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Original Research Article

Keratocyte Dynamics After Surface Ablation Procedures: A Confocal Microscopy-Based Observational Study

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Abstract

Background: Surface ablation laser procedures are widely used for refractive correction; however, they induce significant stromal wound healing responses, particularly affecting corneal keratocytes. Understanding these morphological and quantitative changes is essential for optimizing surgical outcomes and minimizing complications.

Methods: This prospective observational study included 52 patients undergoing surface ablation procedures, including Photorefractive Keratectomy, Laser-Assisted Subepithelial Keratomileusis, and Epithelial Laser In Situ Keratomileusis. Keratocyte density and morphology were assessed preoperatively and at 1 week, 1 month, 3 months, and 6 months postoperatively using In Vivo Confocal Microscopy. Statistical analysis included repeated measures ANOVA, Chi-square test, and Spearman correlation.

Results: A significant reduction in anterior stromal keratocyte density (~29.6%) was observed at 1 week ($p < 0.001$), followed by gradual recovery by 6 months. Qualitative changes, including increased reflectivity (86.5%) and activated keratocytes (75.0%), declined significantly over time ($p < 0.001$). Keratocyte loss correlated negatively with ablation depth ($r = -0.62$, $p < 0.001$). PRK showed greater cellular loss compared to epithelial-preserving procedures ($p = 0.041$). Corneal haze was significantly associated with keratocyte activation ($p = 0.018$). Visual outcomes were favorable, with significant improvement in uncorrected visual acuity ($p < 0.001$).

Conclusion: Surface ablation procedures induce dynamic, depth-dependent keratocyte changes predominantly in the anterior stroma. These alterations are influenced by surgical technique and contribute to postoperative haze, though visual outcomes remain excellent. Understanding these responses may help refine surgical strategies and improve patient outcomes.

Keywords: Surface Ablation, Keratocytes, Corneal Wound Healing, Confocal Microscopy, PRK, Corneal Haze.

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Introduction

Surface ablation laser procedures, including Photorefractive Keratectomy (PRK), Laser-Assisted Subepithelial Keratomileusis (LASEK), and Epithelial Laser In Situ Keratomileusis, are widely employed for the correction of refractive errors such as myopia, hyperopia, and astigmatism[1]. These procedures involve removal of the corneal epithelium followed by excimer laser ablation of the anterior stroma, leading to predictable changes in corneal curvature and visual outcomes [2]. Despite their efficacy and safety, surface ablation techniques induce a cascade of cellular and extracellular responses within the corneal stroma, particularly affecting keratocytes, which play a pivotal role in maintaining corneal transparency and stromal integrity [3]. Corneal keratocytes are specialized quiescent fibroblast-like cells residing within the stromal lamellae. They are responsible for synthesizing extracellular matrix components, including collagen and proteoglycans, essential for corneal clarity [4]. Following epithelial removal and stromal photoablation, keratocytes undergo apoptosis in the anterior stroma within hours of surgery, followed by

proliferation, migration, and differentiation into activated fibroblasts and myofibroblasts [5]. This wound healing response is mediated by cytokines such as transforming growth factor-beta (TGF-β) and interleukins released from injured epithelial cells [6].

Literatures have demonstrated that keratocyte apoptosis can extend up to 50–100 μm into the anterior stroma within the first 24–48 hours post-surgery [7]. Subsequent repopulation begins within days and may continue for several months, often accompanied by phenotypic transformation into myofibroblasts, which are associated with extracellular matrix remodeling and corneal haze formation [8]. Clinically significant stromal haze has been reported in approximately 5–20% of cases following surface ablation procedures, depending on ablation depth, ultraviolet exposure, and postoperative management [9].

Advancements in in vivo imaging modalities, particularly In Vivo Confocal Microscopy, have enabled detailed visualization of keratocyte morphology and density changes following refractive surgery [10]. Literatures have reported reduced keratocyte density in the anterior stroma persisting for months, along with morphological alterations such as increased reflectivity, irregular cell shapes, and activated cellular phenotypes [10,11]. However, variability exists in the extent, duration, and clinical implications of these changes across different patient populations and surgical techniques.

Understanding the temporal and morphological changes of keratocytes following surface ablation is essential, as these alterations directly influence corneal wound healing, refractive stability, and visual outcomes. Despite existing literature, there remains limited data correlating specific morphological patterns of keratocyte changes with clinical parameters in diverse populations. Therefore, the present observational study aimed to evaluate the morphological changes of corneal keratocytes following surface ablation laser surgery, contributing to improved understanding of stromal healing dynamics and potential optimization of postoperative outcomes.

Materials and Methods

Study Design and Setting: This prospective observational study was conducted in the Department of Ophthalmology of a tertiary care center over a period of 24 months from June 2023 to June 2025. The study aimed to evaluate morphological changes in corneal keratocytes following surface ablation laser procedures. All participants were recruited from patients undergoing refractive surgery after fulfilling eligibility criteria. The study adhered to the tenets of the Declaration of Helsinki, and prior approval was obtained from the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrollment.

Study Population: The study included patients aged 18–40 years diagnosed with refractive errors (myopia, hyperopia, or astigmatism) who were scheduled for surface ablation procedures such as Photorefractive Keratectomy, Laser-Assisted Subepithelial Keratomileusis, or Epithelial Laser In Situ Keratomileusis. Patients with stable refraction for at least one-year, normal corneal topography, and adequate corneal thickness were included. Exclusion criteria comprised previous ocular surgery, corneal pathologies such as keratoconus or dystrophies, active ocular infection or inflammation, autoimmune disorders, diabetes mellitus, and use of medications affecting wound healing. Eyes with intraoperative or postoperative complications were also excluded from final analysis.

Preoperative Evaluation: All participants underwent a comprehensive ophthalmic evaluation prior to surgery. This included uncorrected and best-corrected visual acuity assessment, manifest and cycloplegic refraction, slit-lamp biomicroscopy, intraocular pressure measurement using Goldmann applanation tonometry, and dilated fundus examination. Corneal assessment included keratometry, pachymetry, and corneal topography using a computerized corneal analyzer. Baseline corneal cellular morphology and keratocyte density were assessed using In Vivo Confocal Microscopy, focusing on the anterior, mid, and posterior stromal layers.

Surgical Procedure: All procedures were performed under topical anesthesia using standardized aseptic protocols. In PRK, the corneal epithelium was removed mechanically or using alcohol-assisted debridement, followed by excimer laser ablation of the anterior stroma based on the patient's refractive error. In LASEK and Epi-LASIK, epithelial preservation techniques were employed before stromal ablation. The same excimer laser platform and ablation profile were used for all patients to maintain uniformity. Mitomycin-C (0.02%) was applied intraoperatively in cases with higher ablation depth (>75 μm) for 10–20 seconds to reduce postoperative haze, followed by thorough irrigation. A bandage contact lens was placed at the end of the procedure.

Postoperative Management and Follow-up: Postoperatively, all patients received a standardized regimen including topical antibiotics, corticosteroids in tapering doses, lubricating eye drops, and oral analgesics as required. Bandage contact lenses were removed after complete epithelial healing, typically within 4–5 days. Patients were followed up at 1 week, 1 month, 3

months, and 6 months postoperatively. At each visit, clinical examination and visual acuity assessment were performed.

Assessment of Keratocyte Morphology: Morphological evaluation of corneal keratocytes was performed using in vivo confocal microscopy at each follow-up visit. Imaging was conducted under standardized conditions by a single experienced operator to minimize interobserver variability. Multiple high-resolution images were obtained from the central cornea at predefined stromal depths (anterior, mid, and posterior stroma). Keratocyte morphology was assessed based on cell density, reflectivity, cellular shape, and presence of activated phenotypes such as fibroblasts or myofibroblasts. Quantitative analysis included keratocyte density (cells/mm²), while qualitative assessment included grading of cellular activation and stromal reflectivity.

Outcome Measures: The primary outcome measure was the change in keratocyte morphology and density at different postoperative intervals compared to baseline. Secondary outcomes included the association of keratocyte changes with clinical parameters such as ablation depth, type of procedure, and presence of postoperative corneal haze.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS version 20.0). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Normality of data was assessed using the Shapiro–Wilk test. For comparison of keratocyte density across multiple postoperative time points, repeated measures analysis of variance (ANOVA) was applied for normally distributed data, while the Friedman test was used for non-parametric data. Post hoc pairwise comparisons were performed with Bonferroni correction where applicable. Qualitative morphological changes over time were analyzed using the Chi-square test for trend. Intergroup comparison of keratocyte density among different surgical procedures (Photorefractive Keratectomy, Laser-Assisted Subepithelial Keratomileusis, and Epithelial Laser In Situ Keratomileusis) was performed using one-way ANOVA with appropriate post hoc analysis. Correlation between ablation depth and keratocyte density changes was assessed using Spearman's rank correlation coefficient. Association between categorical variables, including keratocyte activation and corneal haze, was evaluated using the Chi-square test or Fisher's exact test as appropriate, while continuous variables between two groups were compared using the independent t-test or Mann–Whitney U test. Preoperative and postoperative visual acuity were compared using paired t-test or Wilcoxon signed-rank test, as appropriate. A p-value of <0.05 was considered statistically significant.

Results

The study included 52 patients with a mean age of 26.8 ± 4.6 years, showing a slight male predominance (57.7%). Myopia was the most common refractive error (75.0%), followed by myopic astigmatism (19.2%) and hyperopia (5.8%). The mean spherical equivalent was −3.85 ± 1.42 D, with an average central corneal thickness of 528.6 ± 27.4 µm.

The mean ablation depth was 68.2 ± 15.7 µm. Among surgical techniques, Photorefractive Keratectomy was the most frequently performed (53.8%), followed by Laser-Assisted Subepithelial Keratomileusis (26.9%) and Epithelial Laser In Situ Keratomileusis (19.3%). Overall, the cohort represented a typical young adult refractive surgery population (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (n = 52)

Variable	Frequency (%)/mean ± SD
Age (years)	26.8 ± 4.6
Gender	
Male	30 (57.7)
Female	22 (42.3)
Type of Refractive Error	
Myopia	39 (75.0)
Myopic Astigmatism	10 (19.2)
Hyperopia	3 (5.8)
Spherical Equivalent (D)	−3.85 ± 1.42
Central Corneal Thickness (µm)	528.6 ± 27.4
Ablation Depth (µm)	68.2 ± 15.7
Type of Procedure	
Photorefractive Keratectomy	28 (53.8)
Laser-Assisted Subepithelial Keratomileusis	14 (26.9)
Epithelial Laser In Situ Keratomileusis	10 (19.3)

D = Diopters; µm = micrometers.

A significant reduction in keratocyte density was observed in the anterior stroma at 1 week postoperatively (642.7 ± 78.9 cells/mm²) compared to baseline (912.4 ± 85.6 cells/mm²), followed by gradual recovery over time, reaching 851.6 ± 69.8 cells/mm² at 6 months ($p < 0.001$). The mid-stroma showed a modest but statistically significant decline with near-complete recovery by 6 months ($p = 0.012$). In contrast, posterior stromal keratocyte density remained largely unchanged throughout the follow-up period ($p = 0.184$). These findings indicate that keratocyte loss and repopulation are predominantly localized to the anterior stromal layers (Table 2).

Table 2: Changes in Keratocyte Density Across Stromal Layers at Different Follow-up Intervals

Stromal Layer	Preoperative	1 Week	1 Month	3 Months	6 Months	p-value
	mean ± SD					
Anterior Stroma	912.4 ± 85.6	642.7 ± 78.9	701.2 ± 80.3	782.5 ± 74.6	851.6 ± 69.8	<0.001
Mid Stroma	756.8 ± 72.1	701.5 ± 68.4	720.3 ± 65.9	735.7 ± 61.2	748.9 ± 59.6	0.012
Posterior Stroma	632.1 ± 61.7	615.4 ± 59.3	620.8 ± 57.6	625.9 ± 55.2	628.7 ± 54.1	0.184

At 1 week postoperatively, a high proportion of eyes demonstrated increased keratocyte reflectivity (86.5%), irregular cellular morphology (78.8%), and presence of activated keratocytes (75.0%).

These changes progressively declined over time, with only 17.3%, 13.5%, and 9.6% of eyes, respectively, showing these features at 6 months (all $p < 0.001$).

The temporal trend suggests an initial phase of cellular activation and stromal remodeling followed by gradual restoration of normal keratocyte morphology (Table 3).

Table 3: Temporal Distribution of Qualitative Morphological Changes in Corneal Keratocytes

Parameter	1 Week	1 Month	3 Months	6 Months	p-value
	Frequency (%)				
Increased Reflectivity	45 (86.5)	38 (73.1)	21 (40.4)	9 (17.3)	<0.001
Irregular Cell Shape	41 (78.8)	34 (65.4)	19 (36.5)	7 (13.5)	<0.001
Activated Keratocytes (Fibroblasts/Myofibroblasts)	39 (75.0)	31 (59.6)	16 (30.8)	5 (9.6)	<0.001

At 1 month postoperatively, anterior stromal keratocyte density was lowest in eyes undergoing Photorefractive Keratectomy (682.5 ± 76.4 cells/mm²), followed by Laser-Assisted Subepithelial Keratomileusis (712.8 ± 70.2 cells/mm²) and Epithelial Laser In Situ Keratomileusis (728.6 ± 68.5 cells/mm²). The difference was statistically significant ($p = 0.041$), indicating relatively better preservation of keratocyte density in epithelial-preserving procedures (Table 4).

Table 4: Comparison of Anterior Stromal Keratocyte Density at 1 Month Among Different Surface Ablation Procedures

Procedure	Mean ± SD (cells/mm²)	p-value
Photorefractive Keratectomy	682.5 ± 76.4	0.041
Laser-Assisted Subepithelial Keratomileusis	712.8 ± 70.2	
Epithelial Laser In Situ Keratomileusis	728.6 ± 68.5	

A significant negative correlation was observed between ablation depth and keratocyte density at 1 week ($r = −0.62$, $p < 0.001$) and 1 month ($r = −0.54$, $p < 0.001$), indicating greater keratocyte loss with deeper ablation. Conversely, a moderate positive correlation was noted between ablation depth and keratocyte recovery at 6 months ($r = 0.48$, $p = 0.002$), suggesting delayed but compensatory repopulation in deeper ablations (Table 5).

Table 5: Correlation Between Ablation Depth and Anterior Stromal Keratocyte Changes

Variable	Correlation Coefficient (r)	p-value
Ablation Depth vs Density Reduction (1 Week)	−0.62	<0.001
Ablation Depth vs Density Reduction (1 Month)	−0.54	<0.001
Ablation Depth vs Recovery at 6 Months	0.48	0.002

Corneal haze was observed in 11 patients (21.2%) at 1 month. Activated keratocytes were significantly more frequent in eyes with haze (90.9%) compared to those without haze (51.2%) ($p = 0.018$). Additionally, mean ablation depth was significantly higher in the haze group (82.6 ± 12.4 µm) than in the non-haze group (63.5 ± 14.8 µm) ($p < 0.001$), indicating a strong association between stromal injury, keratocyte activation, and haze formation (Table 6).

Table 6: Association Between Keratocyte Activation and Corneal Haze at 1 Month

Variable	Haze Present (n=11)	No Haze (n=41)	p-value
	Frequency (%)/mean ± SD		
Activated Keratocytes,	10 (90.9)	21 (51.2)	0.018
Mean Ablation Depth (μm)	82.6 ± 12.4	63.5 ± 14.8	<0.001

There was a significant improvement in UCVA from 0.78 ± 0.21 logMAR preoperatively to 0.04 ± 0.08 logMAR at 6 months ($p < 0.001$). BCVA remained stable with no significant change ($p = 0.312$), indicating preservation of visual quality. Mild corneal haze (grade ≥1) was observed in 11.5% of eyes at 6 months. Overall, the visual outcomes were favorable with minimal long-term complications (Table 7).

Table 7: Visual and Clinical Outcomes Following Surface Ablation Surgery

Parameter	Preoperative	6 Months	p-value
	Frequency (%)/mean ± SD		
UCVA (logMAR)	0.78 ± 0.21	0.04 ± 0.08	<0.001
BCVA (logMAR)	0.02 ± 0.05	0.01 ± 0.03	0.312
Corneal Haze (Grade ≥1), n (%)	—	6 (11.5)	—

UCVA = Uncorrected Visual Acuity; BCVA = Best Corrected Visual Acuity; logMAR = logarithm of minimum angle of resolution.

Discussion

The present study provides a detailed evaluation of corneal keratocyte dynamics following surface ablation procedures, demonstrating a well-defined sequence of early cellular loss, transient activation, and gradual stromal repopulation. The study cohort, comprising predominantly young myopic individuals (mean age 26.8 ± 4.6 years; 75% myopia), is consistent with refractive surgery populations reported in prior studies by Bullimore et al., and Lee et al., thereby supporting the external validity of the findings [12,13].

A principal observation was the marked reduction in anterior stromal keratocyte density at 1 week postoperatively, with a decline of approximately 29.6% from baseline (912.4 ± 85.6 to 642.7 ± 78.9 cells/mm²; $p < 0.001$), followed by progressive recovery to near-baseline levels at 6 months (851.6 ± 69.8 cells/mm²). This pattern is highly consistent with the established model of laser-induced keratocyte apoptosis described by Wilson et al, where epithelial injury triggers interleukin-1–mediated apoptotic pathways in the anterior stroma [14].

Similar reductions in keratocyte density (ranging from 20% to 40%) have been reported in confocal microscopy-based longitudinal studies by Wilson et al., and McLaren et al., reinforcing the reproducibility of this biological response [14,15]. The minimal and statistically insignificant changes observed in the posterior stroma ($p = 0.184$) further confirm that excimer laser–induced injury is spatially localized, predominantly affecting the anterior stromal layers.

The temporal recovery pattern observed in this study, with partial restoration by 1 month and near normalization by 6 months, reflects the dynamic interplay of keratocyte proliferation, migration, and differentiation. However, the persistence of sub-baseline density even at 6 months suggests that stromal remodeling is prolonged, potentially extending beyond the study duration. Comparable findings have been reported in confocal studies by El Zarif et al., and Ramirez-Miranda et al., where complete normalization of keratocyte density may take up to 9–12 months, indicating that structural recovery lags behind clinical improvement [10,16]. Qualitative morphological changes further substantiated the wound healing response. A high proportion of eyes demonstrated increased keratocyte reflectivity (86.5%), irregular morphology (78.8%), and activated phenotypes (75.0%) at 1 week, which declined significantly to 17.3%, 13.5%, and 9.6%, respectively, by 6 months (all $p < 0.001$). These findings reflect the transformation of quiescent keratocytes into fibroblasts and myofibroblasts under the influence of cytokines such as transforming growth factor-beta (TGF-β) [17,18]. Increased reflectivity observed on In Vivo Confocal Microscopy corresponds to heightened metabolic activity and extracellular matrix synthesis [18]. The gradual resolution of these features over time indicates restoration of stromal homeostasis, consistent with previously described healing phases following surface ablation in the reviews by Acosta et al., and Ning et al., [19,20].

Procedure-wise analysis revealed significantly lower anterior stromal keratocyte density at 1 month in eyes undergoing Photorefractive Keratectomy (682.5 ± 76.4 cells/mm²) compared to Laser-Assisted Subepithelial Keratomileusis (712.8 ± 70.2 cells/mm²) and Epithelial Laser In Situ Keratomileusis (728.6 ± 68.5 cells/mm²) ($p = 0.041$). This suggests relatively greater stromal insult in PRK, likely due to complete epithelial removal, which facilitates deeper penetration of inflammatory mediators and enhances keratocyte apoptosis [21]. In contrast, epithelial preservation

in LASEK and Epi-LASIK appears to confer a protective effect, limiting cytokine diffusion and stromal injury [22]. Similar trends have been documented in comparative refractive surgery reviews by Way et al., and Yang et al., supporting the advantage of epithelial-preserving techniques in modulating early wound healing responses [23,24].

The significant negative correlation between ablation depth and keratocyte density at 1 week ($r = -0.62$, $p < 0.001$) and 1 month ($r = -0.54$, $p < 0.001$) highlights the dose-dependent nature of stromal injury. Deeper ablations are associated with greater disruption of stromal architecture and amplified cytokine release, resulting in enhanced keratocyte apoptosis [25]. Interestingly, the moderate positive correlation with recovery at 6 months ($r = 0.48$, $p = 0.002$) suggests a compensatory proliferative response in deeper ablations, possibly mediated by increased activation of stromal progenitor cells. This biphasic response—initial injury followed by regenerative proliferation—has been described in experimental and clinical studies and underscores the adaptive capacity of corneal tissue [26].

A clinically significant finding of this study was the strong association between keratocyte activation and corneal haze formation. Eyes with haze at 1 month demonstrated a markedly higher prevalence of activated keratocytes (90.9% vs 51.2%; $p = 0.018$) and significantly greater ablation depth (82.6 ± 12.4 µm vs 63.5 ± 14.8 µm; $p < 0.001$). These findings corroborate the established role of myofibroblasts in stromal opacity, where excessive extracellular matrix deposition and disorganized collagen architecture lead to reduced corneal transparency [27]. Transforming growth factor-beta plays a central role in this process by promoting myofibroblast differentiation and persistence. The observed incidence of haze (21.2% at 1 month, reducing to 11.5% at 6 months) is comparable to previously reported rates by Torricelli et al., and Wilson et al., particularly in cases with higher ablation depths, and reflects gradual resolution with stromal remodeling [28,29].

Despite these pronounced cellular and morphological alterations, visual outcomes were highly favorable. Uncorrected visual acuity improved significantly from 0.78 ± 0.21 to 0.04 ± 0.08 logMAR ($p < 0.001$), while best-corrected visual acuity remained stable ($p = 0.312$), indicating preservation of visual quality. These findings suggest that microscopic stromal changes do not necessarily translate into clinically significant visual impairment in the majority of cases, likely due to the organized nature of stromal remodeling and effective postoperative management [17].

Limitations

This study has certain limitations. The relatively small sample size (n=52) and single-center design may limit generalizability. Follow-up duration of 6 months may not fully capture long-term keratocyteremodeling and late stromal changes. Lack of randomization between surgical techniques could introduce selection bias. Additionally, reliance on In Vivo Confocal Microscopy, though precise, may have operator-dependent variability despite standardized imaging protocols.

Conclusion

The present study demonstrates that surface ablation laser procedures induce significant, predominantly anterior stromal keratocyte alterations characterized by early apoptosis, transient activation, and gradual repopulation. These changes are strongly influenced by ablation depth and surgical technique, with epithelial-preserving procedures showing relatively favorable cellular outcomes. Keratocyte activation was closely associated with corneal haze formation, highlighting its clinical relevance. Despite pronounced microscopic changes, visual outcomes remained excellent, indicating effective stromal remodeling. These findings enhance understanding of corneal wound healing dynamics and may guide optimization of surgical approaches and postoperative management to minimize complications and improve refractive outcomes.

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