Postrefractive surgery dry eye
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Introduction
One of the most common complications of photorefractive keratectomy (PRK) and laser in-situ keratomileusis (LASIK) is dry eye syndrome [1,2]. Although dry eye after refractive surgery is usually transient, some patients complain of severe symptoms, which may negatively influence their satisfaction with the outcome of the procedure [3,4]. Both keratorefractive procedures have been reported to perturb the ocular surface homeostasis by causing a decrease in corneal sensitivity, tear film instability, decreased aqueous tear production, and corneal and conjunctival epitheliopathy [5]. This review summarizes the recently published literature on the ocular surface changes after keratorefractive surgery and its treatment modalities.

Dry eye syndrome
Dry eye syndrome encompasses diverse etiologies and varies greatly in severity. In addition, correlations between symptoms, clinical signs, and diagnostic test results are variable, making the diagnosis and treatment of this condition challenging [6]. Due to this need, an International Task Force consisting of 17 dry eye expert clinicians was gathered to elaborate diagnostic and treatment guidelines for dry eye syndrome using a Delphi consensus technique [3]. One of the recommendations of the panel was that the term ‘dry eye syndrome’ be replaced with ‘dysfunctional tear syndrome’ to reflect current understanding of the pathophysiology of the disease [3].

DEWS Definition and Classification Subcommittee [7] provided a contemporary definition of dry eye disease supported within a comprehensive classification framework. A new definition of dry eye was developed to reflect current understanding of the disease, and the committee recommended a three-part classification of dry eye, based on etiology, mechanism, and disease stage. These guidelines are not intended to override the clinical assessment and adjustment of an expert clinician in individual cases.

Dry eye syndrome is defined as a disorder of the tear film caused by tear deficiency or excessive tear evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort [8–10]. Diagnosis is made after analyzing patients’ complaints, objective signs, and abnormal results of dry eye.
The quality of life can be significantly affected by dry eye symptoms, as documented by several validated survey instruments [12]. The psychological impact of this chronic condition is suggested by a utility assessment of patients’ willingness to trade years at the end of life for an opportunity to be free of dry eye, which found that the utility of moderate dry eye was similar to that of moderate angina [13].

Etiology

The pathophysiologic definition of dry eye was changed to a dysfunction of the integrated ocular surface-secretory glandular functional unit [14]. Communication between the ocular surface and lacrimal glands occurs through a sensory autonomic neural reflex loop. The sensory nerves innervating the ocular surface connect with efferent autonomic nerves in the brain stem that stimulate secretion of tear fluid and proteins by the lacrimal glands. Ocular surface sensitivity has been found to decrease as aqueous tear production and clearance of tears from the ocular surface decrease. This decrease in surface sensation exacerbates dry eye because sensory stimulated reflex tearing is decreased, resulting in decreased ability of the lacrimal glands to respond to ocular surface insults. Thus, a self-perpetuating cycle between the lacrimal gland and the ocular surface is created [14]. Adequate aqueous tear production and clearance with normal mucous gland function are finely controlled by balancing the innervation of the ocular surface and the tear-secreting glands to prevent surface dryness. The dry eye from keratorefractive surgery results mostly from damage to the corneal sensory nerves. Inflammation plays an important role as well in the pathogenesis of dry eye, and it has been elucidated over the past decade [15]. Decreased tear production and tear clearance lead to chronic inflammation of the ocular surface. This inflammatory response consists of cellular infiltration of the ocular surface by activated T lymphocytes, with increased expression of adhesion molecules and inflammatory cytokines, increased concentrations of inflammatory cytokines in the tear fluid, and increased activity of matrix degrading enzymes such as matrix metalloproteinase MMP-9 in the tear fluid. Significant positive correlation has been observed between the levels of inflammatory cytokines in the conjunctival epithelium and the severity of symptoms of ocular irritation, corneal fluorescein staining, and severity of conjunctival squamous metaplasia in patients with Sjögren’s syndrome keratoconjunctivitis [15].

Tear secretion and tear film instability

Keratorefractive surgery seems to cause tear-deficient dry eye by a neural-based mechanism. Since the usual standard method to evaluate reduced tear volume and tear flow is the Schirmer test, studies have consistently included these data when reporting dry eye incidence [8]. Several recent studies have demonstrated the decrease on corneal barrier, tear secretion, and tear film stability. Polunin et al. [16] showed that the corneal barrier function decreased after PRK and LASIK treatments, and the recovery was more delayed after LASIK than after PRK. Yu et al. [17] investigated the effect of LASIK on tear function in 96 eyes of 58 patients for the correction of myopia. LASIK significantly altered the tear break-up time, Schirmer test values, and basal tear secretion. They also concluded that patients with preexisting tear flow abnormality measured with Schirmer test values less than 10 mm was a significant risk factor for experiencing dry eye symptoms at 1 month after surgery.

Lee et al. [18] compared tear secretion and tear film instability following PRK (36 eyes of 21 patients, ranging from −2.50 to −6.00 D) and LASIK (39 eyes of 25 patients, ranging from −3.25 to −9.75 D). At 3 months following surgery there was significantly decreased tear secretion and tear film stability in LASIK patients compared with PRK patients. Although not statistically significant at 6 months, tear secretion and tear film stability were still decreased in LASIK and these values never reached preoperative levels. Nejima et al. [19] evaluated corneal barrier function, tear secretion, and tear stability after PRK (28 eyes of 15 patients) and LASIK (115 eyes of 59 patients). Both procedures decreased epithelial barrier function, reduced tear secretion, and deteriorated tear film stability ($P < 0.05$). Increases in corneal epithelial permeability were, again, more prolonged after LASIK than after PRK. A significant intergroup difference in permeability was observed 1 month after surgery ($P < 0.05$). In their study, tear break-up time was significantly shorter in the LASIK group than in the PRK group up to 3 months after surgery ($P < 0.045$).

Konomi et al. [20] have shown recently that preoperative tear volume may affect the recovery of the ocular surface after LASIK, increasing the risk of chronic dry eye. In this study, patients were classified into two main outcome groups: the nondry eye group and the chronic dry eye group, on the basis of dry eye status 9 months after surgery. All parameters, except rose bengal staining, were significantly deteriorated after surgery but returned to preoperative levels within 3–9 months. The chronic dry
Corneal sensitivity

Corneal sensitivity is essential for the maintenance of normal corneal structure and function [21]. Inevitably, surgical procedures such as PRK and LASIK induce loss of normal sensitivity which may compromise the protective blink reflex, delay epithelial wound healing, and even induce neurotrophic keratitis or sterile corneal melts [22,23]. In PRK, the damage is to the sensory nerve endings that terminate in the corneal epithelium that is removed by mechanical scraping during the procedure [8]. In both PRK and LASIK, there is additional damage to the nerves in the stroma removed by the laser procedure and the greater the myopic correction, the greater the dry eye symptoms [8]. In LASIK, the superior hinged corneal flap is made through the stroma, transecting the posterior corneal nerve trunks that enter the cornea at the 3 and 9 o’clock positions and provide the sensory innervation to the cornea [24]. Several studies have compared PRK and LASIK in terms of their influence on corneal sensation.

Campos et al. [25] reported that in a series of 14 eyes that had undergone PRK, patients with preoperative myopia of less than −6.50 D recovered 95.7% of central corneal sensitivity after 3 months, whereas patients with severe myopia (more than −9.00 D) recovered 86.2% of the original corneal sensitivity at the same time period.

Chuck et al. [26] evaluated 28 eyes of 18 patients (range 1.50–11.25 D) who underwent LASIK. Preoperative and postoperative corneal sensitivity at the nasal flap hinge, at the central cornea and within the temporal flap edge was measured before and after LASIK for a 3-week period using the Cochet-Bonnetesthesiometer. Corneal sensation initially decreased in all three positions of the flap measured after LASIK and the greatest decrease was in the central cornea. Near preoperative corneal sensation returned by 3 weeks. Furthermore, the degree of sensation loss did not appear to correlate with the ablation depth.

Pérez-Santoja et al. [22] evaluated the recovery of postoperative corneal sensitivity after LASIK (17 eyes of 17 patients, ranging from −3.25 to −6.75 D) and PRK (18 eyes of 18 patients, ranging from −3.12 to −7.00 D) for correction of low myopia. Corneal sensitivity was tested at the center of the cornea, and in four additional central points 2 mm from the corneal center. They showed that corneal sensitivity after LASIK was reduced at the ablation zone during the first months (P < 0.05), and, only after 6 months, it returned to its preoperative values. In the PRK group, corneal sensitivity recovered its preoperative values 1 month after surgery (P > 0.05) except for the central corneal point which took 3 months to recover. Comparing both groups, corneal sensitivity was more compromised after LASIK than PRK during the first 3 months (P < 0.05), except for the nasal central point, although no differences were found between both groups at 6 months (P > 0.05).

Matsui et al. [23] compared the effects of PRK (22 patients, ranging from −2.00 to −7.75 D) and LASIK (13 patients, ranging from −4.38 to −11.00 D) on corneal sensation. After PRK, corneal sensitivity was decreased slightly at 3 days, began to recover at 1 week, and returned to preoperative values at 3 months, but none of the changes was statistically significant (P > 0.05). After LASIK, corneal sensation was significantly decreased at 3 days, 1 week and 1 month; it recovered slightly at 3 months, although it remained significantly less than preoperatively.

Nejima et al. [19] have demonstrated that LASIK induces greater and more prolonged damage to corneal sensation than PRK. After PRK, corneal sensation was significantly deteriorated compared with the preoperative level up to 6 months postoperatively. After LASIK, corneal sensation did not return to the normal level throughout the 12 months postoperatively.

Use of intraoperative mitomycin C

Recently, encouraging results have been reported in reducing haze after high myopic PRK corrections by administering a single intraoperative application of diluted mitomycin C (MMC) solution [27]. Bedei et al. [28] evaluated the prophylactic use of MMC to reduce haze formation and refractive regression after PRK for high myopic defects (over −5.00 D). The application of MMC 0.02% solution immediately after PRK produced lower haze rates and had better predictability and improved efficacy 1 year after treatment. Kyominis et al. [29], however, reported a patient with dry eye after bilateral PRK (−5.50 – 0.50 × 170 left eye and −5.00 – 1.00 × 180 right eye) with MMC treatment in the left eye. The patient developed dry eye symptoms and superficial punctate keratopathy (SKP) in the eye treated with MMC for 15 months postoperatively whereas no evidence was noted in the control eye, except for mild haze. Uncorrected visual acuity was 20/20 in both eyes at 15 months.
**Femtosecond laser**

The solid-state femtosecond laser creates variable thickness and size corneal flaps for LASIK. The femtosecond laser seems to have advantages over mechanical microkeratomes including improved predictability of the flap thickness and diameter, better flap uniformity, better predictability of hinge position and size, astigmatic neutrality, and reduced incidence of epithelial defects, buttonholes, and cap perforation [30]. Mian et al. [2**] have reported dry eye after LASIK in 66 eyes (33 patients) with the femtosecond laser (assessed by the Ocular Surface Disease Index), with values of 22.9% after the first week postoperatively, and 21.9% after the first month ($P < 0.00001$). Overall, symptoms were mild and resolved over the first month. The lower incidence of dry eye signs and symptoms with the femtosecond laser may be attributed to the application of lower suction on the eye and creation of thinner flaps, resulting in a greater residual stromal bed and a decreased corneal denervation. They also demonstrated that loss of central corneal sensation persisted significantly longer than dry eye signs and symptoms and was, in fact, still present at the 1-year postoperative examination. Furthermore, they showed that when performing LASIK with femtosecond laser, either with superior hinge or nasal/temporal hinge position, there was no effect on either corneal sensation or dry eye parameters. In fact, decreased corneal sensation and LASIK-induced neurotrophic epitheliopathy [5] seemed to correlate well with the degree of preoperative myopia, depth of laser treatment, and flap thickness. Rodriguez et al. [31**] have studied the effect of the LASIK procedure performed with femtosecond laser (34 eyes, preoperative spherical equivalent $-3.1 \pm 3.1$ D) and a manual microkeratome (30 eyes, preoperative spherical equivalent $-2.0 \pm 3.8$ D). All patients in both groups showed a decrease in goblet cells after LASIK that recovered after 6 months. At 1 week, 1 month and 3 months, goblet cell counts were lower with the femtosecond group than with microkeratome group ($P < 0.001$). This finding is probably explained because of the length of time that the suction ring exerted pressure on the conjunctiva, which is considerably larger in the femtosecond laser compared with the microkeratome. These changes in the goblet cells may contribute to the development of the ocular surface syndrome after LASIK.

**Preoperative dry eye**

The efficacy and safety of refractive surgery is not necessarily affected by preexisting dry eye. Preexisting dry eye, however, is a risk factor for symptomatic postkeratorefractive surgery dry eye with measurable lower tear function and supra-vital staining of the ocular surface. Preoperative conjunctival staining represents a risk factor for postoperative dry eye, and corneal staining is considered to be a relative contraindication of surgery until the ocular surface has been stabilized. Patients with symptoms of dry eye but no signs of corneal or conjunctival staining are generally good candidates for refractive surgery. Patients who have dry eye symptoms with mild conjunctival staining should be treated accordingly in order to stabilize the ocular surface prior to surgery [15].

Many patients who want to have excimer laser refractive surgery are not able to wear contact lenses because of preexisting dry eye or secondary dry eye caused by long-term contact lens use. Commonly, these patients continue to report dry eye symptoms after surgery, despite an improvement in visual acuity following successful correction of the refractive error [18]. Patients with dry eye syndrome are typically considered poor surgical candidates because of an increased association with postoperative complications, including severe dry eye, fluctuating vision, abnormal wound healing, and persistent epithelial defects which can predispose to an increased incidence of diffuse lamellar and microbial keratitis [5,22,32,33].

Patients without preoperative dry eye may experience symptoms and decreased tear function for several months after keratorefractive surgery. Moreover, patients with preoperative dry eye exhibited more severe symptoms and ocular surface damage after keratorefractive surgery compared with patients without preexisting dry eye, although efficacy and predictability were comparable between these groups [34].

A retrospective study was carried out by Toda et al. [33] in which the patients were preoperatively categorized into two groups – the dry eye group and the non-dry eye group – according to selected criteria for characterization of dry eye. Subsequently, the incidence of complications, loss of best corrected visual acuity (BCVA), and dry eye symptoms/tear function were compared in the two groups postoperatively. No difference was identified in the incidence of intraoperative and postoperative complications and loss of BCVA between groups. Dry eye symptoms and tear function were more compromised in the dry eye group preoperatively and also postoperatively, 1 year after the surgery. Despite this, symptoms and tear function returned to preoperative levels in both groups. The authors suggest that these results may indicate that LASIK may be performed safely and effectively in patients with preoperative dry eye. Albietz et al. [32] examined the relationship between chronic dry eye and refractive regression after LASIK for myopia. The regression after LASIK occurred in 12 (27%) of 45 patients with chronic dry eye and in 34 (7%) of 520 patients without dry eye ($P < 0.0001$). Patients with chronic dry eye had significantly worse outcomes than those without (6 months, $P = 0.004$; 12 months, $P = 0.008$). The risk for regression...
was associated with higher attempted refractive correction, greater ablation depth, and dry eye symptoms after LASIK.

Management

The majority of patients with dry eyes respond to conventional treatment aimed at optimizing the ocular surface microenvironment. The ecosystem of the ocular surface depends on dynamic interactions of healthy adnexae, adequate blink reflex, normal tear production, and ocular surface tissue, consisting mostly of cornea and conjunctiva. Conventional therapeutic options include intensive tear supplements, punctal occlusion, contact lenses, and an appropriate management of the adnexal disease [35].

Artificial tears have been the primary treatment of the postkeratorefractive surgery dry eye [36,37]. Despite attempts to improve composition, artificial tears can never replace those produced by the lacrimal gland. In the last decade, it has been recognized that tears with preservatives may be toxic to the ocular surface epithelium. Therefore, it has been recommended to use preservative-free artificial tears in some cases [9,37]. While artificial tears improve symptoms of dry eye, they do not eliminate the underlying inflammatory process [38].

Meibomian gland dysfunction is another common and critical component of ocular surface inflammation. Patients with meibomian gland dysfunction due to blockage of the glands may also benefit from warm compresses, lid scrubs and massages that would help breaking up the oils and open up the ducts within the glands [11,39]. This particular problem is best controlled with systemic antibiotics, such as doxycycline for a period of 4–6 weeks or more [39]. These antibiotics have shown the capacity of thinning these glands secretions, to maintain the natural flow of their secretions.

Anti-inflammatory therapy using topical corticosteroids has also been reported to be an efficacious therapy for patients with dry eye [36]. Marsh and Pflugfelder [40] reported the efficacy of a topical administration of 1% nonpreserved methylprednisolone for patients with severe dry eye, demonstrating relief from irritation, a decrease in fluorescein staining, and resolution of SPK. While topical steroids may have the most rapid anti-inflammatory action, treatment is not advisable for long-term management because of the side effects of corticosteroids, especially cataract formation and glaucoma [38].

In 2002, the Federal Drug Administration approved cyclosporine for the treatment of dry eye. Cyclosporine 0.05% ophthalmic emulsion was the first treatment to target the underlying pathological mechanism for chronic dry eye: the immune-mediated inflammation. Cyclosporine has minimal side effects compared with steroids and may be used for long periods of time without deleterious effects in the eye [38,41,42]. In addition, cyclosporine offers the advantage of immunomodulation without the risk of corticosteroids’ side effects, as opposed to immunosuppression. This treatment has been shown to increase tear production and reduce inflammation based on T-cell recruitment as well as increasing goblet cell numbers, and preventing lymphocyte infiltration within the lacrimal and accessory glands and conjunctiva [43]. Salib et al. [44] carried out a study to evaluate two treatments for dry eye, and refractive outcomes in patients with dry eye having LASIK. Forty-two eyes of 12 myopic patients (ranging from –1.00 to –10.63 D) with dry eye were treated with unpreserved artificial tears or cyclosporine 0.05% ophthalmic emulsion twice a day beginning 1 month before LASIK. Treatment with the study drug was discontinued for 48 h following refractive surgery and then resumed for three additional months. Statistically significant increases from baseline were found in Schirmer values for artificial tears at 1 month (P = 0.036) and cyclosporine before surgery and 1 week, 1 month, and 6 months after surgery (P < 0.018). Mean refractive spherical equivalent in cyclosporine-treated eyes was significantly closer to the intended target at 3 and 6 months after surgery than in artificial-tear-treated eyes (P = 0.007). Thus, treatment with cyclosporine 0.05% provided greater refractive predictability at 3 and 6 months after surgery than unpreserved artificial tears, according to this study.

Punctal plugs is another tool that appears to be a relatively safe, effective, and reversible method of preserving aqueous and artificial tears on the ocular surface to reduce the signs and symptoms of dry eye [45]. Studies have shown that dry eye patients may often decrease and sometimes eliminate the need for artificial tear preparations [46]. Albietz et al. [47] reported that postoperative ocular surface management, which included the use of punctal plugs when indicated, improved symptoms and goblet cell density in patients who had undergone PRK or LASIK. Since punctal occlusion and topical cyclosporine treat dry eye under different mechanisms, Roberts et al. [48**] carried out a study to examine their efficacy separately and then in combination. They evaluated three treatment regimens consisting of topical cyclosporine twice daily, punctal plugs, and a combination of cyclosporine and plugs over 6 months. As a result, all three treatment groups were effective and increased tear volume to a similar extent over the course of the study. At 1 and 3 months, however, groups that included punctal plugs were superior to cyclosporine alone in improving Schirmer scores. These results are consistent with the known function of punctal occlusion in physical conservation of existing tears. In summary, although all the treatments in this study effectively treated
chronic dry eye, some trends regarding specific modalities are evident. In the near term, punctal occlusion (alone or in combination with cyclopentolate) produced the most rapid improvements in wetness, as assessed by Schirmer testing and patient self-medication with artificial tears, consistent with the tearing-conserving function of punctal plugs. Over the longer term, the cyclopentolate-containing regimen resulted in improvement in the same measures that were statistically indistinguishable from, or were superior to, the plugs-only regimen. Furthermore, only the cyclopentolate-containing regimen significantly improved ocular surface staining over time. These observations are consistent with the known roles of topical cyclopentolate in addressing the underlying immune pathophysiology of chronic dry eye disease. There may be an additive effect of topical cyclopentolate and punctal occlusion, and patients with punctal occlusion may also benefit from adjunctive cyclopentolate.

Autologous serum has also been used as a potential treatment for dry eye. It contains anti-inflammatory agents and MMP inhibitors that are especially useful in patients with autoimmune-associated inflammatory processes, such as Sjögren’s [38,49]. The efficacy of autologous serum application for the treatment of corneal transplantation or other ocular surface disorders [50], such as superior limbic keratitis [51], dry eye in graft-versus-host disease [52], or Stevens-Johnson syndrome [50], has been reported. These studies suggest that autologous serum may improve almost all types of dry eye. Noda-Tsuruya et al. [53] evaluated the efficacy of autologous serum eye drops for dry eye after LASIK. The results showed that break-up time test and vital staining were significantly improved after LASIK in the autologous serum eye drops group, whereas no change was reported in the artificial tear group at 6 months postoperatively. These findings suggest that autologous serum eye drops could be effective for postoperative dry eye induced by LASIK. Toda et al. [34] performed LASIK in three patients who suffered from Sjögren’s syndrome and showed decreased reflex tearing. They inserted punctal plugs and prepared the autologous serum at the first visit of each patient. The LASIK procedure was scheduled to be undertaken after the ocular surface damage was healed by the treatment. LASIK was performed uneventfully, and no complications were observed in any of the patients. These results indicate that LASIK may be safely performed on patients with severe dry eye, if the ocular surface damage is energetically treated before surgery.

Conclusion

LASIK and PRK may exacerbate preexisting dry eye, or trigger a previously nonexistent dry eye. The symptoms after keratorefractive surgery are usually transient but may cause significant discomfort in patients. Attention must be paid to dry eye in candidates undergoing keratorefractive surgery, and appropriate methods of management must be made available to these patients. The incidence of postkeratorefractive procedure dry eye may be reduced by identifying patients at risk for dry eye, maximizing tear film stability preoperatively, and minimizing dry eye through intra and postoperative interventions, both pharmacological and surgical.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 366).

3. There was no difference in corneal sensation between superior-hinged and temporal-hinged flaps at 1 week, 1, 3, 6, and 12 months after surgery. Mild dry eye disease was present early after myopic LASIK with IntraLase laser.
8. Topical cyclopentolate treatment appears to be associated with the cure of symptoms and signs in chronic dry eye patients.
10. A new definition of dry eye was developed, and the committee recommended a three-part classification based on etiology, mechanism, and disease stage.


32 Impression cytology showed a greater reduction in goblet cell populations after IntraLase femtosecond than after microkeratome, probably because of the length of time that the suction ring exerted pressure on the conjunctiva.


41 Perry HO, Donnenfeld ED. Topical 0.05% cyclopentolate in the treatment of dry eye. Expert Opin Pharmacother 2004; 5:2099–2107.


