

Allergic complications with laser-assisted in-situ keratomileusis

Brett P. Bielory and Terrence P. O'Brien

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami – Miller School of Medicine, Palm Beach Gardens, Florida, USA

Correspondence to Terrence P. O'Brien, MD, Bascom Palmer Eye Institute (Palm Beach Campus), University of Miami – Miller School of Medicine, 7101 Fairway Drive, Palm Beach Gardens, FL 33418, USA
Tel: +1 561 515 1544; fax: +1 561 355 8600;
e-mail: tobrien@med.miami.edu

Current Opinion in Allergy and Clinical Immunology 2011, 11:000–000

Purpose of review

This article reviews the complications of laser-assisted in-situ keratomileusis (LASIK) associated with ocular allergy. This review will provide guidance and heighten the need for a more comprehensive allergic evaluation before recommending LASIK procedure to patients. The material provided allows enhanced awareness of the potential postsurgical effects on allergic responses of the ocular surface and management thereof.

Recent findings

Ocular allergy is often underdiagnosed and has been previously reported only in a handful of peer-reviewed journals as the cause for ocular irritation and visual morbidity in post-LASIK dry eye disease. Diffuse lamellar keratitis is one complication of LASIK that has been linked to atopic individuals. LASIK causes significant inflammation in normal eyes, which is only exacerbated in atopic patients. Atopy may be a contributing factor in patients with post-LASIK dry eye symptoms. Further investigation is required to better understand the complications of LASIK in allergic patients.

Summary

LASIK surgery has been associated with increased anterior surface inflammatory processes that include dry eye syndromes and ocular allergy. In addition, poorer outcomes of LASIK procedures have been reported in patients with moderate to severe ocular allergies and chronic forms of allergic conjunctivitis is an absolute contraindication to the LASIK procedure. We propose preoperative and postoperative management algorithms for allergic LASIK candidates.

Keywords

allergy, cornea, laser-assisted in-situ keratomileusis, ocular surface

Curr Opin Allergy Clin Immunol 11:000–000
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1528-4050

Introduction

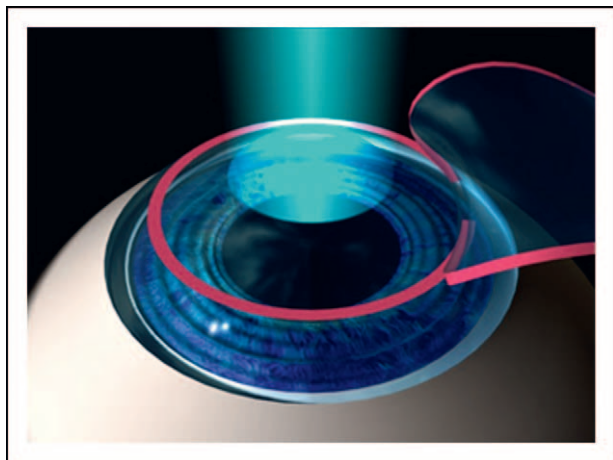
In the past 15 years, laser-assisted in-situ keratomileusis (LASIK) has become the most popular method of surgical vision correction [1]. Adults with stable refraction whose eyeglass prescription has not changed in the past year may be candidates for LASIK. However, before undergoing LASIK, numerous factors have been established as having potential adverse effects on the ocular surface and tear film with LASIK including ocular allergy, contact lens wear, herpetic keratitis, epithelial basement membrane dystrophy, eyelid disease and lid abnormalities, age, sex, and certain medical conditions [2]. Patients may inquire from their allergists about the consequences of photorefractive surgery, especially those with a medical history of asthma, atopic dermatitis, and rhinoconjunctivitis. Allergists may also be involved in the evaluation and management of ocular problems in LASIK-treated patients related to allergy and conditions that mimic or coexist with ocular allergy such as dry eye syndrome (DES). This article reviews the indications, benefits,

and risks of LASIK surgery and gives an overview of the literature associated with atopic disorders associated with potential complications, contraindications, and concerns with laser vision correction procedures.

What is laser-assisted in-situ keratomileusis?

Laser refractive surgery is a corrective corneal procedure that disrupts the corneal tissue, which involves the epithelium and stroma, and thus requires proper wound healing for successful outcome (Fig. 1).

The discipline of refractive surgery embodies various forms of improving the optical focal length in an effort to create the sharpest image on the retina. The change in focus is accomplished by surgical modifications to the corneal surface using a surgical blade (radial keratotomy), excimer laser photoablation [photorefractive keratectomy (PRK), LASEK, LASIK], and intracorneal rings. In particular, LASIK involves the creation of an anterior corneal flap that adheres back into place after laser

Figure 1 Laser-assisted in-situ keratomileusis procedure

Depiction of the LASIK procedure showing the creation of an anterior corneal flap and laser carving into the stromal bed of cornea centrally thereby modifying and enhancing the patient's refraction. LASIK, laser-assisted in-situ keratomileusis.

ablation. From a historical point of view, the original surgical LASIK technique 'keratomileusis', or carving ('mileusis') of the cornea ('kerato'), was first developed as a technique in which a disk of corneal tissue was removed, frozen, milled to the required shape, and sutured back into position.

Indications and benefits of laser-assisted in-situ keratomileusis

Unlike earlier methods of refractive surgery, the use of an excimer laser (wavelength = 193 nm) provides the surgical shaping of the cornea through photoablative decomposition (i.e. LASIK) with minimal postoperative pain and a quick visual rehabilitation (in days) most likely due to corneal flap created during the procedure acting as a natural bandage. LASIK is indicated for myopia, myopic astigmatism, hyperopia, and hyperopic astigmatism. Other indications in which LASIK may be performed are anisometropia and induced refractive errors after other corneal refractive, cataract, glaucoma, retinal, and other ophthalmic surgeries [3].

As LASIK is an elective procedure, relative and absolute contraindications have been established by the American Academy of Ophthalmology (AAO) practice parameters (Table 1) and the American Society of Cataract and Refractive Surgery (ASCRS). Of importance, the US Food and Drug Administration (FDA) and AAO have considered uncontrolled ocular allergy an absolute contraindication to LASIK [4]. Seasonal and perennial allergic conjunctivitis sufferers were not stratified by severity in these practice parameters, although future considerations may be required to stratify the outcomes in order to

Key points

- Although an exact percentage of patients with a history of ocular allergy after laser-assisted in-situ keratomileusis (LASIK) is not directly known, the complexity of this multifactorial disease is likely to be a part of a constellation of symptoms and complications after the procedure.
- Strategies to manage the integrated ocular surface/lacrimal gland functional unit before, during, and after LASIK can optimize outcomes in atopic patients.
- Preoperative uncontrolled ocular allergy is a major risk factor for dry eye after surgery and should be identified prior to surgery.
- Uncontrolled ocular allergy is considered an absolute contraindication to LASIK procedure. Preoperative and perioperative management of ocular allergy may reduce the inflammatory response after LASIK, improve wound healing, and reduce flap complications.
- The strategy for dealing with pre-LASIK allergy is similar to that used with dry eye: detection prior to the procedure is essential in preparing the healthiest possible ocular surface.

maximize the screening of potential laser vision correction patients. Recent reports concluded that LASIK could be performed effectively and safely in selected patients with stable and controlled systemic diseases. Recent studies have investigated the effects of autoimmune disorders on LASIK. Alio *et al.* [5] reported promising post-LASIK visual outcomes of small series ($n=22$) with a history of controlled rheumatic [auto-immune, human leukocyte antigen (HLA)-B27-associated diseases, vasculitis] disease at 6 months after LASIK ($P < 0.001$). However, Moshirfar *et al.* [6] report a poorly significant correlation ($P=0.668$) of incidence rates of uveitis in 10 patients with positive HLA-B27 serology between post-LASIK patients and controls. Cobo-Soriano *et al.* [7] investigated 141 patients with autoimmune disorders, psoriasis, inflammatory bowel disease, diabetes mellitus, and immunosuppressive therapy and found that visual outcomes after LASIK improved in patients with controlled disease.

Ocular surface abnormalities found after laser-assisted in-situ keratomileusis: conjunctival changes

LASIK has been associated with a decrease in goblet cell density and mucin, a stabilizing molecule of the tear film production immediately after the procedure. Reduction in goblet cell density and mucin production can contribute to the Tear Film Dysfunction (TFD) [8]. TFD was most apparent in patients with chronic dry eye symptoms after LASIK [9]. It is possible that some of these patients

Table 1 Contraindications for laser-assisted in-situ keratomileusis procedure

Absolute	Relative
Unstable refraction	Functional monocularly
Certain abnormalities of the cornea (e.g., keratoconus or other corneal ectasias, thinning, edema, interstitial or neurotrophic keratitis, extensive vascularization)	Systemic medications (e.g. isotretinoin, amiodarone, sumatriptan, levonorgestrel implants, colchicine)
Insufficient corneal thickness (<490 μm) for the proposed ablation depth	History of keloid formation
Severe ocular surface disease	History of herpes simplex virus (HSV) or varicella zoster virus (VZV) keratitis (zoster, simplex)
Steven–Johnson’s syndrome	Active ocular infection
Ocular cicatricial pemphigoid	conjunctivitis
Visually significant cataract	scleritis
	Blepharophimosis (small palpebral apertures)
Uncontrolled external disease (e.g. blepharitis, dry eye syndrome, atopy/allergy)	Corneal neovascularization
Uncontrolled glaucoma (especially if bleb present)	Significant dry eye syndrome
Uncontrolled connective tissue or autoimmune disease	Prior incisional or lamellar keratorefractive surgery
	Connective tissue and autoimmune disease
	Systemic or ocular vascular disease
	Large pupil size
	Pregnancy

had underlying allergic symptoms that had not been evaluated. Goblet cell density can take as long as 6 months to return to baseline values after LASIK [8].

Tear changes

The tear film is the most anterior element of the visual system helping to maintain high quality of vision. It is a trilaminar structure consisting of a thin superficial lipid layer, an intermediate aqueous layer, and an underlying mucous layer. After LASIK, goblet cell loss is common secondary to mechanical trauma, thereby altering the mucous layer. Little evidence shows any changes to the lipid or mucin cell layers of the tear film after LASIK. Few studies have shown the direct effects of tear film cytokines after LASIK, such as increases in transforming growth factor- β 1 (TGF- β 1) concentration after epi-LASIK [10] as well as tumor necrosis factor- α (TNF- α) [11], interleukin (IL)-6 [12], Vascular Endothelial Growth Factor (VEGF) [13], platelet derived growth factor (PDGF)-BB [14], and hepatocyte growth factor [15] after PRK. Interestingly, however, ascorbic acid levels in the tear film are lower after LASIK. Tear film osmolarity plays a critical role in causing ocular surface inflammation and eye irritation in patients suffering from tear film dysfunction after LASIK. Hyperosmolar tears lasting longer than 6 months have been documented in post-LASIK and PRK patients [16]. Protease activity is increased, in part, due to elevated osmolarity but also likely due to cytokine imbalance, which together can lead to breakdown of the extracellular matrix and tight junctions.

Complications

The wound healing process includes epithelial–stromal interactions, remodeling of the stromal collagen tissue,

proper blinking, migration and proliferation of epithelial cells, a balance of cytokines and growth factors from tears, and an intact substrate. Certain aspects of inflammation and wound healing have posed a conundrum for physicians, especially to the extent that the two processes may appear to operate in opposition to each other [17]. Theoretically, the various mediators released during the allergic response have an effect on normal healing from refractive surgery causing symptoms such as burning, pruritus, excessive lacrimation, and conjunctival hyperemia. The most common complications after LASIK include dry eye, diffuse lamellar keratitis (DLK), infectious keratitis, epithelial ingrowth, and incomplete flaps. DLK has been reported as a complication in allergic patients, and of more recent interest is the increase in dry eye complaints in allergic patients after LASIK [18,19].

Dry eye

Dry eye is the most common early and late postoperative complication after LASIK surgery. LASIK-induced dry eye is caused by a combination of decreased corneal innervation and chronic ocular surface inflammation. Ocular allergy often aggravates dry eye, compromises contact lens wear, and can be present with glaucoma and other ocular diseases, necessitating multiple therapies. These therapies can lead to contact lens intolerance, irritation, and even a form of ‘conjunctivitis medicamentosa’. Ocular burning is the primary symptom, whereas the signs are staining, reduced tear meniscus, gritty foreign body sensation, keratitis and (rarely) photophobia. It is caused by deficiencies or alterations in any of the components of the tear film, with underlying autoimmune, inflammatory, hormonal, bacterial, and environmental causes. Certain visual tasks, such as working on a computer display terminal, strain the eyes and reduce the

blink rate, thereby depriving the ocular surface of the tear film-replenishing effects provided by the blink. Published studies indicate that up to 20% of adults aged 45 years or more experience dry eye symptoms [20]. The percentage of patients with dry eye 6 months after LASIK ranges from 20 to 48 [21,22]. Persistent post-LASIK dry eye has been estimated to be as high as 28% in Asian eyes and 5% in Caucasian eyes [23]. Nerve fibers in the cornea are important for stimulating tear production. A year after LASIK, subbasal nerve fiber bundles remain reduced by more than half [24]. Some patients experience reactive tearing, in part to compensate for chronic decreased basal wetting tear production. The clinical signs of post-LASIK dry eye include positive vital staining of ocular surface, decreased tear film breakup time and Schirmer test, reduced corneal sensitivity, and decreased functional visual acuity.

Diffuse lamellar keratitis

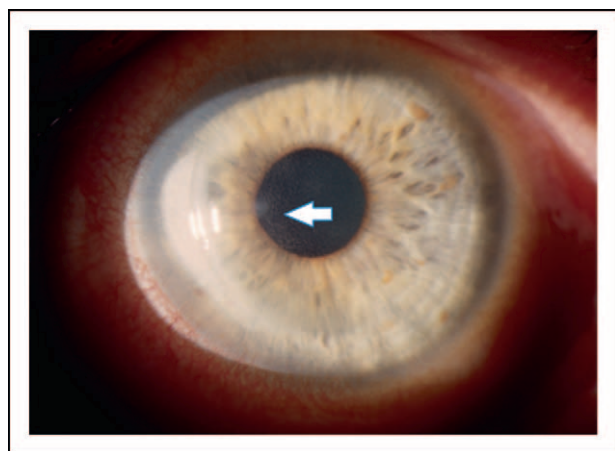
DLK is a noninfectious multifocal corneal, stromal, lamellar inflammation occurring after LASIK in 2–4% of the cases (Fig. 2). Patients present with mild pain, redness, and photophobia in the first week with after surgery [25]. Although the literature for allergy as a risk factor with LASIK is limited, atopy has been thought to be a patient-specific risk factor for the development of DLK, a potentially severe side-effect after bilateral primary LASIK. In a recent study [26], researchers conducted a retrospective, nonrandomized study of 360 patients who underwent same-day bilateral primary LASIK procedure. Atopic patients were defined with positive replies to a preoperative questionnaire ('Do you have any allergies (hay fever) or asthma?'). According

to the study, atopic patients appeared to benefit from preoperative intervention with systemic H1 receptor-antagonists. Ninety-four (26%) of the patients identified themselves as atopic, and 26 of them claimed to have used a nonsedating H1 antagonist. None had reported taking asthma medications alone. Standard postoperative treatments included a mild corticosteroid eyedrop and an 8-methoxy-fluoroquinolone antibiotic applied topically four times daily for 5 days and artificial tears as needed. Although the cause of DLK may not be known, researchers attribute it to a heightened immune response at the lamellar interface, as these atopic patients are secreting excessive cytokines, a heightened pro-inflammatory cascade predisposing these patients to DLK more than nonatopic patients. A 5.85-fold increase in the risk of DLK as complication to LASIK was noted in untreated atopic patients compared with nonatopic patients, yet the risk of DLK among treated atopic patients was not as significant ($P < 0.43$). DLK is not limited only to allergic to disease but also includes autoimmune diseases as well. In a case report of a 42-year-old patient with systemic mastocytosis, moderate myopia and astigmatism who underwent bilateral LASIK developed a 1+ DLK in the left eye that was successfully treated with prednisolone acetate with the eventual achievement of best uncorrected visual acuity of 20/20 in each eye [27], whereas another study [28] described peripheral keratitis in patients with rheumatoid arthritis following LASIK.

Laser-assisted in-situ keratomileusis and allergy

Laser therapy has been known to improve symptoms in patients with nasal allergies [29], but the literature regarding its effect on the ocular surface is limited. A common coexisting disorder with atopic patients is DES, also known as dysfunctional tear syndrome (DTS), a common complication in post-LASIK treatment. DTS is referred to as an abnormality in any of the tear film's three layers (aqueous, lipid, or mucin) due to either decreased tear production or increased tear evaporation leaving the ocular surface unprotected [30,31]. DES can present as its own entity secondary to an intrinsic tear disorder, or in conglomeration with other ocular disorders, procedures, and systemic diseases. Symptoms of DES after LASIK are typically vague and include dryness, burning, ocular pain, photophobia, foreign body sensation, easily fatigued eyes, and blurry vision. Patients initially complain of a mildly injected eye with excessive mucous production and symptoms of gritty sensation as opposed to the allergic symptoms of itching and burning feeling many patients complain of with histamine release onto conjunctiva. Moss *et al.* [32] report an increased incidence (25.2%) of dry eye in an age-adjusted 10-year retrospective review of the elderly population ($n = 572$) with a history of allergy ($P = 0.006$). Due to this overlap

Figure 2 Clinical appearance of diffuse lamellar keratitis ('sands of Sahara')



Post-LASIK DLK at the interface of the flap and stromal bed with a singular nummular area with more concentrated infiltrate (arrow). DLK, diffuse lamellar keratitis; LASIK, laser-assisted in-situ keratomileusis.

between dry eye and ocular allergy, it is strongly suggested that allergy be ruled out in preoperative evaluation of patients seeking laser vision correction with LASIK.

The LASIK procedure disrupts the anchoring complex and alters the curvature of the cornea mounting an impressive acute pro-inflammatory response but a more impressive immune response in allergic sufferers. Within minutes to hours after LASIK, mast cells, macrophages, and infiltrating leukocytes, including eosinophils, neutrophils along with cytokines and other growth factors (TNF, IL-1, IL-8, intercellular adhesion molecule-1), are released from the injured epithelial cells and conjunctiva to the site of the flap incision. Allergic inflammatory disorders, such as those that may affect the surrounding lid, conjunctival mucosa, or even sinuses and release various mediators of inflammation, including histamine, leukotrienes, and neuropeptides, most likely have effects on the local ocular tissue after LASIK, but has not been evaluated.

Corneal refractive surgery inherently stimulates the immune system and can cause multiple types of delayed hypersensitive reactions. Type I reactions, such as allergic conjunctivitis, have been documented as a risk factor for photorefractive keratotomy [33], but interestingly not for LASIK [34]. Asano-Kato *et al.* [34] reported a comparison of LASIK patients with ($n = 49$) and without ($n = 77$) a history of allergic conjunctivitis and failed to find any significant differences between the groups in terms of uncorrected visual acuity after surgery or risk for complications during LASIK. Of note, the literature has not stratified the incidence of corneal refractive surgery among seasonal and perennial allergic conjunctivitis patients. However, Sharwood and Rogers [35] report a single episode of corneal changes due to limbal vernal keratoconjunctivitis (VKC) in a young atopic man after bilateral LASIK procedure. The pathophysiological mechanism proposed includes increased vascularization and lipid deposition to the site of the flap as well as infiltrations of numerous inflammatory mediators, growth factors leukocytes and mast cells to conjunctival epithelium and corneal wound site. The mast cells in acute allergic conjunctivitis are located primarily in the substantia propria, whereas those involved in chronic allergic conditions such as VKC are also found in conjunctival epithelial tissue. Such differences are the most likely causes for a more heightened response after LASIK in chronic allergic conditions, whereby the epithelial tissue is in close proximity to the corneal wound site. Interestingly, type IV (T-cell-mediated) reactions have also been described to complicate LASIK, such as a case of sterile interface keratitis after LASIK in a patient with contact dermatitis of the eyelids [36].

Allergic mediators released after laser-assisted in-situ keratomileusis: potential impact on epithelial health

Ocular allergy has the potential to have an impact on surgical outcomes due to increased incidence of toxicity reactions to medications and their preservatives. The disturbances of any of the following chemical mediators may complicate refractive surgery, though further investigation is required.

Histamine

Histamine, an important mast cell mediator in allergic disorders, may affect extracellular matrix production and cell growth [37]. Sma-related and Mad-related proteins (Smad) modulate extracellular matrix gene expression during wound healing, inflammation, and tissue remodeling that is modulated in conjunctival fibroblasts by histamine and other cytokines released in ocular allergy, IL-4, TGF- β 1, and TNF- α [38*].

Prostaglandin

During the allergic response, the release of tryptase by the conjunctival mast cell via crucial intracellular events (via protease-activated receptor 2) leads to the induction of COX2 and fibroblast proliferation, which is a cornerstone of fibrosis [39]. The expression of COX2 in the corneal epithelium during wound repair is tightly regulated both temporally and spatially [40]. In an animal study [41] evaluating the difference between LASIK and PRK, migrating injured epithelium expressed COX2 until week 4 during post-PRK healing. Central uninjured epithelium as well as stromal keratocytes expressed COX2 from 3 days to 2 weeks after LASIK.

Leukotriene

To our knowledge, no data have been established from investigations of the involvement of leukotrienes in LASIK.

Cytokines

TGF- β , which is increased in the tears of patients with vernal forms of allergic conjunctivitis [42], has also been noted to be increased after LASIK [43] and may also contribute to setting the stage for an ocular conjunctival inflammatory response after LASIK.

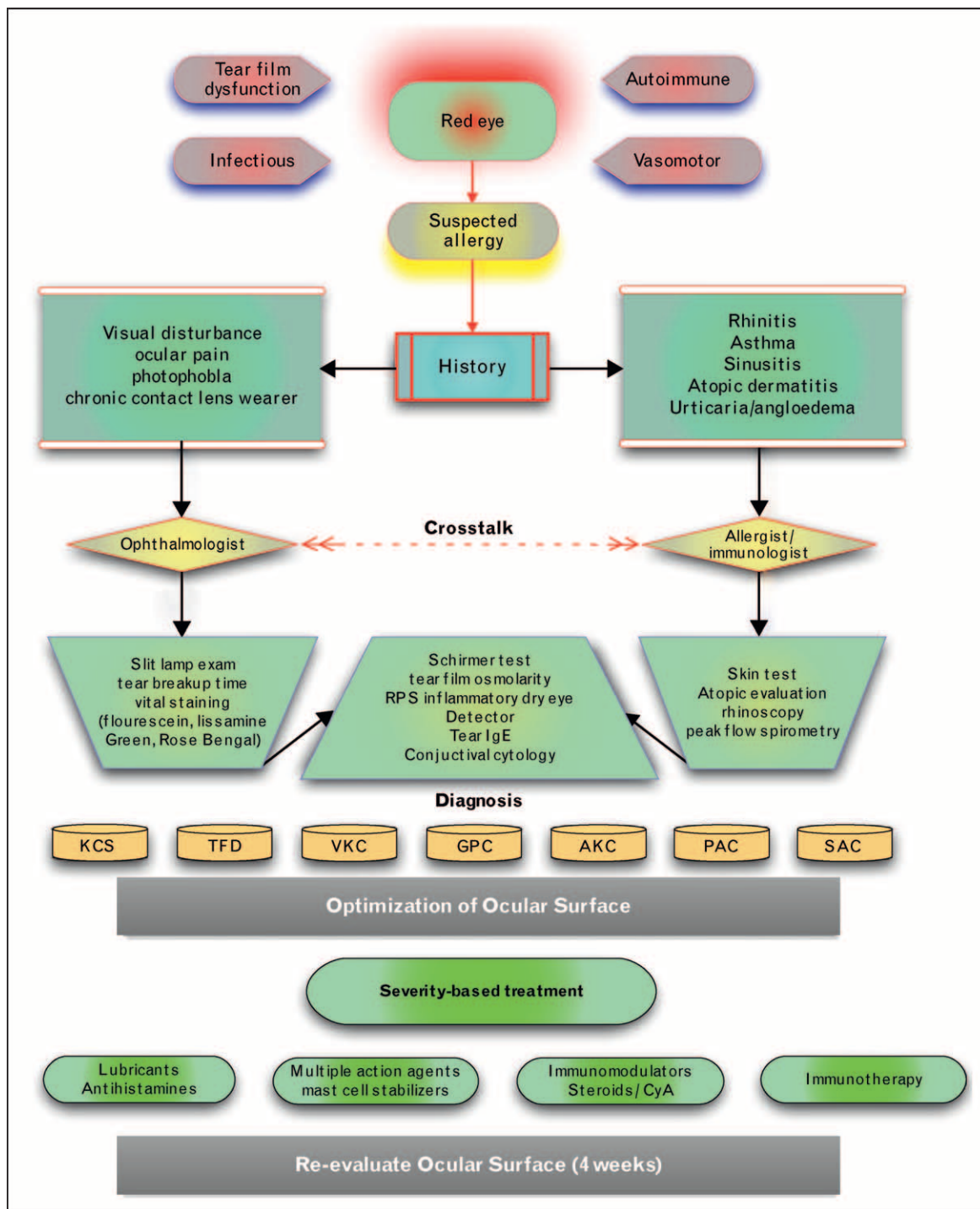
Neuropeptides

Nerve growth factor (NGF), a founding member of the neurotrophin family of neurotrophic factors that control the development, maintenance, survival, and plasticity of peripheral neurons, appears to play an essential role in the development of corneal sensitivity and epithelial wound healing [44]. After LASIK, increased NGF induces a transient inflammatory hyperalgesia in the acute phase augmenting the corneal nerve regeneration.

NGF is activated by the TrkA receptor tyrosine kinase signal transduction pathway very much like the ciliary neurotrophic factor (CNTF), which may play a role in allergic diseases as it has been shown to increase IgE

production from B cells in atopic patients but has not been studied in the cornea [45]. Increased levels of NGF have been reported in VKC [46] but have not been studied in allergic conjunctivitis. Further studies will

Figure 3 Preoperative workup for laser-assisted in-situ keratomileusis candidates with history of allergy



Allergic disorders represent a unique opportunity for allergists/clinical immunologists and eye care providers to collaborate on patients' care in order to maximize outcomes before undergoing the LASIK procedure. The stepwise holistic approach has been modified from the original Joint task Force on Practice Parameters (the American College of Allergy, Asthma & Immunology and the American Academy of Allergy, Asthma & Immunology) for the development of allergic conjunctivitis parameters. LASIK, laser-assisted in-situ keratomileusis; RPS Inflammatory Dry Eye Detector; detects MMP-9 levels in tears. Modified with permission from [50].

require investigation of the role of CNTF in the ocular surface.

Metalloproteinases

Metalloproteinase are integrally involved in angiogenesis, inflammation, and tissue remodeling through their ability to penetrate the extracellular matrix. Specifically, metalloproteinase-9 (MMP-9) has been shown to play a critical role in causing a giant papillary formation dysfunctional tear state in VKC (MMP-2, MMP-3, MMP-9, MMP-10) and after LASIK (MMP-9) [47*], respectively. In addition, MMP-9 expression has been elevated in allergic nasal polyps and staining was associated with eosinophils and CD4 T cells [48]. Leonardi *et al.* [49] assessed multiple mediators and growth factors in tears of active VKC patients using stationary-phase antibody array, which identified previously undetected factors in tears of VKC patients (e.g. MMP-2, MMP-3, MMP-9, MMP-10) and confirmed the presence of a high expression of multiple MMPs, growth factors, and cytokines that contribute to the pathogenesis of conjunctival allergic inflammation.

Management

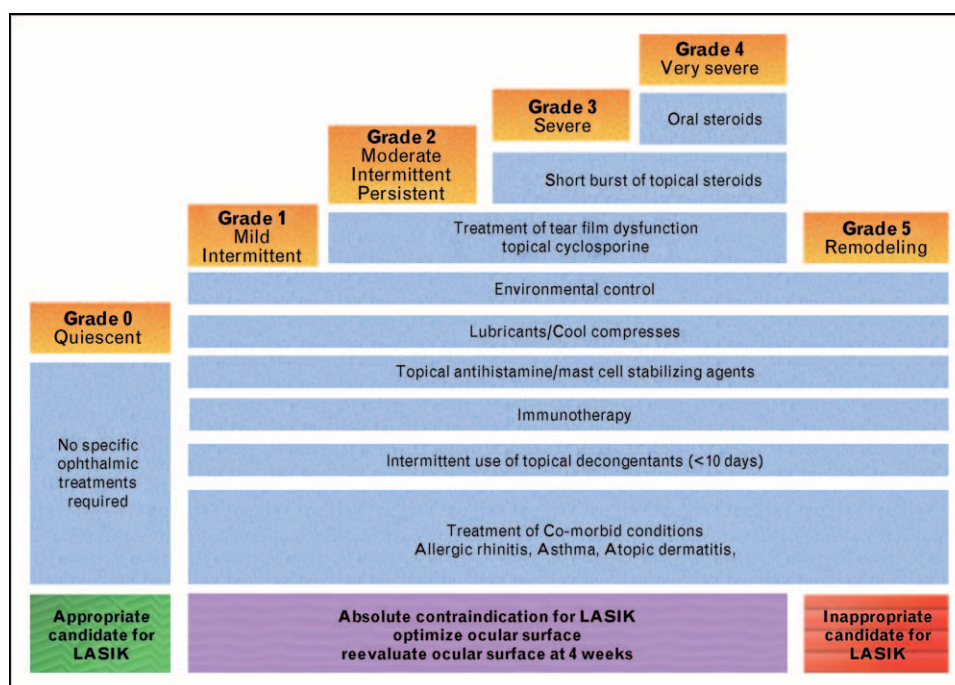
Ocular dryness is a central complaint and complication of refractive surgery most likely found in patients with allergic disorders and prophylactic management is the

gold standard of care. Identification, stratification of risk, and aggressive presurgical management are essential to avoid complications and assure successful outcomes. With careful selection of candidates for LASIK, the procedure can be safely and effectively managed in patients with allergy or dry eye with reduced reflex tearing by aggressive preoperative and postoperative treatments. For allergic patients, optimization of the ocular surface is paramount and treatment with lubricants, antihistamines, immunomodulators, and immunotherapy are all important steps to improving patient satisfaction after LASIK surgery (Fig. 3) [50]. Ocular surface optimization is a multifaceted treatment approach to restore stability of precorneal tear film and allow cellular repair and sustained protection during time between blinks, or the interblink interval. It is important for both allergists and ophthalmologists alike to work in unison when considering a patient with a known history of allergy.

Before laser-assisted in-situ keratomileusis

The protocol for identifying atopic patients preoperatively to help improve patient outcomes after LASIK consists of a complete medical history of asthma, allergic rhinitis, atopic dermatitis, among others, complete physical examination by allergists and ophthalmologists along with a battery of tests (Fig. 3), severity-based treatment (Fig. 4) [50] with lubricants, antihistamines,

Figure 4 Preoperative treatment algorithm for preoperative laser-assisted in-situ keratomileusis candidates



This stepwise approach of ocular allergy patients before LASIK has been modified from the original Joint Task Force on Practice Parameters (the American College of Allergy, Asthma & Immunology and the American Academy of Allergy, Asthma & Immunology) for the developments of allergic conjunctivitis parameters. LASIK, laser-assisted in-situ keratomileusis. Modified with permission from [50].

immunotherapy, and immunomodulators including cyclosporine and corticosteroids such as loteprednol etabonate, which has been shown to be especially effective in allergic conjunctivitis [51], and reevaluation of the ocular surface in 1 month.

However, although helpful in the setting of ocular allergy, autologous serum drops and factor VIII tears [52^{*}] have become increasingly popular for patients who undergo LASIK. Those who still exhibit evidence of ocular allergy (grade 5) or persistent dry eye symptoms are poor candidates for LASIK in that the postoperative dryness will likely be incapacitating and intolerable, as they will suffer from delayed healing because the tears contain factors that promote re-epithelialization. To date, there does not seem to be an advantage of systemically applied over topically applied antihistamines.

After laser-assisted in-situ keratomileusis

In patients with known ocular allergy or dry eye symptoms after LASIK, the main goals of treatment include decreasing inflammation, stabilizing of the tear film, increasing aqueous production, and promoting epithelial cell healing that will ultimately decrease ocular discomfort and improve visual acuity. Current severity-based management for post-LASIK allergy and/or dry eye includes conservative treatment with lid hygiene, artificial tears, topical azithromycin, and oral doxycycline and more aggressive intervention with topical cyclosporine, corticosteroids, and autologous serum along with punctal or canalicular plugs.

Further areas of research including prevalence and mechanistic studies with unique screening methods and patient profiling are required in the management of allergic patients with dry eye and TFD after LASIK. New novel treatment agents such as topical nerve growth factor, fibroblast growth factor, and cytochrome c peroxidase [53] warrant further attention given their potential role in re-epithelialization and accelerated corneal nerve growth.

Conclusion

The status of the ocular surface and tear film in atopic individuals before LASIK can impact surgical outcomes in terms of potential complications during and after surgery, refractive outcome, optical quality, patient satisfaction, and the severity and duration of dry eye. Despite limited studies and literature on the adverse effects of allergy on LASIK, the AAO and ASCRS guidelines consider non-active connective tissue or autoimmune diseases and systemic immunosuppression as relative contraindications and uncontrolled ocular allergy and uncontrolled systemic connective tissue or autoimmune diseases as absolute contraindications to the LASIK procedure.

Acknowledgements

T.P.O.B. is a nonsalaried ad-hoc consultant with Alcon, Allergan, Bausch & Lomb, INSPIRE, ISTA, Santen.

Conflicts of interest

B.B. has no conflicts of interest.

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 (pp. 000–000).

- 1 Duffey RJ, Leaming D. US trends in refractive surgery: 2004 ISRS/AAO Survey. *J Refract Surg* 2005; 21:742–748.
- 2 Albietz JM, McLennan SG, Lenton LM. Ocular surface management of photorefractive keratectomy and laser in situ keratomileusis. *J Refract Surg* 2003; 19:636–644.
- 3 Hori-Komai Y, Toda I, Asano-Kato N, Tsubota K. Reasons for not performing refractive surgery. *J Cataract Refract Surg* 2002; 28:795–797.
- 4 Refractive errors. In: American Academy of Ophthalmology Refractive Errors Panel. San Francisco: Ophthalmology AAO; 2002.
- 5 Alio JL, Artola A, Belda JL, *et al.* LASIK in patients with rheumatic diseases: a pilot study. *Ophthalmology* 2005; 112:1948–1954.
- 6 Moshirfar M, Siddharthan KS, Meyer JJ, *et al.* Risk for uveitis after laser in situ keratomileusis in patients positive for human leukocyte antigen-B27. *J Cataract Refract Surg* 2008; 34:1110–1113.
- 7 Cobo-Soriano R, Beltran J, Baviera J. LASIK outcomes in patients with underlying systemic contraindications: a preliminary study. *Ophthalmology* 2006; 113:1118.e1–1118.e8.
- 8 Rodriguez AE, Rodriguez-Prats JL, Hamdi IM, *et al.* Comparison of goblet cell density after femtosecond laser and mechanical microkeratome in LASIK. *Invest Ophthalmol Vis Sci* 2007; 48:2570–2575.
- 9 Albietz JM, Lenton LM, McLennan SG. Effect of laser in situ keratomileusis for hyperopia on tear film and ocular surface. *J Refract Surg* 2002; 18:113–123.
- 10 Long Q, Chu R, Zhou X, *et al.* Correlation between TGF-beta1 in tears and corneal haze following LASEK and epi-LASIK. *J Refract Surg* 2006; 22:708–712.
- 11 Vesaluoma M, Teppo AM, Gronhagen-Riska C, Tervo T. Increased release of tumour necrosis factor-alpha in human tear fluid after excimer laser induced corneal wound. *Br J Ophthalmol* 1997; 81:145–149.
- 12 Malecaze F, Simorre V, Chollet P, *et al.* Interleukin-6 in tear fluid after photorefractive keratectomy and its effects on keratocytes in culture. *Cornea* 1997; 16:580–587.
- 13 Vesaluoma M, Teppo AM, Gronhagen-Riska C, Tervo T. Release of TGF-beta 1 and VEGF in tears following photorefractive keratectomy. *Curr Eye Res* 1997; 16:19–25.
- 14 Vesaluoma M, Teppo AM, Gronhagen-Riska C, Tervo T. Platelet-derived growth factor-BB (PDGF-BB) in tear fluid: a potential modulator of corneal wound healing following photorefractive keratectomy. *Curr Eye Res* 1997; 16:825–831.
- 15 Tervo T, Vesaluoma M, Bennett GL, *et al.* Tear hepatocyte growth factor (HGF) availability increases markedly after excimer laser surface ablation. *Exp Eye Res* 1997; 64:501–504.
- 16 Lee JB, Ryu CH, Kim J, *et al.* Comparison of tear secretion and tear film instability after photorefractive keratectomy and laser in situ keratomileusis. *J Cataract Refract Surg* 2000; 26:1326–1331.
- 17 Gronert K. Lipid autacoids in inflammation and injury responses: a matter of privilege. *Mol Interv* 2008; 8:28–35.
- 18 Toda I. LASIK and dry eye. *Compr Ophthalmol Update* 2007; 8:79–85; discussion 87–79.
- 19 Toda I, Kato-Asano N, Hori-Komai Y, Tsubota K. Dry eye after LASIK enhancement by flap lifting. *J Refract Surg* 2006; 22:358–362.
- 20 Brewitt H, Sistani F. Dry eye disease: the scale of the problem. *Surv Ophthalmol* 2001; 45 (Suppl 2):S199–S202.
- 21 Shoja MR, Besharati MR. Dry eye after LASIK for myopia: incidence and risk factors. *Eur J Ophthalmol* 2007; 17:1–6.

- 22 Hovanesian JA, Shah SS, Maloney RK. Symptoms of dry eye and recurrent erosion syndrome after refractive surgery. *J Cataract Refract Surg* 2001; 27:577–584.
- 23 Albiatz JM, Lenton LM, McLennan SG. Dry eye after LASIK: comparison of outcomes for Asian and Caucasian eyes. *Clin Exp Optom* 2005; 88:89–96.
- 24 Lee BH, McLaren JW, Erie JC, *et al.* Reinnervation in the cornea after LASIK. *Invest Ophthalmol Vis Sci* 2002; 43:3660–3664.
- 25 Holland SP. Update in cornea and external disease: solving the mystery of 'sands of the Sahara' syndrome (diffuse lamellar keratitis). *Can J Ophthalmol* 1999; 34:193–194.
- 26 Boorstein SM, Henk HJ, Elnor VM. Atopy: a patient-specific risk factor for diffuse lamellar keratitis. *Ophthalmology* 2003; 110:131–137.
- 27 Myrowitz EH. Laser-assisted intrastromal keratomileusis in a patient with systemic mastocytosis. *Optometry* 2008; 79:95–97.
- 28 Lahners WJ, Hardten DR, Lindstrom RL. Peripheral keratitis following laser in situ keratomileusis. *J Refract Surg* 2003; 19:671–675.
- 29 Furukido K, Takeno S, Osada R, *et al.* Study of eosinophil activation in nasal mucosa in patients with perennial nasal allergy: effects of CO2 laser surgery. *Am J Rhinol* 2002; 16:1–6.
- 30 Smith JA, Albeitz J, Begley C, *et al.* The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf* 2007; 5:93–107.
- 31 Lemp MA, Baudouin C, Baum J, *et al.* The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf* 2007; 5:75–92.
- 32 Moss SE, Klein R, Klein BE. Long-term incidence of dry eye in an older population. *Optom Vis Sci* 2008; 85:668–674.
- 33 Yang HY, Fujishima H, Toda I, *et al.* Allergic conjunctivitis as a risk factor for regression and haze after photorefractive keratectomy. *Am J Ophthalmol* 1998; 125:54–58.
- 34 Asano-Kato N, Toda I, Hori-Komai Y, Tsubota K. Allergic conjunctivitis as a risk factor for laser in situ keratomileusis. *J Cataract Refract Surg* 2001; 27:1469–1472.
- 35 Sharwood PL, Rogers CM. LASIK flap interface deposition in limbal vernal keratoconjunctivitis. *Clin Exp Optom* 2008; 91:183–186.
- 36 Macaluso DC, Rich LF, MacRae S. Sterile interface keratitis after laser in situ keratomileusis: three episodes in one patient with concomitant contact dermatitis of the eyelids. *J Refract Surg* 1999; 15:679–682.
- 37 Leonardi A, Radice M, Fregona IA, *et al.* Histamine effects on conjunctival fibroblasts from patients with vernal conjunctivitis. *Exp Eye Res* 1999; 68:739–746.
- 38 Leonardi A, Di Stefano A, Motterle L, *et al.* Transforming growth factor-beta/Smad-signalling pathway and conjunctival remodelling in vernal keratoconjunctivitis. *Clin Exp Allergy* 2011; 41:52–60.
This article investigates the role of different signal proteins in VKC.
- 39 Frungieri MB, Albrecht M, Raemsch R, Mayerhofer A. The action of the mast cell product tryptase on cyclooxygenase-2 (COX2) and subsequent fibroblast proliferation involves activation of the extracellular signal-regulated kinase isoforms 1 and 2 (erk1/2). *Cell Signal* 2005; 17:525–533.
- 40 Amico C, Yakimov M, Catania MV, *et al.* Differential expression of cyclooxygenase-1 and cyclooxygenase-2 in the cornea during wound healing. *Tissue Cell* 2004; 36:1–12.
- 41 Miyamoto T, Saika S, Okada Y, *et al.* Expression of cyclooxygenase-2 in corneal cells after photorefractive keratectomy and laser in situ keratomileusis in rabbits. *J Cataract Refract Surg* 2004; 30:2612–2617.
- 42 Ohtomo K, Ebihara N, Matsuda A, *et al.* Role of TGF-beta in tissue eosinophilia associated with vernal keratoconjunctivitis. *Exp Eye Res* 2010; 91:748–754.
- 43 Chiu EK, Lin AY, Folberg R, Saidel M. Avellino dystrophy in a patient after laser-assisted in situ keratomileusis surgery manifesting as granular dystrophy. *Arch Ophthalmol* 2007; 125:703–705.
- 44 Pepose JS, Johnson EM Jr. Is there a role for neurotrophin treatment of the ocular surface following laser in situ keratomileusis (LASIK)? *Am J Ophthalmol* 2005; 139:1090–1094.
- 45 Kimata H. Ciliary neurotrophic factor preferentially enhances spontaneous IgE production by B cells from atopic patients. *Neuropeptides* 2004; 38:92–97.
- 46 Motterle L, Diebold Y, Enriquez de Salamanca A, *et al.* Altered expression of neurotransmitter receptors and neuromediators in vernal keratoconjunctivitis. *Arch Ophthalmol* 2006; 124:462–468.
- 47 Sambursky R, O'Brien TP. MMP-9 and the perioperative management of LASIK surgery. *Curr Opin Ophthalmol* 2011; 22:294–303.
Reviews MMP-9 utility in the diagnosis and follow-up in patients with post-LASIK dry eye.
- 48 Leonardi A, Brun P, Di Stefano A, *et al.* Matrix metalloproteases in vernal keratoconjunctivitis, nasal polyps and allergic asthma. *Clin Exp Allergy* 2007; 37:872–879.
- 49 Leonardi A, Sathe S, Bortolotti M, *et al.* Cytokines, matrix metalloproteases, angiogenic and growth factors in tears of normal subjects and vernal keratoconjunctivitis patients. *Allergy* 2009; 64:710–717.
- 50 Bielory L, Bonini S, Lambiasse A, Leonardi A. American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology – Joint Task Force, Allergic Conjunctivitis Practice Parameter 2011 (<http://www.allergyparameters.org/>).
- 51 Bielory B, O'Brien T, Bielory L. Management of seasonal allergic conjunctivitis: guide to therapy. *Acta Ophthalmol Scand* (in press).
- 52 Orosz ZZ, Katona E, Facsco A, *et al.* A highly sensitive chemiluminescence immunoassay for the measurement of coagulation factor XIII subunits and their complex in tears. *J Immunol Methods* 2010; 353:87–92.
This article illuminates factor XIII found in tears.
- 53 Scalinci SZ, Scorolli L, Meduri A, *et al.* Effect of basic fibroblast growth factor and cytochrome c peroxidase combination in transgenic mice corneal epithelial healing process after excimer laser photoablation. *Clin Ophthalmol* 2011; 5:215–221.