The Complete Management of the Corneal Collagen Crosslinking (CXL) Patient: Preoperative, Postoperative, and Contact Lenses

Susan J. Gromacki, OD, MS, FAAO
Andrew Morgenstern, OD, FAAO

Disclosure Statement:
Nothing to disclose

Please silence all mobile devices. Unauthorized recording of this session is prohibited.

CXL Is In The Fisheye Lens of FDA

• Currently under investigation
• No timeline on approval
• Insurance will not cover it
• Approved in all European Union Countries
• We can save vision, especially in the pediatric community
• There is a race against time

The many names...

• Corneal Collagen Cross Linking
• Collagen Cross Linking
• CXL
• Holcomb C3R
• CCL
• Ophthalmology Tanning Bed
• Sun

CXL: Indications

• Goal: prevent corneal ectasia from progressing to penetrating keratoplasty
• Indications:
  • Keratoconus
  • Pellucid Marginal Degeneration
  • Post-Refractive Surgery ectasia
  • Corneal melting
  • Infectious keratitis

The Best Candidates

• Keratoconus
  • Mild-to-Moderate
  • Little/no corneal scarring
  • BCVA better than 20/40
  • Young
  • Earlier in the disease
• Post-RK: still changing
• Post-LASIK ectasia: still changing
Patient Selection: Contraindications

- Under age 8
- Corneal thickness < 300-350 um
- Pregnancy or nursing
- Severe central corneal opacities
- Severe dry eye
- Collagen vascular disease
- Prior Herpetic infection
- Poor wound healing
- Autoimmune disease
- Relative contraindication
  * differ per study

Patient Education

- Legal obligation: 10-25% KC corneal transplantation
- Earlier treatment = better for the patient
- Preventing > fixing problems
- Pts. usually still need specs and/or CLs, will need to be refit postop

Pre-Operative Evaluation

- Testing:
  - UCVA
  - Biomicroscopy
  - MRx
  - Pentacam/Topography
  - BCVA
  - IOP
  - DFE
  - Contact Lens Hx
    - Type
    - When last worn
  * differ per study

Research: landmark paper, 1998

- Studied since 1994
- University of Dresden
  - Theo Seiler
  - German Sporel
  - Gregory Wollensak

Diabetes and CXL

- DM + KC = rare
  - Sporel and Seiler, Journal of Refractive Surgery 1999
- Aldehyde sugars in diabetics form natural cross-links but only after prolonged time

History of Corneal Cross Linking

- Theo Seiler, MD
  - Studied Medicine, Mathematics and Physics
  - Professor of Physics and Ophthalmology
  - University of Dresden
  - University of Zurich
  - Early 1990's
  - Uses UV light and a photo sensitizer (typically riboflavin, Vitamin B2) to strengthen bonds in the cornea
  - The Dentist
Corneal Cross-linking (CXL)

- Strengthens/stiffens corneas with UV light and riboflavin drops
- 98-99% effective*


Methods Of Stiffening the Cornea

- UV-irradiation with riboflavin
- Glutaraldehyde
- Alddehyde sugars (14 days)


Riboflavin Absorption Spectrum

Amplification of Cross-Linking Chemistry

Different Devices

- Avedro - USA
- CXLUSA - USA
- Peshke
- IROC Innocross
- Sooft
- Vega X-Link

Web-links are on the [www.ocxls.org](http://www.ocxls.org) site

How much UV light gets into the eye?

Damage thresholds

- 0.65 J/cm²
- 70 J/cm²
- 7.7 J/cm²

Radiant exposures

- 0.46 J/cm² (9 %)
- 0.33 J/cm² (7 %)
- 0.14 J/cm² (2.1 %)
- 0.12 J/cm² (1.9 %)

Radiant Energy is Below Damage Threshold
Real World UV

All Exposed Tissues:
- 170-200 J/cm²/day in 3-4 hrs outdoors
- ~60 J/cm²/day of solar UVA

Cornea:
- 5 J/cm² in 15-20 min in Summer
  CXL exposure = 3 mJ/cm²

How Do We Know UV Ages the Body?

CXL Is Everywhere

We see Collagen Cross Linking EVERYWHERE in our world but NEVER pay attention to it

“Dresden” Technique

What’s The Technique?

How do you do it?

FLEXIBLE, ELASTIC & NOT CROSSLINKED

NOT FLEXIBLE, RIGID & CROSSLINKED

- Anesthetic drops
- Prepare cornea
- Riboflavin drops for 30 mins
- UV light for 30 mins
- Bandage contact lens
- Postop Course: Similar to PRK
Riboflavin 0.1% Drops

15 Min Epi-On Riboflavin Loading Dose
White Light

Photo courtesy of Roy Rubinfeld, MD

UV-A Light 370 nanometer wavelength

Patient’s View of UV Light

So We Know it is Safe
But How Does it Work?

• The collagen in our cornea has links between the layers
• UV light stimulates strengthening between the bonds
  • Takes decades to do it naturally
• We are using UV light activated by riboflavin to stimulate the creation of more cross links

Epi-On vs. Epi-Off

**Epi-On**
- Longer “load time”
- Late stage technique
- More ribo needed
- No epi defect
- Less chance of infection and haze
- No reported complications

**Epi-Off**
- Shorter “load time”
- Early adopted technique
- Less ribo needed
- Large epi defect
- Slower recovery
- Higher risk of infection and haze
- Reported complications
Normal Corneal Epithelium

Barrier to riboflavin penetration of stroma?

Typical Epi-Off CXL

- **Worse** vision for 3-6 months
- **Steeper** Ks
- More compact corneas
- Some haze
- SPEs, pseudodendrites if epi-off

Epi-Off CXL for KCN
Keratometry Over Time


Other Applications of CXL:

- LASIK and CXL
- PRK and CXL
- Post RK Fluctuations
- Cornea-Plastics
- Scleral CXL
- Optic Nerve Head CXL
- Infection
- Intacs - Which currently do the following:
  - Increased K flattening
  - Increased BCVA
  - Increased UCVA

I've heard that Vitamin C can't be used before CXL?
Vitamin C Supplements

• Vitamin C naturally strengthens collagen
• Scurvy is a disease where the lack of Vitamin C leads to an enzymatic breakdown of collagen
• A surplus will possibly be an extra building block for collagen
• Vitamin C therefore will have a synergistic effect
• Many studies do not want their data affected by the addition of Vitamin C
• It is advisable to have your KCN patients that do not have CXL to take daily Vit C

“Moving Pictures” of CXL

LASIK AND CXL

LASIK AND CXL

LASIK Xtra

“Advantages of ReLEx SMILE over LASIK: Increased biomechanical stability and reduced biomechanical variability. Potential benefits of SMILE are the relatively higher biomechanical strength of the remaining cornea as well as a reduction in the variability of the biomechanical effects produced by refractive tissue removal.” – Dan Reinstein

Reinstein concludes that by maintaining corneal strength, indications for refractive surgery may be broadened to larger corrections and thinner corneas.

– Dan Reinstein, ARVO 2014. Images from: https://www.youtube.com/watch?v=mEYs7OAfXh4&feature=youtu.be

LASIK AND CXL

CXL AND INTACS

CXL WITH CK CORNEAPLASTICS

RK FROM COLOMBIA c. 1988

FELLOW EYE POST GRAFT

“Moving Pictures” of CXL

“Moving Pictures” of CXL
“Moving Pictures” of CXL

CK + CXL: Thermokeratoplasty Principles

PiXL: Photorefractive intrastromal CXL

Accelerated Cross-linking

- Original CXL studies at the Dresden Technical University in the late 90s were conducted with 3mW/cm² irradiance, requiring UV treatment time of 30 minutes.
- The Bunson Roscoe Law of Reciprocity states that the photochemical biological effect of ultraviolet is proportional to the total energy dose delivered, regardless of the applied irradiance and time.
- The energy delivered by a UV source is the product of the irradiance of the light source and the delivery time.

Irradiance \( \times \) Time (seconds) = Dose \( \frac{J}{cm^2} \)

3 mW/cm² \( \times \) 30 Minutes = 30 mW/cm² \( \times \) 3 Minutes

Clinical Measurement Of Corneal Biomechanics

Goal: Develop a technique to directly map corneal stiffness properties in a clinical setting

Potential Applications:
- Measure Effect of Cross Linking
- Early Diagnosis of Ectasia
- Pre-Op Screening of Refractive Patients
- Assessment of other tissues
Brillouin Spectroscopy:
Clinical System in Development

Potential Applications:
• Pre-Op Screening of Refractive Patients
• Early Diagnosis of Ectasia
• Measure Effect of Cross Linking

Future Applications:
• More Accurate IOP Measurement
• Assessment of Other Tissues
  • Lens, Lamina, Retina...

POST-OPERATIVE PATIENT MANAGEMENT

Post-Operative Care

• Schedule:
  • 1 day
  • 3-7 days (optional)
  • 1 month (optional)
  • 3 months
  • 6-9 months

*differs per study

Post-Operative Care

• Testing:
  • UCVA
  • Biomicroscopy
  • MRx (3 d→)
  • Penta/Topo (3 d→)
  • BCVA (1 mo→)
  • IOP (1 mo→)

*differs per study

Complications

• Infection
  • Epi-off only reported
• Corneal Haze and Scarring
  • Epi-off only reported
• Progression of disease
• Intraocular Inflammation
• Worsening of refraction
• Inability to tolerate contact lenses
• Need for PKP

Literature Review:
CXL Complications Uncommon

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polhammer M</td>
<td>CRS July 2008</td>
<td>1. Corneal Ulcer · E Coli</td>
</tr>
<tr>
<td>Ramesh I</td>
<td>CRS March 2009</td>
<td>1. Sterile Infiltrate &amp; Melt</td>
</tr>
<tr>
<td>Kymionis G</td>
<td>CRS Nov 2007</td>
<td>1. HSV Keratitis</td>
</tr>
</tbody>
</table>
POST-CXL
VISUAL CORRECTION

Post-CXL CL Pearls

• Wait 2 wks-4 mos po prior to fitting (study and surgeon dependent)
• Combination procedures (CK-CXL, Intacs-CXL) less stable initially
• Healthy anterior segment (many have been wearing CL post CXL)
• Patient Ed: refits may be required
• Always begin with a new refraction, topo, and Ks
  - Fitting should be no different than non-CXL patients—unless cornea and/or refraction change in the future

Contact Lens Design and Material

• Soft
  • Sphere
  • Toric
  • KC-specific designs (NovaKone, Alden, Kerasoft IC, B+L)
• Hybrid
  • ClearKone or UltraHealth (SynergEyes, Inc.)
• GP
  • Small diameter for KC
  • Large corneal for KC, post-RS, PKP
  • Scleral

Scleral Contact Lenses after CXL

<table>
<thead>
<tr>
<th>TABLE 1: Scleral Lens Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>Corneal</td>
</tr>
<tr>
<td>Corneascleral</td>
</tr>
<tr>
<td>Full (Scleral)</td>
</tr>
<tr>
<td>Mini-Scleral</td>
</tr>
<tr>
<td>Large-Scleral</td>
</tr>
</tbody>
</table>

Scleral Lens Fitting

• Vaults the cornea entirely, resting on the bulbar conjunctiva/sclera
• Improved comfort, stability and retention
• Most designs specify 1st BC/sag to insert
  • Your own gross subjective impression: steep, flat or moderate and adjust BC from there
• Fill lens with nonpreserved AT/saline AND NaFL
  • Let lens settle for 20-30 minutes

Central: 100-400 um clearance (use optic section)

Midperiphery-Limbus: clearance (use Co blue light)

Periphery: alignment; no lift-off or vessel blanching

Cases

New Research


DESIGN: To evaluate the long-term results of corneal collagen cross-linking (CXL) in patients with progressive keratoconus (40 eyes, 32 KC) patients.

MAIN OUTCOME MEASURES: BCVA, UCVA, MRSE, max-K, mean-K, CCT, and anterior and posterior elevation at the apex -baseline: 1, 3, 6 months after CXL; 1, 2, 4, and 5 years later.

RESULTS: The mean-K, max-K, UCVA, and astigmatism showed no change over time during these 5 years. After the first year, BCVA, MRSE, and CCT showed no change and stabilized, whereas elevation readings continued to decrease up to 5 years after CXL.

CONCLUSIONS: Treatment of progressive keratoconus with CXL can stop disease progression, without raising any concern for safety, and can eliminate the need for keratoplasty.

Conclusions

New Research

• A Randomized, Controlled Trial of Corneal Collagen Cross-Linking in progressive Keratoconus 3 Year Results
  • Ophthalmology 2014 Witting-Silva, et al.
  • 36 month results of CXL using riboflavin 0.1% solution for 15 minutes with 30 min of UV-A (3mW/cm2)
  • F/U @ 3, 6, 9, 12, 24, 36 month intervals
  • 100 eyes with progressive keratoconus were randomized into CXL treatment or control groups
New Research

• At 36 Months there was a sustained improvement in Kmax, UCVA, BCVA after CXL, whereas eyes in the control group demonstrated further progression.

New Research

• O’Brart DPS, Kwong TQ, Patel P, et al.
• Long-term follow-up of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linking to halt the progression of keratoconus
  *Br J Ophthalmol 2013;97:433-437*
• Abstract
  • To determine long-term efficacy of riboflavin/ultraviolet A corneal cross-linking (CXL)
• Methods
  • 30 patients/eyes who had undergone epi-off CXL were examined 4-6 years later.

New Research

**1 Year**
• spherical equivalent error (SEQ) increased by +0.72 diopters (D) (p<0.002)
• corrected distance visual acuity (CDVA) improved (p<0.005)
• mean simulated keratometry (Sim K) reduced by 0.27D (p<0.04)
• cone apex power (CAP) reduced by 0.4D (p<0.02)
• secondary astigmatism improved (p<0.01)
  compared with preoperative values.

**4-6 Year**
• SEQ increased by +0.82D (p<0.001),
• CDVA improved (p<0.03), mean Sim K reduced by 0.84D (p<0.00001),
• CAP reduced by 1.16D (p<0.0005),
• root mean square (RMS) (p<0.0001), coma (p<0.0001),
• secondary astigmatism (p<0.05) and pentafoil (p<0.05) decreased

Conclusions:

• No treated eyes progressed.
• None lost >1 line of CDVA.
• Seven untreated fellow eyes progressed.

• CXL is safe and effective.

Thank you from your Nation’s Capital