Risk Factors for Epithelial Ingrowth Following Microkeratome-Assisted LASIK

Asaf Friehmann, MD; Michael Mimouni, MD; Arie Y. Nemet, MD; Tzahi Sela, BSc; Gur Munzer, LLB; Igor Kaiserman, MD, MSc, MHA

ABSTRACT

PURPOSE: To analyze the incidence and risk factors associated with epithelial ingrowth following uncomplicated microkeratome-assisted LASIK.

METHODS: All patients who underwent microkeratome-assisted LASIK between January 2006 and December 2014 in a single surgical center were reviewed. Epithelial ingrowth cases were identified and associated factors were assessed.

RESULTS: Overall, 149 (0.49%) of 30,574 cases developed epithelial ingrowth. The epithelial ingrowth group was older compared to controls (35.3 ± 12.3 vs 31.7 ± 10.3 years, P = .001) and had a higher percentage of moderate to high hyperopia (13.7% vs 5.3%, P < .001), early postoperative flap slippage requiring flap repositioning (9.4% versus 2.8%, P < .001), or flap lifting for enhancement (48.6% vs 4.3%, P < .001), were treated with a smaller optic zone (6 mm) (37.7% vs 15.2%, P < .001), with a Moria M2 microkeratome (Moria SA, Antony, France) (70.1% vs 55.5%, P = .02), by low volume surgeons (n < 1,000) (5.8% vs 1.3%, P < .001), in a lower operating room temperature (22.3 ± 1.8 vs 22.8 ± 1.6, P = .005), and with a greater maximum ablation depth (67.3 ± 29.7 vs 57.3 ± 30.3, P < .001). There was a high incidence of epithelial ingrowth in the enhancement group compared to primary LASIK (4.8% vs 0.2%, P < .001). The time between treatments (primary and enhanced LASIK) was significantly greater in the epithelial ingrowth group (mean: 1,110 ± 870 vs 626 ± 662 days, P < .001). There was a significant rise in epithelial ingrowth rates as time between primary and enhancement LASIK increased, peaking at 4 to 5 years (P < .001). In multivariate analysis, flap lifting for enhancement (odds ratio [OR] = 19.5, P < .001), 6-mm optic zone (OR = 2.2, P < .001), moderate to severe hyperopia (OR = 2.4, P = .005), greater ablation depth (OR = 1.005, P < .001), and low volume surgeon (OR = 3.9, P = .01) were associated with epithelial ingrowth (total R² = 15.4).

CONCLUSIONS: The potential risk factors described above may forewarn surgeons as to which individuals merit closer observation for this complication.

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Epithelial ingrowth is one of the most common complications following LASIK and clinically apparent in up to 9.1% of cases. Post-mortem histopathological studies have revealed that some degree of epithelial ingrowth is evident in nearly half of patients following LASIK. Clinical signs of epithelial ingrowth range from subtle interface epithelial pearls or fluorescein pooling at the edge of the flap to devastating complications such as keratolysis or melting of the flap edge. Clinically apparent epithelial ingrowth seems to occur when a route develops under the flap, which allows epithelial cell growth and invasion into the interface. Epithelial ingrowth has been associated with epithelial defects at the time of surgery, history of recurrent corneal erosions, hyperopic LASIK correction, repeat LASIK surgery, flap instability, corneal epithelial basement membrane dystrophy, and a history of ingrowth in the fellow eye.

Over time, new risk factors for the development of epithelial ingrowth may be identified. Specifically, a paucity of data exists regarding the potential risk factors in otherwise healthy eyes. Therefore, the aim of this study was to identify factors that may predict epithelial ingrowth following uncomplicated microkeratome-assisted LASIK surgery.

PATIENTS AND METHODS

All data for the study were collected and analyzed in accordance with the policies and procedures of the Institution.
al Review Board of the Barzilai Medical Center and the tenets of the Declaration of Helsinki.

**Study Participants**

This retrospective study included consecutive patients who underwent bilateral LASIK by multiple surgeons between January 2005 and December 2014 at Care-Vision Laser Centers, Tel-Aviv, Israel. Inclusion criteria were: age 18 years or older; a stable refraction for at least 12 months; intraocular pressure of less than 21 mm Hg; a period without wearing contact lenses (more than 2 weeks for rigid contact lenses and more than 4 days for soft contact lenses); and no history of autoimmune disease, diabetes mellitus, or previous ocular surgery. Patients with myopia up to -12.00 diopters (D), hyperopia up to +6.00 D, or a cylinder of up to 6.00 D were included.

**Surgical Technique**

All patients underwent the following detailed microkeratome-assisted LASIK procedure. One drop of a topical anesthetic (benoxinate hydrochloride 0.4%) was instilled in the conjunctival fornix of the eye prior to surgery, after which an eyelid speculum was inserted. A -1, 0, +1, or +2 suction ring of the Moria microkeratome (Moria SA, Antony, France) was used depending on corneal diameter and steepness. The Moria SBK-90 head created nasal hinge flaps and the Moria M2-90 heads created superior hinge flaps. After cutting and lifting the flap, intraoperative pachymetry measured the post-flap lifting central corneal thickness. The flap thickness was calculated by subtracting the post-flap lifting central corneal thickness from the precutting central corneal thickness. The stromal bed was ablated using Allegretto EX200 or EX500 excimer laser (Alcon WaveLight AG, Erlangen, Germany). Balanced salt solution was used for irrigation before the flap was repositioned. Patients were examined 1 day, 1 week, and 1, 3, and 6 months postoperatively and more if necessary. Patients were encouraged to return for examination if vision deteriorated at any time after surgery, and further treatment was offered free of charge at any time point following surgery. In cases of enhancement, careful flap dissection was performed with a LASIK spatula, then lifted and treatment performed on the stroma, followed by meticulous flap repositioning.

**Data Collection**

The medical files of all eligible patients were reviewed and the following demographic and preoperative information was extracted: age at operation, gender, systemic comorbidities, preoperative sphere, spherical equivalence, preoperative cylinder, mean keratometric power, minimum keratometric power (Kmin), maximum keratometric power (Kmax), and axis.

The following intraoperative information was extracted: type of microkeratome, precutting central corneal thickness, post-flap lifting central corneal thickness (both measured by ultrasonic pachymetry [Sonomed Escalon, New Hyde Park, NY] in the operating room), flap thickness (precutting central corneal thickness – post-flap lifting central corneal thickness), operating room humidity, operating room temperature, suction ring size (-1, 0, +1, or +2), stop value (+7.0, +8.0, +8.5, or +9.0), the involved eye (right or left), and surgeon identity. A low volume surgeon was defined as a surgeon who performed fewer than 1,000 procedures during the study period.

Cases in which clinically evident epithelial ingrowth developed and were of grade 2 or above based on the Probst and Machat criteria were included. If epithelial ingrowth developed following postoperative flap trauma or following an intraoperative complication, they were excluded from additional statistical analyses.

**Statistical Analysis**

Data were analyzed with the Minitab Software (version 17.1.0; Minitab, Inc., State College, PA). For the analysis of continuous data, the Student’s t test was used for normally distributed variables and the Kruskal–Wallis test for nonparametric variables. One-way analysis of variance was used for comparison of multiple group averages. For the analysis of categorical variables, the chi-square or Fisher’s exact test was used and, when applicable, odds ratio (OR) values were calculated.

Finally, a multiple logistic regression analysis, adjusted for year of surgery, was performed in an attempt to determine predictors of epithelial ingrowth. For this purpose, independent variables that reached a significance level of less than .05 in univariate analysis were included. In all analyses, a two-sided P value of less than .05 was considered statistically significant. All presented means are accompanied by their respective standard deviations.

**Results**

Overall, 30,574 eyes of 15,287 patients were included in the final analysis. Of the 149 cases (0.49%) of epithelial ingrowth that were identified, 11 were excluded due to postoperative flap trauma (n = 6) or intraoperative complications (n = 5). Therefore, 138 cases were included in further analyses.

The results of the univariate analyses comparing eyes with and without epithelial ingrowth are depicted in Table A (available in the online version of this article). The epithelial ingrowth group was older (35.3 ± 12.3 vs 31.7 ± 10.3 years, P = .001), had a higher proportion of moderate to high hyperopia (13.7% vs 5.3%, P < .001) (Figure 1), early postoperative flap...
slippage requiring flap repositioning (9.4% vs 2.8%, \( P < .001 \)), or flap lifting for enhancement (48.6% vs 4.3%, \( P < .001 \)), and was treated with a smaller optic zone (6 vs 6.5 or 7 mm) (37.7% vs 15.2%, \( P < .001 \)), with a Moria M2 versus Moria SBK microkeratome (70.1% vs 55.5%, \( P = .02 \)), by low volume surgeons (n < 1,000) (5.8% vs 1.3%, \( P < .001 \)), in a lower operating room temperature (22.3°C ± 1.8°C vs 22.8°C ± 1.6°C, \( P = .005 \)), and with a greater maximum ablation depth (67.3 ± 29.7 vs 57.3 ± 30.3 µm, \( P < .001 \)). Significant differences in rates of epithelial ingrowth were detected in cases performed by less experienced surgeons when compared to more experienced surgeons and among the experienced surgeons themselves (\( P < .001 \)) (Figure 2).

Table 1 depicts the results of the multivariate analysis. Briefly, previous flap relifting for enhancement was the strongest factor associated with epithelial ingrowth (OR = 19.5, \( P < .001 \)). In addition, a small (6 vs 6.5 or 7 mm) optic zone (OR = 2.2, \( P < .001 \)), moderate to severe hyperopia (OR = 2.4, \( P < .005 \)), greater ablation depth (OR = 1.005, \( P < .001 \)), and low volume surgeon (OR = 3.9, \( P < .01 \)) were associated with epithelial ingrowth (total \( R^2 = 15.4 \)).

There was a high incidence of epithelial ingrowth in the enhancement group when compared to primary LASIK (4.8% vs 0.2%, \( P < .001 \)). The time between treatments (primary and enhanced LASIK) was significantly greater in the epithelial ingrowth group when comparing both means (1,110 ± 870 vs 626 ± 662 days, \( P < .001 \)) and medians (974 vs 329 days, \( P < .001 \)). In addition, there was a significant rise in epithelial ingrowth rates as time between primary and enhancement LASIK increased, peaking at 4 to 5 years (\( P < .001 \)) (Figure 3).

**DISCUSSION**

This large cohort study identified preoperative and intraoperative factors associated with epithelial in-
growth, some of which, to the best of our knowledge, have yet to be reported.

In this study, the incidence rate (0.49%) of epithelial ingrowth was somewhat lower than previously reported studies. Wang and Maloney reported an incidence of 0.92% following primary LASIK and 1.7% following cases with previous LASIK treatment. Caster et al. reported epithelial ingrowth in 2.3% of their flap lifting re-treatment cases. This may be a byproduct of a varying definition or cut-off among clinicians as to what meets the definition of epithelial ingrowth. In the current study, we did not include epithelial ingrowth cases that were lower than grade 2 because they are of little clinical significance. 

In the current study, flap relifting for enhancement was the strongest variable associated with epithelial ingrowth (OR = 19.5, \( P < .001 \)). During flap relifting, the surgeon may insert epithelial cells under the flap or the flap may not be correctly realigned with the stromal bed when it is repositioned. Nearly two decades ago, in a comparably smaller cohort, Wang and Maloney reported that the incidence of epithelial ingrowth was nearly two times greater following enhancement when compared to primary LASIK, despite the difference being not statistically significant. Henry et al. reported that the most common factor associated with epithelial ingrowth in their series was previous LASIK surgery, representing nearly two-thirds of their cases of epithelial ingrowth requiring flap lifting. This finding was further substantiated by the findings of several other groups. Interestingly, Chan and Boxer Wachler attempted to identify re-treatment techniques that lower epithelial ingrowth rates. However, they found no significant difference between the different techniques that were investigated. Future studies investigating LASIK enhancement techniques that reduce epithelial ingrowth rates are warranted.

In this study, time between primary LASIK and flap lifting played a major role because the epithelial ingrowth group had nearly two (mean) to three (median) times the amount of time that had gone by when compared to controls. Caster et al. reported that when the flap lifting re-treatment was performed 3 or more years after primary LASIK, the risk for clinically significant epithelial ingrowth increased significantly. Similarly, in the current study, there was a sharp significant rise in epithelial ingrowth rates from 3% to 5% for enhancement performed in the first 3 years after LASIK to approximately 16% for enhancement performed at 4 to 5 years after LASIK. These findings support the speculation that there may be an important change in LASIK flap healing that occurs approximately 3 to 4 years after flap creation, as originally suggested by Caster et al.

In the current study, moderate to severe hyperopia was associated with epithelial ingrowth. This finding is supported by two previous studies that reported that hyperopic primary LASIK was associated with epithelial ingrowth. Furthermore, in vivo confocal microscopy has demonstrated that subclinical epithelial ingrowth is more common following primary hyperopic LASIK. Patients with moderate to severe hyperopia who undergo LASIK demonstrate central steepening that lifts the flap and thus creates a larger gutter at the flap edge, facilitating entry of the epithelial cells. Indeed, Randleman et al. reported preoperative hyperopia as a significant risk factor for epithelial defects during LASIK. It may be that epithelial trauma/microtrauma at the time of surgery and/or epithelial healing barriers (high hyperopic corrections) contribute to subsequent epithelial ingrowth and, as such, they both share common risk factors.

In general, epithelial ingrowth results from misalignment of the flap and stromal bed with an emphasis on the flap edges. To the best of our knowledge, the current study identified several additional parameters associated with epithelial ingrowth that support this concept and have yet to be reported. For instance, a smaller optic zone and a greater maximum ablation depth were associated with epithelial ingrowth. We speculate that both of these variables may lead to more misalignment between the flap and the treated stromal bed and thus easier entrance of epithelial cells under the flap.

In the current study, low volume surgeons had higher epithelial ingrowth rates than the more experienced surgeons. More experienced surgeons are more experienced in repositioning the flap and preventing gaps at the flap margin and there is less chance of flap slippage. This finding is supported by those of Jabbur et al., who reported that epithelial ingrowth was as-
associated with the surgeon’s learning curve. This perhaps indicates that when teaching trainees to perform LASIK surgery, an emphasis should be put on correctly repositioning the flap, verifying that there are no gaps at the edges, and maintaining a clear interface between the lap and stromal bed.21

In this study, we did not analyze and compare the surgical management of different grades of epithelial ingrowth. Treatment depends on severity, where the majority of mild clinically insignificant ingrowth cases (not involving the visual axis) can be managed with observation. In more severe cases, treatment is often surgical and includes flap lift, mechanical removal of the interface epithelial cells by a blade, and replacement of the flap.22 With recurrent episodes of epithelial ingrowth, additional options include flap suture, fibrin glue, or YAG laser treatment.23–27

This study had several limitations. First, despite the large amount of eyes included in this study, one must bear in mind its retrospective nature and the inherent limitations that come with such a study design. Second, it is probable that there are additional factors that may be associated with epithelial ingrowth that were not examined in this study, such as type of laser system used,28 and epithelial defect during surgery.17,18 Furthermore, all patients in the current study underwent microkeratome-assisted LASIK, whereas others have shown that femtosecond laser-assisted LASIK may reduce epithelial ingrowth rates.3,29–33 Finally, some patients may have developed epithelial ingrowth and sought treatment elsewhere; however, patients were encouraged to return immediately at any sign of vision loss or discomfort and were offered further treatments free of charge, and we therefore believe this factor to be negligible.

We presented a large scale study assessing the factors that are associated with epithelial ingrowth following microkeratome-assisted LASIK. Specifically, this study found that flap lifting for enhancement, moderate to severe hyperopia, optic zone of 6 mm, greater maximum ablation depth, and surgeries performed by low volume surgeons are significantly associated with epithelial ingrowth. These potential risk factors may forewarn surgeons as to which individuals merit closer observation for this potentially devastating complication.

**AUTHOR CONTRIBUTIONS**

Study concept and design (AF, MM, IK); data collection (AF, MM, IK); analysis and interpretation of data (AF, MM, IK, AYN, TS, GM); writing the manuscript (AF, MM, IK, AYN, TS, GM); critical revision of the manuscript (AF, MM, IK, AYN); statistical expertise (AF, MM, IK, AYN, TS, GM); supervision (MM)

**REFERENCES**


### TABLE A
Univariate Analysis of Eyes With and Without Epithelial Ingrowth Following Microkeratome-Assisted LASIK

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Epithelial Ingrowth (n = 138)</th>
<th>Control (n = 30,574)</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>58.2%</td>
<td>53.5%</td>
<td>1.2 (0.9 to 1.7)</td>
<td>.28</td>
</tr>
<tr>
<td>Eye (right)</td>
<td>46.4%</td>
<td>50.6%</td>
<td>0.8 (0.6 to 1.2)</td>
<td>.32</td>
</tr>
<tr>
<td>Low hyperopia (0.50 to -2.00 D)</td>
<td>4.6%</td>
<td>3.2%</td>
<td>1.4 (0.60 to 3.30)</td>
<td>.38</td>
</tr>
<tr>
<td>Moderate/high hyperopia (&gt; 2.00 D)</td>
<td>13.7%</td>
<td>5.3%</td>
<td>2.8 (1.70 to 4.70)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>High myopia (&lt; -6.00 D)</td>
<td>10.7%</td>
<td>6.4%</td>
<td>1.8 (1.0 to 3.1)</td>
<td>.04</td>
</tr>
<tr>
<td>Flap repositioning following slippage</td>
<td>9.4%</td>
<td>2.8%</td>
<td>3.6 (2.0 to 6.4)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Flap lifting for enhancement</td>
<td>48.6%</td>
<td>4.3%</td>
<td>20.8 (14.8 to 29.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Moria M2 microkeratome</td>
<td>70.1%</td>
<td>55.5%</td>
<td>1.9 (1.1 to 3.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Optic zone (&gt; 6 mm)</td>
<td>37.7%</td>
<td>15.2%</td>
<td>3.4 (2.4 to 4.8)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Low volume surgeon (n &lt; 1,000)</td>
<td>5.8%</td>
<td>1.3%</td>
<td>4.7 (2.3 to 9.6)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>35.3 ± 12.3</td>
<td>31.7 ± 10.3</td>
<td>–</td>
<td>.001</td>
</tr>
<tr>
<td>Central corneal thickness (µm)</td>
<td>547.7 ± 36.0</td>
<td>543.8 ± 32.0</td>
<td>–</td>
<td>.21</td>
</tr>
<tr>
<td>Maximum ablation depth (µm)</td>
<td>67.3 ± 29.7</td>
<td>57.3 ± 30.3</td>
<td>–</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Mean keratometric power (D)</td>
<td>43.80 ± 1.60</td>
<td>43.80 ± 1.90</td>
<td>–</td>
<td>.98</td>
</tr>
<tr>
<td>Kmin (D)</td>
<td>43.20 ± 1.60</td>
<td>43.10 ± 1.40</td>
<td>–</td>
<td>.84</td>
</tr>
<tr>
<td>Kmax (D)</td>
<td>44.30 ± 1.60</td>
<td>44.10 ± 1.40</td>
<td>–</td>
<td>.34</td>
</tr>
<tr>
<td>CDVA (logMAR)</td>
<td>0.00 ± 0.07</td>
<td>-0.01 ± 0.07</td>
<td>–</td>
<td>.23</td>
</tr>
<tr>
<td>Sphere (D)</td>
<td>-2.11 ± 3.10</td>
<td>-2.43 ± 2.27</td>
<td>–</td>
<td>.23</td>
</tr>
<tr>
<td>Cylinder (D)</td>
<td>-0.83 ± 0.99</td>
<td>-0.78 ± 0.92</td>
<td>–</td>
<td>.59</td>
</tr>
<tr>
<td>Spherical equivalent (D)</td>
<td>-2.55 ± 3.19</td>
<td>-2.78 ± 2.28</td>
<td>–</td>
<td>.42</td>
</tr>
<tr>
<td>Operating room temperature (°C)</td>
<td>22.3 ± 1.84</td>
<td>22.8 ± 1.6</td>
<td>–</td>
<td>.005</td>
</tr>
<tr>
<td>Operating room humidity (%)</td>
<td>38.1 ± 4.3</td>
<td>38.1 ± 3.3</td>
<td>–</td>
<td>.96</td>
</tr>
</tbody>
</table>

CI = confidence interval; D = diopters; Kmin = minimum keratometry; Kmax = maximum keratometry; CDVA = corrected distance visual acuity

*Values are presented as mean ± standard deviation unless otherwise noted.

The Moria M2 microkeratome is manufactured by Moria SA, Antony, France.