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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]