MMP-9 and the perioperative management of LASIK surgery
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Purpose of review
Hyperosmolarity is a central mechanism causing ocular surface inflammation and eye irritation in typical patients suffering from tear dysfunction. Tear composition in dry eyes, or dysfunctional tear syndrome, may destabilize the tear film and cause ocular surface epithelial disease. Increased activity of matrix metalloproteinases (MMPs), especially MMP-9, plays a critical role in wound healing and inflammation and is primarily responsible for the pathologic alterations to the ocular surface that leads to a dysfunctional tear state.

Recent findings
Altered corneal epithelial barrier function is the cause for ocular irritation and visual morbidity in dry eye disease. The increased MMP-9 activity in dry eyes may contribute to deranged corneal epithelial barrier function, increased corneal epithelial desquamation, and corneal surface irregularity.

Summary
Dry eye is one of the most common complications of photorefractive keratectomy and laser in-situ keratomileusis (LASIK). LASIK has both a neurotrophic effect on the cornea and leads to a physical change in corneal shape that results in a change in tear dynamics, leading to ocular surface desiccation. The reduction in tear function after LASIK may induce an increase in osmolarity and consequently raise the concentration of proinflammatory cytokines and MMP-9 in the tear film, which results in dry eyes and insufficient attachment between the corneal flap and the corneal bed. Appropriate diagnosis and management of dysfunctional tear syndrome may lead to less postoperative LASIK complications.

Keywords
dry eyes, dysfunctional tear syndrome, keratoconjunctivitis, laser in-situ keratomileusis, metalloproteinase 9, MMP-9

Introduction
Tear composition in dry eyes, or dysfunctional tear syndrome, may destabilize the tear film and cause ocular surface epithelial disease [1–6]. Increased activity of matrix metalloproteinases (MMPs), especially MMP-9, plays a critical role in wound healing and inflammation [7,8] and is primarily responsible for the pathologic alterations to the ocular surface that leads to a dysfunctional tear state [5,7].

MMPs are a family of 23 zinc and calcium ion–dependent proteolytic enzymes produced by stressed ocular surface and glandular epithelial cells, as well as by the immune cells that infiltrate these tissues. The MMPs are integrally involved in angiogenesis, inflammation, wound repair, and tissue remodeling through their ability to degrade extracellular matrix components [9–11]. These enzymes are subclassified according to their substrates: the collagenases (MMP-1, MMP-8, and MMP-13) degrade fibrillar collagen types I, II, and III; the gela-
MMP-9 tissue inhibitors of metalloproteinases (TIMPs) bind and inactivate the proenzyme [10].

After injury, and in response to the release of cytokines, several MMPs in the cornea are upregulated by transcription or activation [21]. MMP-9 has been found to be of central importance in catalyzing the cleavage of epithelial basement membrane components [19,22]. Additionally, hyperosmolality stimulates the production of inflammatory factors such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and MMP-9 and activates the mitogen-activated protein kinase (MAPK) signaling pathways in the ocular surface epithelial cells [23]. The activation of MAPK signaling pathways is known to stimulate the expression of MMP-9, and the production of inflammatory cytokines, actuation of matrix degrading enzymes, expression of MMP-9, and the production of inflammatory factors such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and MMP-9 and activates the mitogen-activated protein kinase (MAPK) signaling pathways in the ocular surface epithelial cells [23].

**Pathophysiology**

The proinflammatory cytokine IL-1 is an important mediator of inflammation and immunity and is implicated in corneal and ocular surface diseases rosacea, bullous keratopathy, keratoconus, and sterile corneal ulceration [5,25,26]. The precursor and the mature 17-kDa forms of IL-1α are both biologically active, whereas the precursor form of IL-1β possesses minimal biological activity and requires cleavage to the 17-kDa mature form to become active [27]. MMP-9 protein and mRNA was shown to upregulate synergistically in rabbit and human dermal fibroblasts when exposed to a combination of growth factors, IL-1, and TNF-α [28]. MMP-9 is induced by IL-1 in human corneal stromal cells [29]. Tear fluid growth factor and cytokines are secreted by the lacrimal glands and are produced by the epithelial and inflammatory cells that reside on the ocular surface. As tear clearance decreases in dry eye conditions, the concentration of pro-inflammatory cytokines, such as IL-1 increases [5,30].

Solomon et al. [4] demonstrated that dry eye disease is accompanied by an increase in the proinflammatory forms of IL-1 (IL-1α and mature IL-1β). IL-1 is a potent inducer of other inflammatory cytokines such as IL-6, IL-8, and TNF-α and can stimulate the production of MMP-9 by epithelial and inflammatory cells [4,10,31,32]. Previous studies have demonstrated that IL-6 can also induce the expression of MMPs [33,34]. IL-1β is activated in the extracellular environment by a number of proteases, including leukocyte elastase, granzyme A, MMP-2, and MMP-9 [27,35,36]. Further, MMP-9 was found to be the most efficient activator of precursor IL-1β [36]. The stable concentrations of IL-1α and precursor IL-1β in tear fluid after induction of reflex tearing suggests that the lacrimal glands secrete these cytokines.

**Key points**

- Metalloproteinase 9 (MMP-9) is an inflammatory marker that has consistently been shown to be elevated in the tears of patients with dry eyes.
- MMP-9 activity may be a more sensitive diagnostic marker for dry eyes than clinical signs.
- Preoperative dry eye condition is a major risk factor for more severe dry eye after surgery and should be identified prior to surgery.
- Preoperative and perioperative management of inflammation related to dry eyes may reduce dry eyes after laser in-situ keratomileusis, improve wound healing, and reduce flap complications.

**Dry eyes: definition and quality of life**

Historically, the term dry eye implied tear volume deficiency, mainly associated with Sjögren’s syndrome [37–39], but it is now widely appreciated that the majority of dry eye patients do not have associated systemic conditions and many do not have low aqueous tear production [1]. According to the Dry Eye Work Shop (DEWS) definition, dry eyes is 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.

Risk factors for dry eyes include patients taking other medications (e.g., antihypertensives, antidepressants, or hormone replacement therapies) [40], patients with autoimmune inflammatory diseases [41], contact lens wearers [42], laser in-situ keratomileusis (LASIK) and refractive surgery patients [43], and postmenopausal women [44].

Symptoms of dry eyes as described by patients include burning, dryness, foreign-body sensation, ocular pain, blurred vision, photophobia, and visual fatigue. Clinical signs of dry eye include positive vital staining of ocular surface, decreased tear film breakup time and Schirmer’s tests, reduced corneal sensitivity, and decreased functional visual acuity [45]. The discordance between symptoms, clinical signs, and diagnostic test results are inconsistent, making the diagnosis and treatment of this condition challenging [46].

Quality of life can be significantly affected by dry eye symptoms, as documented by several validated survey
Mechanism of action

Hyperosmolarity is a central mechanism causing ocular surface inflammation and eye irritation in typical patients suffering from tear dysfunction [49**]. Dry eye induces inflammation on the ocular surface, evidenced by elevated levels of the inflammatory cytokines, chemokines, adhesion molecules, and MMPs in the tear film and on the ocular surface [3,6,23,50–52]. A significant increase in the concentration and activity of MMP-9 has been reported in the tear fluid of human dry eye patients [4,5,53] as well as in the corneal epithelium and tear fluid of mice with experimental dry eye [54]. MMP-9, in particular, is a nonspecific inflammatory marker that has consistently been shown to be elevated in the tears of patients with dry eyes.

Decreased tear production and tear clearance lead to chronic inflammation of the ocular surface. This inflammatory response consists of cellular infiltration of the ocular surface by activated T lymphocytes, with increased expression of adhesion molecules and inflammatory cytokines, increased concentrations of inflammatory cytokines in the tear fluid, and increased activity of MMP-9 in the tear fluid. Increased MMP-9 expression and activity of MMP-9 causes aggravation of symptoms because they cleave epithelial basement membrane components and tight junction proteins that maintain corneal epithelial barrier function [55–57]. Epithelial damage, along with the progressive lymphocytic infiltration and the released cytokines, induces inflammation and apoptosis. Expression of the proapoptotic markers by the conjunctival epithelium has been found to be high in dry eye [58]. Significant positive correlation has been observed between the levels of inflammatory cytokines in the conjunctival epithelium and the severity of symptoms of ocular irritation, including corneal fluorescein staining, and the severity of conjunctival squamous metaplasia in patients with Sjögren’s syndrome keratoconjunctivitis [59].

Desiccating stress had no effect on levels of TIMP transcripts in the corneal epithelium, suggesting that MMPs are more inducible by dry eye stress than are TIMPs [12]. There are three levels of MMP regulation: transcriptional control, activation of the secreted pro-enzyme, and inhibition of the enzyme by the TIMPs [60,61]. Each MMP is inhibited by at least one of four recognized TIMPs. It has been proposed that MMP activity is related to the ratio of the concentration of an MMP to its TIMP. An altered balance of MMPs and TIMPs has been implicated in the pathogenesis of corneal ulceration and wound healing [62,63]. Although both latent-MMP-9 and TIMP-1 concentrations were elevated in tear fluid obtained from patients with rosacea compared with normal controls, no significant difference in the TIMP-1-to-pro-MMP-9 ratio between the two groups was seen [53].

Experimentally induced dry eye is associated with acutely increased markers of ocular surface inflammation and with epithelial cell apoptosis [51]. MMP-9 produced by the corneal epithelium has been found to impede re-epithelialization of the cornea after experimental thermal injury in animal models [20], and increased MMP-9 activity disrupts corneal epithelial barrier function, produces corneal surface irregularity in an experimental murine model of dry eye [54], and increases production of inflammatory mediators on the ocular surface that is similar to human dry eyes [23,64]. MMP-9 contributed significantly to the altered corneal epithelial permeability in dry eyes, because corneal epithelial barrier function was preserved in experimental dry eye MMP-9 knockout mice [54].

Several human studies demonstrate elevated MMP-9 levels in the tear fluid of patients with dry eyes [53,65]. Expression of MMP-9 by the ocular surface epithelia in normal healthy eyes is low [66]. The normal levels of MMP-9 (ng/ml) in human tears range from 3 to 41 ng/ml (see Table 1). [4,52,67–69,70*]. Increased production of MMP-9 by the corneal epithelium has been

<table>
<thead>
<tr>
<th>Study</th>
<th>Normal controls</th>
<th>Average MMP-9 levels (ng/ml)</th>
<th>Standard deviation (ng/ml)</th>
<th>Upper range (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>Acera et al. [52]</td>
<td>18</td>
<td>23.61</td>
<td>17.4</td>
<td>41</td>
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<tr>
<td>Chotikavanich et al. [87]</td>
<td>16</td>
<td>8.39</td>
<td>4.70</td>
<td>13</td>
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<tr>
<td>Solomon et al. [4]</td>
<td>17</td>
<td>7.2</td>
<td>2.1</td>
<td>9</td>
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<tr>
<td>Leonardi et al. [68]</td>
<td>10</td>
<td>10.5</td>
<td>0.2</td>
<td>11</td>
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<td>Lema et al. [69]</td>
<td>20</td>
<td>6.9</td>
<td>1.4</td>
<td>8</td>
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<td>Honda et al. [70*]</td>
<td>28</td>
<td>22.7</td>
<td>14</td>
<td>37</td>
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<td>Total/average/range</td>
<td>109</td>
<td>13.2</td>
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MMP, matrix metalloproteinase.
found in the eyes of human patients suffering from sterile corneal ulceration [71].

In addition, MMP-9 activity was found to be greater in the tear fluid of patients with ocular rosacea than in normal controls [5]. Ocular rosacea and other dry eye conditions are associated with an increased incidence of recurrent corneal epithelial erosion (RCEE) and sterile corneal stromal ulceration. RCEE has been reported to occur in up to 12% of patients with ocular rosacea [72,73]. Solomon et al. [4] found increased activity of MMP-9 in the tear fluid of patients with meibomian gland disease and Sjögren’s syndrome. MMP-9 concentration and activity is significantly higher in the tear fluid of patients with delayed tear clearance, especially in patients with recurrent corneal epithelial erosion [5].

Chotikavanich et al. [67] showed that levels of MMP-9 in patients with dysfunctional tear syndrome (DTS) were not significantly different between male and female participants and there was no significant difference in the tear MMP-9 activity between each decade of age between 20 and 80 years in both normal controls and dry eye patients. Each DTS group had significantly higher mean levels of tear MMP-9 activity than the normal individuals, and the most severe DTS group (DTS4) was found to have the highest mean MMP-9 activities that were significantly higher than the other DTS groups. These findings indicate that tear MMP-9 activity is significantly elevated, even in mild DTS, and that this may be a more sensitive diagnostic marker than clinical signs. Also, MMP-9 activities strongly correlate with clinical parameters [67]. Additionally, using gelatin zymography of tear fluid samples, Solomon et al. [4] demonstrated minimal or no 92-kDa pro-MMP-9 was observed in normal controls; however, greater levels of pro-MMP-9 were found in tear fluid samples taken from patients with dry eye who had meibomian gland dysfunction (MGD), patients with non-Sjögren’s aqueous tear deficiency, and those with Sjögren’s disease. Further, a quantitative MMP activity assay showed a 66-fold increase in patients with MGD and a 90-fold increase in patients with Sjögren’s disease compared with normal individuals.

**Diagnosis**

It also is widely appreciated that there is little correlation between the symptoms of patients and the clinical test results in dry eye patients [24,38,74].

Tear stability can be evaluated with noninvasive diagnostic technologies [noninvasive tear breakup time (TBUT)] or with application of fluorescein to the tear film to measure tear film breakup time. Schirmer’s tests are used to gauge the volume of tears. There are other methods for analyzing tear interference images [75,76], and technologies such as corneal topography have been used to provide noninvasive tear stability information [77–79]. Even the technique for performing TBUT measurements with fluorescein varies significantly among clinicians depending on whether dye-impregnated strips or commercially available drops are used to perform the test.

A relatively new diagnostic device from TearLab (OcuSense, Inc., San Diego, California, USA) allows for the quantitative measurement of tear osmolarity. Studies of dry eye patients provide well validated cutoff values of 316 mOsm/l [80] or 317 mOsm/l [81] for dry eye disease. Tear osmolarity correlates with increasing severity of dry eye. Also a high correlation is found between tear hyperosmolarity and clinical score.

A rapid, 10-min point-of-care immunoassay that utilizes direct sampling microfiltration technology and detects the presence of elevated MMP-9 in 10 µl of tears, called the RPS InflammaDry Detector (Rapid Pathogen Screening Inc., Sarasota, Florida, USA), is also available. Two antigen-specific antibodies capture MMP-9 antigens in the sample and this complex is trapped at the test line giving rise to a visually observable signal. The intensity of the visual test line correlates with the amount of MMP-9 present in the sample. Since the detection limit of this qualitative test is set at 40 ng/ml, any positive test is indicative of an abnormal level of MMP-9 [82]. Elevated MMP-9 levels in patients with moderate to severe dry eye correlate with clinical examination findings and have even been shown to be a more sensitive diagnostic marker than clinical signs [67].

**Management**

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 short courses of topical steroids or cyclosporine 0.05% drops to optimize the ocular surface, as it has been found to increase goblet cell density [83] and to accelerate the return of corneal sensitivity postoperatively [84].

**Laser in-situ keratomileusis: laser in-situ keratomileusis-associated dry eyes**

Dry eye is one of the most common complications of photorefractive keratectomy (PRK) and LASIK [85,86]. LASIK surgery is the most commonly performed vision correction surgery in the United States [87]. 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 [88] 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.

LASIK-associated dry eye is a major cause of patient dissatisfaction [43,89,90]. Although post-LASIK dry eye is usually short-lived, some patients complain of severe symptoms [1,91]. Other complications, such as fluctuating vision, decreased best spectacle corrected visual acuity, and severe discomfort occurs in approximately 10% of patients [92].

Clinical signs of post-LASIK dry eye include positive vital staining of the ocular surface, decreased TBUT, reduced corneal sensitivity, and the presence of a reduced Schirmer’s tear test score [93–95]. The post-LASIK decrease in TBUT, basal tear secretion, and Schirmer’s scores may persist for months [96,97]. Thus, LASIK has both a neurotrophic effect on the cornea and leads to a physical change in corneal shape that results in a change in tear dynamics, leading to ocular surface desiccation [92].

Preoperative risk factors
Although most patients have reduced basal tear production in the first few months following LASIK, only about half of patients are symptomatic [77,78,93,95–102]. The impact of using traditional methods of dry eye evaluation in the preoperative management of LASIK is variable. Studies have shown that preoperative Schirmer’s scores below 10 mm are associated with postoperative tear dysfunction [95] and Ambrosio [92] showed that preoperative dry eye condition is a major risk factor for more severe dry eye after surgery and should be identified prior to surgery.

Among patients seeking refractive surgery, Toda et al. [103] found that more than 75% of patients interested in refractive surgery had preoperative symptoms or signs of dry eye. Despite having preexisting mild-to-moderate dry eye, a patient can have LASIK performed safely if care is taken to optimize the ocular surface prior to LASIK, and in some cases, if care of the ocular surface is continued after surgery [103–105]. Patients with preexisting tear dysfunction have poorer postoperative ocular surface health and more severe symptoms of tear dysfunction after LASIK and their corneal sensitivities take longer to recover compared to patients without dry eye [95,101,103].

Long-term contact lens wear may also predispose patients to tear film instability before and after surgery [97,101]. Long-term contact lens wearers demonstrate significantly reduced tear secretion and corneal sensitivity before and after LASIK [96,97,106].

Gender has not been shown to be a risk factor for post-LASIK tear dysfunction. Two retrospective studies found significant associations between female gender and chronic post-LASIK tear dysfunction [99,107], yet a prospective study found no association [85]. Age also has not been shown to be an important risk factor for post-LASIK tear dysfunction [85,107].

Although objective clinical signs of tear insufficiency were not demonstrable, patients undergoing LASIK for high myopia reported ongoing dry eye symptoms 2–5 years after surgery [108]. In addition, Asian patients show a higher prevalence of chronic post-LASIK tear dysfunction [109].

Surgical considerations
LASIK-associated dry eye is one of the most frequent LASIK complications, which is believed to be attributable to the transection of large numbers of the afferent sensory nerve fibers in the corneal lamellar cut. This disturbs the lacrimal gland-ocular surface functional unit and promotes the development of LASIK-associated dry eye [77,93,95–101,110]. Corneal sensitivity decreases after LASIK because of surgical amputation and laser ablation of the nerve fibers innervating the central cornea [93,96–98,110–115].

Ablation depth and higher myopic refractive corrections also positively correlate with decreased corneal sensitivity [116,117]. 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 [85,112,118–120].

Suction related to microkeratome use in LASIK leads to altered central corneal shape [121] and loss of goblet cells [99,122], the density of which has been found to decrease immediately postoperatively. Loss of goblet cells results in a subsequent reduction in goblet cell mucin, a stabilizing molecule in the tear film, which, if reduced, may lead to tear film instability [122]. These changes are present in all post-LASIK dry eye patients but are more significant in patients with chronic dry eye symptoms [99]. Goblet cell density may take 6 months to return to baseline values after LASIK [122].

In addition, tear fluorescein clearance time is increased post-LASIK, which may be due to less frequent blinking [96]. Toda et al. [93] found that the blink rate of LASIK patients was decreased by up to 40%, and the difference
in mean blink rate before and after LASIK remained statistically significant at postoperative months 3, 6, and 12.

The possible mechanisms for post-LASIK dry eye may be related to a neurotrophic effect, damage of goblet cells, and altered corneal shape [89]. Previous studies suggest that intraoperative risk factors for developing post-LASIK dry eye include higher refractive correction [116], deeper ablation depth [117], thicker flap [123], superior flap hinge [118], and narrow flap hinge [124].

**Laser in-situ keratomileusis flap-related complications**

LASIK flap analysis indicates that corneal wound healing does not terminate at 3 months after LASIK, and that corneal wound healing likely lasts for a long period following LASIK. This implies that insufficient attachment between the corneal flap and the corneal bed lasts for a prolonged period [125]. Patients have been identified in whom the dislocation of corneal flaps [126,127] or ectasia consisted of a progressive deformation and thinning of the cornea [128] after LASIK, and this appears to be related to corneal wound healing.

In a rabbit model, MMP-2 and MMP-9 were predominantly localized behind the leading edge of migrating epithelium, which may indicate a role for these enzymes in stromal remodeling or early basement membrane assembly [129]. Azar et al. [130] used zymography to compare MMP expression after PRK or LASIK in the rabbit cornea and found that stromal levels of MMP-2 and MMP-9 increased after both procedures, with high MMP-9 expression also localized in the epithelium during re-epithelialization.

Significant expression of MMP-9 is observed in the peripheral LASIK wound margin scar in all eyes analyzed. The presence of MMP-9 may represent a marker of ectasia after LASIK and can lead to ongoing basement membrane remodeling with consequences in the stroma such as prolonged keratocyte apoptosis, which results in decreased synthesis of extracellular components, corneal thinning, and ectasia.

Post-LASIK epithelial ingrowth is associated with elevated MMP-9 [131]. The incidence of epithelial ingrowth is about 1% after LASIK [132] and develops in the interface through one of two known mechanisms for epithelial ingrowth: epithelial invasion and epithelial implantation. Lower endothelial counts, thinner flap thickness, and enhancement are risk factors for the development of epithelial ingrowth [89] through delayed sealing of the flap edge and/or poor adhesion of the flap interface. Epithelial cells under the flap gradually lose their viability over time and finally undergo apoptosis with or without fibrosis. If the sealing of the flap edge is not tight or adhesion of interface is not firm, epithelial cells may survive and proliferate [89].

Epithelial ingrowth develops slowly in the beginning from week 1 to several weeks after LASIK and appears as variously shaped areas of transparent sheets with milky or whitish islands [132]. Although most cases heal spontaneously, some require surgical removal. Epithelial invasion grows in two distinct ways: outside invasion and flap epithelial invasion. The latter type is often seen after enhancement and may be resistant to treatment. Patients with compromised attachment of corneal epithelium before LASIK may develop recurrent corneal erosion, which sometimes requires phototherapeutic keratectomy [89].

**Perioperative ocular surface management**

The reduction in tear function after LASIK may induce an increase in osmolarity and consequently raise the concentration of proinflammatory cytokines and MMP-9 in the tear film [133]. In a dry eye characterized by a reduced tear production and a decreased tear clearance, pro-MMP-9 enzyme is accumulated and activated subsequently in the tears [92]. The importance of inflammation in the pathogenesis of dry eye is underscored by reports that the signs and symptoms of dry eye markedly improve with anti-inflammatory therapies such as glucocorticosteroids and cyclosporine [134,135]. Smith et al. observed a correlation between tear MMP-9 levels and clinical evidence of disease progression [66]. Additionally, cyclosporine was found to significantly decrease the number of meibomian gland inclusions in patients with MGD [136], leading to further tear stabilization.

Many patients who develop LASIK-associated dry eye without prior symptoms or signs of dry eye have a marked response to topical cyclosporine treatment, which treats the underlying inflammation and may benefit nerve regeneration [92]. Cyclosporine inhibits T-lymphocyte proliferation on the ocular surface cells [137,138]. Further, topical cyclosporine treatment significantly decreases the levels of apoptosis and MMP-9 expression in the conjunctival epithelial cells of thyroid patients with dry eye [139]. Patients should be routinely re-examined 4–6 weeks after beginning treatment with cyclosporine. After initiating cyclosporine, symptoms and signs of dry eye will improve in 50–60% of patients within 1 month; however, a significant proportion of patients with chronic dry eye take several months to respond to topical cyclosporine [7,140].

Treatment with anti-inflammatory medications such as topical corticosteroids [141] and topical cyclosporine...
cytokines (IL-1, IL-6, IL-8, TNF-α) have been reported to inhibit MMP-9 [143]. Corticosteroids are global inhibitors of inflammation and have been reported to decrease the production of a number of inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α, GMCSF) and MMP-9 by the corneal epithelium [144].

Therapy of dry eye, with methylprednisolone and doxycycline was shown to preserve the tight junction network, increase corneal smoothness, preserve corneal barrier function, and lead to a reduction in the production and activity of MMP-9 [143]. Corticosteroids are global inhibitors of inflammation and have been reported to decrease the production of a number of inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α, GMCSF) and MMP-9 by the corneal epithelium [144].

Management of the ocular surface during LASIK, as well as long-term management of the tear film and ocular surface, can minimize ocular surface damage and the risk of adverse outcomes, leading to a reduction in the severity and duration of dry eye symptoms and signs [101]. Optimization of the preoperative ocular surface with artificial tears, nutrition supplementation, punctal occlusion, and topical cyclosporine in patients with symptoms or signs of dry eye prior to LASIK decreases the incidence of postoperative symptoms [92]. Konomi et al. [107] suggest that topical anti-inflammatory therapeutics could normalize the ocular surface and improve the quality of the tear film after LASIK. Although topical steroids may have the most potent and rapid anti-inflammatory action, long-term treatment is not advisable because of the side-effects of corticosteroids, especially cataract formation and glaucoma [146]. Cyclosporine, however, has minimal side-effects compared with steroids and may be used for long periods without deleterious effects in the eye [135,146,147].

For patients who develop persistent neurotrophic keratopathy after LASIK, traditional treatment modalities should be implemented including preservative-free artificial tears, punctal occlusion, cyclosporine and azithromycin therapy, bandage contact lenses, autologous serum, and tarsorrhaphy. Autologous serum drops can dramatically increase corneal sensitivity to near normal levels and improve clinical parameters of ocular surface health [49**].

**Conclusion**

Preoperative dry eye or tear film instability is a major risk factor for increased dry eye and should be identified prior to LASIK surgery [92]. MMP-9 is an inflammatory marker that has consistently been shown to be elevated in the tears of patients with dry eyes and may be a more sensitive diagnostic marker than clinical signs [67]. Perioperative management of inflammation related to dry eyes may reduce post-LASIK dry eyes, improve wound healing, and reduce flap complications [92].

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**References and recommended reading**

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

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 308).

This article provides a detailed review of post-LASIK tear dysfunction. This is a significant problem that affects many patients after laser in-situ keratomileusis (LASIK) surgery. The review highlights the importance of understanding the mechanisms underlying tear dysfunction and the potential strategies to mitigate its effects. The article discusses the role of matrix metalloproteinases (MMPs), cytokines, and other factors in the development of post-LASIK tear dysfunction.

Key Points:
- Post-LASIK tear dysfunction is a common issue that affects many patients.
- MMPs and cytokines play critical roles in the pathogenesis of post-LASIK tear dysfunction.
- Understanding the signaling pathways involved is essential for developing effective interventions.
- The article emphasizes the need for further research to identify new targets for treatment.

Implications for Practice:
- Clinicians should be aware of the potential for post-LASIK tear dysfunction and monitor patients accordingly.
- Patients should be educated about the risks and expected outcomes of LASIK surgery.
- Future research should focus on developing personalized treatments based on individual patient characteristics.

References:
This article reviews problems associated with LASIK flap healing. This article correlates MMP-9 response post-LASIK.


This article correlates MMP-9 response post-LASIK.


This article reviews problems associated with LASIK flap healing.


This article demonstrates elevated MMP-9 isolated to LASIK flap.


This is the first article to demonstrate that cyclosporine directly reduces MMP-9 levels.


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