

## Rate of Change of Curvature of the Corneal Stromal Surface Drives Epithelial Compensatory Changes and Remodeling

### To the Editor:

We read with interest the article by Kanellopoulos and Asimellis<sup>1</sup> published in the March 2014 issue that reported the longitudinal change in epithelial thickness after myopic LASIK using spectral-domain anterior segment optical coherence tomography (Optovue, Inc., Fremont, CA). Until recently, epithelial thickness maps had only been reported using Artemis very high-frequency digital ultrasound (ArcScan, Inc., Morrison, CO),<sup>2</sup> so it is encouraging to see this field being expanded with the introduction of optical coherence tomography epithelial thickness mapping. However, we have reservations about the interpretation of some of the results in their study.

The authors link their findings of epithelial thickening after myopic LASIK to their earlier hypothesis<sup>3</sup> that epithelial hyperactivity and re-growth is related to the biomechanics of the cornea and specifically to a thinned cornea such as after excimer laser ablation or in keratoconus. We believe this hypothesis is a misinterpretation of the epithelial response and appears to be based on correlation rather than causation.

In contrast, we believe that all epithelial thickness changes can be explained by a compensatory mechanism that attempts to reestablish a smooth, symmetrical optical surface, which is driven by the rate of change of curvature of the stromal surface such that more epithelial thickness changes occur as the rate of change of curvature increases. The second component of this mechanism is that the outer surface is regulated by the template provided by the blinking action and force applied by the eyelid.<sup>4,5</sup> This hypothesis would appear to be more strongly supported by the existing data on epithelial thickness changes for the following reasons:

1. Increasing the optical zone increases the ablation depth, meaning more tissue is removed. Therefore, there is more corneal thinning and greater reduction in the biomechanical strength of the cornea when using a larger optical zone. The authors' hypothesis thus predicts that there will be more epithelial thickening when using a larger optical zone. However, the amount of epithelial thickening after myopic ablation decreases as the optical zone is increased, as previously described<sup>6</sup> and demonstrated by the lower epithelial thickening found in this study and others using a 6.5-mm optical zone<sup>1,7</sup> compared to that reported using very high-frequency digital ultrasound for a 6-mm optical zone.<sup>2</sup> This is also supported by the reduction in refractive regression when using larger optical zones.<sup>8,9</sup> In contrast, less epithelial thickening in larger optical zones is explained by the rate of change of curvature hypothesis; increasing the optical zone results in a more gradual rate of change of curvature on the stromal surface, which predicts that there will be less epithelial thickening as the optical zone is increased.
2. Epithelial thickness changes have been described after myopic excimer laser ablation,<sup>1,2,6,10-14</sup> hyperopic excimer laser ablation,<sup>15</sup> radial keratotomy,<sup>16</sup> orthokeratology,<sup>17</sup> and in keratoconus,<sup>18</sup> ectasia,<sup>3,19</sup> and cases of highly irregular astigmatism.<sup>20-24</sup> In all cases, there is both epithelial thickening and epithelial thinning; however, the authors' hypothesis only seems to account for epithelial thickening. In contrast, the rate of change of curvature hypothesis predicts that there will always be both and also predicts where each will occur; there will be epithelial thinning to compensate for relative peaks and epithelial thickening to compensate for relative troughs in the stromal surface.
3. From the studies referred to in reason 2, it is known that the ability for the epithelium to compensate for stromal surface irregularities is increased for more localized irregularities. For example, we have previously reported a case of short nasal flap with ablation in which there was a 54- $\mu\text{m}$  difference in epithelial thickness within 1.3 mm.<sup>23</sup> Also, it is well known that the epithelium will compensate to replace stroma that has been lost due to a corneal ulcer, such as a case we reported with an epithelial thickness of 209  $\mu\text{m}$  to compensate for a stromal defect of approximately 1 mm in diameter.<sup>15</sup> In cases such as these, the corneal thinning and change in corneal biomechanics was significantly less than the corneal thinning after a high myopic LASIK correction. Therefore, the authors' hypothesis would predict less epithelial thickening in these cases than after myopic LASIK; however, the epithelial response was much greater. In contrast, the rate of change of curvature hypothesis explains why there is a greater epithelial response for a more localized irregularity.
4. There are dramatic epithelial thickness changes in situations where there is no corneal thinning and no change to corneal biomechanics. One example is a case of the rotation of a malpositioned LASIK free cap in which epithelial changes of greater than 20  $\mu\text{m}$  were observed when scanned 2 days after the free cap rotation procedure.<sup>25</sup> This would not be predicted by the authors' hypothesis, but is explained by the change in the rate of change of cur-

vature of the stromal surface after rotating the free cap. Another example is orthokeratology,<sup>17</sup> where the epithelium thins centrally and thickens in the mid-periphery to fit the template provided by the orthokeratology contact lens. This is an interesting case because although the cornea has not been thinned, the curvature of the stromal surface has not changed either. However, this can be explained by the second aspect of the epithelial compensatory mechanism, that the corneal surface is regulated by the template provided by the eyelid.<sup>4,5</sup> In orthokeratology, the eyelid template is replaced by a contact lens, which then allows the epithelium to thicken to fit the new template.

- To support their hypothesis, the authors cite their previous study investigating epithelial thickness in normal corneas, ectatic corneas, and ectatic corneas treated with corneal cross-linking (CXL).<sup>3</sup> It was found that the overall mean epithelial thickness was greatest in the ectatic corneas and lowest in the normal corneas. It was concluded that the increased biomechanical strength afforded by CXL was the reason why the overall mean epithelial thickness was lower for the CXL ectasia group than in the non-CXL ectasia group. However, the CXL group had also been treated simultaneously with partial topography-guided photorefractive keratectomy. Therefore, the keratoconic cone had been reduced by the simultaneous excimer laser ablation, which would result in less epithelial compensation<sup>18</sup> and a lower overall mean epithelial thickness. The results of this study are therefore explained by the rate of change of curvature hypothesis without the need for referring to corneal biomechanics (the second reference appears to be a study describing optical coherence tomography detection of a demarcation line to measure the effective CXL depth<sup>26</sup>; it is not clear how this reference supports the authors' hypothesis).

Although there is an association between corneal thinning and epithelial thickening in many situations, this does not explain the cause of the epithelial thickness changes and does not appear to be consistent across the range of scenarios for which epithelial changes have been reported. On the other hand, all of the reported epithelial thickness changes can be explained and predicted by considering the rate of change of curvature of the stromal surface and/or changing the outer template provided by the eyelid.

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### Reply:

We would like to thank Reinstein et al. for their letter in regard to our investigative work on epithelial remodeling following myopic LASIK by femtosecond laser,<sup>1</sup> particularly the findings pertaining to a possible correlation between epithelial thickness increase versus attempted myopic correction. Their comments help us clarify further and summarize the recent findings in epithelial thickness imaging.

To properly answer the well-presented and extensively documented points, one has to also consider the

specifics of the optical coherence tomography (OCT) imaging modality employed in our work versus the ultrasound imaging modality employed in the past and used for comparison.

### EPITHELIAL THICKNESS MAPPING: IMAGING TECHNOLOGIES COMPARED

Three-dimensional epithelial thickness maps were introduced using high-frequency ultrasound (HFU) by the system known as Artemis (ArcScan, Inc., Morrison, CO and/or Artemis Medical Technologies Inc., Vancouver, British Columbia, Canada). We also have had the opportunity to work with this exciting technology and report some compelling findings.<sup>2-4</sup>

The recent ability of in vivo epithelial thickness mapping by Fourier-domain anterior segment OCT (AS-OCT) offered by the RtVue-100 (Optovue Inc., Fremont, CA) has further expanded the applicability and clinical importance of epithelial thickness mapping. Among the advantages of the newly emerging modality are the high repeatability,<sup>5,6</sup> ease of use, and acquisition speed. Although the overall acquisition and data visualization still rely on interpolation from raw data derived from several meridional scans, there are specific advantages when one compares the OCT option for epithelial imaging to the HFU option. The first advantage derives from fact that the OCT does not need fluid coupling between the eye and the device. This feature not only facilitates clinical implementation even on the first postoperative day—something that is avoided for reasons of possible wound contamination when the Artemis system is involved—but also makes the acquisition reliable and repeatable. The second is that the OCT imaging of eight meridians is completed in less than a second, which compares to several minutes of successive manual changes (by means of rotating a steering wheel located at the back of the HFU system). The typical number of successive meridional scans required for the HFU imaging is four. Among the possible shortcomings associated with the current state of the OCT-based epithelial imaging is the fact that up to now, imaging is restricted to the central 6-mm corneal diameter, compared, for example, to the 9-mm diameter offered by the HFU system. Another is the fact that the current state of OCT-based epithelial imaging cannot differentiate the tear film, which is “collectively” reported within the epithelial thickness; in comparison, the HFU system may alter the epithelial in vivo state by intense hydration, associated with the capture process that requires the cornea within a “water bath.”

Therefore, a comparison of findings may not always be applicable. Differences in technology may account

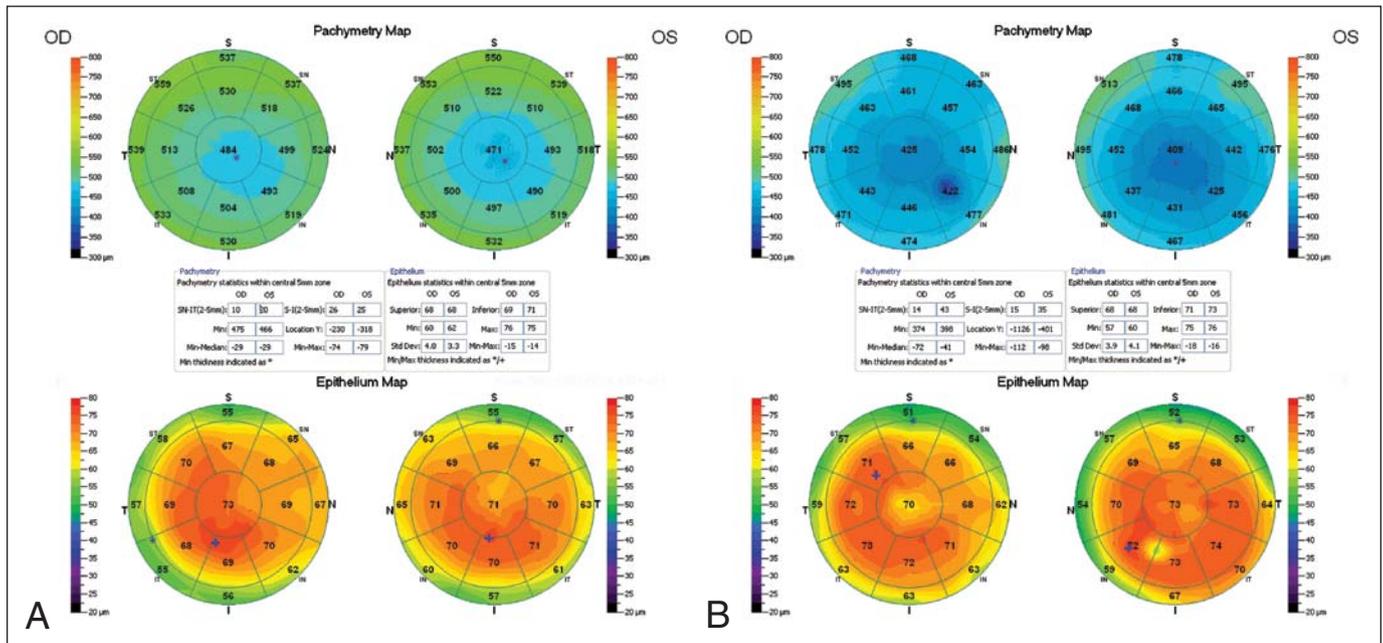
for the possibility that aspects of the epithelial layer distribution may be manifested in a different fashion.

#### EPITHELIAL THICKNESS DISTRIBUTION CHARACTERISTICS

Over the past 5 years, we have extensively investigated AS-OCT imaging inspired from the work previously reported and have employed such routine imaging in all patient visits in our referral type specialized clinical center. Because of this, we have performed more than half a million individual eye scans, employing AS-OCT, and have reported corneal epithelial distribution in large groups of normal patients,<sup>7</sup> patients with dry eye,<sup>8</sup> and patients with keratoconus<sup>9</sup> using epithelial remodeling following cataract surgery,<sup>10</sup> Descemet stripping automated endothelial keratoplasty,<sup>11</sup> cornea collagen cross-linking,<sup>12</sup> and high-myopic LASIK intervention with concurrent prophylactic cross-linking.<sup>13</sup> We have also investigated via the HFU system epithelial thickness mapping in corneas that were normal, ectatic, and ectatic previously treated with CXL.<sup>2</sup> A novel finding of this work was that, in addition to the specific/local epithelial distribution, overall epithelial thickness may be a possible indicator for corneal instability. In our opinion, this hypothesis seems to be a groundbreaking interpretation of the epithelial response to increased oscillation of a biomechanically “weakened” stroma encountered in progressive keratoconus and ectasia. Such a hypothesis will only survive the test of time and multiple corroborative elements of evidence such as a reliable device that may assess corneal biomechanical behavior.

We have encountered several such elements over the course of our extensive investigation, which we would like to summarize:

1. In normal eyes, the epithelial thickness has a near-uniform distribution of approximately 53  $\mu\text{m}$ , ranging between 45 and 60  $\mu\text{m}$ . Epithelial thickness is slightly increased inferiorly. Average topographic variability, expressed by the standard deviation of several points, is 2  $\mu\text{m}$ . The epithelial thickness range (difference minimum – maximum) is -8  $\mu\text{m}$ , ranging from an average minimum of 48  $\mu\text{m}$  to an average maximum of 56  $\mu\text{m}$ .<sup>7</sup>
2. There is a noted overall increase of epithelial thickness in dry eyes (average 58  $\mu\text{m}$ ); however, the topographic variability is comparable to that of normal eyes (average 3  $\mu\text{m}$ ).<sup>8</sup>
3. In corneas characterized by ectasia, there is a noted increase in the spread of thickness values. We have noted an average epithelial thickness range of -23  $\mu\text{m}$  and an average topographic variability of 10  $\mu\text{m}$ .<sup>2,9</sup> Investigation with OCT has verified the compensatory nature of epithelial distribution in response to anterior stromal surface irregularities: indeed, the epithelium is thinner over the steeper ‘conic’ section in a keratoconic eye and thicker over the flatter areas. In addition to this, however, we have noted an overall increase in epithelial thickness, particularly in younger patients with keratoconus.<sup>2</sup>
4. Epithelial thickness remodeling investigated after keratoplasty<sup>11</sup> and cataract surgery<sup>10</sup> has indicated a return to baseline levels after a 3-month interval.
5. Epithelial thickness remodeling following partial anterior cornea normalization and cross-linking (Athens Protocol)<sup>2,12</sup> has indicated that the epithelium is on average thinner compared to untreated eyes with keratoconus, and even compared to ‘normal’ corneas, despite the residual anterior corneal surface abnormality. The only justification for such a manifestation is perhaps the increased stromal rigidity.
6. Epithelial thickness remodeling following LASIK has indicated a slight (average +3  $\mu\text{m}$ ) increase in epithelial thickness.<sup>1</sup> A novel finding has been that the increase was rather non-lenticular (a finding reported by Reinstejn et al.<sup>14</sup>), but more emphasized in the mid-periphery of 5 mm. Of course, the extent of epithelial remodeling over the entire affected area of perhaps up to 8 mm is still not clinically possible with the current state of OCT imaging. A second novel finding has been that the noted increase showed a positive correlation to the amount of attempted myopic correction: the larger the myopic correction, and thus the stromal flattening, the larger the noted epithelial thickness increase.
7. The interpretation of the above finding is, in our opinion, the core of the argument posted by this correspondence. We respectfully disagree to attributing this finding exclusively to the rate of change of curvature and the resultant compensatory response of the epithelium remodeling. The reasons for our different opinion are based on two key findings. First, our investigation of matched groups of myopic ablation, between a ‘standard’ LASIK treatment and a LASIK treatment with concurrent prophylactic in situ cross-linking has indicated that there is no noted increase in epithelial remodeling when the cross-linking is applied.<sup>13</sup> Second, our ongoing investigation of myopic correction applied with photorefractive keratectomy has routinely indicted a drastically different epithelial remodeling. The example in **Figure 1** illustrates corneal and epithelial thickness mapping following 1 year of myopic correction with photorefractive keratectomy. In **Figure 1A** a 28-year-old man received -5.00 diopters of correction and in **Figure 1B** a 27-year-old man received -8.00 D of correction. The remodeled



**Figure 1.** One year postoperative corneal and epithelial thickness mapping of cases that received myopic correction by photorefractive keratectomy. (A) A case of a 28-year-old man who received -5.00 diopters of correction. (B) A case of a 27-year-old man who received -8.00 diopters of correction.

epithelial pattern presented in these cases may not be justified with the compensatory theory for several reasons. First, the epithelial thickness increase is similar in both cases, despite the larger myopic correction, and thus stromal flattening. Second, the noted thickness increase (average +20 μm, compared to preoperative levels) is drastically larger when compared to similar myopic ablations performed with LASIK.<sup>1</sup> Had the compensatory theory been valid in all cases, this is a finding impossible to explain. Therefore, other aspects (in this case the removal of Bowman’s layer) or even a “steeper” transition zone between the ablation and the peripheral cornea that may be “smoother” in LASIK due to some overlying flap masking may also be some important contributing factors.

We believe that the clinical differences observed, despite the possible attribution to the epithelial compensatory response, may not be fully justified with this theory. Our proposed hypothesis of epithelial response being related to corneal rigidity may offer an additional clinical finding, which has a follow-up potential. The anticipated clinical ramifications of this hypothesis is prospectively positive. Nevertheless, we have learned much from the preceding HFU experience and most of the credit of this body of work goes to the discussants.

What we suggest as a clinical pearl to clinicians is that, in our current clinical setting, epithelial and to-

tal corneal three-dimensional mapping has become a critical diagnostic tool in the preoperative assessment of patients undergoing cataract refractive surgery and evaluation of dry eye and multiple other external disease modalities. Epithelial and total corneal mapping has also become an integral tool in monitoring visual recovery and quality of vision in both cataract and refractive surgery cases alongside traditional means of corneal imaging such as Placido-based topography and Scheimpflug tomography.<sup>15</sup>

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