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Post-LASIK Tear Dysfunction and Dysesthesia

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Abstract

Symptoms of tear dysfunction after laser in situ keratomileusis (LASIK) occur in nearly all patients and resolve in the vast majority. Although dry eye complaints are a leading cause of patient discomfort and dissatisfaction after LASIK, the symptoms are not uniform, and the disease is not a single entity. Post-LASIK tear dysfunction syndrome or dry eye is a term used to describe a spectrum of disease encompassing transient or persistent post-operative neurotrophic disease, tear instability, true aqueous tear deficiency, and neuropathic pain states. Neural changes in the cornea and neuropathic causes of ocular surface discomfort may play a separate or synergistic role in the development of symptoms in some patients. Most cases of early post-operative dry eye symptoms resolve with appropriate management, which includes optimizing ocular surface health before and after surgery. Severe symptoms or symptoms persisting after 9 months rarely respond satisfactorily to traditional treatment modalities and require aggressive management. This review covers current theories of post-LASIK dry eye disease, pathophysiology, risk factors, and management options for this disease spectrum of post-LASIK tear dysfunction and neuropathic pain.

Keywords

confocal microscopy; corneal innervation; dry eye; hyperesthesia; laser in situ keratomileusis (LASIK); laser subepithelial keratomileusis (LASEK); photorefractive keratectomy (PRK); precorneal tear film; surface ablation; tear dysfunction syndrome; thin flap LASIK

I. INTRODUCTION

A. Background

Laser in situ keratomileusis (**LASIK**) surgery is the most commonly performed vision correction surgery in the United States.[1] According to the industry market analysis company Market Scope, over one million LASIK procedures are performed annually. Postoperative complications are rare and patient satisfaction is generally excellent, with 98.5% of patients indicating satisfaction when surveyed ≥7 months after LASIK.[2] However, symptoms of dryness and irritation are common early and late postoperative complaints. Signs and symptoms of tear dysfunction occur early in the postoperative period and resolve in nearly all patients by 6–9 months. In a recent review article, Toda reported that signs or symptoms of dry eye after LASIK were found in 50% of patients at 1 week postoperatively, 40% at 1 month, and 20–40% at 6 months.[3] Some patients have clinical signs of tear dysfunction

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without any symptoms. It is likely that post-LASIK tear dysfunction is a qualitatively different disease entity.

Given the large number of patients who undergo LASIK each year, even a very small percentage that develop chronic tear dysfunction represents a substantial number of affected patients. To date, there is no rigorous data on the prevalence of chronic ocular surface disease or irritation or pain symptoms after LASIK. In October 2009, the US Food and Drug Administration launched a study to collect this epidemiological data and to identify predictors of these complications.

For patients who develop signs or symptoms of chronic tear dysfunction that are present 6 months or longer after LASIK, conditions can range from asymptomatic or mild and from easily managed to severe and debilitating. Furthermore, there may be an association between chronic postoperative tear dysfunction and refractive regression.[4]

Although the classic symptoms of tear dysfunction resolve in the vast majority of affected patients, some patients develop chronic post-LASIK tear dysfunction, neurotrophic keratopathy, or neuropathic pain. Anecdotal evidence suggests that post-LASIK ocular surface disease comprises a spectrum, with most affected patients experiencing typical tear dysfunction symptoms, often in the setting of relatively normal or slightly depressed tear production and breakup time metrics. A smaller number of patients fall on each end of the spectrum—some with a persistent and severely hypoesthetic cornea that never approaches normal sensation and may result in neurotrophic keratopathy, and others with abnormal reinnervation and neural sensitization leading to dysesthetic corneas.

In 2006, the Delphi panel proposed the term “dysfunctional tear syndrome” to take into account the many pathophysiologic mechanisms leading to tear film-related ocular surface disease.[5] In 2007, the Dry Eye Workshop Definition and Classification Subcommittee acknowledged that changes in tear composition leading to tear dysfunction are a common feature of dry eye.[6] We propose to use the term *post-LASIK tear dysfunction* to describe the dry eye, discomfort, and ocular surface diseases that develop after LASIK. We suggest that post-LASIK tear dysfunction is probably partly caused by neurally mediated ocular surface changes and, at times, neurally mediated ocular surface changes may be the overriding feature of post-LASIK tear dysfunction.

Figure 1 presents a flowchart for considering the various factors that may contribute to post-LASIK ocular pain, which are discussed in this review.

B. Causes of Post-LASIK Tear Dysfunction and Neuropathic Pain

There are many potential causes of tear dysfunction following LASIK. Some patients may have pre-existing ocular surface disease that is unmasked or exacerbated by surgery. Others may develop medicamentosa secondary to postoperative medications and their preservatives, leading to transient ocular surface disease. Most affected patients develop tear dysfunction secondary to surgery-induced ocular surface changes.

Furthermore, surgical disruption of the corneal afferent nerves leads to early postoperative hypoesthesia. Corneal hypoesthesia disrupts the ocular surface-lacrimal gland functional unit and results in changes of tear film composition and quantity that may contribute to signs and symptoms of tear dysfunction after LASIK.[7] Through a variety of processes, these changes result in tear film hyperosmolarity and ocular surface inflammation. These changes will be addressed in Sections II and III.

Recent studies suggest that neuropathic pain may play a role through early and late changes in the peripheral and central neural pathways, often leading to symptoms suggestive of dry eye and occasionally causing severe ocular surface discomfort. The post-LASIK spectrum of chronic tear dysfunction, neurotrophic keratopathy, and neuropathic pain will be discussed in more detail in Sections II and III.

C. Neural Anatomy of the Cornea

The cornea is endowed with the highest density of sensory nerve endings of any tissue in the body.[8] These nerve endings are the terminal receptors of the sensory corneal nerves. The nerve axons originate at the trigeminal nerve, form a conjunctival plexus near the limbus, and enter the cornea at a depth just below the anterior third of the stroma in a radial distribution around the entire limbus.[9] In humans, these sensory nerves course centripetally through the stroma, penetrate Bowman's layer both centrally and peripherally, branch into finer fibers, and turn at right angles to form a subepithelial nerve plexus. From this subepithelial plexus, branches reach to the basal epithelium and terminate as nerve ending receptors in wing cell layers of the epithelium.[9] These nerve ending receptors are of three main classes: mechanoreceptors, which respond to mechanical force; thermoreceptors, which respond to cooling; and polymodal receptors, which make up the majority of nociceptors and respond to a variety of stimuli, including mechanical, heat, chemical, and endogenous proteins and molecules. Activation of thermoreceptors results in a sensation of cooling, while activation of mechanoreceptors or polymodal receptors results in ocular surface discomfort and pain.[10]

Sensation from the ocular surface is transmitted to the interpretive regions of the brain. Primary corneal sensory nerves travel in the sensory root of the trigeminal ganglion to the pons, where they divide and head to the trigeminal nuclei, synapse with second-order neurons in the dorsal horn of the spinal cord and the medullary horn, then travel to the thalamus via the spinothalamic pathways. From the thalamus, third-order neurons travel to the cortex where the nerve impulses are interpreted as ocular surface pain, irritation or cooling, and to emotive paralimbic areas of the brain.[8,11]

II. OCULAR SURFACE ABNORMALITIES FOUND AFTER LASIK

A. Conjunctival Changes

LASIK has been associated with loss of goblet cells,[12–14] whose density has been found to decrease immediately postoperatively with a subsequent reduction in goblet cell mucin, a stabilizing molecule in the tear film whose reduction may lead to tear film instability.[12] These changes were observed in all groups studied, but are more severe in groups with chronic dry eye symptoms after LASIK.[13] It may take 6 months for goblet cell density to return to baseline values after LASIK.[12]

B. Tear Changes

After LASIK, studies suggest that tear film break up time (**TFBUT**) is decreased,[15–17] and Schirmer scores range from no change to moderate depression.[18,19] The post-LASIK decrease in TFBUT, basal tear secretion, and Schirmer scores may persist for months[15,18,20] and possibly longer.[19,21] Furthermore, tear fluorescein clearance time is increased postoperatively.[15]

Surgical injury to the epithelium during refractive surgery has been shown to alter the tear film cytokine levels. Studies have found an increase in TGF-beta1 concentration post epi-LASIK,[22] and studies post-photorefractive keratectomy have noted increased levels of TGF-

beta1, as well as VEGF,[23] PDGF-BB,[24] TNF alpha,[25] and IL-6.[26] Ascorbic acid levels in the tear film are lower after LASIK.[27]

Hyperosmolar tears lasting more than 6 months have been documented in post-LASIK and PRK patients,[21] although more studies are needed to verify and quantitate the degree and duration of this tear compositional change.

C. Surgically Induced Ocular Surface Changes and Operative Risk Factors

Corneal contour changes postoperatively may lead to abnormal distribution of tears on the ocular surface, which may contribute to the signs and symptoms of ocular surface disease after LASIK.

The role of the LASIK flap hinge location in the development of tear dysfunction has yet to be defined. Creation of the LASIK flap with either a microkeratome or the femtosecond laser truncates the corneal nerves as they course through the cornea. The nerves travelling through the hinge are spared; therefore, placing the hinge at an area of richer innervations may maximize residual corneal sensitivity immediately postoperatively. While one study depicted the main trunks of the corneal nerves entering the cornea at the 3 and 9 o'clock positions, then spreading centrally and anteriorly,[28] subsequent studies have shown the sensory nerves entering the cornea at the limbus at all clock hours, including superiorly and inferiorly.[9,29] Studies have reported conflicting results regarding the effects of hinge location on development of post-LASIK corneal hypoesthesia and dry eye, suggesting that further research is needed to determine the role hinge location plays in post-LASIK tear dysfunction.[16,17,30–32]

Hinge width may have a more important role in subsequent corneal hypoesthesia, although the data is sparse. One study found corneal sensitivity to be reduced and dry eye symptoms to be more severe and of longer duration in patients with a narrower hinge width, although the difference was not significant by the 6-month postoperative visit.[33]

Ablation depth and higher myopic refractive corrections positively correlate with decreased corneal sensitivity,[34,35] with increased likelihood of developing immediate postoperative dry eye symptoms,[16] and with increased likelihood of developing chronic tear dysfunction.[36,37] Higher refractive corrections and deeper ablations likely damage deeper stromal nerves and destroy more neural tissue, leading to delayed regeneration of the subepithelial nerve plexus.

Hyperopic corrections tend to cause a relatively more anesthetic cornea than myopic corrections.[38] This may be due to the more peripheral ablation needed for hyperopic corrections, which likely destroys nerve tissue further from its terminal reach. No study to date has specifically compared risk of developing chronic tear dysfunction or chronic neuropathic pain states after hyperopic versus myopic LASIK.

LASIK flaps created with blade microkeratomes of standard depths of 160–180 microns have been found in many studies to be associated with profound early postoperative relative corneal hypoesthesia, with gradual improvement in sensitivity over months to years, but in some cases never returning to preoperative levels.[18,32,35,39–42] Recent literature suggests that "thin-flap" or "sub-Bowman" LASIK may be associated with less profound postoperative hypoesthesia and with more rapid recovery of sensitivity. Also, the method used to make the LASIK flap may influence recovery of innervation. One recent study comparing thin-flap LASIK performed with a microkeratome versus thin-flap LASIK performed with femtosecond laser found that the femtosecond group had significantly lower incidence of LASIK-induced neurotrophic epitheliopathy (discussed in section II-E) and tear dysfunction symptoms for the first month after surgery.[43] Interestingly, thicker flaps were

not correlated with signs or symptoms of tear dysfunction. A retrospective study that examined the effect of thin-flap femtosecond laser LASIK did not specifically address the issue of LASIK-induced neurotrophic epitheliopathy or tear dysfunction, but did find that corneal sensitivity was only moderately reduced immediately postoperatively and returned to near normal values within 2 months.[44]

D. Preoperative Risk Factors

Patients with preexisting tear dysfunction have poorer postoperative ocular surface health and more severe symptoms of tear dysfunction after LASIK; furthermore, their corneal sensitivities take longer to recover compared to patients without dry eye.[4,20,45] One retrospective cohort study investigating preoperative characteristics associated with dry eye symptoms at the 9-month postoperative examination found that the chronic dry eye cohort had statistically significantly lower preoperative Schirmer test scores than the non-dry eye group.[46] Other studies have shown that preoperative Schirmer scores below 10 mm are associated with postoperative tear dysfunction.[20]

Longterm contact lens wear may also predispose to poorer tear metrics both pre- and postoperatively.[4,18] Furthermore, long-term contact lens wear is associated with decreased corneal sensitivity,[47] and certain patients with tear dysfunction have been found to have relatively less sensitive corneas.[39] It may be that contact lens intolerance is a surrogate marker for preoperative tear dysfunction.

Although older age and female gender, especially post-menopausal, have been found to be risk factors for tear dysfunction, there are conflicting reports on whether female gender is a risk factor for post-LASIK tear dysfunction. One prospective study found no association,[16] whereas two retrospective studies found significant associations between female gender and chronic post-LASIK tear dysfunction.[13,36] Age also has not been shown to be an important risk factor for post-LASIK tear dysfunction.[16,46]

Ethnicity may modulate a patient's risk of developing post-LASIK tear dysfunction. The prevelance of chronic post-LASIK tear dysfunction was reported to be higher in Asian patients.[48]

E. Corneal Nerve Changes

Truncation of corneal nerves via microkeratome or femtosecond laser followed by thermal ablation of corneal sensory nerves typically results in a hypoesthetic cornea immediately post-LASIK, which, in turn, has direct and indirect effects on the ocular surface. This nerve damage likely plays a key role in the early development of LASIK-induced epitheliopathy, and potential abnormal regeneration likely plays a role in the development of post-LASIK tear dysfunction states, as well as post-LASIK ocular surface pain states.

1. Corneal Sensitivity—After LASIK, many patients develop a relatively hypoesthetic cornea, and studies suggest that corneal sensitivity progressively improves and approaches preoperative or "normal" range of sensitivity by 6–12 months when measured with Cochet-Bonnet esthesiometry[18,32,40] and by up to 2 years when measured by gas esthesiometry.[41] A number of studies reported that corneal sensitivity does not return to preoperative or "normal" levels when measured by gas esthesiometry at 14 weeks postoperatively,[42] by Cochet-Bonnet esthesiometry at 6 months postoperatively,[35] or by Cochet-Bonnet at 16 months postoperatively.[15]

Among the studies reporting corneal hyperesthesia with tear dysfunction was one showing that symptoms of ocular surface irritation were associated with hyperesthesia to cooling.[49] A

study of LASIK patients found a transient hyperesthesia of the cornea 1–2 weeks postoperatively when measured with gas esthesiometry.[41]

2. Decreased Blink Rate—Tear fluorescein clearance time is increased post-LASIK, and this may be due to less frequent blinking.[15] Experimental evidence demonstrates that topical anesthetic substantially decreases blink rate.[50] Toda and associates found that the blink rate of LASIK patients was decreased by up to 40%, and the difference in mean blink rate pre- and postoperatively remained statistically significant at postoperative months 3, 6, and 12.[19]

3. Corneal Denervation and Reinnervation

a. LASIK-Induced Neurotrophic Epitheliopathy: Evidence is accumulating that tear dysfunction and other forms of persistent ocular surface disease after LASIK surgery may in large part be neurally mediated. In 2001, Wilson and Ambrosio noted that many post-LASIK patients develop transient symptoms of dry eye, sometimes with blurry vision, that is associated with epithelial erosions on the flap in the setting of relatively normal tear production.[51] They reported that nearly all cases resolved by 6 months and coined the term *LASIK-induced neurotrophic epitheliopathy* (**LNE**) to describe this phenomenon. They postulated that these temporary ocular surface changes were secondary to loss of trophic influence on cornea epithelium caused by cutting the corneal nerves.[51] LNE is now a well-recognized disease that may be associated with complaints of typical dry eye symptoms and fluctuating vision or visual symptoms alone.[52] It is likely that a majority of LASIK patients without preexisting tear dysfunction who develop ocular surface signs or symptoms in the early postoperative period are experiencing LNE.

b. Confocal Microscopy Findings: Confocal microscopy of the cornea after LASIK confirms that corneal nerve density is decreased early postoperatively and increases with time, albeit at a slower rate than return of corneal sensitivity.[53] SJ Lee and associates found that the subbasal nerve fiber density was close to zero for up to 6 months post-LASIK.[54] BH Lee and associates found that at one year after LASIK, the number of subbasal and stromal nerves in the corneal flap were less than half the pre-operative density.[55] While corneal sensitivity post-LASIK has been reported to return to “normal” values by 6–12 months[18,32,40] and 6 months to 2 years,[41] depending of the method of measurement, subbasal nerve fiber density has been reported not to return to preoperative levels by 2 years,[56] by 3 years,[57] or by 5 years[53] in confocal microscopy studies. Subbasal nerve density may never return to preoperative values.

Nerve morphology has also been shown to correlate with corneal sensitivity after LASIK. One study found that low sensitivity in specific corneal areas was associated not only with the absence of nerves seen on confocal images, but was also associated with short nerves lacking connections between nerve bundles.[58] Another study found a significant association in LASIK patients between long nerve fiber bundles and greater sensitivity by noncontact esthesiometry.[59] Finally, one study concluded that “normal” sensation returns to eyes by 6 months post-LASIK, despite a markedly abnormal subbasal nerve plexus with abnormally curved bundles or with thin nerves without the connections between nerve bundles seen in healthy, non surgical eyes.[60]

III. PATHOPHYSIOLOGY OF POST-LASIK TEAR DYSFUNCTION AND NEUROPATHIC PAIN

A. Dysfunction of the Cornea-Lacrimal Gland Functional Unit

The sensory nerves of the cornea and ocular surface create a neural reflex arc through the central nervous system to autonomic fibers innervating the lacrimal glands. The constant and

varying stimulation of the ocular surface nerves regulates both basal and reflex secretion of fluid, electrolytes, and proteins into the tears. It is believed that transection and ablation of corneal sensory nerves during LASIK leads to diminished afferent input into the ocular surface-lacrimal gland functional unit, resulting in a decrease in tear production and a change in tear composition. Post-LASIK changes in this functional unit likely contribute to the decreased TFBUT[15–17] and stable-to-slightly depressed Schirmer scores.[18,19] Tear fluorescein clearance time is increased,[15] while blink rate remains decreased even at 1 year postoperatively.[19] Decreased tearing and blinking may combine to increase evaporative tear loss. Although a true aqueous deficiency state after LASIK in patients with healthy preoperative ocular surface and tear metrics appears to be rare, surgery may exacerbate preexisting aqueous deficiency.

The lacrimal gland is a secretory organ specializing in secretion of the aqueous component of the tear film, as well as the proper mix and concentration of mucins, ions, and proteins, including IgA, lactoferrin, lysozyme, and growth factors, such as epidermal growth factor (**EGF**). The proper relative concentration of these components contributes to maintaining a stable tear film and healthy ocular surface. Disruption of the neural arc by sensory nerve damage during LASIK can alter this delicately balanced system. These alterations result in a qualitative change in tear film composition. It is likely that the modification of the ocular surface-lacrimal gland functional unit and the resultant change in tear film composition plays a central role in tear dysfunction after LASIK.[61]

B. Tear Hyperosmolarity and Ocular Surface Inflammation

Hyperosmolarity has been identified as a central mechanism causing ocular surface inflammation and eye irritation in typical patients suffering from tear dysfunction. Hyperosmolar tears lasting more than 6 months has been documented in post-LASIK and PRK patients.[21] Increased evaporative loss, lacrimal gland hyposecretion, and conjunctival goblet cell loss are likely contributors to post-LASIK increases in tear osmolarity. Hyperosmolarity of the tear film is believed to incite an inflammatory cascade triggering stress-activated kinases, upregulation of inflammatory cytokines and adhesion molecules, actuation of matrix degrading enzymes, and recruitment of T lymphocytes.[62,63] A recent experimental study showed that tear instability is associated with transiently increased hyperosmolarity and can induce ocular surface symptoms and increased concentrations of proinflammatory mitogen-activated protein kinase.[64] LASIK contributes to tear film instability, as TFBUT is decreased. Post-LASIK patients have been found to have decreased goblet cell density and reduced mucin in tears, which further contributes to tear film instability. If left untreated, some cases of persistent ocular surface irritation and hyperosmolarity after LASIK may lead to more permanent changes of the ocular surface. Experimentally induced dry eye is associated with acutely induced markers of ocular surface inflammation and with epithelial cell apoptosis.[65]

LASIK has been associated with loss of goblet cells[12–14] due to mechanical trauma and possibly via inflammatory-induced mechanisms. Interestingly, treatment with anti-inflammatory medications such as topical corticosteroids[66] and topical cyclosporine[67] have been shown to increase goblet cell density in non-Sjogren and Sjogren syndrome-associated tear dysfunction. Furthermore, ocular surface inflammation has been shown to correlate strongly with signs and symptoms of tear dysfunction in patients with Sjogren syndrome.[68]

Damage to corneal nerves from LASIK contributes to tear dysfunction, not just via hyperosmolar tear film but also via neurogenic inflammation. Sensory nerves of the cornea contain neuropeptides, including substance P and calcitonin gene-related peptide (**CGRP**). These neurotransmitters are believed to be trophic factors with important roles in maintaining and renewing corneal epithelium.[9] Substance P and CGRP are released upon

surgically-induced nerve injury, and these pro-inflammatory peptides, as well as other pro-inflammatory mediators, such as growth factors, cytokines and prostaglandins, act on neighboring sensory nerves, lowering their threshold for activation and thus facilitating sensations of ocular surface pain and irritation in the early postoperative period.[8] Release of these neuropeptides may also dilate limbal blood vessels and alter their permeability, changes that contribute to ocular surface inflammation and subsequent immune cell infiltration.[46]

C. Corneal Sensation

A variety of methods have been developed to measure corneal sensation, but, to date, no gold standard method has been established to measure corneal sensitivity. The Cochet-Bonnet esthesiometer utilizes a nylon monofilament of variable length to apply a tactile stimulus to the cornea and selectively activate mechanosensory nerve fibers. More recently, a noncontact gas esthesiometer was developed, which applies a variable force to the cornea via a jet of air. This gas esthesiometer was modified by Belmonte and associates, who added the ability to stimulate thermal and chemical receptors by changing temperature and carbon dioxide concentration of the air jet.[69] As discussed in Section II.E.1, corneal sensitivity has been reported to return at various time points after LASIK, ranging from 6 months to 2 years.[15,18,32,35,40–42]

Altered corneal sensory nerves post-LASIK likely have a crucial role in development of transient and chronic tear dysfunction. Corneal sensitivity appears to be correlated with tear dysfunction in non-LASIK patients, with many studies reporting that affected patients experience relatively hypoesthetic corneas,[39,70–75] and some studies showing a direct correlation between the degree of hypoesthesia and the severity of symptoms.[39] In contrast, hyperesthesia with the gas esthesiometer has been reported with tear dysfunction that may be due to inflammation-induced hyperesthesia and altered corneal barrier function.[76]

Among the studies reporting corneal hyperesthesia with tear dysfunction was one showing that symptoms of ocular surface irritation were associated with hyperesthesia to cooling.[49] A study of LASIK patients found a transient hyperesthesia of the cornea 1–2 weeks postoperatively when measured with gas esthesiometry.[41] Post-LASIK hyperesthesia may be due to neural sensitization and abnormal nerve regeneration, in some cases leading to late and disabling dysesthesia.[76]

D. Neural Inflammation, Sensitization and Neuropathic Pain After Corneal Denervation

LASIK-induced corneal nerve damage causes neurogenic inflammation. This inflammation contributes to peripheral sensitization of functioning sensory nerves and likely facilitates early postoperative pain and, in some cases, a relative hyperesthesia, as noted above. Nociceptor thresholds for firing are plastic and are modulated in part by the type and number of voltage-gated channels in the cell membrane.[8] Sodium ion channels are key players in the generation of action potentials, as the appropriate type of stimulus leads to rapid opening of their channels and sudden influx of positively charged ions.[8] As Rosenthal elucidates in a recent review of corneal neuropathic pain, the number of sodium ion channels in a nociceptor membrane increases in response to persistent stimulation of the nociceptor. The subsequent increased influx of positively charged ions leads, in turn, to a lower threshold for activation.[8] This process of peripheral sensitization results in increased pain sensation at lower thresholds.

Peripheral sensitization is a normal response to injury and allows the individual to take precautions to protect damaged tissue. However, if the sensitized peripheral nerves continue to be stimulated in this environment, central nervous system sensitization can occur. This

develops when the constant torrent of peripheral pain signals to the central nervous system leads to down-regulation of inhibitory impulses and increased ease of transmittance of pain signals through the trigeminal ganglion and pons and to the cortex. Rosenthal notes that, over time, persistent nociceptor pain signaling to the central nervous system can lead to ungoverned neuropathic pain.[8] This neuropathic pain can be persistent and refractory to traditional therapies for tear dysfunction.

The corneal nerves that regenerate 6 months to 2 years after LASIK surgery may be different from pre-existing nerves. Belmonte posits that abnormal nerve regeneration may be responsible for much of the irritation sensation reported after LASIK. He notes that regenerating neurons often form microneuromas with changes in expression of ion channels in the cell membrane and lowered thresholds for firing. Some microneuromas may even fire spontaneously.[77] He proposes that this spontaneous firing, or ectopic firing, by the damaged or regenerating corneal peripheral nerves causes a pain of neuropathic origin, a “phantom cornea,” akin to the pain described by some patients after enucleation or amputation.[10] The ocular surface symptoms some experience after LASIK may be misattributed to tear dysfunction and are, in fact, due to the altered sensitivity and to the ectopic firing of peripheral nerves. Furthermore, Belmonte points out that electrophysiologic studies of corneal nerves in animals after PRK are consistent with the many studies that show an early hypoesthetic cornea after refractive surgery in humans. However, he notes that these same studies found an increase in the frequency of spontaneous nerve firing after persistent corneal stimulation.[10] It may be that the transient post-LASIK hyperesthesia noted by de Paiva and Pflugfelder,[76] as well as the post-LASIK hyperesthesia noted by Gallar et al,[41] are due to peripheral sensitization and ectopic impulses.

Belmonte and Rosenthal, leading experts in the field of corneal neuropathic pain, believe that dry eye symptoms after LASIK should not be attributed to surface dryness but rather to ectopic firing and abnormal responsiveness of peripheral and sensory nerves. Rosenthal states that if this process persists, central sensitization occurs and ultimately severe neuropathic pain, which he classifies as type 2 keratoneuralgia, becomes entrenched (Rosenthal P, personal communication, 2009).

E. Confocal Microscopy Findings

The human subbasal nerve plexus, a dynamic structure constantly migrating and having many interconnections between nerve fibers, may be qualitatively and quantitatively changed by LASIK. This plexus is a planar structure found between the epithelium and Bowman’s layer and therefore can be relatively reliably imaged with confocal microscopy. Resolution of laser scanning confocal microscopes does not allow visualization of individual axons, but does resolve nerve fiber bundles composed of several axons surrounded by Schwann cell sheaths, which appear as linear reflective structures often with branches. Studies of the healthy, nontraumatized plexus in humans suggest that the nerves are continuously migrating centripetally at a rate of up to 26 microns per week.[78] The subbasal nerve architecture disappears after LASIK, but regenerates and, in most patients, corneal sensitivity returns somewhat in parallel with return of visible nerve fiber bundles. The integrity of the subbasal nerves may contribute to development of non-LASIK tear dysfunction. In nonsurgical patients with tear dysfunction, some confocal microscopy studies have found a significantly decreased subbasal nerve density.[79,80] However, others found no difference in density.[81]

Subbasal nerve density and morphology after LASIK have been associated with return of normal corneal sensation. Confocal microscopy of the cornea after LASIK confirms that corneal nerve density is decreased early postoperatively and increases with time, albeit at a slower rate than return of corneal sensitivity.[53] Studies have found that the subbasal nerve

fiber density was close to zero for up to 6 months post-LASIK,[54] and that at 1 year post-LASIK, the number of subbasal and stromal nerves in the corneal flap were less than half the pre-operative density.[55] Corneal sensitivity appears to return to normal within 6 months to 2 years, but this is not mirrored by the return to normal of subbasal nerve fiber density, which does not return to preoperative levels by 2 years,[56] by 3 years,[57] or by 5 years[53] in confocal microscopy studies. Indeed, the subbasal nerve density may never return to preoperative values. Furthermore, it may be that fine nerve fibers are returning to the denervated area and, although too thin to be visualized by confocal microscopy, they are mediating the return of normal sensitivity. Despite this difference in rate of return of nerve density and rate of return of sensitivity, the density of regenerated subbasal nerve fibers do correlate with the return of sensitivity.[54]

Nerve morphology may correlate with corneal sensitivity after LASIK. One study found that low sensitivity in specific corneal areas was associated not only with the absence of nerves seen on confocal images, but was also associated with short nerves lacking connections between nerve bundles.[58] Another study found a significant association in LASIK patients between long nerve fiber bundles and greater sensitivity by noncontact esthesiometry.[59] Finally, one study concluded that normal sensation returns to eyes by 6 months post-LASIK, despite a markedly abnormal subbasal nerve plexus with abnormally curved bundles or with thin nerves without the connections between nerve bundles seen in healthy, nonoperated eyes.[60]

Some patients develop a spectrum of post-LASIK ocular surface neurally mediated disease, including mild but persistent sensations characteristic of tear dysfunction to severe and disabling chronic pain sensations. Confocal microscopy suggests that these patients may have abnormal regeneration of the subbasal nerve plexus. One study found that 2–5 years after LASIK for high myopia, most patients experienced ocular surface discomfort consistent with dry eye syndrome, but in the absence of clinical signs of ocular surface disease and with normal sensitivity when measured with noncontact esthesiometry.[37] Confocal microscopy of these eyes showed abnormal nerve morphology with excessive nerve sprouting. Interestingly, patients with diabetes mellitus and more severe peripheral neuropathy have been found to have more tortuous subbasal nerves.[82] These tortuous nerves may be a marker of nerve regeneration. In our experience, confocal microscopy in LASIK patients experiencing dysethesias sometimes shows an abnormal subbasal plexus with small, branched nerve bundles that lack interconnections and normal length.

Rosenthal believes that neuropathic pain is the underlying mechanism for discomfort in most tear dysfunction states, as well as in post-LASIK dysesthesia. He posits that chronic physiologic pain can lead to refractory neuropathic pain and therefore should be treated early and aggressively (Rosenthal P, personal communication, 2009).

IV. PREOPERATIVE AND POSTOPERATIVE MANAGEMENT OF THE OCULAR SURFACE

Preoperative screening is an important step in identifying appropriate candidates for LASIK. In general, patients should be selected only if they have or can attain excellent preoperative ocular surface health. As discussed earlier, low preoperative Schirmer scores may predispose to postoperative tear dysfunction. Since LASIK surgery is associated with mild decreases in TFBUT, basal tear secretion, and Schirmer scores that may persist for months,[15,18,20] and or longer,[19,21] it is necessary to appropriately screen LASIK candidates for tear dysfunction and to optimize ocular surface health preoperatively. Many patients seeking laser refractive surgery do so because of contact lens intolerance, which is suggestive of tear dysfunction. It is essential to take a thorough patient history, and any

symptoms suggestive of tear dysfunction should make the surgeon wary. Up to 75% of patients seeking refractive surgery may have signs and symptoms of preexisting ocular surface disease.[45] Clinical assessment of the ocular surface with special attention to ocular surface staining, tear volume and quantity, and TFBUT is recommended.

Preoperative management of the ocular surface is essential. Tear dysfunction is a multifactorial disease, so identifying and managing comorbid conditions, such as blepharitis, rosacea, drug toxicity, and exposure keratopathy, is helpful. Treatment of tear dysfunction and lid margin disease may return the ocular surface to health. Artificial tears, especially preservative-free formulations, are useful. Punctal occlusion and nutritional supplements containing omega-3 fatty acids may be appropriate. Some suggest the use of cyclosporine 0.05% drops to optimize the ocular surface preoperatively, as it has been found to increase goblet cell density[83] and to accelerate the return of corneal sensitivity post operatively.[84]

Postoperative management of the ocular surface is also important. Frequent use of preservative-free artificial tears is beneficial, particularly in the early postoperative period when blink rate is decreased. Punctal occlusion may increase tear volume in cases of borderline aqueous tear deficiency. Bandage soft contact lenses may be used in select patients with normal tear production to reduce surface irritation while corneal nerves regenerate.

For patients who develop persistent neurotrophic keratopathy after LASIK, it is useful to pursue traditional treatment modalities for neurotrophic keratopathy, including preservative-free artificial tears, punctal occlusion, bandage contact lenses, and tarsorrhaphy. However, we have found that autologous plasma drops can dramatically increase corneal sensitivity to near normal levels and improve clinical parameters of ocular surface health. Furthermore, confocal microscopy showed an increased diameter and number of subbasal nerves in post-LASIK patients with neurotrophic keratopathy.[85] The Boston Ocular Surface Prosthesis may also be useful. Experimental models, clinical studies, and review articles suggest that there may be a future role for treatment with nerve growth factors,[86–88] topical nerve growth factor plus docosahexaenoic acid,[89] topical naltrexone,[90] fibronectin,[91] and substance P-derived peptide, FGLM-amide and IGF-1,[92] among other substances.

A number of novel therapeutic options exist for patients who are refractory to traditional therapy and for those who develop chronic tear dysfunction symptoms or neuropathic pain. Autologous plasma drops are promising and have been used successfully in some cases to alleviate ocular surface dysesthesia in post-LASIK patients. Treatments that have been used with success for neurotrophic keratitis may have a role for preventing or treating patients with neuropathic corneal pain. The Boston Ocular Surface Prosthesis, which creates a liquid bandage on the cornea, is often the most successful option. In an effort to block or down-regulate corneal neuropathic pain, Rosenthal is currently investigating medications that are placed within the Boston Ocular Surface Prosthesis reservoir to treat pain at the level of the corneal nociceptors (Rosenthal P, personal communication, 2009).

V. OTHER VISION CORRECTION SURGERIES AND POST-OPERATIVE DRY EYE SYMPTOMS

Better preoperative management of the ocular surface and newer surgical techniques have expanded the pool of suitable candidates for vision correction surgeries. Some investigators have even shown successful outcomes without an increased incidence of tear dysfunction symptoms in patients with Sjogren syndrome[93] and in patients with contact lens-associated tear dysfunction.[94] Of the many keratorefractive surgery options available, LASIK appears to have the highest incidence of post-surgery dry eye.

Many clinicians consider photorefractive keratectomy (**PRK**) to have less risk of causing tear dysfunction than LASIK, because corneal sensation returns faster[40,95] and there is less decrease in Schirmer scores after PRK.[21] A comparison of post-PRK and post-LASIK patients showed that the PRK patients had less change from preoperative measurements of tear production, TFBUT, and tear osmolarity.[21] A patient questionnaire study evaluating sensations of ocular surface dryness at 6 months or longer postoperatively found no significant difference between PRK and LASIK groups; about 9% of both groups reported frequent dry eye symptoms, and both groups had a median response of 9 of 10 (10 high) to the question “Are you satisfied with the result of your surgery?”[96]

As discussed in Section III, thin-flap LASIK may produce less post-operative hypoesthesia and more rapid return to normal tear metrics. A prospective contralateral eye study of thin-flap LASIK versus PRK suggested that PRK eyes had less absolute decrease in corneal sensitivity at all postoperative visits and there was no difference in Schirmer scores between the groups[97]; however, these were not primary outcome measures. A long-term follow-up study found that, in one cohort of post-PRK patients at 12 years, 7% had foreign body sensation and 3% had dry eye, presumably based on responses to a subjective questionnaire.[98]

LASEK, which is performed by lifting an epithelial flap, then applying excimer laser ablation to Bowman’s layer and stroma, has many similarities to PRK. LASEK may result in less decrease in corneal sensitivity and in a more rapid recovery than LASIK.[54] This same study found less reduction in corneal nerve density in the LASEK group than the LASIK group.[54] Although post-LASIK patients may describe more severe symptoms consistent with tear dysfunction at all visits for 16 months postoperatively,[15] one study found that LASEK patients noted symptoms of increased ocular surface irritation for 2 months postoperatively with return to baseline at 3 months.[99]

Another study that compared relatively thin-flap LASIK (average flap depth of 130 microns) to LASEK found no difference in postoperative corneal sensitivities at any time point when measured with gas esthesiometry and found no difference in subbasal nerve plexus appearance between the two groups on confocal microscopy at all follow-up visits up to 6 months postoperatively.[100]

Phacoemulsification using a 3.0-mm clear cornea incision is associated with a mild decrease in central corneal sensitivity lasting around 1 week; a relatively more hypoesthetic cornea in the quadrant of the surgical wound returns to near preoperative sensitivity by 3 months postoperatively.[101] Similar to findings in post-LASIK patients, confocal microscopy shows that the subbasal nerve density after phacoemulsification is significantly reduced at all follow-up visits up to 3 months and the density does not recover as quickly as corneal sensitivity. It is possible that degree of relative hypoesthesia would correlate with size of the incision. Phakic IOLs and multifocal IOLs may require larger incisions. However, there are no studies to suggest that cataract or phakic IOL surgery is associated with tear dysfunction or corneal neuropathic pain. The US FDA clinical trial of implantable contact lenses, while not specifically asking about dry eye symptoms, found that 92.4% of respondents were very/extremely satisfied with the results of their surgery at 1 year.[102]

Interestingly, LASIK enhancement procedures are not correlated with an increase in dry eye symptoms or with changes in tear metrics, although enhancements are associated with increased corneal staining and decreased corneal sensitivity.[103]

A study comparing microkeratome to femtosecond laser LASIK did not investigate tear dysfunction, but did find a more rapid recovery in central corneal sensitivity in the

femtosecond laser group.[104] However, the microkeratome flap depth was intended to be 160 microns, whereas the femtosecond laser flap depth was intended to be 110 microns. Interestingly, another study found that patients who underwent flap creation with femtosecond laser (mean flap thickness, 111 microns) had significantly less post-LASIK dry eye symptoms than those who underwent microkeratome flap creation (mean thickness, 131 microns), although in the microkeratome group, there was no significant association between flap thickness and incidence of symptoms.[43] As mentioned previously, the trend toward thin-flap LASIK may result in less postoperative tear dysfunction and neuropathic disease.

No studies were found that investigated the incidence of tear dysfunction or corneal neuropathic pain after astigmatic keratotomy. McDonald reported that conductive keratoplasty for treatment of hyperopia was not associated with postoperative dry eye.[105]

VI. SUMMARY AND CONCLUSIONS

Post-LASIK dry eye represents a spectrum of disease ranging from post-LASIK tear dysfunction syndrome to neurotrophic and neuralgic ocular surface disease. Figure 1 proposes a scheme to identify the causes of post-LASIK eye discomfort. Through a variety of mechanisms, LASIK induces transient ocular surface changes that may lead to permanent ocular surface dysfunction in some patients. Appropriate selection of refractive surgery candidates and aggressive maintenance of ocular surface health are essential in the effort to minimize the risk of longterm tear dysfunction, neurotrophic keratopathy and neuropathic pain after LASIK. Recent advances in refractive surgery techniques and ongoing research in ocular surface therapeutics may reduce the incidence of post-LASIK ocular surface neuropathic disease and may offer relief for those currently suffering.

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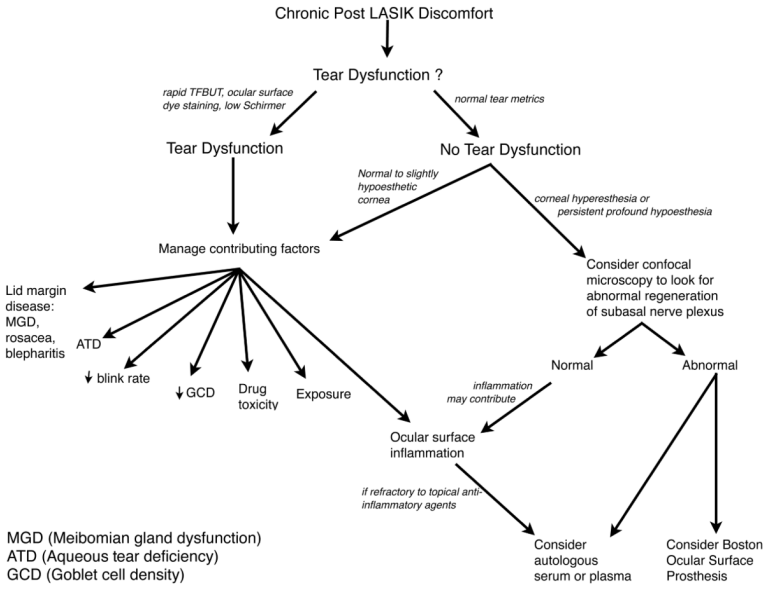

Figure 1.
Flowchart to identify causes of post-LASIK eye discomfort.