ISSN: 2754-4990

Journal of Ophthalmology Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

The Impact of TGF-β on Corneal Stromal Remodeling After LASIK and PRK

Themistoklis Gialelis PhD[1,2*], Aikaterini Mouzaka[3] and Xanthippi Grammatoglou[4]

[1]Department of Biomedical Sciences, Sector of Optics and Optometry, University of West Attica, Greece

[2]First Laboratory of Pathological Anatomy Medical School of Athens Greece

[3]Ophthalmology Department, 251 Air Force General Hospital Athens, Greece

[4]Department of Pathology General hospital of Athens "G.Gennimatas", Athens, Greece

ABSTRACT

Laser refractive surgery- encompassing both LASIK (Laser-Assisted in Situ Keratomileusis) and PRK (Photorefractive Keratectomy) - represents one of the most widely performed elective procedures for correcting refractive errors worldwide. The wound healing response following these interventions involves intricate molecular cascades, with transforming growth factor-beta (TGF-β) playing a pivotal regulatory role in stromal remodeling. This cytokine orchestrates the transformation of quiescent keratocytes into contractile myofibroblasts, modulates extracellular matrix synthesis, and influences the development of corneal haze-a complication that can compromise visual outcomes. The present review examines the mechanistic underpinnings of TGF-β action in corneal wound healing, compares the differential stromal responses between LASIK and PRK, and analyzes the clinical implications of these processes. Understanding TGF- β-mediated pathways provides a foundation for developing targeted therapeutic strategies aimed at minimizing fibrotic responses and optimizing clinical outcomes following refractive surgery. By elucidating the molecular distinctions between these two surgical approaches, we can better predict healing trajectories and tailor interventions to individual patient needs.

***Corresponding author**

Themistoklis K Gialelis, Department of Biomedical Sciences, Sector of Optics and Optometry, University of West Attica, Egaleo Park, Ag Spyridonos str, postal code 12243, Athens, Greece.

Received: March 03, 2026; **Accepted:** March 09, 2026; **Published:** March 17, 2026

Keywords: TGF-β, Cornea, LASIK, PRK, Myofibroblasts, Corneal Haze, Stromal Remodeling, Wound Healing, Extracellular Matrix

Introduction

Laser refractive surgery has fundamentally transformed the management of refractive errors, with millions of procedures performed annually across the globe. Two principal techniques dominate the field: PRK and LASIK. These approaches differ substantially in their surgical methodology-PRK involves complete epithelial removal followed by superficial stromal ablation, whereas LASIK creates a hinged corneal flap before ablating the underlying stromal bed [1]. Despite their proven efficacy in correcting myopia, hyperopia, and astigmatism, both procedures inevitably induce corneal injury that triggers complex wound healing cascades.

The corneal healing response following refractive surgery constitutes a multifaceted biological process involving cellular migration, proliferation, differentiation, and extensive extracellular matrix (ECM) remodeling. Central to these processes is transforming growth factor-beta (TGF- β), a pleiotropic cytokine that regulates cellular behavior and ECM production [2-3]. TGF-β proves particularly critical in mediating the transformation of quiescent keratocytes into myofibroblasts-cells characterized by alpha-smooth muscle actin (α-SMA) expression and contractile properties that can generate disorganized ECM deposition [4]. This myofibroblast- driven response, while essential for wound closure, may lead to corneal haze and suboptimal visual outcomes when dysregulated.

Interestingly, the incidence and severity of corneal haze differ markedly between LASIK and PRK. Clinical observations consistently demonstrate that PRK carries a higher risk of haze formation, particularly in cases involving deeper ablations or higher refractive corrections [5,6]. This disparity stems from fundamental differences in how these procedures affect the epithelial barrier, basement membrane integrity, and the depth of stromal injury. The epithelium and its basement membrane serve as critical regulators of TGF-β availability to stromal keratocytes-a concept that has profound implications for understanding differential healing responses [7,8].

Recent advances in molecular biology have illuminated the specific TGF-β isoforms involved in corneal wound healing, their temporal expression patterns, and the downstream signaling cascades they activate. Three mammalian isoforms exist (TGF-β1, TGF-β2, and TGF-β3), each exhibiting distinct-and sometimes opposing-effects on fibrosis and tissue regeneration [9]. Moreover, therapeutic interventions targeting TGF-β signaling, including topical losartan and anti-TGF-β antibodies, have shown promise in experimental models and early clinical trials [10-14].

This review synthesizes current knowledge regarding TGF-β's role in corneal stromal remodeling following LASIK and PRK. We examine the molecular mechanisms underlying TGF-β action, compare the differential wound healing responses between these two surgical techniques, and discuss emerging therapeutic strategies. By integrating findings from cellular, molecular, and clinical studies, we aim to provide a comprehensive framework for understanding how TGF-β influences refractive surgery outcomes and how this knowledge can be translated into improved patient care.

Mechanisms of TGF-β Action in Corneal Wound Healing

TGF-β Isoforms and Receptor Systems

The TGF-β superfamily comprises multiple isoforms, with TGF-β1, TGF-β2, and TGF-β3 being the predominant forms expressed in mammalian corneal tissue. Each isoform exhibits distinct spatial and temporal expression patterns following corneal injury, and their relative abundance significantly influences the balance between physiological healing and pathological fibrosis [2,8]. Studies examining corneal wound healing after excimer laser keratectomy have documented differential expression of these isoforms, with TGF-β1 and TGF-β2 showing particularly prominent upregulation in the early post-operative period [2].

TGF-β1 has been extensively characterized as a pro-fibrotic mediator. Following corneal injury, TGF-β1 levels increase substantially in the tear film, epithelium, and anterior stroma—regions where myofibroblast differentiation predominantly occurs [3,8]. This isoform potently stimulates keratocyte transformation into myofibroblasts and promotes the synthesis of disorganized ECM components. Experimental studies using anti-TGF-β antibodies have demonstrated that neutralizing TGF-β1 activity can significantly reduce myofibroblast generation and corneal haze formation after PRK [13,15].

TGF-β2 similarly contributes to fibrotic responses, though its role appears more nuanced. Research has shown that TGF-β2 production by corneal epithelial cells can be modulated by the underlying basement membrane composition [7]. In corneas developing stromal fibrosis, delayed regeneration of the epithelial basement membrane correlates with prolonged TGF-β2 expression and sustained myofibroblast presence [7,8]. This observation suggests that basement membrane integrity serves as a critical checkpoint regulating TGF-β2-mediated fibrosis.

In contrast to its pro-fibrotic siblings, TGF-β3 has been implicated in promoting scarless wound healing in various tissues. Studies examining TGF-β3 localization in corneal injury models have revealed distinct expression patterns compared to TGF-β1 and TGF-β2 [9]. TGF-β3 appears to modulate the fibrotic response by influencing the balance between ECM synthesis and degradation, potentially favoring more organized matrix deposition. However, the precise mechanisms by which TGF-β3 exerts its anti-fibrotic effects in the cornea remain incompletely understood and warrant further investigation.

TGF-β isoforms exert their biological effects through binding to heteromeric receptor complexes consisting of type I and type II serine/threonine kinase receptors. Upon ligand binding, the type II receptor phosphorylates and activates the type I receptor, which subsequently propagates intracellular signals through multiple pathways [16]. The specificity of TGF-β signaling depends not only on the isoform involved but also on the cellular context, receptor expression levels, and the availability of intracellular signaling mediators.

Intracellular Signaling and Smad Pathways

Once TGF-β binds to its receptor complex, the activated type I receptor phosphorylates receptor- regulated Smad proteins (R-Smads), specifically Smad2 and Smad3. These phosphorylated R- Smads then form heteromeric complexes with the common mediator Smad4, translocate to the nucleus, and regulate the transcription of target genes involved in ECM production, cellular differentiation, and proliferation [16]. This canonical Smad pathway represents the primary mechanism through which TGF-β exerts its pro-fibrotic effects in corneal stromal cells.

The Smad signaling cascade plays a central role in myofibroblast differentiation. Activation of Smad2/3 leads to increased expression of α-SMA, the hallmark marker of myofibroblasts, as well as enhanced synthesis of collagen types I and III, fibronectin, and other ECM components [4,16]. Studies using gene therapy approaches have demonstrated that overexpression of inhibitory Smad7—which negatively regulates TGF-β signaling by competing with R-Smads for receptor binding—can significantly reduce myofibroblast formation and corneal scarring [16]. In experimental models, targeted AAV5-Smad7 gene therapy reduced α- SMA expression by 93% in TGF-β1-treated human corneal fibroblasts, highlighting the therapeutic potential of modulating this pathway.

Beyond the canonical Smad pathway, TGF-β can activate non-Smad signaling cascades, including mitogen-activated protein kinase (MAPK) pathways, Rho-like GTPase signaling, and phosphatidylinositol-3-kinase (PI3K)/Akt pathways. These alternative routes contribute to the diverse cellular responses elicited by TGF-β and may explain some of the context-dependent effects observed in different corneal cell populations [17]. For instance, the mechanical properties of the ECM and the biomechanical stress experienced by keratocytes can modulate TGF-β signaling through mechanotransduction pathways, creating a complex interplay between biochemical and biophysical cues [18].

The temporal dynamics of TGF-β signaling also merit consideration. Following corneal injury, TGF-β expression exhibits a biphasic pattern, with an initial acute phase characterized by rapid upregulation followed by a prolonged phase of sustained expression in cases developing fibrosis [2,3]. The duration and intensity of TGF-β signaling appear critical in determining whether healing proceeds toward physiological regeneration or pathological scarring. Concentration-dependent effects have been documented, with low TGF-β1 concentrations promoting keratocyte proliferation and migration, while higher concentrations drive myofibroblast differentiation and ECM deposition [19].

Keratocyte-To-Myofibroblast Transformation

The transformation of resident corneal keratocytes into myofibroblasts represents a pivotal event in the wound healing response following refractive surgery. Quiescent keratocytes, which maintain corneal transparency through the production of highly organized ECM and the expression of crystallin proteins that minimize light scattering, undergo dramatic phenotypic changes when exposed to TGF-β in the context of injury [4,17].

This transdifferentiation process occurs in distinct stages. Initially, keratocytes in the vicinity of the wound undergo apoptosis, creating an acellular zone. Subsequently, surviving keratocytes and bone marrow-derived cells migrate into the wound area and proliferate, initially adopting a fibroblastic phenotype characterized by reduced crystallin expression and increased metabolic activity [17]. In the

presence of TGF-β—particularly when combined with mechanical stress and specific ECM components—these fibroblasts further differentiate into myofibroblasts, acquiring α-SMA expression and contractile machinery [4].

Myofibroblasts differ fundamentally from both quiescent keratocytes and activated fibroblasts. They exhibit enhanced contractility, produce large quantities of disorganized ECM (including collagen types I and III rather than the normal stromal collagen type I with its precise fibrillar organization), and generate significant light scattering due to their altered cellular architecture and the ECM they deposit [4,6]. The persistence of myofibroblasts in the corneal stroma correlates directly with the severity and duration of corneal haze [6].

Importantly, myofibroblast differentiation is not irreversible. Studies have shown that when TGF-β signaling is interrupted or when the epithelial basement membrane regenerates (thereby reducing TGF-β availability to stromal cells), myofibroblasts can undergo apoptosis or revert to a more quiescent phenotype [7,8]. This plasticity suggests potential therapeutic windows for intervention, even after myofibroblasts have formed.

The cellular source of myofibroblasts has been debated. While resident keratocytes clearly contribute, evidence also supports the recruitment of bone marrow-derived fibrocytes and the potential contribution of Epithelial-Mesenchymal Transition (EMT) in certain contexts [4]. The relative contribution of these different sources may vary depending on the type and severity of injury, with more extensive wounds potentially recruiting a higher proportion of circulating progenitor cells.

Extracellular Matrix Production and Remodeling

TGF-β profoundly influences ECM composition and organization in the healing cornea. Under physiological conditions, the corneal stroma consists of highly ordered collagen lamellae (primarily collagen type I) arranged in a precise orthogonal pattern that minimizes light scattering and maintains transparency. This organization depends on specific proteoglycans, particularly keratocan, lumican, and decorin, which regulate collagen fibril diameter and spacing [17,20].

Following TGF-β-mediated myofibroblast activation, ECM production shifts dramatically. Myofibroblasts synthesize increased amounts of collagen types I and III, fibronectin, tenascin, and altered proteoglycan profiles [4,20]. This newly deposited matrix lacks the precise organization of normal stromal ECM, resulting in irregular collagen fibril diameters, disrupted lamellar architecture, and increased light scattering-the structural basis of corneal haze [6].

The process of ECM remodeling involves not only synthesis but also degradation and reorganization. Matrix Metalloproteinases (MMPs) and Their Tissue Inhibitors (TIMPs) play crucial roles in this dynamic process. TGF-β influences the expression of multiple MMPs and TIMPs, thereby regulating the balance between matrix deposition and degradation [17]. In the context of refractive surgery, this balance determines whether the cornea achieves stable refractive outcomes with minimal haze or develops progressive scarring.

Recent studies using advanced imaging techniques, including second harmonic generation microscopy and optical coherence tomography, have provided unprecedented insights into stromal remodeling dynamics [20]. These investigations reveal that ECM reorganization continues for months to years after refractive surgery, with gradual improvements in lamellar organization correlating with clinical haze resolution. The regeneration of the epithelial basement membrane appears particularly critical for normalizing ECM remodeling, as it reduces TGF-β penetration into the stroma and promotes the resolution of myofibroblast populations [7,8].

Interestingly, the biomechanical properties of the healing cornea also influence ECM remodeling. The ablation-induced change in corneal curvature and thickness alters the biomechanical stress distribution within the stroma, which in turn affects keratocyte behavior and ECM organization through mechanotransduction pathways [18]. This biomechanical dimension adds another layer of complexity to understanding TGF-β-mediated stromal remodeling and may explain some of the variability in healing responses observed clinically.

Comparison of Remodeling Between LASIK and PRK

Differences in Epithelial Involvement

The most fundamental distinction between LASIK and PRK lies in their treatment of the corneal epithelium and its basement membrane. PRK involves complete mechanical or chemical removal of the central epithelium, followed by direct excimer laser ablation of Bowman's layer and the anterior stroma. This approach creates an epithelial-stromal wound that requires complete re-epithelialization and basement membrane regeneration [7,5]. In contrast, LASIK preserves the epithelium by creating a hinged flap that includes epithelium, basement membrane, Bowman's layer, and anterior stroma; the excimer laser ablation occurs on the deeper stromal bed, after which the flap is repositioned [14,21].

This difference in epithelial handling has profound implications for TGF-β-mediated wound healing. The intact epithelium and basement membrane in LASIK serve as a barrier that limits TGF-β penetration from the tear film into the stromal wound bed [21]. Studies have demonstrated that an intact corneal epithelium is essential for preventing stromal haze after LASIK—when epithelial defects occur, the risk of haze increases substantially, approaching that seen in PRK [21].

Following PRK, the absence of the epithelial barrier allows direct exposure of the stromal wound to tear film components, including elevated concentrations of TGF-β1 and TGF-β2 [3,8]. This unrestricted access of TGF-β to activated keratocytes and stromal fibroblasts promotes robust myofibroblast differentiation. Moreover, the process of epithelial basement membrane regeneration after PRK is gradual, often requiring several weeks to months for complete restoration [7]. During this extended period, the stromal cells remain exposed to pro-fibrotic signals.

Research examining epithelial basement membrane regeneration after PRK has revealed critical insights into the relationship between basement membrane integrity and stromal fibrosis [7,8]. In corneas that develop significant haze, basement membrane regeneration is markedly delayed, with persistent deficiencies in key basement membrane components such as laminin, nidogen, and perlecan. This delayed regeneration correlates with prolonged TGF-β2 expression in the epithelium and sustained myofibroblast presence in the anterior stroma [7,8]. Conversely, corneas that heal without significant fibrosis demonstrate more rapid basement membrane restoration and earlier resolution of TGF-β expression.

The epithelial-stromal interaction extends beyond simple barrier function. The basement membrane actively regulates epithelial

cell behavior, including the production of growth factors and cytokines. Studies have shown that basement membrane-like ECM can inhibit corneal epithelial production of TGF-β2, creating a negative feedback loop that promotes healing resolution [7]. This regulatory mechanism is disrupted in PRK but preserved in LASIK, contributing to the differential fibrotic responses.

Temporal Course of Healing and Myofibroblast Generation

The kinetics of wound healing differ substantially between LASIK and PRK, with important consequences for myofibroblast generation and haze development. Following PRK, re-epithelialization typically requires 3-5 days, during which the stromal wound remains exposed. Myofibroblasts begin appearing in the anterior stroma within the first week post -operatively, reach peak density at 1-2 months, and may persist for 6-12 months or longer in cases developing significant haze [3-6].

In contrast, LASIK healing proceeds more rapidly in terms of epithelial recovery, as the flap repositioning immediately restores epithelial coverage (though flap adhesion and interface healing require additional time). Myofibroblast generation after LASIK is substantially reduced compared to PRK, both in terms of cell density and spatial distribution [14,21]. When myofibroblasts do appear after LASIK, they typically localize to the flap interface and peripheral wound edges rather than the central anterior stroma.

The temporal expression patterns of TGF-β isoforms also differ between these procedures. Studies examining TGF-β expression after excimer laser keratectomy have documented that TGF-β1 and TGF-β2 levels increase rapidly after PRK, with sustained elevation in cases developing haze [2,3]. The magnitude and duration of TGF-β expression correlate with the depth of ablation and the degree of refractive correction. After LASIK, TGF-β expression is generally more modest and transient, consistent with the reduced myofibroblast response [14].

Interestingly, the depth of stromal injury influences healing dynamics in both procedures. Deeper ablations-whether in PRK or LASIK-are associated with more pronounced wound healing responses and higher risks of complications [5]. In PRK, deeper ablations result in more extensive myofibroblast generation and increased haze incidence. In LASIK, deeper ablations (achieved through thinner flaps or greater stromal bed ablation) can compromise biomechanical stability and potentially increase interface complications.

The role of the ablation profile also merits consideration. Surface irregularities created by the excimer laser can influence local wound healing responses, with areas of greater curvature change or surface roughness potentially experiencing enhanced TGF-β signaling and myofibroblast activity [6]. Advanced ablation algorithms and optimized laser parameters have been developed to minimize these irregularities and promote more uniform healing.

Corneal Haze and Clinical Outcomes

Corneal haze represents the most clinically significant manifestation of aberrant TGF-β-mediated wound healing after refractive surgery. This complication occurs far more frequently and severely after PRK than LASIK, reflecting the fundamental differences in their wound healing biology [5,6]. Haze is graded clinically on a scale from 0 (no haze) to 4 (severe haze obscuring iris details), with grades 2 and above typically associated with visual symptoms and reduced best-corrected visual acuity.

The structural basis of corneal haze has been well characterized through histopathological and imaging studies [6]. Haze correlates directly with the presence and density of myofibroblasts in the anterior stroma, along with the disorganized ECM they produce. Myofibroblasts and their associated matrix scatter light due to variations in refractive index, irregular collagen fibril organization, and altered proteoglycan composition. Additionally, surface irregularities resulting from uneven ECM deposition contribute to higher-order aberrations and reduced optical quality [6].

The incidence of clinically significant haze after PRK varies depending on multiple factors, including the degree of refractive correction, ablation depth, patient age, and geographic location (with higher rates reported in populations with greater ultraviolet light exposure) [5]. Modern PRK techniques incorporating prophylactic mitomycin C application have substantially reduced haze incidence, though this intervention carries its own potential risks and does not completely eliminate the problem [22].

After LASIK, clinically significant haze is rare, occurring primarily in cases with epithelial complications, flap irregularities, or interface inflammation [14-21]. The preservation of the epithelial barrier and the deeper location of the ablation (beneath the flap) both contribute to this favorable outcome. However, subclinical interface haze can occur, detectable through careful slit-lamp examination or advanced imaging, though it rarely affects visual function.

Beyond haze, other clinical outcomes differ between LASIK and PRK. PRK typically involves a longer recovery period with more discomfort during epithelial healing, but it avoids flap-related complications such as flap dislocation, striae, or diffuse lamellar keratitis. LASIK offers faster visual recovery and less discomfort but carries risks specific to flap creation. The choice between these procedures depends on multiple factors, including corneal thickness, refractive error magnitude, patient occupation and lifestyle, and surgeon preference.

Long-term refractive stability also relates to wound healing dynamics. Excessive myofibroblast- mediated ECM deposition can lead to regression of refractive effect, particularly after PRK for high myopia [15]. While anti-TGF-β interventions can reduce haze, studies have shown that they do not prevent regression of the photoablative effect, suggesting that different mechanisms underlie these two aspects of wound healing [15].

The Role of the Epithelial Basement Membrane

The epithelial basement membrane has emerged as a critical regulator of corneal wound healing and a key determinant of differential outcomes between LASIK and PRK. This specialized ECM structure, composed primarily of laminin, collagen type IV, nidogen, and perlecan, serves multiple functions: it provides structural support for the epithelium, regulates epithelial-stromal interactions, and acts as a selective barrier controlling the passage of molecules between these compartments [7,8].

In LASIK, the basement membrane remains largely intact (except at the flap edge), preserving its barrier and regulatory functions. This intact membrane limits TGF-β penetration from the tear film to the stromal wound bed and maintains normal epithelial-stromal signaling [21]. The importance of this preservation is underscored by observations that epithelial defects during or after LASIK-which compromise basement membrane integrity-significantly increase the risk of stromal haze [21].

Following PRK, complete basement membrane removal necessitates de novo regeneration. This process proves remarkably complex and prolonged, often requiring 6-12 months for full restoration of normal basement membrane architecture and composition [7,8]. During the regeneration period, the immature basement membrane exhibits altered permeability and reduced capacity to regulate epithelial cytokine production.

Studies comparing fibrotic versus non-fibrotic healing after PRK have revealed striking differences in basement membrane regeneration kinetics [7,8]. Corneas developing stromal fibrosis show significantly delayed basement membrane restoration, with persistent deficiencies in key components. This delayed regeneration correlates with prolonged TGF-β2 expression by epithelial cells and sustained myofibroblast presence in the underlying stroma. In contrast, corneas healing without significant fibrosis demonstrate more rapid basement membrane regeneration, earlier normalization of TGF-β expression, and faster myofibroblast resolution [7,8].

The basement membrane also influences stromal cell behavior through integrin-mediated signaling. Keratocytes and fibroblasts express various integrins that interact with basement membrane components, and these interactions modulate cellular responses to growth factors including TGF-β [17]. The absence or immaturity of the basement membrane after PRK may alter these integrin-mediated signals, potentially enhancing cellular responsiveness to pro-fibrotic stimuli.

Therapeutic strategies aimed at accelerating basement membrane regeneration or providing temporary barrier function during the healing period represent promising approaches for reducing haze after PRK. Amniotic membrane transplantation, for example, provides a temporary basement membrane-like substrate that may facilitate more organized healing, though its clinical utility remains debated [5]. Understanding the molecular mechanisms regulating basement membrane assembly and maturation could lead to more targeted interventions.

Discussion

Therapeutic Strategies Targeting TGF-β

The central role of TGF-β in corneal fibrosis has motivated extensive research into therapeutic strategies for modulating this pathway. Multiple approaches have been investigated, ranging from direct TGF-β neutralization to downstream signaling inhibition and alternative pathway modulation [10-14,23].

Neutralizing antibodies against TGF-β represent one of the earliest therapeutic approaches explored. Studies in animal models demonstrated that topical application of anti-TGF-β antibodies after PRK could significantly reduce myofibroblast generation and corneal
haze [13,15]. However, these antibodies showed limited ability to prevent regression of the refractive effect, suggesting that TGF-β's role in fibrosis is partially independent of its effects on stromal remodeling that influence refraction [15]. Clinical translation of antibody-based therapies has been limited by challenges related to antibody stability, corneal penetration, and potential immunogenicity.

Mitomycin C (MMC), an alkylating agent with antiproliferative and pro-apoptotic properties, has become widely adopted as a prophylactic treatment during PRK to prevent haze formation [22]. While not specifically targeting TGF-β, MMC reduces myofibroblast generation by inducing apoptosis in activated keratocytes and fibroblasts. Clinical studies have demonstrated substantial reductions in haze incidence with MMC use, particularly in high-risk cases involving deep ablations or retreatments [22]. However, concerns persist regarding potential long-term effects on corneal endothelium, keratocyte density, and biomechanical stability, necessitating careful patient selection and dosing protocols [22].

Losartan, an angiotensin II type 1 receptor antagonist widely used for hypertension, has emerged as a promising anti-fibrotic agent for corneal applications [10-14,23]. Losartan inhibits TGF-β-driven fibrosis through multiple mechanisms, including reduced TGF-β1 expression, decreased Smad2/3 phosphorylation, and modulation of ECM remodeling. Preclinical studies in rabbit models have demonstrated that topical losartan significantly reduces myofibroblast generation and late haze formation after PRK [14]. Importantly, losartan appears to preserve normal wound healing while specifically inhibiting pathological fibrosis—a favorable profile compared to more broadly cytotoxic agents like MMC [12,14].

Recent clinical investigations have begun exploring topical losartan for treating established corneal scarring after refractive surgery [10-23]. Early results suggest potential efficacy in reducing haze and improving visual outcomes, even in cases with long-standing scarring. The favorable safety profile of losartan, combined with its established use in systemic medicine, facilitates clinical translation. However, optimal dosing regimens, treatment duration, and patient selection criteria require further investigation [23].

Gene therapy approaches targeting TGF-β signaling represent a more experimental but potentially powerful strategy. Studies using Adeno-Associated Virus (AAV) vectors to deliver Smad7—an inhibitory Smad that negatively regulates TGF-β signaling—have demonstrated remarkable efficacy in preventing corneal scarring in animal models [16]. Targeted AAV5- Smad7 gene therapy reduced α-SMA expression by 93% in TGF-β1-treated corneal fibroblasts and significantly decreased scarring in vivo [16]. While gene therapy faces regulatory and technical hurdles, it offers the potential for sustained therapeutic effects from a single treatment.

Other investigational approaches include decorin (a natural TGF-β-binding proteoglycan), hepatocyte growth factor (which antagonizes TGF-β effects), and small molecule inhibitors of TGF-β receptor kinases. Each approach offers distinct advantages and limitations, and combination strategies may ultimately prove most effective.

Limitations and Future Directions

Despite substantial progress in understanding TGF-β's role in corneal wound healing, important knowledge gaps remain. The relative contributions of different TGF-β isoforms, their temporal dynamics, and their interactions with other growth factors and cytokines require further elucidation. Most studies have focused on TGF-β1, with less attention to TGF-β2 and TGF-β3, yet emerging evidence suggests these isoforms may have distinct and potentially opposing effects [9].

The cellular heterogeneity of the wound healing response also deserves greater attention. Keratocytes, bone marrow-derived fibrocytes, and potentially epithelial-derived cells through EMT may all contribute to the myofibroblast population, but their relative importance and differential responses to TGF-β remain unclear. Single-cell transcriptomic approaches could provide unprecedented insights into this cellular diversity and identify

novel therapeutic targets.

The biomechanical dimension of corneal wound healing represents another frontier. The altered stress distribution following refractive surgery influences cellular behavior through mechanotransduction pathways that interact with TGF-β signaling [18]. Understanding these biomechanical-biochemical interactions could lead to surgical technique modifications or adjunctive therapies that optimize healing by modulating the mechanical environment.

Patient-specific factors influencing wound healing responses require better characterization. Age, genetic background, environmental exposures (particularly ultraviolet light), systemic health conditions, and medications all potentially affect TGF-β-mediated healing, yet our ability to predict individual healing trajectories remains limited. Developing predictive biomarkers or risk stratification tools could enable personalized therapeutic approaches.

The long-term consequences of anti-fibrotic interventions also warrant careful study. While reducing excessive fibrosis is desirable, TGF-β plays important roles in normal tissue homeostasis, and complete inhibition could have unintended consequences. The ideal therapeutic approach would selectively prevent pathological fibrosis while preserving physiological wound healing—a nuanced goal requiring sophisticated understanding of the molecular switches that distinguish these processes.

Finally, translating promising preclinical findings into clinical practice faces multiple challenges. Animal models, while invaluable, do not perfectly recapitulate human corneal wound healing. Differences in corneal anatomy, healing kinetics, and environmental factors between species necessitate careful validation in human studies. Moreover, the regulatory pathway for novel ophthalmic therapeutics is rigorous, requiring substantial evidence of safety and efficacy.

Future research directions should include: (1) comprehensive characterization of TGF-β isoform- specific effects using isoform-selective inhibitors or genetic models; (2) investigation of combination therapeutic strategies that target multiple aspects of the fibrotic cascade; (3) development of sustained-release drug delivery systems to maintain therapeutic levels throughout the critical healing period; (4) application of advanced imaging techniques to enable non-invasive monitoring of wound healing and early detection of aberrant responses; and (5) large-scale clinical trials of promising anti-fibrotic agents with long-term follow-up to assess both efficacy and safety.

Conclusions

Transforming growth factor-beta occupies a central position in the molecular choreography of corneal wound healing following refractive surgery. This pleiotropic cytokine orchestrates the transformation of quiescent keratocytes into contractile myofibroblasts, drives the synthesis of disorganized extracellular matrix, and ultimately determines whether healing proceeds toward transparent regeneration or opaque scarring. The differential wound healing responses observed between LASIK and PRK stem fundamentally from differences in epithelial barrier integrity and basement membrane preservation-factors that profoundly influence TGF-β availability to stromal cells.

PRK, by removing the epithelium and necessitating complete basement membrane regeneration, creates conditions favoring robust TGF-β signaling and myofibroblast differentiation. The prolonged period of basement membrane immaturity allows sustained TGF-β exposure to stromal cells, increasing the risk of corneal haze-particularly in cases involving deep ablations or high refractive corrections. In contrast, LASIK preserves the epithelial barrier and basement membrane (except at flap edges), limiting TGF-β penetration to the deeper stromal wound bed and substantially reducing myofibroblast generation and haze formation.

Understanding these mechanistic distinctions has important clinical implications. It explains the differential risk profiles of these procedures, guides patient selection and surgical planning, and provides a rational basis for developing targeted therapeutic interventions. The emergence of anti-fibrotic strategies-including topical losartan, mitomycin C, and experimental gene therapies-offers hope for further reducing complications and expanding the safety envelope of refractive surgery.

Nevertheless, significant challenges remain. The complexity of TGF-β signaling, with multiple isoforms, diverse cellular targets, and intricate interactions with biomechanical and environmental factors, defies simple therapeutic manipulation. The goal is not to eliminate TGF- β signaling entirely-which would compromise normal wound healing-but rather to modulate it precisely, preventing pathological fibrosis while preserving physiological repair. Achieving this nuanced control requires deeper understanding of the molecular switches that distinguish these processes.

Looking forward, the integration of molecular biology, advanced imaging, biomechanics, and clinical investigation promises to yield increasingly sophisticated approaches to managing corneal wound healing. Personalized medicine approaches, guided by genetic and biomarker profiling, may enable prediction of individual healing trajectories and tailoring of interventions to patient-specific risk factors. Novel drug delivery systems could provide sustained therapeutic levels throughout the critical healing period, while combination strategies might target multiple nodes in the fibrotic cascade for enhanced efficacy [24-30].

Ultimately, the goal is clear: to harness the regenerative capacity of the cornea while preventing the fibrotic complications that can compromise visual outcomes. By continuing to unravel the molecular mechanisms of TGF-β action and translating these insights into clinical practice, we move closer to this goal-offering patients the benefits of refractive surgery with ever-improving safety and predictability. The journey from bench to bedside is long and challenging, but the progress achieved thus far provides reason for optimism that the next generation of refractive surgical techniques and adjunctive therapies will further minimize complications and maximize visual outcomes.

References

1. Salomão MQ, Wilson SE (2010) Femtosecond laser in laser in situ keratomileusis. Journal of Cataract and Refractive Surgery 36: 1024-1032.
2. Kaji Y (1998) Expression of transforming growth factor beta superfamily and their receptors in the corneal stromal wound healing process after excimer laser keratectomy. British Journal of Ophthalmology 82: 456-463.
3. Mita (1998) Effects of transforming growth factor beta on corneal epithelial and stromal cell function in a rat wound healing model after excimer laser keratectomy. Graefe's Archive for Clinical and Experimental Ophthalmology 236: 834-843.

4. Wilson SE (2012) Corneal myofibroblast biology and pathobiology: generation, persistence, and transparency. Experimental Eye Research 99: 78-88.
5. Spadea L (2019) Main Complications of Photorefractive Keratectomy and their Management. Clinical Ophthalmology 13: 2305-2315.
6. Netto MV (2019) Stromal haze, myofibroblasts, and surface irregularity after PRK. Experimental Eye Research 82: 788-797.
7. Oliveira HB (2022) Epithelial Basement Membrane Regeneration After PRK-Induced Epithelial-Stromal Injury in Rabbits: Fibrotic Versus Non-fibrotic Corneal Healing. Journal of Refractive Surgery 38: 108-116.
8. Oliveira HB (2021) TGFβ1 and TGFβ2 proteins in corneas with and without stromal fibrosis: Delayed regeneration of apical epithelial growth factor barrier and the epithelial basement membrane in corneas with stromal fibrosis. Experimental Eye Research 202: 108325.
9. Shiju TM (2023) Transforming growth factor beta-3 localization in the corneal response to epithelial-stromal injury and effects on corneal fibroblast transition to myofibroblasts. Experimental Eye Research 237: 109631.
10. Wilson SE (2025) Topical Losartan in the Treatment of Stromal Scarring After Refractive Surgery. Journal of Refractive Surgery 41: 312-319.
11. Abdelghaffar W (2025) Topical losartan ophthalmic drops - a review of corneal wound healing and topical losartan for managing corneal haze and potential future indications. Graefe's Archive for Clinical and Experimental Ophthalmology 263: 789-02.
12. Villabona-Martinez (2025) Insights from animal studies exploring the efficacy and safety of topical losartan, in prophylaxis and treatment of corneal scarring fibrosis. Biomedicine & Pharmacotherapy 183: 117857.
13. Thom SB (1997) Effect of topical anti-transforming growth factor-β on corneal stromal haze after photorefractive keratectomy in rabbits. Journal of Cataract and Refractive Surgery 23: 1324-1330.
14. Sampaio LP (2022) Losartan Inhibition of Myofibroblast Generation and Late Haze (Scarring Fibrosis) After PRK in Rabbits. Journal of Refractive Surgery 38: 788-795.
15. Møller-Pedersen T (1998) Neutralizing antibody to TGFβ modulates stromal fibrosis but not regression of photoablative effect following PRK. Current Eye Research 17: 736-747.
16. Gupta A (2017) Targeted AAV5-Smad7 gene therapy inhibits corneal scarring in vivo. PLOS ONE 12: e0172928.
17. West-Mays JA, Dwivedi DJ (2006) The keratocyte: corneal stromal cell with variable repair phenotypes. The International Journal of Biochemistry & Cell Biology 38: 1625-1631.
18. Dupps WJ, Wilson SE (2006) Biomechanics and wound healing in the cornea. Experimental Eye Research 83: 709-720.
19. Wang J (2011) Concentration-dependent effects of transforming growth factor β1 on corneal wound healing. Molecular Vision 17: 2835-2846.
20. Kivanany PB (2018) Assessment of Corneal Stromal Remodeling and Regeneration after Photorefractive Keratectomy. Scientific Reports 8: 12580.
21. Nakamura K, Kurosaka D, Bissen MH, Tsubota K (2001) Intact corneal epithelium is essential for the prevention of stromal haze after laser assisted in situ keratomileusis. British Journal of Ophthalmology 85: 209-213.
22. Arranz-Marquez E, Teus MA (2019) A Critical Overview of the Biological Effects of Mitomycin C Application on the Cornea Following Refractive Surgery. Advances in Therapy36: 786-797.
23. Burgos BB, Mercedes MS, Pilar PG, Mayte AG, Pedro AV, et al. (2026) Topical Losartan in Ophthalmology: Rationale, Experimental and Clinical Evidence, and Emerging Clinical Applications. Journal of Clinical Medicine 15: 1354.
24. Bühren J, Lana N, Jennifer NS, Shawn K, Scott M, et al. (2009) Optical effects of anti-TGFβ treatment after photorefractive keratectomy in a cat model. Investigative Ophthalmology & Visual Science 50: 634- 643.
25. Wu M, Yan Wang (2018) The Wound Healing Responses and Corneal Biomechanics after Keratorefractive Surgery. In Wound Healing - Current Perspectives. IntechOpen https://www.intechopen.com/chapters/64239.
26. Poulsen ET (2009) LASIK surgery of granular corneal dystrophy type 2 patients leads to accumulation and differential proteolytic processing of transforming growth factor beta-induced protein. Molecular Vision 15: 1972-1982.
27. Mohan RR (2008) A novel method for generating corneal haze in anterior stroma of the mouse eye with the excimer laser. Experimental Eye Research 86: 235-240.
28. Jester JV (2006) An Eye on Repair. In Principles of Regenerative Medicine. Academic Press 227-246.
29. Salomão MQ, Wilson SE (2009) Corneal Molecular and Cellular Biology Update for the Refractive Surgeon. Journal of Refractive Surgery 25: 459-466.
30. Safi H, Seitz B, Flockerzi E, Flockerzi FA, Dash L (2021) Haze Nach PRK (Without the use of mitomycin C) On a cornea pretreated with DALK and LASIK-Clinical and histopathological findings. Clinical Monthly Journal of Ophthalmology 240.

Copyright: ©2026 Themistoklis K Gialelis, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.