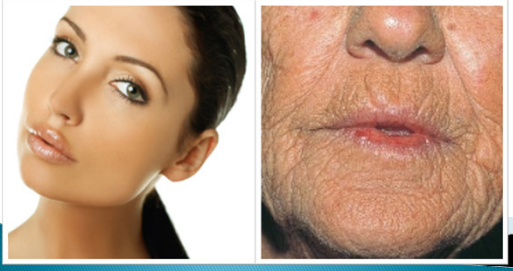
Optometrists Guide to Corneal Collagen Cross-linking



Bill Tullo, OD, FAAO Diplomate
Vice-President of Clinical Services – TLC Vision
33386-PO 1 Hour

Financial Disclosure

- Bill Tullo, OD has no financial interests in any of the products or companies discussed in this program

Corneal Ectasia – Causes

- Naturally-existing Corneal Pathology
  - Forme Fruste Keratoconus
  - Keratoconus
  - Pellucid Marginal Degeneration
- Surgically induced Pathology

  Mechanical Instability
  - Post- LASIK ectasia
  - Post-PRK ectasia

  Abnormal Collagen fibrils vs biomechanical destabilization

Keratoconus

Progressive corneal steepening and thinning in the absence of refractive surgery

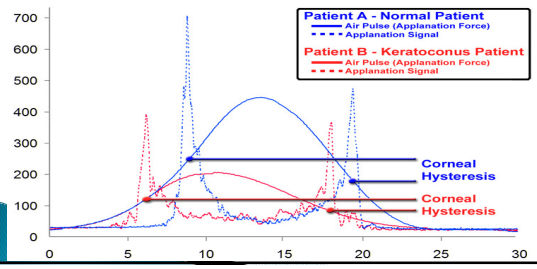
Keratoconus

- Adolescent onset
- Progresses over 10-20 years
- Incidence
  - 1/2,000 in general population
- Prevalence: 1/430
  - 2% in patients seeking surgical correction of refractive errors
- About 20% of patients with KC require corneal transplantation
- KC is the indication for 5000 (15%) corneal transplants performed each year in the US

[1]Kennedy
[2]Nielsen, K., et al., Acta Ophth
[3]Nesburn AB, et al., Keratoconus Diag
[4]2006 EBAA Eye Banking Statistical Report

Characteristics of Keratoconus

- Reduced corneal rigidity in eyes with keratoconus – Corneal Hysteresis



Who is NOT at Risk?

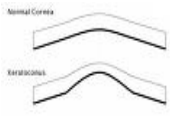
- Reduced likelihood of keratoconus progression with age (physiological cross-linking)[1]
- Diabetes protects against development of keratoconus – glycation[2]
- Cigarette smoking protects against development of keratoconus – unknown toxins in cigarette smoke protects against development of keratoconus[3]

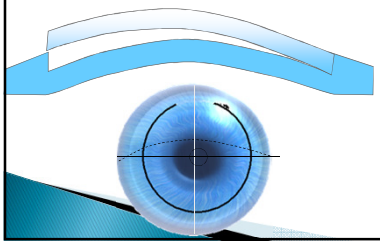


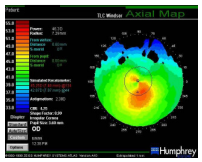
[1]Malik et al., Biochem. Biophys. Acta, 1992
[1]Malik et al., Biochem.
[2]Seiler et al., Graefe's Arch Clin
3 Spoerl et al. J Refractive Surg. 2003

Risks of Post-Surgical Ectasia

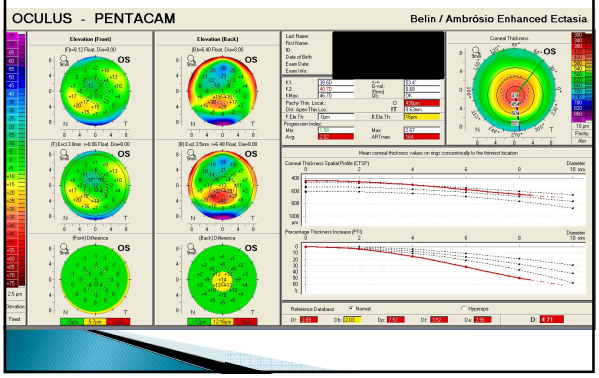
- Flap Thickness/Diameter
- Ablation Depth
- Irregular topography







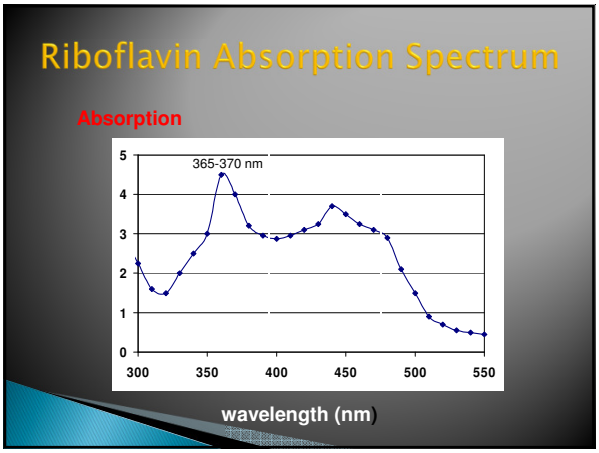
Post-Surgical Ectasia – Tomography



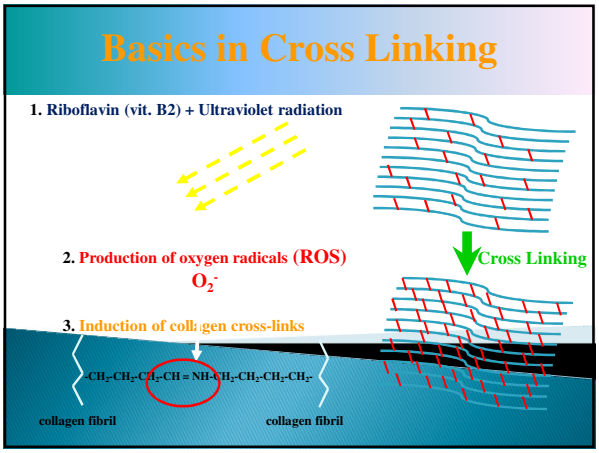
Methods of Stiffening the Cornea

- *Glutaraldehyde* crosslinking (prosthetic heart valves)
- *Formaldehyde* (pathology specimens)
- *Aldehyde sugars*
- *UVA*-induced crosslinking (dentistry)

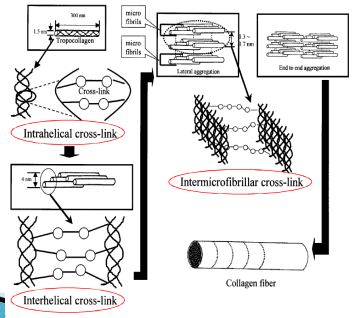
Riboflavin Absorption Spectrum



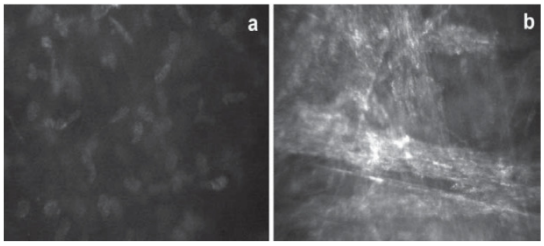
Basics in Cross Linking



Sites For Collagen Cross-Linking



Confocal Micrograph at 300 microns



Pretreatment **30 Days Post Treatment**

Collagen Cross-Linking History

- Studied since 1994
  - University of Dresden
    - T Seiler, E Spoer, G Wollensak
    - 23 eyes (Maximum K values 48-72D) treated
    - In ALL treated eyes, the progression of Keratoconus stopped
    - 70% reduction of K readings by 2.01 D
    - 1.14D reduction of refractive error
    - 65% improvement in Visual Acuity (3.6 lines Caprorossi et al)

Induction of Cross-links in Corneal Tissue

EBERHARD SPOERL*, MICHAEL HUHLE AND THEO SEILER

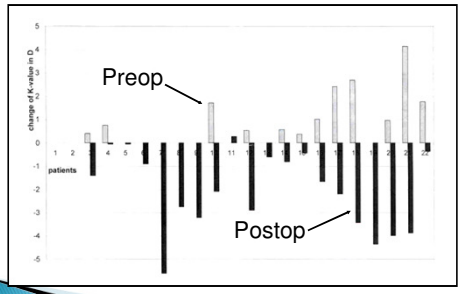
Department of Ophthalmology, University of Dresden, Dresden, Germany

Important Questions

- Does it really work?
- Is it really safe?
- How long does the effect last?
- Does the epithelium have to be removed?[1]
- What is the best protocol?

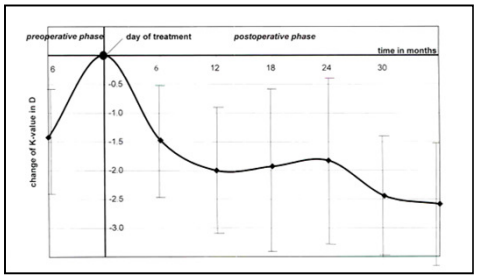
[1]Chan et al., J. Refract. Surg.)

Cross-Linking and Keratoconus Keratometric Change



Wollensak, Spoerl, and Seiler, AJO 135:620, 2003.

Cross-Linking and Keratoconus Keratometry Over Time



Wollensak, Spoerl, and Seiler, AJO 135:620, 2003.
Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross [illegible] Am J Ophthalmol. 2010 Apr;149(4):585-93

Clinical Studies

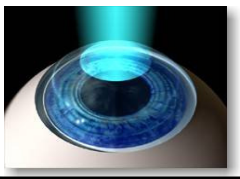
- 687 Peer-reviewed literature citations
- 96% of eyes show topographic stability
- Average flattening 1.7D of max-K
- Flattening effect reduced max-K > 54D

Dresden Protocol

UVA dosage 3 mW/cm2
for 30 minutes

0.1% riboflavin

Remove Epithelium



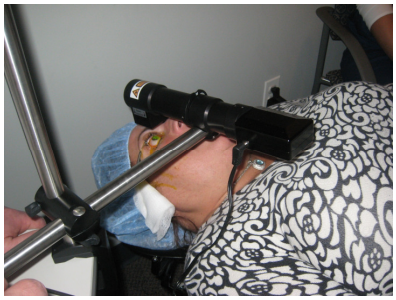
Riboflavin 0.1% Drops

1 drop q2 min x 30 min

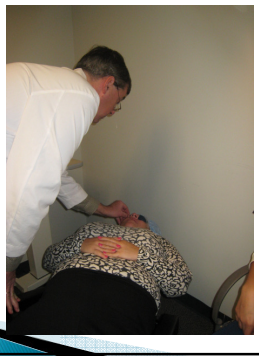
Fluorescence in Anterior Chamber

UV-A Light 370

UV Light for 30 Minutes



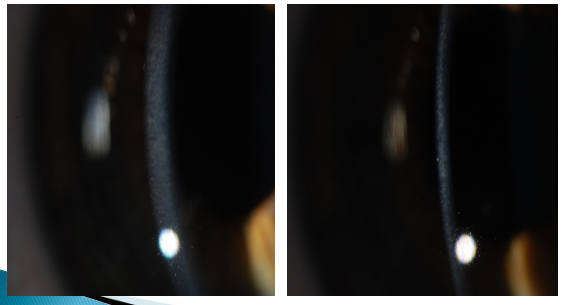
Bandage Contact Lens



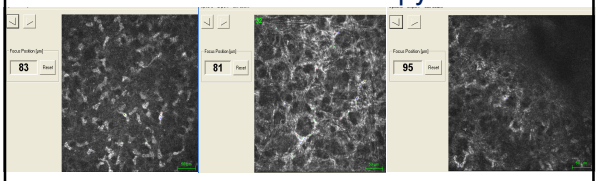
CXL – Possible Side Effects

- Endothelial Cell Loss
- Crystalline lens opacity
- Pain
- Infection
- Delayed Epithelial healing
- Retinal damage
- **Stromal Haze**

Haze



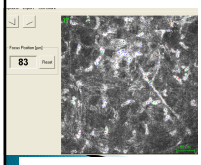
Confocal Microscopy



Pre op

1 m postop

3 m postop



- Apoptosis 300 µm deep after CXL
- Repopulation takes 6 months

6 m postop

Courtesy of Dr. Caporossi,

Minimal Corneal Thickness

- 400 microns when using 3.0 mW/cm2 and Dextran based Riboflavin
- Thicken a thin cornea with hypoosmotic riboflavin not safe[1]
- Stromal haze peaks at 1 month post-op and decreases significantly between 3 and 12 months[2]

1.Hafezi F. Limitation of Collagen Cross-Linking With Hypoosmolar Riboflavin Solution: Failure in an Extremely Thin Cornea. Cornea. 2011 Mar 8.

2. Greenstein SA, Fry KL, Bhatt J, Hersh PS Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. J Cataract Refract Surg. 2010 Dec;36(12):2105-14

Conclusions – CXL

- Halts progression of ectatic corneal diseases
  - Decreases corneal curvature and thickness
  - Regularizes corneal surface
  - Improves UCVA and BSCVA
  - Effect lasts indefinitely
- Offers safe and effective treatment for conditions with no currently available treatment and may avoid
  - 15% of corneal transplants
  - Disability, cost, loss of productivity, CTL

Regulatory Status

- International
  - CE Mark since 2006
  - Distributed internationally
- United States
  - Investigational
  - Combination product
    - Device: UVA light source
    - Drug: Riboflavin

CXL FDA Studies

- > 27 total FDA studies
- 13 US studies

- FDA Grants Riboflavin Orphan Drug Status 10/10
  - Avedro – 7 years of exclusive rights
  - 1/12 FDA Expedited Review Request

Ideal CXL Study Candidate

Young patients with good history expected to progress if untreated

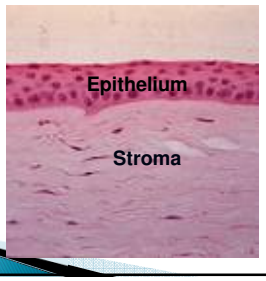
- Age ≤ 35 yr
- Kmax ≤ 56 D
- Pachymetry > 400 microns
- Health History Non-smoker/Non-diabetic
- Corneal signs Scissoring or Thinning
  - No or few Vogt's striae
  - No or little scarring
- Keratoconus/Ectasia History Rapidly progressive disease
  - At least 3 months of topographic history preferred

ACOS CXL Study

- Multicenter (100 sites), randomized
- Keratoconus and Ectasia after Refractive Surgery
- > 12 yrs old and evidence of KC on topography
- Minimum Pachymetry > 375 microns
- 3 treatment groups
  - Epi-removal – 15 mW/cm^2 x 8 minutes
  - Epi-removal – 30 mW/cm^2 x 4 minutes
  - Epi-removal – 45 mW/cm^2 x 2 min 40 sec

Normal Corneal Epithelium

Barrier to riboflavin penetration of stroma



Riboflavin

- Epithelium-OFF
  - 0.1% Riboflavin with 20% Dextran
  - VibeX Rapid – 0.1% riboflavin with hydroxypropyl methylcellulose
  - Reduced corneal thinning allow treatment of corneas as thin as 325 microns
- Epithelium-ON (Transepithelial)
  - Paracel – BAC opens epithelial junctions
  - VibeX Xtra – 0.1% riboflavin

Transepithelial Epi-On CXL

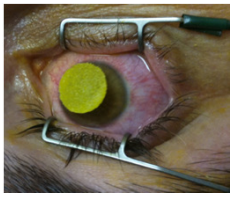
- Mechanical Disruption
  - Daya Disruptor
- Chemical Disruption
  - BAK
  - Tetracaine
  - EDTA
  - 20% Alcohol
- Permeability Enhancers
  - Cellulose or sodium phosphate
- Iontophoresis

Epi-on ParaCel Protocol

- 1. Apply topical anesthetic to the cornea.
- 2. Insert lid speculum using standard clinical techniques.
- 3. Apply **2-4 drops** of **ParaCel** to coat the cornea. Apply an additional drop **every 90 secs** for a total soak of **4 mins.**
- 4. Rinse cornea completely with VibeX XtraTM.
- 5. Apply sufficient **VibeX Xtra** to coat the cornea and repeat this procedure **every 90 secs** for a total of **6 mins**.
- 6. Initiate UV treatment using the KXL SystemTM for **2 mins 40 secs at 45mW/cm2**, applying 1-2 drops of BSS as needed during irradiation.
- 7. Rinse cornea completely with BSS.
- 8. Remove speculum using standard clinical techniques.

Trans-epithelial CXL – CXL-USA

- Riboflavin 1% with gum cellulose Q2 min:
  - From local compounding pharmacies
- Topical Tetracaine with BAK provided Q2 to 5 min
- Corneal Protector sponge used
- 60-80 minutes of Riboflavin drops required



Corneal Protector Sponge

William Trattler, MD

SUMMARY EPI-ON CXL

- Benefits:
  - Faster visual recovery & less pain
  - Reduced risk of pain & haze
  - Reduced risk of infection & slow re-epithelialization
  - Very good clinical results
    - Even in keratoconus patients in their 50's and 60's
- Downside:
  - Longer procedure (30-50 min longer)
  - Insufficient Riboflavin penetration can lead to UVA over-exposure and damage to ocular structures.
  - Can not combine with simultaneous topo-guided PRK

Intacs with Sequential CXL

- Effects of both treatments are synergistic
  - Increased K flattening
  - Increased BCVA
  - Increased UCVA

- Kamburoglu G, Ertan A: Intacs Implantation with Sequential CXL Treatment in Postoperative LASIK Ectasia. *J Refractive Surg. 2008*:24:7:S726-S729
- Chan CC, Sharma M, Wachler BS: Effect of inferior-segment Intac with and without C3-R on keratoconus. *J Cataract Refract Surg.* 2007;33:75-80.

CLX & PRK

- Simultaneous CXL & PRK more effective than sequential CXL & PRK
- PRK before CXL better than PRK after CXL

Kanellopoulos AJ, Binder PS. Management of Corneal Ectasia After LASIK with Combined, Same-Day, Topography-Guided Partial Transepithelial PRK and Collagen Cross-Linking: The Athens Protocol. J Refract Surg. 2010 Nov 5:1-9.

Kanellopoulos AJ Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. J Refract Surg. 2009 Sep;25(9):S812-8

Athens Protocol

- Topographically Guided Transepithelial PRK
  - Treat 70% corneal astigmatism
- 0.02% Mitomycin-C 20 seconds
- 0.1% riboflavin sodium phosphate x 10 minutes
- 370nm 3.0 mW/cm^2 x 30 minutes

LASIK Xtra

- Use of modified CXL protocol for LASIK patients
- All LASIK patients vs. “at risk”
  - Thin corneas
  - Irregular topography
  - High myopia
- Stabilize hyperopic LVC?

LASIK Xtra Shinagawa Protocol

- 1. After ablation, sufficient VibeX Xtra™ is applied to coat the stromal bed
- 2. Following a 90 second soak, VibeX Xtra is thoroughly flushed from the eye using BSS
- 3. The flap is carefully replaced, and the cornea is irradiated with the KXL®device at 45mW/cm2 for 90 seconds

Keratoconus in Younger Patients

- Poorer prognosis
- Faster progression
- Increased probability of PK
- Higher risk of PK rejection
- **MUST DIAGNOSE KERATOCONUS AS EARLY AS POSSIBLE!!**

Keratoconus Treatment

- Early Keratoconus – progressive topography or tomography minimal reduced BCVA
  - CXL as soon as Dx confirmed
- Moderate Keratoconus – progressive topography or tomography moderate reduced BCVA
  - Consider CXL / Intacs
- Advanced Keratoconus – pachymetry less than 400 microns
  - Intacs if stable with CL refit
  - PK as last resort

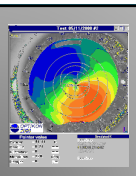
Future Directions

- Transepithelial CXL
- High Irradiance CXL
- Oxygen Enhanced CXL
- Accelerated CXL with Pulsed Illumination
- Intrastromal CXL
- LASIK Xtra & PRK Xtra
- Topographic Guided – CXL
- Alternative Agent CXL
- Selective CXL

CXL Myths

- **Wait till ectasia progresses before CXL**
- **Older patients don't benefit from CXL**
- **Insurance will pay for CXL soon**
- **The epithelium must be removed for CXL**
- **CXL effect is temporary**
- **CXL not approved because it's dangerous**
- **Epithelium has to be removed for CXL**

NKCI
National Keratoconus Institute



"The Mission" :

- Comprehensive KC Education for ECP's
- Resource for all KC Patient's Needs
- Provide Comprehensive Care for KC Patients in Conjunction with Affiliated ECP's
- Advancement of Knowledge re-KC Through Clinical Research Leading to Ongoing Improvement in the Care of KC Patients


THANKS!