Corneal Curvature Gradient Determines Corneal Healing Process and Epithelial Behavior

We read with great interest the article by Kanellopoulos and Asimellis[1] and the subsequent correspondence with Reinstein et al.[2] with the debate regarding the law that drives epithelial remodeling and the healing process.

Kanellopoulos and Asimellis explained their findings of epithelial thickening after myopic LASIK with their hypothesis that epithelial behavior is related to the biomechanics of the cornea and that a thinned cornea (in cases of large myopic ablation) might be more susceptible to epithelial hyperactivity and regrowth. Conversely, Reinstein et al. suggested that all epithelial thickness changes can be explained by a compensatory mechanism that is driven by the rate of change of curvature of the stromal surface. This last finding was presented in an article by our group that defined the rate of change of curvature as the corneal curvature gradient.[3] In particular, the curvature gradient is a topography map aimed to evaluate the rate of change in curvature over the corneal surface. In that article, we demonstrated that the initial curvature gradient after excimer ablation predicts the change in tangential curvature over the subsequent 12 months in areas where the initial tangential curvature is the greatest. When the curvature gradient is high, the surface curvature modification remains in progress even months after the ablation.

We believe the hypothesis by Kanellopoulos and Asimellis (that biomechanics could play a role in corneal healing) is interesting and we cannot exclude it, but it currently lacks validation with preclinical and clinical studies that separate the possible biomechanical effect from the curvature gradient change. With the current evidence we believe that all epithelial thickness changes, even those described by Kanellopoulos and Asimellis, could be explained by a change in the curvature gradient.

We would like to divide the categorical evidence into Clinical, Cell Morphology, Modelling, and Real Life.

CLINICAL

The role of changing epithelial thickness as a key factor in the pathogenesis of the regression after refractive surgery, both LASIK and photorefractive keratectomy (PRK), is well known. In particular, it has been shown that central epithelial thickness increases after myopic PRK and LASIK in the region of central flattening and decreases in mid-periphery over the steepened area of

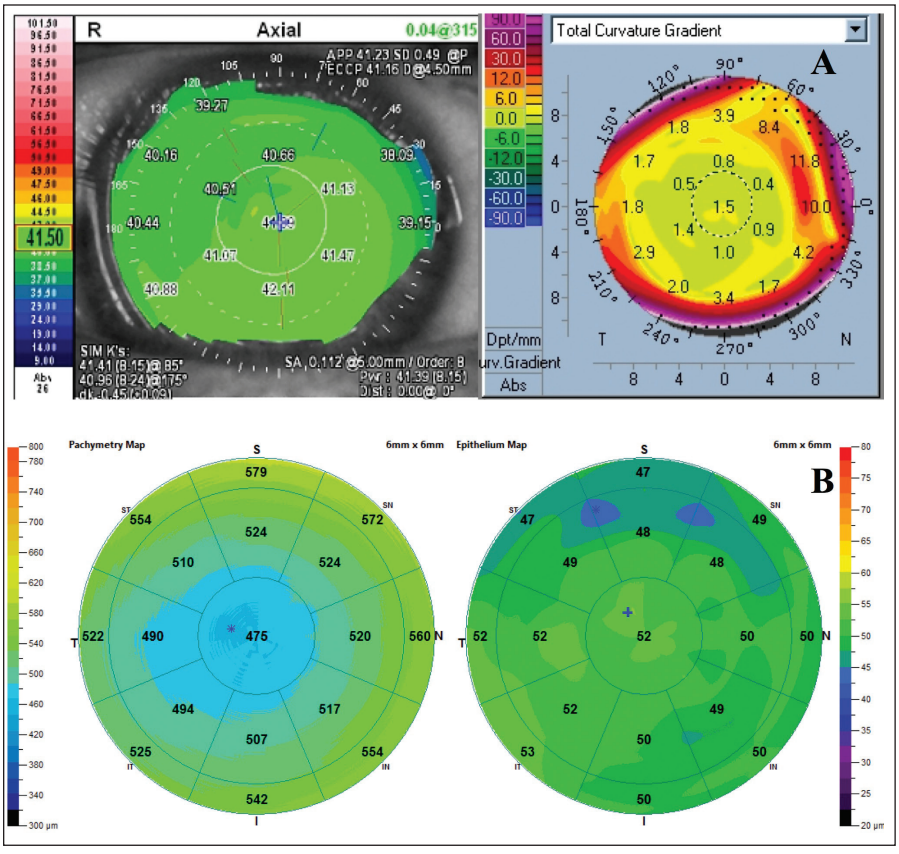

Figure 1. Demonstrating that it is possible to obtain a thinned cornea after refractive surgery with normal thickness epithelium only if the curvature gradient is normal. (A) A post-refractive surgery map with low gradient and smooth transition between optical zone and transition zone with Axial and Total Curvature Gradient topography map. (B) A thin cornea after refractive surgery with normal thickness epithelium evaluated by anterior segment optical coherence tomography pachymetry and epithelial thickness map.

the "red ring." In addition, after hyperopic LASIK the epithelium tends to thicken in the region of the ablation, accounting for refractive regression. These areas are where there is a high curvature gradient.

Cell Morphology

The change in epithelial thickness has been hypothesized to be due to a change in tension in the epithelial cells[4] and the inhibition of migration of the epithelial cells by contact with the neighboring cells.[5] This finding was well described by Dierick and Missotten,[4] who hypothesized that surface shape was influenced by tension in the epithelial cells, resulting in a hyperplasia of the epithelium in areas of flatter curvature until the growth pressure is balanced by the pressure between adjacent cells. In the presence of bulging or an increase of curvature, the tension exerted between the cells will induce thinning of the epithelium. Conversely, to our knowledge there is no preclinical study that supports the idea of any influence of biomechanics and thinned cornea in the epithelial behavior.

Modelling

A mathematical model introduced by Huang et al.[5] described epithelial "smoothing" after refractive surgery. The theory at the base of this study was that epithelial cell migration followed a law similar to the passage of solute across a concentration gradient. Similarly, the authors agreed that contact inhibition could be an explanation of epithelial behavior and that high curvature gradient leads to regression. Interestingly, at the end of the discussion they suggested creating a transition zone with a gradual change in curvature; otherwise, creating an abrupt change in curvature would create a peak in radial curvature that will induce large epithelial thickness response. This proposal was due to the clinical and theoretical finding that the ablation tends to regress with high curvature gradient.

Real Life

It is possible clinically to see a patient with thinned cornea after refractive surgery with normal thickness epithelium only if the curvature gradient is normal (**Figure 1**) or, as described by Reinstein et al.[2], a normal thickness cornea with dramatic changes in epithelial thickness that are explained with the curvature gradient theory. These findings contradict the hypothesis of Kanellopoulos and Asimellis.

For these reasons, although there is frequently an association between corneal thinning and change in epithelial thickness, this does not explain epithelial behavior and does not appear to be reliable to predict all reported epithelial changes. Conversely, as reported, all epithelial thickness changes can be explained and predicted by a corneal curvature gradient remodeling that has solid preclinical and clinical evidence, with ultrasound, topography, and optical coherence tomography.

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The authors have no financial or proprietary interest in the materials presented herein.

Reply:

We appreciate the commentary by Vinciguerra et al. on our previous reply on the same subject, and would like to thank the authors for their continued interest in our investigative work regarding corneal epithelial remodeling.

Over the past several years we have consistently employed high-frequency scanning ultrasound imaging (Artemis; ArcScan, Inc., Artemis Medical Technologies Inc., Vancouver, British Columbia, Canada) and/or Fourier-domain anterior segment optical coherence tomography (RTVue 100; Optovue, Fremont, CA) for the purpose of corneal evaluation in the clinical assessment of nearly every patient. Both devices provide epithelial thickness maps. As a result of this work, we have reported corneal epithelial distribution in large groups of normal, dry eye, and keratoconic patients. We have also investigated epithelial remodeling following cataract surgery, Descemet's stripping automated endothelial keratoplasty (DSAEK), corneal collagen

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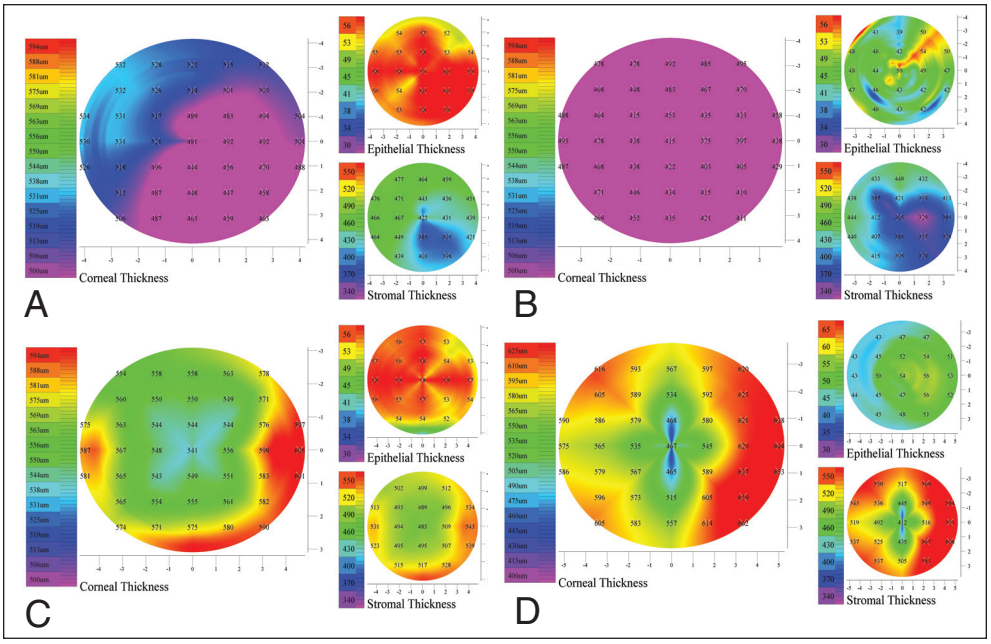

Figure 1. (A, C) Two cases of young, not treated keratoconic eyes and (B, D) two cases of keratoconic eyes subjected to the Athens Protocol, a procedure that combines partial stromal ablation and high-fluence cross-linking. Images were obtained with high-frequency scanning ultrasound imaging (Artemis; ArcScan, Inc., Artemis Medical Technologies Inc., Vancouver, British Columbia, Canada). For the treated eyes, images correspond to 9-month postoperative imaging. The top right corner of each report corresponds to the epithelial thickness maps. Comparison of the epithelial thickness maps indicates an overall increased epithelial thickness in the keratoconic eyes.

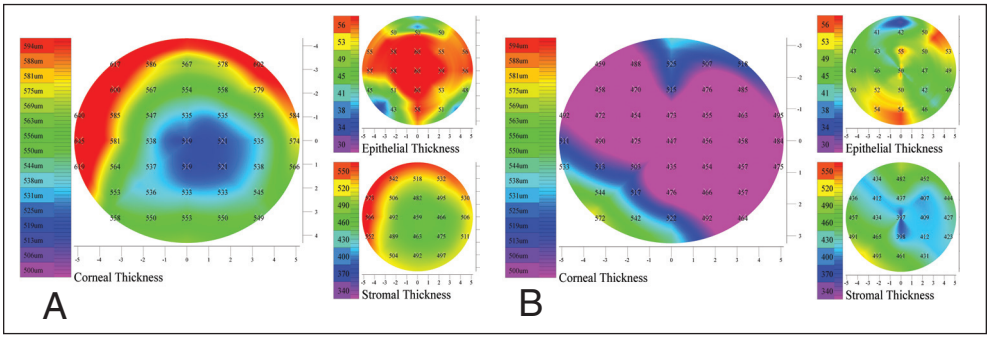

Figure 2. Contralateral example of a young keratoconic patient. (A) The untreated right eye of the patient. (B) The treated left eye of the patient (subjected to the Athens Protocol), 9 months postoperatively. Comparison of the epithelial thickness maps (top right corner of both reports) suggests that reduced epithelial thickness corresponds to the eye treated with cross-linking.

cross-linking,[1] myopic LASIK,[2] and high-myopic LASIK with concurrent prophylactic cross-linking.[3]

There is little doubt that there is postoperative near- and long-term epithelial remodeling following corneal refractive interventions. Specifically in regard to LASIK, our work[2] confirmed previous findings documenting epithelial thickening. A novel finding in our work was that the increase was not lenticular, but more emphasized in the mid-periphery of 5 mm. The epithelial thickness increase appears to correlate to the amount of attempted myopic correction: the larger the myopic correction (and thus the stromal flattening), the larger the localized epithelial thickness increase. The above findings do not contradict the well-known and modeled epithelial thickness remodeling pattern. It is perhaps a human biological "compensatory memory" mechanism that attempts to reverse the iatrogenic flattening of the natural shape of the cornea, which is altered for refractive purposes.

However, an important aspect that has not been discussed in this current correspondence is that we have also extensively investigated epithelial remodeling following interventions that modulate corneal biomechanics (ie, corneal cross-linking [CXL][1,4] Another novel finding was that the epithelium in such cross-linked keratoconic corneas appears to be on average thinner compared to untreated keratoconic corneas and even compared to "normal" corneas, despite the residual anterior corneal surface abnormality. The only justification for such a manifestation perhaps is the increased stromal rigidity: we suggested that an overall increased epithelial thickness may be an indicator for corneal instability, whereas a decreased epithelial thickness may indicate increased corneal stability.

Figure 1 presents two cases of young, untreated keratoconic eyes and two cases of keratoconic eyes subjected to the Athens Protocol, a procedure that combines partial stromal ablation and high-fluence cross-linking.[1,5] **Figure 2** presents a contralateral example of a young keratoconic patient, showing the untreated right eye and the treated left eye of the patient (which was subjected to the Athens Protocol procedure) 9 months postoperatively. It is evident from these examples that epithelial thickness is influenced by corneal biome-

chanics, and not just by corneal curvature gradients. The cross-linked examples shown indicate, beyond reasonable doubt, that the overall corneal epithelial thickness in the cross-linked corneas is much thinner when compared to untreated keratoconic corneas.

We also compared stand-alone LASIK and LASIK combined with prophylactic high-fluence cross-linking,[3] investigating the connection between epithelial thickness and corneal rigidity. If the epithelial thickness changes were governed solely by changes in anterior surface curvature gradients, the two groups would have displayed similar epithelial remodeling patterns, but they did not. The epithelial thickening was drastically more pronounced in the non-CXL LASIK cases, especially for higher myopias corrected. The findings strongly suggest that corneal biomechanics play a role in epithelial remodeling.

In our opinion, the link between epithelial remodeling and corneal biomechanics cannot be ignored. This appears to be a groundbreaking interpretation of the epithelial response to increased oscillation of a biomechanically "weakened" stroma encountered in progressive keratoconus and ectasia. Our proposed link between epithelial response and corneal rigidity may offer an additional clinical screening element, which has a follow-up potential. The anticipated clinical ramifications of this hypothesis are prospectively positive.

In addition, the examples of myopic correction applied with photorefractive keratectomy (PRK) indicate a drastically different epithelial remodeling pattern. The differences in epithelial remodeling presented in these cases may not be solely justified with the curvature gradient compensatory theory for several reasons. First, the epithelial thickness increase is similar in both cases, despite the large difference in myopic correction, and thus difference in effective stromal flattening. Second, the noted thickness increase (average +20 µm, compared to preoperative levels) is drastically larger when compared to similar LASIK myopic ablations.[2] Had the gradient compensation theory been valid in all cases, this is a finding difficult to explain. Perhaps other aspects specific to PRK—the removal of Bowman's layer and possibly a steeper transition zone between the ablation zone and the peripheral cornea that may be smoother in LASIK due to some overlying flap "masking"—may be among other factors that contribute to these differences. In addition, induced dry eye may also be among the contributing factors. The curvature change is still a valid theory, but it appears that it may not be the only one.

Therefore, we respectfully disagree with the "all" in the statement "all epithelial thickness changes, even those described by Kanellopoulos and Asimellis, could be explained by a change in curvature gradient."

It would be of great interest to this subject to evaluate epithelial remodeling after an alternate laser corneal refractive surgical technique: the small incision lenticule extraction (SMILE) procedure. In situ all femtosecond laser lenticular removal procedures for the correction of myopia hold the promise of affecting the anterior biomechanical stability less than LASIK and not interrupting significantly the superficial nerve fiber plexus of the cornea. Epithelial remodeling in SMILE cases may further enlighten us in regard to additional mechanisms involved in epithelial remodeling following curvature changes, in addition to neurotrophic dry eye and/or biomechanical changes.

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