal contour contribute to DED. This is mediated by the abnormal tear film distribution that occurs across the irregular corneal surface, as well as the altered contact that is present between the irregular cornea and eyelids during blinking.[9,24]

Refractive Procedures and Tear Film Parameters

The relationship between corneal refractive surgery, postoperative tear film dysfunction and DED, varies significantly between refractive procedures. The associations and outcomes reported in the literature are highly dependent on study methodology, parameters examined and duration of follow-up [Table 1].[5-6,8-10,15,19,22,25-31] Parameters used to assess tear film dysfunction include tear film indices, corneal sensation and corneal nerve morphology. These factors can be evaluated through objective measures such as—reflex and basal tear secretion, tear meniscus height, and volume and tear break up time (TBUT), or also through subjective measures such as dry eye symptoms.[32,33]

a. Laser assisted in-situ keratomileusis [LASIK]

Of all the kerato-refractive procedures available, LASIK is associated with the highest incidence and severity of postoperative DED.[10,19] The mechanisms by which LASIK affects the ocular surface are multifactorial, with Batat L *et al*.[25] demonstrating

Table 1: Refractive procedures and their association with dry eye disease

Study	Number of eyes	Study design	Parameters examined	Follow up	Conclusion
De Paiva CS et al.[5] 2006	70	Single-center, prospective randomized clinical trial	Fluorescein tear breakup time (TBUT), corneal fluorescein staining evaluation, measurement of precorneal sensitivity by the Belmonte modified noncontact gas esthesiometer, and the Schirmer 1 test.	1 week, 1 month, 3 months, 6 months	LASIK surgery can precipitate dry eye symptoms in patients with no history of dry eye disease. The risk of developing dry eye disease increases with depth of ablation.
Denoyer A et al.[6] 2015	60 in each group (SMILE & LASIK)	Prospective, comparative, non-randomized clinical study	Ocular Surface Disease Index (OSDI), TBUT, Schirmer I test, tear osmolarity measurements, together with an overall severity score, corneal esthesiometry for morphology and functional assessment of corneal innervation and subbasal nerve imaging using in vivo confocal microscopy (IVCM).	1 month, 6 months	LASIK causes greater impairment to corneal and conjunctival innervation compared to SMILE. LASIK is therefore associated with a greater risk of postoperative DED.
Donnenfeld ED et al.[8] 2004	108	Prospective	Lissamine green corneal and conjunctival staining, Schirmer I test, TBUT and corneal sensations using masked Cochet-Bonnet esthesiometry	1 week, 1 month, 3 months, 6 months	Narrow LASIK flap hinges are associated with reduced corneal sensation compared to wide LASIK flap hinges.
Edward YW et al.[9] 2000	96	Prospective, comparative, nonrandomized interventional study	Dry eye symptoms, standardized Schirmer test values, basal tear secretion test, and TBUT	Day 1, 1 week, 1 month	Dry eye symptoms are common after myopic LASIK surgery and patients with pre-existing tear flow abnormalities are at the greatest risk of experiencing postoperative dry eye symptoms.
Lee JB et al.[10] 2000	36 (PRK) and 39 (LASIK)	Prospective	Schirmer test values, TBUT, and tear osmolarity	3 months, 6 months	A greater decrease in tear secretion was observed with LASIK compared to PRK.
Salomão MQ et al.[15] 2009	113 (femtosecond laser) and 70 (microkeratome)	Prospective randomized controlled trial	Flap thickness assessed by intraoperative ultrasonic pachymetry. LASIK-induced neurotrophic epitheliopathy (LINE) severity grading and slit lamp biomicroscopy for dry eye assessment	Day 1, 1 week, 1 month, 3 months, 9 months	LASIK flaps formed using femtosecond laser were associated with a lower incidence of post-LASIK dry eye disease.
Konomi K et al.[19] 2008	24	Prospective	TBUT, Schirmer I and II tests, rose bengal staining, central corneal sensitivity, nucleus-to-cytoplasmic ratio, and goblet cell density	1 week, 3 months, 9 months	Poor preoperative tear volume may affect the recovery of the ocular surface and increase the risk of chronic dry eye disease after LASIK.
Rodriguez AE et al.[22] 2007	34 (femtosecond laser) and 30 (microkeratome)	Prospective, nonrandomized, masked study	Suction ring contact duration intraoperatively and conjunctival impression cytology for- goblet cell density, epithelial cell morphology, and inflammatory cells	1 week, 1 month, 3 months	LASIK results in a reduction in the density of conjunctival goblet cells. A greater reduction in goblet cell density is associated with the use of a microkeratome compared to femtosecond laser.
L Battat et al.[25] 2001	48	Prospective, non-comparative case series	Tear fluorescein clearance, corneal fluorescein staining, Schirmer 1 test, and corneal and conjunctival sensitivity, corneal surface regularity (SRI) using topography instrument	Day 7, 1 month, 2 months, 6 months, 12 months, 16 months	Sensory denervation of the ocular surface after bilateral LASIK disrupts ocular surface tear dynamics and causes dry eye symptoms.
Shoja MR et al.[26] 2007	190	Retrospective	TBUT, corneal staining, corneal sensitivity test, and Schirmer I test	1 month, 3 months, 6 months	Females and patients with high refractive errors are at an increased risk of developing dry eye disease after myopic LASIK.

Contd...

Table 1: Contd...

Study	Number of eyes	Study design	Parameters examined	Follow up	Conclusion
Sauvageot P *et al.*[27] 2017	22 (LASIK) and 22 (PRK)	Prospective, comparative observational study	Tear osmolarity, the OSDI questionnaire, Schirmer I test, corneal sensitivity, TBUT, and corneal fluorescein staining	3 months, 6 months, 12 months	The effect of femtosecond laser-assisted LASIK PRK on the ocular surface are similar.
Patel S *et al.*[28] 1999	22	Prospective	Central corneal sensitivity using non-contact corneal aesthesiometer, tear lipid layer by optical interferometry, and tear volume using the phenol red cotton thread test	14 weeks	A greater reduction in corneal sensation at the ablated zone was observed with LASIK compared to PRK.
Mian SI *et al.*[29] 2009	66	Prospective randomized contralateral-eye study	Central Cochet-Bonnet esthesiometry, OSDI questionnaire, Schirmer I test, TBUT, corneal fluorescein, and conjunctival lissamine green staining	1 week, 1 month, 3 months, 6 months, 12 months	No association between LASIK flap hinge position, angle, or thickness and dry eye disease was identified.
Donnenfeld ED *et al.*[30] 2003	104	Prospective randomized self-controlled trial	Masked Cochet-Bonnet esthesiometry, lissamine green corneal and conjunctival staining, Schirmer I test, and TBUT	1 week, 1 month, 3 months, 6 months	Superiorly located LASIK flap hinges are associated with a more significant reduction in corneal sensation compared to nasally located LASIK flap hinges.
Wang B *et al.*[31] 2015	47 (SMILE) and 43 (FS-LASIK)	Prospective, non-randomized, observational study.	Salisbury Eye Evaluation Questionnaire (SEEQ) and TBUT	1 month, 3 months, 6 months, 12 months	SMILE produces less dry eye disease than FS-LASIK at 6 months postoperatively but demonstrates similar degrees of dry eye disease at 12 months.

derangements in tear fluorescein clearance, corneal fluorescein staining, aqueous tear production (via Schirmer 1 test), and reduced corneal and conjunctival sensation. The formation of a stromal flap also disrupts the contour and integrity of the ocular surface, destabilizing the tear film which leads to a reduction in TBUT.[34] Whilst reflex tear production is acutely elevated in the immediate postoperative period, Schirmer's test is subsequently reduced following LASIK.[10] Tear osmolarity has also been found to be elevated postoperatively and the barrier function of the cornea impaired.[10] These indices remain affected for a variable period of time postoperatively, with normalization typically occurring between three and six months

Corneal sensation is invariably reduced following LASIK and plays an important role in post-LASIK DED, particularly that which persists beyond one-month, postoperatively. Corneal sensation is typically reduced for three months after surgery leading to a suppression of blink frequency and reduction in basal and reflex tear production.[9,12,19,28,35,36] There is however, a significant variation in the time taken for corneal sensation to recover, which may occur over three weeks to fourteen months.[25,26,29] The morphological recovery of corneal nerves following LASIK is delayed relative to the recovery of functional sensation.[37,38] Short, non-branching, nerve fibers become visible approximately three months following surgery, with synapses between fibers visible by six months.[39,40] Stromal and central sub-basal nerve fiber bundles are absent immediately post-LASIK, since they are transacted during flap formation and stromal photoablation.[41] It takes up to five years for the density of sub-basal and stromal nerves to reach preoperative levels[42] and the morphology of these fibers often remains persistently

abnormal, being atypically narrow and curved with an abnormal branching pattern[43]

Post-LASIK DED is also influenced by LASIK flap structure, specifically the location and width of the flap hinge. Whilst the corneal nerves are truncated during the formation of the flap, nerves coursing through the hinge are spared.[8] Narrow hinges are therefore associated with greater corneal anaesthesia as demonstrated by Donnenfeld *et al.*[30] Additionally, Feng *et al.*[4] reported that horizontally oriented hinges affect corneal sensation less than vertically oriented hinges at three months after surgery; however, no difference was seen at 6-months. Nasally located hinges are associated with improved recovery of corneal sensation, Schirmer's test and TBUT values when compared to superiorly located hinges at 6-months postoperatively.[8,30,44,45] This may reflect the anatomical distribution of the long posterior ciliary nerves (LPCN) and the preservation of their fibers that occurs along the orientation of these hinges. It must however be noted, that a number of studies have failed to find an association between hinge location and postoperative DED[29,46,47]

Ablation depth has been proposed as an important factor contributing to postoperative tear film derangement.[48] LASIK, which utilizes a relatively thin tissue flap, may produce less postoperative hypoesthesia and more rapid normalization of tear film metrics, relative to other corneal refractive procedures.[49] High myopic correction, which mandates a deeper ablation depth, is associated with reduced corneal sensation[50] and an increased prevalence of postoperative dry eye symptoms. This is due to increased damage sustained by deep stromal nerves, leading to delayed regeneration of the

sub-epithelial nerve plexus. Hyperopic correction requires greater peripheral ablation which likely damages peripheral nerve trunks, and thus tends to cause relatively greater corneal anesthesia compared to that in myopic correction.[48] However, no study has specifically compared the risk of developing chronic tear dysfunction following hyperopic and myopic LASIK surgery

Both corneal sensation and corneal barrier function are more severely affected following LASIK than PRK or LASEK in the first three months following surgery.[34,51] Furthermore, contrary to previously described observations, LASIK enhancement procedures have not been shown to be associated with an increase in dry eye symptoms or with a change in tear film metrics compared to standard LASIK surgery[52]

A LASIK flap can be fashioned using either a microkeratome or femtosecond laser, with surgery performed using a microkeratome carrying a significantly higher risk of postoperative DED.[15] Femtosecond laser is associated with a more rapid postoperative recovery of corneal sensation and rehabilitation of the ocular surface.[15] One particular issue, associated with the use of a microkeratome suction ring, is the intraoperative trauma sustained by conjunctival goblet cells. This significantly reduces goblet cell density during the first three months postoperatively, thus impairing mucin layer of the tear film.[22] Additionally, a microkeratome suction ring also causes trauma to the conjunctival nerves, resulting in reduced conjunctival sensation for up to 18 months.[25] Lastly, as LASIK flaps constructed using femtosecond laser are thinner, trauma to the anterior stromal afferent sensory nerves is minimized.[15,53] It must be noted however, that these associations are not universally reported through the literature, with at least one study finding no favorable relationship between femtosecond laser and DED.[54]

b. Photorefractive keratectomy [PRK]

In comparison to LASIK, PRK is associated with a reduced risk of postoperative tear film dysfunction. One study, comparing DED in post-PRK and post-LASIK patients, found that tear production, TBUT, tear osmolarity, corneal barrier function, and corneal sensation were less deranged in PRK patients.[10,24,34,51] This is possibly due to the preservation of the LPCN and more rapid regeneration of corneal nerve fibers, in particular the sub-basal corneal nerve plexus[42] that occurs following PRK.[36,51] PRK also appears to be associated with favorable measures of corneal sensation when compared to thin-flap LASIK, however no significant difference in Schirmer scores between the two has been observed.[48] Other studies, on the other hand, have failed to find a significant difference in tear film dysfunction or DED at 6-months following PRK or LASIK.[19,36,48]

c. Laser epithelial keratomileusis [LASEK]

In comparison to LASIK, LASEK enjoys a favourable DED risk profile during the first three months after surgery.[55] TBUT typically returns to its preoperative state within two months, while fluorescein staining returns to its preoperative state within four to six weeks.[55] Similarly, there is almost full recovery of corneal sensation within two months, which is more rapid than that occurs with LASIK. This may reflect greater nerve preservation following LASEK.[56] This recovery time is consistent with subjective dry eye symptoms postoperatively, which are worst during the first two months after surgery.[56]

Advantages of LASEK over thin-flap LASIK are less clear, with no significant difference in postoperative corneal sensation or confocal sub-basal nerve plexus morphology being observed between the two procedures.[56]

d. Small incision lenticule extraction and femtosecond lenticule extraction [SMILE & FLEx]

SMILE is a flapless procedure that induces minimal inflammation or damage to the LPCN and as such, enjoys a favorable DED risk profile. However, given that it is a relatively novel technique, these observations are tempered by the current lack of long-term data regarding the procedure. Additionally, the benefits of SMILE appear to be largely subjective, with some studies finding no significant difference in objective tear film parameters between SMILE and femtosecond-LASIK (FS-LASIK).[57,58] However, Elmohamady et al. compared postoperative ocular surface parameters among SMILE, LASIK, and FS-LASIK and observed that the severity and duration of DED after LASIK and FS-LASIK was significantly greater than that after SMILE.[59] SMILE is associated with improved tear film stability at 3, 6, and 12 months postoperatively, in comparison to FS-LASIK.[31] Furthermore, a meta-analysis, comparing corneal sensation following SMILE and FS-LASIK, found that postoperative corneal sensation recovered more rapidly in SMILE patients in the first three months post-operatively; however, no significant difference was observed at six months.[60]

Meiyan et al. compared post-LASIK versus post-SMILE tear film stability and found TBUT to be reduced for three months post-operatively in SMILE patients compared to six months in FS-LASIK patients.[61] SMILE patients were also found to have significantly less corneal fluorescein staining than FS-LASIK patients.[61] Corneal sensation is also better preserved following SMILE compared to FLEx, however derangements in tear film stability are equal between these two procedures.[62] These findings are thought to occur due to improved preservation of corneal stromal nerve fibers associated with SMILE. Subjectively however, FS-LASIK and SMILE appear to be equally associated with dry eye symptoms, as measured using the ocular surface disease index (OSDI), with symptoms typically peaking in the first month post-surgery before improving.

Management

1. **Preoperative considerations**
   Patient selection and preoperative evaluation

Careful patient selection and preoperative assessment to identify those at high risk of postoperative DED is essential to ensure successful surgical outcomes. This also provides clinicians with the opportunity to manage reversible causes of DED and optimize ocular surface, facilitating more accurate preoperative measurements and biometry

Stable refraction over a 12-month period, in patients over 18 years of age, with a normal anterior segment, and adequate corneal thickness are mandatory inclusion criteria. The relationship between gender, ethnicity, and postoperative DED is uncertain. Asians and females—especially post-menopausal—have been reported to be at an increased risk of postoperative tear dysfunction[26]

Potential candidates should be carefully evaluated for presence of pre-existing DED or tear film abnormalities, given the association between preoperative tear film dysfunction and postoperative DED. Patients with preoperative Schirmer test scores below 10 mm are at significant risk of postoperative DED.[9] Furthermore, the recovery of corneal sensation is particularly slow in patients with preoperative tear film dysfunction, highlighting the importance of identifying such patients prior to surgery[63]

Patients should also be evaluated to exclude the presence of concurrent conditions including cataract, glaucoma, and other external diseases, which may limit the utility of refractive surgery.[64] Similarly, coexistent corneal pathology including dystrophies, degenerations, and keratopathies—such as neurotrophic keratopathy following viral keratitis, should be excluded.[21] It is essential that patients with ocular allergy are also identified, owing to their poorer postoperative outcomes and higher incidence of diffuse lamellar keratitis experienced by this cohort.[65,66] Long-term contact lens wear predisposes to reduced corneal sensation and poor tear film metrics postoperatively; whilst preoperative contact lens intolerance, is a significant risk—per se, for postoperative tear film dysfunction.[21,67] As such, these patients should be carefully assessed and if required, surgery deferred until the ocular surface has normalized[48]

Ocular complications of diabetes mellitus and systemic autoimmune diseases including Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematous, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease, and Bechet's disease should all be excluded.[68] As a general principle, such conditions should be well controlled for at least six months prior to undergoing corneal refractive surgery.[64] LASIK is well tolerated in diabetic patients who have tight glycemic control and have not had any prior ocular or systemic complications.[66] Sjogren's syndrome should be considered a contraindication, even if mild in severity, since it can lead to severe DED postoperatively.[69] Corneal refractive surgery should not be performed in patients with acquired immunodeficiency syndrome (AIDS), ocular complications related to human immunodeficiency virus (HIV) infection, or in patients who are noncompliant with HIV medications[21]

Derangement of ocular surface is one of the commonest complications of refractive surgery. The severity can be worse in patients with pre-existing ocular surface disorders. Thus, it is imperative to identify such patients preoperatively so as to optimize the ocular surface with appropriate treatment before proceeding with refractive procedure. Management of ocular surface disease and inflammation can be achieved using topical cyclosporine,[70,71] topical azithromycin 1%,[72] and corticosteroids[73,74] in addition to oral doxycycline.[72] Prior to surgery, a detailed ocular surface assessment should be performed, which includes an assessment of the tear film meniscus height and volume, TBUT, ocular surface fluorescein staining and Schirmer's test.[5,21,22,25,30] The lid margins should be carefully examined for evidence of blepharitis and meibomian gland dysfunction, which can predispose to postoperative keratitis or infection.[75] This may be managed conservatively using lid hygiene measures, warm compresses and lid massage. A short course of oral doxycycline or topical azithromycin may also be administered

Analysis of tear film stability has been used with promising results in an attempt to identify patients who are at high risk of postoperative DED.[76,77] Future advances may enable tear osmolarity, lactoferrin, and MMP-9 to be incorporated into the preoperative assessment, offering greater accuracy in prognosticating the risk of postoperative DED.

2. Postoperative management

Lubrication of the ocular surface, in addition to topical anti-inflammatory therapy remains the standard treatment for DED following corneal refractive surgery. Treatment can then be discontinued once the tear film has normalized. However, in cases of chronic DED, patients may need to continue therapy for a longer duration. Treatment options that may be considered in the management of DED, can be summarized as follows:

- *Tears Substitutes*

Frequent administration of preservative-free lubricants is considered the mainstay of treatment in mild to moderate DED, particularly where there is deficiency of the aqueous layer. However, in more severe cases, tear substitutes therapy may be augmented with additional agents. A wide range of substances are used to produce tear substitutes, using cellulose derivatives such as—hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), polyvinyl derivatives such as polyvinyl alcohol (PVA), chondroitin sulphate, and sodium hyaluronate. These agents work by increasing the viscosity, hydration, and lubrication of ocular surface and as such, the efficacy of these substances largely depends on their retention time, viscosity, and adhesion to ocular surface

CMC has been shown to be more effective in post-LASIK DED when compared with HPMC 0.3% and dextran 0.1% in bicarbonate buffer.[78] Preservative free hyaluronic acid (HA) 0.15% has also been shown to be efficacious in reducing post-LASIK dry eye, owing to its water retention and viscoelastic properties and its ability to promote corneal epithelial wound healing.[79] Other formulations containing CMC 0.5% and HA 0.1%, organic osmolytes, glycerine, and erythritol, have also been used.[80] The dosing schedule varies from QID to hourly for a period of 3-12 months, depending on the severity and nature of tear film dysfunction. A bandage contact lens can be used in conjunction with tear substitutes to reduce ocular surface irritation and provide symptomatic relief in the immediate postoperative period.[21,81]

- *Punctal plugs*

Tear substitutes can be augmented with punctal occlusion, particularly in patients with aqueous tear deficiency, which acts by reducing tear drainage via the nasolacrimal system. Temporary punctual occlusion can be achieved with collagen, silicone or acrylic plugs, while punctal cautery can be used to achieve permanent occlusion if required.[82] In addition to improved lubrication of ocular surface, punctal occlusion can also improve visual acuity by influencing the curvature, surface tension, volume and dynamics of the tear film, resulting in reduction of lower and higher order aberrations.[83]

- *Anti-inflammatory agents*

Topical anti-inflammatory medications suppress the cytokine mediated ocular surface inflammation, improving the quality of tear film and promoting restoration of ocular surface.

This reduction in inflammation results in increased goblet cell density and accelerated recovery of corneal sensations, allowing the tear film to recover.[70,71] Cyclosporin A administration, one month prior to surgery and three months postoperatively is associated with improved Schirmer test scores and refractive results.[71] A short course of topical corticosteroid eye drops can also be used to alleviate DED, however they are not appropriate for long-term use owing to their potential side effects including cataract development and raised intraocular pressure[77]

Other anti-inflammatory drugs that have been shown to be efficacious include rebamipide and diquafosol.[84,85] Rebamipide reduces the concentration of inflammatory cytokines in tears,[85] while diquafosol ophthalmic solution 3% stimulates fluid and mucin secretion from conjunctival epithelial and goblet cells.[84] Koh *et al*. described the effective use of combined therapy consisting of diquafosol tetrasodium and sodium hyaluronate for improved visual performance and dry eye symptoms post-LASIK.[86]

- *Treatment of Meibomian gland dysfunction (MGD)*

Patients with coexistent MGD often suffer more severe DED following refractive procedures. Hot compresses supplemented with tear substitutes and topical antibiotics providing gram-positive coverage constitute an effective therapy. When self-management of MGD is insufficient, thermal pulsation treatment such as LipiFlow (TearScience, Morrisville, NC, USA) or intense pulsed light (IPL), M22 (Lumenis Ltd, Israel) may be effective.[87,88]

- *Other treatment modalities*

In severe cases of DED following LASIK, scleral contact lenses have been shown to offer symptomatic relief.[89,90] The role of amniotic membrane transplantation has also been examined by Dua *et al*. However, whilst this intervention reduced corneal haze on examination, no improvement in visual acuity occurred.[91] Autologous serum, which contain growth factors and anti-inflammatory mediators, may also benefit patients with DED associated with corneal refractive surgery.[92,93] These benefits must be weighed against the cost and logistics of therapy. Lastly, a potential role for nerve growth factors including topical naltrexone, fibronectin, substance *P* – derived peptides, FGLM-amide and IGF-1 has been identified.[94] Further research and development will be required for these trophic factors to be utilized in clinical practice.

Future Directions

A better understanding of the pathophysiology and mechanism of dry eye in post refractive surgery patients, has led to newer insights in the diagnosis and management of these cases. High resolution, anterior segment spectral-domain optical coherence tomography (AS – SD OCT) is increasingly being used to measure the tear meniscus and therefore offers an opportunity to characterize tear film abnormalities and DED in a better way. Corneal confocal microscopy, ocular response analyzer (ORA) and Corvis® ST are other promising diagnostic techniques with the potential to identify tear film abnormalities at an early stage.

Tear Film and Ocular Surface Society Dry Eye Work Shop II (TFOS DEWS II) has suggested the potential utility of biologic compounds such as lubricin (proteoglycan-4), recombinant human nerve growth factor, tumor necrosis factor *α*– stimulated

gene/protein-6, interleukin-1 receptor antagonist, anti-tumor necrosis factor-*α* therapy, and anti-interleukin—17 in the management of DED. These treatments are promising and offer the potential to change the management of post-refractive surgery dry eye disease. It should be noted that most of these agents have been investigated in animal models only and therefore human trials are required to fully assess their therapeutic potential.[95]

Conclusion

Tear film abnormalities and consequent DED continue to be the most frequent complication of corneal refractive surgery. Fortunately, a majority of patients achieve total or partial resolution within one year following surgery. Thorough preoperative assessment is essential to facilitate the appropriate selection of surgical candidates. Post-operative management is largely conducted in a stepwise manner with preservative-free artificial tears constituting a central component in the therapeutic approach. Anti-inflammatory agents such as topical cyclosporine A and/or punctal occlusion can be used to augment supplemental tears if required. Adequate and timely management of postoperative tear film abnormalities is paramount, since it reduces the risk of further postoperative complications, controls dry eye symptoms, and promotes visual rehabilitation.

Conflicts of interest
There are no conflicts of interest.

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