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Refractive surgery and dry eye

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Abstract

Refractive surgery is one of the most common elective surgeries performed worldwide. The incidence of dry eye disease (DED) after corneal refractive surgery varies among different studies. Pre-existing untreated DED has been identified as a risk factor for postsurgical dry eye symptoms. On the basis of both evidence and clinical experience, some recommendations for ocular surface and DED management pre- and post-refractive surgery are described. In aqueous deficiency Dry Eye Disease, preservative-free lubricating drops should be preferred, in addition to ointment and gel forms. Topical anti-inflammatory agents (Cyclosporine 0.1%, hydrocortisone phosphate, fluorometholone) should be used for 3–6 months in cases of ocular surface damage. The therapy of evaporative DED includes lifestyle modifications, lid hygiene (either performed by the patient or offered as professional lid hygiene by the physician), use of lubricating eye drops with lipid components, topical and/or systemic antibiotic treatment with anti-inflammatory properties and Intense Pulsed Light (IPL-) Treatment for meibomian gland dysfunction.

Keywords

Diseases of the ocular surface < cornea / external disease, diseases of the ocular surface: lid inflammation affecting the ocular surface < cornea / external disease, complications of refractive surgery < refractive surgery, corneal procedures for astigmatism < refractive surgery, corneal procedures for myopia < refractive surgery

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Impact of refractive surgery on dry eye disease

Refractive surgery is one of the most common elective surgeries performed worldwide. According to statistics released by the Refractive Surgery Council, the number of laser vision correcting procedures in the U.S. has grown year by year, with approximately 1 million procedures performed in 2021 (LASIK, SMILE, and PRK), with LASIK being the most widespread.[1] The reason for the dominance of LASIK on the U.S. refractive market could be because it is a safe and effective procedure that offers many advantages over other types of refractive surgery, including fast and painless visual rehabilitation, no subepithelial corneal haze, and less regression. With the introduction of femtosecond laser LASIK (FS-LASIK), the incidence of complications has decreased, with a more predictable flap diameter, thickness, and hinge width than with microkeratomes.[2] On the other hand, small incision lenticule extraction (SMILE) is a flap-free procedure based on creating a stromal lenticule in the corneal stroma with a FS system and removing it through a small side cut. The shape of the lenticule is selected to correct the refractive error.[3] Although they are a well-established procedure, dry eye remains one of the

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most common transitory complications after excimer laser surgery.[4–17]

The incidence of dry eye disease (DED) after corneal refractive surgery varies among different studies, partly because of the different diagnostic criteria and partly because of different refractive techniques. In a study conducted by Toda et al., symptoms and signs of dry eye after LASIK were found in 50%, 40%, and 20% to 40% of patients at 1 week, 1 month, and 6 months after surgery, respectively.[4] It is typically time-dependent and self-limited; the chronic form of the disease is rare, as the incidence is approximately 0.8% in patients that have undergone LASIK,[4] but may have a negative effect in the individual quality of life, being responsible for discomfort and refractive regression during the short-term recovery period after surgery. Knowing the pathogenesis and the risk factors of DED may help identify patients at risk and prevent complications, thus improving patient satisfaction.

In a retrospective study comprising 25,317 eyes of patients who underwent keratorefractive surgery, Shehadeh-Mashor suggested LASIK treatment, female gender, older age, lower preoperative refractive error, and lower preoperative BCVA as potential risk factors for developing symptomatic dry eye disease during the first 6 postoperative months.[5]

The pathophysiology of DED after refractive surgery is multifactorial and may be related to 3 major mechanisms: damage to the corneal nerves, alteration of goblet cells, and corneal curvature changes.

Damage to the corneal nerves

The damage of the corneal nerves appears to be the leading cause, resulting in decreased corneal sensitivity, reduced blinking, tear film instability, and hyperosmolarity.[3–17]

The cornea is one of the most densely innervated tissues in the human body; corneal sensory nerves originate from the ophthalmic division of the trigeminal ganglion, principally through the nasociliary nerves and long ciliary branches. These nerves enter the cornea at the limbus in thick nerve trunks, branching and running parallel to form the stromal plexus, with fibers forming the sub-basal corneal plexus in the basal and superficial epithelial layers.[18,19] These sensory nerves play a crucial role in corneal homeostasis, maintaining the structural and functional integrity of the entire surface of the eye, controlling reflex tear production, blinking, and releasing trophic factors (NGF, NT-3, NT-4, BDNF, CNFT, GDNF, TrK).[19] In FS-LASIK the flap created by the femtosecond laser cuts the sub-basal nerve bundles and the deeper anterior stromal nerve, causing a temporary partial denervation of the cornea with interruption of the cornea-trigeminal nerve-brainstem-facial nerve-lacrimal gland reflex.[10,18] Deeper laser ablation, greater flap diameter and depth, and hinge width can affect the extent of the nerve damage and therefore the risk of post-operative DED.[7,8] Only fibers in the hinge position are spared, but the effect of the hinge position in DED is not well understood. Some authors have postulated that horizontal-hinge flaps (nasal or temporal) result in faster recovery than vertical-hinge flaps (superior).[20,21] In a meta-analysis, Feng et al. suggested that hinge location may have some effect on corneal sensation but no significant difference in DED symptoms 6 months after surgery, whereas Huang et al. hypothesized that corneal sensation and dry eye parameters will not differ with different hinge positions because corneal nerves are distributed uniformly around the circumference of the cornea.[18,22–25]

Small incision lenticule extraction (SMILE) is a flapless technique in which a side-cut tunnel of 3–5 mm is used to remove a stromal lenticule created by a femtolaser, preserving the sub-basal plexus and the anterior stroma except in the region of the small incision. According to recent studies, SMILE has the advantage of preserving more corneal nerves than does FS-LASIK.[9]

In photorefractive keratectomy (PRK), there is no flap creation, but the excimer photoablation of the epithelium and anterior stroma damages the corneal nerve endings in the sub-basal plexus with preservation of the deeper stromal nerves.[4,15,26] Lee demonstrated that signs and symptoms of dry eye are fewer in PRK than in LASIK at 6 months postoperatively, whereas Bower et al. studied dry eye manifestations prior to and post-PRK or LASIK and found that in both procedures signs and symptoms of dry eye significantly changed over time, with more participants experiencing DED 12 months postoperatively in the PRK group than in the LASIK group.[4,27]

Denervation can also produce tear film changes with an impairment in lacrimal function. In fact, denervation can lead to an increase in tear film osmolarity, with an accumulation of inflammatory mediators such as IL-1 and matrix metalloproteinase 9, causing inflammation and keratocyte apoptosis which result in pain modulation and amplification of neural signals.[26,28,29]

Conjunctival goblet cell disfunction

Conjunctival goblet cells are specialized epithelial cells that secrete mucins onto the ocular surface, forming the innermost layer of the tear film. These cells are essential for producing a high-quality tear film for maintaining wettability on the ocular surface. Mucins reduce friction of the ocular tissue and protect the eyeball from harmful substances and pathogens.[30]

Corneal nerve disruption produces an alteration in membrane-associated mucin expression on the epithelium with a resultant reduced goblet cell mucin. The damage of conjunctival goblet cells is amplified in FS-LASIK and SMILE techniques, caused by ring pressure during

suction, thus increasing the vicious cycle of DED.[10,16,26,31,32]

Corneal curvature changes

Changes in corneal topography can contribute to the pathogenesis of DED after refractive surgery via a dual mechanism of modification of the relationship between the eyelids and corneal surface due to the corneal curvature changes and irregularities of the corneal surface. In some corneas, in fact, local convexities of the corneal surface are seen.[4,14,17,27] Furthermore, in PRK the irregularity of the corneal epithelium during recovery can exacerbate tear film impairment.[10,31]

All the above-mentioned mechanisms can contribute to signs and symptoms of dry eye, which is the main cause of postoperative patient dissatisfaction. Symptoms of dry eye may be triggered while corneal nerves are regenerating because of the increased activity and activated corneal sensory nerves during the healing process.[27,33]

Several studies have compared the signs and symptoms of dry eye after the available refractive procedures.

A recent meta-analysis published by Shambi et al., based on 14 studies, compared tear breakup time (TBUT) and tear secretion before and after surgery in a 6–12-and/or 24-month follow-up period, showing a significant reduction in both parameters postoperatively in patients who underwent LASIK, and a nonsignificant reduction with SMILE and PRK.[34]

Kobashi et al. compared dry eye after SMILE and FS-LASIK, analyzing ocular surface integrity and innervation by means of Schirmer's test, TBUT, ocular surface disease index (OSDI), tear osmolarity, corneal sensitivity, and corneal sub-basal nerve density. They concluded that SMILE offers a lower risk of alteration in ocular surface homeostasis and lesser risk of developing post-operative dry eye during the 1–6-month observation period than FS-LASIK.[8]

Similarly, a metanalysis conducted by Shen based on 5 cohorts and one RCT, which included 291 eyes treated with SMILE and 277 eyes treated with FS-LASIK in a 6-month period, showed significantly higher TBUT scores in the SMILE group than in the LASIK group at all follow-up visits, whereas statistically significant decreases in the Schirmer's I test (SIT) in both SMILE and FS-LASIK groups were found at six months postoperatively, compared with preoperative values. OSDI revealed significantly lower values in the SMILE group with respect to the FS-LASIK group at all time points, with scores returning to preoperative values in the SMILE group at six months postoperatively.[13]

As previously reported by Shambi et al., tear film osmolarity did not change significantly in either group postoperatively compared to preoperatively. In conclusion, this metanalysis did not show an obvious superiority of SMILE, although SMILE patients may have milder subjective symptoms in the first months after surgery.[34]

Corneal sensitivity changes during the first months postoperatively. Indeed, Denoyer et al. compared corneal sensitivity between FS-LASIK and SMILE, measuring corneal nerve density, number of long fibers, and branching at 1 month and 6 months postoperatively with in vivo confocal microscopy (IVCM). They found that all parameters were significantly higher in the SMILE group than in the LASIK group 1 and 6 months after surgery, concluding that the SMILE procedure has a less pronounced impact on the ocular surface and corneal innervation than does LASIK. However, the corneal sensitivity at 6 months in both groups appeared not to be different than that obtained in healthy controls, suggesting a progressive recovery of the normal values in both procedures.[9,35]

Recchioni et al. confirmed these findings by studying corneal nerve morphology at 1 month postoperatively with IVCM using ACCMetrics software. They found a reduction of up to 75% in the sub-basal corneal nerve after FS-LASIK, whereas in the SMILE group the impact was less, with a reduction of up to 23%.[11]

In light of this evidence, we can affirm that postoperative dry eye syndrome is quite common, but most patients experiencing it transiently and spontaneously recover. There are many published reports on this topic, but recognition of the real incidence still presents a challenge, because of the differences in diagnostic criteria in both literature and practice and the difficulty in objectifying the symptoms. Therefore, early diagnosis and timely, appropriate clinical management are crucial to improve patient comfort and satisfaction. The advantages of a flapless technique, such as SMILE, include the preservation of corneal biomechanical properties, the reduced incidence of dry eye, the low impact on corneal sensation, the nerve sparing with consequent preservation of corneal sensitivity and the absence of flap-dislocation risk in contact trauma.

Impact of dry eye disease on refractive surgery outcomes

The prevalence of dry eye disease varies depending on the definition and patient population characteristics. Studies report rates ranging from approximately 5% to 60% in patients with symptoms, with or without signs of DED.[36,37]

Similarly, there is a high prevalence of preoperative DED in patients presenting for refractive surgery;[38] for example, in the Patient-Reported Outcomes With Laser In Situ Keratomileusis (PROWL)-1 and PROWL-2 studies, 45% and 56% of patients, respectively, were affected by DED symptoms with at least a mild Ocular

Surface Disease Index (OSDI) score prior to refractive surgery.[39,40]

Pre-existing untreated DED has been identified as a risk factor for postsurgical dry eye symptoms.[41–43] When referring a patient to refractive surgery, it is crucial to make a careful examination of the ocular surface. Early recognition of dry eye signs may lead the surgeon to choose a specific refractive technique or, in severe cases, to even discourage the patient. In any case, the prompt correction of ocular surface alterations is crucial for obtaining a successful surgery and long-term satisfaction of the patient. Multiple factors may interfere with the surgical outcomes.

Pre-surgical clinical examination of the patient

Lid examination. The presence of lid margin abnormalities should be assessed and an adequate early treatment should be recommended to the patient before considering refractive surgery. The main reason is the fact that lid margin alterations present multiple risk factors for the surgical outcome. Anterior blepharitis presents a potential increased risk factor for the development of an infection of the surgical wounds and of the flap.[44] Moreover, the microbiota may trigger the activation of an inflammatory response, which could alter the post-surgical course.[45]

Posterior blepharitis and meibomian gland dysfunction (MGD) are characterized by irregularities of the lid margins and by the presence of local inflammation. In case of PRK, this could cause alterations of the epithelial regrowth, with disturbance of the post-surgical visual acuity and overall poor patient satisfaction. If LASIK is performed, the irregularities of the lid margin could interfere with the healing of the corneal flap and even cause alterations of the adherence of the flap or sterile infiltrates.[46,47] Moreover, when MGD occurs, the presence of altered lipids may cause the release of esterases and lipases by commensal bacteria which are present in the eyelids, resulting in epithelial irritation and triggering proinflammatory cytokine release, thus promoting a vicious cycle of inflammation, which could modify the post-surgical healing processes.[48]

While the features of the outer lid margins are more commonly considered in the clinical practice, the inner face of lid should not be neglected. Superior and inferior lid eversion is an indispensable practice in the preliminary examination of the ocular surface. Tarsal conjunctiva irregularities, such as papillae or follicles, may play a role in maintaining an inflammatory condition of the ocular surface, causing potential damage and disturbing vision.[49]

Conjunctival fibrosis may be a consequence of chronic inflammatory processes of the ocular surface. These alterations, often occurring after prolonged chronic conjunctivitis, can interfere greatly with post-surgery healing processes.[50] Tarsal papillae, commonly detected in contact lens wearers and in allergic/atopic patients, are a sign of Ig-E mediated inflammation; in fact, the pathogenesis of papillae is due to the activation of conjunctival fibroblasts by the release of cytokines from T-helper 2 cells.[51] In the case of chronic use of contact lenses, the prolonged rubbing on the lens of the tarsal epithelia causes alterations of the epithelial-lamina propria junction, leading to the creation of tarsal irregularities and papillae.[52] Another common finding in tarsal conjunctiva is lid wiper epitheliopathy (LWE). The "lid wiper" region is considered the area responsible for the spread of tear film over the ocular surface between blinks, and extends from the line of Marx to the subtarsal fold. It can be observed as a linear area of staining after the instillation of vital dyes. Histologically, it is characterized by parakeratinization phenomena, due to different causes, including poor lubrication of the ocular surface, alterations of the blinking rate, incorrect use of contact lenses, and other environmental factors.[53] The clinical relevance of LWE in the presurgical examination is multifold: first of all, it can be a sign of sub-clinical inflammation of the ocular surface, thus indicating the necessity for a proper pre-surgical treatment; secondly, the epitheliopathy itself may interfere deeply with the healing processes after refractive surgery, causing corneal opacities and epithelial defects.

Vital dyes for the study of the ocular surface. The use of vital dyes is a key approach in the observation of alterations of the ocular surface.[54] Fluorescein sodium is widely used in clinical practice to evaluate epithelial defects of the ocular surface. Its action is related to the loss of integrity of the epithelial cells, mainly when alterations of the tight junctions occur. Fluorescein allows the simultaneous examination of corneal and conjunctival alterations, providing a complete observation of the ocular surface with one test. Moreover, the use of a yellow filter within the blue light of the slit lamp enhances the visualization of the defects.[55]

Rose bengal and lissamine green are both effective in the detection of conjunctival alterations, by binding mucins of altered glycocalyx and offering information on subclinical cellular damage and inflammation. In any case, the toxicity and irritating effects of rose bengal (affecting the viability of healthy proliferating corneal epithelial cells) has recently led ophthalmologists to prefer lissamine green dye, which has a better safety and tolerability profile.[56] Today, the combined use of fluorescein sodium and lissamine green is considered very efficient in the identification of epithelial alterations of the ocular surface.[57]

When performing a staining of the ocular surface by means of a vital dye, it is very important to assess the grade of severity of the alterations. For this reason, several classification systems have been studied. The Van Bijsterveld score, National Eye Institute (NEI)/Industry Workshop, Collaborative Longitudinal Evaluation of Keratoconus (CLEK) schema, area-density

combination index, Oxford score, and ocular staining score (SICCA classification) are systems that are widely accepted by the scientific community.[58–63]

Testing in a clinical setting. In addition to the slit lamp examination, it is very useful to perform some non-invasive tests to study the ocular surface before surgery, in order to promptly recognize its subclinical or pauci-symptomatic impairment.

Among others, Schirmer's test is very common in clinical practice. It provides information regarding the quantity of tear production, by collecting tears with specific paper strips that are placed on the inferior lid margin, between the middle and the outer third, performed with or without topical anesthetic drops.

Also, the hyperosmolarity of tears is considered an important sign of dry eye. It can be examined with the help of a chip-on-lab tool that provides a quantitative numerical value, obtained by collecting tears with a specific probe.[64,65] The matrix metalloproteinase 9 (MMP-9) test can also add interesting information about subclinical inflammation. In fact, MMP-9 is an endopeptidase that is involved in the cellular turnover, and is over-released in case of cellular damage.[66]

Using the commercial clinical device, it is possible to obtain a positive/negative response as to the high presence of MMP-9 in the ocular surface of the patient.[67,68] In the pre-surgical setting, a test of corneal sensitivity should not be neglected. It is known that the impairment of corneal nerves is one of the etiopathological factors that can trigger the inflammatory cascade of dry eye disease.[69] Moreover, a valid corneal sensitivity is necessary for the post-surgical healing processes, particularly in the case of LASIK. For this reason an accurate evaluation of the corneal sensitivity, by using a contact or non-contact esthesiometer, is highly recommended.

Contraindications related to dry eye. Uncontrolled DED is an absolute contraindication to refractive surgery. The definition may vary greatly and is dependent on both objective and subjective parameters. Patients should be aware that dry eye may worsen after all types of refractive surgery and that this condition often deteriorates with increasing age.[70] These concepts should be explained thoroughly to patients before performing refractive surgery. Preoperative treatment of patients affected by initial forms of DED results in increased patient satisfaction.[71]

Uncontrolled ocular allergy is an absolute contraindication to laser vision correction (LVC) and can exacerbate DED.[72] Patients should be screened for history of atopy, asthma, allergic conjunctivitis and rhinitis, and atopic dermatitis.[73] Blepharitis is often associated with DED and should be aggressively treated before and after surgery. If treatments are unable to significantly control lid disease, laser vision correction should be avoided.[74] Cicatricial conjunctivitis, either caused by ocular cicatricial pemphigoid or associated with other factors (e.g., ocular burns, infections, drug reactions) is an absolute contraindication for refractive surgery due to the often poor prognosis and unpredictable evolution of the disease.

Systemic diseases such as rheumatoid arthritis, collagen vascular diseases (CVD), Sjogren's syndrome, Graves' disease and other thyroid disorders, or diabetes may be associated with DED. DED associated with these systemic diseases must be controlled. CVD are a group of autoimmune diseases comprising rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polychondritis, Sjogren's syndrome, and the seronegative spondyloarthropathies. Uncontrolled CVD is an absolute contraindication to laser vision correction (LVC), as these patients are at high risk for post-operative dry eye, corneal thinning, melts, irregular healing, and keratitis. Whereas in the past autoimmune conditions were considered an absolute contraindication to refractive surgery, different retrospective case series have confirmed excellent results with no major complications in patients with inactive or stable disease.[75–77] Uncontrolled diabetic disease is an absolute contraindication to LVC, as it can be associated with delayed epithelial healing, persistent epithelial defects, and neurotrophic changes after refractive surgery.[78–80] In a complete review of literature regarding LASIK in diabetic patients, Simpson et al. recommend rigorous criteria for diabetic individuals seeking LVC. These include excellent metabolic control of diabetes (with HgA1c < 7.9%) for at least 12 months prior to surgery, no evidence of ocular complications, such as neurotrophic keratopathy or diabetic retinopathy, and no evidence of uncontrolled systemic disease (renal impairment and diabetic neuropathy).[81]

Neurotrophic keratopathy, exposure keratopathy, and herpetic keratitis. In patients with a history of neuropathy, all forms of refractive surgery can lead to corneal nerve damage and may predispose towards development of neurotrophic keratopathy. Recent studies show that the impact on corneal nerves following refractive surgery may be long-lasting.[82,83] Patients should be screened for the various risk factors (e.g., previous neurosurgery, diabetes, herpetic keratitis, contact lens abuse). Surgeons should set an extremely low threshold for contraindicating refractive surgery in patients with a history of neurotrophic keratopathy. LVC should be avoided in patients affected by exposure keratopathy determined by lagophthalmos, proptosis, and lid malposition. LVC is generally contraindicated in patients with a history of herpetic keratitis (both herpes simplex and zoster), since excimer lasers have been associated with viral reactivation in animal models and humans.[84–86] Furthermore, herpetic keratitis is often associated with neurotrophic keratopathy, and recurrences may lead to severe visual impairment with stromal scarring. Even though successful outcomes have been described in

small case series when antiviral prophylaxis was performed, we suggest avoiding surgery in patients with a positive history of herpetic keratitis for all of the aforementioned reasons.[87]

Use of systemic medications. An accurate patient history regarding medications being taken is fundamental. The following drug categories are associated with dry eye: antihistamines, tricyclic antidepressants, selective serotonin reuptake inhibitors, diuretics, and beta-blockers.[88–90]

Dry eye and refraction. Obtaining accurate subjective refractive measurements is fundamental for planning LVC. Patients affected by DED often have an altered quality of vision with an unstable tear film, determining increased higher order aberrations after blinking and a consequent fluctuation of vision.[91] This leads to accommodation, in an attempt to obtain better vision quality, and may be associated with ocular fatigue.[92] Refraction tests are partially conditioned by data obtained from other examinations such as autorefractometry and corneal tomography/topography. In the presence of dry eye, the quality of acquisitions can be significantly altered and may have even more relevant consequences in patients who undergo topography-guided treatments. In the presence of inadequate exam quality, dry eye should be assessed and treated, and measurements should be repeated once a healthy ocular surface has been restored.

Recommendation for management

On the basis of both evidence and clinical experience, the "Dry Eye and Refractive Surgery" subcommittee of the DROPS workshop formulated some recommendations for ocular surface and DED management pre- and post-refractive surgery.

The most relevant pre-operative actions could be:

- To implement a combination of detailed clinical history, basic tests for tear film analysis, and new advances in diagnostic imaging
- To graduate the severity of DED. In cases of severe dry eye disease, it is always recommended to not perform refractive surgery
- To avoid refractive surgery when corneal nerve damage is documented and a neuropathic DED is present
- To treat Dry Eye before surgery in cases of moderate or mild DED

The most relevant post-operative actions could be:

- To treat Dry Eye based on the deficiency of the tear film

In aqueous deficiency Dry Eye Disease, preservative-free lubricating drops should be preferred, in addition to ointment and gel forms. Topical anti-inflammatory agents (Cyclosporine 0.1%, hydrocortisone phosphate, fluorometholone) should be used for 3–6 months in cases of ocular surface damage. The therapy of evaporative DED includes lifestyle modifications, lid hygiene (either performed by the patient or offered as professional lid hygiene by the physician), use of lubricating eye drops with lipid components, topical and/or systemic antibiotic treatment with anti-inflammatory properties and Intense Pulsed Light (IPL-) Treatment for MGD.

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