Role of epithelial hyperplasia in regression following photorefractive keratectomy

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Abstract

Aim—To determine the relation between epithelial hyperplasia and regression of effect after photorefractive keratectomy (PRK).

Methods—Seventy unilaterally treated patients with PRK were examined. All eyes had been treated with the Summit excimer laser 27 (SD 7) months previously with zone diameters of 4.1 to 5.0 mm. The untreated fellow eyes served as controls. Epithelial thickness was measured centrally with a thin slit optical pachometer and manifest subjective refraction was performed.

Results—The epithelium was 21% thicker in the treated eye (p<0.0001). The relation between refractive regression and epithelial hyperplasia was significant (r=0.41; p<0.001).

Conclusions—Epithelial hyperplasia after PRK correlated with the myopic shift (including hyperopia reduction) after treatment with the Summit laser. A model is proposed suggesting that both subepithelial and epithelial layers contribute to regression in the Summit treated eyes with 18 μm of epithelial hyperplasia contributing each dioptre of regression.

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Surgical procedures

All patients had PRK performed for myopia by one of four surgeons (BT, DE, PF, HHN). All surgeries were performed in Stockholm, Sweden. Surgical factors are summarised in Table 1.

The surgical procedure was preceded by topical anaesthesia with amethocaine (tetra-caine) 0.5%, and marking of the treatment zone. With the patient fixating an internal fixation target within the laser, a 5.0 mm radial keratotomy marker with cross hairs was centred on the entrance pupil and pressed on the cornea to delineate the treatment zone. Removal of the central corneal epithelium was performed manually with a Beaver blade (Becton Dickinson, AcuteCare, Franklin Lakes, NJ, USA). With the patient again fixating the same target, PRK was performed with the Summit argon fluoride laser with spectral emission at 193 nm and pulse frequency fixed at 10 Hz. The pulse energy resulted in a radiant exposure of 180 mJ/cm². The number of pulses was computed by a proprietary algorithm. All subjects had less than 1 D of astigmatism and
Reasons why subjects remained unilaterally treated

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number (% of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual refraction error</td>
<td>13 (41)</td>
</tr>
<tr>
<td>Monovision by choice</td>
<td>22 (31)</td>
</tr>
<tr>
<td>Haloes around lights at night</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Surgery of fellow eye booked</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Waiting for sufficient time between eyes</td>
<td>0</td>
</tr>
<tr>
<td>Not needed in other eye</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Financial strain</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

Statistical analysis

Pearson's product moment regression analysis was used to determine relations between two sets of data. A paired Student's t test was used to test for differences between eyes in the same subject. A proportions test was used to detect differences between two percentages. A one way analysis of variance (ANOVA) was used to test for significant differences in epithelial hyperplasia among regression groups. The Student Newman Keuls test was used to determine which of these groups were different.
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A 95% confidence level was chosen to denote statistical significance and all statistical tests were two tailed.

Results

EPITHELIAL THICKNESS

The mean epithelial thickness in the PRK eye was 69 (SD 8) μm (range 52–95 μm) and in the control eye was 57 (7) μm (range 38–75 μm). The epithelium in the PRK eye was significantly thicker by 12.10 μm (21%) compared with the control eye (p<0.0001; 95% confidence interval 9.35 to 14.3 μm).

Figure 1 Postoperative refractive error (D) over time (months). Figures in brackets represent the sample size at each time point. Error bars represent standard deviations.

Figure 2 Total regression (D) versus epithelial hyperplasia (μm). The thick line represents the regression line.

Figure 3 Mean amount of epithelial hyperplasia (μm) versus total regression divided into groups of 1 D steps for the Summit eyes. The means (SD) are shown in the bars.

Discussion

The aim of this study was to determine the contribution of epithelial hyperplasia to refractive regression after PRK. Owing to the cross sectional nature of the study design, subjects who were unilaterally treated were chosen so that the untreated eye could be used as a control. The authors acknowledge that this group of patients may not be representative of PRK patients in general as the study group had chosen not to have their fellow eye treated.

It has been postulated that regression is caused by epithelial hyperplasia and/or development of new stromal collagen. Some authors have suggested that reduction of the initial overcorrection is due to epithelial hyperplasia and that stromal regeneration is the major source of the remaining regression. It has also been proposed that regression is related to the formation in the laser created 'bowl' of a subepithelial layer containing hyaluronic acid and other glycosaminoglycans which can alter corneal hydration and consequently affect corneal curvature. Wilson et al hypothesised that the healing of the corneal epithelium during the early postoperative period results in an artificial and temporary hyperflattening of the corneal contour which would occur if the epithelium was thicker in the periphery than in the centre of the ablation, giving apparent initial overcorrection. They also suggested that a more pronounced stromal swelling at the wound edge could account for the apparent but temporary overcorrection.

The results of this study show that refractive regression is related to the central epithelial hyperplasia occurring postoperatively in eyes treated with small (5 mm or less) ablation zones. This regression consists largely of a reduction in hyperopia occurring in the early postoperative months (Fig 1). Since all of the subjects in this group were examined 12 months after the operation, it is not possible to confirm the time course of epithelial hyperplasia. However, based on the refractive data collected

MANIFEST SUBJECTIVE REFRACTION

Figure 1 shows the mean refractive results over 36 months.

EPITHELIAL HYPERPLASIA VERSUS REGRESSION

The relation between epithelial hyperplasia and total regression was highly statistically significant (r=0.41; p<0.001, Fig 2). Calculation of the relation between epithelial hyperplasia and regression based on the equation derived in Figure 2 predicts that without hyperplasia there is a regression of 1.56 D, and for each additional 10 μm of hyperplasia there is 0.55 D of regression (18 μm for each dioptre of regression).

Figure 3 shows the mean epithelial hyperplasia grouped by the amount of total regression (ANOVA, p <0.001). There was a statistically significant difference in epithelial hyperplasia (a) between groups with total regression from 0.00 D to 3.00 D and the group with greater than 4.00 D of total regression, and (b) between groups with total regression from 0.00 D to 2.00 D and the group with regression of 3.12 D to 4.00 D.
and the correlation of the refractive regression with the measured epithelial hyperplasia, it seems reasonable to hypothesise that most of the hyperplasia develops in the early postoperative months since this is when the greatest rate of reduction in hyperopia occurs. In quantitative histological studies of epithelial thickness after PRK in monkeys, Beuerman et al found that the epithelium increased in thickness over the first year reaching maximum thickness at 12 months after operation with inconsistent changes thereafter. Others have found histological evidence of hyperplasia within the first month after ablation.\(^4\)\(^5\) Reduction of the initial overcorrection because of epithelial hyperplasia has also been proposed by different authors.\(^6\)\(^7\)

It has been proposed in this study that in the absence of epithelial hyperplasia there was 1.56 D of regression, and for each 18 \(\mu\)m increase in epithelial thickness there was a 1 D increase in regression. This model of regression suggests that there is a non-epithelial component accounting for approximately 1.50 D of regression and the remainder of the regression is due to epithelial hyperplasia. Although stromal thickness was measured it was not possible to evaluate its relation to refractive error since the thickness of the stroma postoperatively is dependent on the amount of myopia that was corrected.

The results of this study show that central epithelial hyperplasia occurs postoperatively in eyes treated with small (5 mm or less) ablation zones. The retrospective refractive data on the study patients show that most of regression occurs in the early postoperative months as the hyperopic overcorrection subsides. Since it is clear that regression after PRK must be due to the treatment zone 'filling in' with tissue, it is not unreasonable to suggest that this tissue is at least in part the epithelium as others have shown histologically. The significant correlation found in this study between refractive regression and measured epithelial hyperplasia suggests that the two findings are related. A model of the relation between epithelial hyperplasia and regression was proposed stating that approximately 1.50 D of regression was due to non-epithelial elements (a subepithelial lenticule and/or stromal remodelling) and that for each 18 \(\mu\)m of epithelial hyperplasia an additional 1 D of regression occurs. Postoperative studies of topographical epithelial, subepithelial, and stromal thickness are needed to better delineate the contribution of the different corneal layers to regression.

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