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Post-LASIK dry eye

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Abstract

Laser-assisted *in situ* keratomileusis (LASIK) is a frequently performed corneal refractive surgery with excellent refractive outcomes. The most common complication of LASIK is dry eyes, with virtually all patients developing some degree of dryness in the immediate postoperative period. Identifying preoperative dry eyes, and conscientious attention and treatment in the perioperative time period, can lead to enhanced patient satisfaction and more accurate visual outcomes. Improved understanding of the development of dry eyes after LASIK will advance our understanding of the complex pathophysiology of dry eye disease.

Keywords

cornea; corneal nerves; dry eye; dry eye disease; dry eye syndrome; keratitis sicca; laser *in situ* keratomileusis; LASIK; refractive surgery

Dry eye disease (DED) is a commonly encountered diagnosis in ophthalmology, but is poorly understood, difficult to define, and lacks a unique diagnostic test. The International Dry Eye Work Shop (DEWS) recently defined DED as “a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface” [1]. It can be caused by either inadequate tear production or excessive tear evaporation. Dry eye symptoms range from mild ocular irritation to severe discomfort, photophobia and vision loss. Clinical signs of dry eye include evidence of decreased aqueous tear production, decreased tear volume on the ocular surface, increased rate of tear evaporation, and increased tear osmolarity. There is often a mismatch noted between the severity of signs and symptoms in patients with dry eyes.

Laser-assisted *in situ* keratomileusis (LASIK) is a safe and effective surgical option for treatment of refractive errors [2]; however, dry eyes are a remarkably frequent consequence of LASIK surgery, with up to 95% of patients experiencing symptoms of dry eyes after corneal refractive surgery [3]. Although signs and symptoms of dry eyes are most common in the immediate postoperative period and are usually only transient in nature, a small

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proportion of individuals develop chronic and severe dry eyes that can be quite refractory to traditional dry eye treatments.

The epidemiology, pathophysiology and treatment options for dry eye after LASIK will be reviewed here in an effort to improve the understanding of the etiologic factors and our ability to minimize development of severe dry eyes, and improve treatment of post-LASIK dry eyes. Through improved understanding of iatrogenically induced post-LASIK dry eyes, it is hoped that we will also expand our understanding of the pathophysiology of other forms of DED as well.

Epidemiology

Dry eye symptoms are fairly common in patients prior to LASIK, very often due to dry eye-associated contact lens intolerance leading patients to seek alternate methods of refractive error correction. The prevalence of dry eye symptoms prior to undergoing LASIK is estimated to be between 38 and 75% [4,5].

Post-LASIK, it has been widely shown that a majority of patients complain of dry eye symptoms, especially in the early postoperative period [3,6–9]. Immediately after LASIK, 95% of patients report some dry eye symptoms [3]. Dry eye symptoms are reported in as high as 60% of patients 1 month after LASIK [3,7]. Post-LASIK dry eye usually peaks in the first few months after surgery, and then symptoms begin to improve in the vast majority of patients at 6–12 months after surgery. Corneal refractive surgeons also report dry eyes as the most common complication of LASIK [10].

Quality of life can be severely affected by dry eyes. Utility assessment quantifies patient preferences with regards to any health state or disease, allowing comparison across patient populations and across disease states. Patients with moderate-to-severe dry eyes report utility scores similar to patients with moderate-to-severe angina, or hospital dialysis [11,12]. Lesser degrees of dry eyes are also associated with significant morbidity, with utility scores of patients with mild DED equivalent to those who suffer from severe migraines [12,13]. Dry eyes are a primary reason for patient dissatisfaction after LASIK surgery. Two independent retrospective studies evaluating post-LASIK patient referrals to tertiary ophthalmology care centers identify approximately 30% of these patients with dry eyes [14,15].

Pathophysiology

Dry eye disease has a complex and multifactorial etiology. The ocular surface and lacrimal gland are a functional unit that work together to maintain the tear film and ocular surface environment [16]. Specifically, there is a complex interaction between the afferent sensory nerves of the ocular surface and the efferent autonomic nerves to the lacrimal gland that modulate both tear composition and secretion. Any factor that disrupts this relationship will lead to tear dysfunction and an increase in the concentration of the tear film (hyperosmolarity) that has been shown to cause inflammation and apoptosis of the epithelium.

There are multiple theories as to how LASIK contributes to the pathophysiology of dry eyes. The main proposed cause is iatrogenic corneal nerve damage. LASIK disrupts both the dense sub-basal nerve plexus and stromal corneal nerves in the creation of the anterior stromal flap and excimer laser ablation of the cornea.

Loss of conjunctival goblet cells has also been identified after LASIK, likely due to direct damage from the suction device used during creation of the LASIK flap [17]. Damage to the goblet cells occurs with both microkeratome- and femtosecond laser-created flaps [18–20].

Postoperative inflammatory changes may also contribute to post-LASIK dry eyes [8]. Inflammation at or near the nerve endings may directly stimulate pain through either pressure or other direct action on the nerve. Alternatively, inflammation could exacerbate a pre-existing dry eye state, destabilizing the tear film through cytokine-mediated reduction in tear film quality. Ocular surface dryness is known to be associated with chronic inflammation of the ocular surface, and the presence of inflammatory cytokines in the tear film and conjunctival epithelium [21]. It is hypothesized that the inflamed postsurgical state could contribute to propagating inflammation on the ocular surface.

Finally, the LASIK-induced change in corneal shape may affect the relationship between the eyelids and ocular surface and lead to abnormal tear distribution during blinking [3,22]. A corneal iron line can sometimes be seen within the area of the LASIK flap, reflecting an alteration in the surface tear dynamics of the cornea [23].

Dry eye risk factors & preoperative management

Identifying patients at risk for severe post-LASIK dry eye is crucial to improve comfort and optimize surgical outcomes. Prior to surgery, LASIK candidates should have a thorough examination, including detailed evaluation of the ocular surface and careful questioning about dry eye symptoms. Components of the examination especially important to note include the tear meniscus, tear quality, tear break-up time, presence of lid disease, Schirmer testing, and any ocular surface staining. Although there is no single diagnostic test for dry eyes, there is increasing evidence that tear osmolarity testing can provide crucial information about dry eye severity [24,25], and may be of value in identifying patients at risk for post-LASIK dry eye. Symptoms that should be elicited include feelings of dryness, grittiness, irritation or tired eyes. It is also of value to inquire about vision fluctuations, especially in conjunction with blinking, and any eye symptoms that seem worse towards the end of the day. Patients should be appropriately counseled with realistic expectations about the immediate postoperative worsening of dry eyes and the potential for long-term symptomatic postoperative dry eyes.

Any ocular surface abnormalities noted before surgery should be treated prior to proceeding with surgery. A retrospective study that compared patients who either did or did not have preoperative ocular surface treatment prior to undergoing LASIK showed reduced dry eye symptoms in patients with more aggressive management [26]. All patients should be instructed regarding adequate lubrication of the ocular surface, and at-risk patients should be started on a regimen prior to LASIK and monitored for therapeutic efficacy prior to surgery. Punctal plugs can be considered preoperatively to reduce the tear drainage rate. Also, either cyclosporine or corticosteroid eye drops can be considered preoperatively to treat the inflammatory component of dry eyes [27]. Lid margin disease should be identified and treated preoperatively. Preoperative management of any existing issues will improve tear function and overall ocular surface health, and thereby improve the accuracy of the preoperative measurements and postoperative visual outcomes.

There is no way to predict the severity of post-LASIK dryness for any individual patient, but pre-existing dry eye is a known risk factor for post-LASIK ocular surface staining, more prolonged and severe dry eye symptoms, and delayed recovery of corneal sensation [3,20,28–30]. Other factors that have been associated with increased risk of dryness include female sex [31,32], Asian ethnicity [33], contact lens use [34], eyelid anomalies [35] and

diabetes [36]. Finally, higher refractive correction and deeper stromal ablation have been associated with increased severity of post-LASIK dry eyes in some studies [5,31].

Post-LASIK tear film

Numerous studies have reported findings of decreased tear amount or tear quality after LASIK. Although the study designs and specific dry eye parameters differ by study, most agree that there is objective evidence of worsening of dry eye clinical signs after LASIK. The studies differ greatly in length of follow-up, and there is no uniform consensus as to when these signs begin to improve, although most studies indicate approximately 6–12 months after surgery.

An early prospective study investigating the effect of LASIK on tear function in 96 eyes of 58 patients found significant differences in basal and reflex tear secretion and tear break-up time after LASIK [3]. The study also found that pre-LASIK Schirmer score correlated with the level of dry eye symptoms after LASIK [3]. However, the study only included 1 month of follow-up. Another study of 115 eyes of 59 patients with slightly longer follow-up confirmed that reduced tear secretion and tear film stability persisted until at least 3 months after surgery [37].

Among studies with longer follow-up, there was more variability of results. One study revealed reduced tear secretion and tear film stability, as well as increased tear osmolarity that persisted until 6 months post-LASIK [22]. A study evaluating dry eye after hyperopic LASIK showed reduced tear film volume until 3 months, with subsequent resolution to preoperative levels by 6 months [32]. Another study found no significant postoperative differences in either tear secretion or stability with noninvasive tear film testing, although the authors state there was a great deal of variability between individual eyes [38].

Several studies followed patients until 9 months after LASIK. One small prospective study found that conjunctival goblet cell density, tear secretion and tear film stability all worsened immediately postoperatively, but then improved by 3 months postoperatively [20]. For the patients that continued to have dry eye problems at the 9-month follow-up, preoperative Schirmer score was found to be predictive for dry eyes. There was also a significant difference in the postoperative tear break-up time measurement at both 3 and 9 months between patients whose symptoms improved compared with those who maintained chronic ocular surface dryness [20]. A small retrospective study found no such relationship, with tear secretion improved to preoperative levels by 9 months postoperatively [34].

A retrospective case–control study compared 19 post-LASIK patients with punctate epithelial erosions in their flap postoperatively to 19 concurrent patients without ocular surface stain and found no significant difference in tear production as measured by Schirmer score at 1, 3 and 6 months after LASIK. Since there was no difference in actual tear production, the authors presume that the staining is more likely due to neurotrophic epitheliopathy [39,40].

Post-LASIK corneal sensation

Healthy corneal sensation is a requirement for maintaining communication of the ocular surface–lacrimal gland functional unit. The afferent sensory nerves that mediate the sensitivity of the ocular surface come from the ophthalmic division of the trigeminal nerve. They penetrate the cornea peripherally and form a dense sub-basal nerve plexus from which terminal nerve endings enter into the epithelium [41]. Corneal denervation is believed to be the most significant cause of post-LASIK dry eyes [21].

Laser-assisted *in situ* keratomileusis induces corneal nerve damage in the process of flap creation and the excimer laser stromal ablation. LASIK-induced damage to the sensory nerve fibers of the cornea decreases basal and reflex tearing, slows the blink rate and impairs the neurotrophic effect on corneal epithelial cells [42]. Sensory denervation of the ocular surface disrupts the tear apparatus and causes irritative symptoms [8]. Decreased corneal sensation is associated with decreased aqueous tear secretion, resulting in reduced reflex tear secretion, and a cycle of dryness [43]. A phenomenon of LASIK-induced neurotrophic epitheliopathy has also been described in which corneal staining occurs in the absence of aqueous tear deficiency, implying that LASIK-induced corneal denervation affects factors other than exclusively lacrimal gland tear production [39,40,44].

Corneal sensitivity has repeatedly been shown to be decreased after LASIK [8,20,31,34,37,42,45–52], but various studies have identified different rates of recovery of sensation. Time to recovery to preoperative sensation levels ranges from 3 weeks [53] to sustained corneal sensation abnormalities at 12–16 months after surgery [8,37,54]. Several studies converge on the recovery of pre-operative levels of sensation at the 6–9 month range [20,31,34,52], similar to the time scale of post-LASIK recovery of tear secretion and tear quality.

The clinical correlations of decreased corneal sensation after LASIK are difficult to interpret owing to varying study designs and inconsistent conclusions in the existing studies. Some studies identify correlations between decreased sensation and worse dry eye signs/symptoms [8,34], while others find no such relation [20,46].

Post-LASIK corneal nerve morphology

In vivo confocal microscopy (IVCM) can be used to identify and characterize the sub-basal nerve plexus and stromal corneal nerves in living subjects in a noninvasive and repeatable manner. Using this technology, several studies have investigated the morphologic changes of corneal nerves following corneal refractive surgery.

The pattern of sub-basal nerve regeneration has been described, with nerve regeneration beginning in the peripheral cornea and extending centrally [55]. Short unconnected nerve fibers become visible approximately 3 months after LASIK, with some interconnections between these segments becoming visible by 6 months postoperatively [50,56,57].

A prospective study of patients who underwent LASIK for high myopia revealed an 82% decrease in sub-basal nerve density immediately post-LASIK, followed by a subsequent gradual increase over time [58]. However, even 2 years after LASIK, nerve density remained significantly decreased [58]. Another prospective study followed patients with serial IVCM evaluations for 5 years after LASIK [59]. Sub-basal nerve density was reduced by 51, 35 and 34% at 1, 2 and 3 years after LASIK, respectively. At 5 years after surgery, sub-basal nerve density was still reduced from pre-operative levels, although this was not statistically significant [59]. A single case report of a patient who had LASIK 15 years previously showed a regenerated sub-basal nerve plexus [60]. However, despite the regeneration of sub-basal nerves, many post-LASIK patients have persistent altered corneal morphology years after surgery, with nerves described as thinner, more curved and with abnormal branching [61].

Corneal stromal nerves are more variable and therefore more difficult to quantify; however, systematic evaluation of stromal nerves after LASIK has identified a decrease in the number of nerves in the anterior stromal flap that is most severe immediately postoperatively [62]. Stromal nerve density remains abnormal in the anterior cornea 3 years after LASIK, with no decrease noted in the stromal nerves of the posterior corneal bed [62].

Several studies have performed corneal evaluations in conjunction with IVCM assessment of corneal nerve appearance. Most studies find no direct correlations between corneal nerve regeneration and recovery of corneal sensation [50,56,63,64]. In general, corneal sensation is found to recover to preoperative levels within the first year after surgery, but corneal nerve morphology continues to be abnormal. Only one study found that recovery of corneal sensation correlated with regeneration of corneal nerves [65].

Refractive outcomes with dry eyes

Dry eyes can substantially affect a patient's perception of their surgery and their level of satisfaction [14,15], but refractive outcomes in patients with dry eyes still tend to be quite good. A study evaluating early refractive outcomes of patients with preoperative dry eyes found that patients with pre-LASIK dry eyes had slightly decreased visual acuity on the first postoperative day that resolved by 1 week postoperatively [66]. Several studies indicate no significant difference in refractive outcomes in patients with pre- or postoperative dry eyes. One retrospective study compared patients with and without preoperative dry eyes and found no difference in uncorrected distance visual acuity or best corrected distance visual acuity, or incidence of intra- or post-operative complications other than increased rate of dry eye symptoms and signs [28]. Two prospective studies evaluating a total of 76 eyes of 42 patients found no correlation between depth of corneal ablation and loss of corneal sensation [34,53].

Of interest, chronic dry eye is associated with refractive regression after both myopic and hyperopic LASIK [32,67], but not to clinically significant levels. This effect was noted to be lessened in patients who were treated with an aggressive, scheduled regimen of moisturizing drops [30] or cyclosporine eye drops [68].

Variations in LASIK surgical technique

Since post-LASIK dry eyes are strongly associated with surgical corneal nerve damage, alterations in surgical technique have been hypothesized to modulate the degree of induced dry eye. Studies have shown variable results in the effect of altering the LASIK surgical parameters.

The use of the femtosecond laser for LASIK flap creation has been FDA approved since 2001. Although more expensive than the traditional microkeratome, the femtosecond laser provides more accurate, more reliable and safer LASIK flap creation [69]. Several studies have been performed to assess the effect of femtosecond laser use on the incidence of dry eyes after LASIK, with some evidence for decreased signs and symptoms of dry eyes after femtosecond LASIK [70]. However, there is evidence of significantly lower conjunctival goblet cell density, as measured by impression cytology, in those who had femtosecond flaps compared with microkeratome flaps in the first 3 postoperative months, with goblet cell density improving over 6 months after surgery to preoperative levels [18]. The authors presume a greater loss of goblet cells early after surgery in the femtosecond group due to the longer duration of the suction device on the eye during flap creation [18]. Of note, the role of goblet cells in DED is not fully understood and the clinical ramifications of reduced goblet cell density are not well-established.

Flap hinge position has been compared in several prospective studies. One study found significant differences in dry eye signs and symptoms and corneal sensation between superior and nasal-hinged microkeratome LASIK flaps, with the nasal hinge group having fewer problems with dry eyes and faster resolution of corneal sensation loss [71]. Other studies did not find any differences in dry eye parameters when varying the hinge position in this manner [5,72,73]. One study used the femtosecond laser to vary flap hinge position

from superior to temporal, but also did not find an effect of hinge position on dry eye parameters or corneal sensation [54].

Wider LASIK hinge size was associated with faster improvement of corneal sensation in one study [74], but varying LASIK flap hinge width with a femtosecond laser had no effect on corneal sensation or dry eye signs and symptoms [75]. Variations in flap thickness are also not associated with an appreciable effect on corneal sensation or dry eye signs and symptoms [70,75]. Lifting a LASIK flap for an enhancement procedure had no significant effect on dry eye signs or symptoms, but did lead to a decrease in corneal sensitivity that was maintained throughout the 6 months of post-enhancement follow-up [29].

A prospective study of patients with femtosecond-flap myopic LASIK reported an increase in dry eye signs and symptoms after surgery that resolved within the first 3 months after LASIK. Corneal sensation, however, remained decreased throughout the 1 year follow-up [54,75]. The authors postulate that a lower degree of suction on the eye, thinner flaps and increased residual stromal bed may contribute to a lower rate of dryness and faster recovery than with microkeratome [54].

Special population: rheumatologic disease

Patients with rheumatologic conditions are usually excluded from corneal refractive surgery owing to concern for worsening corneal inflammation and possible corneal melt. These patients are also at high risk for pre- and post-operative dry eyes. Few studies have evaluated the effect of LASIK on dry eyes in these patients.

A retrospective review of patients with controlled rheumatic diseases who underwent LASIK showed good outcomes without any vision-threatening complications. Interestingly, 14% of eyes required an enhancement procedure, consistent with other studies that demonstrate an association of dry eyes with regression of refractive effect [32,67]. Moderate persistent dry eye developed postoperatively in 10% of these patients [76].

Two small studies reported the results of patients with Sjogren’s syndrome who underwent LASIK. Two patients with well-controlled Sjogren’s syndrome developed severe and difficult-to-treat dry eyes and refractive regression [77]. Another report of three patients with Sjogren’s syndrome who were treated with punctal occlusion and/or autologous serum drops both before and after bilateral LASIK all had good refractive results and were satisfied with their surgical outcomes [78].

Post-LASIK dry eye treatment

Many patients with post-LASIK dry eyes do well with conventional treatments for dry eyes. Artificial tears are the initial therapy, especially in sensitive postoperative eyes and in cases in which patients use drops more than four times a day, where the use of preservative-free drops should be encouraged [79]. Unfortunately, artificial tears do not always provide sufficient relief.

Punctal occlusion can be performed after LASIK to assist with improving the amount of time that tears stay on the ocular surface. Punctal plugs are a safe, effective and reversible treatment for dry eyes [80]. Patients with more prolonged symptoms, and especially those who have had improvement of dry eye signs and symptoms with plugs, can also consider thermal punctal occlusion [81].

Tear quality should also be addressed in post-LASIK dry eye patients. Meibomian gland dysfunction can significantly contribute to ocular surface discomfort and inflammation of

the ocular surface, and should be identified and treated. Conservative treatment measures include warm moist compresses and gentle lid massage or scrubs [82]. Some patients also benefit from a course of oral tetracycline, usually doxycycline, for its anti-inflammatory effect on the skin and meibomian glands [82]. Topical azithromycin eye drops have also shown some promise as a treatment for meibomian gland dysfunction [83].

Dry eye disease involves an inflammatory component and anti-inflammatory therapy is a mainstay of treatment for moderate-to-severe dry eyes [84]. Although treatment for dry eyes can include a short course of topical corticosteroid eye drop, this is not a good long-term measure owing to potential side effects of increased intraocular pressure and cataract formation. Cyclosporine A 0.05% ophthalmic emulsion is a topical anti-inflammatory that can be used safely and effectively to treat post-LASIK dry eyes [42]. These drops have been shown to increase tear production, decrease inflammation and increase goblet cell numbers in individuals with dry eye [85]. When compared with artificial tear use in a randomized double-masked prospective trial, cyclosporine A 0.05% for 1 month prior to LASIK and 3 months after was associated with increased Schirmer score and improved refractive result, although there was no difference in dry eye symptoms or visual acuity [68].

In cases of dry eyes that do not improve with the above treatments, other options exist. Autologous serum eye drops comprise a patient's own serum mixed with sterile saline solution in an eye drop. This provides a unique source of growth factors and anti-inflammatory factors that have been shown to improve dry eye signs and symptoms in a variety of dry eye conditions [86], and have been shown to be safe and effective for use in post-LASIK dry eyes [87]. A comparison of serum tears and artificial tears in post-LASIK dry eye patients showed improved tear break-up time and less ocular staining in the serum tear group at the 6-month time point [87].

Another treatment option for severe cases of dry eyes is scleral contact lenses. Scleral gas-permeable contact lenses have been shown to improve comfort in patients with post-LASIK dry eyes [88]. The prosthetic replacement of the ocular surface (PROSE) is a prosthetic device that supports a healthy environment for the ocular surface. PROSE has been shown to provide improvement in dry eye signs and symptoms in a variety of dry eye conditions [89].

There has been some preliminary interest in the potential use of topical nerve growth factor for the treatment of post-LASIK dry eyes. Nerve growth factor has both neurotrophic and immune-modulator effects and could be useful to treat corneal nerve damage after LASIK [90]. There may even be a role for nerve growth factor or other neurotrophins to assist with healing of corneal nerve damage in the early postoperative period [90]. However, there are still challenges in making this type of treatment accessible to the cornea. There is also a subset of post-LASIK dry eye patients with aberrant nerve regeneration and corneal neuropathy that might benefit from treatment for neuropathic pain [91].

Expert commentary

Post-LASIK dry eye is extremely common and can be a significant problem for affected patients and their eye-care providers. Patients should be examined carefully prior to LASIK for any signs of ocular surface disease, and treated to optimize the ocular surface in order to increase both the accuracy of surgery and the patients' postoperative comfort. Careful attention should be taken during surgery to minimize ocular surface damage.

In patients with symptomatic post-LASIK dry eyes, symptoms and signs should be treated aggressively to optimize visual outcomes, speed visual recovery and improve comfort. Treatment modalities mirror those for other forms of DED, including tear supplementation, punctal occlusion and anti-inflammatory therapies. More severe dry eyes can also be treated

with autologous serum tears or specialized contact lenses and ocular prostheses. Most patients will improve over the 6–12 months following surgery; those who do not improve in that timeframe will often have long-term symptoms of dry eyes.

Five-year view

In recent years there has been increasing research into the role of corneal nerve damage in the development of post-LASIK dry eyes. In the coming years, there will be improved insight into the role of corneal nerve abnormalities in the development and perpetuation of dry eyes. It is likely that more targeted treatment towards nerve healing will be developed and will assist with treatment for post-LASIK dry eyes. The additional insight gained from investigations of post-LASIK dry eyes is also likely to enhance our understanding, and perhaps treatment, of other forms of DED.

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Key issues

- Dry eye signs and symptoms are the most common complication of laser-assisted *in situ* keratomileusis (LASIK), occurring in a vast majority of patients.
- Pathophysiology is multifactorial, including damage to the corneal nerves and conjunctival goblet cells, and postoperative inflammatory changes.
- Preoperative risk factors include pre-existing dry eye signs and symptoms.
- Although usually temporary, the symptoms of post-LASIK dry eyes can be quite troublesome and lead to decreased satisfaction with surgical outcomes.
- Most studies indicate clinical signs of dry eye and corneal sensation recover to preoperative levels approximately 6 months to 1 year after surgery.
- Current treatment of post-LASIK dry eyes depends on tear supplementation, punctal occlusion and medications used for dry eye disease.
- Improved understanding of iatrogenic dry eye after LASIK might improve our understanding of the pathophysiology of dry eye disease in the general population.