Ocular interventions, such as surgical procedures and contact lenses, can alter the ocular surface environment and induce tear film instability. It has been reported that postoperative tear function after cataract,1 strabismus,2 ptosis,3 photorefractive keratectomy (PRK),4 and LASIK5–7 surgeries is sometimes compromised by uncomfortable dry eye symptoms. Based on reports concerning the association between ocular surgeries and dry eye, LASIK is the most common procedure that influences postoperative tear film status. Therefore, in this review I will focus on LASIK, which is well known to cause postoperative dry eye, and will discuss the possible mechanisms involved in this condition.

LASIK has become a very popular form of refractive surgery in recent years. This is because it is a safe, effective, and well-established procedure that offers many advantages over other types of refractive surgery, including fast and painless visual rehabilitation, less regression, and no subepithelial corneal haze. With improvement in the techniques and instruments used in LASIK, the incidence of complications has decreased. Clinical outcome, safety, and patient satisfaction from modern LASIK with advanced technology have been found to be significantly better than when LASIK was first introduced about 30 years ago.8

Although the outcomes have improved dramatically, we should continue doing our best to prevent and quickly treat even minor complications of refractive surgery such as LASIK. Postoperative dry eye affects approximately 50% of patients at 1 week postoperatively, 40% at 1 month, and 20% to 40% at 6 months.9,10 Although post-LASIK dry eye is temporary, some patients complain of severe symptoms that can negatively influence their satisfaction with the outcome. Therefore, we need to understand the nature of post-LASIK dry eye and devise strategies for its management.

CLINICAL FEATURES OF POST-LASIK DRY EYE

History

In the past, we have encountered many LASIK patients who complain of dry eye-like symptoms, such as discomfort, ocular fatigue, dryness, and red eye, in the early postoperative period; however, these symptoms disappeared over time. LASIK-induced neurotrophic epitheliopathy (LINE), a clinical entity, was first described by Wilson et al.,11 who observed rose bengal staining and fluorescein staining of the ocular surface for several months after LASIK. Subsequently, we reported in a retrospective study that dry eye symptoms and tear functions worsened for at least 1 month after LASIK, and we defined this condition as post-LASIK dry eye.8 We think that post-LASIK dry eye and LINE may partly share the same etiology. Around this time, other researchers published findings on “post-LASIK dry eye,” which is now recognized as a common complication after LASIK.5,12,13

Symptoms

The symptoms of post-LASIK dry eye include typical dry eye symptoms, such as dryness, irritation, ocular fatigue, and red eye. We believe that decreased visual acuity is more pronounced in post-LASIK patients than in other patients with...
Dry Eye After LASIK

Postoperative slit lamp photo of a LASIK patient. SPK can be observed.

During various activities, such as driving, working on a computer, and reading. We defined “functional visual acuity (FVA)” as the visual acuity after 10 seconds of keeping the eye open. After full refractive correction, the visual acuity of patients is tested by determining the smallest Landolt ring that can be recognized by them. During the experiment, the monitor continuously displays various Landolt rings, and patients register their responses using a joystick. If a patient answers correctly, the next ring shown will be the same size as the previous one; however, if a patient answers incorrectly or fails to answer in 2 seconds, the next ring shown will be larger (Fig. 2). People with a stable tear film show good FVA, whereas patients with an unstable tear film after LASIK sometimes show decreased FVA. This indicates that patients need to exercise caution while driving in the early postoperative period.

Prognosis

Post-LASIK dry eye usually lasts for at least 1 month. Tear function and dry eye symptoms improve to preoperative levels thereafter. However, a small number of patients still experience chronic dry eye symptoms more than 1 year after LASIK. Bower et al. evaluated the occurrence of chronic post-LASIK dry eye lasting more than 1 year, and found that the incidence was 0.8%.

It is not easy to predict the severity of post-LASIK dry eye in a given patient. Previous studies and our clinical impressions suggest that preoperative or intraoperative risk factors for developing post-LASIK dry eye include preexisting dry eye, Asian race, female sex, higher refractive correction, deeper ablation depth, thicker flap, superior flap hinge, and narrow flap hinge.

Mechanisms Involved in Post-LASIK Dry Eye

Although the mechanisms involved in post-LASIK dry eye are not completely understood, temporary denervation of the cornea caused by flap creation, and the resulting decreased corneal sensitivity, may be associated with the condition. Corneal sensitivity decreases significantly for 3 months after LASIK. Observation of the intracorneal nerves with a confocal microscope revealed that regeneration of nerve fibers occurred within 3 to 6 months after LASIK. This regeneration occurs concurrently with the recovery of corneal sensitivity after LASIK. We hypothesize that decreased corneal sensitivity may affect the corneal-lacrimal gland and corneal-blinking reflex loops, which in turn may decrease tear secretion and blinking. Since meibomian lipid secretion is controlled by blinking, a reduced blink rate may prevent proper meibomian gland secretion and/or excretion, which leads to tear evaporation and delayed tear clearance. Alternatively, neural disruption of the cornea may alter cell membrane-associated mucin expression on the epithelium, leading to decreased tear stability. Ablamowicz et al. suggested in their review that alteration in expression of membrane-associated mucin can occur in various ocular surface disease states, including dry eye. Song et al. reported that the expression of membrane-associated mucins such as MUC-4 in the conjunctiva was lower in neurotrophic states in mice and caused dry eye, suggesting that disruption of the neural network has important effects on ocular surface homeostasis.

Although post-LASIK dry eye is a temporary complication, as corneal sensitivity measured with a Cochet-Bonnet esthesiometer appears to return to preoperative values by 6 months after LASIK, a small number of patients complain of dry eye symptoms longer. Previous studies of intrastromal nerve fibers with a confocal microscope found that the number of reinnervated corneal fibers at 1 year postoperatively remains...
less than half of the number before LASIK.\textsuperscript{22} We suspect that incomplete reinnervation may be in part associated with chronic dry eye symptoms after LASIK, although cases of chronic post-LASIK dry eye are rare.

Recently, another refractive surgical option, small incision lenticule extraction (SMILE), has emerged.\textsuperscript{27} This is a flapless procedure in which an intrastromal lenticule is created with a femtosecond laser (VisuMax; Carl Zeiss Meditec AG, Germany) and removed manually via a 3-mm vertical side cut. The vertical cut of the cornea is much shorter than the length of a LASIK flap, and preserves the corneal nerves. Many studies, including meta-analyses, found that SMILE is less invasive to the corneal nerves and reduces the incidence of postoperative dry eye compared to femtosecond LASIK.\textsuperscript{28–30}

In these studies, dry eye symptoms and TBUT were significantly better in SMILE; however, the Schirmer values and tear osmolality did not differ between LASIK and SMILE. The postoperative tear secretion after SMILE determined by the Schirmer test varied among the previous studies. Li et al.\textsuperscript{31} and Zhang et al.\textsuperscript{32} reported that the Schirmer values decreased for several months after SMILE, whereas other researchers did not detect any significant changes after SMILE.\textsuperscript{33–35}

Li et al.\textsuperscript{36} evaluated corneal reinnervation and the corresponding corneal sensitivity after SMILE and femtosecond laser-
LASIK (FS-LASIK), with in vivo confocal microscopy. They found that in both groups, the subbasal nerve density decreased after surgery as compared to the preoperative values; however, the reduction in subbasal nerve density was significantly less in the SMILE-treated eyes than in the FS-LASIK-treated eyes at 1 week, 1 month, and 3 months postoperatively. The reductions for the two groups were not significantly different at 6 months. Although corneal sensitivity significantly decreased postoperatively in both groups, the reduction was significantly greater in FS-LASIK-treated groups at 1 week, 1, 3, and 6 months.

These data support the hypothesis that corneal denervation plays a major role in post-LASIK dry eye. However, mechanisms other than corneal denervation may also be involved in the development of post-LASIK dry eye. As discussed later, dry eye is milder after LASIK enhancement by flap lifting. This fact is not consistent with a neurotrophic effect functioning as the only mechanism for post-LASIK dry eye. One possible explanation is that changes in corneal curvature and smoothness may alter the friction between the cornea and lid, resulting in tear film instability. Alternatively, the pressure exerted by the patient interface of the femtosecond laser may damage conjunctival goblet cells and reduce mucin secretion (Fig. 3).

**POST-LASIK OCULAR SURFACE PAIN**

Dry eye-like symptoms after LASIK, especially long-lasting chronic symptoms, may not be a single entity. Previous studies indicated there are at least two entities, chronic post-LASIK tear dysfunction and neuropathic pain. The former is a chronic dry eye condition, as mentioned earlier. The latter is thought to be a pathological postoperative pain state, caused by abnormal reinnervation and neural sensitization leading to dysesthetic cornea after corneal nerve injury. LASIK-induced corneal nerve damage causes neurogenic inflammation, which contributes to peripheral sensitization of sensory nerves and resulting in a relative hyperesthesia. The number of sodium ion channels in the nociceptor membrane increases in response to persistent stimulation of nociceptors, which in turn decreases the threshold for activation. If these sensitized peripheral nerves continue to be stimulated, central nervous system sensitization can finally occur. As a result, patients suffer from persistent pain. This state falls in the same category as the persistent post-surgical pain that can occur after a variety of surgical interventions, such as C-section, knee replacement, inguinal hernia repair, and mastectomy.

Post-LASIK ocular surface pain is not associated with tear dysfunction and cannot be treated with conventional dry eye management. The mechanism for development of post-LASIK ocular surface pain is unknown, but is suspected to involve an interaction between genetic disposition and environmental factors. Further research is needed to understand the mechanisms, treatments, and prevention of this rare but devastating condition.

**DRY EYE AFTER LASIK ENHANCEMENT**

If post-LASIK dry eye is caused only by the loss of neurotrophic effects, it should recur after enhancement by flap-lifting. We have retrospectively examined symptoms and tear functions after enhancement. As compared to pre-enhancement values, the dry eye symptoms, Schirmer value, and TBYT remained unaltered, and fluorescein staining increased slightly after enhancement. We concluded that post-enhancement dry eye is absent or considerably milder than dry eye after initial LASIK, in which tear secretion and TBYT decreased postoperatively.

In contrast, corneal sensitivity decreased for 3 to 6 months after enhancement as they did after initial LASIK, indicating that other mechanisms in addition to neurotrophic effect may be involved in post-LASIK dry eye. We suspect that the reasons for milder dry eye symptoms and signs observed after enhancement could be as follows: the neurotrophic effects lost after the first surgery had not recovered by the time of enhancement; dry eye symptoms and signs were masked by artificial tears, which were continuously used after the first surgery; other factors, such as a change in the corneal curvature caused by refractive correction, alter tear stability, and such changes are much greater after the first surgery. To support the first theory, Calvillo et al. reported that intracorneal nerve fibers do not recover in number even 1 year after LASIK. As mentioned earlier, transient elevation of pressure on the conjunctiva, induced by the suction ring of a femtosecond laser or a microkeratome at the initial LASIK, may cause damage to the conjunctival goblet cells and alter mucin expression. These data support the hypothesis that corneal denervation plays a major role in post-LASIK dry eye.

**SAFETY AND EFFECTIVENESS OF LASIK FOR PATIENTS WITH PREEXISTING DRY EYE**

If LASIK itself induces dry eye, the question arises whether LASIK can be performed safely and effectively on patients with preexisting dry eye. We conducted a retrospective study in which we categorized patients into 2 groups based on information collected preoperatively—a dry eye group and a non-dry eye group—in accordance with the Japanese criteria for characterization of dry eye. We then compared the incidence of complications, loss of best corrected visual acuity (BCVA), dry eye symptoms, and tear functions in the 2 groups postoperatively. We did not find any difference in the incidence of intra- and postoperative complications and loss of BCVA between the groups. We were particularly careful regarding epithelium-related complications, such as epithelial defect and epithelial ingrowth, but their incidence did not increase in the dry eye group. In contrast, dry eye symptoms and tear functions were more compromised in the dry eye group pre- and postoperatively, until 1 year after surgery. However, the symptoms and tear functions returned to preoperative levels even in the dry eye patients. For further verification, postoperative uncorrected visual acuity and refraction in the two groups were compared, but no difference was found. These results suggest that LASIK can be performed effectively in patients with dry eye. However, preexisting dry eye is a risk factor for severe postoperative dry eye with reduced tear function, more vital staining of the ocular surface, and more severe symptoms. Liang et al. concluded that severe and refractory dry eye can develop after LASIK in patients with well-controlled early-stage Sjogren syndrome. Therefore, careful patient-selection should be conducted before performing LASIK on patients with preexisting dry eye. LASIK should not be recommended for patients whose ocular surface staining does not improve with preoperative treatment. Phakic intraocular lenses and SMILE might be considered as alternatives for these high-risk dry eye patients. For any type of refractive surgery, strict informed consent is mandatory before surgery.

**MANAGEMENT OF POST-LASIK DRY EYE**

The treatments for post-LASIK dry eye are the same as those for non-post-LASIK dry eye. Current management methods are listed and briefly explained below. Since post-LASIK dry eye is temporary, these treatments are usually only necessary for a...
few months, and can be discontinued later in most patients. However, some patients need to continue these treatments for chronic symptoms.

Tear Supplements

Preservative-free artificial tears are fundamental to the treatment. We prescribe 0.3% hyaluronic acid 5 times a day for 1 month and 0.1% hyaluronic acid or saline-based lubricants thereafter. Recently, we and others found that a 3% diquafosol tetrasodium ophthalmic solution (DIQUAS ophthalmic solution 3%, Santen Pharmaceutical Co. Ltd, Osaka, Japan), a purinergic P2Y2 Receptor agonist, which stimulates water and mucin secretion from conjunctival epithelial cells and goblet cells, is effective for post-LASIK dry eye. Another mucus supplement, rebamipide (MUCOSTA, Otsuka, Tokyo, Japan), is effective at stabilizing the precorneal tear film and protecting the ocular surface.

Antimicrobial Agents

Cyclosporine 0.05% ophthalmic emulsion (Restasis, Allergan, Inc, CA, USA) is known to be effective for patients with chronic dry eye whose tear production is suppressed by inflammation. Although it is not clear whether inflammation is involved in the mechanism of post-LASIK dry eye, it has been reported that a better refractive outcome was achieved with topical cyclosporine compared to unpreserved artificial tears in patients with post-LASIK dry eye. Rebamipide is known to have antimicrobial effects as well.

Ointments and Eye Patches

Some people keep their eyelids slightly open while sleeping, but most of them are asymptomatic. However, their ocular surfaces would be more fragile after LASIK, and this could easily lead to complications associated with epithelial involvement, such as SPK, epithelial defects, recurrent erosion, delayed wound healing of the flap edge, and epithelial ingrowth, which in turn induce severe symptoms. We instruct these patients to use an ointment and eye patches at bed time for a month after LASIK. These patients often have incomplete blinking during the daytime. We instruct them to blink properly, especially when they are involved in intense tasks, such as video display terminal work.

MGD Management

Patients with preexisting MGD often experience more severe dry eye and excessive tear evaporation after LASIK. Hot compresses with a warm towel or a disposable eyelid-warming device are effective in such cases. We instructed our LASIK patients to use disposable eyelid-warming devices for 5 min, twice a day for 2 to 4 weeks postoperatively, and found that TBUT and dry eye symptoms improved. In the patients for whom self-management of MGD is insufficient, a thermal pulsation system, LipiFlow (TearScience, Morrisville, NC, USA) and an intense pulsed light system (IPL), M22 (Lumenis Ltd, Israel), are other options to consider.

Punctal Plugs and Autologous Serum Eye Drops

If artificial tears are not effective, intensive care with punctal plugs or autologous serum eye drops are considered for the treatment of post-LASIK dry eye. We have come across many cases in which persistent SPK with astigmatism improved only with punctal plugs for both puncta (Figs. 1C, 1D).

Future Directions

Post-LASIK dry eye is one of the most common post-operative complications of ophthalmic surgeries. Neural changes in the cornea play a major role in the development of this condition. This suggests that other ophthalmic surgeries, especially those of the cornea, could also cause post-operative dry eye. Although it is usually temporary, postoperative dry eye can induce not only uncomfortable symptoms but also refractive changes and decreased quality of vision, which could affect patients’ satisfaction, even when the outcome is objectively successful. Furthermore, if post-operative ocular surface pain develops, the patients suffer from chronic pain, which does not have an effective treatment. Therefore, prevention as follows is important:

1. If patients have preoperative dry eye, all possible treatments for SPK, MGD, incomplete blinking, and short TBUT should be performed before surgery.
2. If preoperative dry eye is not controlled satisfactorily, other refractive surgical options, such as phakic IOILs or SMILE, should be considered.
3. Novel treatment with agents that have neuroprotective or neuromodulatory properties may be considered after ophthalmic surgery to manage the symptoms associated with neurotrophic effects.
4. Attention must be paid to even subtle dry eye signs and symptoms after surgery, and appropriate methods of management must be implemented as early as possible.

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References

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