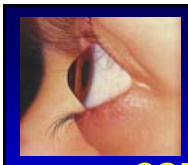
Clinica Oculistica
Dipartimento di Chirurgia e Medicina Traslazionale
Dir. Prof. S. Rizzo

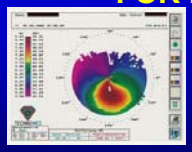
Azienda Ospedaliero Universitaria Careggi

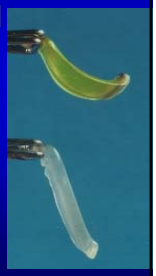
Cheratocono:
indicazioni al cross-linking ed alla chirurgia

Eleonora Favuzza



CORNEAL COLLAGEN CROSS LINKING FOR KERATOCONUS





WHY CAN CXL BE USEFUL IN KERATOCONIC CORNEA?

- Corneal stability decreases in keratoconus (Andreassen 1980, Meek 2005)
- In keratoconus corneal tensile strength is reduced by about 36%

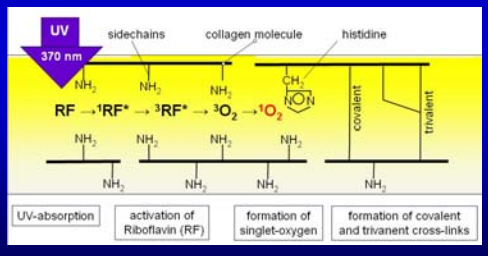
CORNEAL COLLAGEN CROSS LINKING

PHOTOPOLYMERIZATION PROCESS OF STROMAL FIBERS BY THE COMBINED ACTION

- **PHOTOSENSITIZING SOLUTION** (RIBOFLAVIN OR VITAMIN B2 0,1% in DEXTRAN 20%)
- **UVA** FROM A SOLID STATE UVA SOURCE

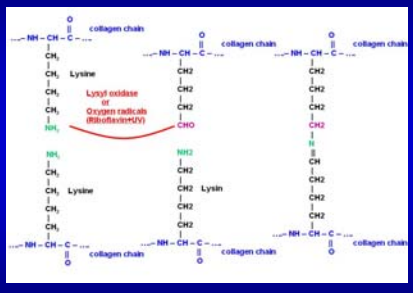
RIBOFLAVIN

- Absorption peak of UV-irradiation at 370 nm
- Photosensitizer is excited and generates reactive oxygen species (Singulet oxygen)
- The ROS can react with various molecules inducing chemical covalent bonds



Spoerl, 2011

BIOCHEMICAL REACTION
Oxidative Desamination

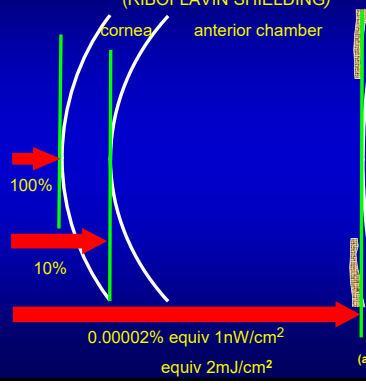


These chemical covalent bonds form bridges between amino groups of collagen fibrils (type II photochemical reaction)

RIBOFLAVIN (VIT. B2)

- Acts as a photo-sensitizing agent, inducing the production of reactive oxygen species
- It can absorb UV radiation, giving an effective eye structure protection

More than 90% of the UV-light is absorbed in the cornea but it is the riboflavin in anterior chamber that reduces the UV-intensity to a level that is a FACTOR OF 1000 SMALLER than the official safety level (RIBOFLAVIN SHIELDING)



(according to *Theo Seiler*)

COLLAGEN CROSS-LINKING FOR KERATOCONUS

- **WHAT REALLY HAPPENS?**

CXL: BIOMECHANICAL CHANGES

- Increase in mechanical rigidity (≈ 300%) in corneas after Riboflavin-UV induced XL

Gkika M, Int Ophthalmol 2011

CXL

Clinical & Experimental Ophthalmology

Clinical and Experimental Ophthalmology 2010; 38: 49–56 doi: 10.1111/j.1442-9071.2010.02207.x

Original Article

Effects of riboflavin/UVA corneal cross-linking on keratocytes and collagen fibres in human cornea

Rita Mencucci MD,[1] Mirca Marini PhD MD,[2] Iacopo Paladini MD,[1] Erica Sarchielli PhD,[2] Eleonora Sgambati PhD,[2] Ugo Menchini MD[1] and Gabriella B Vannelli PhD MD[2]

[1]Department of Oto-Neuro-Ophthalmological Surgical Sciences, Eye Clinic, [2]Department of Anatomy Histology and Forensic Medicine – University of Florence, Policlinic of Careggi, Florence, and [3]Department of Health Sciences, University of Molise, Campobasso, Italy

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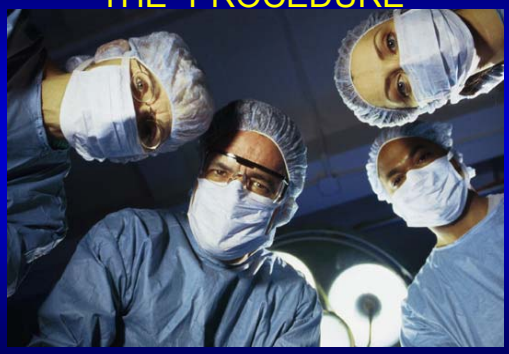
journal homepage: www.elsevier.de/acthis

Lectin binding in normal, keratoconus and cross-linked human corneas

Rita Mencucci[a], Mirca Marini[b], Gherardo Gheri[b], Debora Vichi[b], Erica Sarchielli[b], Laura Bonaccini[b], Stefano Ambrosini[b], Giorgia D. Zappoli Thyrion[c], Iacopo Paladini[a], Gabriella B. Vannelli[b], Eleonora Sgambati[d,*]

CXL: AS-OCT

THE “PROCEDURE”



PATIENT PREPARATION

- Instillation of a miotic agent (Pilocarpina 2%) at least 30 min before surgery
- Topical anesthesia (Lydocaine 4% drops 15 min before)

SURGICAL TIMING

- Epithelial removal (blunt spatula): 9 mm diameter
- Solution:RICROLIN
  (Riboflavin vitamin B2+0,1% - Dextrane 20%)
- Soaking time 15 -20 min without UV-A
- UVA Source: CBM X LINKER UVA 370 nm
- Exposure period of 6 times x 5 min

REMOVAL OF EPITHELIUM

Riboflavin(hydrophylic) does not penetrate through epithelium (hydrophobic)

Epithelium acts as UV-protector and absorbs some UV-energy

Indications for KC Progression per Published CXL Literature

TIME: within 1 year

- Topography
  Kmax. 1.00 D ++++
- Refraction
  Cyl. 1.00 D +++
  SEQ 0.50 D
- Contact lens change
  1 or 2 /year ++
- CCT decrease ? [5%] +
- History of subjective decrease of vision +

Prof. Joseph Frucht-Pery, 2011

Our CXL primary indications:

- Age: 10-40 years
- Clinical and instrumental progression (Refractive, topographic, Pachimetric, Aberrometric) in the last 6-12 months
- Thinnest point above 400µ
- No scarring

The Most Common Predictors for KC Progression

- poorer manifest refraction
- young age from 10 to 20 years

- rubbed eyes
- corneal scar
- not white race

Prof. Joseph Frucht-Pery, 2011

CXL Contraindications

- Thinnest point below 400 µ
- Central corneal opacity
- Undetectable KC progression in the last 12 months
- Age over 42 years (under investigation)

Contraindications in Literature

Ocular

- Ocular Surface Disease
  - severe dry eye
  - delayed epithelial healing
- Corneal HSK
- Endothelial disorders
- Infections

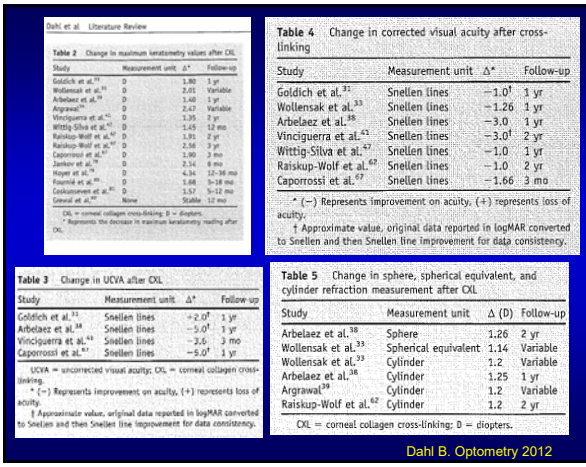
General

- Pregnancy (estrogens may decrease biomechanical stability)
- Connective Tissue Disease
- Concomitant Autoimmune Disease

Prof. Joseph Frucht-Pery, 2011

CXL Results at least 1 yr FU

- Kmax: reduction approx 1D
- BCVA: improvement approx 1 Snellen line
- UCVA: variable
- Refractive parameters (spherical equivalent, cylinder): variable changes, approx <2D



Dahl et al. Literature Review

Table 2 Change in maximum keratometry values after CXL

Study	Measurement unit	Δ*	Follow-up
Goldich et al.[31]	D	1.80	1 yr
Wollensak et al.[33]	D	2.01	Variable
Arbelaez et al.[38]	D	1.48	1 yr
Argrawal[39]	D	2.47	Variable
Vinciguerra et al.[41]	D	1.35	2 yr
Wittig-Silva et al.[42]	D	1.45	12 mo
Raiskup-Wolf et al.[62]	D	1.91	2 yr
Raiskup-Wolf et al.[63]	D	2.56	3 yr
Caporrossi et al.[67]	D	1.90	3 mo
Jankov et al.[78]	D	2.14	6 mo
Hoyer et al.[79]	D	4.34	12–36 mo
Fournié et al.[80]	D	1.68	9–18 mo
Caiskunonen et al.[81]	D	1.57	9–12 mo
Grewal et al.[82]	None	Stable	12 mo

CXL = corneal collagen cross-linking; D = diopters.
* Represents the decrease in maximum keratometry reading after CXL.

Table 4 Change in corrected visual acuity after cross-linking

Study	Measurement unit	Δ*	Follow-up
Goldich et al.[31]	Snellen lines	−1.0†	1 yr
Wollensak et al.[33]	Snellen lines	−1.26	1 yr
Arbelaez et al.[38]	Snellen lines	−3.0	1 yr
Vinciguerra et al.[41]	Snellen lines	−3.0†	2 yr
Wittig-Silva et al.[42]	Snellen lines	−1.0	1 yr
Raiskup-Wolf et al.[62]	Snellen lines	−1.0	2 yr
Caporrossi et al.[67]	Snellen lines	−1.66	3 mo

* (−) Represents improvement on acuity, (+) represents loss of acuity.
† Approximate value, original data reported in logMAR converted to Snellen and then Snellen line improvement for data consistency.

Table 3 Change in UCVA after CXL

Study	Measurement unit	Δ*	Follow-up
Goldich et al.[31]	Snellen lines	+2.0†	1 yr
Arbelaez et al.[38]	Snellen lines	−5.0†	1 yr
Vinciguerra et al.[41]	Snellen lines	−3.6	3 mo
Caporrossi et al.[67]	Snellen lines	−5.0†	1 yr

UCVA = uncorrected visual acuity; CXL = corneal collagen cross-linking.
* (−) Represents improvement on acuity, (+) represents loss of acuity.
† Approximate value, original data reported in logMAR converted to Snellen and then Snellen line improvement for data consistency.

Table 5 Change in sphere, spherical equivalent, and cylinder refraction measurement after CXL

Study	Measurement unit	Δ (D)	Follow-up
Arbelaez et al.[38]	Sphere	1.26	2 yr
Wollensak et al.[33]	Spherical equivalent	1.14	Variable
Wollensak et al.[33]	Cylinder	1.2	Variable
Arbelaez et al.[38]	Cylinder	1.25	1 yr
Argrawal[39]	Cylinder	1.2	Variable
Raiskup-Wolf et al.[62]	Cylinder	1.2	2 yr

CXL = corneal collagen cross-linking; D = diopters.

Dahl B. Optometry 2012

CXL: Treatment failure

KC progression following treatment: 7.6% after 1y

Risk factors:

- Corneal thickness below 400 microns
- Kmax over 58 D

Hovakiman, J Ophthalmol 2012
Dhawan , J Ophthalmol 2011
Koller, JCRS 2009

CXL Complications

- Infectious Keratitis (Case reports)
  - Bacterial
  - Acanthamoeba
  - Herpetic (UV exposure? Mechanical trauma? Corticosteroids?)
- Stromal haze
- Sterile infiltrates
- Delayed epithelial healing

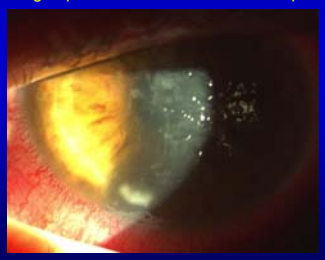
Hovakiman, J Ophthalmol 2012
Dhawan , J Ophthalmol 2011
Koller , JCRS 2009

CXL Complications

Sterile infiltrates: 7.6% (Koller 2011)

•Individual hypersensitivity reaction to Riboflavin or UVA

•SFC ag deposition in areas of static tear pooling



Hovakiman, J Ophthalmol 2012
Dhawan , J Ophthalmol 2011
Koller, 2011

TE CXL : NEW HOPE ?

► **intact epithelium** = barrier for riboflavin

Further possibilities

- Intrastromal application of riboflavin (Pockets)
- Injection of riboflavin into the stroma (microneedles)
- Epithel-Disruptor/scratches+Ricrolin-TE
- Iontophoresis
- Pharmacologic change of tight-junctions with
  - Benzalkoniumchloride, Chlorobutanol, EDTA

Spoerl 2011

Iontophoresis

Riboflavin is charged negatively.

Spoerl 2011

CXL & Iontophoresis

Its advantages over standard epi-off CXL are:

• the reduction of patient's discomfort

•lower risk of infectious keratitis

•the shortening of the treatment duration.

Iontophoresis-assisted CXL

- As this technique has been recently introduced, long-term follow up clinical studies are still lacking.
- From the first clinical reports (Vinciguerra et al., 2014b; Buzzonetti et al., 2015; Bikbova and Bikbov, 2016), with a limited follow up and functional parameter evaluation, ionto-CXL seems to reduce keratoconus progression, but with a lower efficacy than standard CXL.
- Moreover, previous experimental studies on human eye bank and rabbit corneas (Vinciguerra et al., 2014a; Mastropasqua et al., 2014a; Mencucci et al., 2015) found a greater and deeper riboflavin penetration after iontophoresis-assisted corneal imbibition than after TE-CXL, even if without reaching the concentration obtained after epithelial debridement.

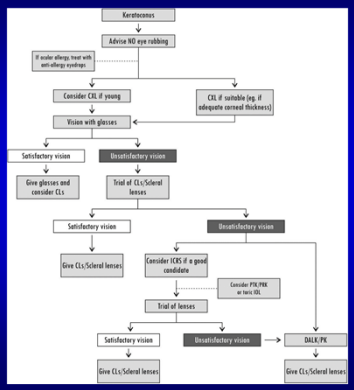
CONCLUDING REMARKS

- CXL is the only available treatment directed at the underlying pathology in keratoconic cornea
- CXL creates new covalent cross-links between collagen fibrils, thus stiffening and stabilizing the cornea
- It remains unclear whether the changes in cornea stability will be permanent or time limited
- The long term effects of standard and modified protocols should be reviewed with longer follow-up

STADIAZIONE DINAMICA

	Preclinico	1° Stadio	2° Stadio	3° Stadio	4° Stadio
Età		17 – 20 anni	17 – 20 anni	Variabile	Variabile
Visus		Es.: OD 10\10 naturale OS 8\10 nat 10\10 corr.	Es.: OD 10\10 –0.50 sf. OS 8\10 –0.50 sf = –1 cil.	OD 10\10 l.ac. OS 10\10 l.ac.	OD 7\10 l.ac. OS 3\10 l.ac.
Familiarità	+\– negativa				
Miopia\Astigmatismo		< 5 D	> 5 / <8 D	>8 / <10 D	Non misurabile
K Readings		< 48 D	< 51 D	> 53 D	> 55 D
Pachimetria		Normale	> 400 µ	200 / 400 µ	< 200 µ
RMS Coma Zywave µ	> 0.45/<0.81	> 0.70 / <1.02	>0.94 (eseguibile 50% casi)	Non eseguibile	Non eseguibile
Coma Corneal Wavefront µ	> 0.30/<0.70	> 0.55/< 1.28	> 0.89/< 2.72	> 1.94/< 3.56	> 3.12
µ Coma Cornea/ Astig. Topogr.	> 0.23//<0.42	> 0.41/< 0.72	> 0.65/< 0.94	> 0.79/< 1.14	> 1.03
µ Coma Cornea/ µ Astig. Aberrom.	> 0.2/<0.6	> 0.54/< 1.12	> 1.00/< 1.88	> 1.75/< 2.55	> 2.28
Microscopia Confocale		Cellule epiteliali allungate	Aumento spessore epitelio	Fibre collagene alterate	Opcaità ipermiflettenti
Cicatrici		No	Strie Vogt	Strie Vogt	Cicatrici
Soluzioni ottiche	Occhiali, lenti corneali anche usa e getta	Occhiali, lenti semirigide	Lenti corneali semirigide	Lenti corneali semirigide	
Soluzioni chirurgiche			Intacs, Epi, Lamellare	Lamellare, Perforante	Perforante
Informazione chirurgica	No	No	Generica	Orientamento chirurgico	Possibilità chirurgiche
Scelta chirurgica	No	No	No	Si\No Esigenze personali	Si
Controlli	6 mesi se età < 25 aa, 12 mesi in età > 25 aa	6 mesi età < 25, 1 anno età > 25	6 mesi età < 25 aa, 12 mesi età > 25 aa		

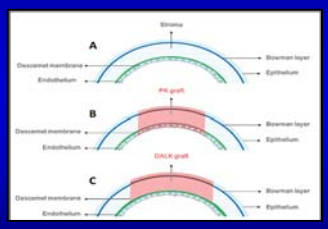
Keratoconus: management



Gomes JAP Global Consensus on Keratoconus and Ectatic Diseases, Cornea 2015;34:359–369

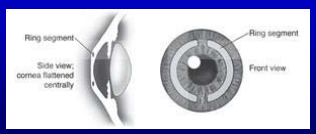
Keratoconus: surgical treatment

- ICRS (Intrastromal corneal ring segments); Keraring
- PK (Penetrating Keratoplasty)
- DALK (Deep Anterior Lamellar Keratoplasty)



ICRS

reduce the corneal steepening and astigmatism associated with keratoconus



IRCS: indications

– clear central cornea
– contact lens intolerance
– the cornea should be at least 450 µ thick at the insertion site

Shabayek MH, Alió JL : Intrastromal corneal ring segment implantation by femtosecond laser for keratoconus correction. Ophthalmology. 2007 Sep;114(9):1643-52
Piñero DP, Alio JL: Intracorneal ring segments in ectatic corneal disease - a review. Clin Experiment Ophthalmol. 2010 Mar;38(2):154-67

IRCS-Outcome

- Improvement of best spectacle corrected visual acuity (BSCVA) in >50% of cases.
- More studies are needed to delineate the aberrometric effects of ICRS
- Improved CL tolerance
- Do not halt keratoconus progression

Shabayek MH, Alió JL : Intrastromal corneal ring segment implantation by femtosecond laser for keratoconus correction. Ophthalmology. 2007 Sep;114(9):1643-52
Piñero DP, Alio JL: Intracorneal ring segments in ectatic corneal disease - a review. Clin Experiment Ophthalmol. 2010 Mar;38(2):154-67

IRCS-Outcome

- Implantation is reversible
- Complications (rare): segment decentration or extrusion, corneal haze, corneal neovascularization

Shabayek MH, Alió JL : Intrastromal corneal ring segment implantation by femtosecond laser for keratoconus correction. Ophthalmology. 2007 Sep;114(9):1643-52
Piñero DP, Alio JL: Intracorneal ring segments in ectatic corneal disease - a review. Clin Experiment Ophthalmol. 2010 Mar;38(2):154-67

Keratoconus: corneal transplantation

- Excellent postop visual acuity (20/25-20/20)

Despite anatomical clarity, the transplanted eye may be optically degraded due:

- Astigmatism (suture adjustment/removal, ~1 year follow-up)
- higher-order wavefront aberrations (++trefoil)
- Interface haze (DALK)

Tamaguchi T, Cornea 2015;34(Suppl):S128–S135

PK

Fig. 2 Slit-lamp image of a keratoconic eye after penetrating keratoplasty with a double continuous suture

Arnalich-Montiel *et al. Eye and Vision* (2016) 3:2

DALK vs PK

- DALK: retention of healthy recipient corneal endothelial cells
  - ➢ absence of corneal endothelial cell immune rejection
- ➢ DALK: higher resistance to trauma
- ➢ PK: open-sky procedure
- Similar postoperative visual outcome (especially with bared Descemet), but sometimes DALK<PK, even in presence of transparent graft
- DALK: more challenging for the surgeon

Tamaguchi T, Cornea 2015;34(Suppl):S128–S135