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MAJOR REVIEW

Corneal Inflammation Following Corneal Photoablative Refractive Surgery With Excimer Laser

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Abstract. Millions of surface ablation excimer laser surgeries are performed worldwide. The normal cornea, when photoablated, reacts in a way specific to this process. The fundamentals of this biological reactivity are based on the normal structure of the photoablated cornea and on the energy delivered by the laser. This leads to a new type of inflammation and wound healing. We systematically review the literature relating inflammation to photoablative procedures and its wound healing consequences and offer guidelines on treatment corneal inflammation following corneal photoablative surgery. (**Surv Ophthalmol 58**:11–25, 2013. © 2013 Elsevier Inc. All rights reserved.)

Key words. corneal inflammation • excimer laser • LASIK • PRK • refractive surgery

I. Relevance of Corneal Inflammation Following Photoablative Procedures

Modifying corneal curvature by using excimer laser implies tissue injury and consequently a wound-healing response. This phenomenon affects the refractive outcome and can be responsible for visual impairment. Understanding inflammatory and healing reactions after photoablations is essential for the safety and accuracy of the procedures.

After destroying keratocytes and the extracellular matrix, photorefractive procedures activate stromal corneal fibroblasts to produce cytokines and chemokines that may modulate wound healing.[54] Several chemokines are involved in the recruitment and activation of inflammatory cells in the corneal wound-healing process.[118,119] Stimulated keratocytes can produce chemokines that potentially initiate severe corneal inflammation, leading to corneal haze and other adverse sequelae.[27,64,104]

Although the inflammatory and healing response is lower after laser assisted in situ keratomileusis (LASIK) than after photorefractive keratectomy (PRK), all refractive surgery procedures activate of corneal cells and the release of cytokines that modulate the corneal inflammatory and healing processes. Pain, delayed visual recovery, and corneal haze are the most frequent complications; the cellular, molecular, and neural regulatory phenomena associated with postoperative inflammation and wound healing are likely to be involved in flap melting, epithelial ingrowth, and regression. For these reasons, corticosteroid or non-steroidal anti-inflammatory agents are always used to minimize inflammation in the postoperative period.[54]

II. Corneal Inflammation and Corneal Healing in LASIK and PRK

Keratocyte activation induced by LASIK has a short duration compared with that reported after PRK. Regardless of the method of flap formation, all corneas show early morphological changes in keratocytes located below the flap.[94]

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LASIK and laser-assisted subepithelial keratectomy seem to be less traumatic than PRK because less tear transforming growth factor (TGF-b) is released and expressed in the early postoperative days, indicating that these techniques stimulate corneal cell activation differently.[41,53,62]

Leonardi, et al studied the changes in the levels of chemokines in tears after LASIK.[54] Their results can be summarized as follows.

- In tears before surgery (i.e., normal):
  - Interleukin (IL)-8 was the only cytokine consistently present in all patients, and the levels of Th1-type and Th2-type cytokines were low or below detection limits.
- After surgeries:
  - Tear IL-12, although at low levels, increased 1 hour postoperatively, probably as a result of corneal dendritic cell stimulation.
  - Eotaxin (a chemokine involved in the recruitment of eosinophils, monocytes, and mast cells) was increased in tears 24 hours postoperatively. Eotaxin has been shown to be produced by keratocytes and conjunctival fibroblasts, but not by corneal and epithelial cells. In the in vitro model, eotaxin was detectable at baseline and 24 hours after treatment, when corneal fibroblasts were growing during the healing process.
  - Monocyte chemoattractant protein (MCP)-1 and IL-8 were significantly increased 24 hours after laser treatment, confirming that stimulated corneal fibroblasts produce these factors after injury. IL-8, produced by keratocytes and neutrophils, was shown to contribute to the development of diffuse lamellar keratitis in an animal model. Overexpression of these chemokines may be responsible for noninfectious LASIK complications.
  - The symptom score after surgery was correlated only with IL-6 tear levels, indicating that this cytokine is directly involved in the development of postsurgical inflammation and in the wound-healing process.

The inflammatory response associated with the corneal healing process after excimer laser PRK is characterized predominantly by macrophage infiltration.[79] Macrophages play a central role in the innate immune response by engulfing, processing, and destroying foreign invaders. Macrophages also play a crucial role in cell-mediated immune responses as antigen presenting cells that initiate specific immune responses; as a source of various cytokines and growth factors; or as effector inflammatory cells to perform inflammatory, tumoricidal, or microbicidal activity. In addition, macrophages can secrete elastase and collagenase and ingest dead tissue or degenerated cells.[78,113] Therefore, it is not surprising that macrophages are present in the cornea following excimer laser PRK.

During the laser procedure, there are no foreign antigens or infectious factors. Thus, the macrophage may be recruited to the ablation site as an effector cell to engulf cellular debris and assist reorganization of the laser sculpted cornea.

Langerhans cells remained relatively stable after excimer laser PRK. This is consistent with the lack of antigen presenting activity in the excimer laser–related corneal recovery process. Furthermore, the mechanism by which corticosteroids substantially reduced haze intensity could be related to their effect on macrophages.[79]

III. Anatomical and Optical Consequences of Corneal Inflammation Following LASIK and PRK: Clinical Aspects, Confocal Microscopy Findings, and Wound-healing Reaction

The process of wound repair and the impact of healing response seen after PRK differs from that observed after LASIK.

A. PHOTOREFRACTIVE KERATECTOMY

During PRK the corneal epithelium is physically or chemically debrided. After that, Bowman's layer and part of the anterior stroma is ablated by excimer laser. A few hours later, re-epithelization begins from the periphery, and the process is completed in 3–4 days.[12,47] One week after surgery the first sprouts of subepithelial plexus and the stromal trunks appear, although some authors report these changes begin 1 or 2 months postoperatively.[12,43]

Re-innervation starts from the periphery in the form of thin branches so that that the subepithelial plexus is reformed 6–8 months later, but always containing morphological abnormalities (Fig. 1). The neural regeneration is relatively fast because of inflammation and the direct interaction of the ablated fibres with the neurotrophic factors produced by the regenerating epithelium. Hypoesthesia during the 3 first months is a consequence of the initial loss of nerve fibers, although some investigators find almost normal sensitivity 1 month after PRK.[99]

The stromal repair is responsible for the transparency and refractive outcome. An acellular layer is appreciable between 25 and 100 microns of depth immediately after PRK caused by apoptosis of the anterior keratocytes.[115]

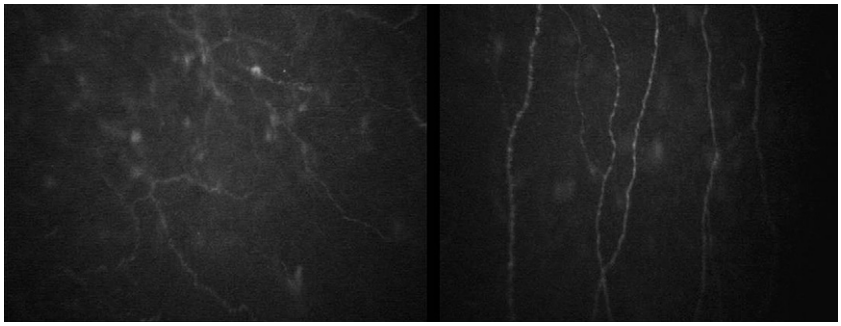

Fig. 1. Confocal microphotographs of a normal subepithelial plexus (*right*) and morphological abnormalities in the nerves after ablation (*left*).

Different cytokines and matrix metalloproteinases related to inflammation and wound repair play an important role in the changes in the keratocyte population and in the production of extracellular matrix (ECM). Some of these cytokines seem to proceed from the tear.[107–110] This cellular disappearance is followed by a progressive repopulation from the subjacent activated keratocytes that migrate into the ablated stroma during the first weeks after surgery. These cells transform into myofibroblasts and are associated with an increase in ECM, being responsible for new collagen creation. It is assumed that the surgically induced apoptosis and the keratocyte repopulation, activation, and transformation regulate both normal wound healing and the formation of haze.[59,70]

Usually the healing response is more evident in the first 30–50 microns between 1 and 3 months after procedures, with the deeper area of the corneal stroma remaining unaltered. Even in cases with complete transparency of the cornea, some morphological alterations can be seen over 30 months after PRK. The intensity of these phenomena is lower after the sixth month, however.[12,59] An inadequate healing response with large amounts of activated keratocytes and an exaggerated production of ECM produces haze, which is described as a subepithelial opacity with variable degrees of intensity that alters visual function by decreasing contrast sensitivity and visual acuity.

The presence of activated keratocytes and the synthesis of types III and IV of new collagen that is anatomically structured in an abnormal way are clearly documented (Fig. 2). Before the use of mitomycin C (MMC), some haze was frequent, but only patients suffering pathological healing developed clinically relevant haze.[9] The intensity of haze is greater during the first 6 months after PRK, tending to decrease in the following 12–24 months.[12] Its development can be modified by using postoperative steroids, and its can be prevented with intraoperative topical application of MMC.[12,89] Adequate control of the postoperative inflammatory response is essential for preventing its formation.

The corneal surface is normally fully covered by a thin layer of epithelium by 3–4 days after surgery. Many authors have pointed out the impact of the relationship between the epithelium and the surface of the ablated stroma.[12,70] When the re-epithelization is delayed, subepithelial haze is greater.[47] The impact of the interaction of the wound healing–epithelium has been demonstrated after the observation that laser-assisted subepithelial keratectomy (LASEK)-treated eyes showed less keratocyte apoptosis, myofibroblast transformation, and upregulation in the synthesis of chondroitin sulphate than PRK-treated eyes.[10]

Haze has been studied using confocal microscope (CM) and confocal microscopy through focusing (CMTF) analysis:

- Depth: In most cases the haze is located between 60 and 150 microns from the ocular surface. CMTF allows measurement of the thickness of this opaque layer, such maneuver

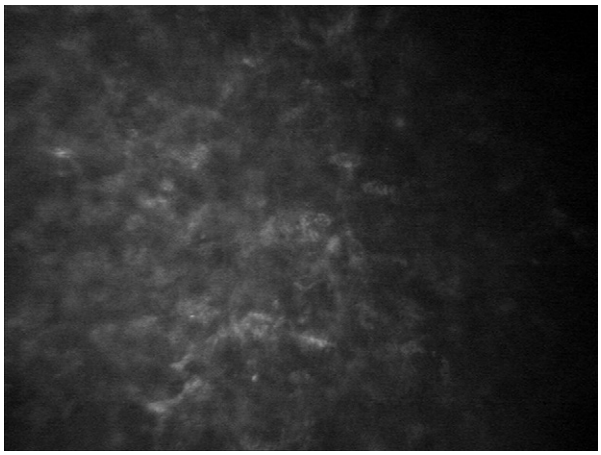

Fig. 2. Activated anterior keratocytes and abnormal extracellular matrix in a patient with subclinical haze after photorefractive keratectomy.

being essential before performing phototherapeutic keratectomy.

- Optical density: In 1997, Möller-Pedersen, et al first used CM for measuring the density of haze. The degree of opacity is estimated by calculating the peak of luminous reflectivity (Wound Healing Opacity –World Health Organization-index) that can observed be after the CMTF analysis.[30,36,37,43,70]

B. LASIK

Although the wound-healing process is similar for surface ablations and for LASIK, the differences in the surgical techniques clearly determine the inflammatory response and the intensity, location, and wound repair. Significant inflammatory cell infiltration is noted in both PRK and LASIK, but appears to be greater in PRK.[118]

Some other differences include the absence of the interaction between stroma and regenerating epithelium and the absence of cytokines and biological active substances present in the fluid tear. As the subepithelial nerve plexus is not ablated, less pain and neurogenic inflammation, but a more delayed recovery of corneal sensitivity, occurs with LASIK.

On the other hand, in LASIK a deeper ablation level (which respects the most anterior keratocytes) produces less intense keratocyte activation and clinically detectable haze. Finally, the presence of a new virtual space—the surgical interface—allows the collection of liquid or particles, the spread of inflammatory cells, or the inoculation and proliferation of microorganisms during the postoperative period.

In the same way as in the surface ablations, confocal microscopy is a useful tool for helping to understand the tissue phenomena that occurs after LASIK. CMTF analysis records precise corneal and flap thickness. The depth of ablation and flap thickness have been related to different degrees of luminous reflectivity in the CMTF profiles. Thinner flaps mean that photoablations are performed on more superficial keratocytes. As the capability of these cells to be activated and transformed into myofibroblasts is greater, a larger peak of reflectivity can be appreciated after performing thin flaps even when haze is not detectable clinically.[30,36,37,99] Using CM it is possible to evaluate the surgical interface, the stromal bed, the nervous regeneration, the corneal and flap thickness and, finally, the luminous reflectivity, which is an indirect way to evaluate corneal transparency (Fig. 3).

1. Flap and Stromal Thickness

The remaining stromal bed and the flap thickness are important parameters to be taken into account

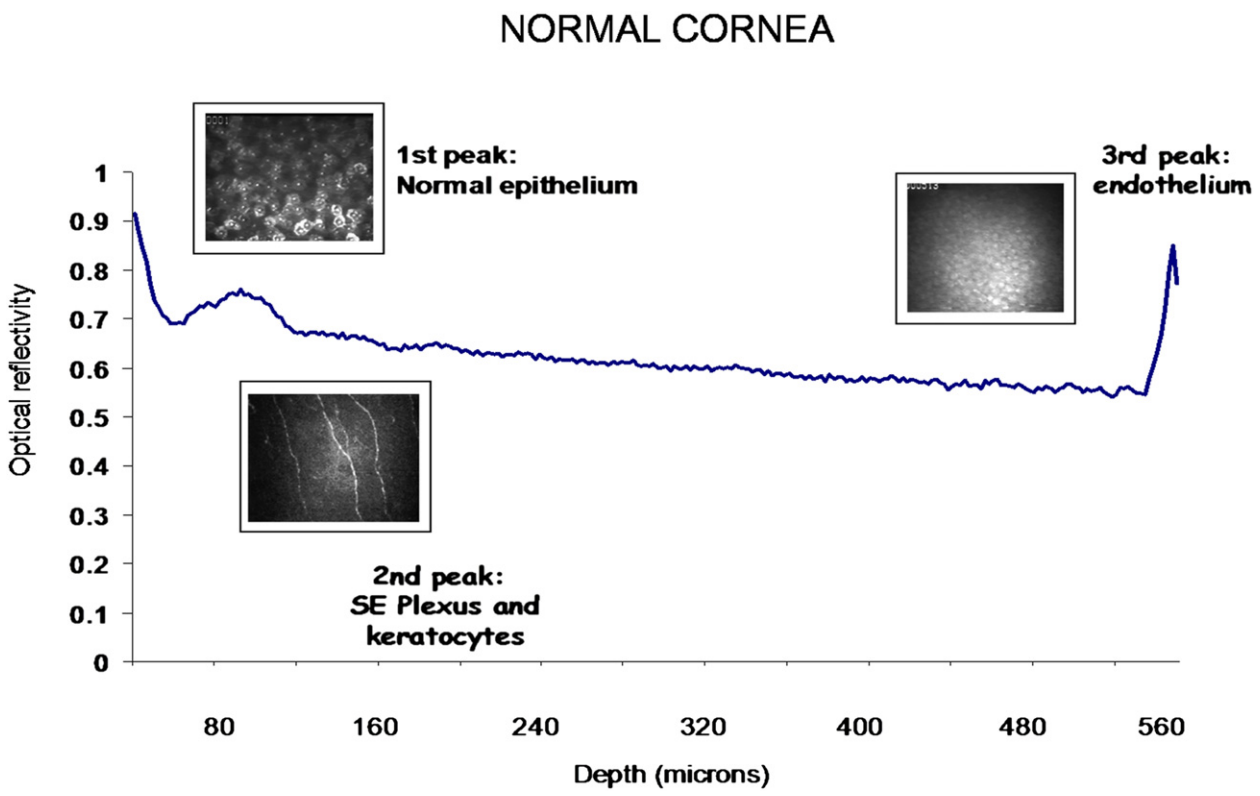

Fig. 3. Confocal microscopy through focusing (CMTF) graph in a normal cornea. The confocal microscope software creates a bidimensional graph. The horizontal axis represents the corneal thickness in microns and the vertical axis shows the optical reflectivity.

when planning retreatment with LASIK. The possibility of intraoperative error when lifting an ultrathin flap or the need to leave between 250 and 300 microns of corneal stroma make an accurate estimation of the thickness of these structures obligatory. The accuracy of CMTF analysis for performing precise pachymetries of the natural or artificial sublayers of the operated corneas has been studied. It has been suggested that the flap thickness influences the corneal transparency. Is well known that the keratocyte population present in the most anterior part of the stroma is more able to suffer activation, apoptosis, and transformation into myofibroblasts, and to produce ECM and haze (Figs. 4 and 5).[36–38,56] The profile of optical reflectivity obtained by using this technique significantly differs from that observed in a cornea operated on with a surface ablation technique (Fig. 6).

Significant amounts of cytokines and inflammatory mediators in the most anterior part of the stroma have been reported[115]; as there is not an increase in reflectivity in all LASIK eyes with thin flaps, however, this implies that an individual susceptibility explains the different healing responses.[36]

2. Analysis of the Stromal Changes

A significant decrease in the density of the anterior keratocytes is clearly seen early after LASIK. The cellular disappearance is greater in the most superficial areas (in the posterior flap and anterior retroablation layer, the regions adjacent to the lamellar cut) and has been related to apoptosis, the loss of communication between the keratocytes, the presence of inflammatory cells, and denervation.

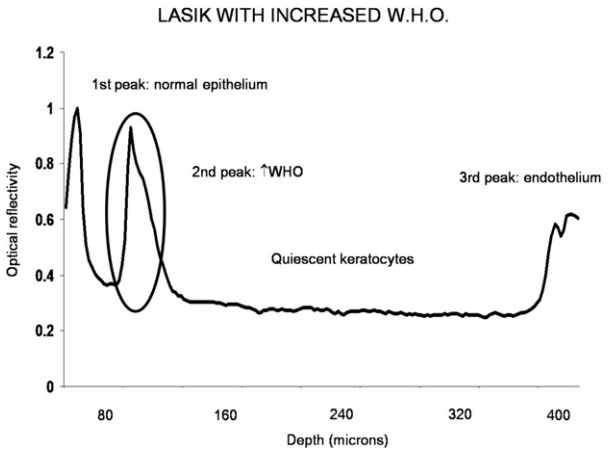

Fig. 4. Confocal microscopy through focusing (CMTF) graph in a cornea operated with LASIK and suffering a subclinical degree of haze. The peak which is inside the ellipse represents the increased optical reflectivity generated by the mild opacity which is produced by the activation of anterior keratocytes and abnormal extracellular matrix.

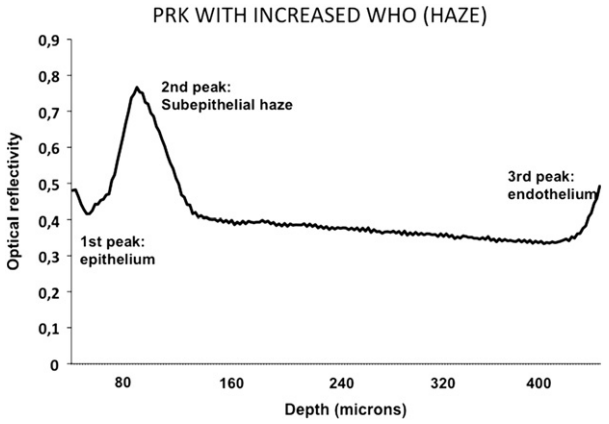

Fig. 5. Confocal microscopy through focusing (CMTF) graph after photorefractive keratectomy. It was possible to appreciate mild haze (1–2) at the slit-lamp. The amount of luminous reflectivity must be considered regarding that corresponding to epithelium and endothelium. respectively.

Keratocytes that die in the anterior stroma following the lamellar cut are replenished in 2–4 days by proliferation and migration. The replenishing cells are activated myofibroblastic keratocytes that produce collagen, hyaluronic acid, growth factors modulating epithelial healing, and other components of the wound-healing response.[20,28,83,114,117]

On the other hand, some studies have found that the cellular density remains altered for over 12 months after LASIK and even decreases with time. The impact of these observations on the biomechanical stability of the corneas in the long term is not yet clarified.[69]

A study from our team found that the opacity index related to the wound-healing process after photoablative surgery was greater in eyes operated by surface ablations (LASEK) and in LASIK with flaps thinner than 100 microns. This increase is subclinical

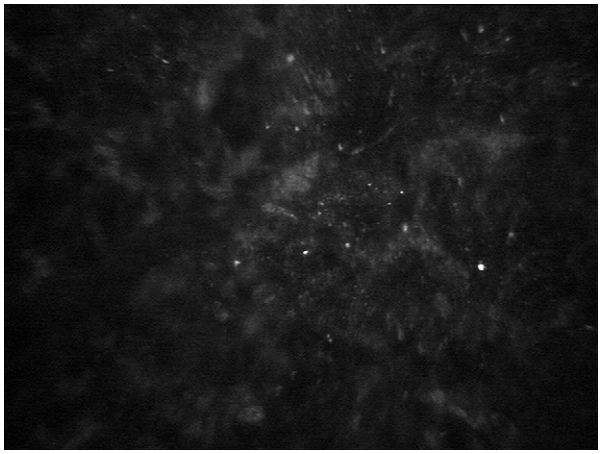

Fig. 6. Confocal microscopy of the LASIK interface. Particles are visible as small hyper reflective (*white*) dots.

because it is hardly visible biomicroscopically, but we have also demonstrated an impact on contrast sensitivity.[30] Even considering their limited impact on the visual outcome after LASIK, these findings have the same pathophysiolgy as haze after PRK, namely, the exaggerated activation of anterior keratocytes.

3. Nerve Regeneration

Although the first regenerating sprouts can be appreciated in the wound at the first week after LASIK, the nerve density low until 6–8 months after the surgeries, and the pattern is, even at that time, abnormal. Nerve regeneration and recovery of the corneal sensitivity is slower after LASIK than after surface ablations.[36,42,60]

4. The Interface

The morphological specific changes that can be observed with CM occur between 15 and 50 microns of depth. Apart from the previously mentioned changes in keratocyte density, it is possible to see inflammatory cells and necrotic spindle-shaped debris if diffuse lamellar keratitis occurs, microfolds in the Bowman's layer in 96% of cases, and hyperreflective particles in all (Fig. 5).[36,60,106] The nature of these particles varies: they can be metallic, plastic, or organic, but they do not have an impact on visual function and do not cause an inflammatory responses under normal conditions.[29,60,83,99,106]

IV. Pharmacological Management of Inflammation Following Surface Ablation Procedures

In the usual management of postoperative inflammation, high-dose topical steroids are used during the first week. Some authors recommend carrying on with non- absorbable corticosterioids such as fluormetholone to modulate the inflammatory response, and therefore the wound-healing process, for longer periods, in particular after surface ablations.

When combining topical steroids and nonsteroidal anti-inflammatory drugs (NSAIDs), there is an increased risk of suffering corneal melting and even ocular perforation.[66] As NSAIDs alone are not enough for controlling postoperative inflammation after PRK, their use appears inefficient and potentially hazardous. Other substances are currently being tested in the laboratory to control postoperative inflammation.[11]

The outcome and stability of PRK can be improved by controlling keratocyte apoptosis. This can be achieved by inhibiting the transmission of the apoptosis signal from the damaged corneal epithelium to the keratocytes, thus attenuating cell activation. Omega-6 essential fatty acids have been used to control the release of the mediators of the inflammation and to stimulate tear production.[84]

A. EFFECT OF MMC

The appearance of haze has been one of the complications that have limited the use of PRK or photoablative surface ablations for deep ablations to correct higher refractive errors. The greater incidence of haze after PRK when compared to LASIK can be explained in part because PRK acts more on superficial stroma where the density and the capability of the keratocytes to be activated is much greater. As noted earlier, these cells transform into myofibroblasts and can produce ECM and haze.[115]

The topical intraoperative application of MMC has been used as cytostatic agent and to avoid excessive scarring in surgical procedures such as the treatment of conjunctiva-cornea intraepithelial neoplasia or for the prophylaxis from bleb failure in glaucoma surgery. Complications have been controlled by a better knowledge of appropriate dosage. MMC is an alkylating agent with cytotoxic and antiproliferative effects that reduces the myofibroblast repopulation after laser surface ablation and, therefore, reduces the risk of postoperative corneal haze.[100]

Topical intraoperative MMC has been successfully used during surface photoablative procedures to reduce the incidence and intensity of haze.[89,92,120] MMC has proved to be efficient in preventing haze even in PRK to correct residual errors after penetrating keratoplasties[14,52] or in radial keratotomy.[15,46] MMC has been used prophylactically not only to avoid haze after primary surface ablation, but also therapeutically to treat pre-existing haze.[100]

No relevant ocular or systemic adverse effects have been reported. A delay in epithelial healing has been observed in 3.5% of the treated corneas, but such incidence does not increase the risk of postoperative haze.[48] MMC has also been used in certain special circumstances during LASIK surgery.[49,50,105]

The prophylactic effect seems to be the result of a reduction in the activation of keratocytes and their transformation into myofibroblasts,[45] but it seems that in the long term the use of 0.02% topical MMC has no significant side effects on corneal keratocyte density and morphology compared to standard PRK, as documented by in vivo corneal confocal microscopy.[67]

Some dosage-dependent endothelial damage has been demonstrated experimentally after the application of different concentrations of MMC over mechanically denudated corneal stroma. It has been pointed out as well that MMC is detectable in the

aqueous humor of the hen eye after topical application in PRK-treated eyes and in eyes with intact epithelium.[103]

Some clinical studies have demonstrated that a significant reduction in the endothelial cell density (ECD) can be found after using 0.02% MMC during PRK, proportional to the time of exposure.[71,77] In fact, if the drug application is no longer than 15 seconds, such toxic ECD reduction is not appreciated.[8] It seems that for moderate myopia and shallow depth, low-dose MMC (0.002%) appears to be as effective as the classic concentration of 0.02%.[102]

Furthermore, a case of clinically relevant haze after retreatment with photorefractive keratectomy with MMC following LASIK has been recently published.[61] The authors suggest applications of over 15 seconds in such cases. Even taking into account these issues, the use of 0.02% MMC during surface ablations is routine in most refractive surgery units because of its ability to prevent haze formation.

V. Specific Clinical Entities

A. DIFFUSE LAMELLAR KERATITIS

1. Clinical Appearance, Classification, and Prevalence

Diffuse lamellar keratitis (DLK) is a multietiologic syndrome characterized by an inflammatory reaction confined to the interface of eyes operated on by LASIK surgery that appears during the first week after surgery.[40,57,58,91] In 1998, Smith and Maloney published 13 cases in 12 patients who presented with diffuse multifocal infiltrates between the second and sixth day after LASIK that were limited to the interface without anterior or posterior extension and accompanied by pain, photophobia, red eye, and tearing. All disappeared without sequela after being treated with antibiotics or fluormetholone.[91]

Several terms have been used for this entity: *Sahara sands syndrome* because of the granulated and undulated pattern, *PostLASIK interface keratitis, nonspecific and diffuse interstitial keratitis*, and *diffuse intralamellar keratitis*; the term DLK, however, is the most frequently used.[57,58]

Since the first cases of this condition were described, it has been recognized that the syndrome can occur either in isolated cases or in epidemic outbreaks.[57] Cluster DLK has been defined as a concentration of diffuse lamellar keratitis in one session or operating room. Johnson, et al proposed considering a single case described in a surgical session as sporadic and more than one case as a cluster.[40,98] The incidence of sporadic DLK ranges between 0.58% and 3.54%, but may reach 50% in clusters.[1,4,5,16,19,21,22,24,34,39,44,51,68,74,76,81,86–88,90,101,112,116,121]

We review this topic considering the physiopathology of and prophylactic measures for DLK and share our experience in managing this entity.

a. Classification

Linebarger, et al in 1999 proposed a classification taking into account the severity and location of the lamellar interface inflammation:[58]

- Stage 1: Presence of white granular infiltrates at the periphery of the flap outside the visual axis. The incidence is 1/25–1/50 cases.
- Stage 2: Visual axis is affected. The incidence is 1/200 cases.
- Stage 3: The pattern of white cell infiltration appears condensed in the visual axis, and this is often associated to a decrease in the visual acuity of less than two Snellen lines. The incidence is 1/500 cases (Fig. 7).
- Stage 4: Severe lamellar keratitis with stromal melting due to the enzymatic digestion caused by the collagenases produced by white cells. This results in stromal volume loss and hyperopic shift. The incidence is approximately 1/5,000 cases (Fig. 8).

In 2000, Johnson, et al proposed another classification based on the extent of centripetal migration of inflammatory cells and whether the occurrence is sporadic or in a cluster.[40]

- Type I was designated as scarce affectation of the center and was subdivided into IA (sporadic) and IB (cluster). An association between epithelial defects and DLK seems to exist especially in type IA.
- Type II involves the visual axis and is subdivided into IIA (sporadic) and IIB (cluster). The occurrence of clusters is an important factor when managing DLK. Type IIB is associated

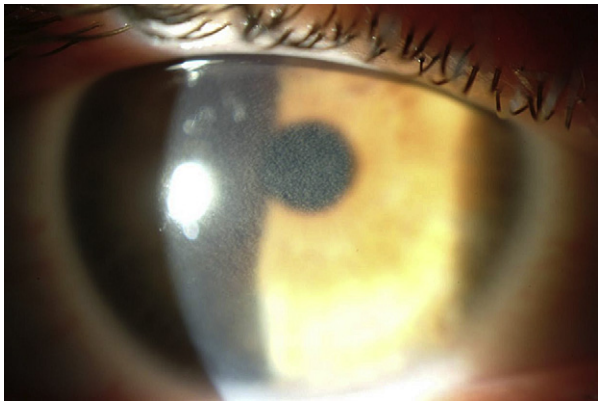

Fig. 7. Aspect of a diffuse lamellar keratitis stage 3 at the slit-lamp examination.

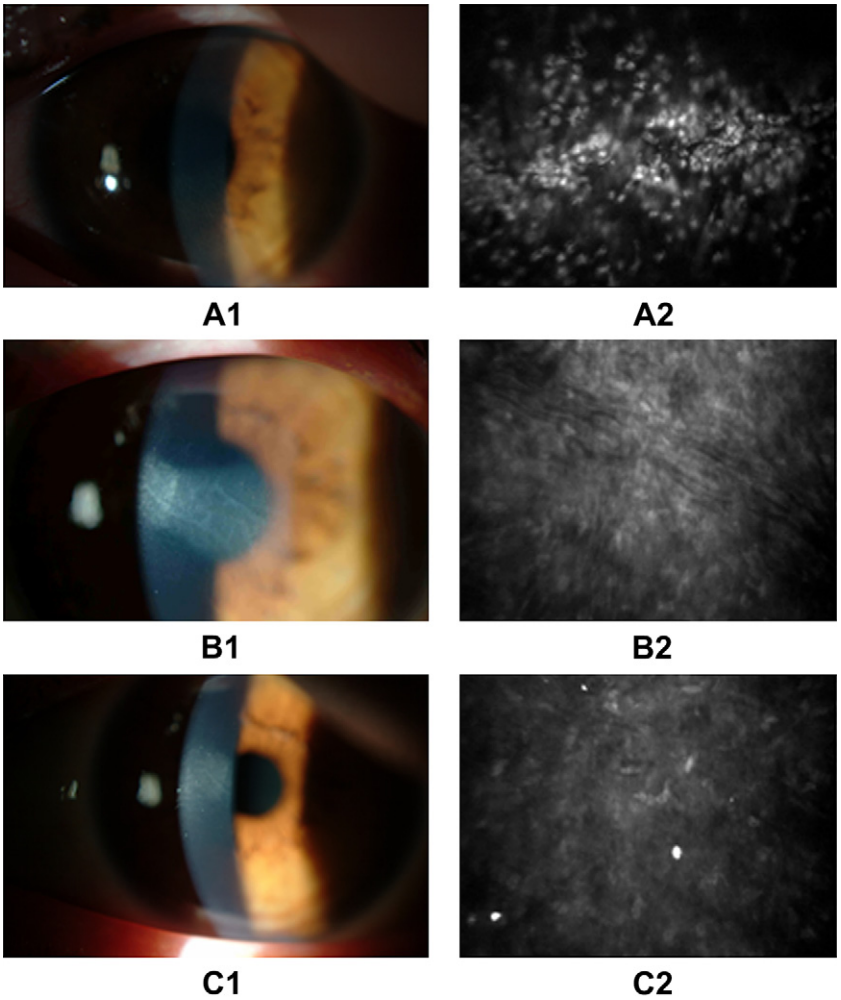

Fig. 8. Full slit-lamp and confocal microscopy evolution in a diffuse lamellar keratitis stage 4 case belonging to our series. Left side column of pictures (*A1*, *B1*, and *C1*) show the biomicroscopic aspect at 24 hours, first month, and third month, respectively. Right images (*A2*, *B2*, and *C2*) correspond to confocal microscopy exams done the same day as the photographs were taken.

with a greater risk of visual loss and is strongly related to endotoxins.[40]

Bühren and coauthors proposed a 4 stage classification based on confocal microscopy in relation to the findings under the slit lamp. With this technology we can study the resulting inflammatory activity (Table 1). Figure 8 shows a full slit-lamp and confocal microscopy evolution in a DLK stage 4 case belonging to our series.

2. Etiopathogeny

A great variety of causes has been proposed for DLK, but the prognosis differs between clusters and sporadic cases. Scars involving central cornea with irregular astigmatism, hyperopic shift, and loss of best-corrected visual acuity are more frequent in clusters.[40] Clusters have been attributed to sterilization problems, the cleaning of instruments, or environmental issues such as ventilation air circuits in the operating room or toxic substances touching the eye during surgeries.[5,21–24,35,40,51,76,90,91,111,121] Epithelial defects, bleeding, trauma, and surface or intraocular inflammation have been described as potential causes of sporadic, early, or even late-onset DLK after LASIK.[2,19,39,40,44,57,68,74,81,85,88,101,116]

a. Lipopolyscharide endotoxin of Gram-negative bacteria

Holland, et al[23] proposed that lipopolysaccharide endotoxin is most likely to provoke epidemics of DLK, and this has been clinically and experimentally tested in many studies.[7,22–24,55,82,98,101,111] Gram-negative bacteria and endotoxins are frequently present in water supplies, and although the bacteria are killed during heat sterilization, the endotoxins remain and can therefore be transferred by LASIK instruments into the flap interface.[82] In the majority of short-cycle autoclaves, the water reservoir cannot be removed for

TABLE 1

The Four Stages of Diffuse Lamellar Keratitis

DLK Stage	Biomicroscopic Findings	Confocal Microscopy
1	Diffuse peripheral infiltration without central involvement	Granulocytes and monocytes in the anterior stroma of the flap and interface
2	Diffuse infiltration with central involvement	Granulocytes and monocytes in the anterior stroma of the flap and interface with involvement of the central area, spindle-shaped reflective bodies
3	Clusters of white cells involving the central area of the cornea	Infiltrates spread over the anterior stroma of the flap with accumulation of inflammatory debris and spindle-shaped reflective bodies
4	Folds, corneal opacity	Absence of inflammatory cells, stromal folds, and keratocyte activation; highly reflective images

The four stages are as described in Bühren et al.[4a]
DLK = diffuse lamellar keratitis.

cleaning. A new model machine (Statim 7000; SciCan Inc, Canonsburg, PA, USA) allows the extraction of the water reservoir.

b. Other agents

Metallic particles were initially thought to produce DLK, but later studies did not find an inflammatory reaction around these particles when inserted at the interface of operated rabbits. Bissen-Miyajima et al think plastic particles may be a cause.[3] Other suggestions are the presence on the instruments of trace amounts of detergents such as Palmolive ultra 100%, Klenzyme 100%, or sterilizing substances as glutharaldehide, or lubricant oils on the microkeratome blade.[26,40,57,121]

c. Associated conditions

DLK is more likely to occur in atopic patients, even those on antihistamines.[4] Meibomium gland secretions and exotoxins of *S. aureus* present in patients with chronic blepharitis have been linked to DLK, because of the ability of these toxins to promote lymphocyte T activation and an inflammatory response. For this reason careful cleaning of the lid margins is recommended before surgery.[13,25]

d. Epithelial defects

A strong association between DLK and intraoperatory epithelial defect has been reported, with an increase in the risk of DLK between 13 and 24 times compared to eyes with undamaged epithelium.[40,85,88]

e. Others

We first described the association between DLK and higher levels of energy when using femtosecond laser for creating flaps during LASIK.[33,35] This condition is now rare as the result of low energy use in the 30 and 60 Khz femtolasers currently marketed. In a large series of DLK outbreaks, we found that several factors can act simultaneously to generate an epidemic and that a dramatic reduction in the incidence can be achieved after applying a progressive strategy acting at all levels of the surgical procedure, even when the exact cause of the outbreak could not be determined.[32]

3. Differential Diagnosis

The following entities can be involved in the differential diagnosis:[2]

a. Epithelial ingrowth

Epithelial cells appear at the interface without inflammatory signs in the form of a few scattered fine translucent cells. The cells are more transparent and fewer than would be present than in diffuse lamellar keratitis. In addition, a smaller area is affected.

b. Microbial keratitis

Acute microbial keratitis presents with decreased visual acuity, pain, and, injection. Microbial keratitis does not respect the boundaries of the flap interface. A single or dominant focus may extend anteriorly into the flap and posteriorly into the stroma. Conjunctival/ciliary injection, epithelial defects over the infiltrate, and inflammatory cells in the anterior chamber are also present. DLK can be distinguished from microbial infiltrates by clinical presentation and course.

c. Nonmicrobial interface opacities

Nonmicrobial interface opacities are common in the first postoperative weeks and are related to tear film debris or foreign particles from the microkeratome, blade, sponge, or air. Interface debris can also be caused by powder on the gloves, Meibomian secretions, or blood from cut pannus. It is normally not difficult to recognize these interface opacities. The foreign bodies are usually well tolerated, although they may sometimes be a nidus for infection or inflammation. If

inflammation is present, flap repositioning and foreign body removal may be considered.

4. Treatment

Linerbarger recommended intensive topical steroids (methyl-prednisolone acetate 1% hourly during the day and dexamethasone ointment at bedtime) for stages 1 and 2. The patients should be seen 48 hours later for evaluation and to begin tapering.

For stage 3, early flap lifting and careful irrigation of the interface remove white cells and avoids stromal melting. Cultures can be taken if microbial keratitis is considered. After flap lifting, the same routine of topical steroids must be applied.[58,111] Hoffman added systemic corticosteroids (oral prednisone 40–80 mg each day) for the initial management of stage 3.[21]

Although initially a similar protocol was described for stage 4, it was soon seen that flap lifting increased the possibility of stromal volume loss, and as a result, worsened the visual prognosis by hyperopic shift and irregular astigmatism. In the same way, if central toxic keratopathy (see subsequent discussion) is suspected, the application of high doses of topical steroids may be contraindicated given its non inflammatory nature.[72,73,95] Some authors therefore recommend waiting until the eye heals itself and the hyperopic shift resolves rather than subject the patient to any invasive procedures.[58,73,95]

It has been reported that the prophylactic use of hourly postoperative prednisolone acetate and dexamethasone sodium during an epidemic resulted in a significant decrease in the rate of DLK.[6] A preventive effect has not been demonstrated with hourly fluorometholone on a patient's fellow eye if the first eye developed sporadic DLK.[65]

B. CENTRAL TOXIC KERATOPATHY: CLINICAL APPEARANCE, PATHOPHYSIOLOLOGY, AND TREATMENT

There is some discussion about whether DLK stage 4 is an independent entity that should be called central toxic keratopathy (CTK) as the pathogenesis of the tissue damage may be different from DLK,[18,95] or whether it could be considered as a spectrum of disorders forming part of a single syndrome.[80]

It has been proposed that CTK differs from DLK stage 4 in the absence of inflammation and in an affectation of flap stroma without interface infiltration. Affected eyes present central stromal opacification within 1 week of laser refractive surgery, resulting in stromal thinning and a hyperopic shift in most eyes. The opacity clears without treatment, and the remaining refractive error can be corrected with later enhancement surgery without recurrence of the opacity. CTK can also occur after PRK.

C. TRANSIENT LIGHT SENSITIVITY SYNDROME

1. Clinical Features and Prevalence

The description *transient light sensitivity syndrome* (TLSS) has been coined to describe a clinical condition characterized by unusual photosensitivity with normal visual acuity several weeks after an otherwise uneventful LASIK with the femtosecond laser that typically responds to topical treatment with steroids or cyclosporine. Other proposed designations includes *delayed acute photophobia*, *track-related iridocyclitis and scleritis syndrome*, and *good acuity plus photophobia*. In TLSS slit-lamp examination is unremarkable, with normal tear film, no hyperemia, flare, or inflammation inside the interface. The prevalence of TLSS has been reported to range between 0.2% and 2.8%.[75,97] The combined use of the lowest possible energy surgical settings together with an intensive postoperative regimen of topical steroids for the first few days after femtosecond laser flap creation have decreased the incidence of TLSS.

2. Physiopathology

The etiology of TLSS is unknown, but there are clues that point towards an inflammatory origin. The mechanisms that have been proposed include inflammation caused by necrotic cellular debris or subproducts of the gas bubbles, cykotines migrating from the flap interface to the perilimbal sclera and iris base, or activated keratocytes in the interface.[17,97] In fact, the femtosecond laser has been associated with a higher postoperative inflammatory reaction and fibrosis adjacent to the flap margin compared to microkeratomes.[93] In a recent study of TLSS, Stonecipher, et al observed a five-fold reduction of the incidence (from 1% to 0.2%) after lowering in laser energy settings by 20%.[97]

In 2006 we published the results of a prospective study conducted over 756 eyes operated by using femtosecond laser. We observed that the incidence of DLK in the postoperative period was significantly related to TLSS development. DLK was 10 times more frequent in eyes that later developed TLSS. This again suggests that increased inflammation in the postoperative period may increase the incidence of TLSS and supports its inflammatory origin.[75]

3. Therapeutic Approach

Intensive steroidal therapy after femtosecond LASIK seems to be useful for prevention and

treatment of TLSS. Another finding of our study was a decrease of the incidence of the TLSS after increasing the postoperative regimen of steroids while using similar levels of energy in the creation of the flap. The incidence of TLSS dropped seven-fold, from 2.8% to 0.4%.[75]

VI. Outcomes of Photoablative Refractive Surgery with Excimer Laser Complicated by Corneal Inflammation

The noninfectious inflammations after photoablative procedures have limited the visual outcomes. Post PRK haze was frequent from the thermal effects of the old excimer laser units and before using MMC. When deep ablations are avoided and MMC is prophylactically used during surgeries, haze that impairs visual acuity is rare today.[61,63,89,92,96,120] Although the density of the corneal haze usually decreases over time, nonabsorbable steroids and, if necessary, lamellar surgery or phototherapeutic keratectomy can be used.

The impact of DLK on visual function varies with the severity, therapeutic approach, and the occurrence of an epidemic. Although DLK stages 1 and 2 rarely affect the refractive or visual outcome of LASIK, DLK stages 3 and 4 can induce hyperopic shift, irregular astigmatism, and loss of best-corrected visual acuity.

We recently studied the impact of an outbreak of DLK on the refraction, visual abilities, and corneal aberrations of a group of over 200 cases and concluded that this is uncommon with early diagnosis and adequate treatment.[31] This is consistent with other studies of clusters or sporadic DLK.[51,98]

VII. Conclusion

Adequate management of postoperative inflammation is essential after photorefractive procedures. Successful modulation of the biochemical inflammatory process and cellular wound healing response seems to be important after surface procedures for to achieve an excellent visual outcome. Finally, early detection and a suitable therapeutic approach can prevent undesirable sequelae of specific inflammatory conditions such as DLK, CTK, or TLSS.

VIII. Method of Literature Search

Articles regarding inflammation and refractive surgery were identified through a multistage systematic approach. First, we conducted a computerized search of the Medline database using PubMed (www.pubmed.com). Last search was performed in June 2011. A comprehensive search was made using the terms: *excimer laser, surface ablation, advanced surface ablation, photorefractive keratectomy, PRK, laser-assisted subepithelial keratectomy, laser subepithelial keratomileusis, LASEK, epi-LASIK, LASIK, laser in situ keratomileusis*, and all of those terms followed by "*AND*" and the following: *corneal inflammation, corneal wound healing, corneal infection, bacterial keratitis, diffuse lamellar keratitis, DLK, central toxic keratopathy , CTK, transient light sensitivity syndrome,* and *TLSS.*

Second, all entries were critically reviewed and those considered to be of significance were used, including those written in English, Spanish, and French, and also those from the non-English literature if an English abstract was available. Next, we reviewed the reference section of each article, to detect other studies not captured by the Medline search. Once these articles were critically reviewed, they were included if they were considered to add additional data or to refute previous information.

IX. Disclosure

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Outline

I. Relevance of corneal inflammation following photoablative procedures
II. Corneal inflammation and corneal healing in LASIK and PRK
III. Anatomical and optical consequences of corneal inflammation following LASIK and PRK: clinical aspects, confocal microscopy findings, and wound-healing reaction
  A. Photorefractive keratectomy
  B. LASIK
    1. Flap and stromal thickness
    2. Analysis of the stromal changes
    3. Nerve regeneration
    4. The interface
IV. Pharmacological management of inflammation following surface ablation procedures
  A. Effect of MMC
V. Specific clinical entities
  A. Diffuse lamellar keratitis
    1. Clinical appearance, classification and prevalence
      a. Classification
    2. Etiopathogeny
      a. Lipopolyscharide endotoxin of Gram-negative bacteria
      b. Other agents

c. Associated conditions
d. Epithelial defects
e. Others

3. Differential diagnosis

a. Epithelial ingrowth
b. Microbial keratitis
c. Nonmicrobial interface opacities

4. Treatment

B. Central toxic keratopathy: clinical appearance, pathophysiolology, and treatment

C. Transient light sensitivity syndrome

1. Clinical features and prevalence
2. Physiopathology
3. Therapeutic approach

VI. Outcomes of photoablative refractive surgery with excimer laser complicated by corneal inflammation

VII. Conclusion

VIII. Method of Literature Search

IX. Disclosure