CXL Experts' Meeting

Epi-on and epi-off applications

Koppen C MD, PhD
Antwerp, Belgium

Zurich, December 2nd 2016

No financial interest

Universiteit Antwerpen

UZA
kennis / ervaring / zorg

Transepithelial or epi-on CXL

Addresses the limitations and safety issues of epi-off CXL:

- No wound related complications

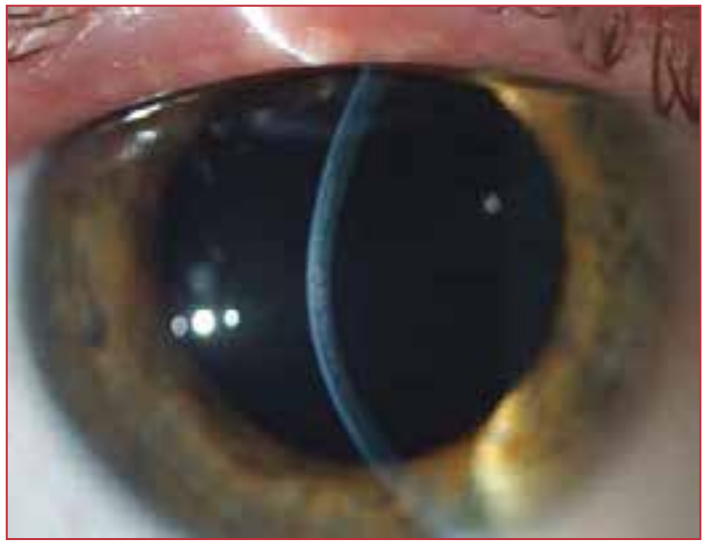


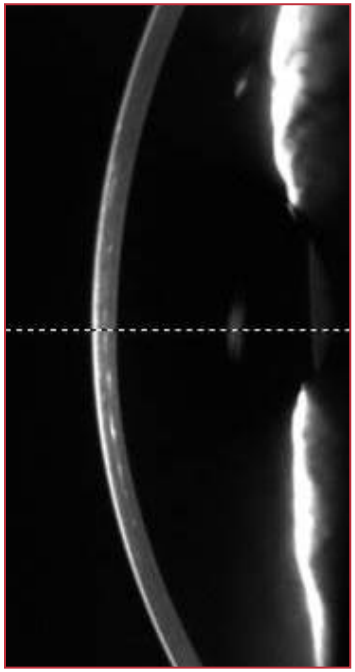

Koppen C, Vryghem J et al. Keratitis and corneal scarring after UVA/riboflavin cross-linking for keatoconus. J Refract Surg. 2009;25:S819-823.
Koppen C et al. Riboflavin/UVA cross-linking for keratoconus in Down syndrome. J Refract Surg. 2010;26:623-624.

Transepithelial or epi-on CXL

Addresses the limitations and safety issues of epi-off CXL:

- No wound related complications
- Less deep effect (demarcation line at ± 100 versus 300 µm)
  - *Less toxicity for the stroma and keratocytes (haze)*





Greenstein SA, et al. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. J Cataract Refract Surg 2010;36:2105-14.

Raiskup et al. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. J Refract Surg. 2009;25:S824-8.

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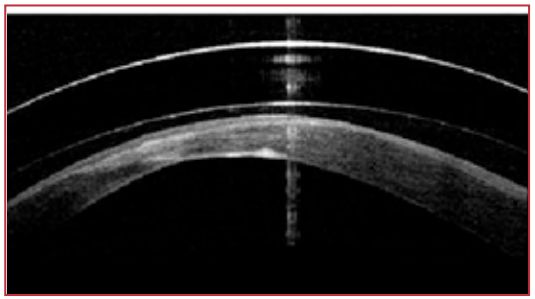
  - *Lower dosage at the level of the endothelium*
    - thin corneas < 400 µ stroma



    - thinning throughout the procedure 87 ± 40 µm 60-min CXL treatment

Holopainen et al. Transient corneal thinning in eyes undergoing corneal cross-linking. Am J Ophthalmol. 2011;152:533-6.

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  - *Down patients*
  - *Very young patients*

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- Shorter interruption of contact lens wear

Transepithelial or epi-on CXL

But what about efficacy?

1. Riboflavin is a large hydrophylic molecule that cannot penetrate through an intact epithelium

2. Intact epithelium blocks about 20% of UV rays

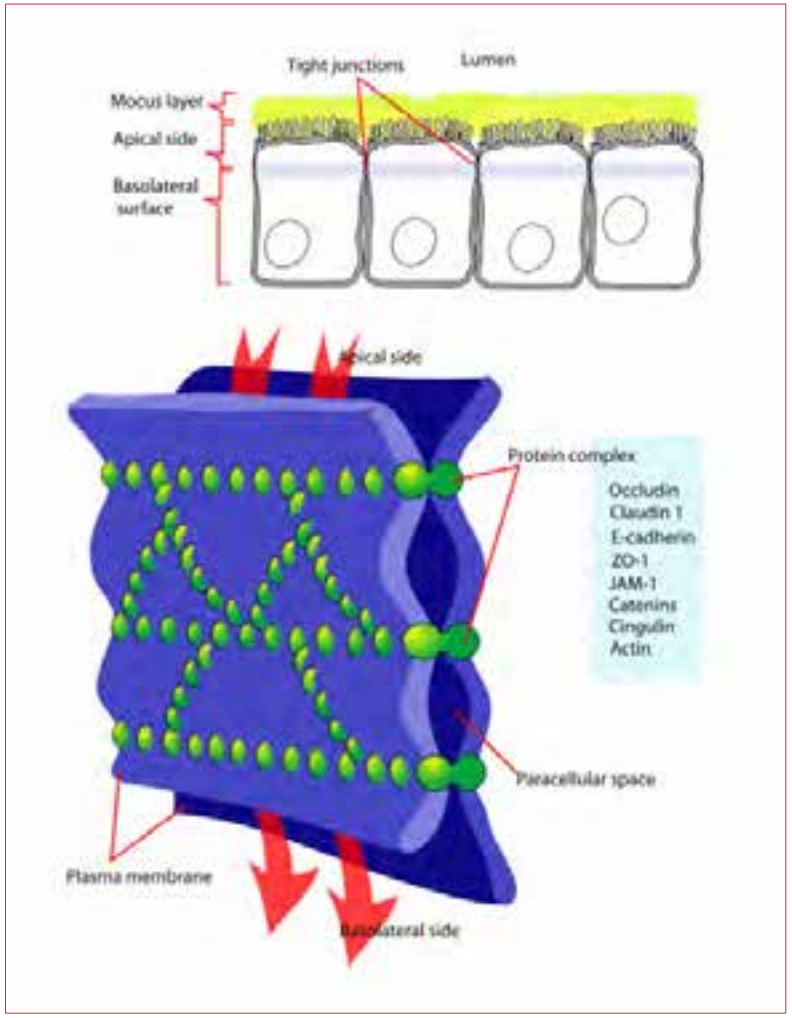


Image from:http://php.med.unsw.edu.au/cellbiology/index.php?title=2009_Lecture_8

TE CXL: Pharmacological modification of epithelial permeability

- *Wollensak et al have studied the TE CXL treatment in rabbits using the protocol proposed by Boxer Wachler and Pinelli:*
  - Pretreatment with Proparacaine 0.5% every 5' for 30' (BAC 0.005% preserved), followed by standard instillation of riboflavin in dextran 30' and UVA 365 nm 3mW/cm^2 30'
- Conclusions of this rabbit experiment:
  - *Biomechanical effect reduced by about 1/5 compared to standard CXL*: increase in rigidity 62% for TE-CXL versus 320% for standard CXL
  - *Cytotoxic damage restricted to anterior 200 µm stromal depth*

Pinelli R. Corneal collagen crosslinking: is it necessary to remove the epithelium? Journal of the intraocular implant and refractive surgery society, India. 2008;4:28-34
Wollensak G et al. Biomechanical and histological changes after corneal crosslinking with and without epithelial debridement. J Cataract Refract Surg. 2009;35:540-6.

Refractive and topographic results of BAC-assisted TE CXL

Prospective study[1] on 53 eyes of 38 patients stage I – III
Statistical analysis for a follow up of 18 months

- *Efficacy? Statistically significant changes?*
  - DCVA improved
  - majority of parameters including K max on EyeSys remained stable
  - K max on Pentacam and I-S value on Placido based topography deteriorated
- *Failures*: 7/53 eyes (13%) versus
  - standard CXL (own results): 2/27 eyes (7%)
  - epi-off CXL in the literature: 7.6%[2]
- Haze: none, *complications: none*

[1]*Koppen et al. Refractive and topographic results of benzalkonium chloride-assisted transepithelial crosslinking. J Cataract Refract Surg. 2012;38:1000-5.*
[2]*Koller et al. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg. 2009;35:1358-62.*

TE CXL with Ricrolin TE (Riboflavin 0.1%, trometamol and EDTA)

Efficacy?

- TE CXL appeared to halt progression, with a statistically significant improvement in visual and topographic parameters

...

- Functional results after TE CXL showed keratoconus instability, in particular in pediatric patients 18 y old and younger – 50% of pediatric patients were retreated with epi-off CXL after 12 months of follow-up
- This technique does not effectively halt keratoconus progression in children compared to standard CXL

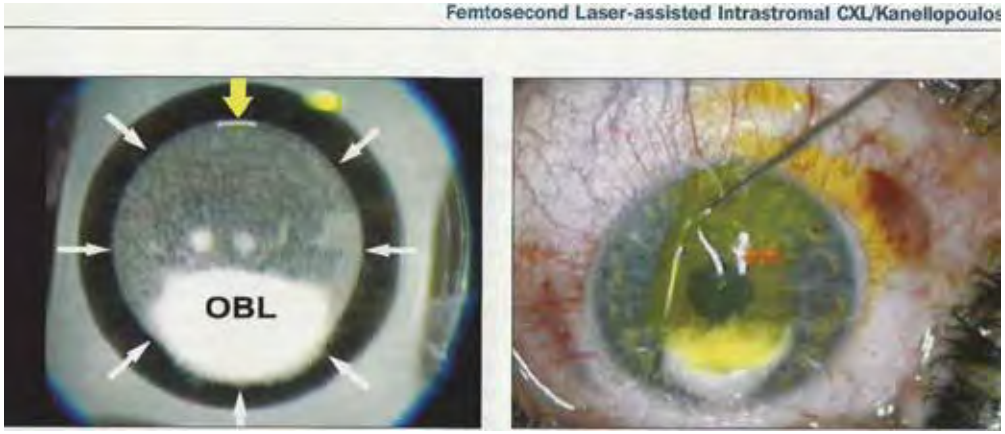
... basic research is lacking

Filippello et al. Traneptihelial corneal collagen crosslinking: bilateral study. J Cataract Refract Surg. 2012;38:283-91.
Caporossi et al. Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results. J Cataract Refract Surg. 2013;39:1157-63.
Buzzonetti et al. Tranepithelial crosslinking in pediatric patients: early results. J Refract Surg. 2013;28:763-7.

Other methods of TE CXL

Epithelial disruptor

Intrastromal pocket (femtolaser)



Rechichi et al. Epithelial-disruption collagen crosslinking for keratoconus: one-year results. J Cataract Refract Surg. 2013;39:1171-8.

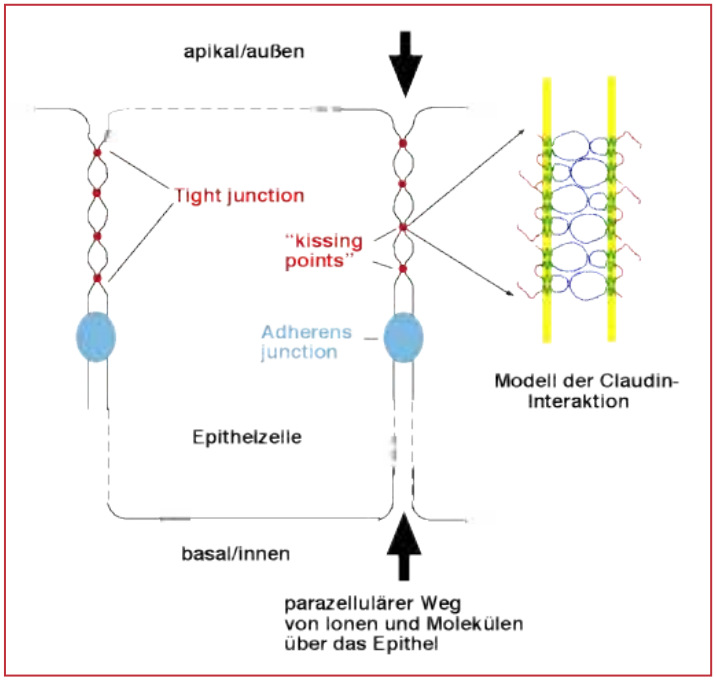
Wollensak et al. Biomechanical efficacy of collagen crosslinking in porcine cornea using a femtosecond laser pocket. Cornea. 2014;33:300-5.

TE CXL: research on pharmacological modification of epithelial permeability

- Animal experiments by Spoerl et al: TE CXL using riboflavin 0.1% in NaCl 0.44% with BAC 0.01% results in the same biomechanical effect as standard epi-off CXL

Structure of tight junctions is modified -> changes in paracellullar transport lead to increased permeability for riboflavin

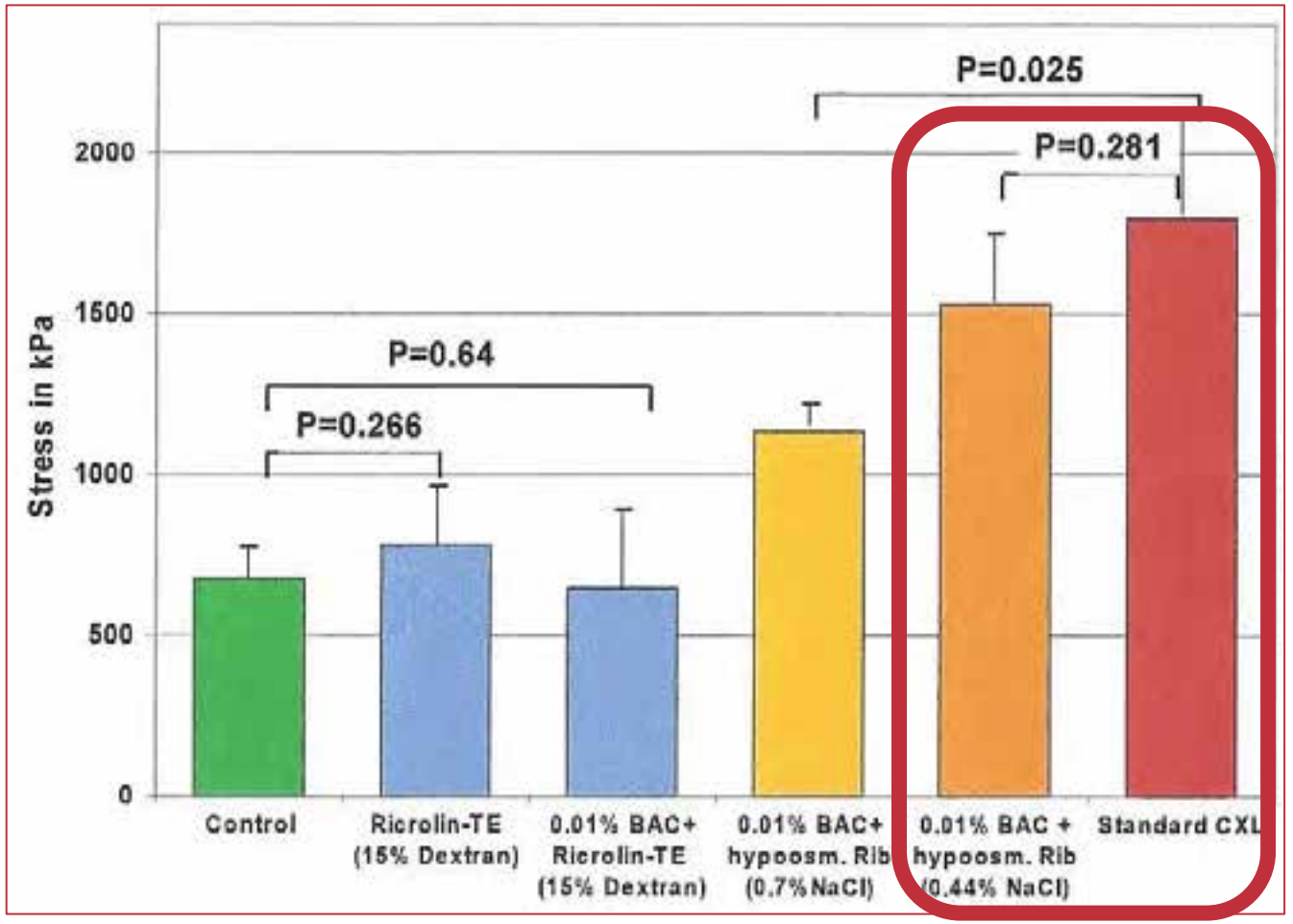
- Dextran ⬇ ribo transport
- NaCl 0.44% ⬆ ribo transport



Kissner et al. Pharmacological modification of the epithelial permeability by benzalkonium chloride in UVA/riboflavin corneal collagen cross-linking. Curr Eye Res. 2010;35:715-21.

Raiskup et al. Riboflavin osmolar modification for transepithelial corneal cross-linking. Curr Eye Res. 2012;37:234-38.

TE CXL: research on pharmacological modification of epithelial permeability



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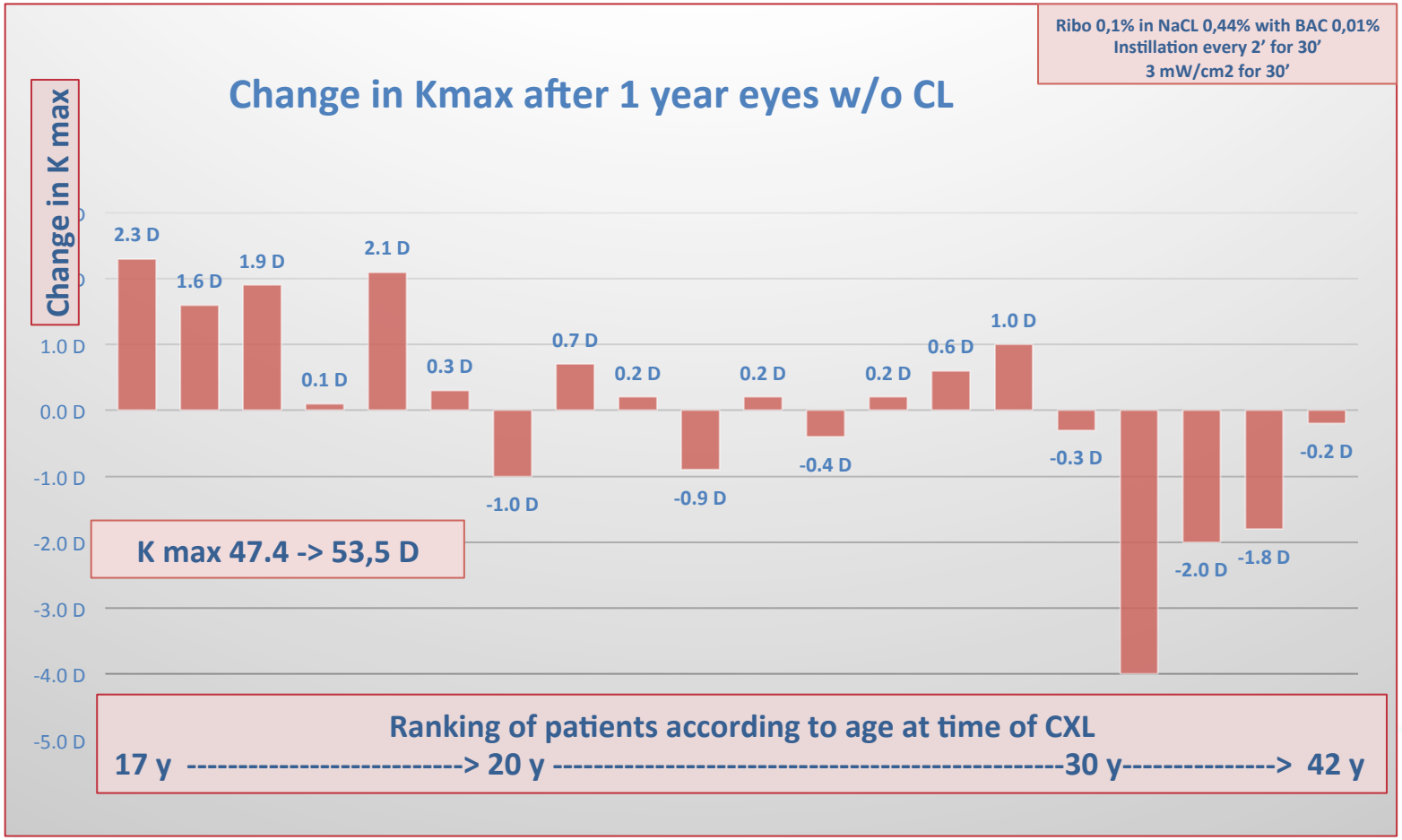
TE CXL with ribo 0,1% in NaCl 0,44% with BAC 0,01% (preliminary results)

- Prospective study on 20 eyes of 15 patients stage I - III

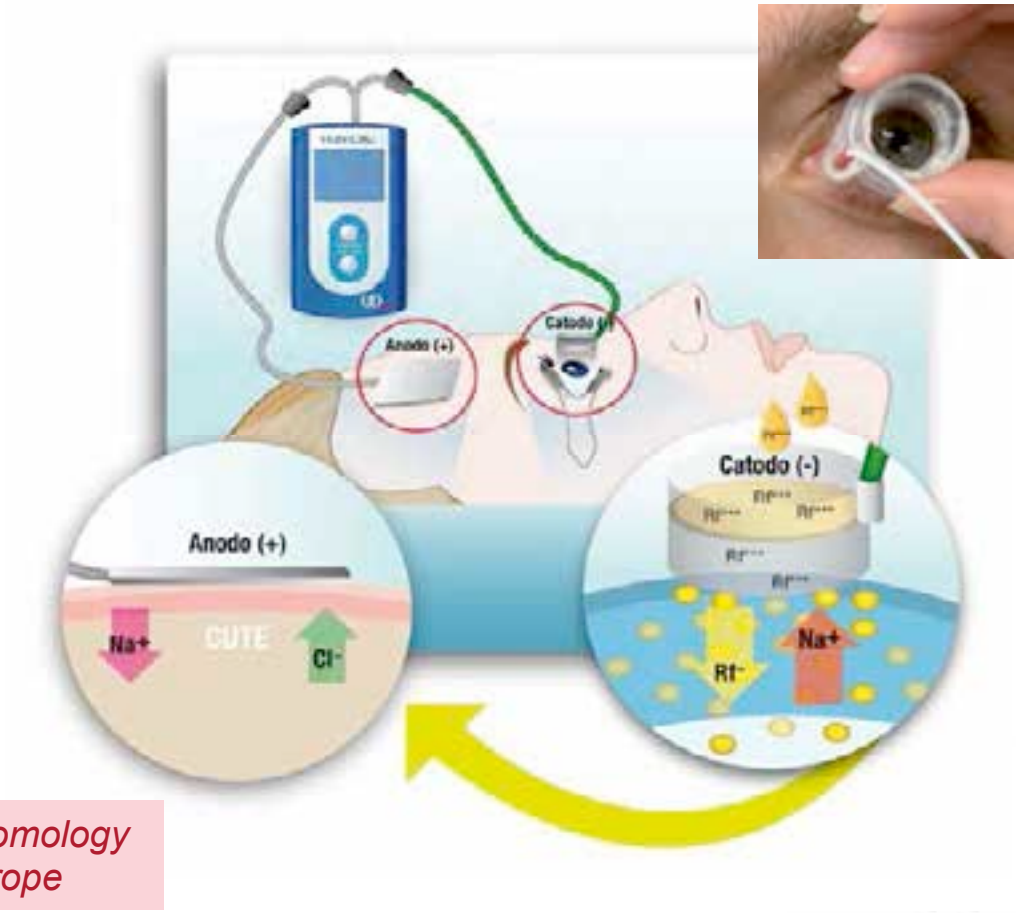


Koppen, unpublished results, 2014.

TE CXL iontophoresis: principle

Iontophoresis

- physical process in which ions flow in a medium driven by an electric field



2012 Ophthalomology Times Europe

TE CXL iontophoresis: stromal uptake

Iontophoresis

- *TE iontophoresis imbibition yielded greater and deeper riboflavin saturation with respect to conventional epi-on,.. but did not reach concentrations obtained with standard epi-off*

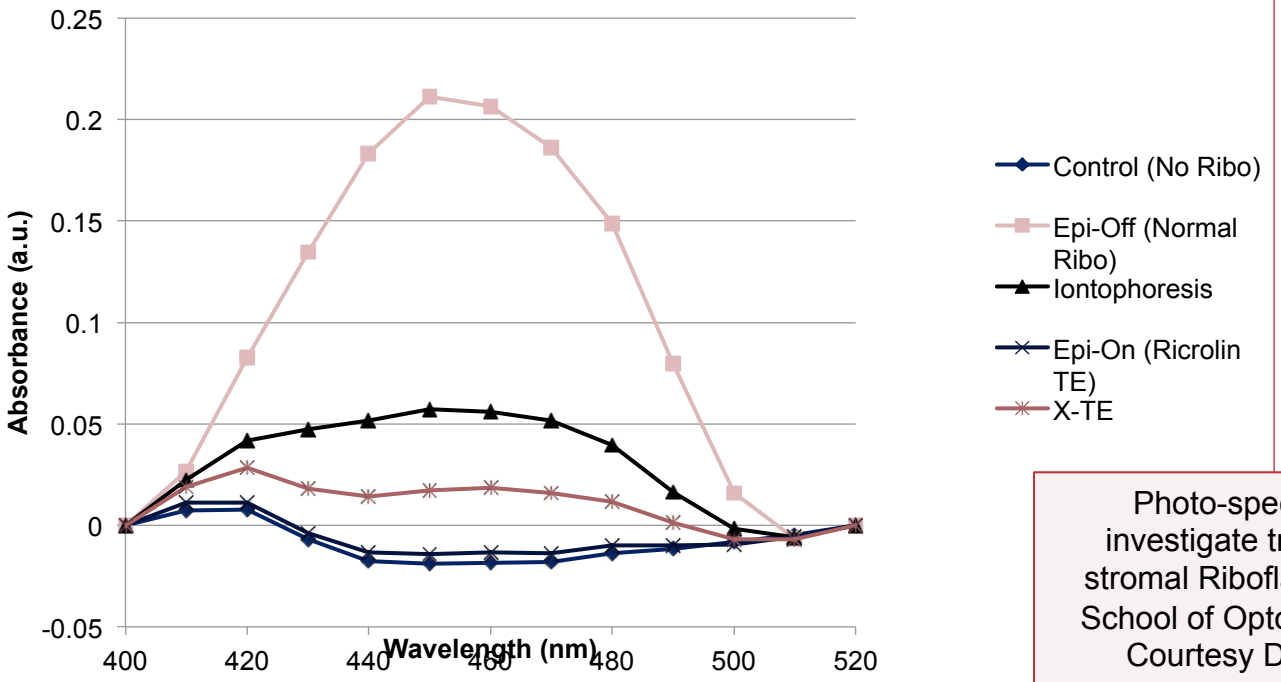


Photo-spectrometry to investigate trans-epithelial stromal Riboflavin absorption School of Optometry, Cardiff - Courtesy David O'Brart

Mastropasqua L et al. Corneal cross-linking: intrastromal riboflavin concentration in iontophoresis-assisted imbibition versus traditional and transepithelial techniques. Am J Ophthalmol. 2014;157:623-30.

TE CXL iontophoresis: CXL effect

Iontophoresis

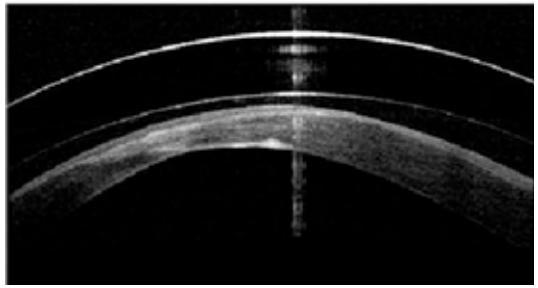
- Ex vivo biomechanical studies on rabbit and human cadaveric corneas showed an increase of the biomechanical resistance of human cornea comparable to that obtained with the standard epi-off crosslinking procedure
- Preliminary clinical results of iontophoresis assisted corneal CXL are promising: keratoconus progression is halted without significant complications

TE CXL: conclusions

Epi-on CXL is safer than the standard epi-off procedure

Efficacy, however, remains the weakness:

Dosage UVA irradiation



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Combination with accelerated CXL

Epithelial thickness profile

Oxygen

EVIDENCE-BASED CXL

Epi-on, higher UV power, shorter treatment tantalise, but only epi-off is proven. *Howard Larkin reports*

Despite many experiments with corneal crosslinking (CXL) technologies designed to preserve the epithelium and shorten the procedure, the traditional method involving epithelium removal and 30 minutes of 3mW/cm² ultraviolet radiation remains the only proven CXL treatment for keratoconus, Frederik Raiskup MD, PhD, FEBO told the XXXII Congress of the ESCRS in London.

Dr Raiskup noted some promising tests of various epi-on, high-power radiation and iontophoresis CXL approaches. But some early studies ar
long-term clinical st
safety and efficacy ar

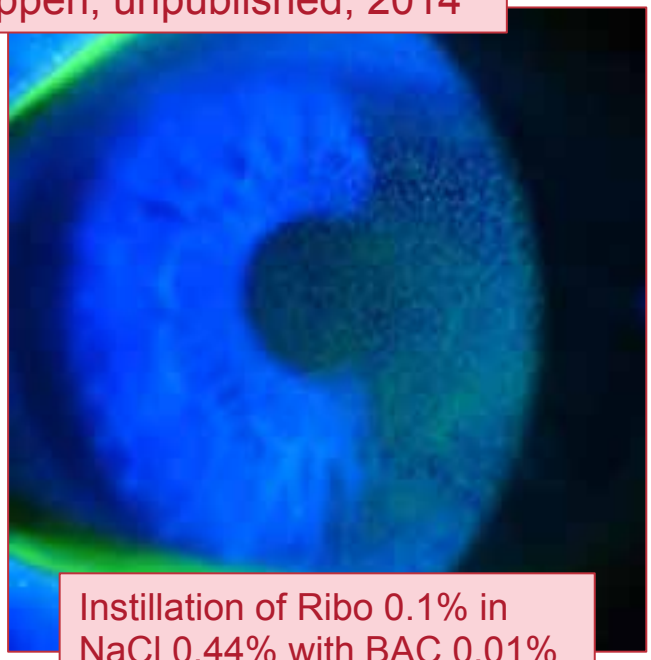
Cornea without epithelium soaked with riboflavin during CXL procedure

Courtesy of Frederik Raiskup MD, PhD, FEBO

TE CXL: enhancement of permeability versus preservation of integrity of the epithelium

- Standardization: exact composition of drops, method of application, duration of application,…

Koppen, unpublished, 2014



Instillation of Ribo 0.1% in NaCl 0.44% with BAC 0.01%

Gatzoufias et al, JRS 2016

Instillation of Ribo 0.25% with BAC 0.01%

- There is a thin line between epi-on and epi-off

Raiskup et al. Riboflavin osmolar modification for transepithelial corneal cross-linking. Curr Eye Res. 2012;37:234-38.