Epithelial Measurement and Healing

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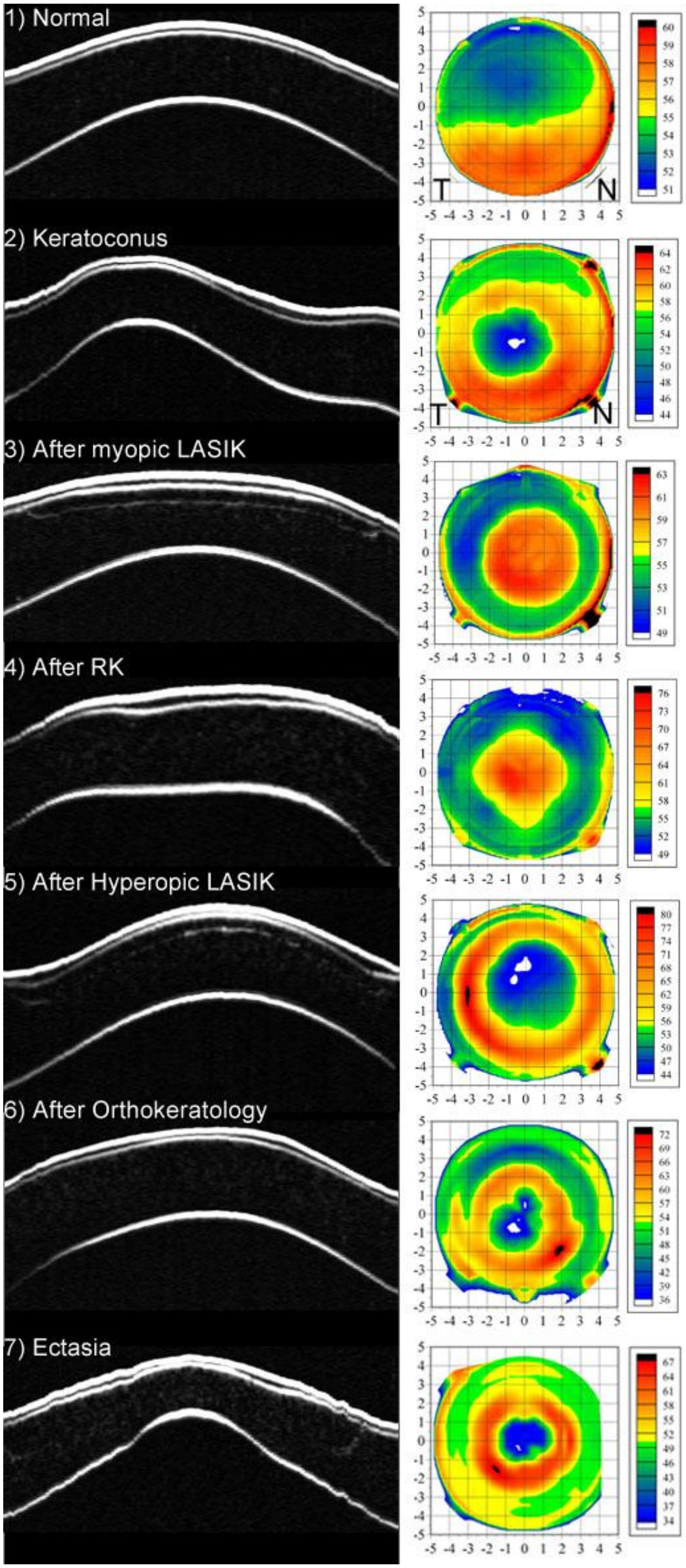
Introduction

The corneal epithelium is a highly active, self-renewing layer; a complete turnover occurs in approximately 5 to 7 days.[1] Despite this high turnover rate, the epithelium must maintain the same thickness profile over time to maintain corneal power and, hence, ocular refraction. As described by Alfred Vogt in 1921,[2] it is known that the corneal epithelium has the ability to alter its thickness profile to compensate for changes in stromal surface curvature in order to try and re-establish a smooth, symmetrical optical surface. Understanding this epithelial compensatory mechanism is crucial to fully understand how the cornea will respond to different conditions and surgical procedures. As the refractive index of epithelium and stroma are sufficiently different (1.401 vs. 1.377),[3] the epithelial-stromal interface constitutes an important refractive interface within the cornea, with a mean power contribution estimated at approximately -3.60 D.[4] Therefore, knowledge of the epithelial thickness profile and how it may change after corneal surgery could positively contribute to the accuracy of refractive corneal and intraocular lens surgery.

Understanding the Predictable Behavior of the Corneal Epithelium

Before looking at more complicated situations, it is useful to consider the epithelial thickness profile in a population of normal eyes.[5] Somewhat surprisingly, we demonstrated using VHF digital ultrasound that the epithelium was not a layer of homogeneous thickness as had previously been thought, but followed a very distinct pattern; on average the epithelium was 5.7 µm thicker inferiorly than superiorly, and 1.2 µm thicker nasally than temporally, with a mean central thickness of 53.4 µm. This non-uniformity seems to provide evidence that the epithelial thickness is regulated by eyelid mechanics and blinking, as we suggested in 1994.[6] We postulated that the eyelid might effectively be chafing the surface epithelium during blinking and that the posterior surface of the semi-rigid tarsus provides a template for the outer shape of the epithelial surface. During blinking, which occurs on average between 300 to 1500 times per hour,[7] the vertical traverse of the upper lid is much greater than that of the lower lid. Doane[8] studied the dynamics of eyelid anatomy during blinking and found that during a blink the descent of the upper eyelid reaches its maximum speed at about the time it crosses the visual axis. As a consequence, it is likely that the eyelid applies more force on the superior than inferior cornea. Similarly, the friction on the cornea during lid closure is likely to be greater temporally than nasally as the outer canthus is higher than the inner canthus (mean intercanthal angle=3°), and the temporal portion of the lid is higher than the nasal lid (mean upper lid angle=2.7°).[9] Therefore, it seems that the nature of the eyelid completely explains the non-uniform epithelial thickness profile of a normal eye.

Epithelial thickness changes have been described after myopic excimer laser ablation,[10-12] hyperopic excimer laser ablation,[13] radial keratotomy,[14] orthokeratology,[15] intra-corneal ring segments,[16] irregularly irregular astigmatism after corneal refractive surgery,[17-20] and in keratoconus[21-23] and ectasia.[24] Figure 1 shows the epithelial thickness profile in a number of different situations.


1) Normal
60 59 58 57 56 55 54 53 52 51
T
N
2) Keratoconus
64 62 60 58 56 54 52 50 48 46 44
T
N
3) After myopic LASIK
63 61 59 57 55 53 51 49
4) After RK
76 73 70 67 64 61 58 55 52 49
5) After Hyperopic LASIK
80 77 74 71 68 65 62 59 56 53 50 47 44
6) After Orthokeratology
72 69 66 63 60 57 54 51 48 45 42 39 36
7) Ectasia
67 64 61 58 55 52 49 46 43 40 37 34
-5 -4 -3 -2 -1 0 1 2 3 4 5

In all of these cases, the epithelial thickness changes are clearly a compensatory response to the change to the stromal surface and can all be explained by the theory of eyelid template regulation of epithelial thickness. Compensatory epithelial thickness changes can be summarised by the following rules:

1. The epithelium thickens in areas where tissue has been removed or the curvature has been flattened (e.g. central thickening after myopic ablation[10-12] or radial keratotomy[15] and peripheral thickening after hyperopia ablation[13]).
2. The epithelium thins over regions that are relatively elevated or the curvature has been steepened (e.g. central thinning in keratoconus,[21-23] ectasia[24] and after hyperopic ablation[13]).
3. The more irregular the topography, the more epithelial remodelling will have occurred.
4. The amount of epithelial remodelling is defined by the rate of change of curvature of an irregularity; there will be more epithelial remodelling for a more localized irregularity.[17, 19, 20] The epithelium effectively acts as a low pass filter, smoothing small changes almost completely, but only partially smoothing large changes.

The rate of change of curvature is really the key to understanding the entirely predictable epithelial response. This can be appreciated by the fact that there is almost twice as much epithelial thickening after a hyperopic ablation[13] compared with a myopic ablation,[11] and the total epithelial compensation for small, very localized stromal loss such as after a corneal ulcer.[13] Similarly, the effectiveness of a trans-epithelial PTK procedure increases as the localization of the irregularities increases (see more later).[20]

Rate of Change in Epithelial Thickness

The other aspect of the changes in the epithelial thickness profile described above is the speed at which the changes occur. This turns out to be extremely fast with dramatic overnight changes having been demonstrated after myopic LASIK[12] and complete epithelial remodeling one day after flap rotation of a free cap.[25] Orthokeratology is another example of this, as it has been shown that the refractive changes are mainly due to epithelial thickness changes; overnight, the lenses compress the central cornea to induce central epithelial thinning and allow paracentral epithelial thickening.[15] Therefore, the temporary nature of the effect demonstrates the speed of epithelial remodeling as it returns to its natural state.

The epithelial thickness changes observed in orthokeratology add more weight to the theory that the epithelium remodels to fit the template in front of the cornea. In orthokeratology, the template normally provided by the posterior surface of the semi-rigid tarsus is replaced by a contact lens that is designed to fit tightly to the center of the cornea and loosely paracentrally. Therefore, the epithelium is chafed and squashed by the lens centrally while the epithelium is free to thicken paracentrally where the lens is not so tightly fitted.

After myopic LASIK, we have previously shown that the epithelial thickness continues to change during the first 3 months, after which it remains completely stable.[12] Overnight, there is central epithelial thickening of approximately 1 to 2 µm, but paracentral epithelial thinning of approximately 4 to 6 µm – we postulated that this thinning was in response to edema. Between 1 day and 1 month, the epithelium thickened across the entire 7 mm diameter zone by up to 5 µm, with more pronounced thickening within the central 4 mm. Between 1 month and 3 months, the epithelium continued to thicken in the central 7 mm diameter zone by approximately an additional 1 µm. These epithelial changes partially explain the regression seen after myopic LASIK in the first 3 months and agree with the common finding that refractive stability is attained after 3 months.[26]

Applications of Epithelial Thickness Mapping

Epithelial changes such as those described above will have an impact on the ocular refraction, however, the biggest clinical impact of epithelial changes is to corneal front surface topography; since the epithelium compensates for stromal irregularities, the presence of an irregular stromal surface is either partially or totally masked from corneal front surface topography. Therefore, corneal front surface topography does not always tell the whole story, and in some cases does not provide the necessary information to establish a correct diagnosis.

1. Keratoconus Screening

In keratoconus, the epithelium remodels to follow a distinctive epithelial donut pattern, characterized by a localized central zone of thinning surrounded by an annulus of thick epithelium, demonstrating that the epithelium compensates for the underlying stromal cone by thinning over the cone and thickening around the cone.[21-23] In early keratoconus, the epithelial doughnut pattern will act to minimize the extent of the cone on the front corneal surface and potentially fully compensate the stromal surface irregularity and render a completely normal front corneal surface.[27] Therefore, epithelial thickness mapping has the potential to exclude the appropriate patients by detecting keratoconus earlier or confirming keratoconus in cases where topographic changes may be clinically judged as being “within normal limits”. Secondly, epithelial thickness profiles may be useful in excluding a diagnosis of keratoconus despite suspect topography; epithelial thickening over an area of topographic steepening implies that the steepening is not due to an underlying ectatic surface.

2. Limits for Hyperopic Steepening

It is currently assumed that hyperopic LASIK should be limited according to postoperative curvature as too much steepening can result in epitheliopathy or apical syndrome; it is generally accepted that the postoperative curvature should not exceed 49.00 to 50.00 D.[28] However, we have previously suggested that central epithelial thickness may be a more useful indicator as it is a direct measurement of the potential risk of apical syndrome, which occurs once the epithelium is too thin (less than 25 µm).[13] Therefore, using epithelial thickness measurements, hyperopic retreatments might be performed without risk of apical syndrome while also allowing some patients to have retreatment who would otherwise have been rejected for further surgery due to high keratometry postoperatively.

3. Trans-epithelial PTK / Stromal Surface Topography-guided Custom Ablation

Despite all the advances in corneal topography and ocular wavefront measurement, it is not always possible to diagnose the cause of subjective visual complaints by these means alone because the compensatory epithelial thickness changes act to partially mask the true stromal surface irregularity (described above). In 1994, we coined *Reinstein’s Law of Epithelial Compensation* for irregular astigmatism:[29] “Irregular astigmatism results in irregular epithelium”. If a patient presents with stable irregular astigmatism, by definition the epithelium has reached its maximum compensatory function by thinning over peaks and thickening over troughs in the stromal surface. As mentioned earlier, the epithelium can compensate almost completely for very localized irregularities. Therefore, topography or wavefront-guided treatments may lead to a sub-optimal treatment plan and potentially make things worse.[20] Instead, we need a method to target the irregularities masked by the epithelium, something that is achieved, by definition, by trans-epithelial PTK.[17, 19, 20] The only disadvantage of trans-epithelial PTK is that it is limited to treat only the proportion of the stromal irregularities compensated for by the epithelium, so more than one procedure is often required. The final solution in repair treatments is going to be a custom ablation profile based on stromal surface topography, something which can be measured by subtracting the epithelial thickness profile from the front corneal surface topography.

4. Improved IOL Power Calculation after Corneal Refractive Surgery

Given the lenticular nature of epithelial remodeling after corneal refractive surgery, the postoperative epithelium will make a contribution to the refractive effect of the cornea. However, the epithelial thickness profile after a myopic ablation will have the opposite effect to that after a hyperopic ablation, while also being correlated to the amount of correction – and studies have demonstrated this exact result of undercorrection in post-myopic eyes and overcorrection in post-hyperopic eyes.[30] Therefore, consideration of epithelial thickness profiles into IOL power calculation formulae has the potential to further improve accuracy.

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