Save the Cornea!
Keratoconus and Corneal Crosslinking

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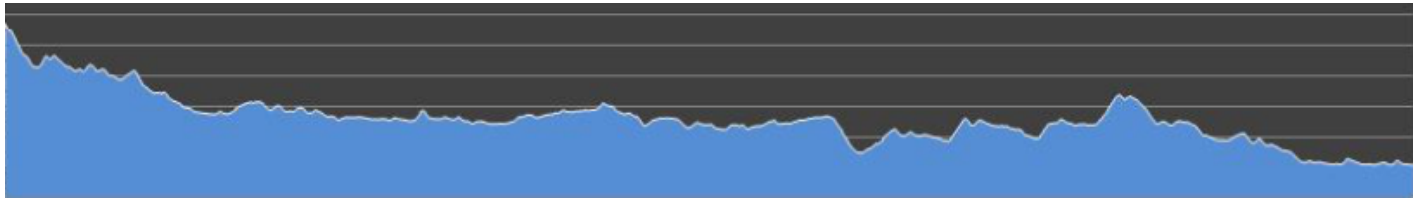
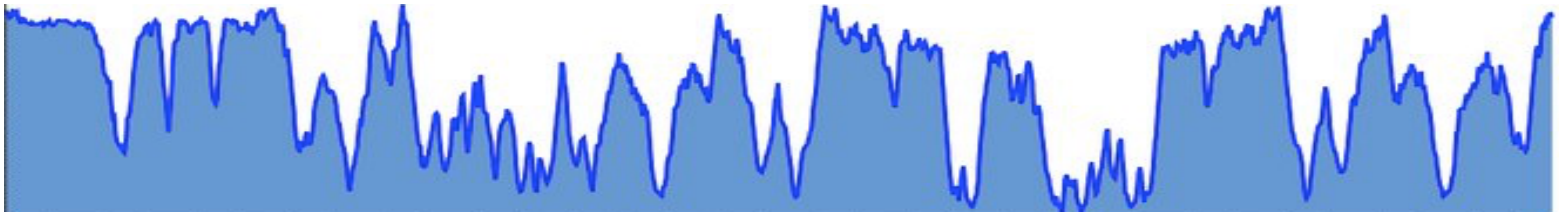
Disclosures

None





Outline

- Brief overview of keratoconus / corneal ectasia
- Brief history of corneal cross-linking
- Review classic approach and results
- Potential improved methods
  - Epi-On
  - Accelerated
- Cross-Linking Plus
- Summary

Corneal Ectasias

Dilation or distension of a tubular structure

- Group of non-inflammatory conditions which alter the normal architecture (shape) of the cornea
- Includes:
  - Keratoconus- axial ectasia- most common
  - Keratoglobus- uniform, particularly peripheral ectasia
  - Pellucid Marginal Degeneration - peripheral ectasia, thinning along inferior band
  - Terriens Marginal Corneal Degeneration - perilimbal ectasia
  - Post-Refractive Surgery Ectasia

Corneal Ectasias

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  - **Post-Refractive Surgery Ectasia**

Pellucid Marginal Degeneration (Not FDA Approved)

Cagil N, Sarac O, Yesilirmak N, Caglayan M, Uysal BS, Tanriverdi B.Transepithelial Phototherapeutic Keratectomy Followed by Corneal Collagen Crosslinking for the Treatment of Pellucid Marginal Degeneration: Long-term Results. Cornea. 2019

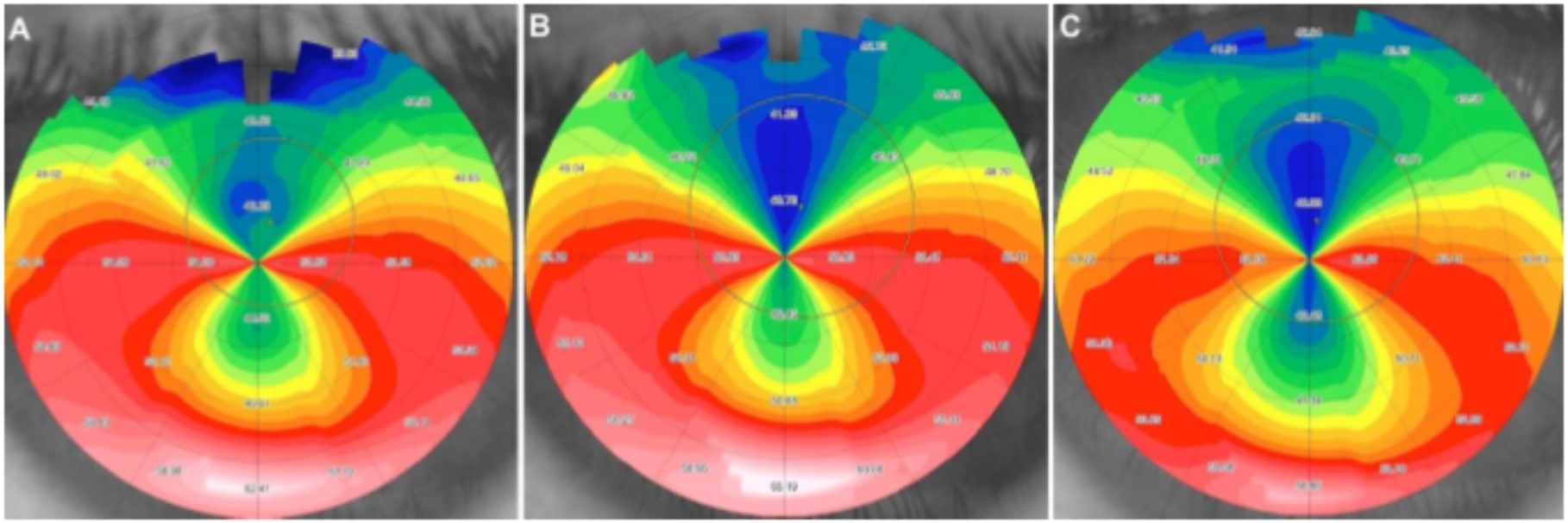


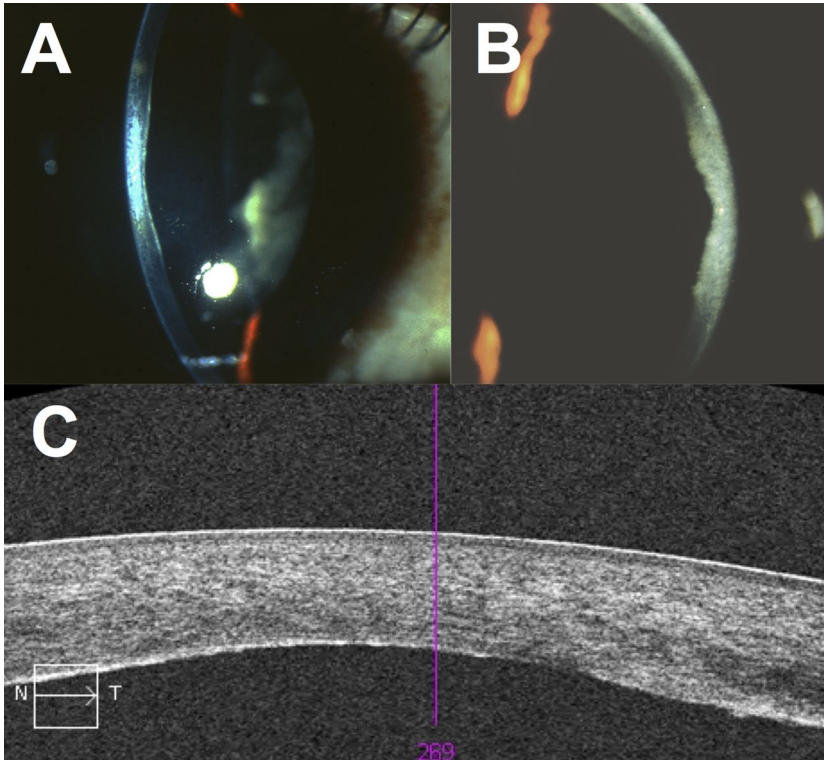
FIGURE 3. Sagittal curvature maps demonstrating the changes in inferior corneal steepening (A), baseline (B), last visit before corneal collagen crosslinking (1 year after baseline examination) (C), and 36 months after corneal collagen crosslinking. Kmax was 62.41 D, 65.19 D, and 56.85 D; MCT was 551 μm, 534 μm, and 498 μm; cylinder was −3.00 D, −4.00 D, and −3.50 D; UDVA (logMAR) was 0.70, 1.30, and 1.0; BDVA (logMAR) was 0.22, 0.40, and 0.30 at the baseline, last visit before, and 36-months after corneal collagen crosslinking, respectively.

Posterior Keratoconus

Congenital Opacities of the cornea
STUMPED classification

S	**Sclerocornea**
T	**Tears in Descemet's Membrane**
	Congenital glaucoma
	Birth trauma
U	**Ulcer**
	Herpes simplex virus
	Bacterial
	Neurotrophic
M	**Metabolic** (rarely present at birth)
	Mucopolysaccharidoses
	Mucolipidoses
	Tyrosinosis
P	**Posterior corneal defect**
	Peters' anomaly
	Posterior keratoconus
	Staphyloma
E	**Endothelial Dystrophy**
	Congenital hereditary
	Posterior polymorphous corneal dystrophy
	Stromal: congenitial stromal corneal dystrophy
D	**Dermoid**

Waring GO and Rodrigues MM, Congenital and neonatal corneal abnormalities. In Tasman, Jaeger eds. Duane's Ophthalmology, CD-Rom. Philadelphia: Lippincott, Williams and Wilkins; 2002.



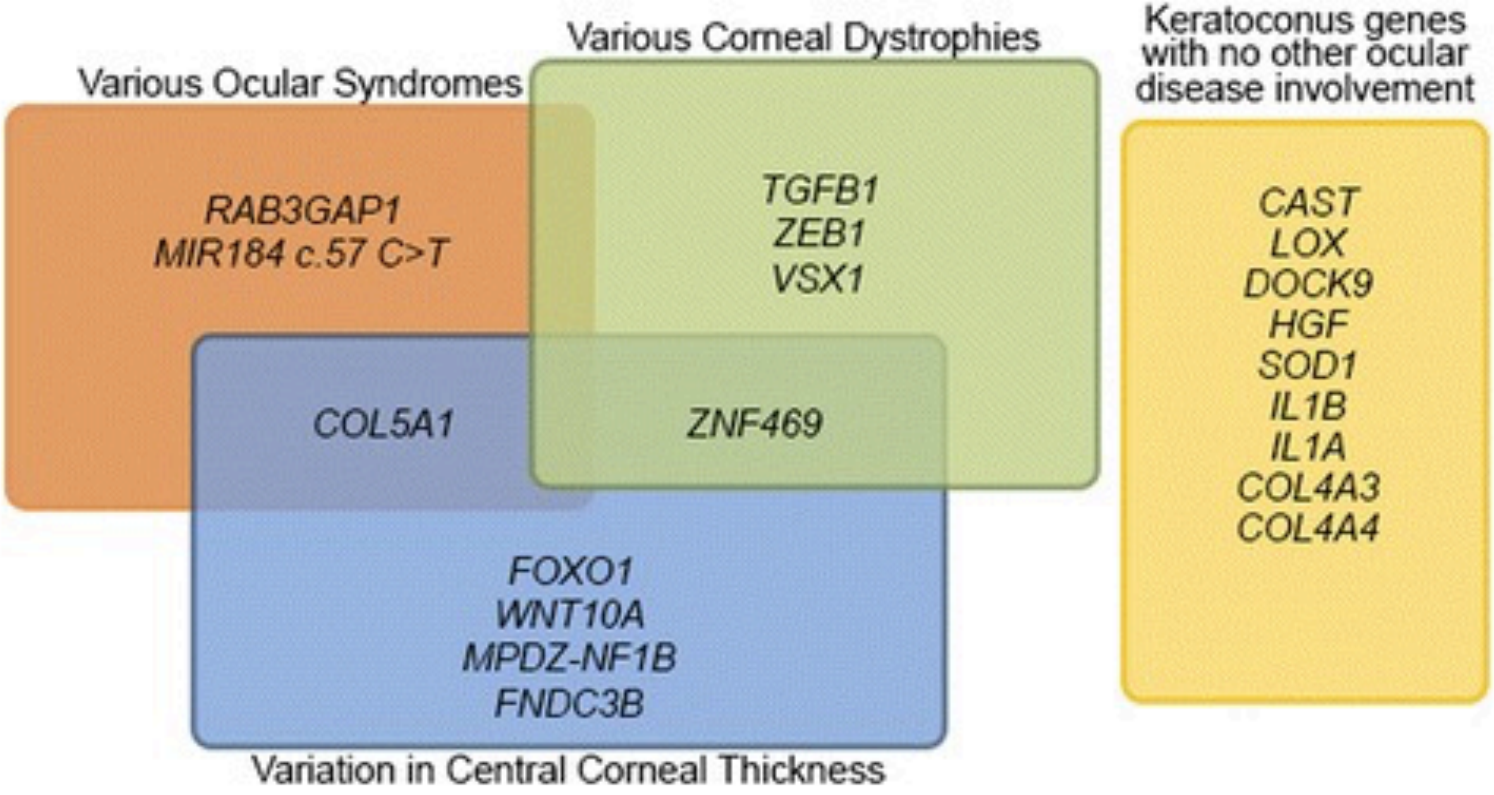
Silas MR, Hilkert SM, Reidy JJ, Farooq AV. Posterior keratoconus. Br J Ophthalmol. 2018 Jul;102(7):863-867.

Keratoconus

- Prevalence is 50-230/100,000
- No predictable hereditary pattern - some families seem to show dominant transmission
- Will have (+) FHx in 6-8% of cases
- All races affected, female preponderance
- The genes implicated potentially include *VSX1*, *miR-184*, *DOCK9*, *SOD1*, *RAB3GAP1,* and *HGF.*
- Etiology is currently unclear
- Likely **multifactorial** since there are many associated syndromes which have KC as an end result

Genetics in Keratoconus: where are we?

Yelena Bykhovskaya[1,2], Benjamin Margines[2] and Yaron S. Rabinowitz[1,23*]



Extra cost of care for a patient with keratoconus: $24,168

Increased Prevalence of KC

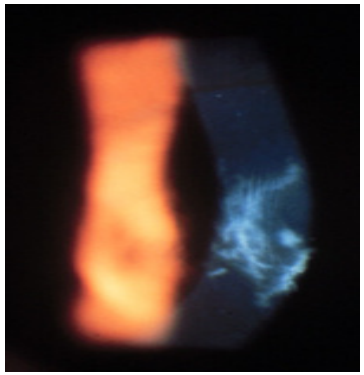
- Down Syndrome
- Marfan Syndrome
- Floppy eyelid syndrome
- Leber congenital hereditary optic neuropathy
- MVP
- Ehlers-Danlos
- OI- type I
- Laurence-Moon-Bardet-Biedl syndrome
- In association with other congenital anomalies of the eye
- Atopic Dermatitis
- Vernal Keratoconjuctivitis
- Retinitis Pigmentosa
- Infantile tapetoretinal degeneration
- Aniridia
- Cutis Laxa

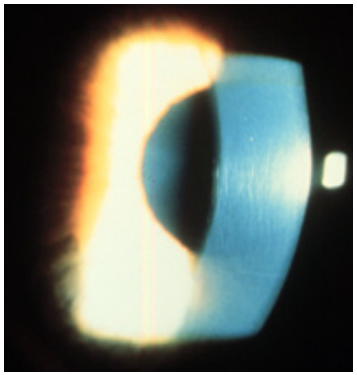
Natural History of KC

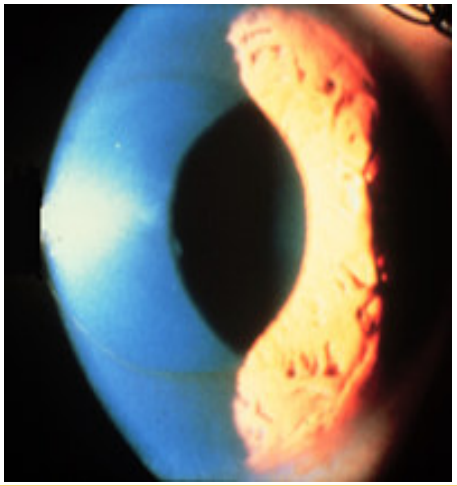
- Manifests usually at puberty
- **Highly variable progression**
- **Asymmetric**
- Gradual thinning of the cornea - central
- Protrusion of corneal apex - forming a cone
- Development of high myopic errors
- Development of high irregular astigmatism
- **Progression slows and stabilizes by age 40 in many patients**

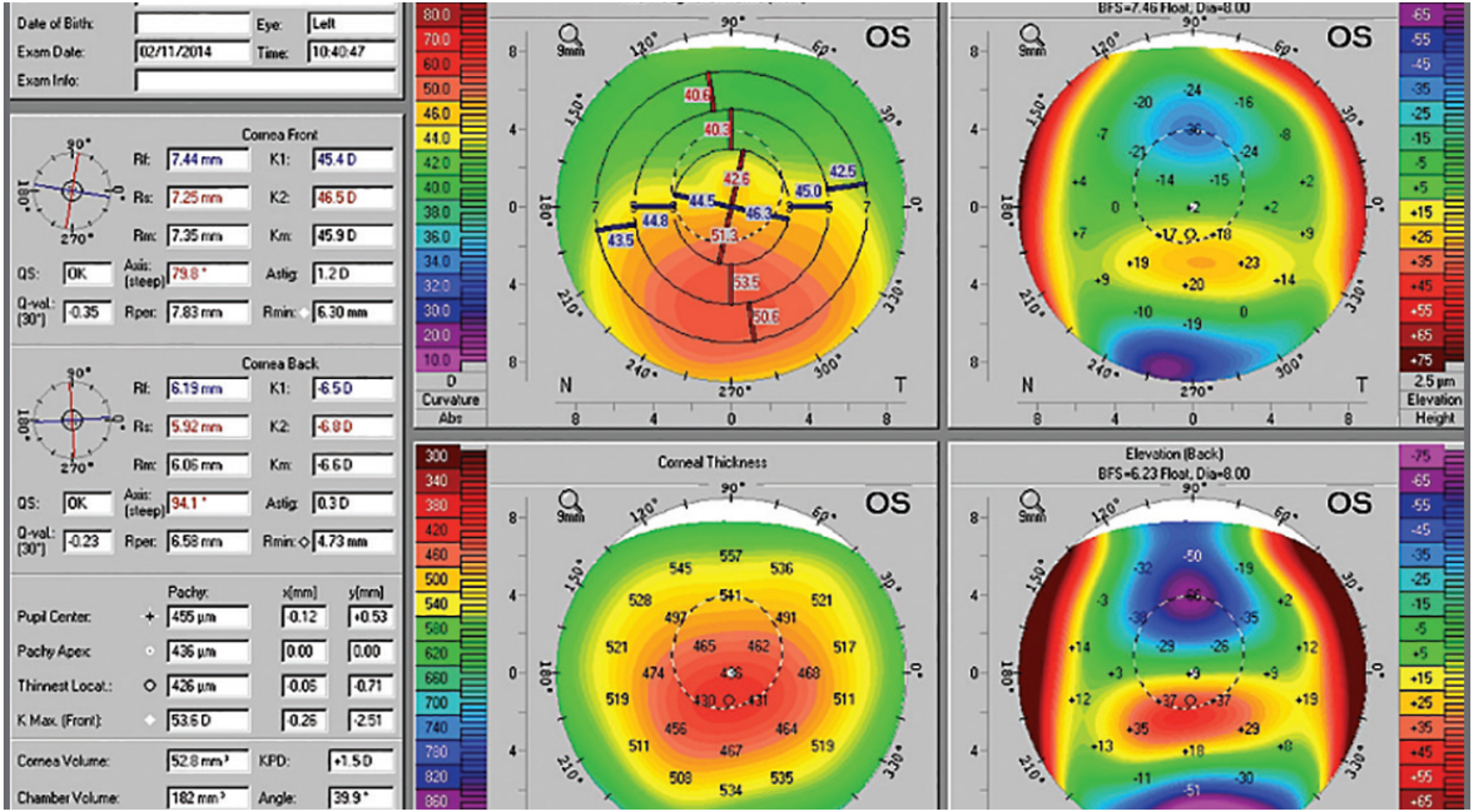
Signs of Keratoconus

- Scissoring of the Light Reflex
- Munson's Sign
- Fleischer Ring
- Vogt's Stria
- Anterior Corneal scarring
- Hydrops







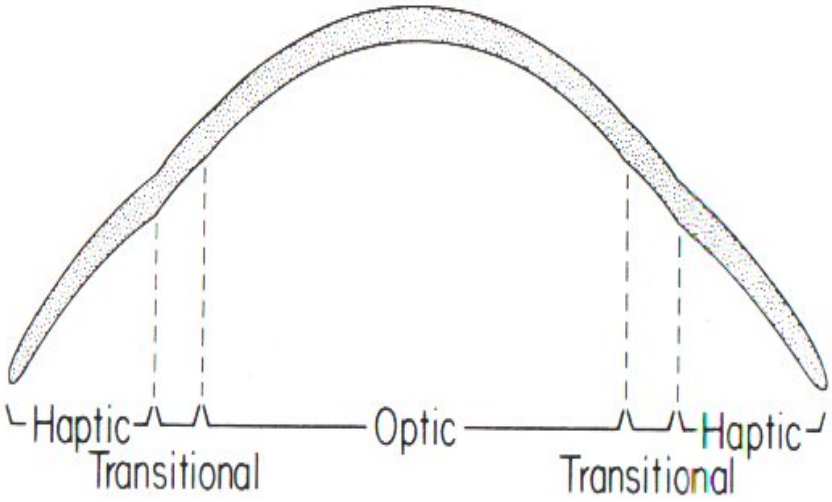

Date of Birth:
Eye: Left
Exam Date: 02/11/2014
Time: 10:40:47
Exam Info:
Cornea Front
Rf: 7.44 mm
K1: 45.4 D
Rs: 7.25 mm
K2: 46.5 D
Rm: 7.35 mm
Km: 45.9 D
QS: OK
Axis: (steep) 79.8°
Astig: 1.2 D
Q-val: (30°) -0.35
Rper: 7.83 mm
Rmin: 6.30 mm
Cornea Back
Rf: 6.19 mm
K1: -6.5 D
Rs: 5.92 mm
K2: -6.8 D
Rm: 6.06 mm
Km: -6.6 D
QS: OK
Axis: (steep) 94.1°
Astig: 0.3 D
Q-val: (30°) -0.23
Rper: 6.58 mm
Rmin: 4.73 mm
Pachy: x[mm] y[mm]
Pupil Center: 455 µm 0.12 +0.53
Pachy Apex: 436 µm 0.00 0.00
Thinnest Locat.: 426 µm -0.05 -0.71
K Max. (Front): 53.6 D -0.26 -2.51
Cornea Volume: 52.8 mm³
KPD: +1.5 D
Chamber Volume: 182 mm³
Angle: 39.9°
OS
Curvature Abs
Corneal Thickness
Elevation (Back)
BFS=7.46 Float, Dia=8.00
BFS=6.23 Float, Dia=8.00
2.5 µm
Elevation Height

Traditional Management of KC

- Spectacle Correction - mild cases
- Therapeutic Contact Lenses - most cases
- Lamellar or Penetrating Keratoplasty - advanced cases. When CL's don't give satisfactory correction
- Intracorneal Rings and / or Nodulectomy - specific treatment of subepithelial scar formation done to allow continued use of CL's (superficial keratectomy) when fit or comfort are unacceptable

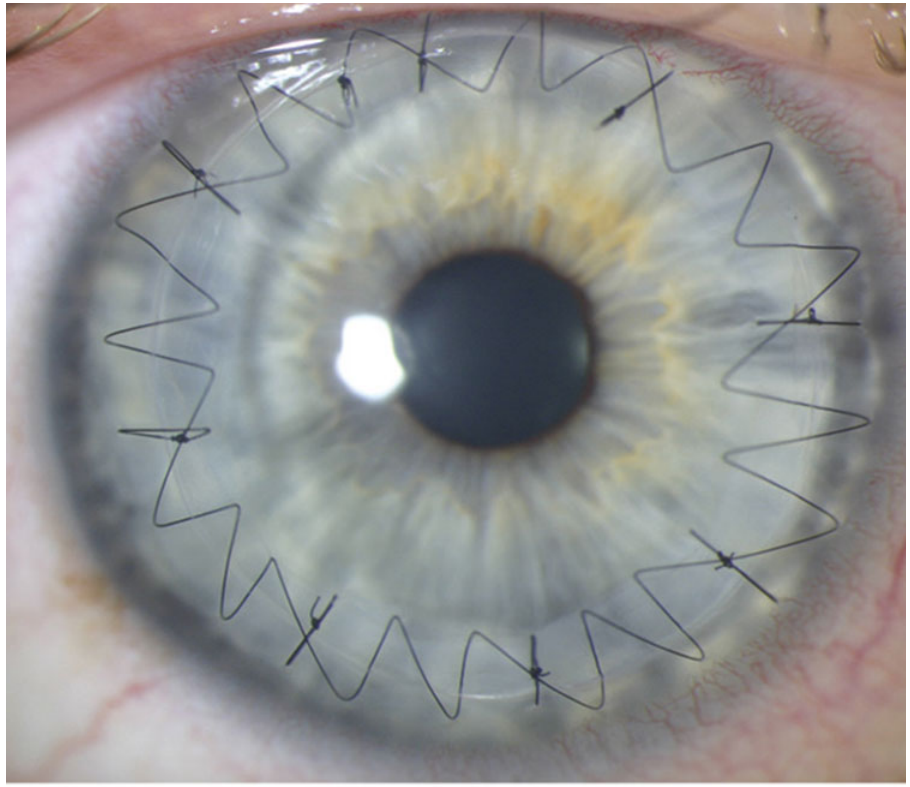
Contact Lenses

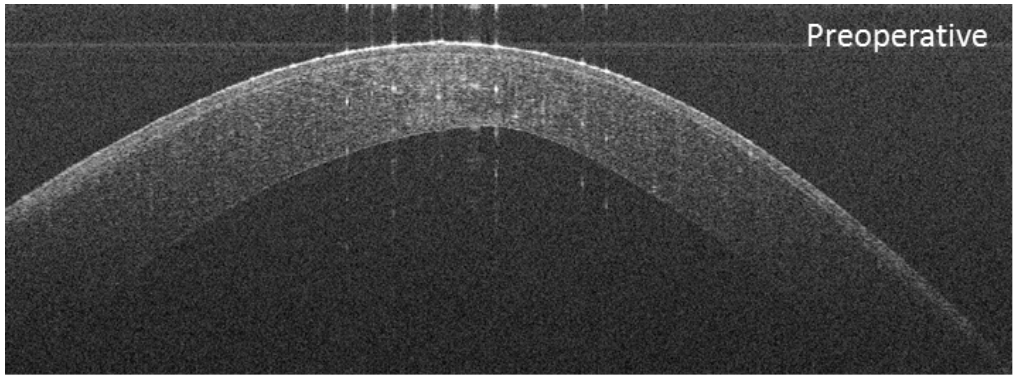
- RGP Scleral Contacts
  - Does not depend on corneal topography
  - Central optic dome
  - Peripheral haptics rest on sclera
  - Work well when RGP lenses have failed due to poor centration or abrasion

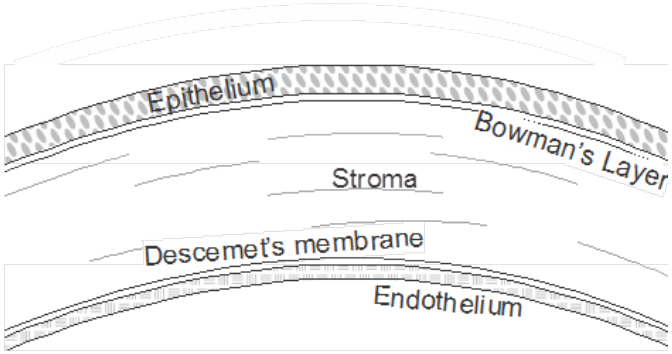


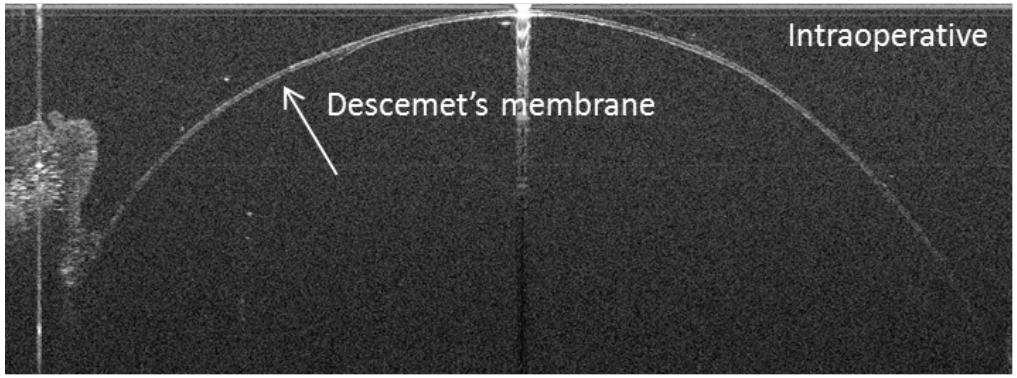
Lamellar or Penetrating Keratoplasty

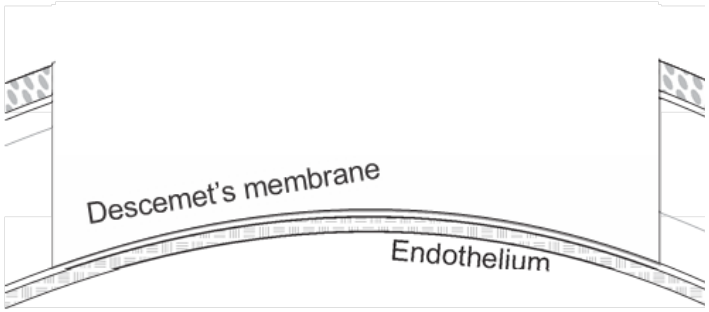
- Indicated if contact lenses have failed
- Major consideration is whether the patient is actually disabled by corneal disease
- Likelihood that surgery will correct the problem

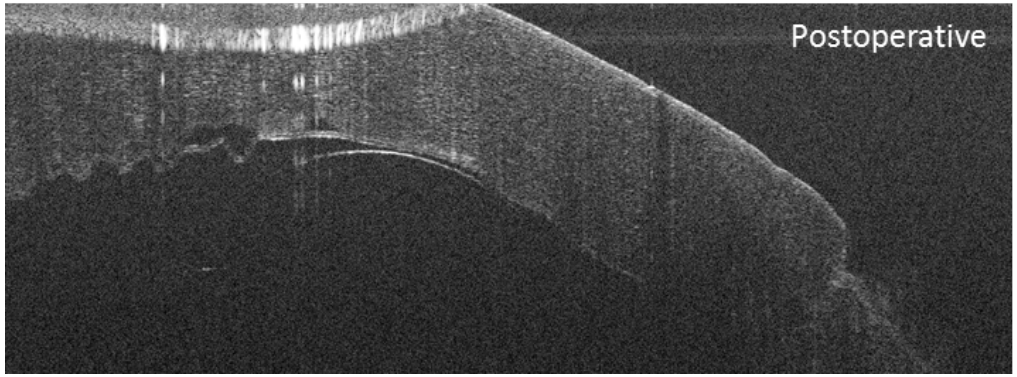


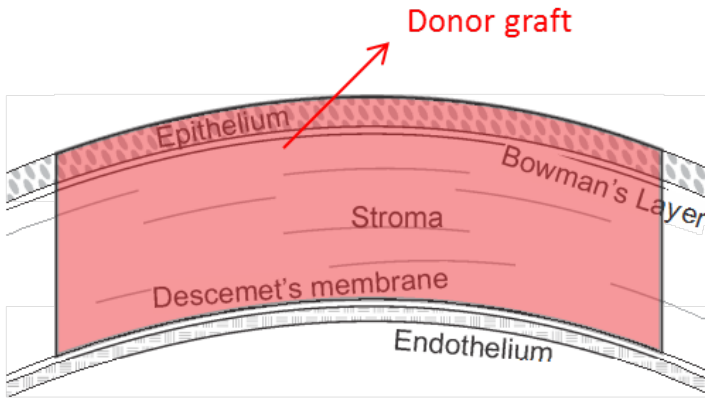

Preoperative


Epithelium
Bowman's Layer
Stroma
Descemet's membrane
Endothelium

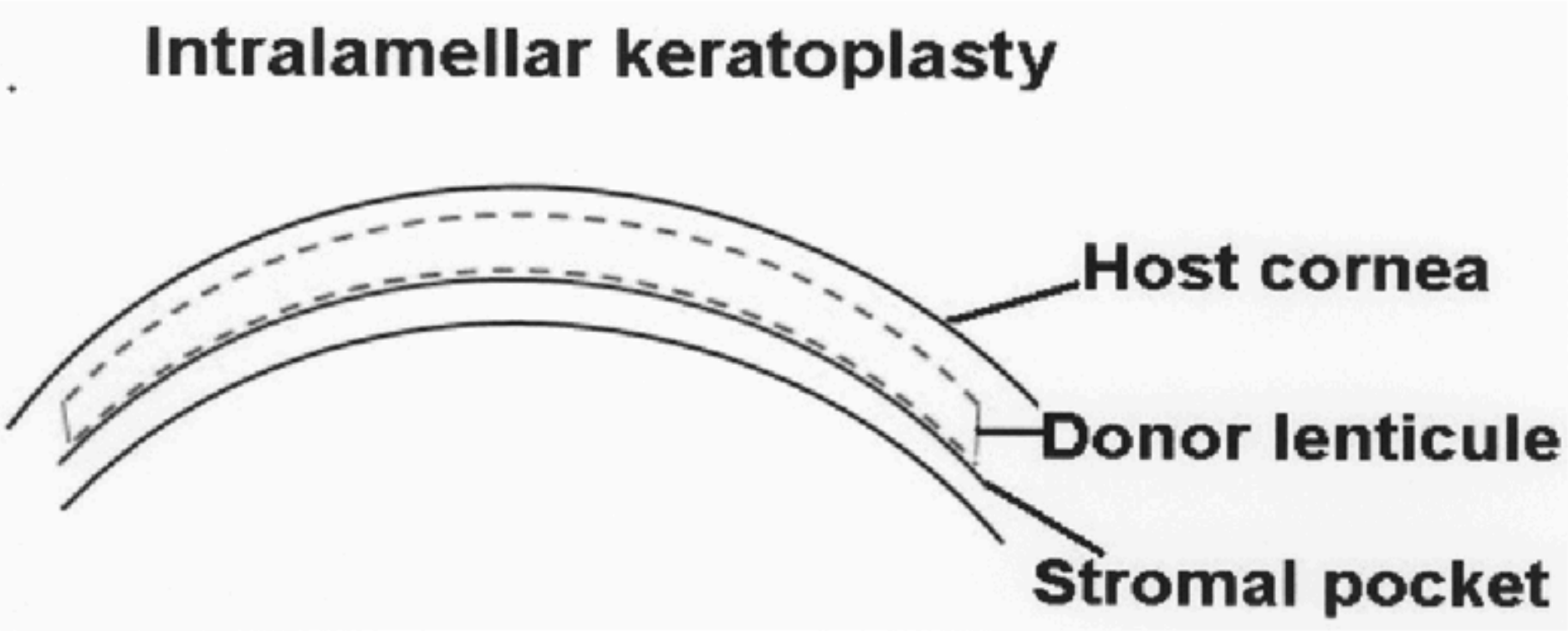

Intraoperative
Descemet's membrane


Descemet's membrane
Endothelium


Postoperative


Donor graft
Epithelium
Bowman's Layer
Stroma
Descemet's membrane
Endothelium

Tan, Bryan U., Tracy L. Purcell, L. F. Bloomfield Torres and David J. Schanzlin. “New surgical approaches to the management of keratoconus and post-LASIK ectasia.” Transactions of the American Ophthalmological Society 104 (2006): 212-20 .



Bowman's Layer Transplantation

van Dijk K, Liarakos VS, Parker J, Ham L, Lie JT, Groeneveld-van Beek EA, Melles GR. Bowman layer transplantation to reduce and stabilize progressive,advanced keratoconus. Ophthalmology. 2015

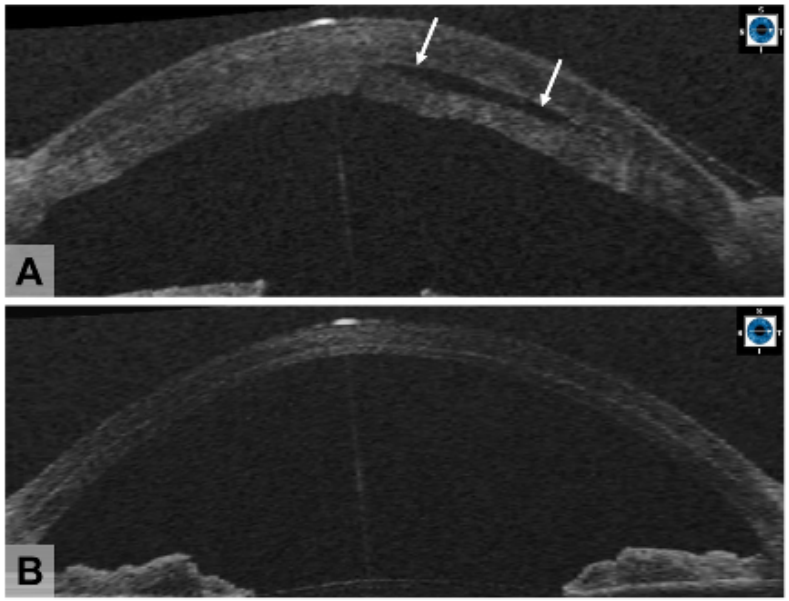
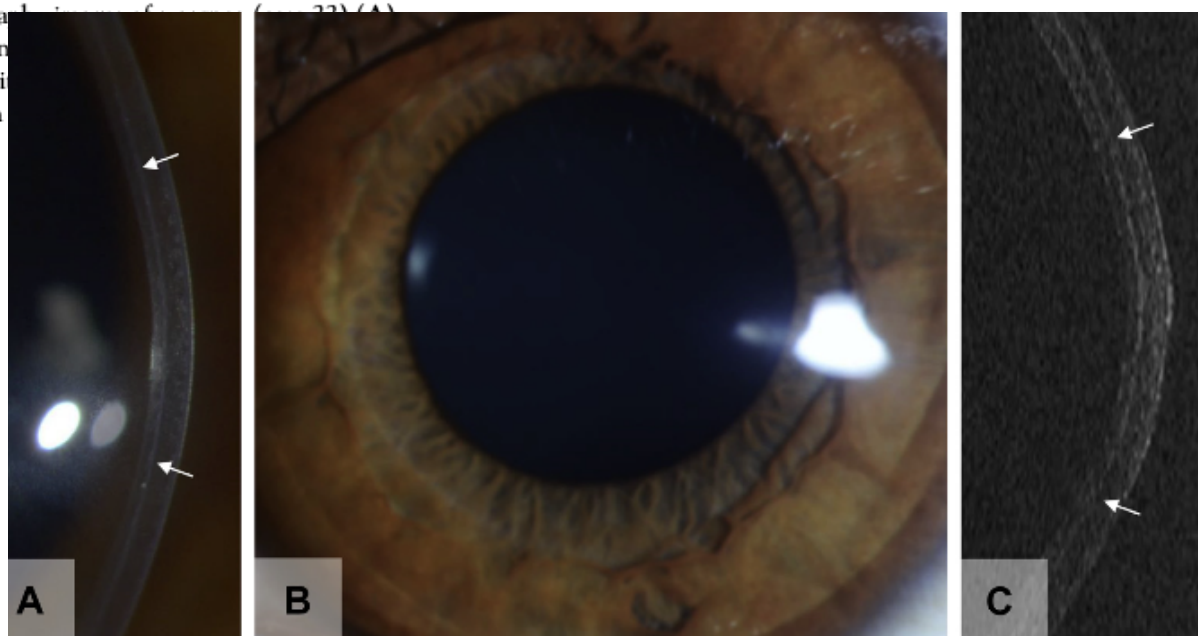


Figure 1. Optical coherence tomogra
immediately after Bowman layer tran
gery. **A**, Note the intrastromal cavi
surgery. **B**, These disappeared within



Biomechanical and biochemical differences between normal and keratoconus corneas

- Modified configuration of stromal collagen
- Decreased thickness
- **Increased expression of lysosomal and proteolytic enzymes**
- **Decreased concentration of protease inhibitors**
- Differences in elasticity causing **decreased stiffness**
- Possibly secondary to decreased number of **collagen cross-links** and molecular bonds between neighboring stromal proteoglycans
  - Daxter and Fratzal, 1997; Radner et al., 1996; Meek et al., 2005
  - Rehany, 1982
  - Sawaguchi et al., 1989; Zhou et al., 1998
  - Kao et al., 1982; Kenny et al., 1997
  - Nash et al., 1982; Andreassen et al., 1988; Edmund, 1988
  - Wollensak, Ihme, and Seiler, 1982; Wollensak and Buddecke, 1998

Collagen Crosslinking Mechanisms

- **Collagen fibrils crosslink naturally as part of their maturation process**
  - Oxidative deamination of ε-amino group of a single lysine or hydroxylysine by lysyl oxidase
  - Aldehyde produced forms cross-links with a specific lysine or hydroxylysine in adjacent collagen monomers
- Non-enzymatic reaction of glycation
  - **Increase in cross-sectional area of collagen fiber** Occurs in **aging and diabetics**
  - Type II diabetes has protective effect on development and progression of keratoconus

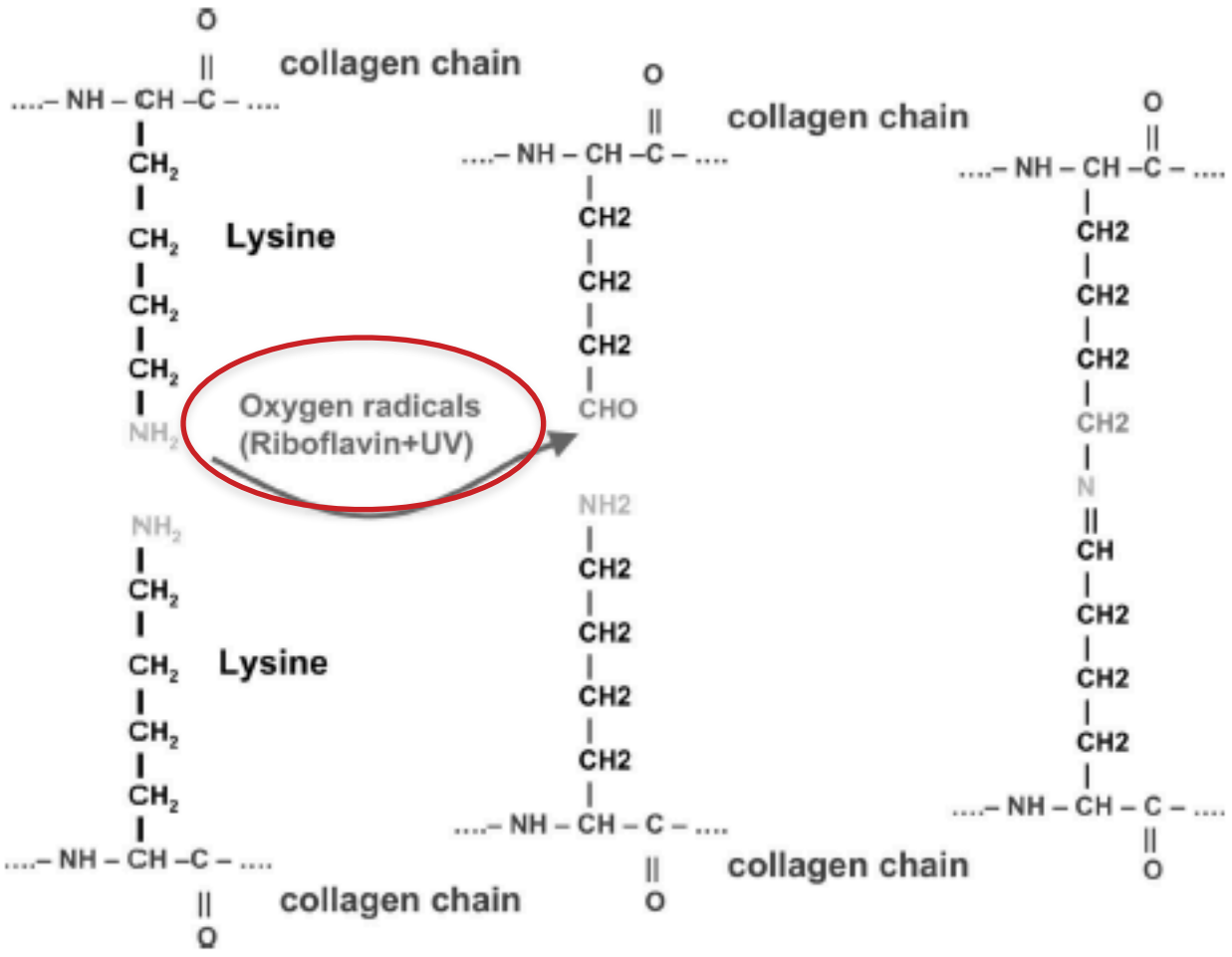
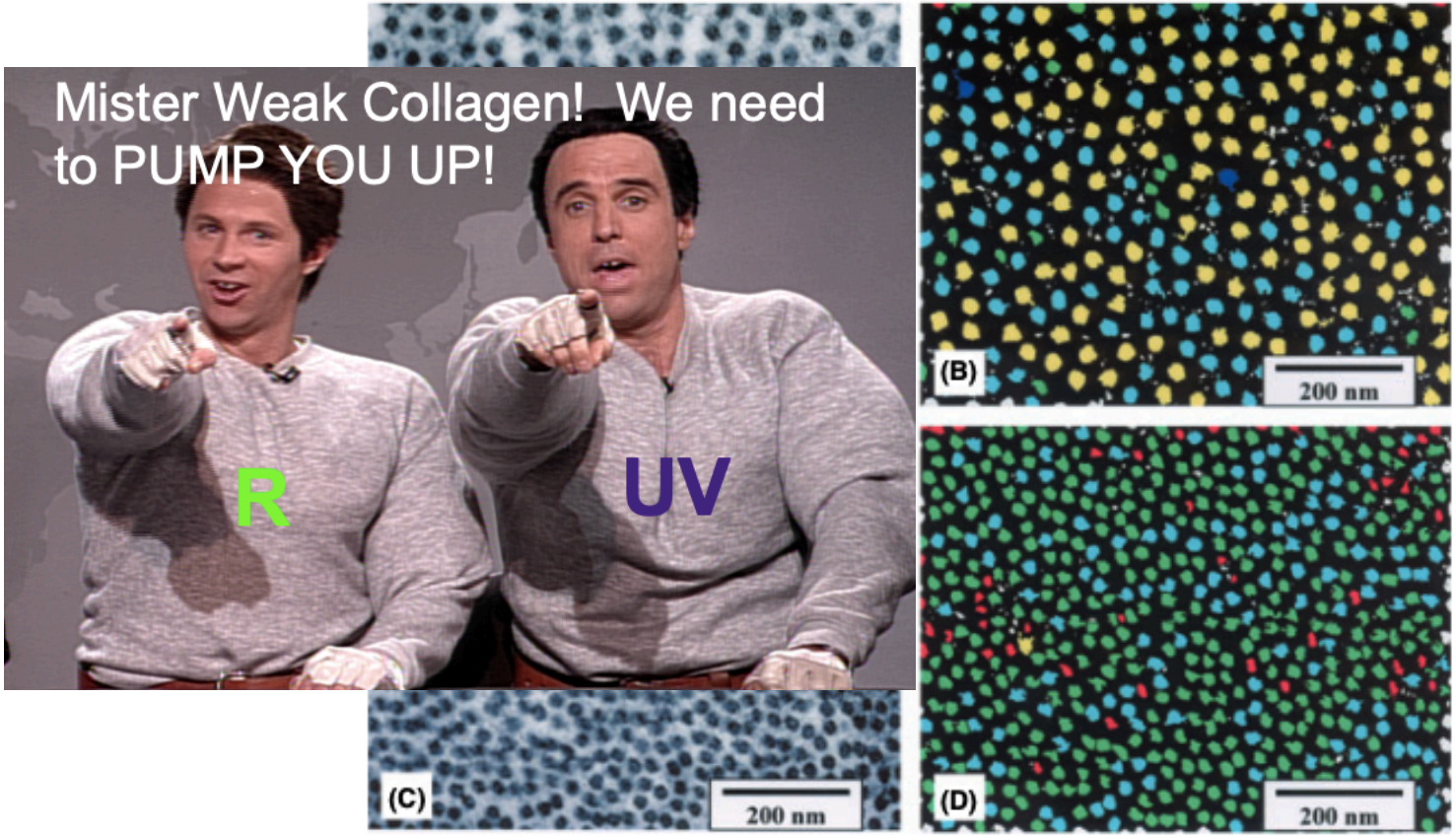


FIGURE 2. Schematic of the photochemical reaction of cross-linking of collagen caused by production of oxygen radicals by riboflavin and UVA light inducing a change at the end of an amino group. Afterward, these reactive groups can form new covalent bonds.

Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea* 2007;26(4):385-9.



Normal

Collagen Fibril
24.8 nm

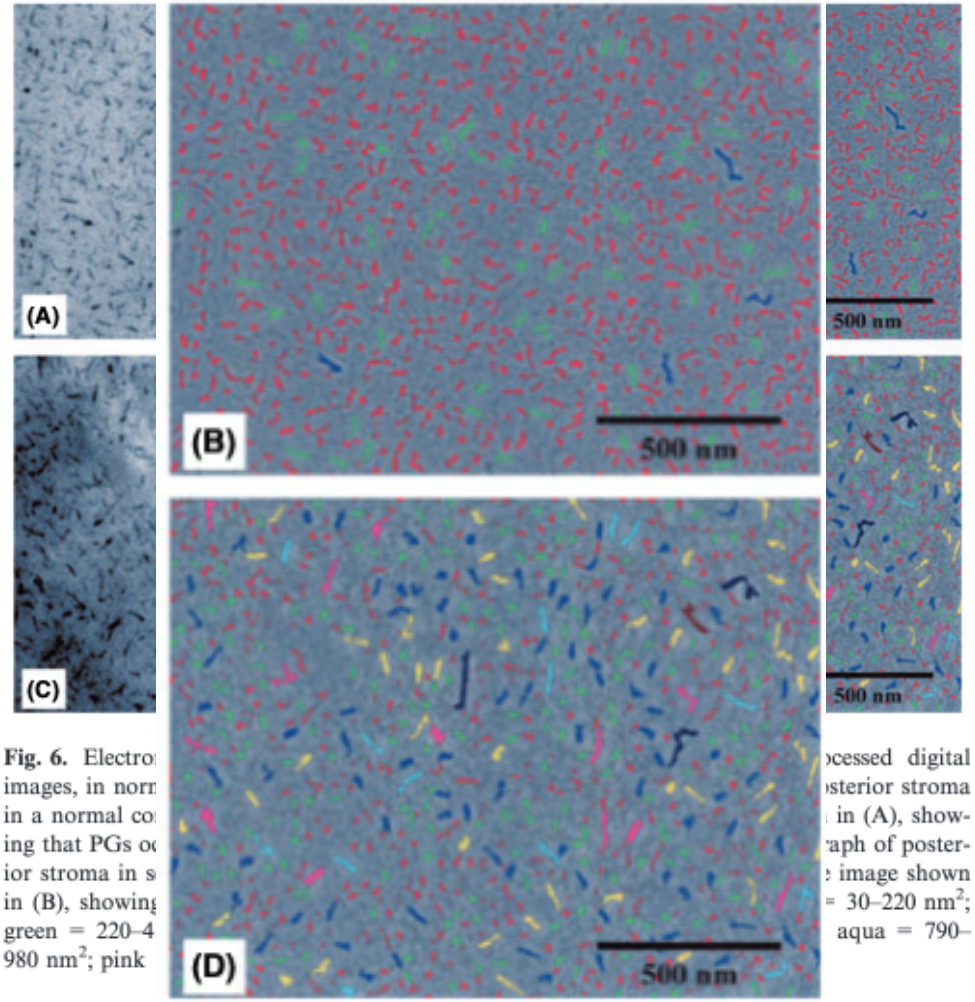
Keratoconus

22.0 nm

Fig. 3. Electron micrographs of collagen fibrils (CFs) and processed digital images of normal and keratoconus corneal tissue. (A) Electron micrograph of posterior stroma of a normal cornea. (B) Digital image obtained after processing the image in (A), showing large CF diameters in the normal cornea. (C) Electron micrograph of posterior stroma in severe keratoconus. (D) Processed image obtained after processing the image in (B), showing small CF diameters in severe keratoconus. Red = 15–20 nm; green = 20–25 nm; aqua = 25–30 nm; yellow = 30–35 nm.

Akhtar S, Bron AJ, Salvi SM, Hawksworth NR, Tuft SJ, Meek KM. Ultrastructural analysis of collagen fibrils and proteoglycans in keratoconus. Acta Ophthalmol. 2008 Nov;86(7):764-72.

Proteogylcans



Normal

Keratoconus

Fig. 6. Electro
images, in norm
in a normal co
ing that PGs oc
ior stroma in s
in (B), showing
green = 220–4
980 nm^2; pink
ocessed digital
sterior stroma
in (A), show-
aph of poster-
image shown
= 30–220 nm^2;
aqua = 790–

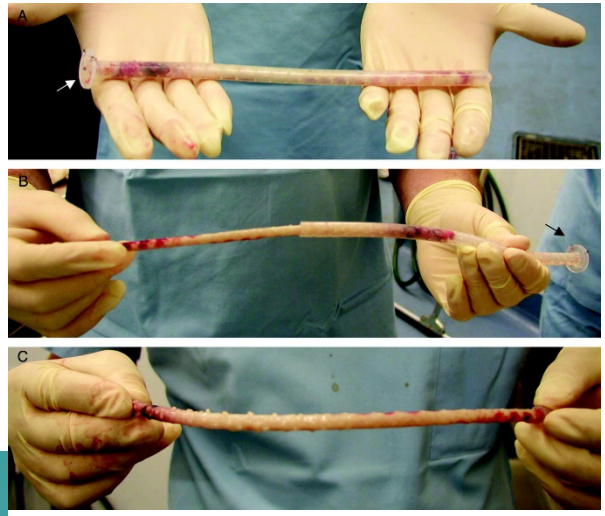
Akhtar S, Bron AJ, Salvi SM, Hawksworth NR, Tuft SJ, Meek KM. Ultrastructural analysis of collagen fibrils and proteoglycans in keratoconus. Acta Ophthalmol.2008 Nov;86(7):764-72.

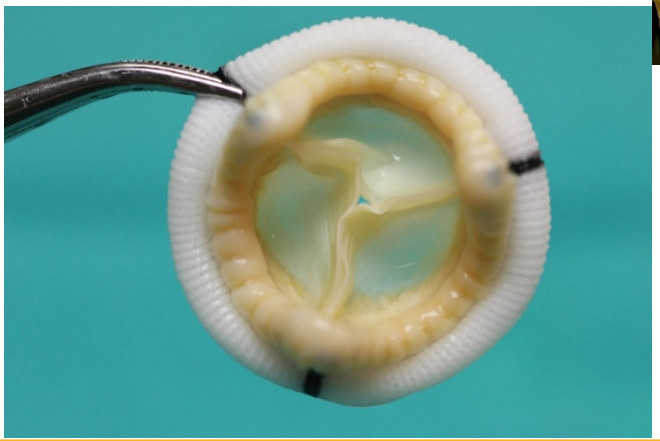
CXL Use in Biological Processes

- Inter and intra molecular crosslinking is found in many biological processes
  - Crosslinking of fibrin in **blood clots**
  - Crosslinking of collagen in **tendons** for increased tensile strength
  - Crosslinking in **cataractous lenses**
    - Leads to increased rigidity and increased weight of crystallin proteins

Medical Uses of CXL

- Increase the stability and reduce the biodegradation of collagen-based biomaterials for bioprostheses
  - Porcine heart valves
  - Blood vessel prosthesis
  - Dural substitutes
  - Meniscal allografts





Crosslinking via Aldehyde Rxns

- **Cardiovascular prostheses**
  - Nimni, 1988
- **Tympanic membrane reconstruction using cross-linked temporalis fascia**
  - Perkins and Bui, 1996
- **Treatment of vocal cord immobility**
  - Remache, 1995
- **Meniscal allografts**
  - Wisnewski et al., 1988

UV mediated

- With and without photosensitizers
- **Irradiated bovine cartilage for nasal reconstruction**
  - Ersek and Derlem, 1988
- Crosslinking of collagen gels for potential use in **synthetic epikeratoplasty**
  - Milne and Zika, 1992
- **Collagen implant as a dural substitute**
  - Pietrucha, 1991

Photopolymerization

- A monomer substrate in the presence of a photoinitiator can polymerize by way of cross-linkage in presence of UV source
- Used in **industry** to generate highly cross-linked materials
  - **Epoxy coatings**
  - **Optical lenses**
  - **Optical fiber coatings**
  - **Dental materials (to harden fillings)**

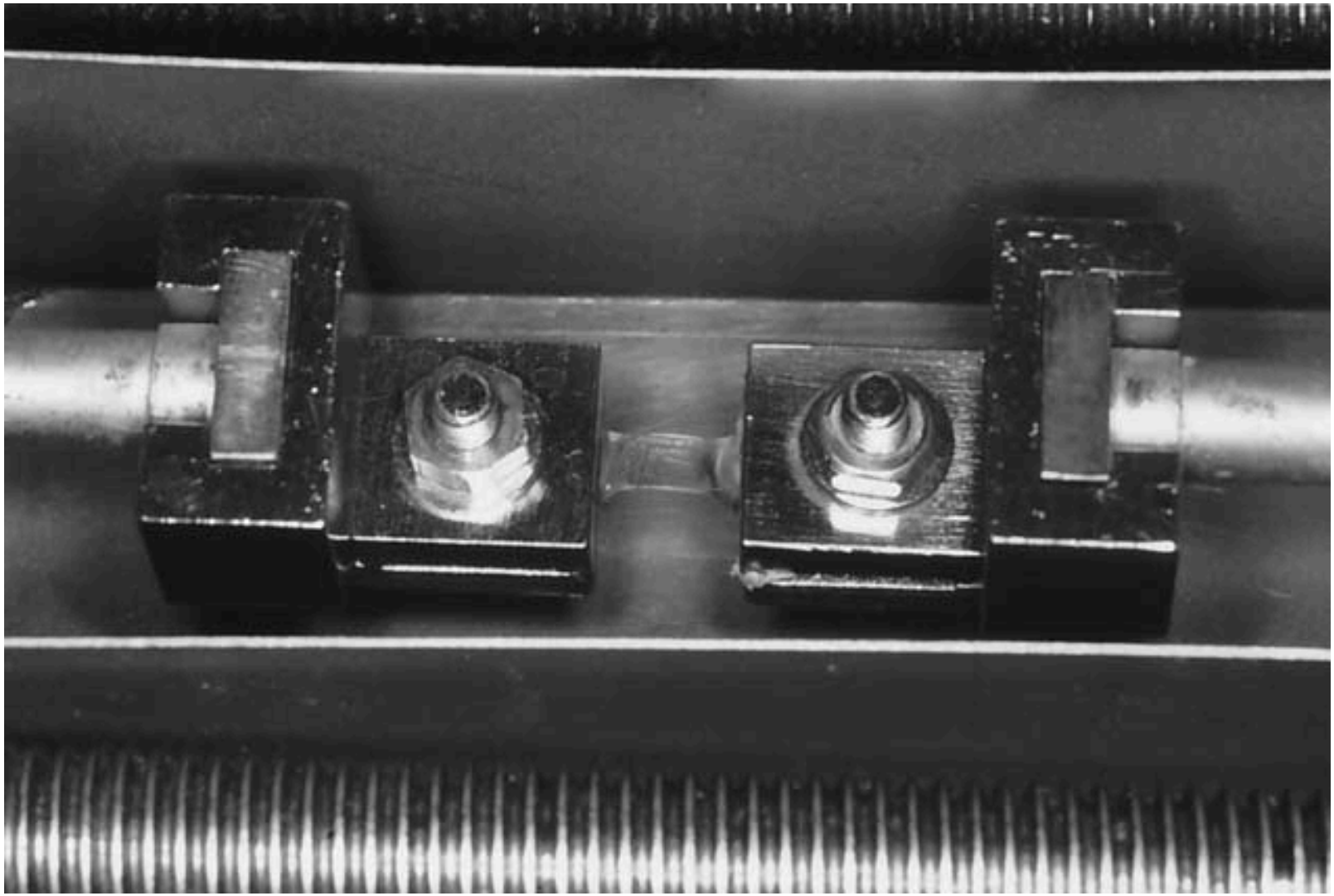
Corneal Collagen Crosslinking

- Seiler, Spoerl, and Wollensak in 1996
  - University of Dresden in Dresden, Germany
  - Assess the value of stromal cross-link induction to increase corneal stiffness
  - Possible treatment for keratoconus

Induction of Cross-links in Corneal Tissue

- Spoerl E, Huhle M, Seiler T. *Exp Eye Res* 1998.
- 160 pig eyes with CCT less than 1 mm
- Epithelium removed
- Incubated in various solutions
  - Riboflavin
  - Glutaraldehyde
  - Karnovsky sln (glutaraldehyde and formaldehyde)
    - Penetrates faster
- Exposed to various wavelengths of light
  - Mercury lamp: 254 nm and 90 W/m^2 intensity
  - Xenon lamp: 365 nm, 436 nm and 20 W/m^2
  - Sunlight: estimated 85 W/m^2

Stress-Strain Measurements



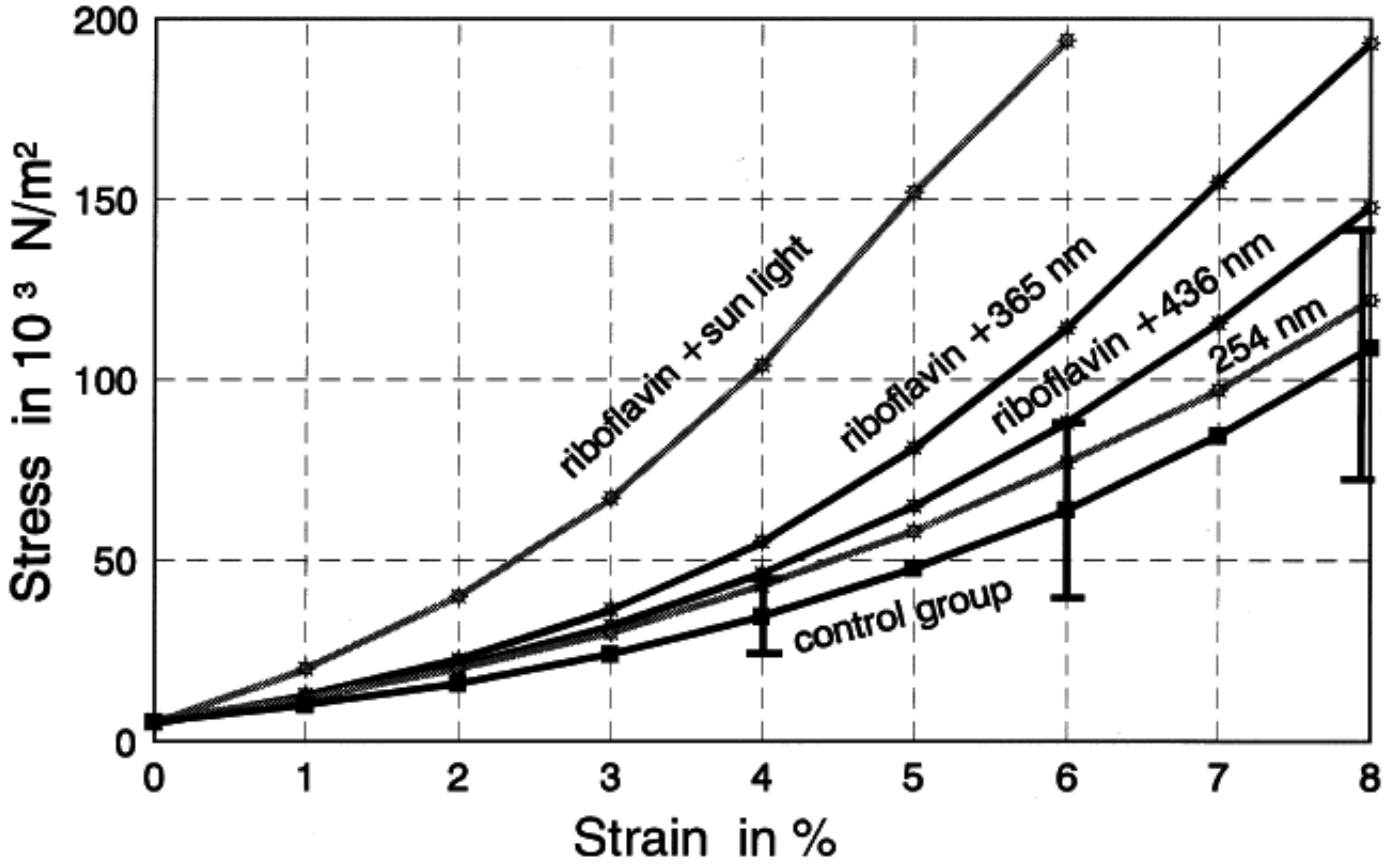


FIG. 1. Influence of UV-radiation and riboflavin on the stress-strain relation of the cornea (group 1, 2, 4 and 9). Treatment with UV light (254 nm) alone does not reach an effect and riboflavin/436 nm produce only a weak significant stiffness of the cornea. Riboflavin/sunlight and riboflavin/365 nm show a high significant effect.

Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res*. 1998;66:97–103.

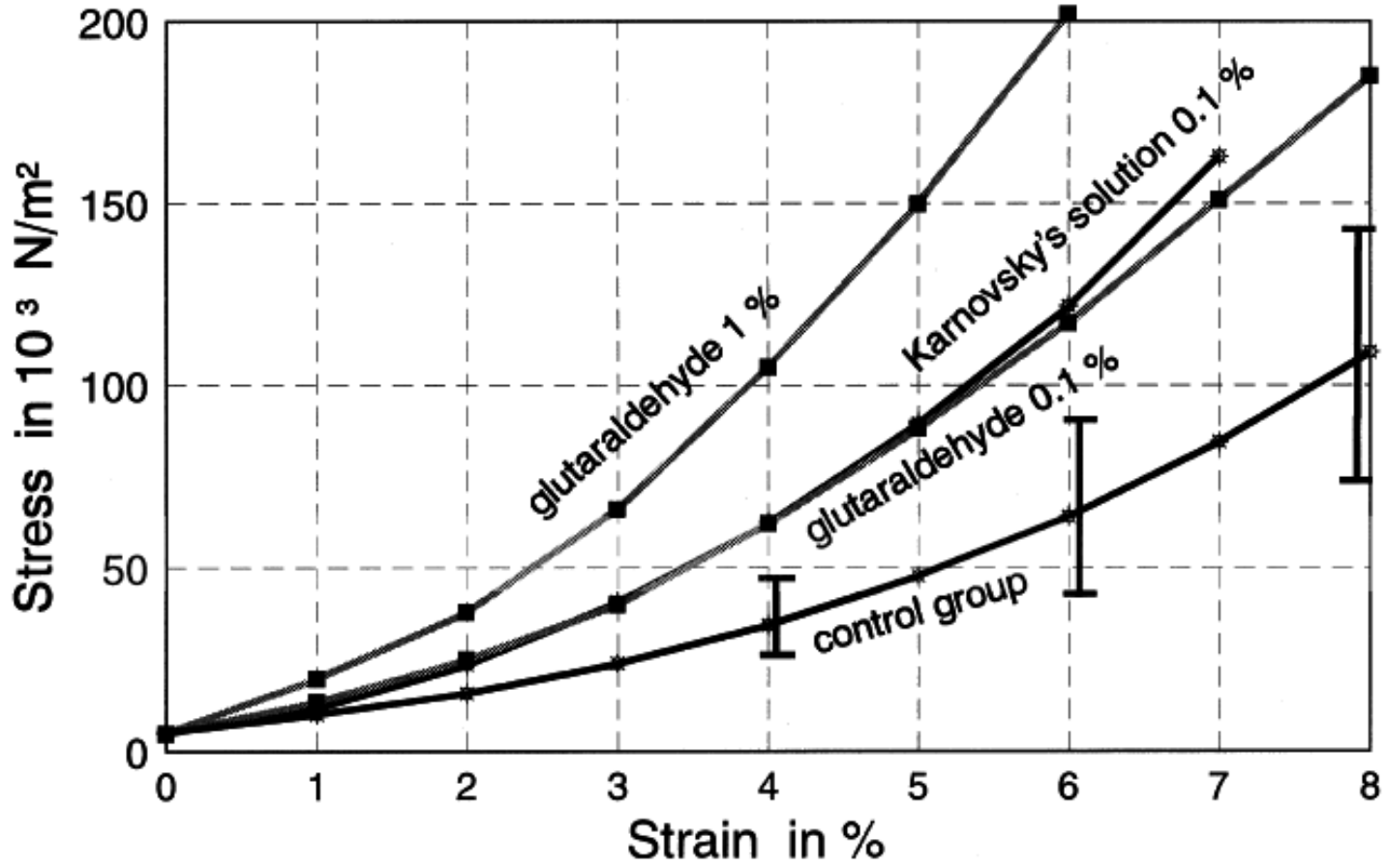


FIG. 2. Influence of glutaraldehyde and Karnovsky's solution on the stress-strain relation of the cornea (group 6, 7, 8 and 9). In spite of the high standard deviation the increase of stiffness is statistically significant for all treatments.

Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res*. 1998;66:97–103.

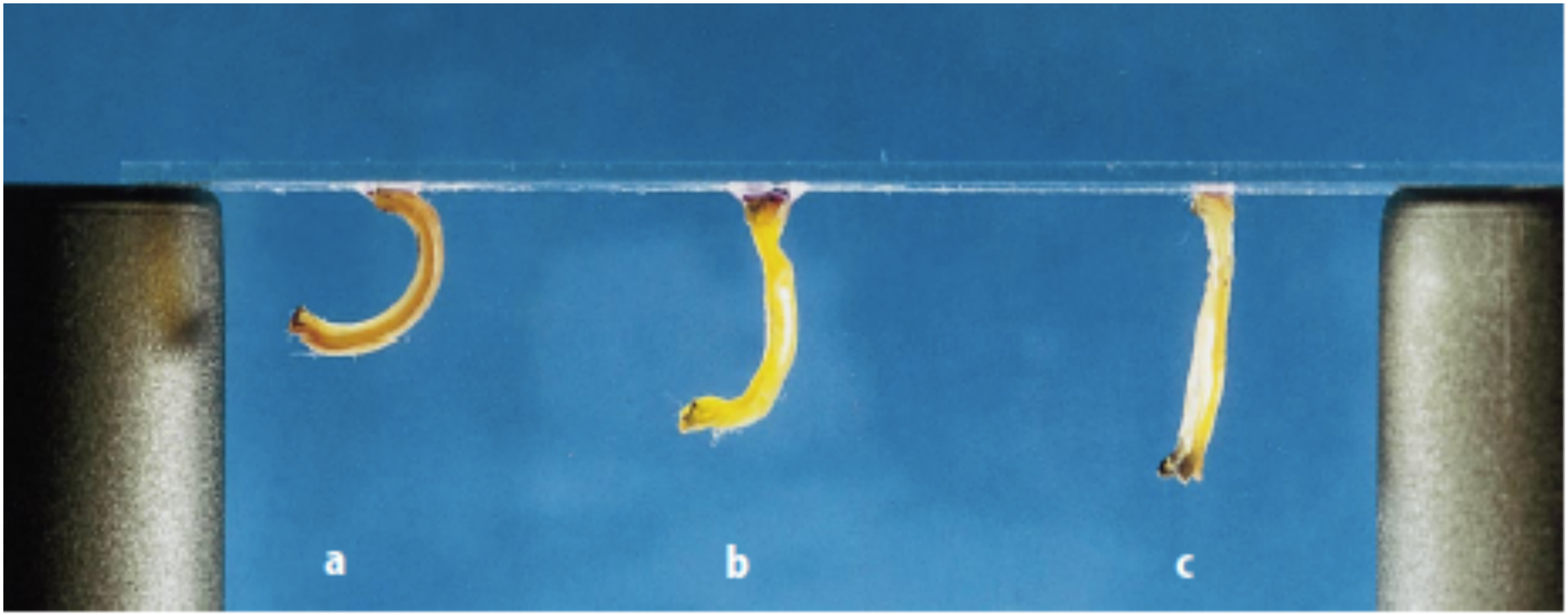


Abb. 4a–c ▲ Demonstration des Biegeverhaltens der Hornhaut.
(a) mit Glutaraldehyd behandelt, (b) mit Riboflavin und UV-Strahlung behandelt und (c) unbehandelt

Spoerl E, Schreiber J, Hellmund K, et al. Untersuchungen zur Verfestigung der Hornhaut am Kaninchen. *Ophthalmologe*. 2000;97:203–206.

Crosslinking in Rabbit Corneas

- Spoerl et al. *Ophthalmologe* 2000.
- **28 rabbits (1 treated eye, 1 control eye)**
  - 19 with **riboflavin-UV**(365 nm, 2 mW/cm^2) for 45 minutes
  - 9 eyes with **0.075% glutaraldehyde** for 20 min
- 1 month and 3 months stress-strain measurements and compared to the fellow eye
- Glutaraldehyde stress-strain at 1 month was higher in the treated corneas by a factor of 1.3
- **Riboflavin-UV increased stress-strain by a factor of 1.6 at 1 month, and by 1.3 at 3 months**
- Corneas remained clear and was no inflammation

Aldehyde Reactions vs. UV / Riboflavin

- Concern for corneal opacity
  - 0.1% Karnovsky's soln in rabbits caused transient subepithelial opacity lasted 3 weeks
- Concern for other potential side effects such as inflammation, cataracts, toxicity
- Stress-strain measurements were not statistically significant at 1 month in rabbits
- Only form cross-links in superficial 200 μm

Crosslinking in Human Corneas

- Wollensak, Spoerl, Seiler. *Am J Ophthalmol* 2003
- 23 eyes of 22 patients with maximum K value 48-72 diopters (fellow eye as control)
- Riboflavin and UVA (370 nm, 3 mW/cm^2) for 30 minutes
- Follow up intervals of 6 months
- Vision, topography, slit-lamp, endothelial cell density, and photos
- Follow-up between 3 months to 4 years

Results

- Corneal and lens transparency, endothelial cell density, and IOP remained unchanged
- In treated eyes, **progression of KCN was stopped**
- **16/23 eyes (70%), reduction in maximal K readings by 2.01 D**
- Refractive error improved by 1.14 D
- Vision improved slightly in 15 eyes (65%) by average of 1.26 lines

Effects of Crosslinking

- **Increase in corneal collagen fiber diameter by 12.2% in anterior stroma to 4.6% in posterior stroma**
  - 4.5% increase in diameter in aging subjects
- Increase in collagen diameter by 3.96 nm does not lead to loss of transparency
- **Increased rigidity** by 70% in porcine corneas and **330% in human corneas**
  - Durability of stiffness effect unknown
  - Collagen turnover is 2-3 years, may need retreatment
- **Increased resistance to collagenases**
  - Increased collagenase activity in KCN

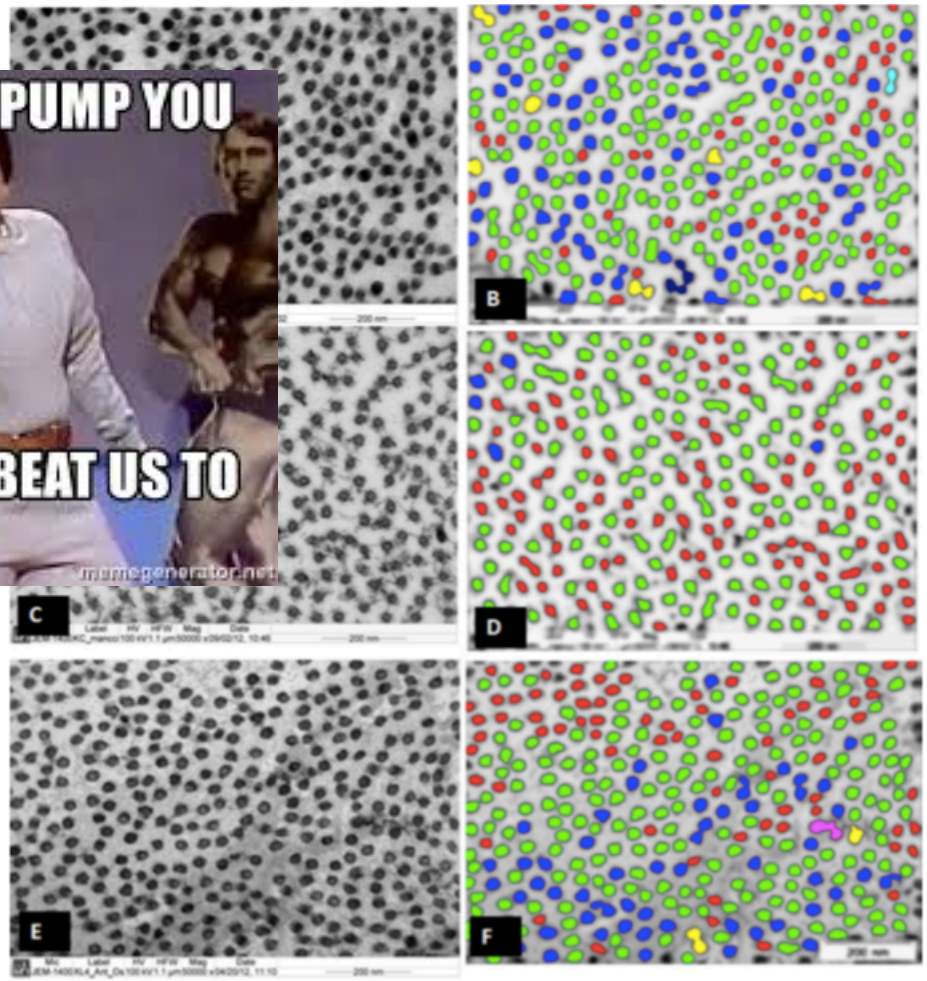


Figure 3. Electron micrograph and digital images of the collagen fibrils of normal, keratoconus (KC), and cross-linked (CXL) corneas. **A**: Electron micrograph of collagen fibrils which are present in the normal human corneas. **B**: Digital image obtained after processing the image shown in **A**. **C**: Electron micrograph of the collagen fibrils which are present in the KC corneas. **D**: Digital image is obtained after processing the image shown in **C**. **E**: Electron micrograph of collagen fibrils which are present in the CXL corneas. **F**: Digital image obtained after processing the image shown in **E**. The images were displayed by using color coding to demonstrate the distribution of the variable diameters of collagen fibrils. Collagen fibril color coding: Red=10–15 nm, Green=15–20 nm, Blue=20–25 nm, Yellow=24–30 nm, Aqua=30–35 nm, Pink=35–40 nm, Brown=40–45 nm.

Normal Cornea

Collagen Fibril Diam
23.74 nm

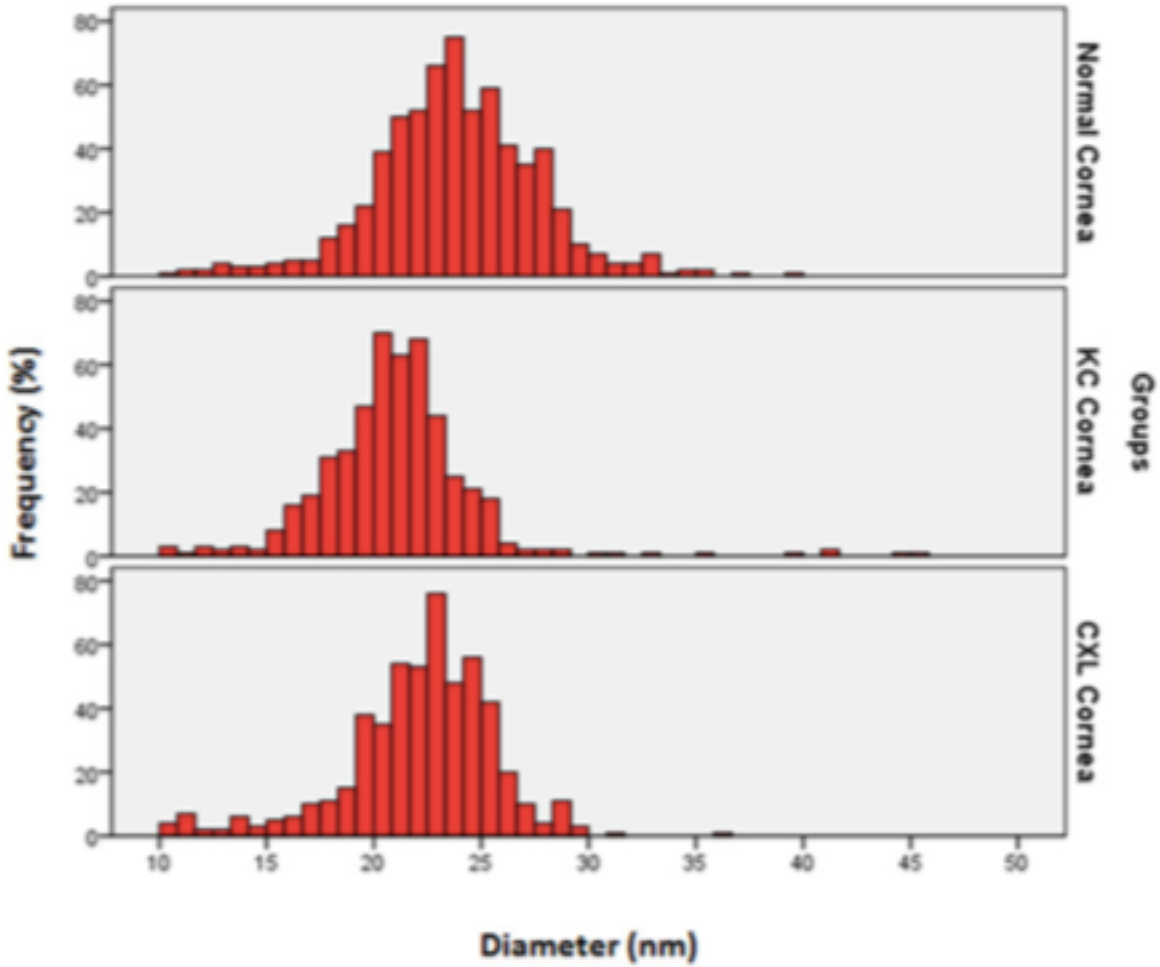
Keratoconus

20.99 nm

Crosslinked

22.57 nm

Akhtar S, Almubrad T, Paladini I, Mencucci R. Keratoconus corneal architecture after riboflavin/ultraviolet A cross-linking: ultrastructural studies. Mol Vis.2013 Jul 19;19:1526-37.



Normal Cornea

Keratoconus

Crosslinked

Akhtar S, Almubrad T, Paladini I, Mencucci R. Keratoconus corneal architecture after riboflavin/ultraviolet A cross-linking: ultrastructural studies. Mol Vis.2013 Jul 19;19:1526-37.

Summary of efficacy studies (shortterm)

Authors	Year of Publication	Type of Study	Number of participants	Duration of follow-up
Caporrosi et al	2006	Prospective, non-randomized	10 eyes of 10 patients	6 months
Hoyer et al	2008	Retrospective	153 eyes of 111 patients	Min: 12 months
Wittig-Silva et al	2008	Prospective, non-randomized	66 (treatment=33, control=33) eyes of 49 patients enrolled	12 months (only 9 patients in treatment group completed 12 months follow-up)
Raiskup-Wolf et al	2008	Retrospective	241 of 130 patients	Min: 6 months
Jankov et al	2008	Prospective, non-randomized	25 eyes of 20 patients	4-7 months
Vinciguerra et al	2009	Prospective, non-randomized	28 eyes of 28 patients	12 months
Agrawal	2009	Retrospective	37 eyes of 25 patients	Min: 12 months
Grewal et al	2009	Prospective, non-randomized	102 patients	12 months

10 Year Results

- 34 eyes of 24 patients
- 2 eyes (5.8%) required retreatment at 5 and 10 yrs
- Apical K: Decreased from 61.5 D to 55.3D
- Mean Astigmatism: Decreased from 5.7 to 4.0 D
- 1 eye (2.9%) developed a permanent corneal scar
- **13 eyes (38.2%) had persistent anterior stromal haze that was not visually significant**
- ECC: Increased from 2214 cells/mm^2 to 2831.

Raiskup et al, JCRS 2015

CXL in Pediatric Patients: Long-Term Results

- 377 eyes of 336 patient (Age 18 yrs or less)
- Standard Dresden Protocol
- F/U from 2 to 6.7 years
- Reduced Ast. From 7.22 to 6.13D
- **Steepening of K Max (> 1D) occurred in 24% of eyes by 4 years**

Padmanabhan et al Cornea 2018

Endothelial Cell Damage

- Wollensak et al. *J Cataract Refractive Surgery* 2003.
- 34 rabbit eyes treated with 0.1% riboflavin and various endothelial UVA doses 0.09-0.5 mW/cm^2 (370 nm) or UVA alone
- 6 eyes enucleated at 4 hours remainder at 24 hours to look for apoptosis
- In corneas less than 400 µm, the endothelial UVA dose reached a cytotoxic level of 0.36 mW/cm^2 using the standard surface UVA dose of 3 mW/cm^2

Endothelial Cell Damage Reduced Fluence for thin Corneas

- In thinner corneas with **at least 350 µm** corneal thickness
  - **reduced surface UVA dose of 3.6 J/cm² (2 mW/cm² instead of 3)**
  - lowest dose to produce a mechanical stiffening effect and increase resistance to enzymatic digestion
- The endothelial UVA dose would then be only 0.54 J/cm² (0.3 mW/cm²)

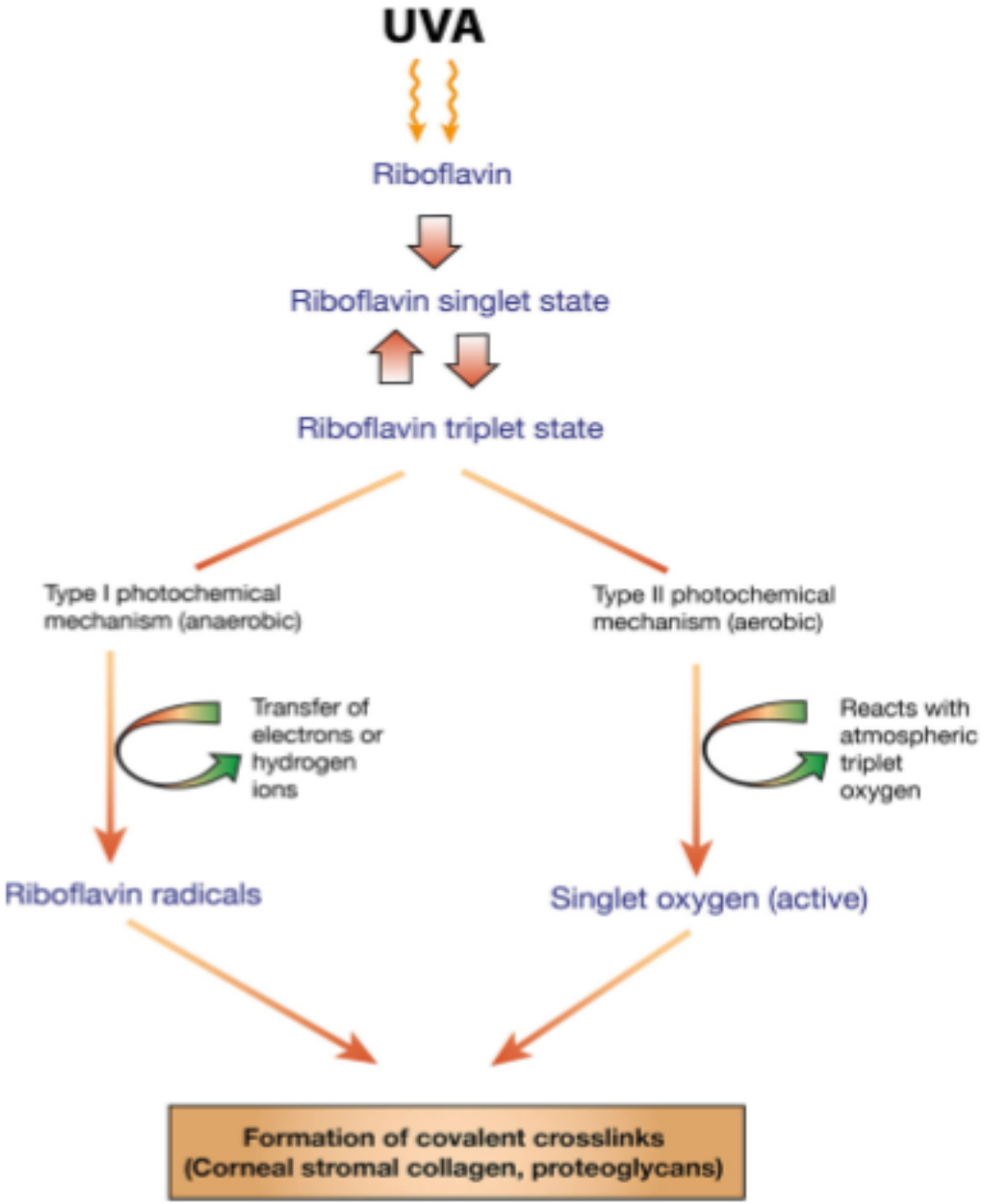
Keratocyte Damage

- Wollensak et al. *Eye* 2004.
- Cell cultures from porcine keratocytes treated with 0.025% riboflavin and various UVA (370 nm) 0.4-1.0 mW/cm^2 or UVA alone
- Evaluated for cell death after 24 hours
- **For riboflavin-UVA cytotoxic irradiance level at 0.5 mW/cm^2**
  - 10 fold lower than cytotoxic irradiance of 5 mW/cm^2 for UVA alone
- **Reached in human corneas at 300 µm** using surface irradiance of 3 mW/cm^2
- Keratocyte apoptosis
  - transient corneal edema
- After 6 months, repopulation of entire stroma with normal keratocytes
  - **Late migration of fibroblasts results in flattening**

Riboflavin

- Non-toxic, water soluble, penetrates stroma easily **(But NOT epithelium)**
  - In keratocyte study, no cell death with riboflavin alone
- **Provides adequate shielding effect at 370 nm**
  - maximum absorption by riboflavin at this wavelength
- Generates sufficient free radicals to induce cross-links
- Intramolecular rather than intermolecular cross-links
  - Collagen fibrils run parallel with equal distance b/w them
  - **Increase in collagen diameter after crosslinking**
- Osmolarity may be adjusted (ex. dextran 20%) to control corneal swelling / thinning

Subasinghe SK, Ogbuehi KC, Dias GJ. Current perspectives on corneal collagen crosslinking (CXL). Graefes Arch Clin Exp Ophthalmol. 2018 Aug;256(8):1363-1384.



Direct UV Damage

- Depends on wavelength, irradiance, time
- **Photokeratitis occurs at 270 to 315 nm (UVB 290-320)**
- **For cataract between 290 and 365 nm**
  - has a higher energy because of a shorter wavelength than UVA
  - for short UV times, antioxidative mechanisms in lens to reduce damage
- Retina by thermal or blue light 400–1400 nm
- Irradiance damage threshold
  - 70 J/cm^2 for the lens
  - 42 J/cm^2 for the cornea
  - 4.3 mW/cm^2 for the retina
- Crosslinking procedure uses 370 nm at 3 mW/cm^2 for 30 minutes

Riboflavin Has 2 roles

- **Participates** with UV light and oxygen in the crosslinking process
- **Shields** the posterior cornea and other structures of the eye from the toxic effects of UV radiation

Riboflavin Shielding

- Endothelium, lens, and retina are exposed to a residual UV radiant exposure that is less than 1 J/cm^2
- **In the corneal stroma it enhances the absorption of UV coefficient by a factor of 5**
  - 95% compared to 32% w/o and 50% absorption in the lens
- Limits the UV irradiance through a 400 µm-thick stroma to 0.18 mW/cm^2 at the endothelial level
  - 2 times lower than the damage threshold of 0.35 mW/cm^2

Riboflavin UV Absorption

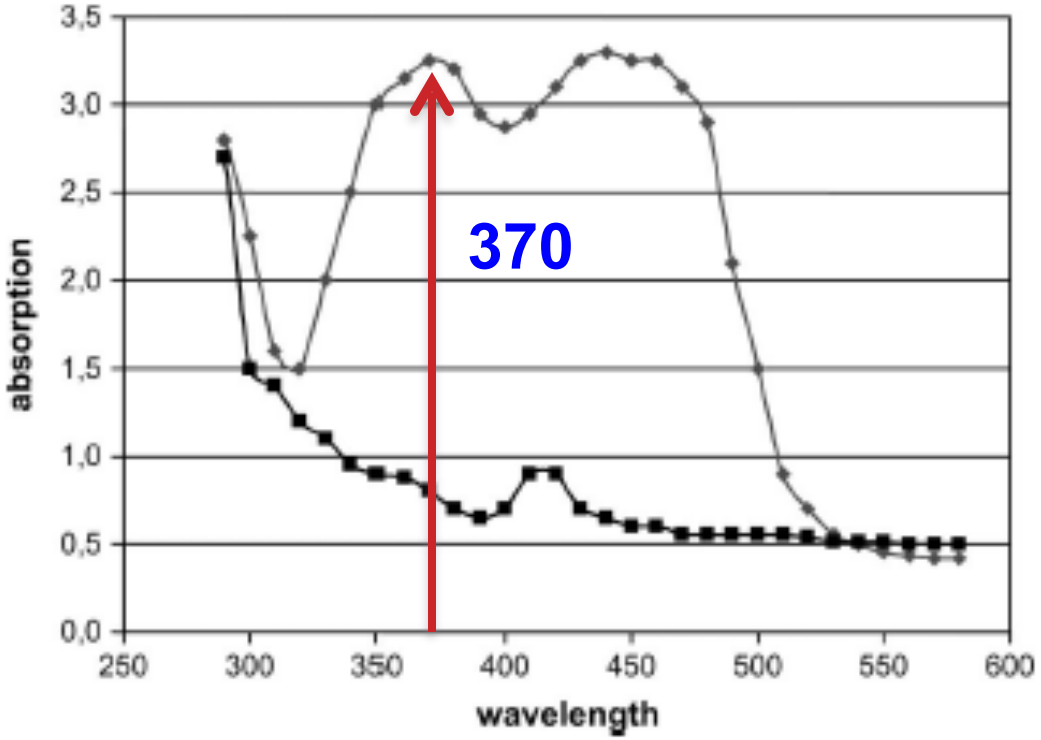


FIGURE 1. Absorption spectrum of the porcine cornea with and without riboflavin. Three absorption maxima could be selected, but the one <300 nm is not acceptable because of potential DNA damages, and the maximum at ~450 nm may be dangerous because of the blue light hazard to the retina.

Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea* 2007;26(4):385-9.

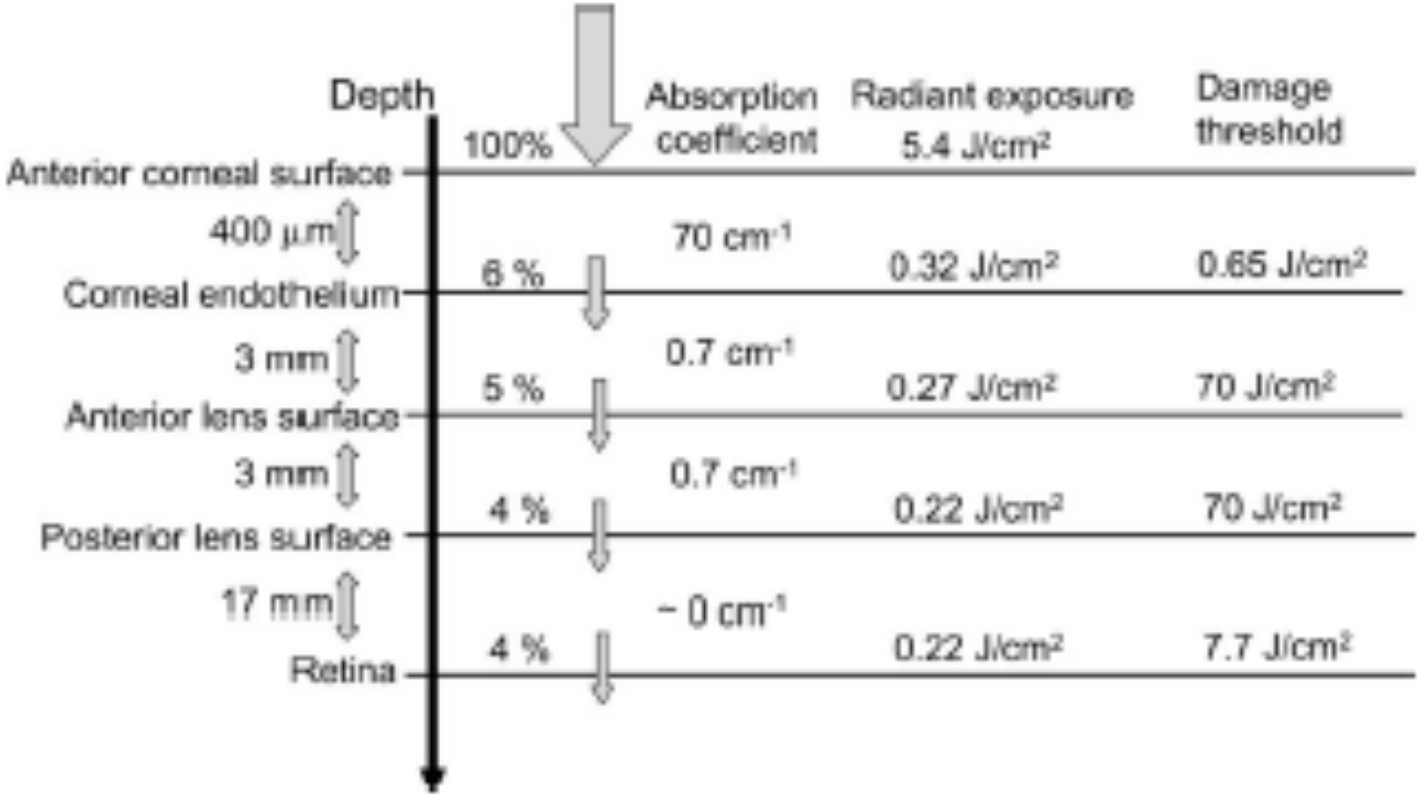
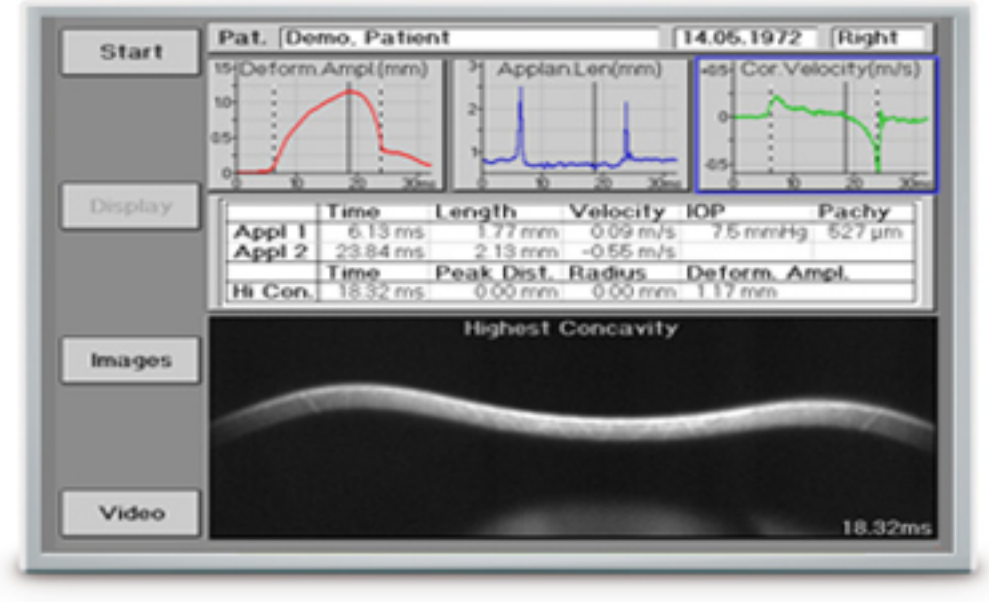


FIGURE 5. Radiant exposures, transmission, and damage thresholds for different ocular media for a human eye after 30 minutes of riboflavin application.

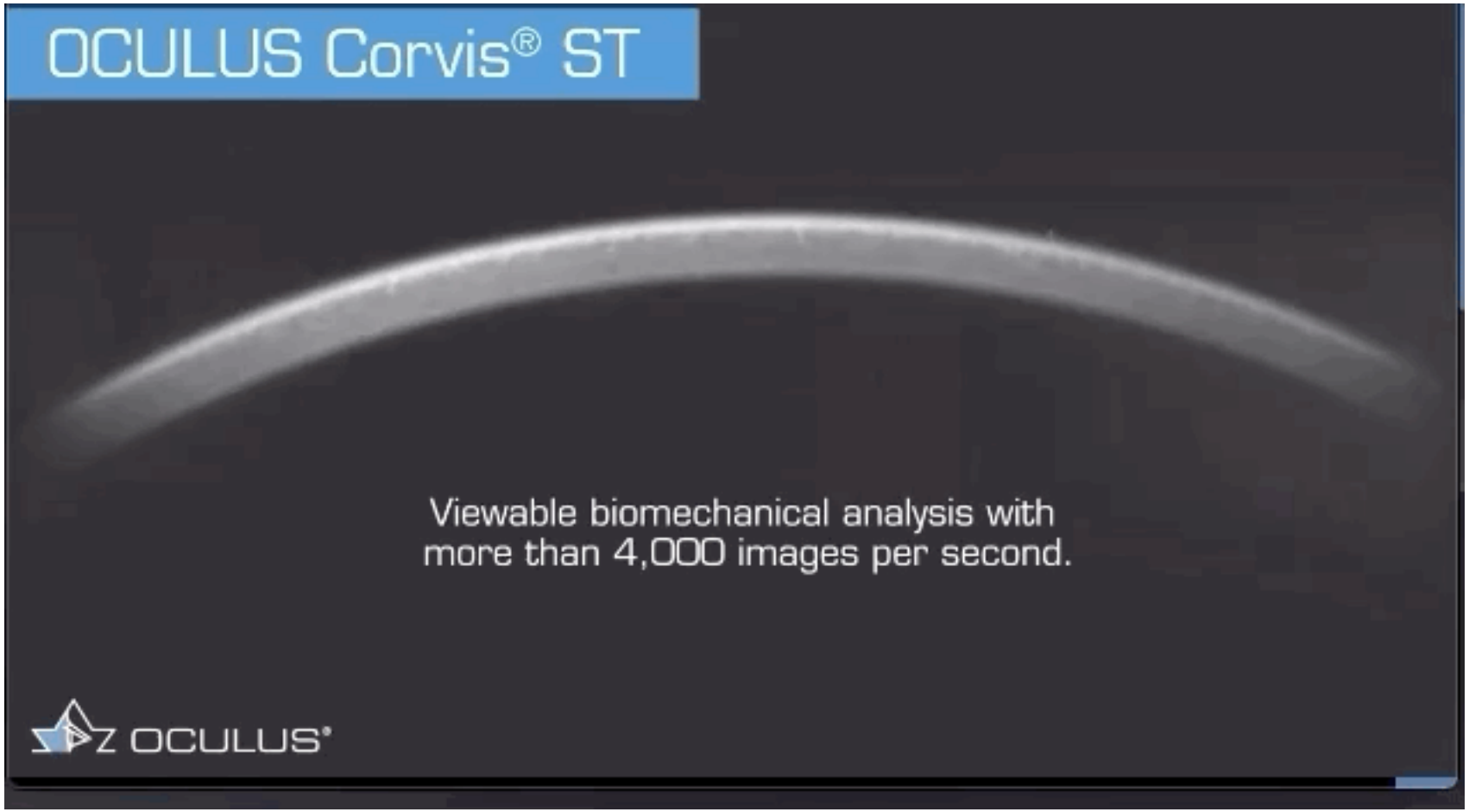
Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea* 2007;26(4):385-9.

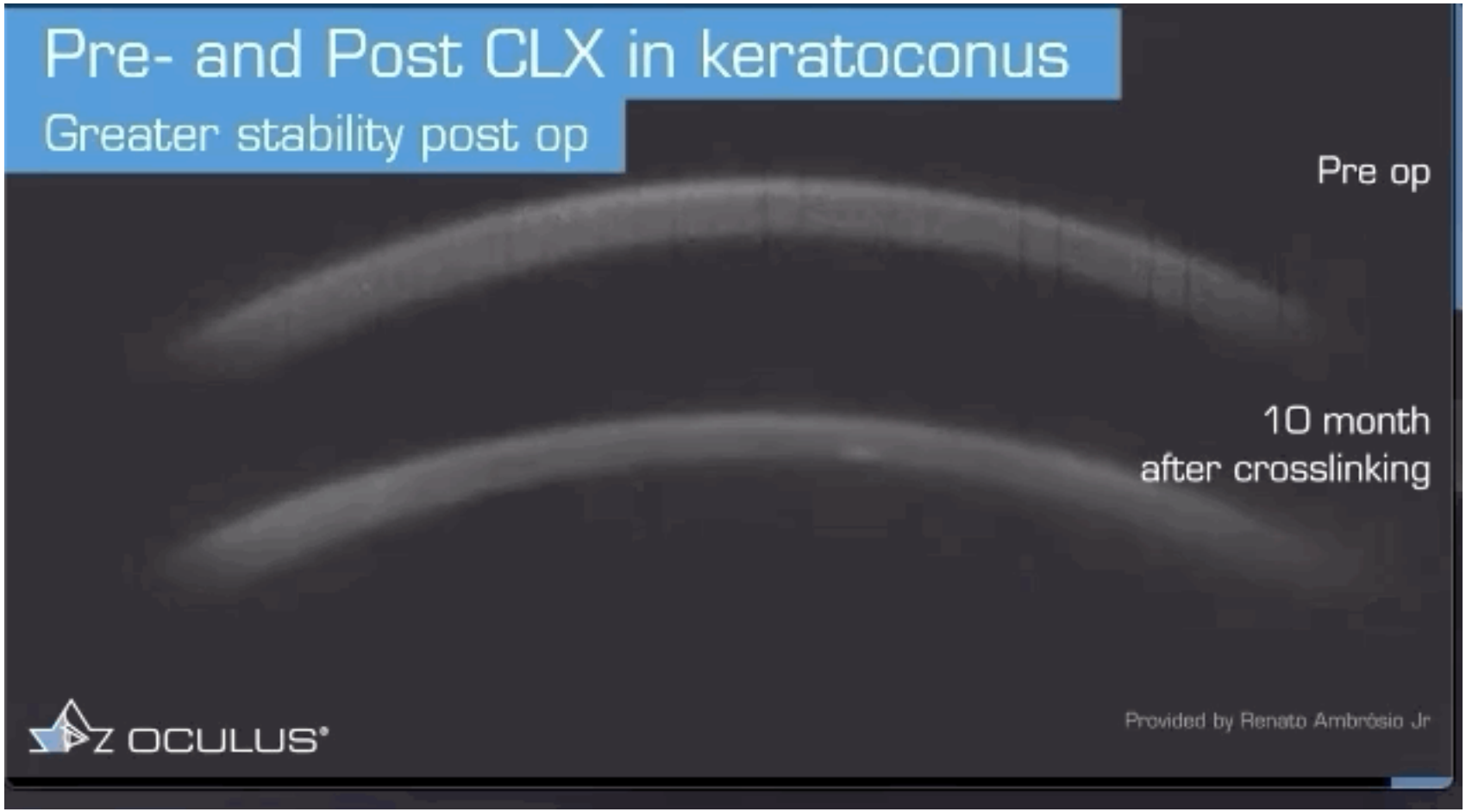
Biomechanical Measures

Corvis - ST



Exame Corvis - ST


OCULUS Corvis® ST
Viewable biomechanical analysis with
more than 4,000 images per second.
OCULUS


Pre- and Post CLX in keratoconus
Greater stability post op
Pre op
10 month
after crosslinking
OCULUS
Provided by Renato Ambrósio Jr

Dresden Procedure
Wollensak, Spoerl, and Seiler (2003)

- Topical anesthetic
- Remove the central 8-10mm of the epithelium
- Apply riboflavin solution (0.1% riboflavin-5-phosphate and 20% dextran T-500) to the corneal surface 30 minutes
- 30 minute exposure to 370 nm UVA with an irradiance of 3 $mWcm^{-2}$.
- Apply riboflavin every 5 min during the exposure

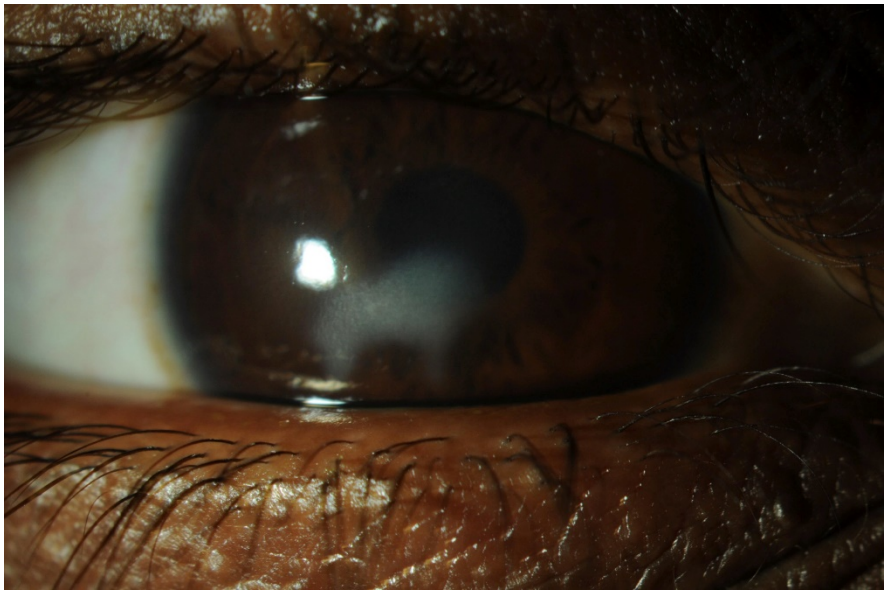
Avedro

- FDA Approved
- Dresden protocol
- Indications
  - Keratoconus
  - Post refractive surgery ectasia
  - Age 14 – 65
  - Documented progression in the past year
  - Pachymetry of 400 u or greater
- Contraindications
  - Pregnant or women who are breastfeeding

Contraindications

- Corneas thinner than 400 microns
- Prior herpetic infection is a contraindication because it may result in viral reactivation
- Concurrent infection
- Severe corneal scarring or opacification
- History of poor epithelial wound healing
- Severe ocular surface disease (ex. dry eye)
- Autoimmune disorders
- Rosacea

Complications



- Rare
- Delayed healing
- Sterile infiltrates
- Infection
- Corneal scarring
- Endothelial damage / corneal edema
- Progression of keratoconus

CXL can treat infections and cause infections..

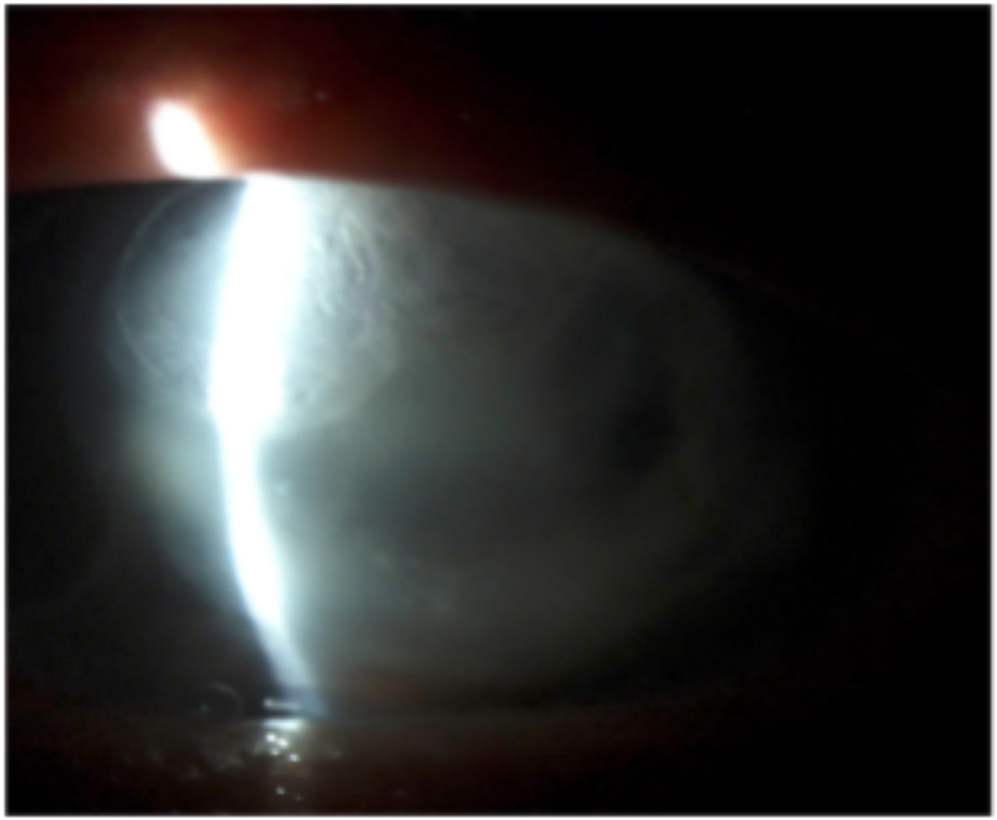


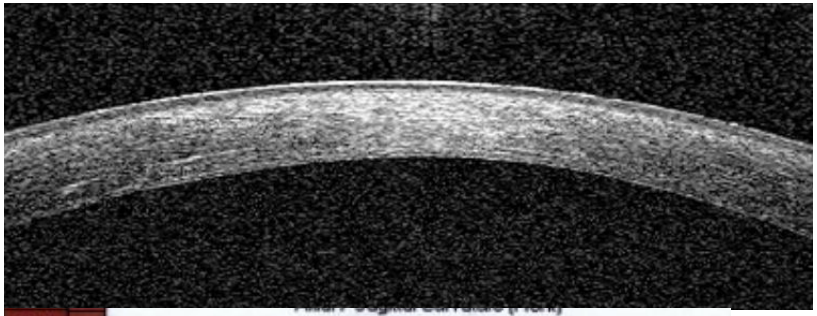
Fig. 2. Left eye of Case-1 showing area of perforation supported by the corneal glue and therapeutic bandage CL.

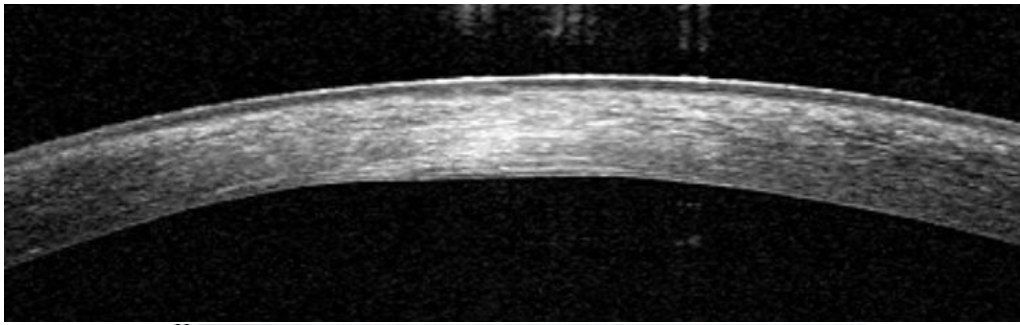
Rana M, Lau A, Aralikatti A, Shah S. Severe microbial keratitis and associated perforation after corneal crosslinking for keratoconus. Cont Lens Anterior Eye.2015 Apr;38(2):134-7.

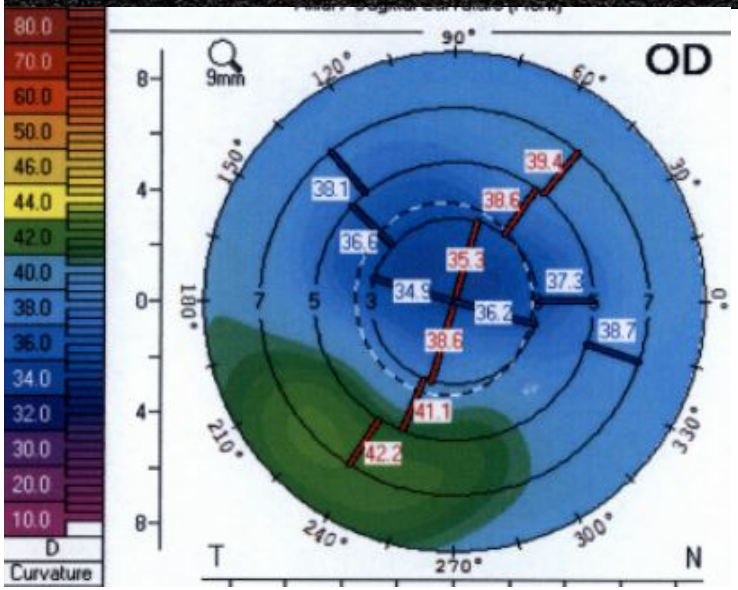
Results

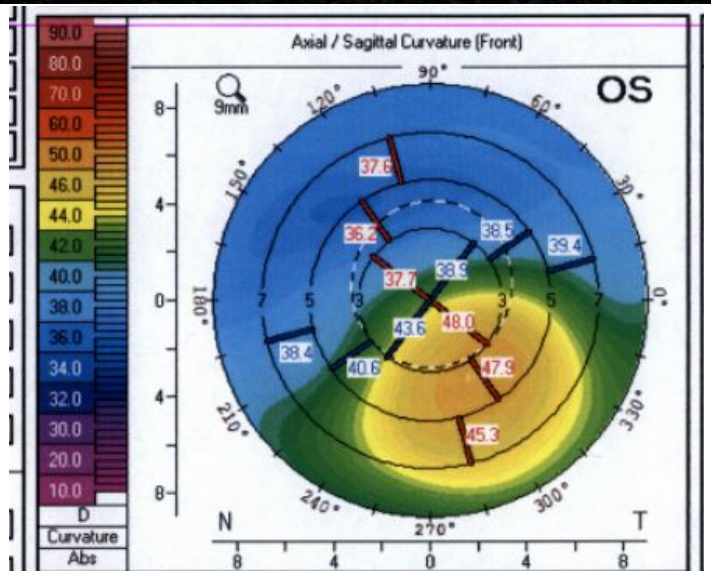
- Over 90% of all eyes in clinical trials show stability
- About half will show slight improvement
- Serious complications are rare(?)
- In rare cases where progression is found the treatment may be repeated

Ten-plus years s/p CXL
Severe flattening - 35 - 38D
Full thickness corneal haze
BDVA OD 20/80 OS 20/100









Problems with the Dresden CXL Procedure

- Takes forever!
- Post-op pain

Accelerated Crosslinking

- 30 mWcm^2 UVA source (Compared to 3)
- Reduced time
- Oxygen is necessary to produce free radicals
- Pulsed delivery
- Customized / variable systems

Cornea • Volume 38, Number 6, June 2019

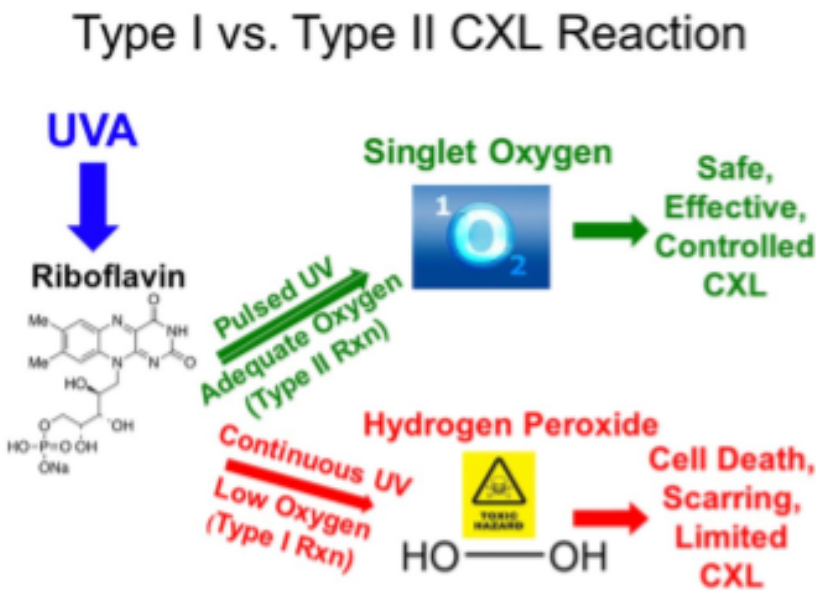
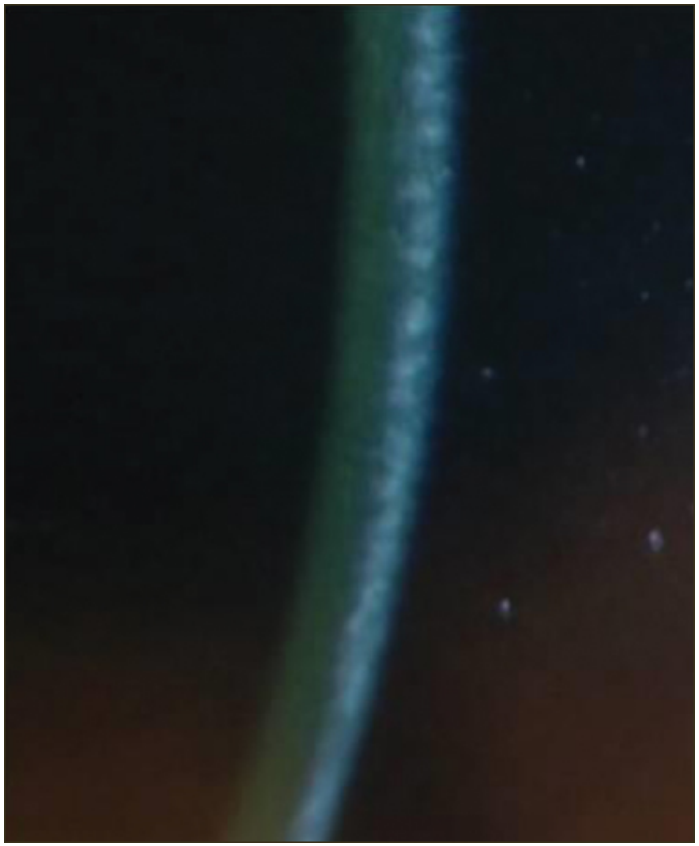


FIGURE 5. Schematic description of the 2 main types of CXL photochemical reactions. Type II is less toxic than type I.

Rubinfeld RS, Caruso C, Ostacolo C. Corneal Cross-Linking: The Science Beyond the Myths and Misconceptions. Cornea. 2019 Jun;38(6):780-790.

Epithelium ON CXL
Less Pain

- The epithelium is a barrier to riboflavin penetration
- Topical anesthetics to breakdown the epithelial barrier
- Prolonged riboflavin loading times
- Special riboflavin formulations



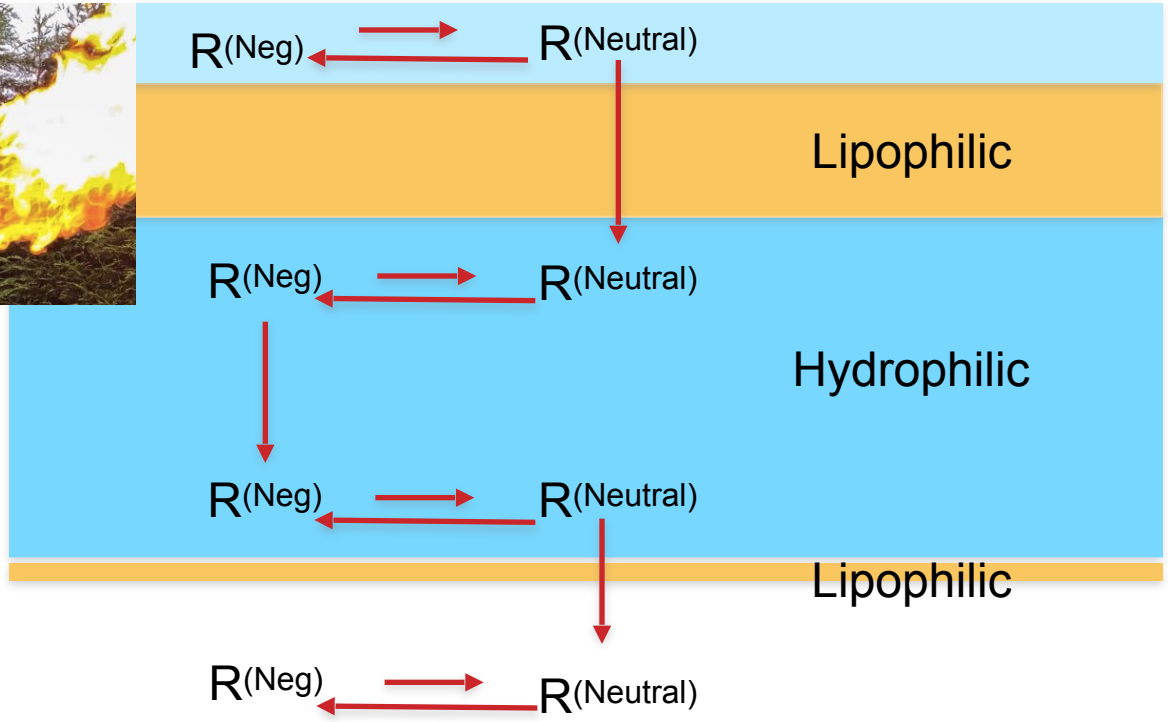
Epithelium ON CXL
Less Gain

- AJO 2015 RCT of Epi-On vs Epi-Off
  - 23% of epi-on showed KCN progression in the first year compared to **none** of the epi-off eyes
  - Epi-Off had increased surgical complications
- Eye and Contact Lens 2017
  - Pediatric population (12-18 years)
  - Epi-Off: Stable or improved – 94.4%
  - Epi-On: Stable or improved – 66.6%

Soeters N, Wisse RP, Godefrooij DA, Imhof SM, Tahzib NG. Transepithelial versus epithelium-off corneal cross-linking for the treatment of progressive keratoconus: a randomized controlled trial. Am J Ophthalmol. 2015 May;159(5):821-8.

Eraslan M, Toker E, Cerman E, Ozarslan D. Efficacy of Epithelium-Off and Epithelium-On Corneal Collagen Cross-Linking in Pediatric Keratoconus. Eye Contact Lens. 2017 May;43(3):155-161.

The Corneal Sandwich Dilemma



Tears

Epithelium

Stroma

Endothelium

Aqueous

Tetracaine

Benzalkonium chloride

Alcohol

EDTA

Quantitative analysis of corneal stromal riboflavin concentration without epithelial removal

Roy S. Rubinfeld, MD, MA, R. Doyle Stulting, MD, PhD, Glenwood G. Gum, MS, PhD, Jonathan H. Talamo, MD

Figure 1. Proprietary sterile delivery device before hydration.

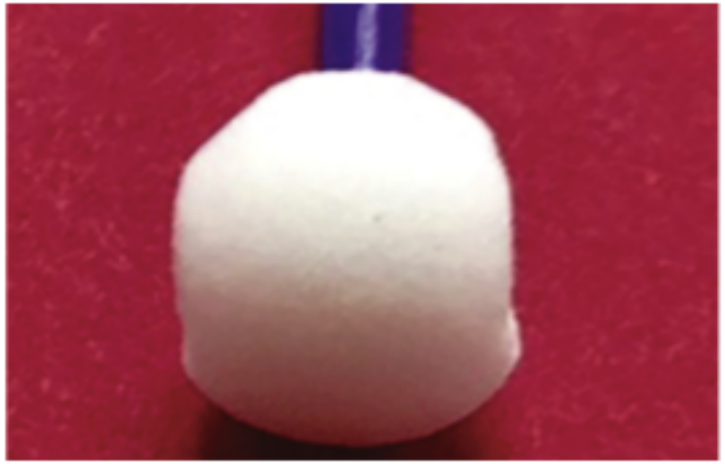


Figure 2. Proprietary device after hydration with no sharp edges to induce epithelial disruption.

Rubinfeld RS, Stulting RD, Gum GG, Talamo JH. Quantitative analysis of corneal stromal riboflavin concentration without epithelial removal. J Cataract Refract Surg. 2018 Feb;44(2):237-242.

Corneal crosslinking without epithelial removal

R. Doyle Stulting, MD, PhD, William B. Trattler, MD, Jonathan M. Woolfson, MD, Roy S. Rubinfeld, MD, MA

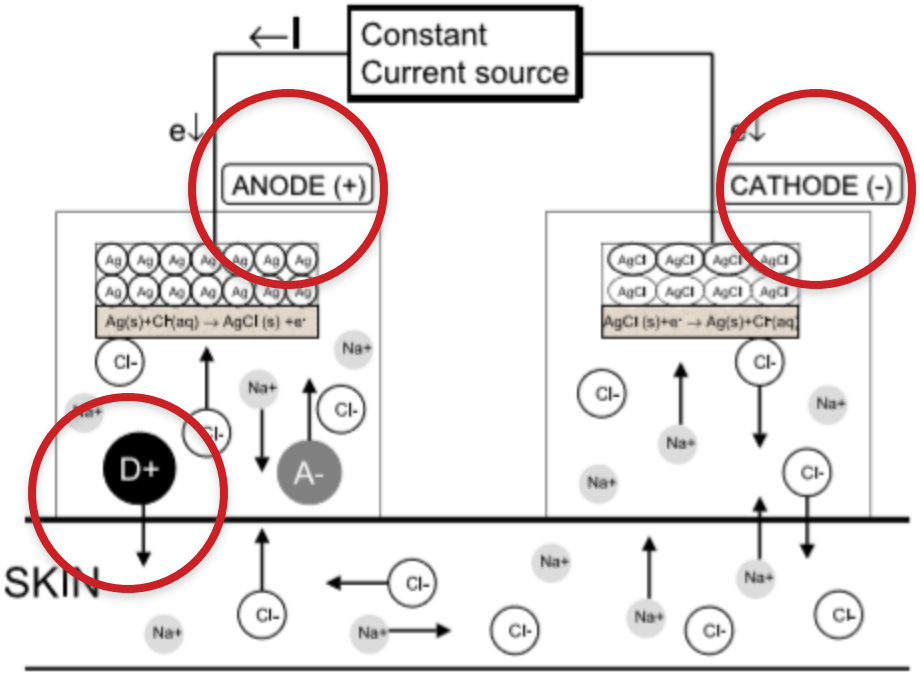
J Cataract Refract Surg 2018

- 512 eyes of 308 patients with keratoconus
- 80 eyes of 55 patients with Post LASIK ectasia
- Results:
- Vision Improved on average 1 to 1.5 lines at 1 and 2 yrs
- K_{max} decreased by 1/2D at 2 years
- No eyes progressed
- No eyes had sight threatening complications

Stulting RD, Trattler WB, Woolfson JM, Rubinfeld RS. Corneal crosslinking without epithelial removal. J Cataract Refract Surg. 2018 Nov;44(11):1363-1370.

Iontophoresis

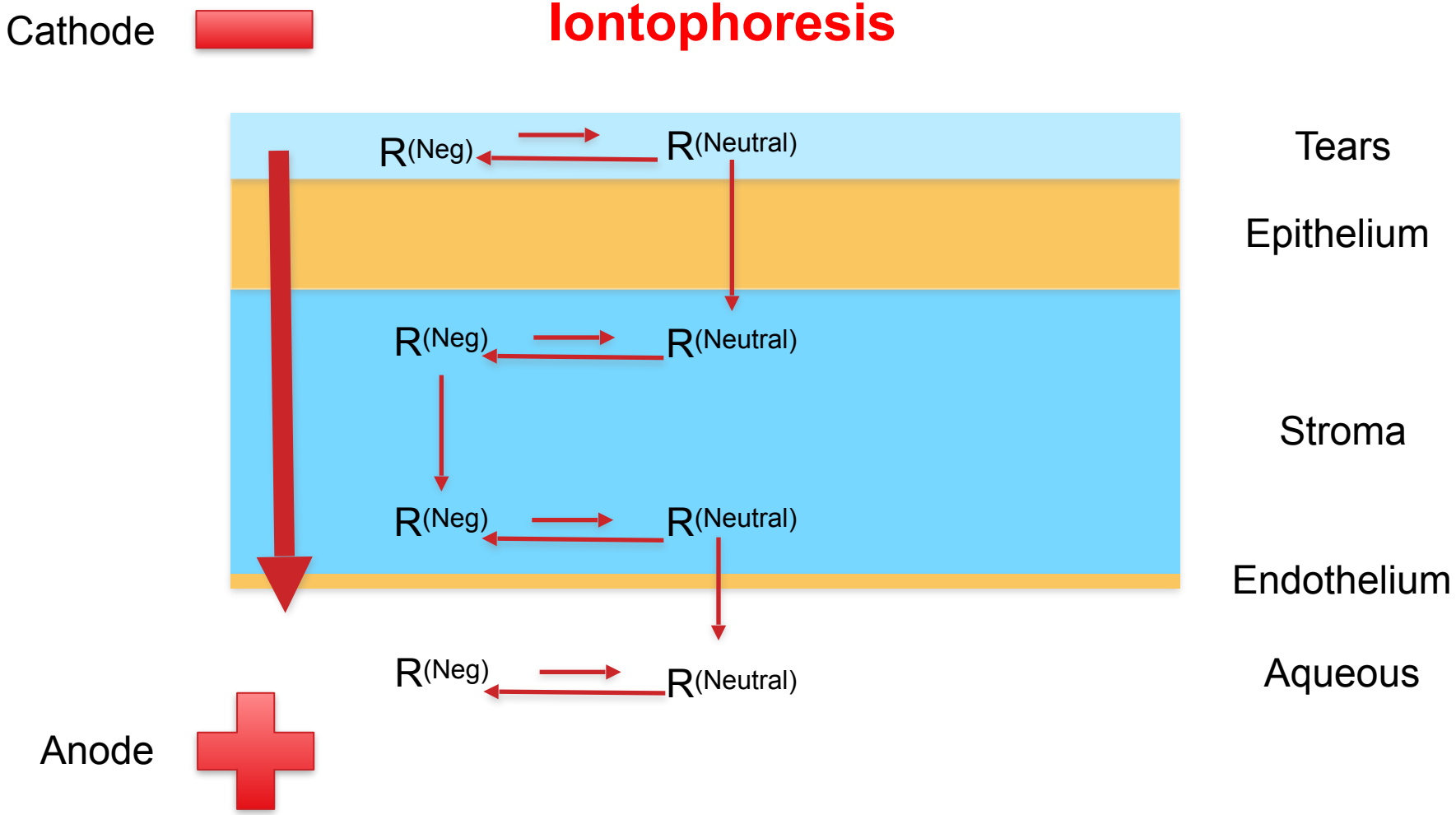
- Riboflavin is negatively charged and has low molecular weight



Kalia YN, Naik A, Garrison J, Guy RH. Iontophoretic drug delivery. Adv Drug Deliv Rev. 2004 Mar 27;56(5):619-58.

The Corneal Sandwich Dilemma

Iontophoresis



Conventional Corneal Collagen Cross-Linking Versus Transepithelial Diluted Alcohol and Iontophoresis-Assisted Corneal Cross-Linking in Progressive Keratoconus

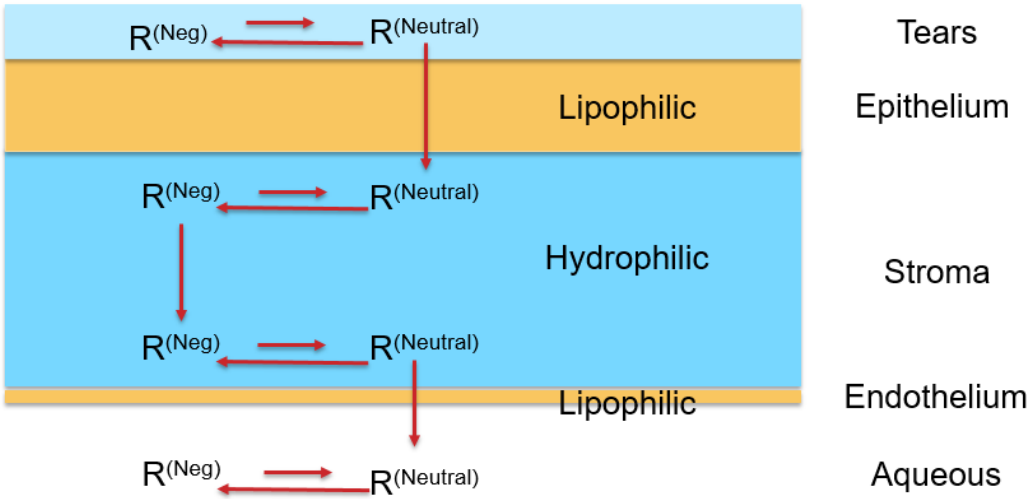
Kamil Bilgihan, MD, Nilufer Yesilirmak, MD,* Yesim Altay, MD,† Armagan Yuvarlak, MD,* and Huseyin Baran Ozdemir, MD**

FIGURE 1. A, Application of 10% alcohol solution for 10 seconds and position of the positive electrode. B, Negative electrode within a 9-mm barrel and filled 0.2% riboflavin solution. C, Penetration of riboflavin into the corneal stroma.

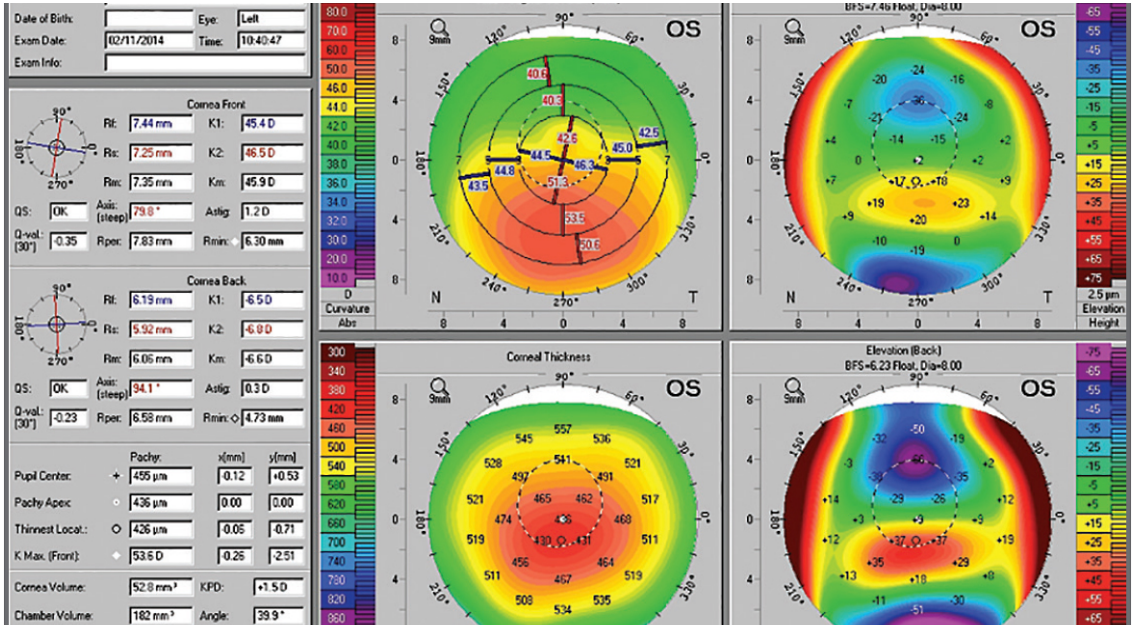
Bilgihan K, Yesilirmak N, Altay Y, Yuvarlak A, Ozdemir HB. Conventional Corneal Collagen Cross-Linking Versus Transepithelial Diluted Alcohol and Iontophoresis-Assisted Corneal Cross-Linking in Progressive Keratoconus. Cornea. 2017 Dec;36(12):1492-1497.

Other Agents / Delivery systems

- Iontophoresis
- Rose Bengal and Green Light
- Genipin
- Decorin
- Oral Riboflavin?

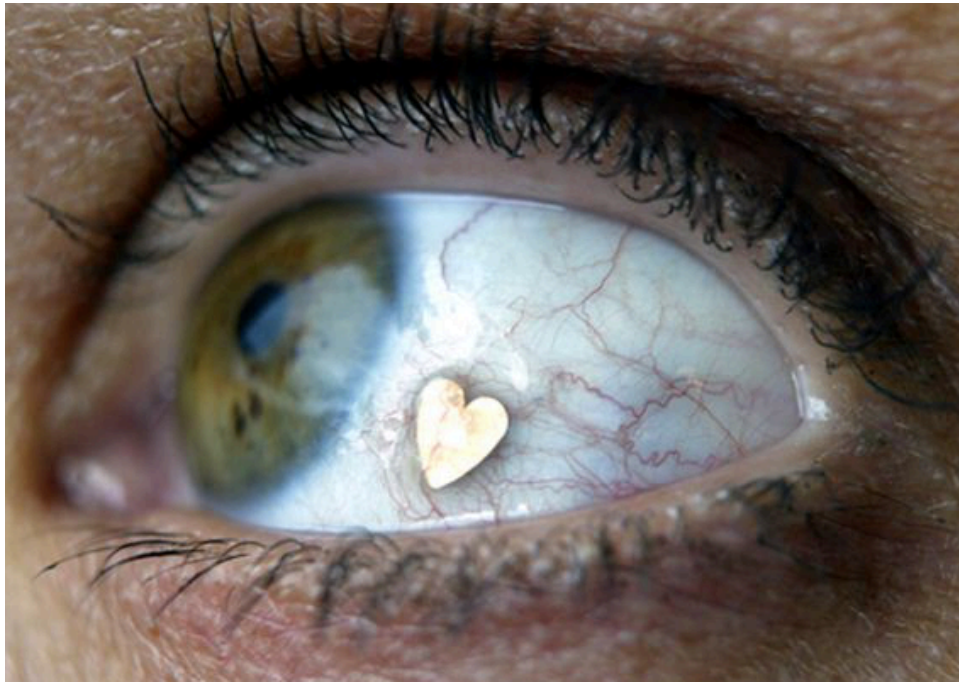


The problem with crosslinking....



Crosslinking PLUS
Crosslinking combined with…..

- **LASIK / SMILE**
- **PRK / PTK**
- **ICR**
- **Phakic IOL**



Accelerated CXL with LASIK

- After the laser ablation and while the flap remained open, a drop of riboflavin 0.1% solution was applied to the corneal bed within 1.5 minutes of ablation.
- The corneal flap is repositioned and allowed to adhere.
- The CXL device was used to apply UVA light within 3 minutes of flap closure for 3 minutes at a power of **30 mw/cm2** (total dose 5.4 j/cm2).
- At the end of the procedure, a bandage contact lens was placed

Celik HU, Alagöz N, Yildirim Y, Agca A, Marshall J, Demirok A, Yilmaz OF. Accelerated corneal crosslinking concurrent with laser in situ keratomileusis. J Cataract Refract Surg. 2012 Aug;38(8):1424-31.

Evaluation of the Effectiveness of Cross-Linking Combined With Photorefractive Keratectomy for Treatment of Keratoconus

Mohammed Iqbal, MD, Ahmed Elmassry, MD,† Ahmed Tawfik, MD,‡*
Mervat Elshabrawy Elgharieb, MD,§ Osama Mohiey El Deen Al Nahrawy, MD,§
Ashraf Hassan Soliman, MD,¶ Hisham A. Saad, MD, FRCS (Glasg),‖
*Hosam A. Ibrahim Elzembely, MD,** Ahmed Mohamed Saeed, MD,†† Osama Ali Mohammed, MD,**
Ahmed Gad Kamel, MD, and Islam Saad El Saman, MD**

Cornea 2018

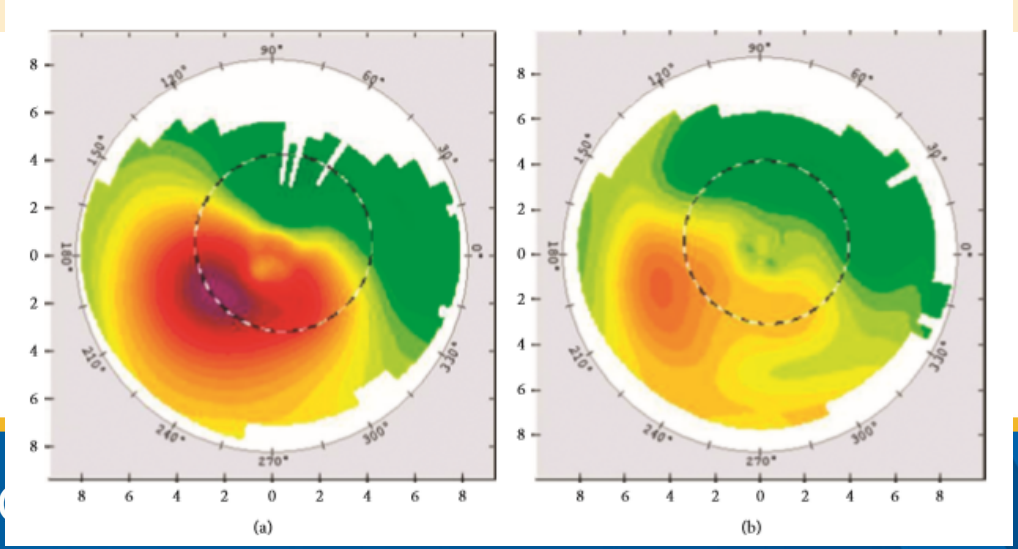
- Non-Topo-guided PRK
- Goal was to reduce up to 5 D of myopia /astigmatism and **leave 400 microns**
- Accelerated epi-off CXL
- **14% of eyes had delayed epithelial healing** of one week or longer and were associated with corneal haze
- **6.3% had progressive keratoconus**

Combined PTK / PRK / CXL for Post-LASIK ectasia

Zhou W, Wang H, Zhang X, Tian M, Cui C, Li X, Mu G. Management of Corneal Ectasia after LASIK with Phototherapeutic Keratectomy Combined with Photorefractive Keratectomy and Collagen Cross-Linking. J Ophthalmol. 2019 Feb 18;2019:2707826.

- PTK – 50 micron 8.5 mm zone (Wavelight EX 500 – Alcon)
- PRK – Topoguided – Irregular ast. and partial refractive Tx while staying within the corneal flap
- CXL – Dresden protocol

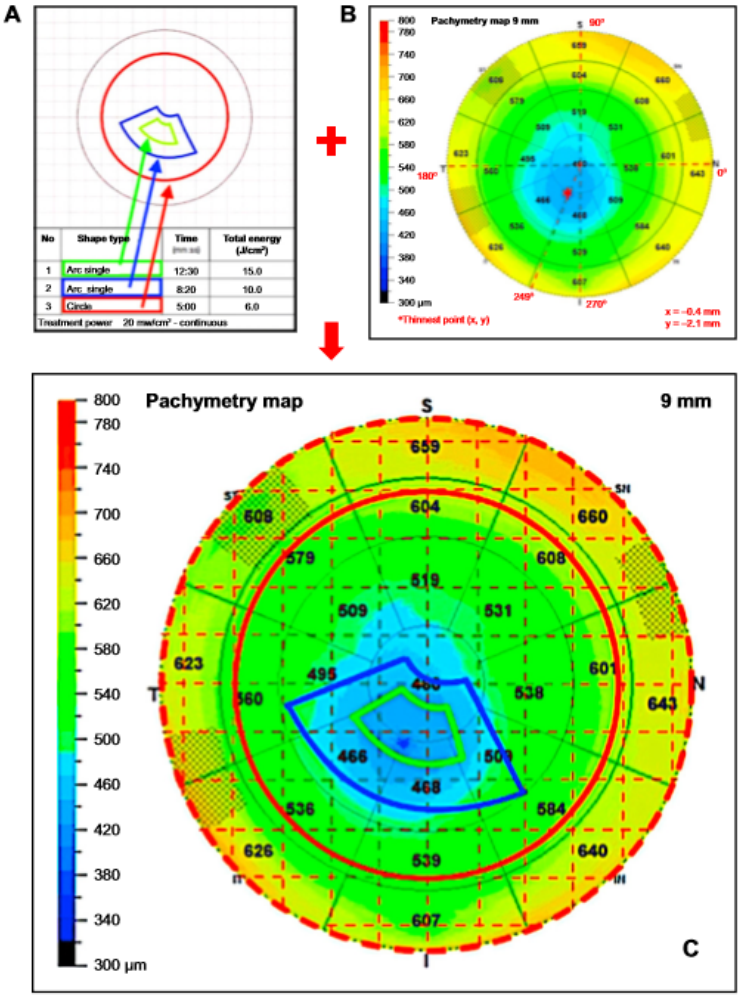
- Results -12 patients – Post op 24 months
- UDVA (mean) improved 20/150 to 20/60
- Steep K (mean) improved 45.675 to 42.612



Combined PRK / PTK /CXL Enhanced Athens protocol -2019

Kanellopoulos AJ. Management of progressive keratoconus with partial topography-guided PRK combined with refractive, customized CXL - a novel technique: the enhanced Athens protocol. *Clin Ophthalmol*. 2019;13:581–588.

- Topo-guided partial photorefractive keratectomy (Transepithelial PRK) for **max of 30 microns** of removal (Wavelight EX500 excimer laser – Alcon)
- 7 mm 50 micron PTK for epithelial removal
- **0.02% MMC for 20 sec**
- Roboflavin 0.1% for 5 min
- **UV 20 mW/cm2 variable pattern (KXL-II - Avedro)**



Kanellopoulos AJ. Management of progressive keratoconus with partial topography-guided PRK combined with refractive, customized CXL - a novel technique: the enhanced Athens protocol. *Clin Ophthalmol*. 2019;13:581–588.

Combined PRK / PTK /CXL
Enhanced Athens protocol -2019-
Results

Kanellopoulos AJ. Management of progressive keratoconus with partial topography-guided PRK combined with refractive, customized CXL - a novel technique: the enhanced Athens protocol. *Clin Ophthalmol*. 2019;13:581–588.

- 27 eyes - post op 36 – 42 months
- UDVA improved from 20/80 to 20/25
- Steepest corneal meridian decreased:
  - Mean 54.18 to 45.04
- 2 eyes with delayed epithelial closure (9 days)

Staged Approach

Document indications for CXL

Perform CXL

Document stability over 6 months

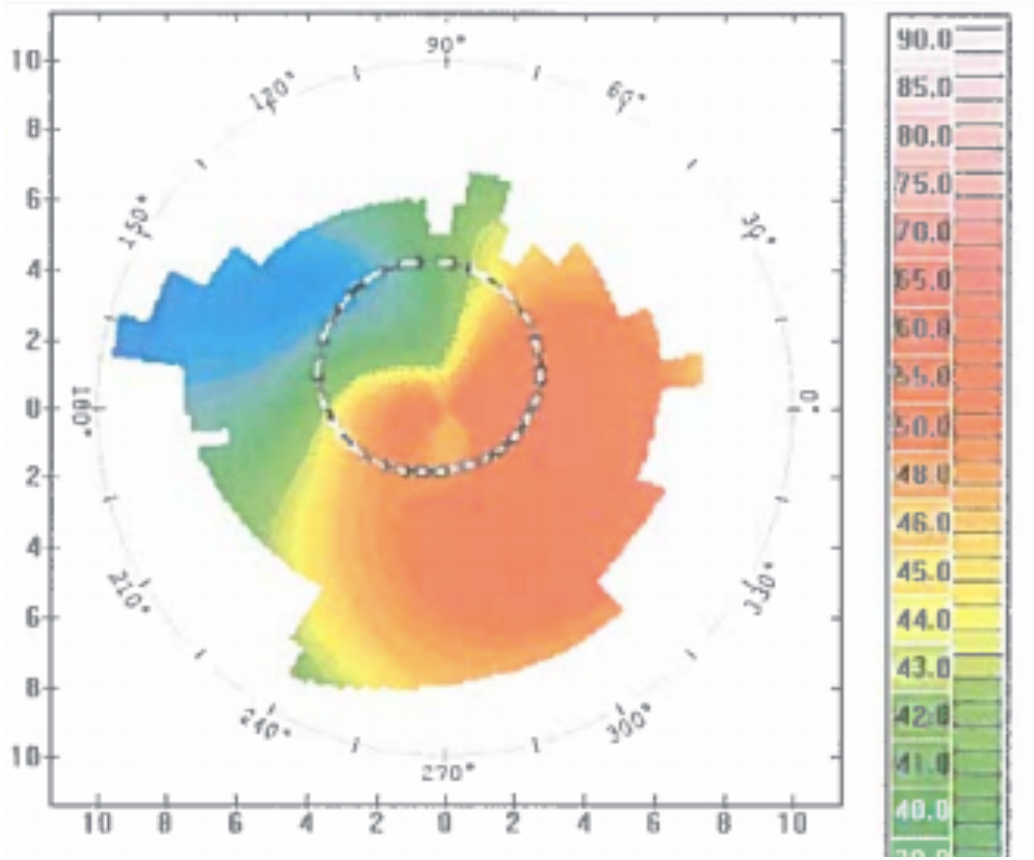
Trial of spectacle / CL correction

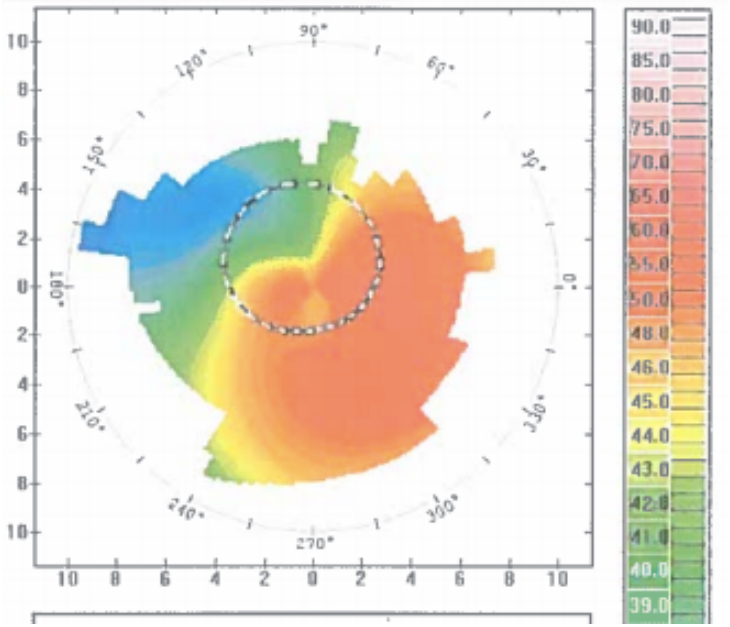
Topo-guided transepithelial PRK to:

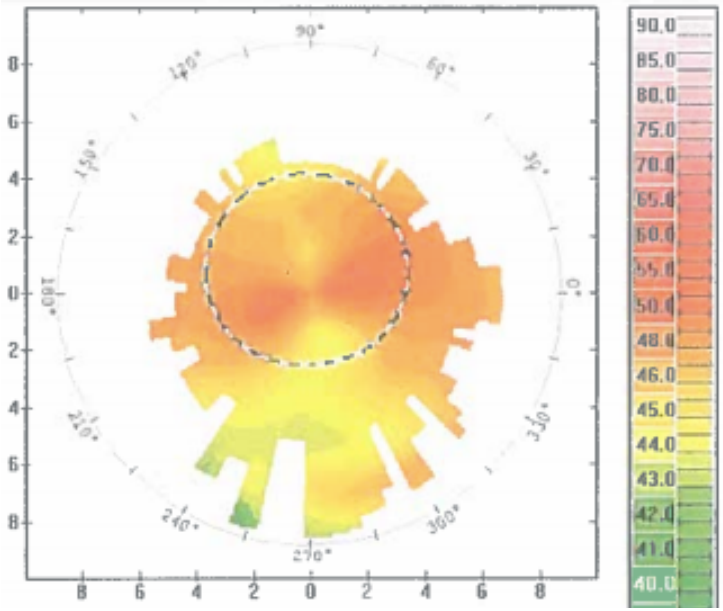
Reduce irregular astigmatism only

5 years s/p Epi-Off CXL for Post-Lasik Ectasia

Pre Op: -3.00 -3.75 X 135 20/50





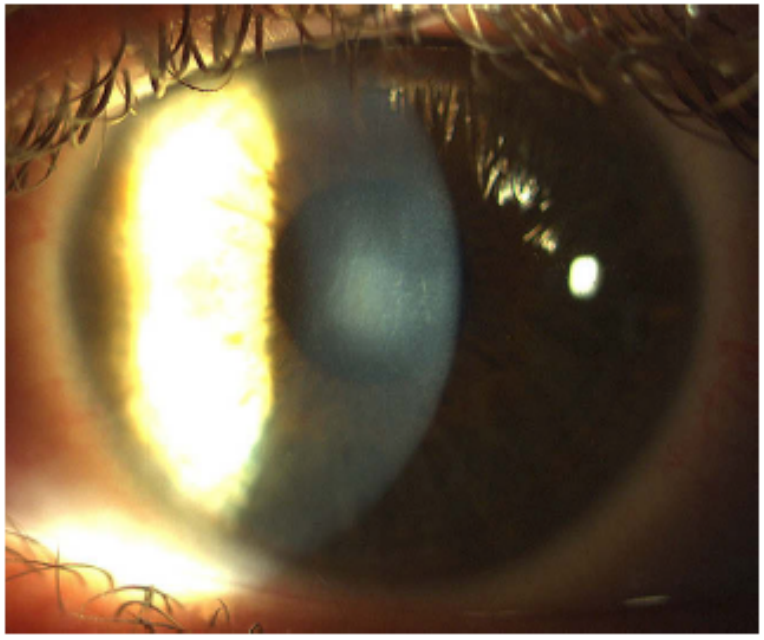


Pre Op: -3.00 -3.75 X 135 20/50

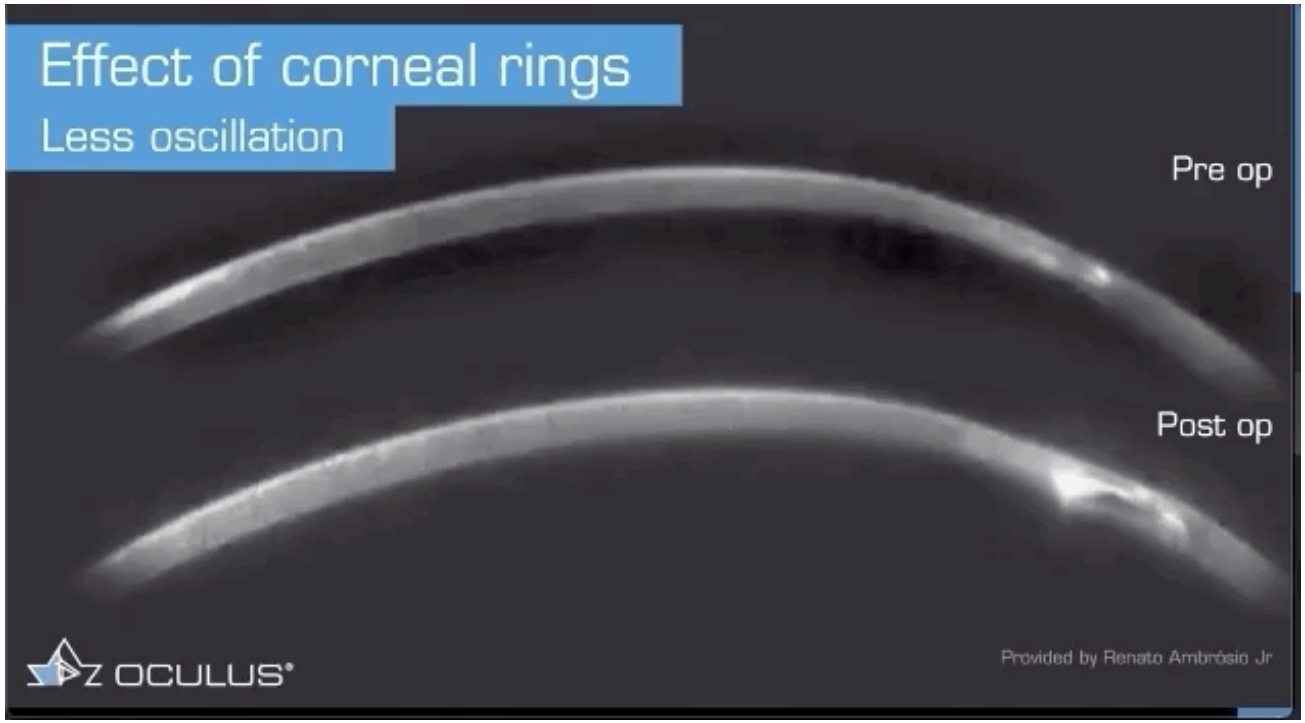
Post Op: +0.75 -2.00 X 120 20/25

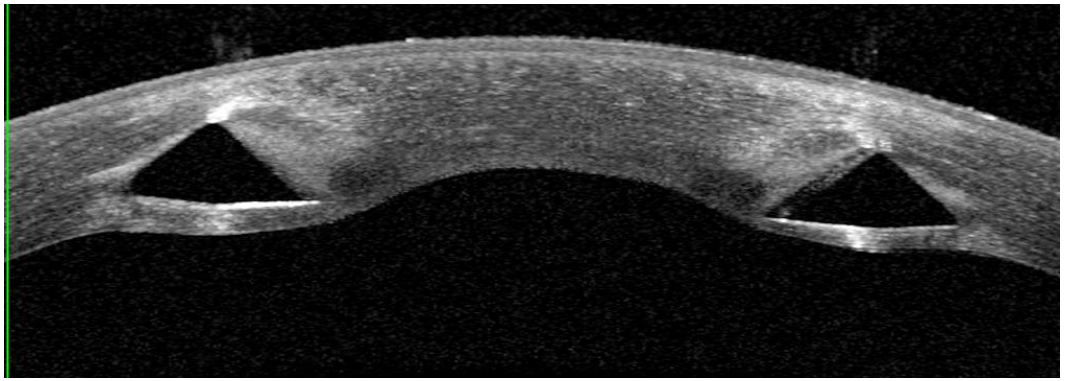
More surgery = increased risks

- **Guell et al,** J Refract Surg. 2014 Apr;30(4):286-8.
- **Late onset of a persistent, deep stromal scarring after PRK combined with corneal cross-linking in a patient with forme fruste keratoconus.**



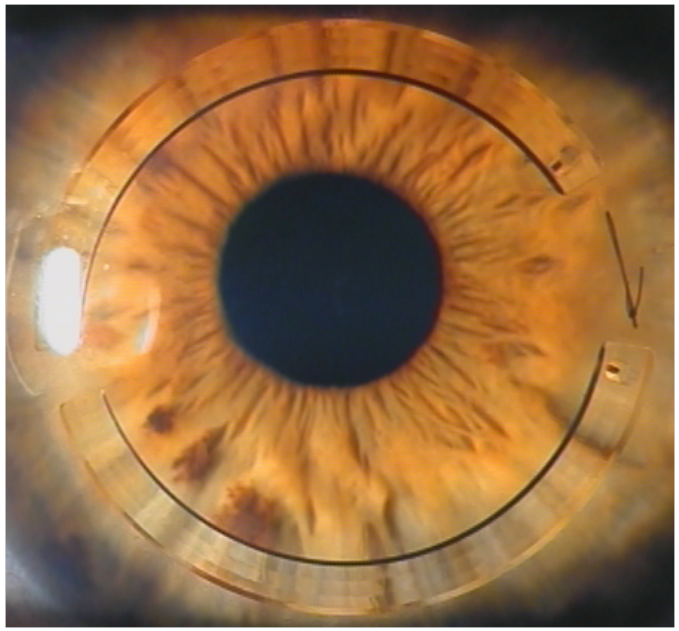
Intracorneal Rings





Intracorneal Ring Segments

- **Additive Procedure**
- **Avoids visual axis**
- **Timing**
- **ICR / CXL**
- **CXL > ICR**
- **ICR > CXL**



Appropriate Sequence of Combined Intracorneal Ring Implantation and Corneal Collagen Cross-Linking in Keratoconus: A Systematic Review and Meta-Analysis

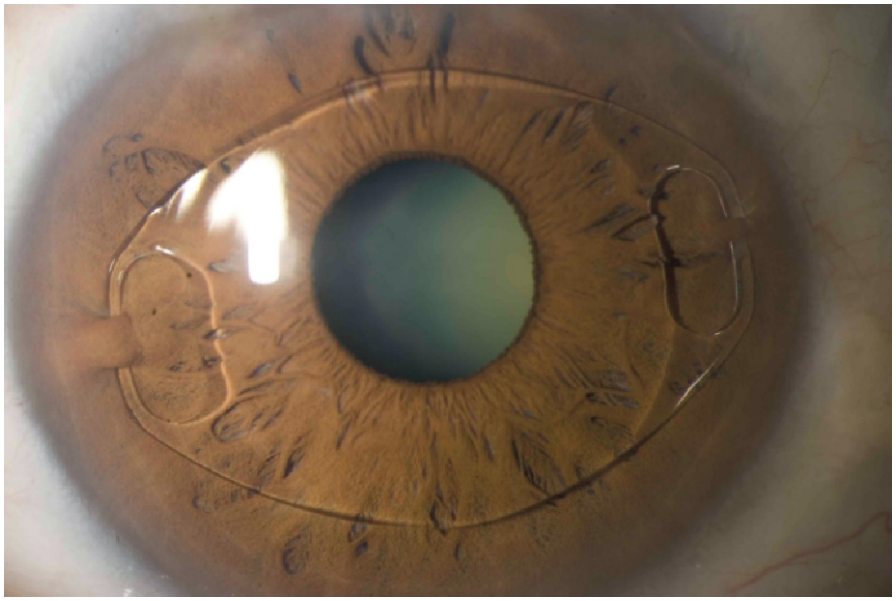
Hassan Hashemi, MD, Azam Alvani, MSc,† Mohammad A. Seyedian, MD,† Mehdi Yaseri, PhD,‡ Mehdi Khabazkhoob, PhD,§ and Hamed Esfandiari, MD¶*

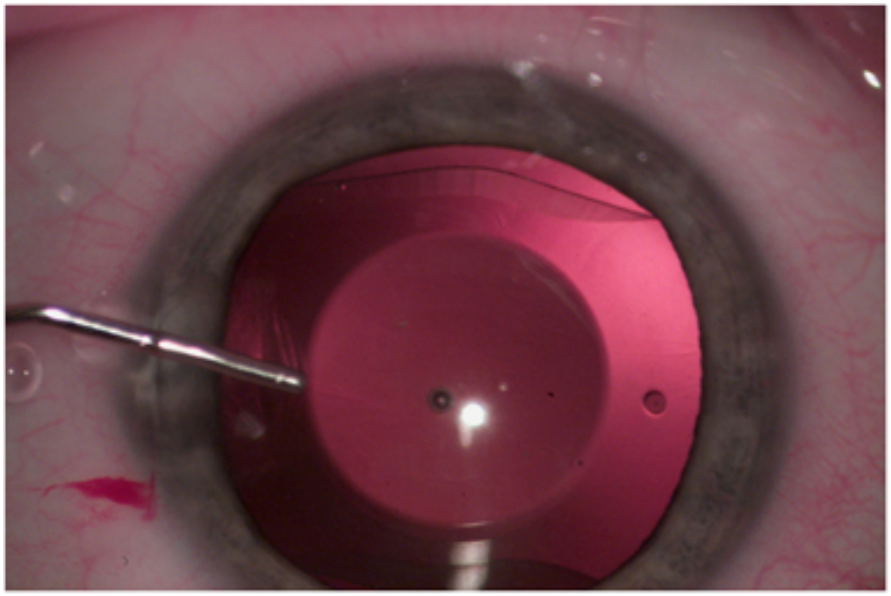
- No difference in terms of astigmatism and corrected VA
- Simultaneous procedures achieved superior corneal flattening and spherical correction

Hashemi H, Alvani A, Seyedian MA, Yaseri M, Khabazkhoob M, Esfandiari H. Appropriate Sequence of Combined Intracorneal Ring Implantation and Corneal Collagen Cross-Linking in Keratoconus: A Systematic Review and Meta-Analysis. Cornea. 2018 Dec;37(12):1601-1607.

Phakic IOL

- Myopia correction
- After CXL
- After Topo-guided PRK?





Summary

- CXL is effective and reasonably safe for progressive KCN or post-refractive ectasia
- Large-scale / long-term data is not yet available
- CXL alone
  - Epi OFF –FDA Approved Protocol
  - Epi ON
  - Accelerated CXL

Summary

- **Consider additional interventions either simultaneously or sequentially**
  - ICR
  - Topo Guided PRK
  - Phakic IOL
- **Keratoplasty / CL / Glasses still play a role**

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Thank You