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Review

Biomechanics and wound healing in the cornea☆

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Abstract

The biomechanical and wound healing properties of the cornea undermine the predictability and stability of refractive surgery and contribute to discrepancies between attempted and achieved visual outcomes after LASIK, surface ablation and other keratorefractive procedures. Furthermore, patients predisposed to biomechanical failure or abnormal wound healing can experience serious complications such as keratectasia or clinically significant corneal haze, and more effective means for the identification of such patients prior to surgery are needed. In this review, we describe the cornea as a complex structural composite material with pronounced anisotropy and heterogeneity, summarize current understanding of major biomechanical and reparative pathways that contribute to the corneal response to laser vision correction, and review the role of these processes in ectasia, intraocular pressure measurement artifact, diffuse lamellar keratitis (DLK) and corneal haze. The current understanding of differences in the corneal response after photorefractive keratectomy (PRK), LASIK and femtosecond-assisted LASIK are reviewed. Surgical and disease models that integrate corneal geometric data, substructural anatomy, elastic and viscoelastic material properties and wound healing behavior have the potential to improve clinical outcomes and minimize complications but depend on the identification of preoperative predictors of biomechanical and wound healing responses in individual patients.

Keywords: cornea; biomechanics; wound healing; refractive surgery; ectasia; haze; hyperopic shift; regression; LASIK; PRK; PTK

1. Introduction

The structural and reparative properties of the cornea are essential to its function as a resilient, yet transparent, barrier to intraocular injury. Because the cornea is also the scaffold for the major refractive surface of the eye, any mechanical or biological response to injury will also influence optical performance. Consequently, the same mechanisms responsible for preserving ocular integrity can undermine the goals of achieving predictable and stable visual outcomes after keratorefractive surgery.

Even in an era of high-precision treatment algorithms, discrepancies between intended and realized visual outcomes are common. The shape-subtraction model of photokeratectomy that forms the basis of LASIK and PRK ablation routines (Munnerlyn et al., 1988) assumes a biologically and biomechanically inert cornea (Roberts, 2000) and does not account for non-idealities in the laser-tissue interaction. While empirical modifications to algorithms and major advances in laser delivery platforms have improved the statistical predictability of LASIK and PRK, the ability to anticipate confounding biological responses at the level of the individual patient remains limited. In some cases, a predisposition to mechanical instability or abnormal regulation of healing can lead to serious complications such as keratectasia or loss of corneal transparency (severe haze). The goal of research in this setting is to improve outcomes and reduce complications by discerning details of the biomechanical and wound healing pathways, identifying measurable predictors of individual responses and developing therapeutic models for controlling or compensating for these factors.

In this review, we highlight selected basic and practical considerations in corneal biomechanics and wound healing specific to the setting of photoablative corneal surgery, which

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accounts for the vast majority of all refractive surgery done today. These processes are approached temporally to distinguish between immediate biomechanical effects, later wound healing effects and ongoing biomechanical-wound healing interactions that help create a new steady state. Ultimately, biomechanical and wound healing responses are linked in time and space and are described separately only for the sake of clarity.

2. Corneal biomechanics

It is evident from incisional refractive surgery that the cornea is not mechanically inert. The role of biomechanics is therefore important to consider in routine LASIK or surface ablation procedures and in special cases where the biomechanical status of the cornea is abnormal (for example, after any previous refractive surgery or after penetrating keratoplasty). Biomechanical changes can manifest clinically as immediate corneal shape changes, shape instability over time and increased sensitivity to shape changes from stimuli such as altered hydration, hypoxia and subsequent injury or surgery. The relative impact of biomechanics and wound healing increases when wavefront-guided treatments of higher-order aberrations are attempted (Netto and Wilson, 2004; Roberts, 2002; Wilson et al., 2003b). Fig. 1 describes an approach to biomechanical problems in the cornea that illustrates a relationship between the corneal structure, its material properties, the nature of the mechanical injury and the structural and optical responses. This approach is expanded in the following paragraphs.

2.1. Foundations of the biomechanical response

2.1.1. Corneal architecture

Of the five anatomic layers of the cornea, only Bowman's layer and the stroma contain collagen fibrils. These layers thus provide the majority of the cornea's tensile strength. The epithelium is attributed a minimal role in this tensile strength, and its removal causes little or no change in the anterior corneal curvature (Litwin et al., 1991). The extensibility and low stiffness of Descemet's membrane ensure its laxity over a broad range of intraocular pressures (IOP) (Jue and Maurice, 1986), which may serve to prevent transmission of stromal stresses to the endothelium. The role of Bowman's layer, an 8 to 12-μm-thick a cellular condensation of stroma with more randomly-oriented collagen fibrils (Komai and Ushiki, 1991), has been a subject of controversy (Seiler et al., 1992; Wilson and Hong, 2000). Although some have proposed a structural role distinct from that of the stroma, extensiometry studies suggest that removal of Bowman's layer does not measurably alter the mechanical properties of the cornea (Seiler et al., 1992).

The mechanical response of the cornea to injury is dominated by the stroma. On a weight basis, the stroma is approximately 78% water, 15% collagen and 7% non-collagenous proteins, proteoglycans and salts (Maurice, 1984). Three hundred to five hundred lamella run from limbus to limbus and are stacked with angular offsets; this orientation becomes increasingly random in the anterior stroma where significantly more oblique branching and interweaving are noted (Komai and Ushiki, 1991). Interlamellar branching is also more extensive in the corneal periphery than in its center (Polack, 1961; Smolek and McCarey, 1990). Interweaving of collagen bundles between neighboring lamellae provides an important structural foundation for shear (sliding) resistance (Ehlers, 1966) and transfer of tensile loads between lamellae (Fig. 2) (Dupps and Roberts, 2001; Roberts, 2000). In addition, X-ray diffraction studies provide evidence of a predominantly

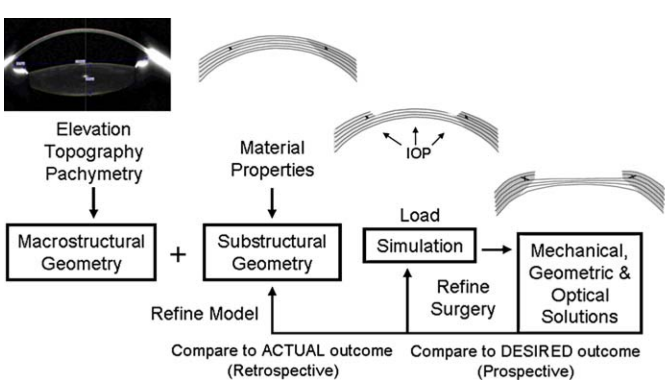

Fig. 1. An approach to biomechanical modeling of surgery and disease in the cornea. Disease is simulated by alteration of the substructural components or their material properties. Surgery is simulated by imposing an ablation profile or incisions. The model is optimized retrospectively by comparing model simulations to analogous experiments in tissue or clinical models. A model optimized with clinical data can then be used prospectively to design and evaluate patient-specific treatment algorithms.

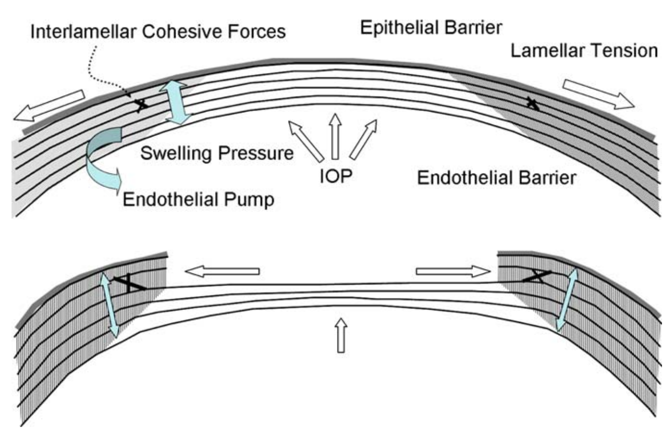

Fig. 2. Major biomechanical loading forces in the cornea and a model of biomechanical central flattening associated with disruption of central lamellar segments. A reduction in lamellar tension in the peripheral stroma reduces resistance to swelling and an acute expansion of peripheral stromal volume results (Dupps and Roberts, 2001; Roberts, 2000, 2002). Interlamellar cohesive forces (Smolek, 1993) and collagen interweaving (Komai and Ushiki, 1991), whose distribution is greater in the anterior and peripheral stroma and is indicated by grey shading, provide a means of transmitting centripetal forces to underlying lamellae. Because the central portions of these lamellae constitute the immediate postoperative surface, flattening of the optical surface occurs, resulting in hyperopic shift. The degree of flattening is associated with the amount of peripheral thickening (Dupps and Roberts, 2001). This phenomenon is exemplified clinically by PTK-induced hyperopic shift but is important in any central keratectomy, including PRK and LASIK. Simultaneous elastic weakening of the residual stromal bed may occur (Guirao, 2005), and the threshold for inducing irreversible (plastic) or progressive (viscoelastic) steepening (or ectasia) is a matter of great clinical concern.