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Corneal epithelial adhesion abnormalities associated with LASIK*[1]

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Abstract

Purpose

To assess the clinical characteristics, incidence, and pathologic correlation of corneal epithelial adhesion abnormalities encountered during LASIK.

Design

Prospective noncomparative interventional case series.

Participants

Five hundred consecutive eyes of 268 patients undergoing primary LASIK procedures by one surgeon utilizing the Moria LSK One microkeratome and VISX Star S-2 excimer laser.

Methods

Corneal epithelial adhesion was assessed immediately preoperatively using a cellulose surgical sponge (adhesion test), and the incidence, extent, and location of epithelial defects occurring during the microkeratome incision of the corneal flap were recorded. Epithelial specimens from 7 corneas requiring debridement of dysadhesive epithelium were examined by transmission electron microscopy.

Main outcome measures

The characteristics of the study population (age, gender, contact lens use, relevant ocular surface or systemic disease, refractive error, keratometry, pachymetry) and the microkeratome-related variables (head selection and vacuum level) were compared with the results of the preoperative epithelial adhesion test, the development of intraoperative epithelial effects (size and location), and the postoperative outcome.

Results

Epithelial defects were sustained by 51 corneas (10.2%), and among these, 31 (6.2%) were microdefects and 20 (4.0%) were macrodefects. The adhesion test was positive (indicative of compromised adhesion of epithelium to stroma) in 20 (64.5%) corneas with microdefects, but false negatives (epithelial defect despite negative adhesion test) occurred in 11 cases (35.4%). The adhesion test was positive in 16 (80%) of corneas having macrodefects, with 4 (20%) false negatives. Thus, the overall positive predictive value of the adhesion test was 59%, and the percentage of positive prediction was 92% (Bayes' theorem). Among all other outcome measures assessed, only corneal flap thickness seemed a potential risk factor, as 40 (78.4%) epithelial defects were associated with the creation of a 180-μm-thick flap, whereas 10 (19.6%) were associated with a 160-μm-thick flap and only 1 (2%) occurred with a 130-μm flap. These trends were not, however, statistically significant ($P = 0.15$, Fisher exact test). Transmission electron microscopy of all epithelial debridement specimens disclosed consistent abnormality of the basement membrane adhesion complex, as thickened and multilaminated basement membrane remained adherent to the intact epithelial sheet.

Conclusions:

Corneal epithelial dysadhesion and defects occurring in the course of LASIK surgery may be associated with an intrinsic compromise of the basement membrane adhesion complex, as evidenced clinically by the adhesion test and demonstrated pathologically by duplicated

basement membrane.

Article Outline

• Materials and methods
• Results
• Discussion
• References

Problems encountered during LASIK range from the minor difficulties of superficial punctate keratitis to the major complications of sterile or infectious keratitis.[1, 2 and 3] A somewhat common but usually innocuous occurrence is the development of corneal epithelial defects during the traverse of the microkeratome. [4] Such defects are reported to increase the risk of postoperative epithelialization of the intrastromal interface, diffuse lamellar keratitis, and irregular astigmatism. [5, 6 and 7] Yet, aside from a single report [8] and an unpublished study (Belin M. Experience with the Moria LSK One single-use microkeratome. Presented at: American Society of Cataract & Refractive Surgery Annual Meeting, May, 2001; San Diego), current reviews [1, 2 and 3] and texts [4] make only limited reference to the problem. Having particular interest in corneal epithelial adhesion, [9, 10 and 11] we sought to define the clinical characteristics, incidence, and pathology of LASIK-related corneal epithelial adhesion abnormalities.

Materials and methods

In this prospective, noncomparative, interventional case series, 500 consecutive primary LASIK procedures performed by a single surgeon (KRK) between October 2000 and September 2001 were studied. Each patient was examined preoperatively by the operating surgeon, and eyes with a history of recurrent corneal erosion and/or biomicroscopic evidence of anterior basement membrane dystrophy (map–dot–fingerprint), major keratoconjunctivitis sicca, decreased corneal sensation, corneal exposure, or chronic blepharitis were excluded from study, as these criteria also comprised contraindications for LASIK surgery. Eyes with previous excimer photorefractive keratectomy (PRK) and undergoing subsequent LASIK enhancement were also excluded. Eyes with prior penetrating keratoplasty or radial keratotomy were included if their corneal surface appeared normal by slit-lamp biomicroscopy.

The overall study population comprised 500 eyes of 268 individuals (140 males and 128 females) with an average age of 47 years (range = 23–64). Among 411 myopic eyes, the average preoperative spherical equivalent refractive error was –3.8 diopters (D) (range = –1.5 to –10.25), and average keratometry was 44.2 D (range = 38–48). Among 89 hyperopic eyes, the average preoperative spherical equivalent refractive error was +2.7 D (range = +1.0 to +6.75), and average keratometry was 42.4 D (range = 39–46). Approximately half (49%) of the subjects had worn soft hydrophilic or rigid gas permeable contact lenses. Three eyes had received penetrating keratoplasty, whereas 3 had undergone radial keratotomy. Only 3 individuals (6 eyes) had diabetes mellitus, 5 (9 eyes) had prior hyperthyroidism, and 5 (10 eyes) reported allergies.

All LASIK procedures were performed at either Laser Eye Consultants of Boston (Boston, Massachusetts) or Eye Health Vision Center (North Dartmouth, Massachusetts) utilizing identical protocols and instrumentation. In particular, preoperative anesthesia comprised a single drop of proparacaine hydrochloride 0.5% instilled approximately 5 minutes before surgery, followed by a single drop of tetracaine hydrochloride 0.5% (Ciba, Duluth, GA) immediately before insertion of the lid speculum. Several drops of balanced salt solution (BSS) were applied to prevent drying of the corneal surface as the patient was positioned beneath the operating microscope of the excimer laser.

For purposes of this study, the surgeon then assessed corneal epithelial–stromal adhesion (the adhesion test) as follows: a cellulose surgical sponge (Weckcel [Edward Weck, Research Triangle Park, NC] or Merocel [Medtronic Solan, Jacksonville, FL]) was moistened with BSS, applied gently to the inferior midperipheral corneal surface, and stroked 3 times tangentially in a temporal–nasal direction. The same maneuver was then repeated on the superior midperipheral corneal surface. If the corneal epithelium retained its adhesion to the underlying stroma, the adhesion test was graded as negative. If, however, the corneal epithelium shifted position, formed corrugated folds, or developed a break, the adhesion test was graded as positive.

Irrespective of the adhesion test result, the fixation ring of the Moria LSK One microkeratome (Moria, Inc., Antony, France) was applied, the corneal surface was irrigated with carboxymethyl–cellulose sodium 0.5% (Refresh Plus, Allergan, Irvine, CA), and a nasally hinged corneal flap was incised with the microkeratome. Depending upon the preoperative corneal pachymetry and predicted stromal ablation depth, the microkeratome head selected was designated either 100, 130, or 150 (thereby creating a flap thickness of 130, 160, or 180 μm, respectively). During the withdrawal stroke of the microkeratome, the vacuum level of the suction ring was either maintained (high) or reduced (low) according to randomization independent of adhesion test result or occurrence of epithelial dysadhesion during the microkeratome incision. If both eyes of a patient were to undergo LASIK, either simultaneously or sequentially, then one eye was subjected to high vacuum while the other eye sustained low vacuum. A new microkeratome blade was always utilized for each surgical procedure.

After microkeratome withdrawal and removal of the suction ring, the corneal flap was reflected nasally, the stromal ablation was performed, and the flap was repositioned, followed by interface irrigation with balanced salt solution and stroking of the flap from nasal to temporal with a moist cellulose surgical sponge. If an epithelial defect developed, then the dysadhesive fragments were debrided with fine jeweler's forceps. Minor epithelial fragments from microdefects (<2×2 mm) were discarded, but epithelial sheets from macrodefects (>2×2 mm) occurring in 7 eyes were immediately immersed in either 10% formalin or half-strength Karnovsky's fixative and prepared for transmission electron microscopy. The location and dimensions of the epithelial defects were recorded. In cases developing macrodefects of the epithelium and/or defects involving the visual axis, a bandage soft contact lens was applied. At the conclusion of surgery, intracanalicular collagen implants were always inserted in the superior and inferior puncta, as is our standard operative procedure. Postoperatively, all eyes received fluorometholone (FML, Allergan) and either ofloxacin (Ocuflox, Allergan) or tobramycin (Tobrex, Alcon, Ft. Worth, TX) 4 times a day for 1 week. Patients were typically examined at postoperative day 1, week 1, and months 1, 3, and 6. Interim visits were performed as indicated for management of epithelial defects or other unanticipated events. For all eyes, uncorrected and best-corrected visual acuities, performance of enhancement or other secondary procedures, and development of

complications were recorded. All patients were observed for a minimum of 1 month postoperatively. Statistical analyses for differences between means were performed using the Fisher exact test. The percentage of positive prediction and the positive predictive value of the adhesion test were calculated using Bayes' theorem.

Negative controls for morphologic study included epithelial specimens from 2 corneas undergoing excimer laser PRK in which epithelial–stromal adhesion was diminished by application of 20% ethanol to the corneal surface for 15 seconds. In both cases, there was neither historical nor biomicroscopic evidence of corneal epithelial dysadhesion, and the intraoperative epithelial adhesion test was negative. Positive controls comprised epithelial specimens from 2 corneas undergoing PRK, which exhibited both biomicroscopic signs of anterior basement membrane dystrophy and a positive epithelial adhesion test.

Results

Epithelial defects were sustained by 51 corneas (10.2%) of 36 patients. Among these, 31 (6.2%) were microdefects (<2×2 mm) occurring in 26 patients, whereas 20 (4.0%) were macrodefects (>2×2 mm) occurring in 16 patients. Microdefects were usually a uniocular phenomenon, as developed in 21 of 26 (80.8%) patients, with 5 (19.2%) patients exhibiting bilateral microdefects. Macrodefects were also predominantly unilateral, as observed in 12 of 16 (75%) patients, with 5 (25%) patients demonstrating bilateral macrodefects. Microdefects developed equally among males and females (13 vs. 13), whereas macrodefects were somewhat more common in females than in males (11 vs. 5). Although no defects developed in patients younger than 30 years, individuals with defects did not otherwise differ in age from the overall study population.

All defects developed during the forward cutting stroke of the microkeratome. Microdefects invariably occurred at the superior margin of the flap, whereas macrodefects were usually superior (9 cases) but also occurred centrally (3 cases) and inferiorly (4 cases), suggesting more generalized epithelial dysadhesion. After flap replacement and epithelial debridement, soft contact lenses were applied in all 20 macrodefect cases and in 15 of 31 microdefect cases. The adhesion test was positive for dysadhesion in 20 of 31 (62%) corneas developing microdefects, but false negatives (i.e., epithelial defect despite negative adhesion test) occurred in 11 cases (38%) (Table 1). The adhesion test was positive in 16 (80%) of corneas sustaining macrodefects, with false negatives in 4 (20%). Among all 61 corneas with positive adhesion tests, there were 25 (41%) false positives (i.e., no epithelial defect despite positive adhesion test), but among all 439 corneas with negative adhesion tests, there were only 15 (3.4%) false negatives (i.e., epithelial defect despite negative adhesion test). Thus, the adhesion test proved highly accurate in detecting epithelial dysadhesion, especially in corneas developing macrodefects, and is highly predictive in detecting normal epithelial adhesion (P<0.001). The positive predictive value of the adhesion test was 59%, whereas the percentage of positive prediction was 92%. (Importantly, there was also no correlation between the location in which the adhesion test was performed and the position of the subsequent epithelial defect. Thus, performance of the adhesion test did not provoke development of the epithelial defects.)

Table 1. Adhesion Test Results Versus Epithelial Defect Occurrence

	Adhesion Test	
	Positive	Negative
Microdefect	20 (64.5%)	11 (33.5%)
Macrodefect	16 (80%)	4 (20%)
No defect	25 (5.6%)	424 (94.4%)

P<0.0001 for false positive versus true negative, Fisher exact test.

The occurrence of epithelial defects seemed dependent upon the selection of the microkeratome head utilized and corneal flap thickness thereby created. Specifically, 40 defects were associated with the 150 head (180-μm flap, used in 366 cases overall), 10 defects developed with the 130 head (160-μm flap, used in 100 cases), and only 1 defect occurred with the 100 head (130-μm flap, used in 34 cases). Thus, incidences of defects were 10.9% with the 150 head, 10.0% with the 130 head, and 2.9% with the 100 head.

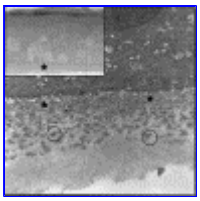
From another perspective, among all defects, 78.4% were associated with the 150 head, 19.6% with the 130 head, and 1.96% with the 100 head. Despite this trend, these differences were not statistically significant ($P = 0.15$).

Complications in this series were rare. Diffuse lamellar keratitis occurred in 5 eyes (1.0%): 4 cases unassociated with epithelial defects and 1 case associated with a microdefect. Neither interface epithelialization nor infectious keratitis was encountered.

Enhancements have been required thus far in 26 eyes (5.2%). Importantly for the purpose of this study, neither complications nor enhancements were increased in patients with epithelial defects.

Epithelial defects were also unassociated with preoperative refractive error or keratometry, with intraoperative use of high versus low vacuum during microkeratome withdrawal, and with postoperative visual acuity relative to the overall study group. There was insufficient prevalence of either ocular surface disease (including keratitis sicca) or systemic disease to afford comparison.

Morphologic findings in the dysadhesive epithelium were remarkably consistent for all 7 cases studied. In particular, the intact epithelial sheets displayed nearly continuous basement membrane that remained uniformly adherent to the intact basal cell plasma membrane (Figure 1 and Figure 2). This basement membrane material ranged in thickness from 0.5 to 5.0 μm and was usually multilaminated to as many as 10 layers with interspersed anchoring fibrils, plus fibrillar collagen and amorphous material. In contrast, negative control specimens of normal corneal epithelium removed at PRK demonstrated no attached basement membrane or extracellular material (Fig 3), whereas positive control specimens from corneas with anterior basement membrane dystrophy exhibited multilaminated basement membrane of approximately 2 μm in thickness that had remained adherent to the epithelium (Fig 4), and thus were morphologically identical to the specimens from LASIK-related epithelial defects.



(58K)

Figure 1. Corneal epithelial debridement specimen from a 40-year-old female who developed a macrodefect during LASIK. **Inset,** Phase contrast microscopy discloses an intact epithelial sheet with an underlying thick layer of extracellular material (*) (stain, toluidine blue; original magnification, ×1200). **Main figure,** By transmission electron microscopy, the basal epithelial cells (above) are intact, and adherent to the cell membrane is an extremely thickened (≈5 μm) aberrant layer of multilaminated basement membrane (*) interspersed with clustered anchoring fibrils (○) and fibrillar collagen (original magnification, ×17 500).

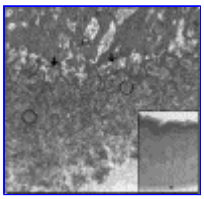


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Figure 2. Corneal epithelial debridement specimen from a 50-year-old female who developed a macrodefect during LASIK. **Inset,** Phase contrast photomicrograph shows an extracellular layer (*) attached to the basal surface of the intact epithelial sheet (stain, toluidine blue; original magnification, ×1200). **Main figure,** Transmission electron microscopy resolves this approximately 3.6-μm-thick extracellular layer to be comprised of multiple basement membrane layers (arrows), anchoring fibrils (○), and fibrillar collagen (original magnification, ×30 000).

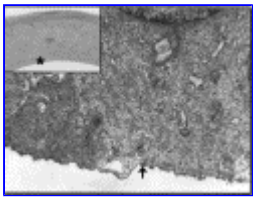

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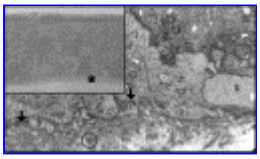
Figure 3. Corneal epithelium removed from a 37-year-old female undergoing photorefractive keratectomy. **Inset,** By phase contrast microscopy, although the epithelial sheet remains intact, the basal surface (*) is apparently devoid of extracellular material (stain, toluidine blue; original magnification, ×900). **Main figure,** Transmission electron microscopy of the basal epithelial surface confirms that the basal epithelial cell plasma membrane is largely intact and displays hemidesmosomes (arrow), but no basement membrane is associated (original magnification, ×30 000).



(39K)

Figure 4. Corneal epithelium debrided from a 45-year-old male with epithelial basement membrane dystrophy. **Inset,** Phase contrast microscopy demonstrates an intact epithelial sheet with attached extracellular material (*) (stain, toluidine blue; original magnification, ×1200). **Main figure,** By transmission electron microscopy, duplications of basement membrane plus anchoring fibrils and fibrillar material are observed to remain adherent to the basal epithelial cell plasma membrane (arrows) (cf. Figure 1 and Figure 2) (original magnification, ×26 000).

Discussion

While performing LASIK, corneal epithelial defects occurring during the microkeratome incision are not uncommon. To minimize their development, several preventive strategies are recommended, including contraindication of LASIK in patients with known epithelial basement membrane (map–dot–fingerprint) dystrophy, preoperative optimization of concomitant ocular surface disorders (typically, dry eye or chronic blepharitis), avoidance of excessive intraoperative topical anesthetic use, lubrication of the corneal surface before the microkeratome pass, and release of suction ring vacuum during microkeratome withdrawal.[4 and 5] Utilizing all these approaches, we nonetheless observed an epithelial defect incidence of 10.2%, comprising 6.2% microdefects (<2×2 mm) and 4.0% macrodefects (>2×2 mm). This rate of occurrence is remarkably similar to that observed by M. Belin (Experience with the Moria LSK One single-use microkeratome. Presented at: American Society of Cataract & Refractive Surgery Annual Meeting, May, 2001; San Diego), who encountered 10.1% epithelial defects while utilizing the same microkeratome system as in the current study. In the only other published study of which we are aware, Smirennaia et al [8] reported only 1.6% of LASIK cases with intraoperative epithelial damage.

As such epithelial abrasions typically resolve without sequelae, they are considered more of a nuisance problem than a true complication. Yet, in rare instances, the occurrence of diffuse lamellar keratitis, microbial keratitis, interface epithelialization, and irregular astigmatism have been reported.[5, 6, 7 and 8] Utilizing copious irrigation during flap repositioning, debridement of all loose epithelial fragments, therapeutic soft contact lenses (especially for macrodefects), and topical medications (including antibiotics, corticosteroids, nonsteroidal anti-inflammatory agents, and lubricants), we have fortunately avoided such complications.

Among all risk factors surveyed (including patient age, gender, ocular surface or systemic disease, prior corneal surgery, preoperative refractive error, keratometry or corneal thickness, and postoperative visual acuity), only corneal flap thickness (as a function of the microkeratome head utilized) seemed related to epithelial dysadhesion. In particular, though 78.4% of defects were associated with 180-μm flaps, versus 19.6% with 150-μm flaps versus 1.96% with 100-μm flaps, the relative rates of epithelial defect formation in these same subsets were 10.9%, 10.0%, and 2.9%, respectively, a trend that was not statistically significant. Interestingly, these findings are also consistent with those of Belin (Belin M. Experience with the Moria LSK One single-use microkeratome. Presented at: American Society of Cataract & Refractive Surgery Annual Meeting, May, 2001; San Diego), who experienced 75% of epithelial defects associated with 180-μ flaps, versus 25% with 160-μm flaps versus 0% with 130-μm flaps. Although the explanation for this observation is uncertain, it might be speculated that having a thicker corneal flap requires greater compressive effect of the microkeratome head, which exerts a higher shear force at the corneal surface.

The bilaterality of epithelial defects in conjunction with the results of the epithelial adhesion

test suggests that certain individuals are predisposed to develop epithelial dysadhesion. In particular, bilateral epithelial microdefects occurred in 19% of patients and macrodefects developed in 25% of patients undergoing bilateral LASIK. The epithelial adhesion test was positive (abnormal) in 64.5% of microdefect eyes and in 80% of macrodefect eyes. These tendencies, although suggestive, were not statistically significant, given the 35.5% and 20% false-negative adhesion test results for microdefects and macrodefects respectively. Yet, in the overall context, the epithelial adhesion test proved highly significant ($P<0.0001$) as a useful screening technique, for among the 439 eyes with negative adhesion tests, only 15 (3.4%) developed epithelial defects (false-negative test). In the clinical context, therefore, the observation of a positive adhesion test might encourage the selection of a microkeratome head to produce a thinner flap and/or alert the surgeon to the likelihood of impending epithelial adhesion problems.

Given these findings, should we conclude that microdefects are somewhat random events due to mechanical variations of surgical technique, whereas macrodefects are the consequence of an intrinsic defect of epithelial–stromal adhesion? Are there corneas whose clinically occult compromise of the basement membrane complex renders them an accident waiting to happen? Indeed, the consistent ultrastructural features of the epithelial debridement specimens of macrodefect cases strongly suggest this possibility. In particular, although age-related thickening and even multilaminar duplication of basement membrane in the normal human cornea are known to occur, such changes typically result in basement membrane thickness of only 0.1 to 0.5 μm for individuals of up to 55 years of age.[12 and 13] In all macrodefect specimens examined here, basement membrane thickness of at least 0.5 μm to as much as 5.0 μm was evident, comprised of multilaminar duplications of the lamina densa with anchoring fibrils and fibrillar collagen interspersed, thereby having the identical ultrastructural morphology of the aberrant basement membrane complex of corneas with epithelial basement membrane dystrophy [9, 14 and 15] (cf. Fig 4) or diabetes mellitus.

Equally compelling as the abnormal morphology of the epithelial adhesion complex is the retention of the anomalous basement membrane material by the dysadhesive epithelial sheet. In particular, when normal epithelium is mechanically separated (e.g., scraped) from the underlying stroma, the basement membrane is retained on the stromal surface, and the basal surface of the epithelial cell layer is devoid of basement membrane material[11] (cf. Fig 3). Epithelial scraping of corneas with epithelial basement membrane dystrophy [9 and 15] or diabetes mellitus, [16] in contrast, results in separation of the entire abnormal basement membrane complex from the stromal surface and its continued adhesion to the basal epithelial cell surface, exactly as encountered in our macrodefect epithelial specimens. Laibson [17] has suggested that the incidence of epithelial basement membrane dystrophy is perhaps 5% in the general population. Hence, it is inevitable that individuals who are asymptomatic for this dystrophy will undergo LASIK. Our findings, moreover, extend this supposition to propose that there exist individuals subclinically affected by epithelial basement membrane dystrophy who are not only asymptomatic but who are also without biomicroscopic evidence of the dystrophy until challenged by the stress of microkeratome-induced shear on the corneal surface. In such cases, perhaps appreciation of the epithelial adhesion test, plus creation of a thin corneal flap and meticulous management of any subsequent epithelial defect, should nonetheless optimize the LASIK outcome.

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