

## Stromal Opacity After Cross-linking

### To the Editor:

The same stromal opacities found in the rabbit study by Salomão et al,<sup>1</sup> which appeared in the June 2011 issue of the *Journal of Refractive Surgery*, have been previously described as frequent but asymptomatic complications after corneal cross-linking (CXL) in cases of steep corneas with keratometry values >54.00 diopters (D).<sup>2-4</sup> Raiskup et al<sup>4</sup> demonstrated that infusion with a hypo-osmolar riboflavin solution preserved corneal tissue from stromal opacity development even in severe keratoconus cases with ultra-thin corneas, with no reduction of CXL effectiveness. The same phenomenon was observed by our group<sup>5</sup> in patients with postoperative LASIK ectasia. Corneas were plumped with hypotonic riboflavin before CXL irradiation.<sup>6</sup> None of the patients developed any stromal opacity, despite their mean central corneal thickness (CCT) was less than the recognized safe cut-off depth of 400  $\mu\text{m}$ . We found that the usual development of deep stromal opacities after CXL was related to a reduction of CCT at 1 month after CXL.

Therefore, we decided to study CCT behavior during CXL in 45 corneas with keratoconus. Mean patient age was 27 years (range: 19 to 37 years). After 20 minutes of soaking with 0.1% riboflavin solution (10 mg riboflavin-5-phosphate in 20% dextran-T-500 10 mL), all corneas with CCT <350  $\mu\text{m}$  were plumped to 400  $\mu\text{m}$  with a hypo-osmolar solution (riboflavin-5-phosphate) for a mean time of 8 minutes.

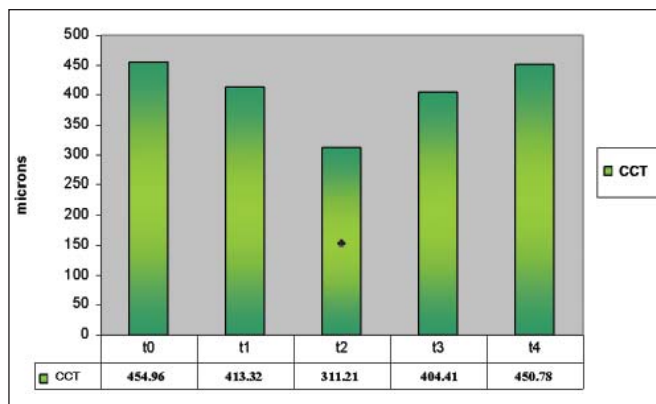
Intraoperative CCT was measured with ultrasound pachymetry after epithelial removal (t1), after 20 minutes of riboflavin infusion (t2), after corneal expansion (t3), and at the end of irradiation (t4) (Fig). Posterior stromal opacity formation was evaluated by anterior segment optical coherence tomography up to 12 months postoperatively.

No significant difference ( $P=.003$ ) was found after epithelium removal. A mean CCT reduction of 102.11  $\mu\text{m}$  was measured after 20 minutes of riboflavin infusion ( $P<.00001$ ). No significant change in CCT was measured at the end of corneal expansion ( $P=.51$ ) or irradiation ( $P=.016$ ).

Eyes were also divided into 3 groups of 15 eyes each according to preoperative CCT (group I <450  $\mu\text{m}$ , group II between 450 and 500  $\mu\text{m}$ , and group III >500  $\mu\text{m}$ ). The decrease in CCT after the first 20 minutes of riboflavin infusion was significantly higher in group III, with a 28% CCT reduction. Groups I and II showed a 22% and 25% decrease in CCT, respectively.

None of the patients presented intraoperative, early, or late postoperative complications such as deep stromal opacities for up to 1 year after CXL.

We therefore concluded that CCT reduction during



**Figure.** Variations in mean central corneal thickness (CCT) at different time points during corneal cross-linking in 45 corneas (mean patient age: 27 years). t0 = preoperative, t1 = after epithelial removal, t2 = after 20-minute riboflavin infusion ( $P<.001$ ), t3 = after corneal expansion, t4 = end of irradiation

the soaking phase could be a predictive factor for the potential development of stromal opacity after CXL. Because CCT can be measured during the entire CXL procedure, we recommend testing each cornea after the soaking phase and eventually swelling corneas with a CCT <350  $\mu\text{m}$  to avoid stromal scar formation and visual impairment. It is also interesting to note that the thickest corneas thinned at a higher rate than the thinnest, most likely because thick corneas have more interlamellar and interfibrillar spaces and become more dehydrated during the CXL procedure.

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

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## Association of Corneal Indices for the Detection of Ectasia-susceptible Corneas

### To the Editor:

The recent article by Wei et al,<sup>1</sup> which appeared in the October 2011 issue of the *Journal of Refractive Surgery*, highlights the low incidence of forme fruste keratoconus and describes some of its corneal characteristics measured with the Orbscan II (Bausch & Lomb, Rochester, New York). In their prospective study, the authors included 111 patients with clinical keratoconus and found that only 5 (4.5%) had unilateral keratoconus without any clinical or topographic (including objective topographic assessment) sign of keratoconus in the fellow eye.<sup>1</sup> They found that normal fellow eyes of eyes with keratoconus have greater irregular optical surfaces compared to normal eyes and supposed that these fellow eyes may show a certain low-expressivity morphologic feature of keratoconus.

In 2010, we published an article describing the topographic and tomographic properties of forme fruste keratoconus.<sup>2</sup> Our study included 40 corneas with forme fruste keratoconus (normal corneas based on the Corneal Navigator system of the OPD-Scan [NIDEK Co Ltd, Gamagori, Japan] with clinical keratoconus in the contralateral eye) that were compared to 72 normal corneas and 31 corneas with keratoconus. The irregularity index measured at 3 mm reached  $1.25 \pm 0.38$  in the forme fruste keratoconus group and was significantly higher compared to the normal group. Irregularity at 5 mm, central and thinnest pachymetry, vertical position of the thinnest point, and maximal central anterior elevation were also statistically different between the normal group and forme fruste keratoconus group. Additionally, we considered the thinnest point as a center location to obtain the posterior elevation of the thinnest point and the percentage of increase in thickness from the thinnest point to the periphery (corneal spatial profile). These parameters were different between the two groups.

In their study, Wei et al<sup>1</sup> reached an area under the receiver operating curve of 0.860 using the irregularity at 3 mm to discriminate between the forme fruste keratoconus and normal eyes. Our study<sup>2</sup> showed that one index alone can hardly reach a high sensitivity and specificity in the detection of forme fruste keratoconus. However, the combination of multiple corneal indices in one discriminant function allowed the differentiation between the normal group and forme fruste keratoconus group with a sensitivity of 92.5% and specificity of 92%. More recently, this discriminant function was able to retrospectively classify a cornea that develops ectasia after LASIK despite normal pre-

operative parameters and good postoperative stromal bed thickness as forme fruste keratoconus.<sup>3</sup> It would be interesting to see how the pachymetric progression graphs appear in Wei et al's forme fruste keratoconus group and what would be the gain in the sensitivity and specificity of forme fruste keratoconus detection by adding and combining these parameters. As the frequency of unilateral keratoconus is low, reports such as the one by Wei et al and international cooperation will help determine specific indices for the diagnosis of ectasia-susceptible corneas.

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### Reply:

Saad and Gatinel recently stated that one index alone can hardly reach a high sensitivity and specificity in the detection of forme fruste keratoconus or ectasia-susceptible corneas.<sup>1,2</sup> In their study, they described and compared topography and tomography indices, as well as the central to periphery percentage of thickness increase and the percentage of anterior and posterior curvature modification in three groups of corneas classified as normal (LASIK with 2-year follow-up), forme fruste keratoconus, and keratoconus by specular topography, on the basis of the artificial intelligence of the Corneal Navigator (NIDEK Co Ltd, Gamagori, Japan), and combined those indices in discriminant functions to detect mild ectatic corneas. They found that those indices generated from corneal thickness and curvature measurements over the entire cornea and calculations of the percentage of thickness increase and the percentage of anterior and posterior curvature variation from the thinnest corneal thickness to the periphery can identify mild forms of keratoconus that are not detected by Placido topography. However, as the studied indices showed some degree of overlap in normal and pathologic corneas, it could not be concluded that any single parameter taken alone is suffi-

cient to distinguish a normal from a suspect cornea. The authors believe that evaluating those indices in conjunction with the parameters provided by Placido topography may help in creating an artificial intelligence more sensitive and specific for the detection of at-risk corneas. This is in agreement with our previous report.<sup>3</sup> In this report, four main videokeratography patterns of clinical keratoconus tested the ability of the KCI and KSI indices to detect keratoconus. The results show that no single index is expert in detecting keratoconus or ectasia-susceptible corneas. In our opinion, one needs to look at a combination of corneal topography pattern and quantitative indices in screening for mild cornea ectasia. Our recent study<sup>4</sup> highlights the ability of the irregularity at 3 mm to discriminate topographically normal fellow eyes of unilateral keratoconus. It does not conclude that a single parameter is sufficient to distinguish a suspect from a normal cornea.

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