

# Preoperative Characteristics and a Potential Mechanism of Chronic Dry Eye after LASIK

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**PURPOSE.** To determine whether measurable preoperative characteristics predispose patients to chronic dry eye after laser in situ keratomileusis (LASIK).

**METHODS.** The study consisted of 24 eyes of 24 patients who underwent LASIK. Tear breakup time, Schirmer testing with and without anesthesia, rose bengal staining, central corneal sensitivity, nucleus-to-cytoplasmic ratio, and goblet cell density were evaluated 2 weeks before and 1 week, 3 months, and 9 months after surgery. Patients were classified into two outcome groups, the nondry-eye group (NDEG) and the chronic dry-eye group (CDEG), on the basis of dry eye status 9 months after surgery. The authors tested whether preoperative values of each parameter were associated with the development of chronic dry eye.

**RESULTS.** All parameters, except rose bengal staining, deteriorated significantly after surgery but returned to preoperative levels within 3 to 9 months. The CDEG had significantly lower preoperative Schirmer test values with and without anesthesia and were delayed in recovery after surgery in goblet cell density, rose bengal staining, Schirmer test values without anesthesia, and tear breakup time. Results of preoperative Schirmer tests without anesthesia positively correlated with tear breakup time 9 months after surgery.

**CONCLUSIONS.** Preoperative tear volume may affect recovery of the ocular surface after LASIK and may increase the risk for chronic dry eye. (*Invest Ophthalmol Vis Sci.* 2008;49:168–174) DOI:10.1167/iovs.07-0337

Many patients have taken advantage of the fast and relatively painless recovery of vision, the lower probability of regression of refractive correction, and the absence of subepithelial haze<sup>1</sup> provided by laser in situ keratomileusis (LASIK) compared with photorefractive keratectomy. However, LASIK

can affect the health of the ocular surface by decreasing corneal sensation,<sup>2</sup> tear secretion, tear quality, corneal and conjunctival epithelial integrity, and conjunctival goblet cell density.<sup>3</sup> These alterations decrease tear film stability<sup>4</sup> and may lead to dry eye symptoms during the first 6 months after surgery.<sup>1,2,5,6</sup> Despite the recovery of the ocular surface, a small number of patients continue to have chronic dry eye symptoms. If it is possible to identify preoperative characteristics of the tear film or ocular surface that induce a delay in recovering from dry eye after LASIK, it may be possible to start treatment for dry eye before surgery and to minimize the postoperative complications or, at a minimum, to better identify patients at high risk and counsel them accordingly. In the present study, we measured time-dependent changes in conjunctival morphology and clinical parameters of tear function before and after LASIK. Our goal was to determine whether preoperative characteristics of the tear film or ocular surface could delay recovery or predict the development of chronic dry eye syndrome after LASIK.

## METHODS

We enrolled 24 eyes of 24 patients who were undergoing LASIK at the Massachusetts Eye and Ear Infirmary between June 2002 and November 2003. This research followed the tenets of the Declaration of Helsinki. The Human Studies Committee of the Massachusetts Eye and Ear Infirmary, the Schepens Eye Research Institute, and the Department of the Army approved the study protocol, and all patients gave written informed consent. Inclusion criteria were that patients be between 21 and 40 years of age, be qualified for LASIK for myopia (<10 diopters) or hyperopia, fill out dry eye questionnaires, and be evaluated on subsequent visits. Patients were excluded from the study if they had severe dry eye with Schirmer test values (with anesthesia) <1 mm, had a history of arthritis or connective tissue disease, were pregnant, or were part of another dry eye study. All patients had a superior-hinge corneal flap.

A suspension of topical steroid (1% prednisolone acetate 4 times daily) and a topical antibiotic (ciprofloxacin 4 times daily) was routinely prescribed for 1 week after surgery. Among the clinical assessments we performed were Schirmer test with and without anesthesia, sodium fluorescein tear breakup time, central corneal sensitivity, rose bengal staining, and impression cytology from the nasal and superior bulbar conjunctiva twice within 2 weeks before LASIK and at 1 week, 3 months, and 9 months after LASIK. The Schirmer test with and without anesthesia was performed before and after instilling a drop of 0.4% oxybuprocaine hydrochloride into the conjunctival sac by placing a standard Schirmer test strip in the inferior cul-de-sac for 5 minutes and measuring the length of the wet portion. Tear breakup time was measured as the number of seconds between the last complete blink and the first visible disturbance of the precorneal film, as visualized at the slit lamp. We used the Cochet-Bonnet esthesiometer to measure central corneal sensitivity. The instrument consists of a nylon monofilament 6 cm long and 0.12 mm in diameter. Patients looked straight ahead and notified the examiner when they felt the top of nylon filament touch the center of the cornea. The measurement started at 6 cm and the length of the filament decreased by 5-mm increments to increase its rigidity until a positive response was obtained. The length

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of the filament that produced the first positive response indicated the central corneal sensitivity and was converted to  $\text{g}/\text{mm}^2$  using the conversion table provided by the manufacturer. To evaluate the damage to the ocular surface, rose bengal dye solution was instilled into the conjunctival sac, and the staining pattern was graded from 0 to 3 (0, negative; 1, scattered minute; 2, moderate spotty; 3, diffuse blotchy staining) in the temporal conjunctiva, cornea, and nasal conjunctiva. The values for each location were summed and ranged from 0 (negative) to 9 (diffuse blotchy staining in all these areas).

We obtained impression cytology specimens from the nasal and superior bulbar conjunctiva using the method of Tseng et al.<sup>7</sup> Briefly, a  $5 \times 8$  mm piece of cellulose filter paper was placed on the superior or nasal bulbar conjunctiva to include an area located 3 to 6 mm from the limbus. After a number of gentle and uniform compressions, the paper was peeled and stored at  $-80^\circ\text{C}$ . Specimens were stained with hematoxylin/eosin and periodic acid-Schiff reagents.<sup>7</sup> The length of the nucleus and the cell of non-goblet cells was measured, and the number of goblet cells counted by the National Institutes of Health Image J processing program.<sup>8,9</sup> The nucleus-to-cytoplasm ratio (N/C ratio) of five non-goblet cells and the goblet cell density were calculated from five areas of each specimen in a double-blind manner. We calculated the mean of the goblet cell density and the N/C ratio from each patient at each visit in both the nasal and the superior areas and summed these to obtain an overall N/C ratio and goblet cell density. The average of the two preoperative values for conjunctival morphologic parameters (N/C ratio, goblet cell density) and clinical parameters (Schirmer test with/without anesthesia, tear breakup time, central corneal sensitivity, and rose bengal staining) signified the "preoperative" value.

### Time-Dependent Changes in the Conjunctival Morphology and the Clinical Parameters after LASIK

We calculated the mean value for each parameter at each postoperative visit (at 1 week, 3 months, 9 months after LASIK) and compared these to the mean preoperative value of each parameter. These comparisons were made using the paired *t*-test for conjunctival morphologic parameters and the Wilcoxon matched pairs test for clinical parameters.

### Preoperative Characteristics of Chronic Dry Eye after LASIK

To investigate which preoperative parameters might influence the development of chronic dry eye after LASIK, patients were assigned to either of two groups based on dry eye status at 9 months after surgery. For these analyses, we excluded two patients who missed their visits at 9 months after surgery. The chronic dry-eye group (CDEG) was classified according to alternative definitions: (1) modified Japanese criteria<sup>10</sup> (whereby patients had to have a Schirmer test without anesthesia  $\leq 5$  mm or tear breakup time 5 seconds or less, or both, or they had to have a fluorescein score  $\geq 1$  or a rose bengal score  $\geq 3$  or both); (2) McMonnies questionnaire score  $> 14.5$ <sup>11</sup>; and (3) based on the dry eye symptom questionnaire developed by Oden et al.<sup>12</sup> For the Oden questionnaire, the scores for questions 2 (constantly = 6, often = 4, sometimes = 2, and never = 0) through 5 (yes = 6, no = 0) were summed and then multiplied by 0.16. Those with scores of 4.15 or greater were considered to have dry eye. Those who did not satisfy these criteria constituted the nondry-eye group (NDEG). In the modified Japanese criteria in our study, we included subjects who would have been classified as having either "definite dry eye" or "probable dry eye" in the original Japanese dry eye criteria.

Values in each of the measured tear film and ocular surface parameters were compared between NDEG and CDEG by Student's *t*-tests. Age, sex (ratio of female to male), and spherical equivalent were also compared between these two groups by the  $\chi^2$  test (for sex) and Student's *t*-test (for others). To investigate which preoperative parameters correlated with tear film stability at 9 months after surgery, we calculated the correlation between each preoperative parameter and

the tear breakup time at 9 months after surgery using the Pearson correlation coefficient.

We used a mixed models linear regression procedure to compare repeated measures of study parameters between the CDEG (as defined at 9 months, by either Japanese criteria or McMonnies questionnaire) and the NDEG. In these models, we tested whether the pattern of change in each parameter over time was different between the CDEG and the NDEG. We also estimated the mean difference for each parameter between CDEG and NDEG subjects before surgery and at each postoperative time point.

## RESULTS

### Description of Patients

Patient ages ranged from 21 to 39 years (mean  $\pm$  SD,  $32.29 \pm 1.06$  years). The ratio of females to males was 13/11. Preoperative spherical equivalents ranged from  $-7.75$  to  $+4.25$  diopters (mean absolute value of spherical equivalents,  $4.072 \pm 0.414$  diopters).

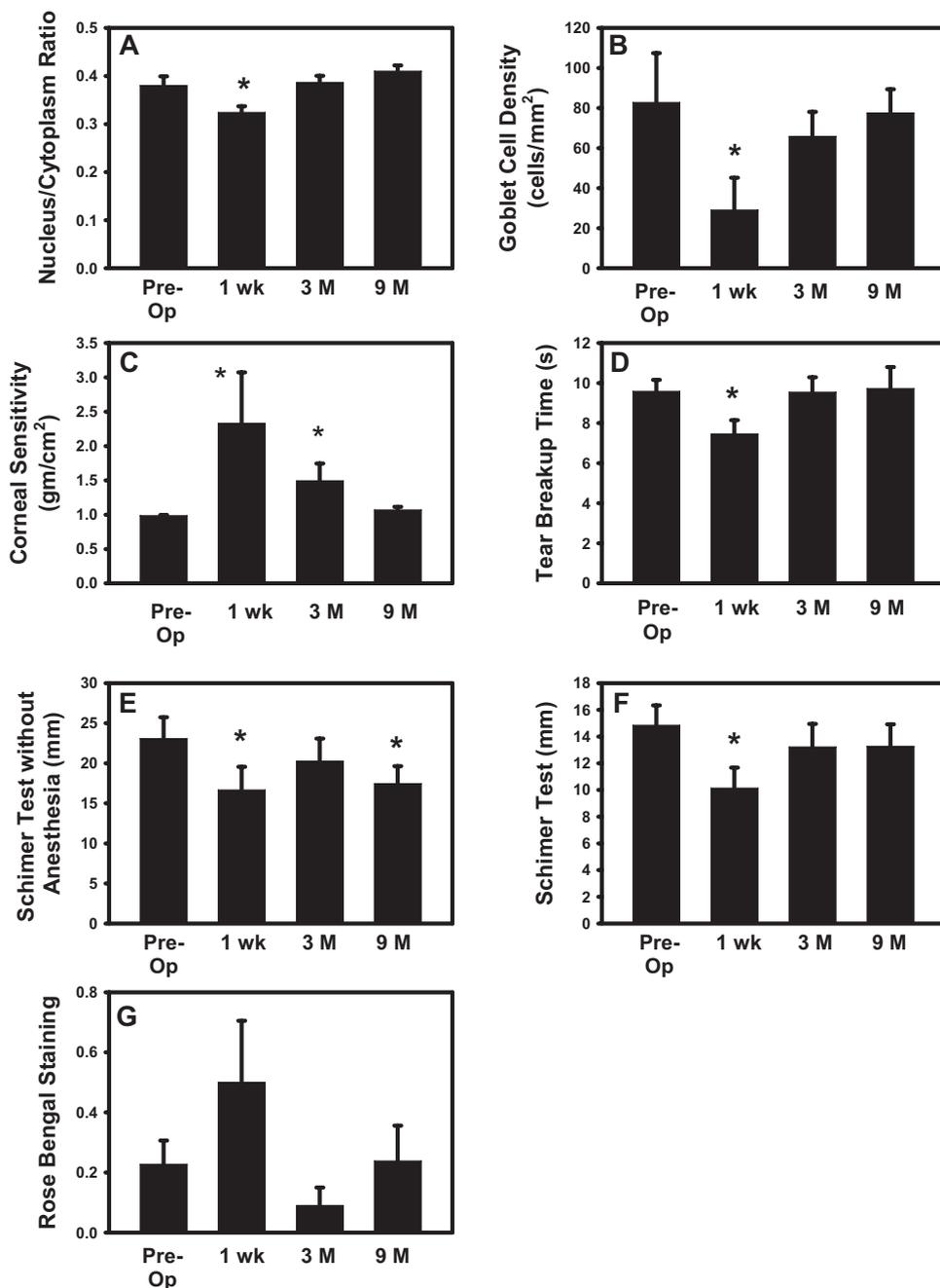
### Time-Dependent Changes in Conjunctival Morphology and Clinical Parameters

Before surgery, the N/C ratio was 0.38; this ratio decreased significantly to 0.32 1 week after surgery ( $P = 0.02$ ) and recovered to the preoperative value 3 months after surgery (Fig. 1A). Goblet cell density, tear breakup time, and Schirmer testing with anesthesia followed the same postoperative pattern of being significantly lower 1 week after surgery ( $P = 0.002$ ,  $<0.0001$ ,  $<0.0001$ , respectively; Figs. 1B, 1D, 1F) and then statistically indistinguishable from baseline levels at 3 months. In contrast, central corneal sensitivity—calculated as the central corneal threshold values, the values obtained when Cochet-Bonnet esthesiometer values were converted from cm to  $\text{g}/\text{mm}^2$ —was significantly increased at 1 week and at 3 months after surgery ( $P = <0.0001$ , at each time point) and fully recovered to baseline values 9 months after surgery (Fig. 1C). A higher central corneal threshold value indicates lower corneal sensitivity. We observed a significant decrease in the Schirmer test without anesthesia at 1 week ( $P = 0.0009$ ). Although similar to the other tests, the Schirmer test without anesthesia values returned to the preoperative level 3 months after surgery. However, it was significantly lower than baseline 9 months after surgery ( $P = 0.014$ ; Fig. 1E). Rose bengal staining score appeared to increase 1 week after surgery, though the change was not statistically significant ( $P = 0.094$ ). This value had recovered to the preoperative level 3 and 9 months after surgery (Fig. 1G).

### Preoperative Characteristics of Chronic Dry Eye after LASIK

The preoperative value in every measured parameter was compared between the NDEG and the CDEG using each classification (Table 1). Seven patients were classified as having chronic dry eye based on the modified Japanese criteria, whereas four patients were classified as having chronic dry eye with the McMonnies Questionnaire and five were put in the CDEG based on the Oden questionnaire. Using the Japanese criteria, the CDEG had significantly lower preoperative values than the NDEG for Schirmer test with and without anesthesia ( $P = 0.02$  and  $0.013$ , respectively). No other preoperative differences were observed between these two groups. When either the McMonnies or the Oden questionnaire was used for classification, there was no significant difference between the CDEG and the NDEG in any preoperative parameter (Table 1).

To observe how chronic dry eye develops after LASIK, values from patients were compared between the NDEG and



**FIGURE 1.** Time-dependent changes in conjunctival morphology and clinical parameters. Impression cytology was performed on eyes from 22 patients (12 females/10 males) and the nucleus to cytoplasm ratio for non-goblet cells (A) and goblet cell density (B) were determined. In addition, the same eyes were analyzed for corneal sensitivity by Cochet-Bonnet esthesiometer (C), tear breakup time with sodium fluorescein (D), Schirmer test without (E) and with (F) anesthesia, and rose bengal staining (G) before LASIK (Pre-op) and 1 week, 3 months, and 9 months after LASIK. Values are means  $\pm$  SEM. Asterisk: statistically significant difference.

the CDEG, defined by the modified Japanese criteria at each time of measurement in each parameter (Fig. 2). In this comparison, we used the Schirmer test without anesthesia for evaluation of tear secretion because this test is thought to reflect both basal and stimulated tear secretion and would evaluate the total capacity for tear secretion more adequately than the Schirmer test with anesthesia. No statistically significant difference was detected between the NDEG and the CDEG before or after surgery for the N/C ratio (Fig. 2A), goblet cell density (Fig. 2B), central corneal sensitivity (Fig. 2C), or rose bengal staining (Fig. 2F). There were significant differences between NDEG and CDEG 3 and 9 months after surgery in tear breakup time ( $P = 0.025$  and  $P = 0.0002$ , respectively; Fig. 2D). In addition the differences between NDEG and CDEG were significant at all time points in the Schirmer test without anesthesia ( $P = 0.013$ ,  $P = 0.009$ ,  $P = 0.008$ , and  $P = 0.009$  for baseline, 1 week, 3 months, and 9 months after LASIK,

respectively; Fig. 2E). The analysis comparing the CDEG, classified by the McMonnies questionnaire, with the NDEG gave similar results, though there was no statistically significant difference between the NDEG and the CDEG, possibly because of very small numbers (data not shown).

Because of the theoretical interrelationship of various measures of the state of the ocular surface unit, we next determined whether there was a correlation between preoperative values in each parameter and values for tear breakup time 9 months after surgery. In this analysis, we observed a significant positive correlation between the preoperative Schirmer test without anesthesia and tear breakup time 9 months after LASIK ( $r = 0.504$ ;  $P = 0.02$ ; Fig. 3). However, exclusion of one patient with the highest values for both measures (Schirmer, 53 mm; tear breakup time, 25 seconds) resulted in a reduction of this correlation ( $r = 0.38$ ;  $P = 0.10$ ). We did not find significant correlations in any of the other preoperative param-

TABLE 1. Preoperative Characteristics of Chronic Dry Eye after LASIK

Parameter	Modified Japanese Criteria			McMonnies Questionnaire			Oden Questionnaire		
	NDEG n = 15	CDEG n = 7	P	NDEG n = 18	CDEG n = 4	P	NDEG n = 17	CDEG n = 5	P
Age (years)	32.73 ± 1.29	32.71 ± 2.24	NS	32.78 ± 1.25	32.5 ± 2.63	NS	33.18 ± 1.25	31.20 ± 2.48	NS
Female/male	8/7	4/3	NS	8/10	4/0	NS	9/8	3/2	NS
Spherical equivalent (D)	-3.26 ± 0.95	-3.47 ± 0.45	NS	-3.41 ± 0.79	-2.97 ± 0.77	NS	-3.46 ± 0.71	-2.90 ± 1.74	NS
CCS (g/mm <sup>2</sup> )	0.98 ± 0.01	0.99 ± 0.02	NS	0.98 ± 0.01	0.98 ± 0.02	NS	0.99 ± 0.01	1.00 ± 0.03	NS
Schirmer + (mm)	17.12 ± 2.07	10.43 ± 1.64	0.02*	15.57 ± 1.76	12.38 ± 4.48	NS	26.74 ± 3.45	14.20 ± 3.32	NS
Schirmer - (mm)	27.47 ± 3.69	15.29 ± 2.48	0.013*	24.53 ± 3.34	19.24 ± 3.68	NS	16.98 ± 2.11	8.7 ± 0.77	NS
Tear breakup time (s)	10.17 ± 0.66	9.29 ± 1.27	NS	10.19 ± 0.65	8.50 ± 1.43	NS	9.68 ± 0.77	10.6 ± 0.85	NS
GCD (cells/mm <sup>2</sup> )	87.78 ± 38.87	69.43 ± 19.28	NS	86.88 ± 31.85	59.51 ± 33.93	NS	87.42 ± 31.88	57.19 ± 32.71	NS
N/C ratio	0.38 ± 0.02	0.39 ± 0.04	NS	0.39 ± 0.02	0.36 ± 0.06	NS	0.39 ± 0.02	0.36 ± 0.05	NS

CCS, central corneal sensitivity; Schirmer -, Schirmer test without anesthesia; Schirmer +, Schirmer test with anesthesia; GCD, goblet cell density; NS, not significant (P > .05).

\*Statistically significant difference.

eter with tear breakup time at 9 months after surgery. (Data for patients 2 and 7 are identical and thus are overlaid with one another.)

Also of interest were possible correlations between preoperative Schirmer values without anesthesia and the values of other clinical parameters 9 months after LASIK. In these anal-

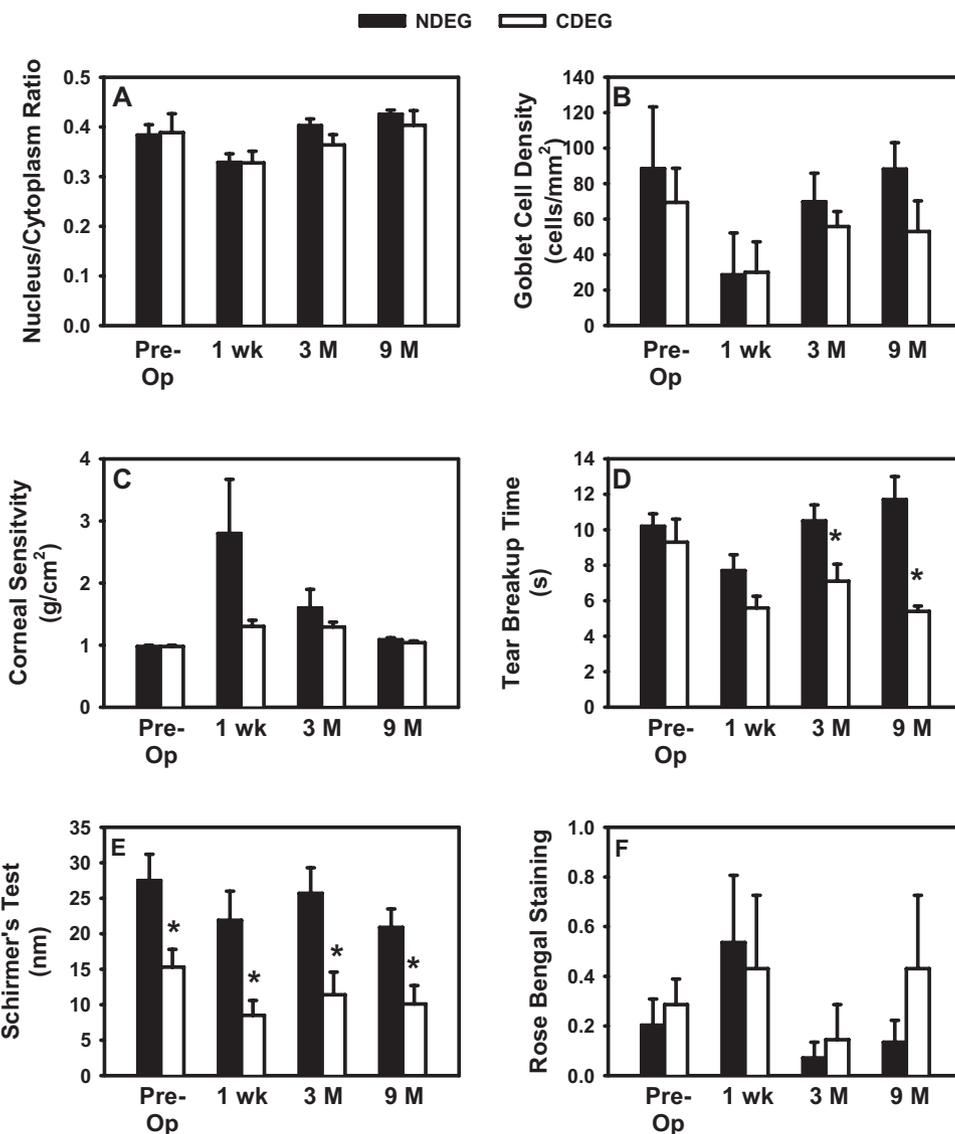
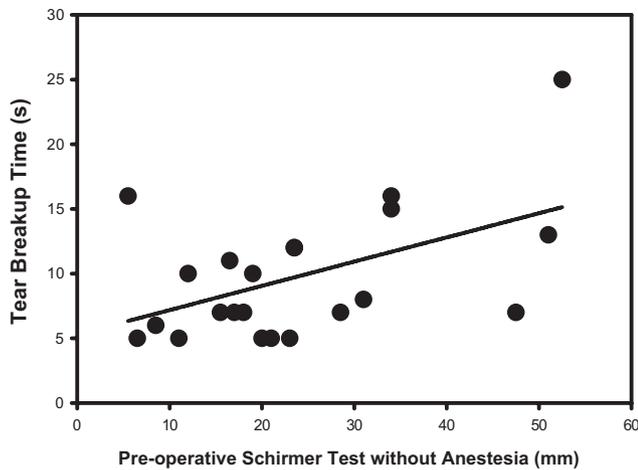


FIGURE 2. Changes in conjunctival morphology and clinical parameters of nondry eye and chronic dry-eye groups. Patients were classified as either NDEG (solid bars) or CDEG (open bars) based on the modified Japanese criteria. Impression cytology was performed on eyes from 22 patients (12 females/10 males), and the nucleus to cytoplasm ratios for nongoblet cells (A) and goblet cell density (B) were determined. In addition, the same eyes were analyzed for corneal sensitivity by Cochet-Bonnet esthesiometer (C), tear breakup time with sodium fluorescein (D), Schirmer test without anesthesia (E), and rose bengal staining (F) before LASIK (Pre-op) and 1 week, 3 months, and 9 months after LASIK. Values are means ± SEM. Asterisk: statistically significant difference.



**FIGURE 3.** Correlation between preoperative Schirmer test and postoperative tear breakup time. Mixed models linear regression analysis was used to determine correlation between preoperative tear breakup time and postoperative Schirmer test 9 months after LASIK. Data for patients 2 and 7 are identical and thus are overlaid with one another.

yses, in addition to the significant correlation noted for TBUT, a significant correlation also occurred with the postoperative Schirmer level ( $r = 0.722$ ;  $P < 0.0001$ ), as did a more modest correlation with postoperative corneal sensitivity that was not statistically significant but that indicated a tendency for those with lower preoperative Schirmer values to have a lower threshold and thus higher corneal sensitivity 9 months after LASIK ( $r = 0.381$ ;  $P = 0.08$ ).

Finally, for the Schirmer test without anesthesia, our more statistically robust repeated measured analysis suggested that the pattern of change over time was similar in the CDEG group compared with the NDEG ( $P = 0.81$ ) because the CDEG had consistently lower Schirmer test scores before surgery and at each postoperative visit. Averaged across all visits, Schirmer test scores in the CDEG were 12 mm lower than in the NDEG ( $P = 0.01$ ). Results were similar when the Oden questionnaire was used to determine classification into the CDEG or the NCDEG ( $P = 0.05$ ).

In contrast, we observed a significant difference in the pattern of change in TBUT over time between CDEG, as defined by the Japanese criteria and NDEG ( $P = 0.04$ ). More specifically, TBUT was significantly shorter in the CDEG than in the NDEG at the 3-month ( $P = 0.04$ ) and the 9-month ( $P = 0.0002$ ) follow-up visits, whereas there were no significant differences between these groups at baseline ( $P = 0.97$ ) or 1 week after surgery ( $P = 0.18$ ). Results based on dry eye classification using the McMonnies questionnaire were similar ( $P = 0.03$  and  $P = 0.04$ ) for differences between groups in mean TBUT at 3 and 9 months, respectively. Classification based on the Oden questionnaire failed to reveal any significant postoperative differences in TBUT between the groups ( $P = 0.65$ ,  $0.52$ , and  $0.16$  for 1 week, 3 months, and 9 months, respectively).

In similar models, we observed that the pattern of change in corneal sensitivity appeared to vary between the CDEG and the NDEG, with patients classified based on the Oden questionnaire, though this difference was not statistically significant ( $P = 0.06$ ). Nonetheless, patients in the CDEG had lower corneal sensitivity at 1 week ( $P = 0.003$ ) and 3 months ( $P = 0.02$ ) after surgery, but levels were statistically indistinguishable between these groups at 9 months ( $P = 0.99$ ). In contrast, no significant differences were observed when patients were classified based on the Japanese criteria ( $P = 0.24$ ,  $P = 0.49$ ,  $P = 0.93$  at 1 week, 3 months, and 9 months, respectively) or

the McMonnies questionnaire ( $P = 0.17$ ,  $P = 0.39$ ,  $P = 0.93$  at 1 week, 3 months, and 9 months, respectively).

## DISCUSSION

We observed time-dependent changes in the conjunctival morphology and clinical parameters of tear function before and after LASIK. More specifically, transient changes in all parameters occurred that were consistent with the development of transient dry eye after LASIK. It is considered that these generally short-term changes are induced by denervation of the cornea, inflammation caused by surgical trauma, and contour changes of the ocular surface.<sup>1,3,13,14</sup> In the present study, these measurable changes in the tear film/ocular surface recovered, on average, to be statistically indistinguishable from preoperative levels by 3 months after surgery in all parameters.

However, even in this limited sample, we identified a number of patients who continued to have chronic signs or symptoms of dry eye. To investigate the background of the development of chronic dry eye after LASIK, we classified patients into two groups on the basis of dry eye status at 9 months after surgery using three different classifications. In the modified Japanese criteria clinical test values are used. In the McMonnies questionnaire, patients are classified on the basis of age, sex, dry eye symptoms, habits, medications, and the presence of chronic illness.<sup>11,15</sup> In the Oden questionnaire (also known as the Dry Eye Epidemiology Project questionnaire), patients are classified based on use of eyewashes, compress drops, frequency of dry eye symptoms, presence of dry mouth, ocular allergies, contact lens wear, and physician diagnosis.<sup>12</sup> For both the McMonnies and the Oden questionnaires, a score is given depending on the frequency of symptoms. The Dry Eye Workshop<sup>16</sup> evaluated dry eye questionnaires that had previously been used in randomized clinical trials or that were tested or used in epidemiologic studies and had undergone some validation. Both the McMonnies and the Oden questionnaires were reviewed and characterized.

Despite the fact that we classified patients on the basis of dry eye status 9 months after surgery, we found a significant difference in the preoperative values in the Schirmer test between the NDEG and the CDEG, suggesting that preoperative tear volume, perhaps mediated through a decreased reserve of lacrimal or conjunctival function or responsiveness, affects recovery from transient dry eye induced by LASIK. Although the direction in the changes in Schirmer test between the NDEG and the CDEG was the same in the analyses of the McMonnies and the Oden questionnaires and the modified Japanese criteria, no preoperative significant difference between NDEG and CDEG was detected in the McMonnies and Oden questionnaire analyses, most likely because there were fewer patients in the dry eye category. As might be expected, for 2 of the 3 classification systems, we also observed significant differences in tear breakup time at 3 months and 9 months after surgery between the group who developed chronic dry eye and the group who did not.

Several reports have now suggested that cutting corneal nerves during LASIK may suppress tear secretion from the lacrimal gland, mucin expression on the corneal epithelium, and blinking frequency because these are driven by the neural reflex mediated by corneal sensitivity.<sup>14,17,18</sup> After LASIK, corneal nerves are decreased up to 90% in the flap and the subbasal area.<sup>19</sup> Subbasal nerves begin to recover 3 to 6 months after surgery and are 50% of the original preoperative density 2 years after surgery.<sup>20–23</sup> There is some difference in nerve regeneration, depending on the area of the cornea examined. Nerves in the nasal cornea have long fiber bundles at all time points after surgery, including 2 hours. In the temporal area nerves begin to show long fiber bundles 3 months after surgery, and in the central cornea nerves are short and uncon-

nected even 6 months after surgery.<sup>22</sup> The time-dependent changes in all measured values that we observed in all patients support this theory. Values for central corneal sensitivity, Schirmer test with and without anesthesia, and tear breakup time showed transient deterioration just after surgery, but all recovered to preoperative levels by 3 months. However, it remains unlikely that the loss of corneal nerves and their slow regrowth alone can explain the development of chronic dry eye after LASIK.

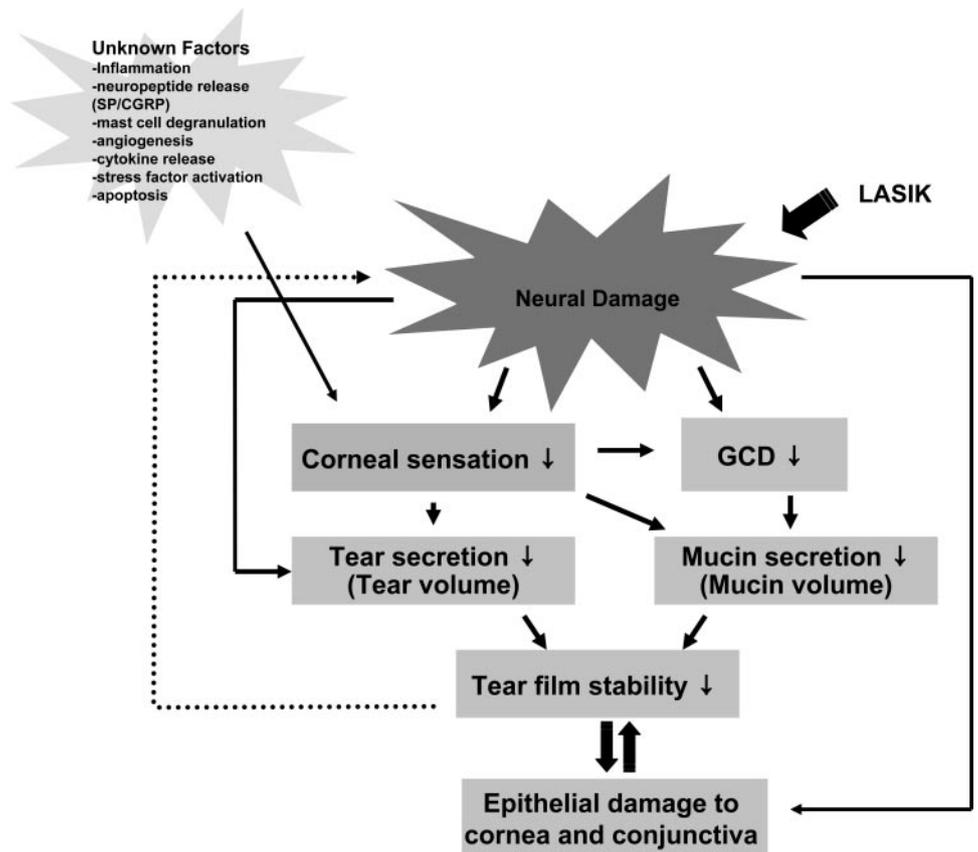
In the Cullen Symposium<sup>24</sup> and the recently published summary from the Dry Eye Workshop,<sup>25</sup> the role of decreased neural stimuli in the pathogenesis of aqueous deficient dry eye disease was summarized. Loss of corneal nerves such as occurs with LASIK can lead to dry eye disease by two mechanisms, first by causing increased tear osmolarity and second by inducing neurogenic inflammation. Both mechanisms lead to ocular surface inflammation. Loss of neural stimuli increases tear osmolarity by decreasing lacrimal gland protein, electrolyte and water secretion, and conjunctival secretion of electrolytes and water. Increased tear osmolarity (hyperosmolarity) induces ocular surface inflammation by activating nuclear factor kappa B (NF-κB) and the stress-activated protein kinases, including extracellular related kinase (ERK, also known as p44/p42 mitogen-activated protein kinase [MAPK]), c-Jun N-terminal kinase (JUNK), and p38 MAPK.<sup>24,26</sup> Activation of these stress kinases causes the production of cytokines and chemokines such as IL-1β and TNF-α, matrix metalloproteinases (MMP) such as MMP-9, adhesion molecules, and proapoptotic factors. These stimuli alter the ocular surface and set up another inflammatory process that includes the recruitment of blood-borne inflammatory cells that degrade the basement membrane, releasing growth factors that stimulate angiogenesis.<sup>26</sup> In addition, the inflammatory response causes epithelial damage by apoptosis, goblet cell loss, and loss of the glycocalyx and its mucins.<sup>27</sup> Chronic dry eye in humans and dogs<sup>28</sup> or acute dry eye in

mice<sup>29</sup> has been shown to induce apoptosis of ocular surface cells.<sup>30</sup>

For neurogenic inflammation, damage to the sensory nerves in the cornea causes release of the sensory neurotransmitters substance P (SP) and calcitonin gene-related peptide (CGRP) from the nerve endings. SP and CGRP lead to inflammation of the ocular surface by causing mast cell degranulation, dilation of blood vessels in the limbus, and increased vascular permeability.<sup>31</sup> Degranulating mast cells release cytokines such as TNFα and other factors that increase the sensitivity of mast cells to SP. A triangle of paracrine activation is formed by neuropeptides, mast cells, and cytokines that eventually contribute to cellular infiltration by immune cells such as eosinophils, natural killer cells, leukocytes, macrophages, and lymphocytes. Thus, LASIK destroys corneal nerves leading to hyperosmolarity and neurogenic inflammation leading to tear instability, a vicious circle that drives aqueous-deficient dry eye disease.

An additional factor altered after LASIK could also account for the chronic dry eye that occurs in some patients with decreased tear secretion. Tear proteins, including IgA, lactoferrin, lysozyme, and growth factors such as epidermal growth factor and transforming growth factor α at appropriate concentrations, are important for normal ocular-surface maintenance, but their levels may be decreased after LASIK. The occurrence of any combination of these factors (loss of nerves, hyperosmolar tears, neurogenic inflammation, loss of lacrimal gland secretory proteins) in some patients may tip the balance to chronic dry eye.

Taking all these factors into consideration, we propose the following potential mechanism to explain our findings (Fig. 4). In all patients who underwent LASIK, corneal sensitivity, tear volume, goblet cell density, and integrity of corneal and conjunctival cells deteriorated soon after LASIK because of surgical stress. Changes in the tear film, as described, induced acute dry eye. Patients with a high preoperative Schirmer test values were able



**FIGURE 4.** Schematic diagram of possible mechanism leading to post-LASIK dry eye. LASIK causes neural damage that results in decreased corneal sensitivity, tear volume, and goblet cell density. Corneal and conjunctival cells deteriorate as a result of damage from the tear hyperosmolarity and inflammation causing acute dry eye. A high preoperative Schirmer test value indicates the ability of the tear film and the ocular surface to recover quickly; patients do not develop chronic dry eye. In contrast, a lower preoperative Schirmer test value indicates the inability of the tear film and ocular surface to recover because repair of the ocular surface cells could be delayed by the prolonged inflammation or apoptosis because of an insufficient amount of tears. GCD, goblet cell density.

to recover quickly from this stress; ocular surface damage repaired itself, and chronic dry eye did not develop. In contrast, patients with lower preoperative Schirmer test values were unable to recover because repair of the ocular surface cells needed for maintenance of the tear film layer might have been delayed by prolonged inflammation or apoptosis, possibly because of insufficient tear volume. In other words, we theorize that a reduced preoperative tear volume induces an imbalance of various factors that maintain ocular surface health and invites a vicious circle of ocular surface and tear film deterioration.

Consistent with this hypothesis, we found that an increasing preoperative Schirmer test without anesthesia positively correlated with an increasing tear breakup time at 9 months after surgery. According to our results, patients had to have preoperative values greater than 20 mm on the Schirmer test without anesthesia if patients they were to be expected to have values exceeding 10 seconds in tear breakup time at 9 months after LASIK. This suggests that an abundance of preoperative tear volume may be needed for adaptability to the stress after LASIK. Our study raises the hypothesis that preoperative tear volume plays an important role in long-term ocular surface integrity after LASIK. Thus, preoperative values in the Schirmer test without anesthesia might be predictive of chronic dry eye after LASIK. Recently, successful use of artificial tears has been reported for dry eye symptoms after LASIK.<sup>1,3,32</sup> It is also possible that topical anti-inflammatory therapeutics could normalize the ocular surface and improve the quality of the tear film after LASIK. Further investigations are needed to evaluate our hypotheses.

In conclusion, LASIK causes reversible changes in conjunctival morphology and clinical parameters that are consistent with dry eye. The magnitude of the preoperative tear volume (inferred from clinical testing) may affect the recovery of the ocular surface after LASIK such that a large tear volume decreases the likelihood of chronic dry eye after LASIK. Preoperative Schirmer test values without anesthesia appeared to be predictive of the development of chronic dry eye after LASIK.

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