

# Corneal Cross-linking for Keratoglobus Using Individualized Fluence

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## ABSTRACT

**PURPOSE:** To present a case of bilateral progressive keratoglobus that was successfully arrested with corneal cross-linking (CXL) applying the sub400 individualized fluence protocol.

**METHODS:** Case report.

**RESULTS:** A 36-year-old man with bilateral progressive keratoglobus and no history of eye rubbing presented with a corrected distance visual acuity (CDVA) of 20/200 in the left eye. Progression in the left eye was confirmed using previously taken corneal topographies and comparing them to

high-resolution Scheimpflug imaging, high-speed dynamic Scheimpflug imaging, and anterior segment optical coherence tomography. Epithelium-off CXL was performed in the left eye using individualized fluence that was adapted to the thickness of the corneal stroma immediately prior to irradiation (sub400 protocol). Postoperative follow-up of 32 months showed stabilization of keratometric values and no endothelial cell loss.

**CONCLUSIONS:** The sub400 epithelium-off CXL protocol using individualized fluence may arrest progressive keratoglobus and might represent a novel therapeutic approach for the management of keratoglobus.

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**K**eratoglobus is a corneal ectasia that typically occurs bilaterally and is characterized by a generalized stromal thinning across the entire cornea.<sup>1</sup> Although classified as a congenital disorder and often associated with connective tissue diseases such as Marfan syndrome and Ehlers-Danlos syndrome (type VI in particular),<sup>2</sup> recent reports suggest that keratoglobus

may also be acquired and associated with vernal keratoconjunctivitis atopy, blepharitis, corneal traumas, dysthyroid eye disease, and extreme eye rubbing.<sup>3-6</sup>

Keratoglobus treatment is challenging, largely due to the reduced thickness across the entire cornea. Several complex surgical techniques have been proposed for the management of advanced keratoglobus,

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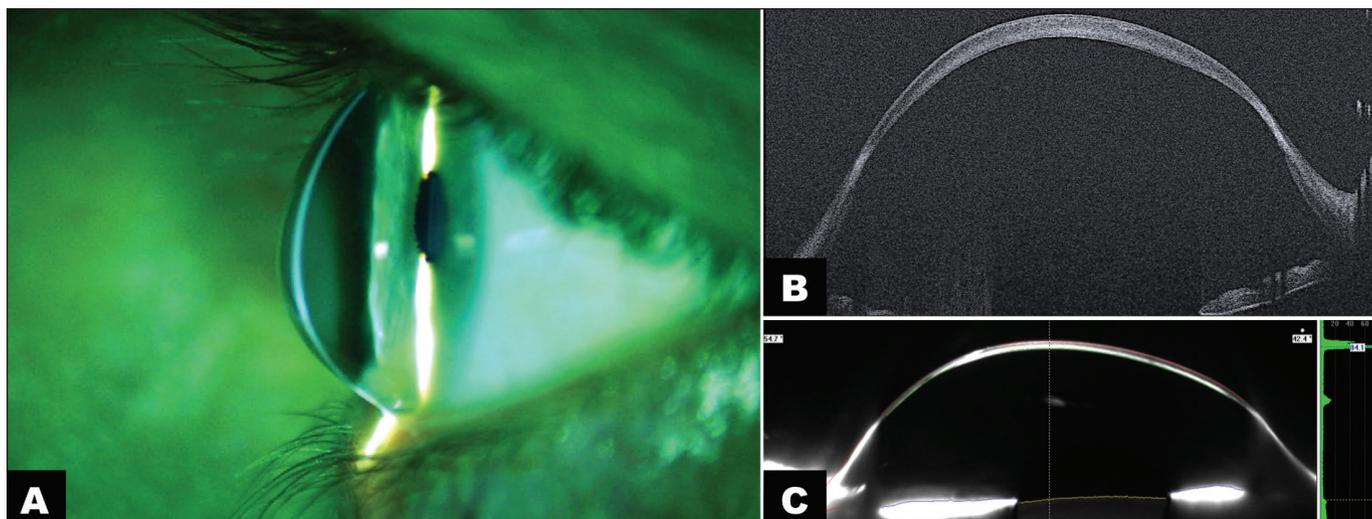
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**Figure 1.** (A) Slit-lamp, (B) anterior segment optical coherence tomography, and (C) Scheimpflug image of the left cornea before corneal cross-linking show marked thinning in the periphery, but also in the central cornea.

usually with the purpose of restoring corneal structural integrity and introducing some degree of visual rehabilitation, sometimes in conjunction with scleral contact lenses.<sup>7-9</sup> However, because peripheral thickness is often severely compromised in keratoglobus, such techniques often have increased intraoperative and postoperative risks.<sup>8</sup> Lamellar surgeries have increased chances of intraoperative microperforations or macroperforations, and may also result in interface-related issues in the postoperative period.<sup>10</sup> Penetrating keratoplasties with large corneal grafts lead to not only technical difficulties in the placement of peripheral sutures, but also an increased risk of endothelial rejection due to a loss of immune privilege, limbal stem cell disruption, and angle structure disruption.<sup>10</sup> Additionally, it is often the case that more than one surgical procedure may be required, which delays the patient's visual recovery.<sup>8,10</sup>

Corneal cross-linking (CXL) is frequently and successfully used to treat corneal ectasias such as keratoconus and pellucid marginal degeneration—both of which appear to share a common pathogenesis—and there are now several new treatment algorithms validated for cross-linking thin keratoconic corneas.<sup>11,12</sup> We used the sub400 individualized fluence CXL protocol<sup>11</sup> to halt keratoglobus progression in the case report presented below.

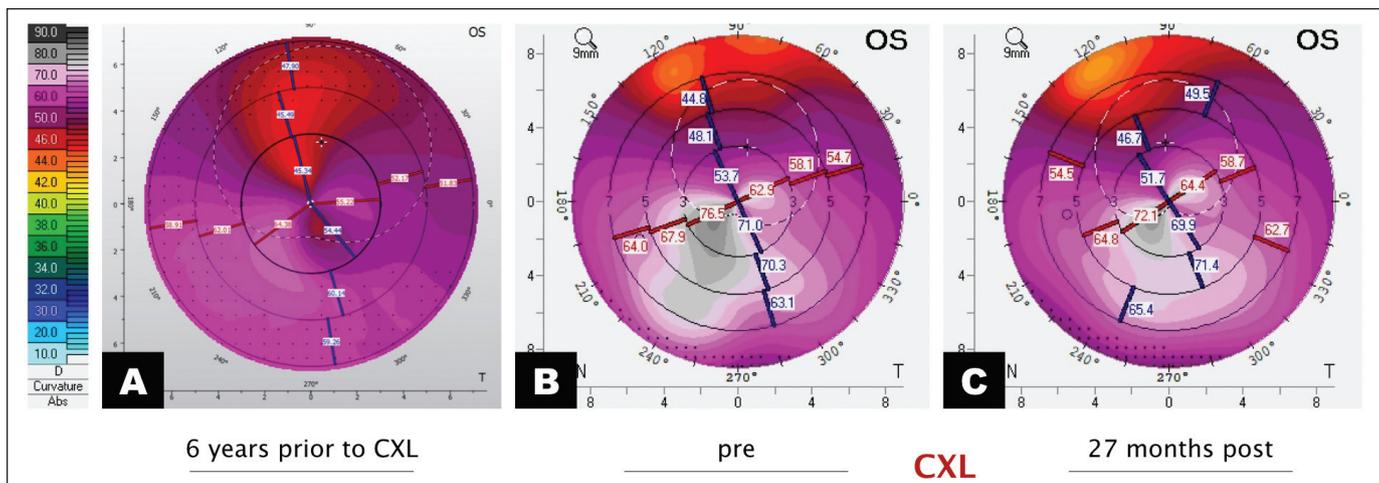
### CASE REPORT

A 36-year-old man presented with bilateral corneal ectasia in November 2016, reporting that ectasia was diagnosed when he was 16 years old. He had no history of allergic disease or eye rubbing but presented with a marfanoid habitus, hypermobile joints, and scoliosis.

At initial presentation, ophthalmological examination of the left eye showed an apical scar, Vogt striae in the paracentral deep stroma, and a corrected distance visual acuity of 20/200 with a subjective refraction of  $-8.25 -0.25 \times 120^\circ$ . The diagnosis of ectasia was established using anterior segment optical coherence tomography (MS-39; CSO Italia) and Scheimpflug imaging (Pentacam; Oculus Optikgeräte GmbH). The left eye showed signs of keratoglobus with substantial stromal thinning over the entire cornea (**Figure 1**). Minimum corneal thickness was 244  $\mu\text{m}$  and maximum keratometry readings reached 81.90 diopters (D) (**Figure 2B**). The patient also reported a continuous deterioration of his visual acuity in the left eye over the previous 6 years: in 2010, Placido-based topography showed mean keratometry values of 53.40 D and maximum keratometry values of up to 65.80 D (**Figure 2A**), and in 2011, corrected distance visual acuity of the left eye was 20/50 with a subjective refraction of  $-7.50 -3.00 \times 110^\circ$ .

Examination of the right eye revealed a crescent-shaped scar in the mid-peripheral inferior corneal stroma and a topographical bow-tie pattern and thickness distribution typical of pellucid marginal degeneration.

CXL was proposed and later performed in the left eye in December 2016 and in the right eye in May 2017. The procedures were performed as follows<sup>11</sup>: after application of proparacaine and oxybuprocaine eye drops, a speculum was inserted, and a 9-mm diameter region of the epithelium, centered over the pupil, was carefully removed using a hockey knife. After removal of the speculum, 0.1% hypoosmolar riboflavin (Ricrolin+; SOOFT Italia) without dextran or hydroxypropyl methylcellulose was instilled every 2 minutes to soak the cornea for 20 minutes.



**Figure 2.** Corneal topographies of the left cornea showing progressive keratoglobus prior to corneal cross-linking (CXL) and flattening at 32 months after CXL. (A) Placido-based topography 6 years prior to CXL shows a mean keratometry value of 53.40 diopters (D) and a maximum keratometry value of up to 65.80 D, whereas (B) Scheimpflug-based topographies taken immediately prior to CXL show a mean keratometry value of 64.70 D and a maximum keratometry value of up to 81.90 D. (C) At 32 months after CXL, mean and maximum keratometry readings were 63.90 and 80.60 D, respectively.

**TABLE 1**  
**CXL Methods**

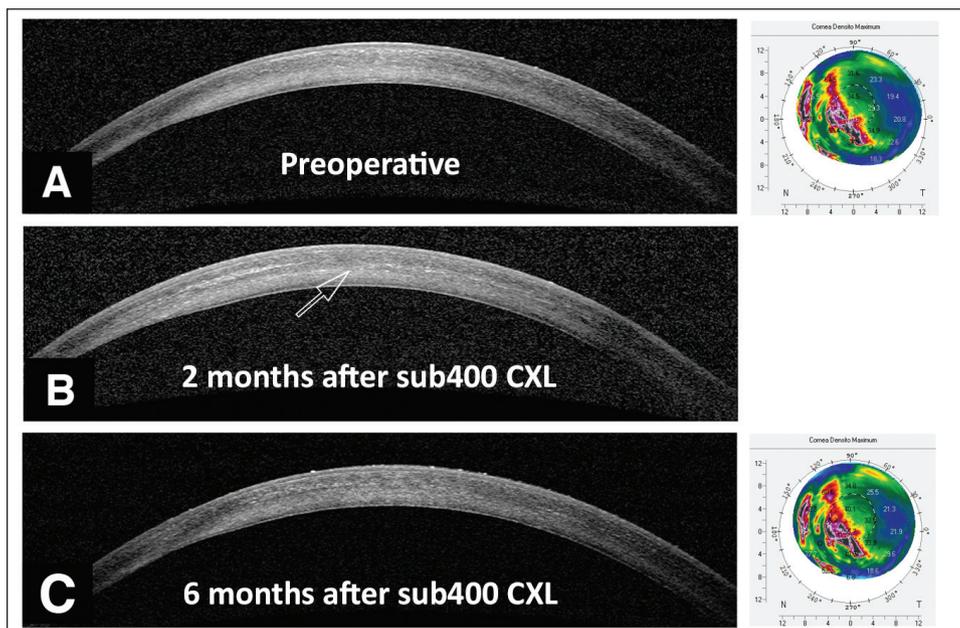
Parameter	Variable
Treatment target	Keratoglobus
Fluence (total) [J/cm <sup>2</sup> ]	0.36
Soak time and interval (minutes)	20 (q2)
Intensity (mW/cm <sup>2</sup> )	3
Treatment time (minutes)	2
Epithelium status	Off
Chromophore	Riboflavin (Ricola+; SOOFT Italia)
Chromophore carrier	None
Chromophore osmolarity	Hypo-osmolaric
Chromophore concentration	0.1%
Light source	CXL-365 Vario (SCHWIND eye-tech-solutions)
Protocol modifications	Using individualized fluence
Protocol abbreviation in manuscript	None

*CXL = corneal cross-linking*

In the following, only the intervention in the left eye is described. Corneal stromal thickness was measured every 5 minutes using ultrasound pachymetry over the area of the corneal stroma that had previously been identified as the thinnest. Minimum corneal pachymetry in the left cornea was 244  $\mu\text{m}$  prior to and 211  $\mu\text{m}$  after the manual abrasion. During riboflavin soaking, minimum corneal thickness was 209  $\mu\text{m}$  after

5 minutes, 225  $\mu\text{m}$  after 10 minutes and 228  $\mu\text{m}$  after 15 minutes. After 20 minutes of soaking with riboflavin (Ricola+) and immediately prior to irradiation, the left cornea showed a minimum stromal thickness of 231  $\mu\text{m}$ . The cornea was then exposed to continuous ultraviolet-A light with an intensity of 3 mW/cm<sup>2</sup> and an irradiation time of 2 minutes using our published and clinically validated algorithm and an irradiation diameter of 9 mm.<sup>11,12</sup> No additional riboflavin was applied during irradiation. The protocol details are summarized in **Table 1**.

A bandage contact lens was applied immediately after the procedure and remained in place for 4 days. Postoperative medication included tobramycin–dexamethasone eye drops three times daily (Tobradex; Novartis Pharma) for the first 4 days; ketorolac (Acular; Allergan, Inc.) for the first 2 postoperative days; and oral analgesia with paracetamol and ibuprofen. After 4 days, the bandage contact lens was removed and a remaining erosion of 2  $\times$  3 mm was observed in the absence of signs of infectious keratitis. Topical eye drops were stopped and replaced by ofloxacin ointment (Floxal; Bausch & Lomb Switzerland). Full reepithelialization occurred at day 8 after CXL, which is slightly slower compared to CXL reepithelialization times in keratoconic eyes with corneas thicker than 400  $\mu\text{m}$ . The remainder of the postoperative period was uneventful. A demarcation line was observed in the corneal stroma at 200  $\mu\text{m}$  of depth at 2 months after the procedure (**Figure 3B**). At 6 months after the procedure, both optical coherence tomography imaging and Scheimpflug densitometry showed no evidence of persistent haze or scarring (**Figure 3A** and **Figure 3C**).



**Figure 3.** Optical coherence tomography and densitometry measurements (A) pre-operatively and at (B) 2 months and (C) 6 months after the sub400 corneal cross-linking (CXL) procedure. The arrow indicates the depth of the demarcation line at 2 months after the sub400 epithelium-off CXL procedure.

Twelve months after bilateral CXL was performed, the patient's corrected distance visual acuity with spectacles was unchanged at 20/200 in the left eye and subjective refraction was  $+1.25 -2.00 \times 73^\circ$ . Maximum keratometry was 80.60 D in the left eye, and corneal thickness at the thinnest point was 243  $\mu\text{m}$ . The cornea showed no signs of endothelial decompensation under slit-lamp examination, and endothelial specular microscopy was not possible in this cornea. At the last visit at 32 months after CXL in the left eye (**Figure 2C**), the patient presented with stable refraction and similar maximum keratometry readings. Following adaptation of scleral lenses, visual acuity was 20/20 when the spectacles were worn.

### DISCUSSION

The treatment of keratoglobus is challenging due to the profound stromal thinning over the entire cornea. As a result of both thinning and protrusion, patients experience high myopia with irregular astigmatism (the main cause of poor vision in these patients) and this is difficult to treat with refractive correction. Due to the extreme thinning and fragility of the cornea, many patients initially present with corneal perforations, which can occur either spontaneously or following even minimal trauma.<sup>4</sup>

Myopia and irregular astigmatism can be corrected partially with scleral contact lenses, but surgical options are limited. Conventional penetrating keratoplasty is extremely difficult and inexorably doomed to failure due to the extreme peripheral corneal thinning, which is associated with an increased risk of endothelial rejection, loss of immune privilege, limbal stem cell disruption,

angle structure disruption, and tectonic instability. More recently, large limbus-to-limbus corneal grafts have been used to overcome the issue of peripheral stromal thickness. However, these techniques, besides being technically challenging, also lead to the loss of immune privilege and may require long-term immunosuppression.<sup>10</sup> Spontaneous tears in Descemet's membrane (acute hydrops) may occur, which can result in acute presentations of pain, tearing, photophobia, and a sudden diminution of vision.<sup>13</sup>

CXL is a treatment modality that reinforces the stroma biomechanically<sup>14</sup> and has been successfully applied in other members of the family of ectatic corneal diseases: keratoconus, pellucid marginal degeneration, and postoperative ectasia. In many cases, hypoosmolar riboflavin is used to swell the stroma. Due to its extreme stromal thinning (less than 300  $\mu\text{m}$  across large areas of the cornea), keratoglobus represents the only remaining ectatic disease that, until now, was untreatable with CXL, even when using hypoosmolar solution to swell the corneal stroma to a thickness suitable for CXL.<sup>15,16</sup> Because of this, we used our newly developed sub400 protocol to treat these eyes with keratoglobus.<sup>11</sup> Using our previously published algorithm,<sup>12</sup> the sub400 protocol takes into account riboflavin distribution and oxygen availability in the corneal stroma and adapts the overall fluence to the individual stromal thickness of the patient.<sup>12</sup> We observed stabilization of the ectatic process with a follow-up of 32 months in the absence of any clinical signs of endothelial decompensation. A potential explanation for stabilization might be that, apparently, the cross-linking reaction was able to biomechanically

cally strengthen the collagen fibril microstructure of the anterior part of the corneal stroma. Accordingly, a demarcation line was observed at 200 µm of depth at 2 months after the procedure using our approach of individualized fluence.<sup>11</sup> By adapting the fluence to the individual minimal thickness, the risk of endothelial decompensation and persistent haze or scarring is not increased in extremely thin corneas, but rather is similar to the “usual” risk encountered in corneas with a thickness of greater than 400 µm.

Whether or not keratoglobus represents an independent disease or rather is an extreme manifestation of pellucid marginal degeneration or even keratoconus is controversial.<sup>1</sup> In our patient, we observed keratoglobus in the left eye and a topographical appearance similar to pellucid marginal degeneration in the right eye, similar to an observation made by Karabatsas and Cook.<sup>17</sup>

Our report shows the first successful application of CXL in keratoglobus, and stabilization of the disease up to 32 months after CXL using the individualized sub400 CXL protocol.<sup>11,12</sup> This may suggest that CXL has the potential to become a viable treatment modality in the management of keratoglobus.

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