Epi-on Iontophoresis CXL latest clinical data

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HUMANITAS
CENTRO OCULISTICO

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UNIVERSITY

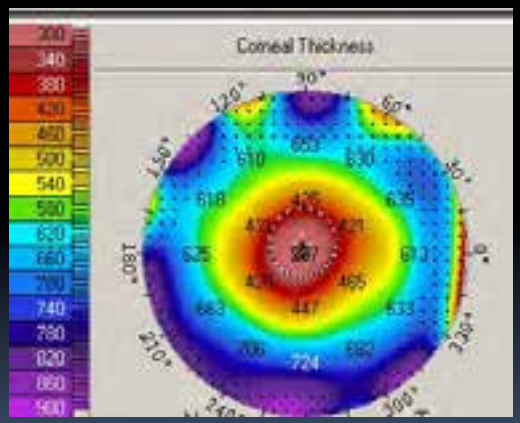
Financial interest

Consultant

Nidek, Oculus, Schwind,

Epi Off→CONS

- Pain
- Risk of Infections

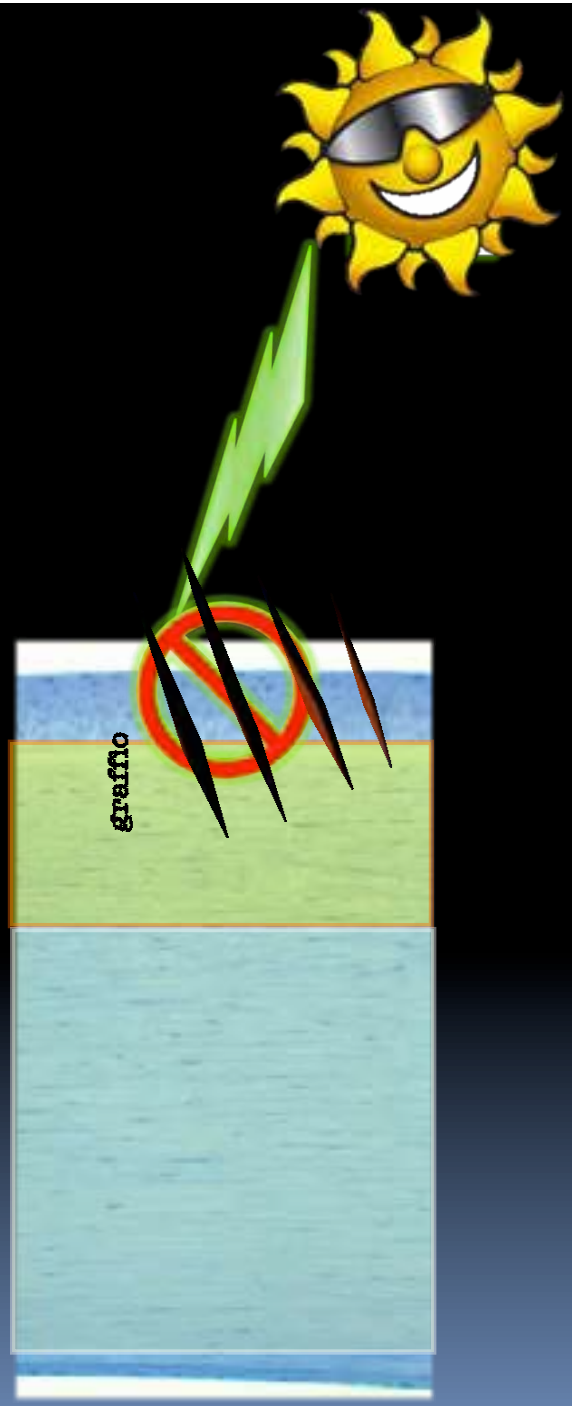


- Slow visual acuity recovery
- Problems with thin corneas(swelling solutions)

Vinciguerra et al Ophthalmology (2013)

Epithelium and CXL (1)

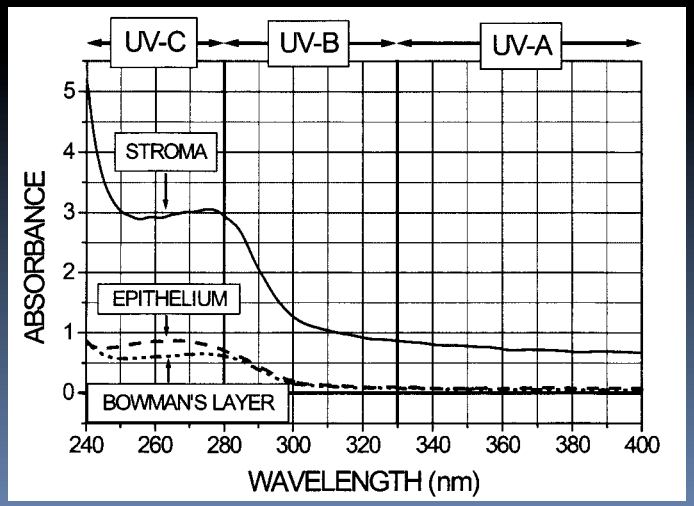
- Epithelium with riboflavin 85% UV[1]
- Epi-on with scratch provides good impregnation and results[2]
- Reduced efficacy (1/5) if epi-on [3]
- Epi induces increase of Max Stress e Young's modulus of 35.9% e 15.4% more than epi-on[4]



1) Baiocchi et al. J Cataract Refract Surg (2009)
2) Alhamad et al J Cataract Refract Surg (2012)
3) Wollensak et al. J Cataract Refract Surg (2009
4) Tao et al. Biomed Res Int (2013)

Epithelium and UV (2)

- Kolazsvari et al: Epithelium blocks only UV wavelenght < 300 nm[1] !!!
- Bottos et al: epithelium reduces CXL principally because of the reduced impregnation with riboflavin



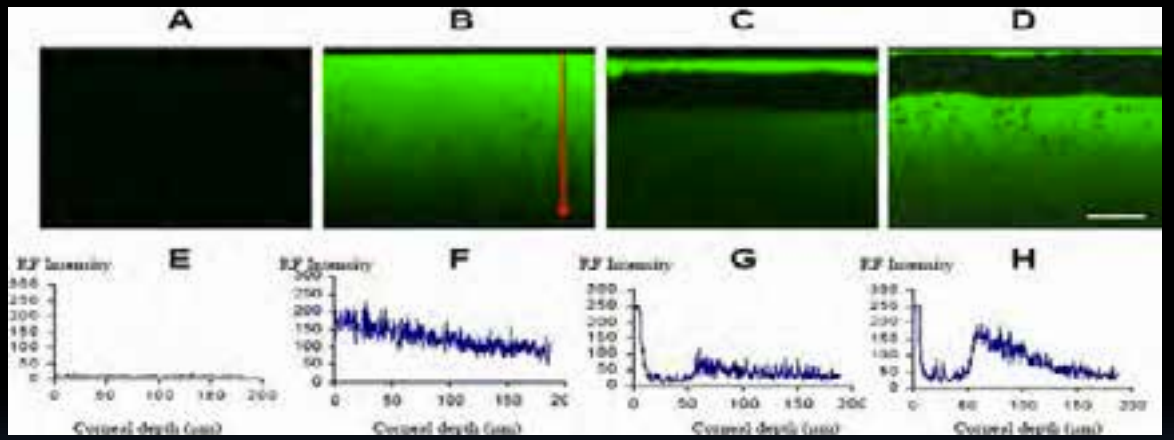
1)Kolozsvári L et al . Invest Ophthalmol Vis Sci. 2002
2) Bottós et al. Arq Bras Oftalmol (2011)

CXL and epithelium (3)

- Zhang et al

Epithelial cells are not enriched with riboflavin

IOVS 2012



What makes CXL unpredictable? The obtained concentration of riboflavin in to the cornea

- Poor riboflavin concentration leads to:
  - Corneal opacity
  - Superficial demarcation line
  - Weak biomechanical outcomes
  - Weaker refractive improvement
  - Unsafe corneal stability

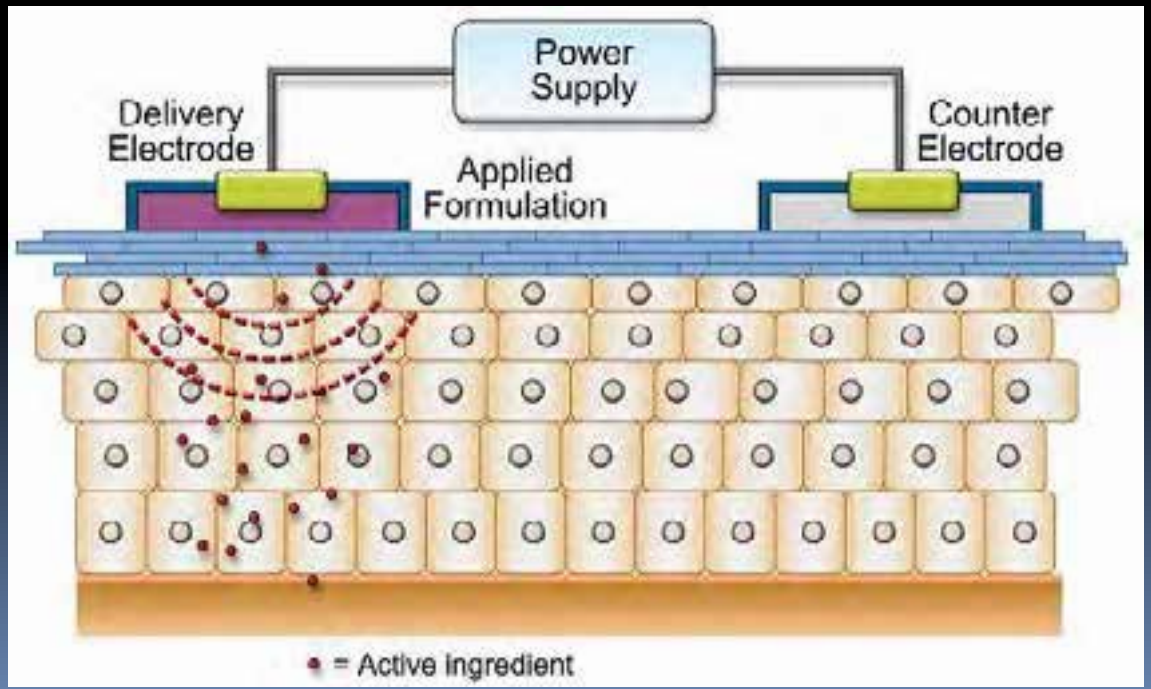
Ways to improve riboflavin penetration in to the cornea

- Epi off
- Increase concentration
- Ipotonic solution
- Without dextran
- Increase soaking time
- Corneal suction ring to get a constant riboflavin layer on the cornea

IONTOPHORESIS

Iontophoresis

Iontophoresis is a non-invasive technique in which a small electric current is applied to enhance ionized drug penetration into tissue. The drug is applied with an electrode carrying the same charge as the drug, and the ground electrode, which is of the opposite charge, is placed elsewhere on the body to complete the circuit. The drug serves as a conductor of the current through the tissue



Riboflavin is a perfect"candidate" for iontophoresis as it has a small molecular weight (476 Da), negatively charged at physiological pH and high solubility in H_2O.

Iontophoresis technique

- An anular suction ring of 9 mm in diameter, acts as special electrode, is placed on the cornea and connected to a DC generator powered by batteries. DC will emit a current of 1 mA
- Low suction is created by a syringe connected to the ring
- Ring is then filled with 0,5 mL the solution of Riboflavin (TEB).
- Another electrode is placed on the forehead
- The duration of the iontophoresis is 5 minutes

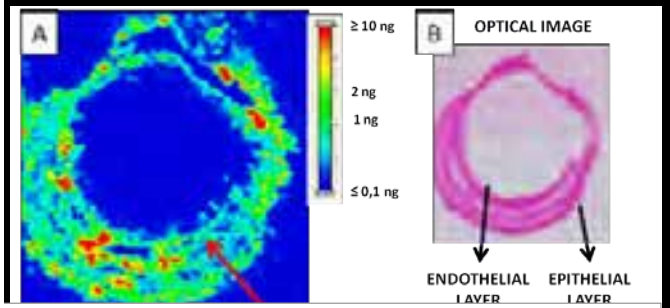
"RICROLIN + for iontophoresis in combination with UV-A irradiation at 10 mW/cm2 for 9 minutes

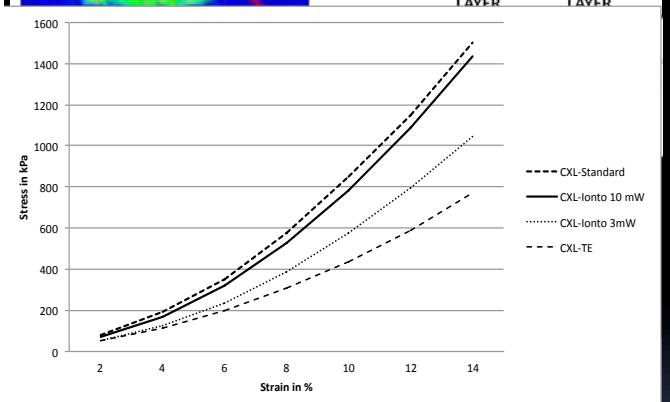
Iontophoresis

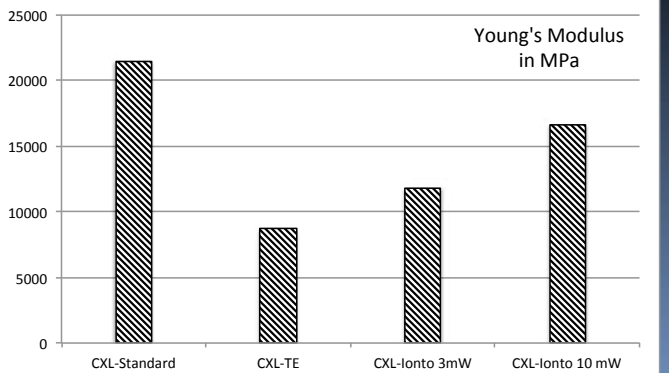
Research Article

Imaging Mass Spectrometry by Matrix-Assisted Laser Desorption/Ionization and Stress-Strain Measurements in Iontophoresis Transepithelial Corneal Collagen Cross-Linking

Paolo Vinciguerra,[1] Rita Mencucci,[2] Vito Romano,[3] Eberhard Spoerl,[4] Fabrizio I Camesasca,[1] Eleonora Favuzza,[2] Claudio Azzolini,[5] Rodolfo Mastropasqua,[6] and Riccardo Vinciguerra[1,5]







- Increase in stress strain and Young's modulus
- Lower than epi-off
- Good Riboflavin concentration (lower than epi-off)

	TE	B3	B10	IONTO 10	GRID
Number	3	3	3	2*	1/1**
Impregnation	Ricrolin TE	Ricrolin TE B solution	Ricrolin TE B solution	Ricrolin TE B solution	Ricrolin TE B solution
Imregnation Time	30 min	30 min	30 min	10 min	30 min
Irradiation Power	3mW/cm²	3mW/cm²	10mW/cm²	10mW/cm²	3mW/cm²/10mW/cm²
Irradiation Time	30 min	30 min	10 min	10 min	30/10 min
Iontophoresis	NO	NO	NO	YES	NO
Grid-removal epithelium	NO	NO	NO	NO	YES

*one cornea excluded because too thick **one cornea treated with 3mW/cm² and one with 10 mW/cm²

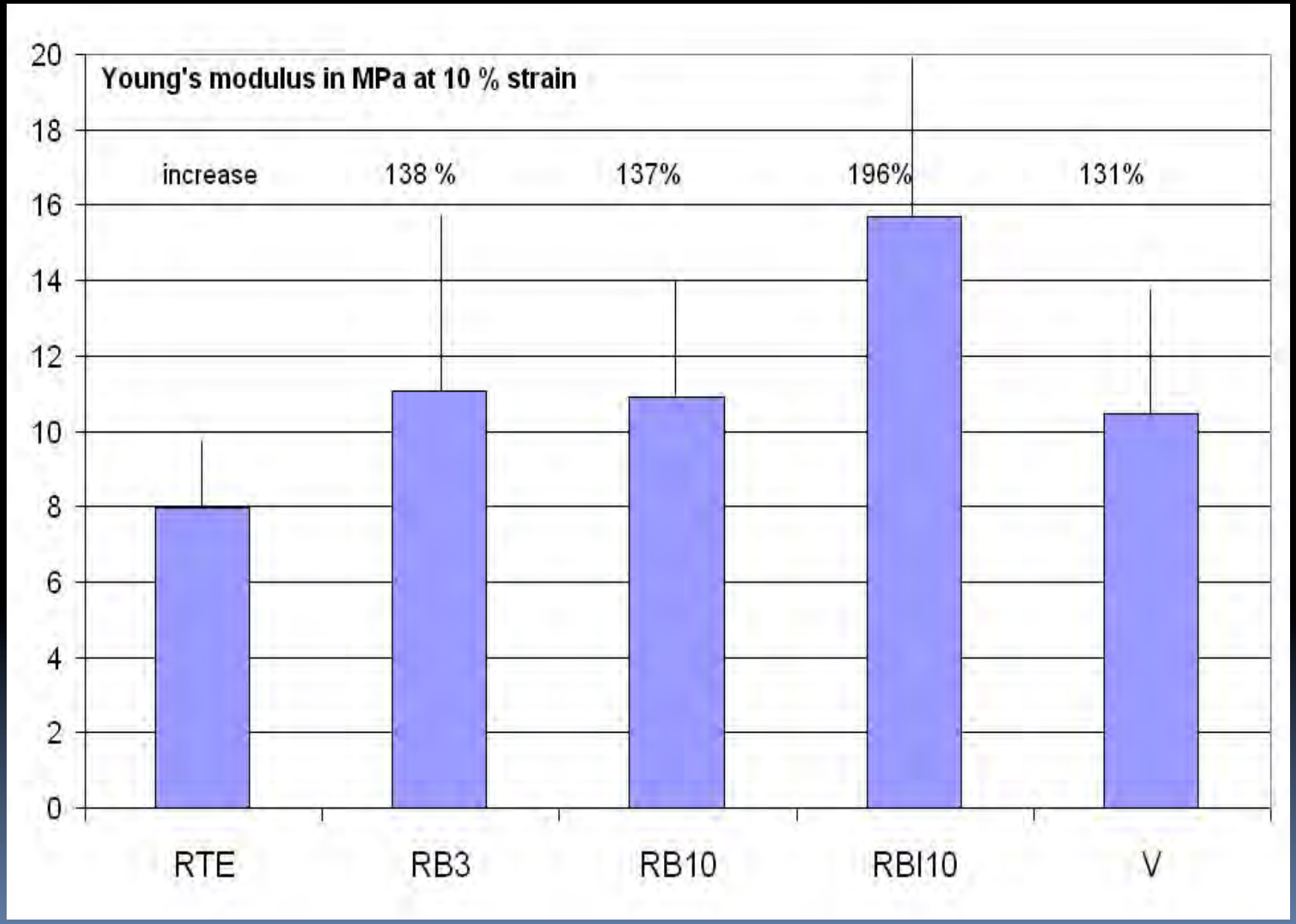
Stress strain analysis

- **UNIVERSITY OF DRESDEN, Prof Spoerl**

- Vertical strips of 5 mm wide were cut from the cornea (superior to inferior) and clamped in the stress-strain device.
- The distance of the clamps were 7 mm, the load 5 N and the preload 20 mN. The thickness of the corneas were measured with a pachymeter (PACH-PEN-XL).
- Static stress-strain measurements of the corneas were performed using a microcomputer-controlled biomaterial tester with a pre-stress of $10x10^3$ Pa"
- The stress stain curves were fitted with an exponential function and the Young's modulus were calculated.

Corneal pachymetry

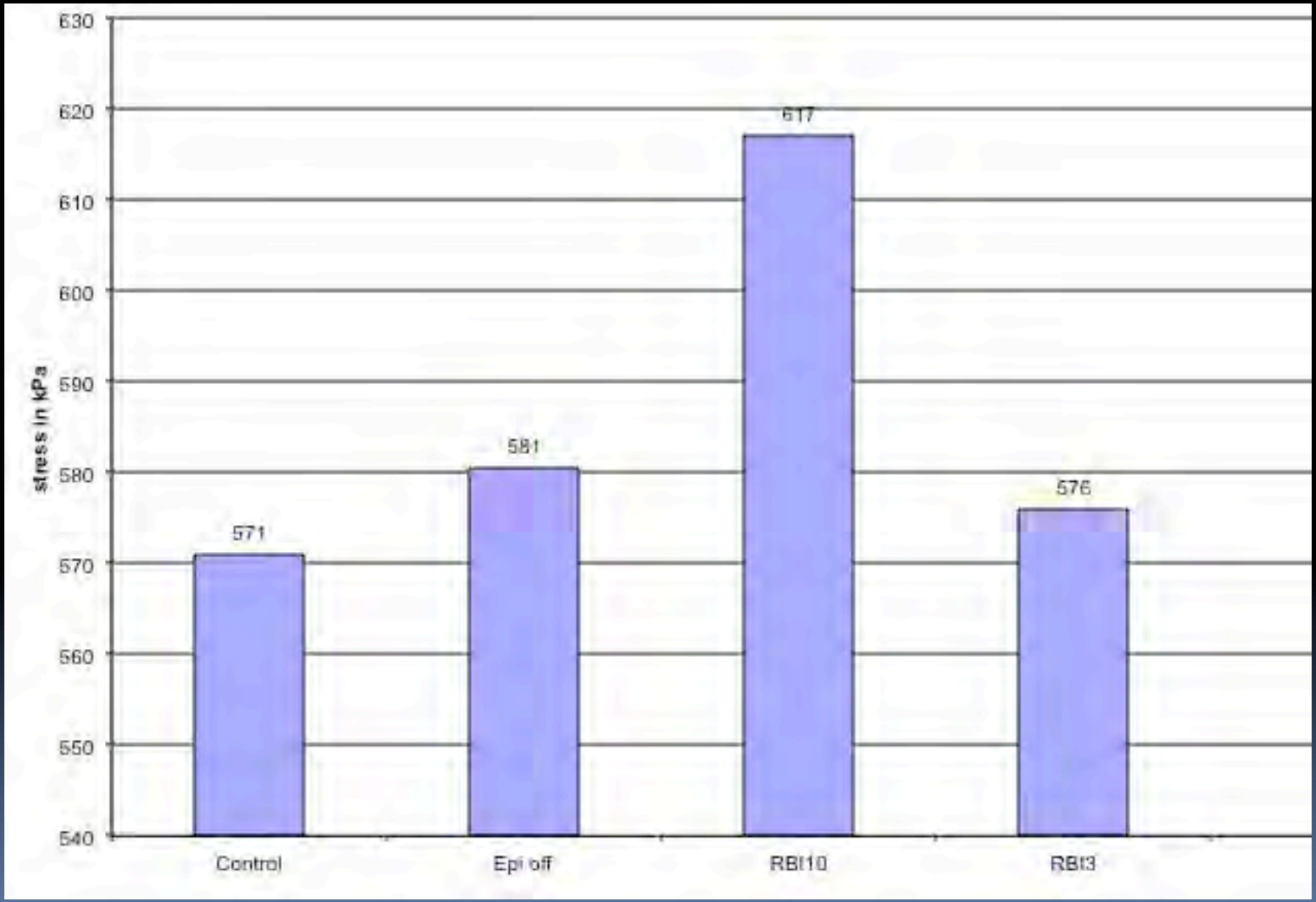
The thicknesses of the corneas were measured with an ultrasound pachymeter.

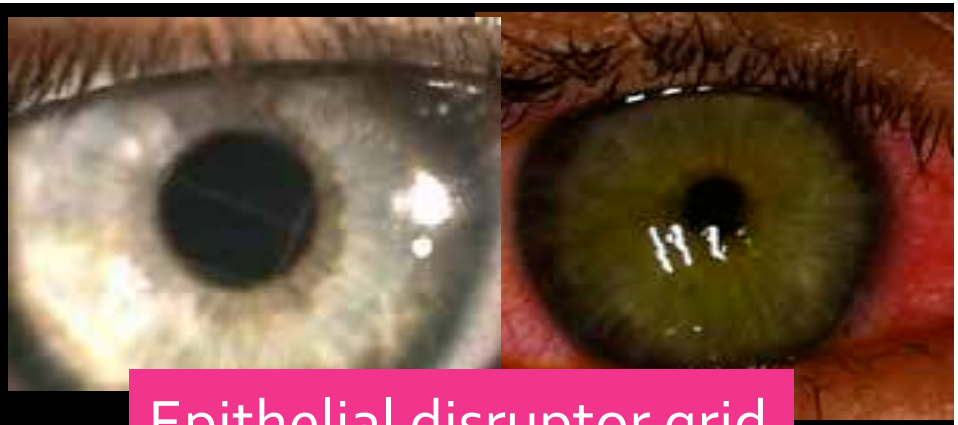

Young's modulus in MPa at 10 % strain
increase
138 %
137%
196%
131%
20
18
16
14
12
10
8
6
4
2
0
RTE
RB3
RB10
RBI10
V

	Control	Standard epi off	Ionto 3 mW	Ionto 10 mW
Number	4	4*	4	4
Impregnation	Ricrolin	Ricrolin	Ricrolin TE B solution	Ricrolin TE B solution
Impregnation Time	30	30 min	30 min	10 min
Irradiation Power	0mW/cm²	3mW/cm²	10mW/cm²	10mW/cm²
Irradiation Time	0 min	30 min	9 min	9 min
Iontophoresis	NO	NO	YES	YES
removal epithelium	YES	YES	NO	NO

*one cornea excluded from the analysis for abnormal data

Stress Strain analysis

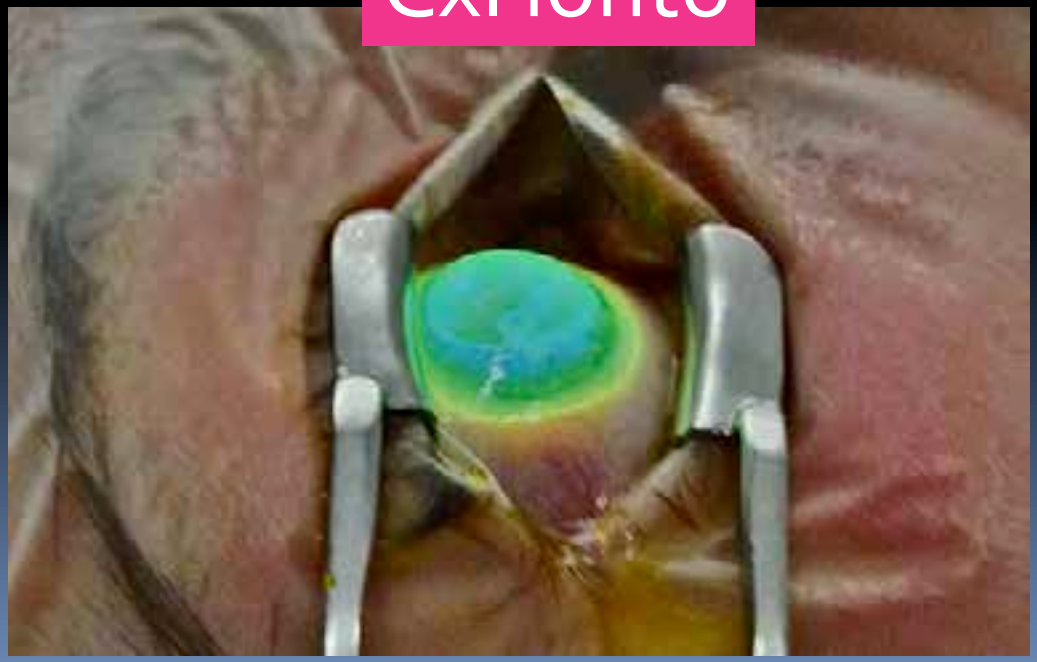




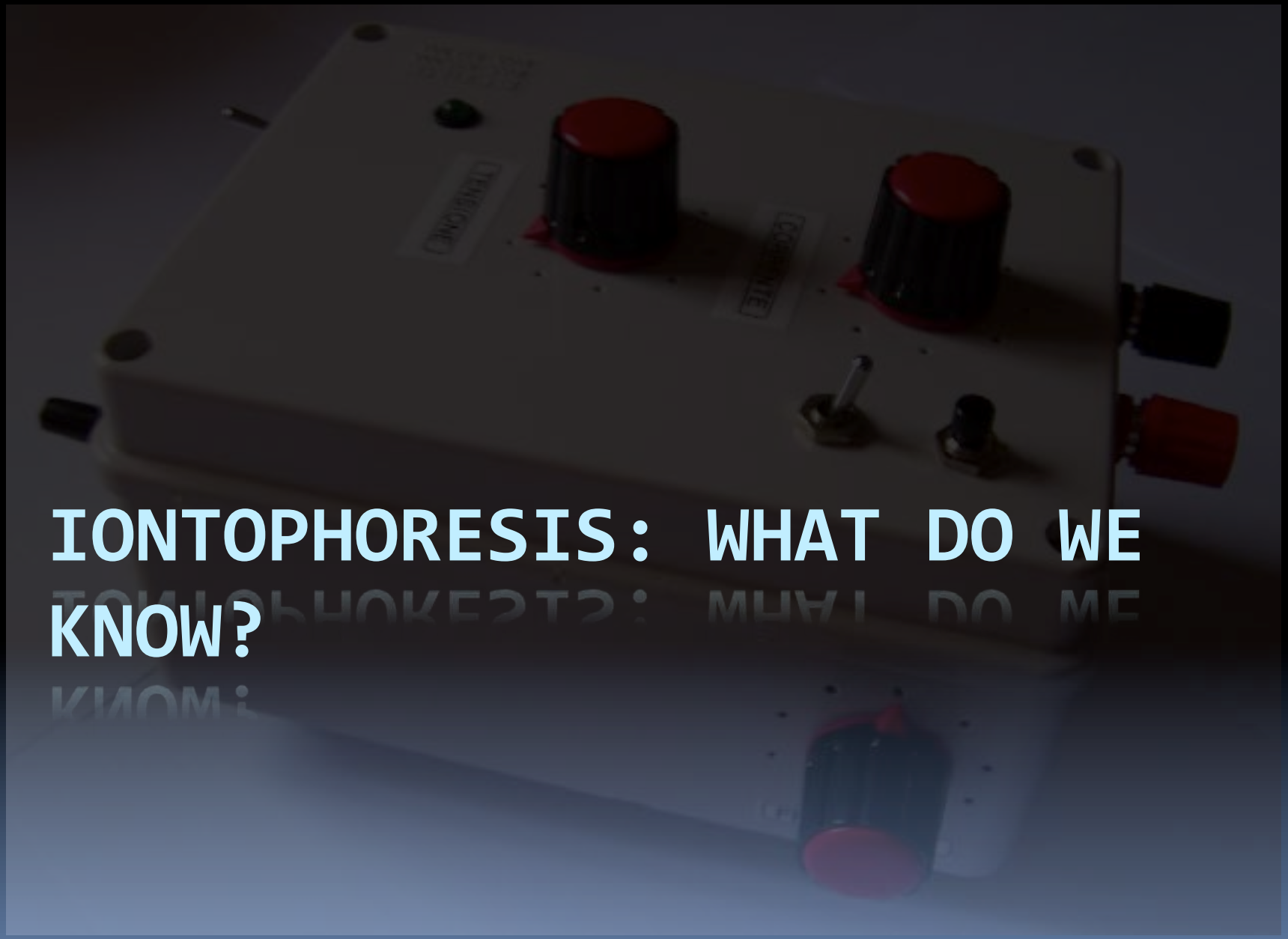
Epithelial disruptor grid

With Vinciguerra Ring

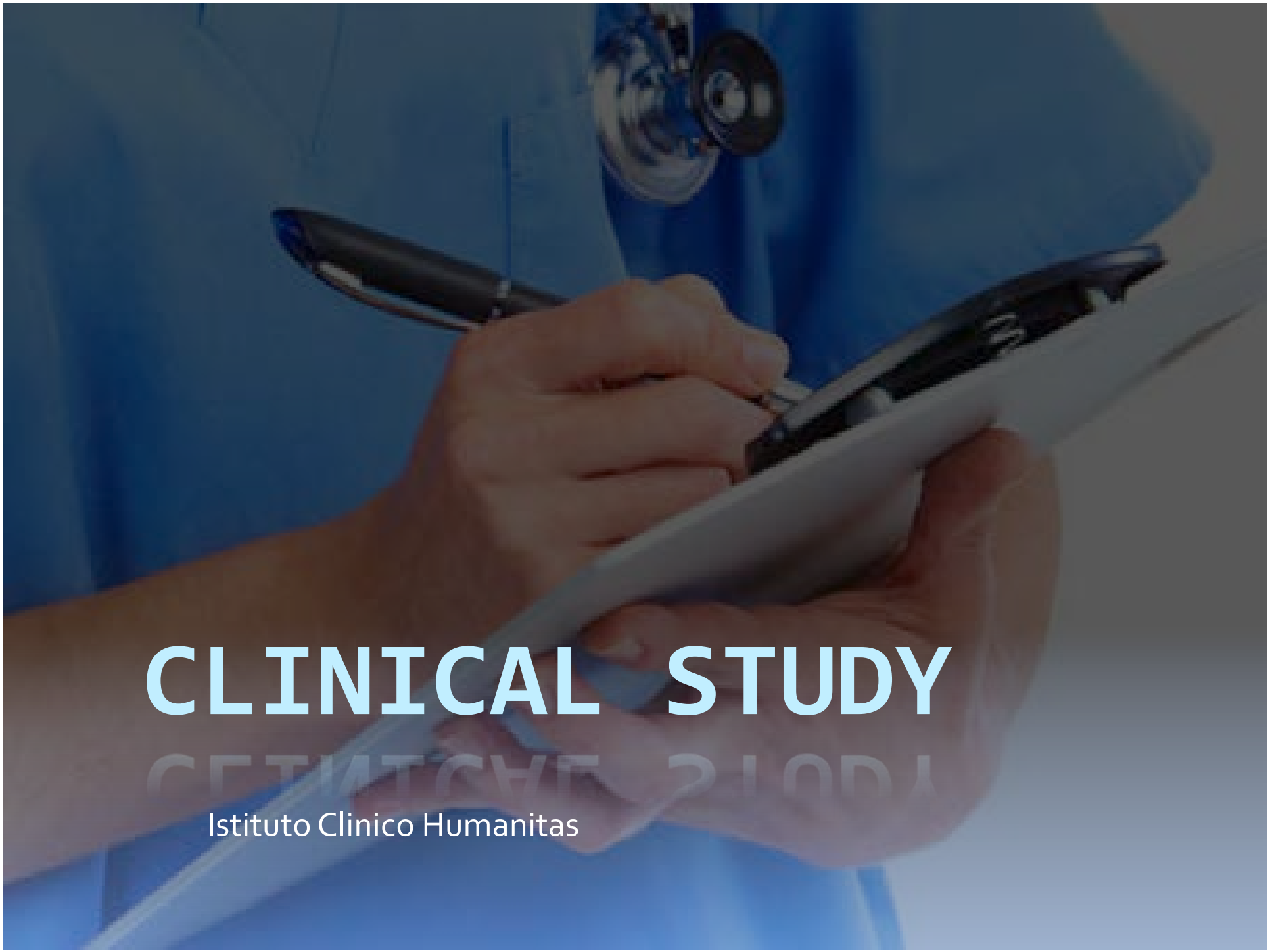
Cxl ionto



the UV stimulated fluorescence is greater than epi off /on & grid removal epithelium



IONTOPHORESIS: WHAT DO WE KNOW?


CLINICAL STUDY
Istituto Clinico Humanitas

JRS 2016

SURGICAL TECHNIQUE

Transepithelial Iontophoresis Corneal Collagen Cross-linking for Progressive Keratoconus: Initial Clinical Outcomes

Paolo Vinciguerra, MD; J. Bradley Randleman, MD; Vito Romano, MD; Emanuela F. Legrottaglie, MD; Pietro Rosetta, MD; Fabrizio I. Camesasca, MD; Raffaele Piscopo, MD; Claudio Azzolini, MD; Riccardo Vinciguerra, MD

ABSTRACT

PURPOSE: To report initial clinical results of transepithelial corneal collagen cross-linking with iontophoresis (I-CXL).

METHODS: Twenty eyes of 20 patients diagnosed as having progressive keratoconus who underwent I-CXL were included in this prospective non-randomized clinical study. Corrected distance visual acuity (CDVA), spherical equivalent and cylinder refraction, various corneal topography and Scheimpflug tomography parameters, aberrometry, anterior segment optical coherence tomography, and endothelial cell count were assessed at baseline and at 1, 3, 6, and 12 months postoperatively.

RESULTS: CDVA improved significantly at 3, 6, and 12 months postoperatively (logMAR difference of -0.07 ± 0.01, -0.09 ± 0.03, and -0.12 ± 0.06, respectively; $P < .05$). Aberrometry remained stable during follow-up and a trend toward improvement was noted. All topographic parameters (including maximum keratometry) were stable during the follow-up, but exhibited a positive non-significant trend toward improvement. Minimum corneal thickness values were stable for up to 12 months postoperatively. None of the patients showed a progression of keratoconus. Endothelial cell counts did not change significantly ($P > .05$).

CONCLUSIONS: Preliminary results up to 1 year postoperatively indicate the efficacy of I-CXL in stabilizing the progression of this degenerative disease combined with significant improvement of CDVA. I-CXL, which spares the corneal epithelium, has the potential to become a valid alternative for halting the progression of keratoconus while reducing postoperative patient pain, risk of infection, and treatment time in select patients; however, the relative efficacy of this technique compared to standard epithelium-off techniques remains to be determined.

[*J Refract Surg*. 2014;30(11):746-753.]

Corneal collagen cross-linking (CXL) is able to change the biomechanical properties of corneas and is currently the only treatment that can potentially slow or block the progression of ectatic disease.[1,2] Long-term follow-up studies on CXL mostly refer to the standard technique, which entails epithelial debridement to allow riboflavin penetration in the corneal stroma.[1,3] Epithelial removal causes pain[4] and a higher risk of corneal infection,[5] as well as visual loss for the first few months after treatment.[2,3] To avoid these drawbacks, transepithelial corneal collagen cross-linking (TE-CXL) was developed. The transepithelial protocol currently used employs a specially formulated riboflavin solution (Ricrolin TE; SOOFT, Montegiorgio, Italy) in which two enhancers (ie, trometamol and sodium ethylenediaminetetraacetic acid) are added to help riboflavin penetration in the corneal stroma.[6] However, results of TE-CXL are limited and have not achieved the same efficacy as standard CXL, frequently due to inadequate riboflavin penetration.[7-10]

The use of enhancers may not be the only way to increase riboflavin penetration through the epithelium. In other specialties (ie, dermatology), iontophoresis has been adopted for a long time. It is a non-invasive technique in which a small electric current is applied to enhance an ionized drug's penetration.

Preclinical results have shown that CXL with iontophoresis (I-CXL) is able to increase the concentration of riboflavin in the corneal stroma when compared to TE-CXL[11-13] with

From the Eye Center, Humanitas Clinical and Research Center, Rozzano, Italy (PV, EFL, PR, FIC, RP, RV); the Department of Ophthalmology, Emory University, Atlanta, Georgia (JBR); the Department of Ophthalmology, Second University of Naples, Naples, Italy (VR); and the Department of Surgical and Morphological Sciences, Section of Ophthalmology, School of Medicine, University of Insubria, Varese, Italy (CA, RV).

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Dr. Paolo Vinciguerra is a consultant for Nidek, Inc. and Oculus Optikgeräte GmbH. The remaining authors have no financial or proprietary interest in the materials presented herein.

Dr. Randleman did not participate in the editorial review of this manuscript.

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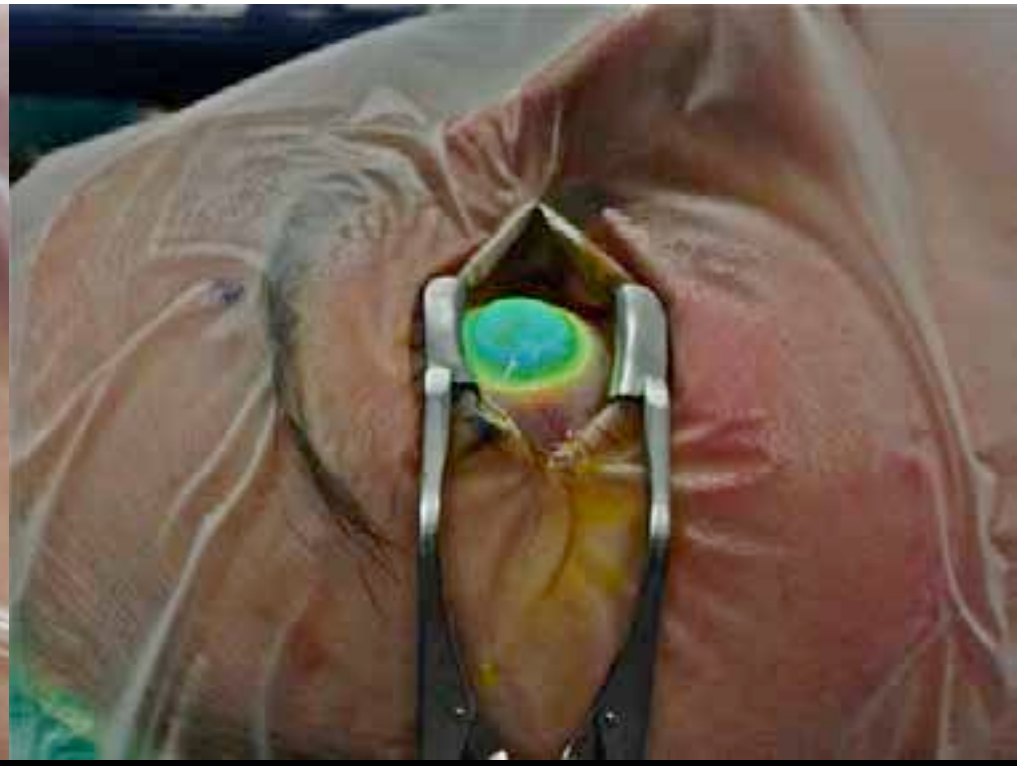
doi:10.3928/1081597X-20141021-06

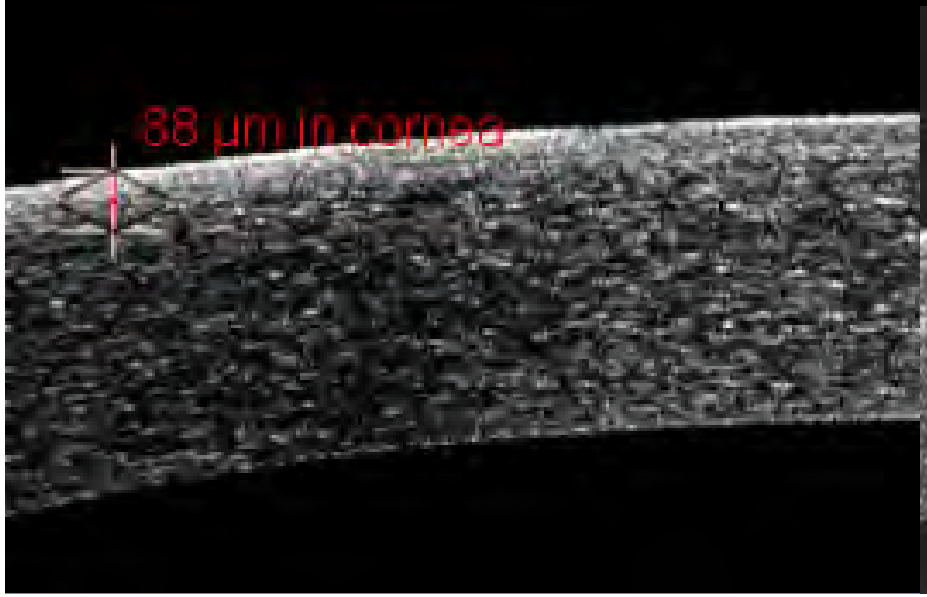
Materials and Methods

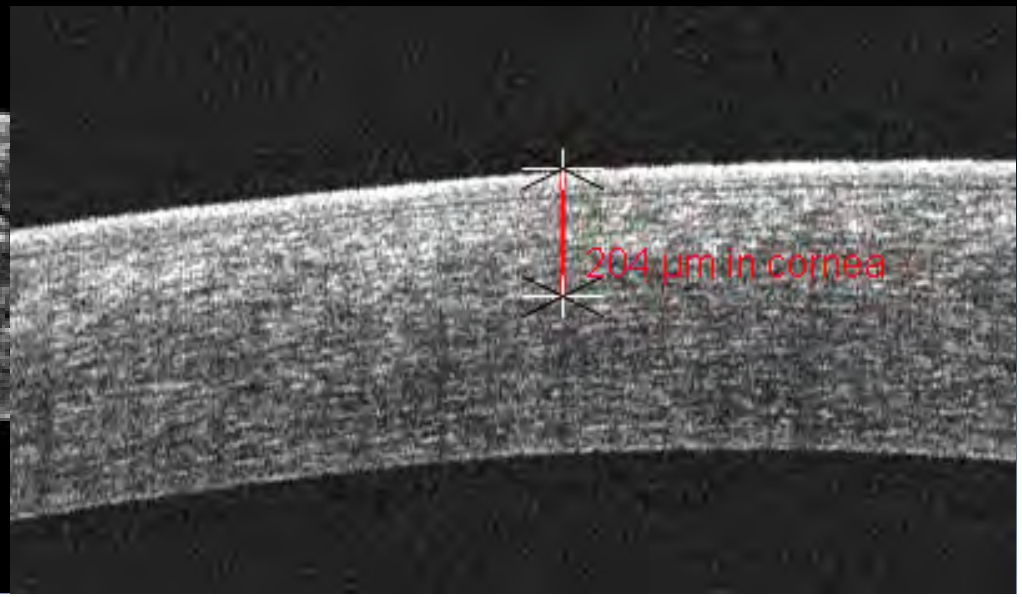
- 20 eyes of 20 patients with progressive keratoconus
- Progression proved with differential maps
- Age >18 years
- Follow up 12 months



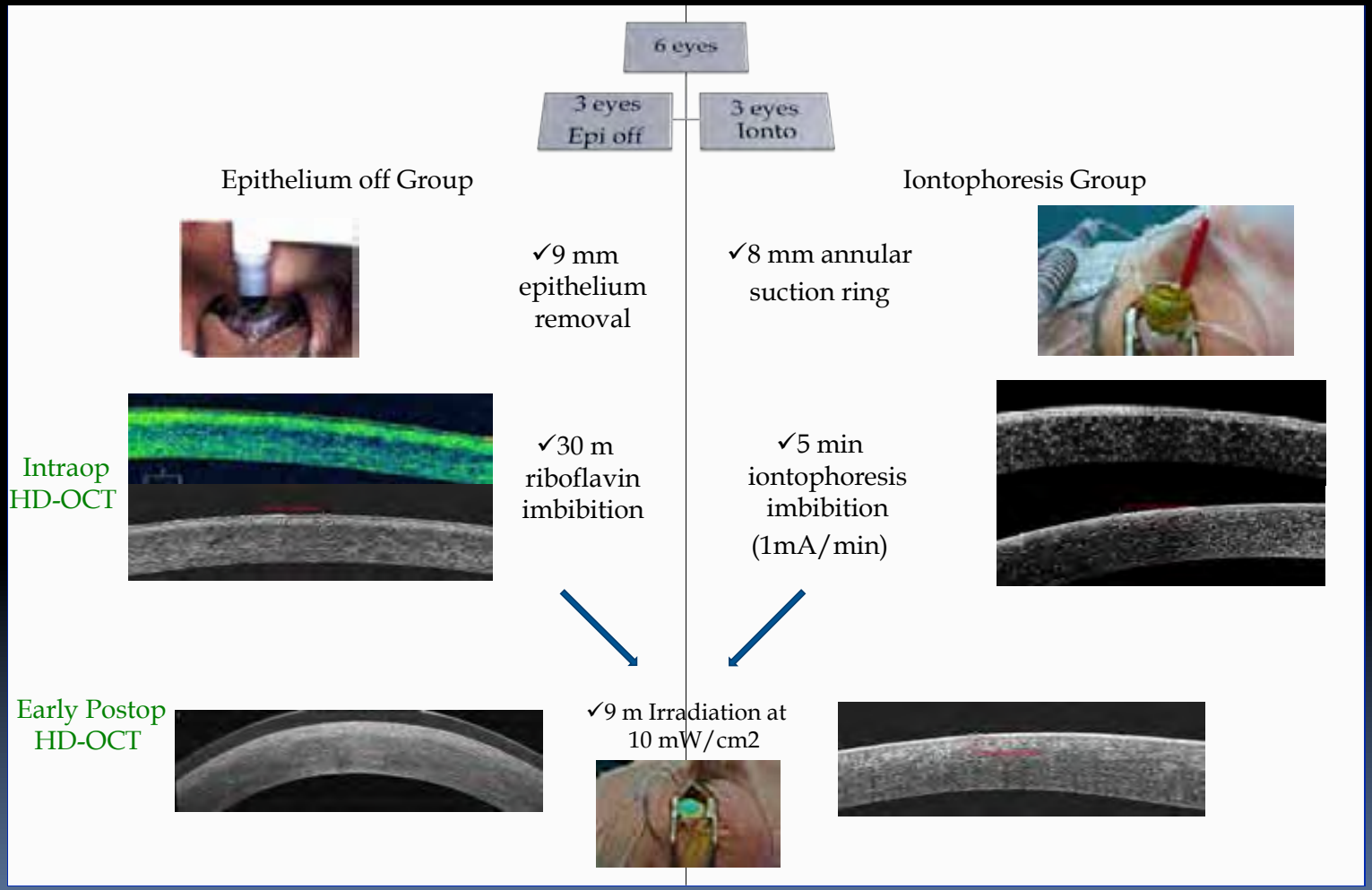
-HD-OCT after impregnation

-HD-OCT after irradiation





IntraOp OCT



Vinciguerra et al J Refract Surg (2013)

High Fluence Iontophoretic Corneal Collagen Cross-linking: In Vivo OCT Imaging of Riboflavin Penetration

To the Editor:

We read with interest the excellent article by Malhotra et al.[1] regarding in vivo estimation of riboflavin penetration using anterior segment optical coherence tomography (OCT). The article evaluates the effect of complete versus grid-like epithelial removal on riboflavin penetration during collagen cross-linking (CXL) in vivo using hand-held OCT. Twenty eyes of 20 patients were imaged intraoperatively at 30 and 60 minutes after starting the procedure. Results showed

eratively using high-resolution OCT. The epithelium was removed completely in the central 9-mm zone in 3 eyes (epi-off group), whereas riboflavin penetration through intact epithelium was promoted by an iontophoresis device in the remaining 3 eyes (iontophoresis group). The iontophoresis device for corneal application (8 mm in diameter) is placed on the cornea using an annular suction ring (low suction created by a syringe connected on the suction annulus). The device is filled with approximately 0.5 mL solution from the open proximal side, until the electrode (stainless steel mesh) is covered (**Figure 1A**). The device is connected to a constant current generator (I-ON XL, Sooft, Italy) set at 1 mA (the total dose of 5 mA × min is monitored by the generator).

2. High fluence iontophoretic corneal collagen cross-linking: in vivo OCT imaging of riboflavin penetration.

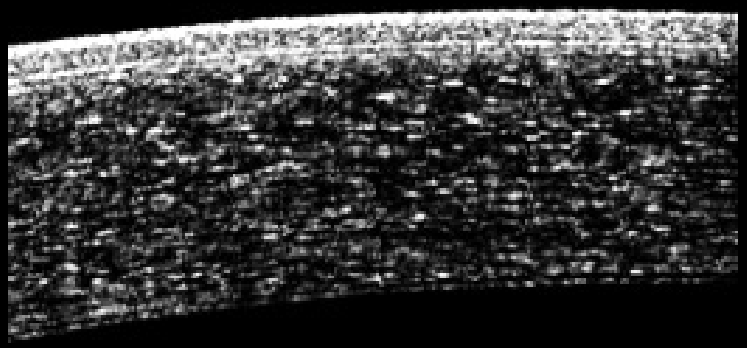
Vinciguerra P, **Rechichi** M, Rosetta P, Romano MR, Mastropasqua L, Scorcia V, Azzolini C, Vinciguerra R.

J Refract Surg. 2013 Jun;29(6):376-7. doi: 10.3928/1081597X-20130509-01. No abstract available.

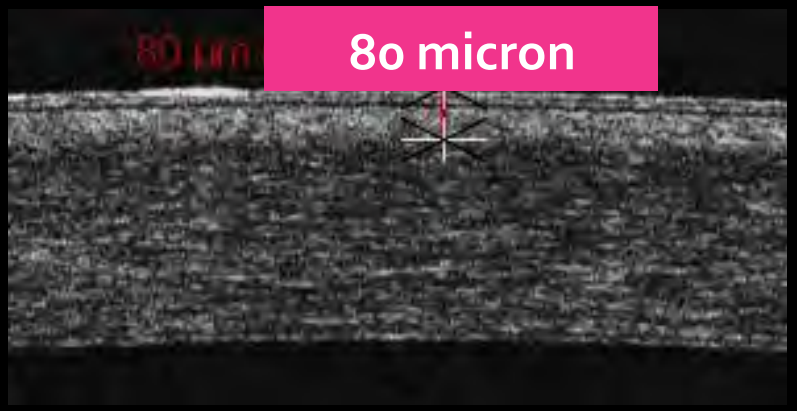
PMID: 23739828 [PubMed - indexed for MEDLINE]

Related citations

Normal cornea



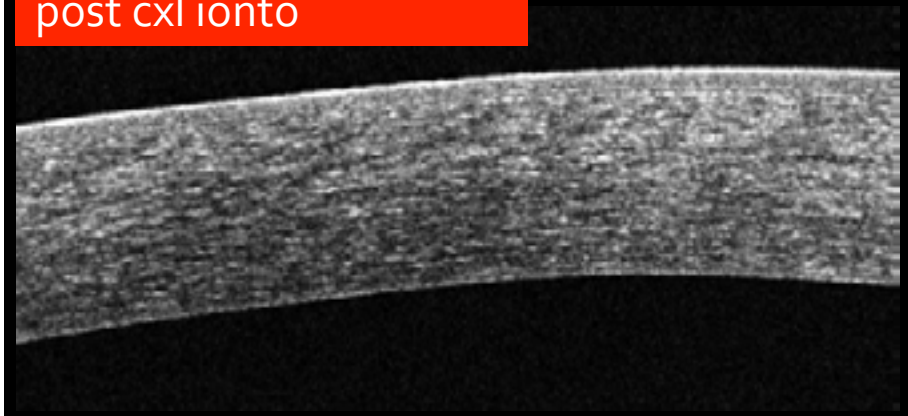
Epi off after 30 min imbibition and irradiation



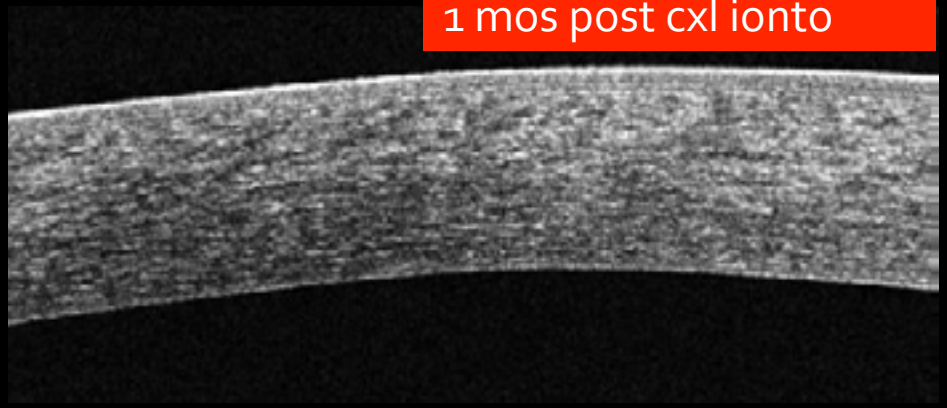
IONTO riboflavin penetration after 5 minutes of impregnation

IONTO riboflavin penetration follow up

post cxl ionto



1 mos post cxl ionto



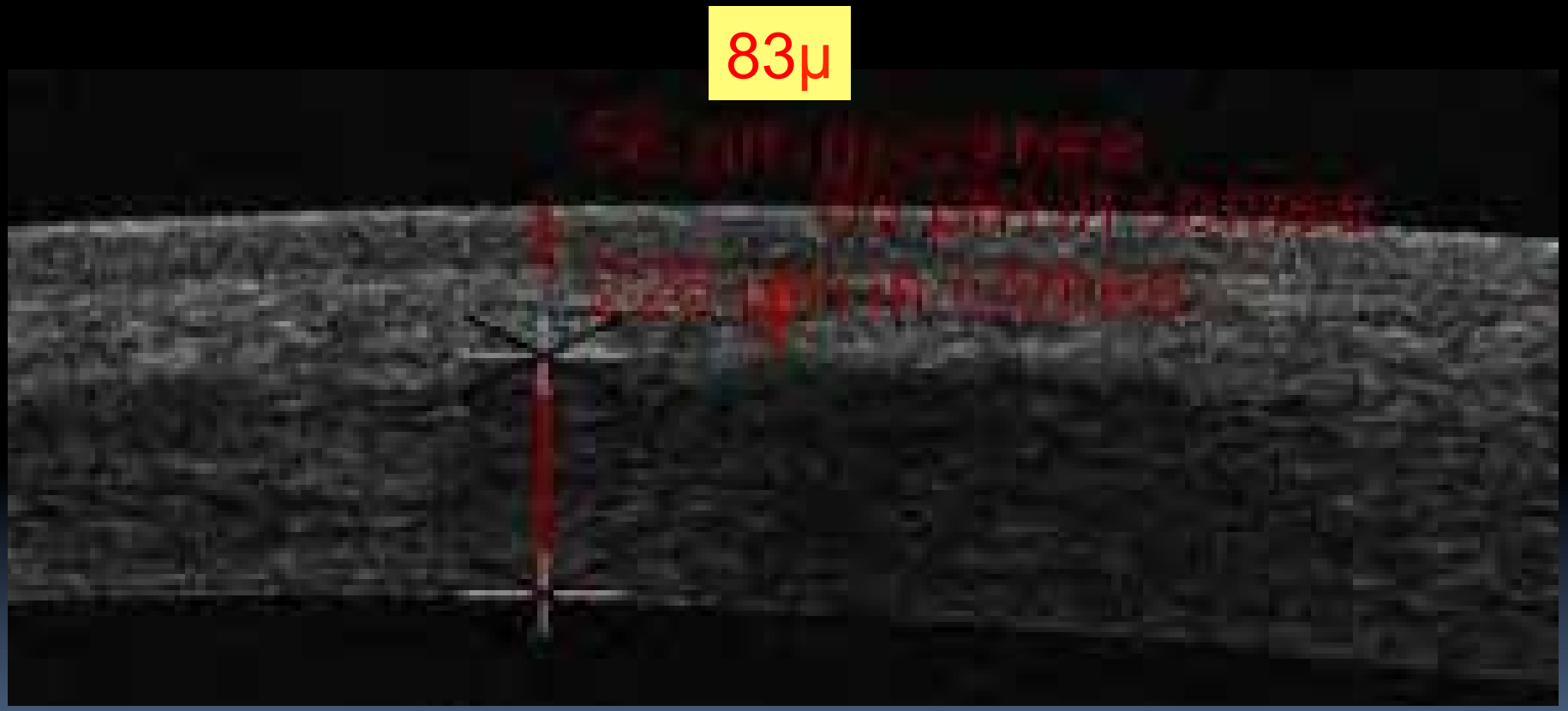
Sometimes demarcation line is evident only after 3 mos post Cxl iontophoresis

3 mos post cxl ionto

Demarcation line 196 µ in cornea

Standard Demarcation line in Epi off CXL

CxI Epi on demarcation line variable depth and less homogeneous



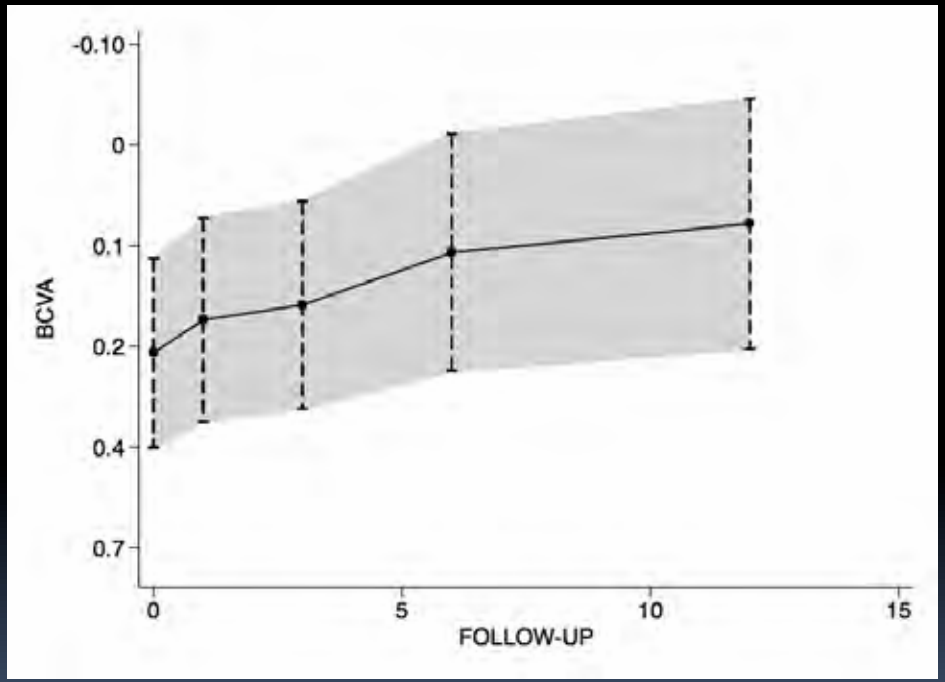
Demarcation line 392 micron

Parameters!!

	Baseline	1 month	3 months	6 months
CDVA	0.6(0.22)	0.61(0.22)	0.67(0.23) *	0.77(0.24) *
Sphere error	-2.1(2.03)	-1.95(2.13)	-2.1(2.6)	-1.8(3.3)
Cylinder	-3.07(1.44)	-3.3(1.46)	-3.32(1.58)	-3.5(1.77)
AK	58.5 (4.26)	59.03(3.4)	58.8(3.10)	58.1(4.1)
SAI	6.5(3.3) *	6.9(3.4)	6.77(3.10)	6.1(3.3)
SI	8.9(5.4)	9.02(5.4)	9.88(4.77)	9.6(5.4)
ECD. cell/mm^2	2436(132.32)	2497(224.8)	2549(172.1)	2401 (209.3)
ISV	100.3(33.1)	103.2(30.2)	99(29.4)	103.3(32.2)
IVA	1.02(0.38)	1.059(0.36)	1.02(0.35)	1.06(0.38)
KI	1.27(0.11)	14.7(42.6)	1.27(0.11)	1.29(0.13)
CKI	1.08(0.04)	1.08(0.04)	1.08(0.04)	1.08(0.04)
IHA	24.6(14.03)	26.6(29.8)	19.6(11.7)	22.5(16.6)
IHD	0.09(0.05)	0.1(0.04)	0.1(0.1)	0.1(0.04)
Rmin	5.8(0.63)	5.8(0.5)	5.8(0.6)	5.9(0.72)
Pachmin	444(42.1)	444(40.0)	447(45.3)	452(40.1)
HOA	1.07(0.53)	1.1(0.49)	1.1(0.45)	0.9(0.39)
Coma	2.2(1.11)	2.33(1.01)	2.35(0.81)	1.91(0.88)
Absph	0.349(0.448)	0.40(0.54)	0.41(0.43)	0.34(0.48)

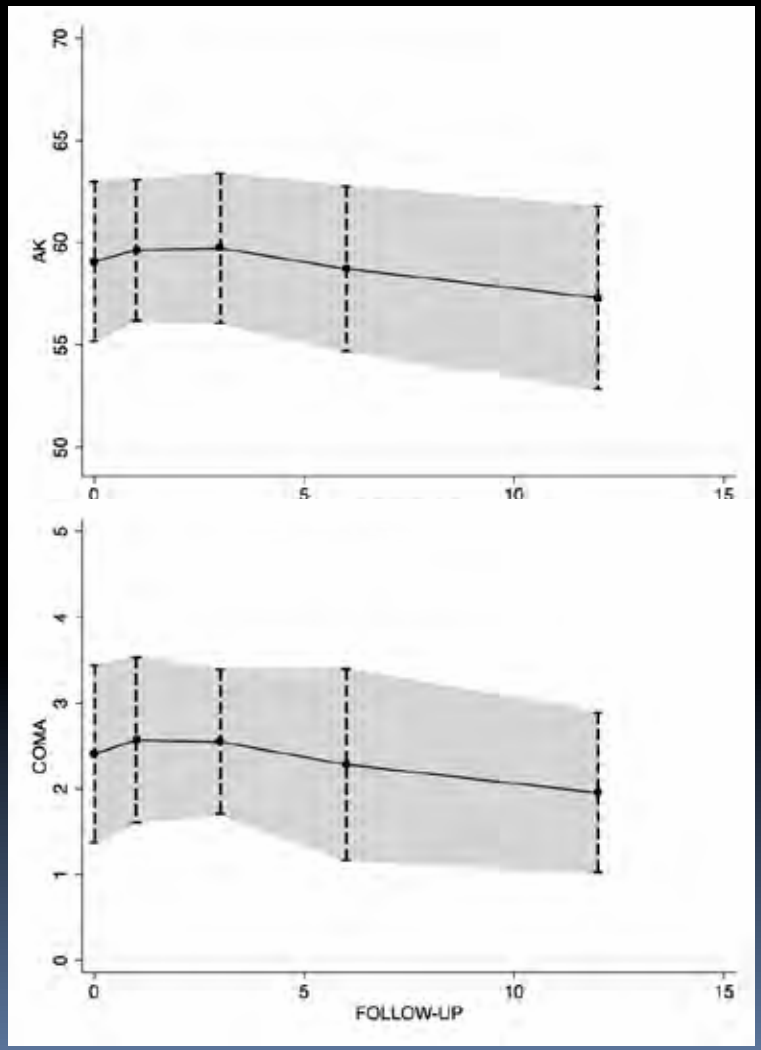
Results

- Significant improvement of of BCVA at 3, 6 and 12 months of follow up
- reduction of HOA, AK.



Risultati

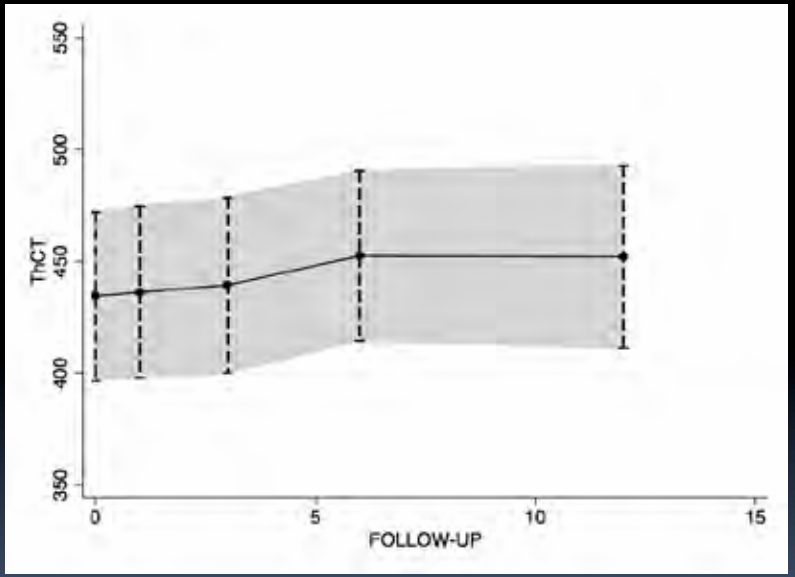
- Reduction of HOA and AK.



Numbers

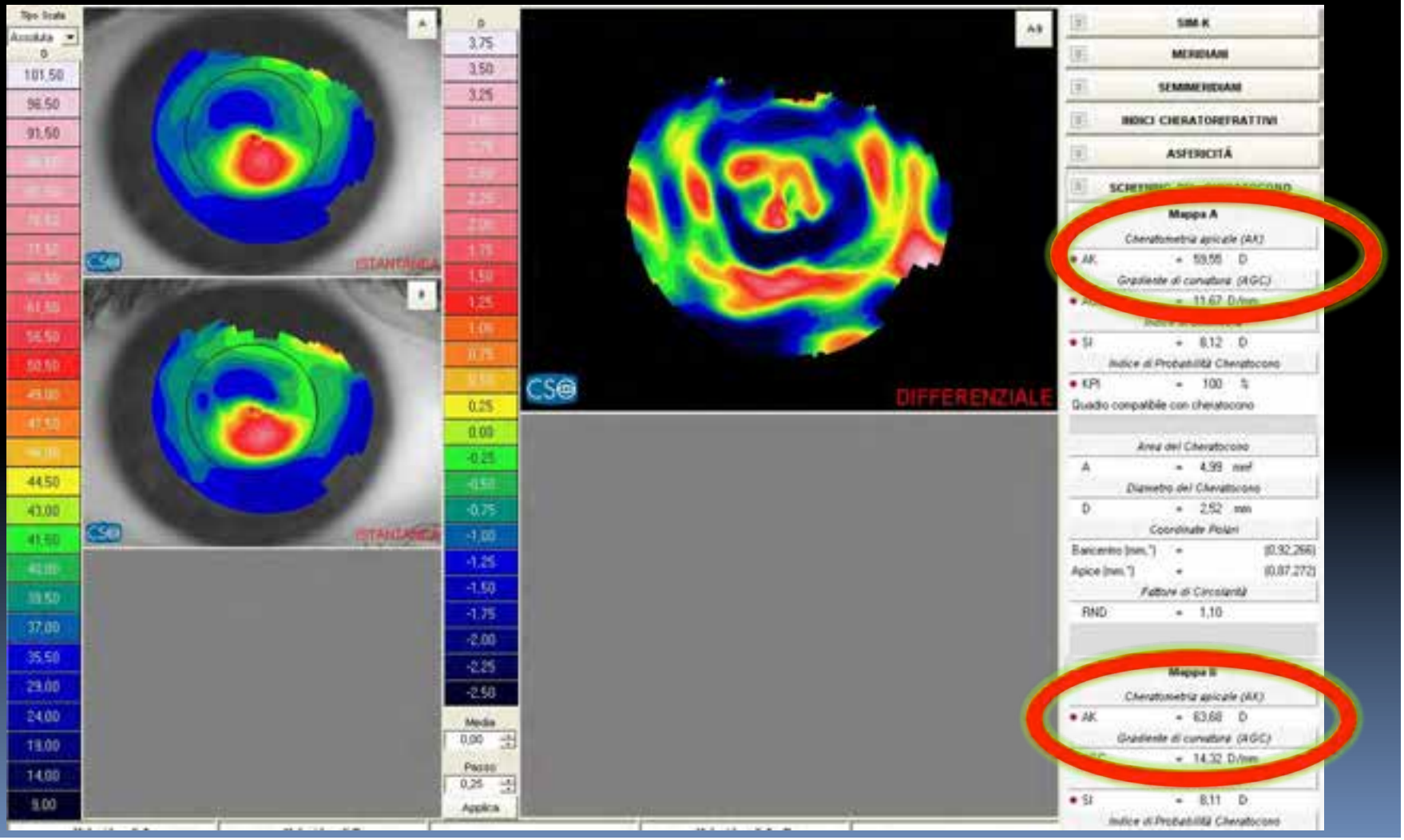
- Stable pachymetry
- Endothelial cell count stable

Pachimetria



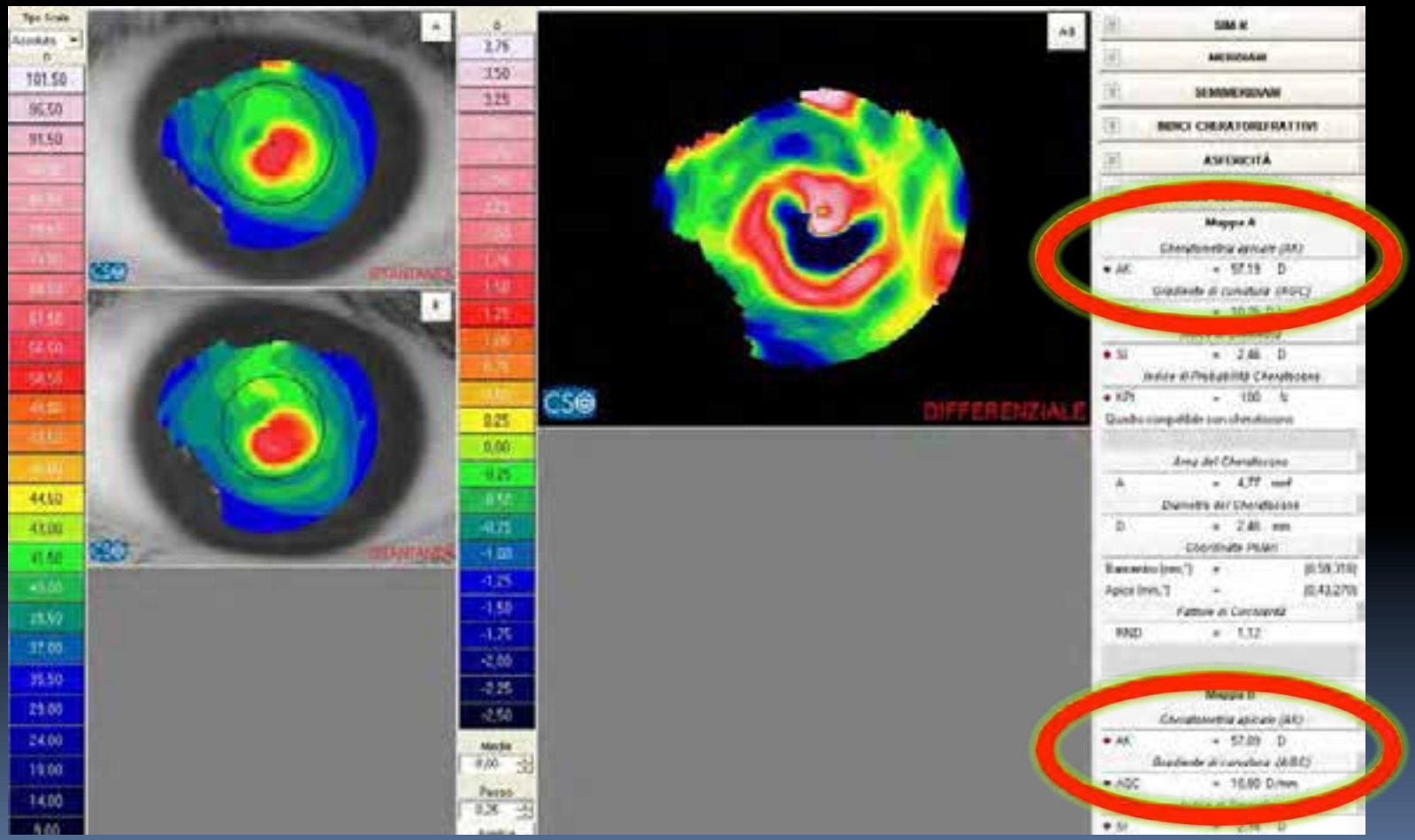
Patients are not only numbers…

RB

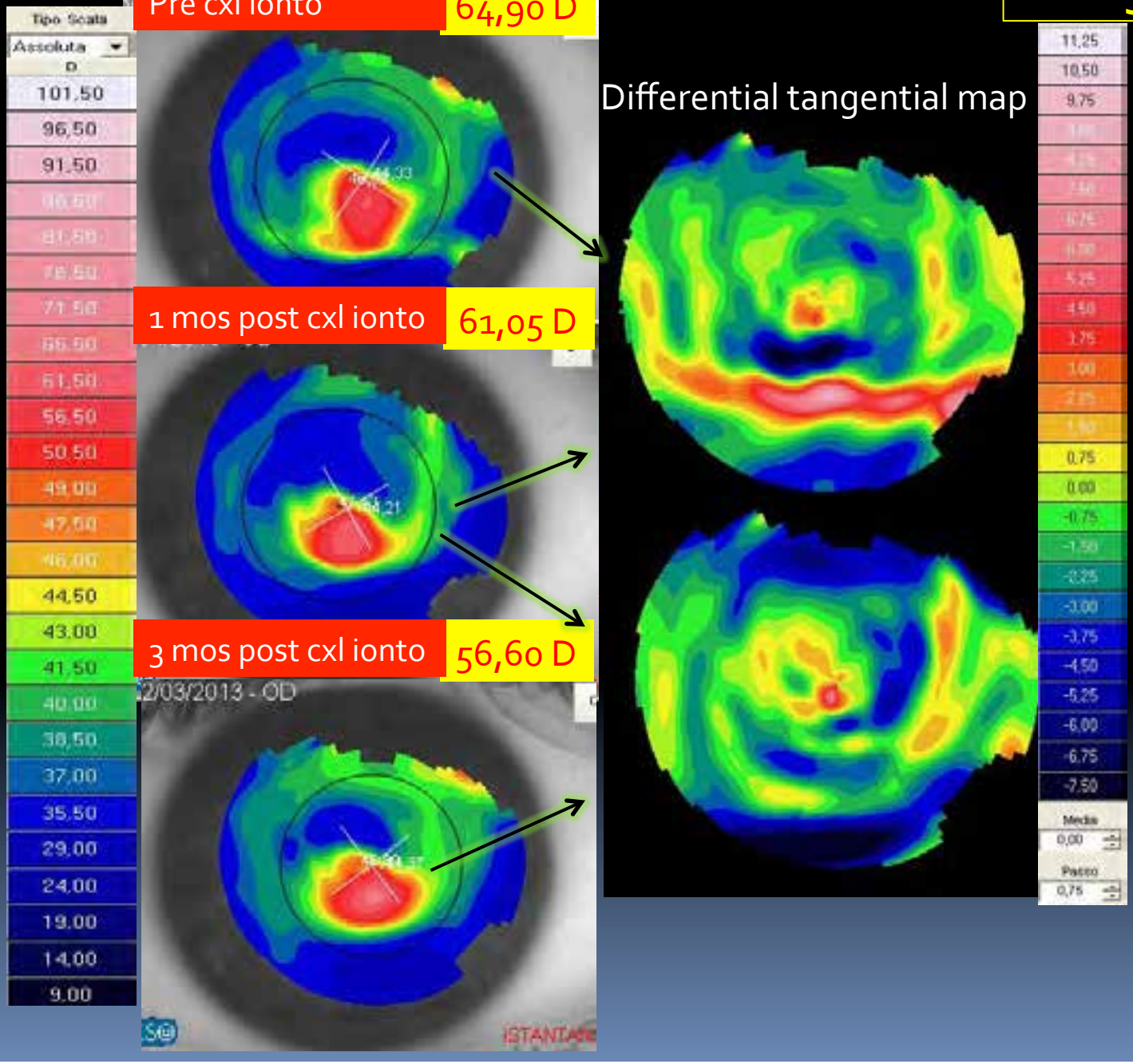


Patients

GF

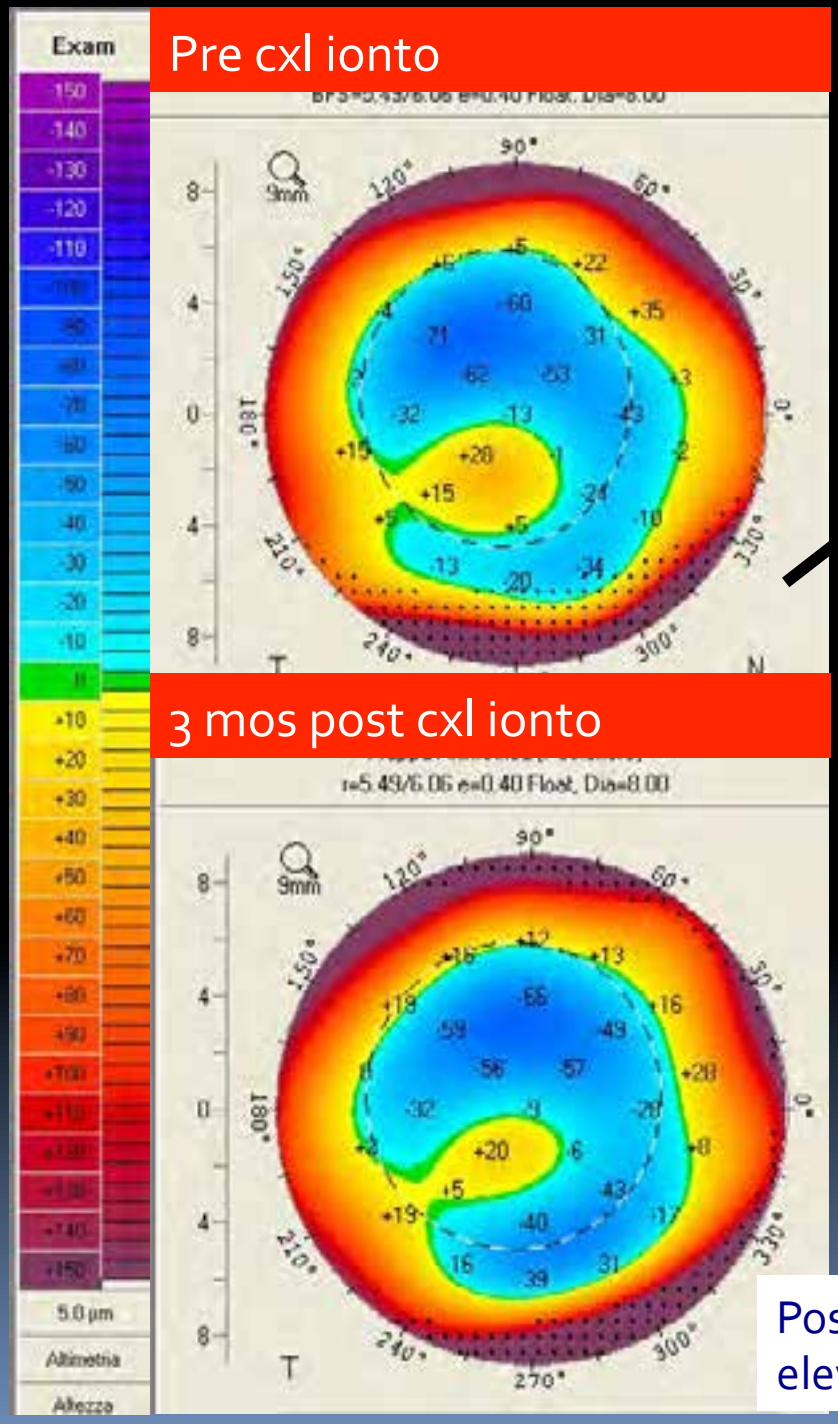


Tangential map



- Reduction of curvature 1-3 mos post-op

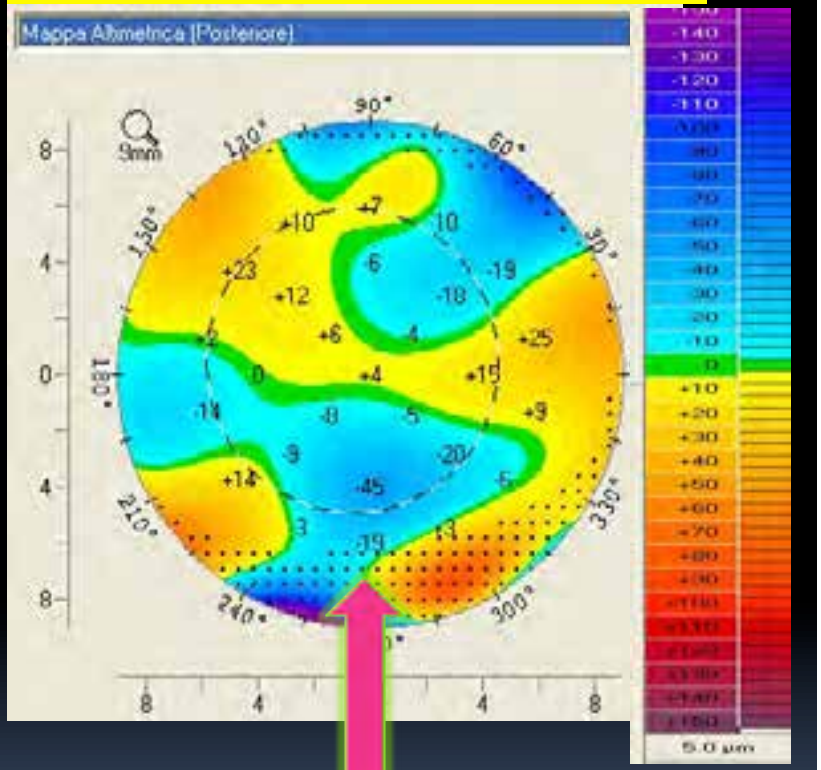
Pre cxl ionto



3 mos post cxl ionto

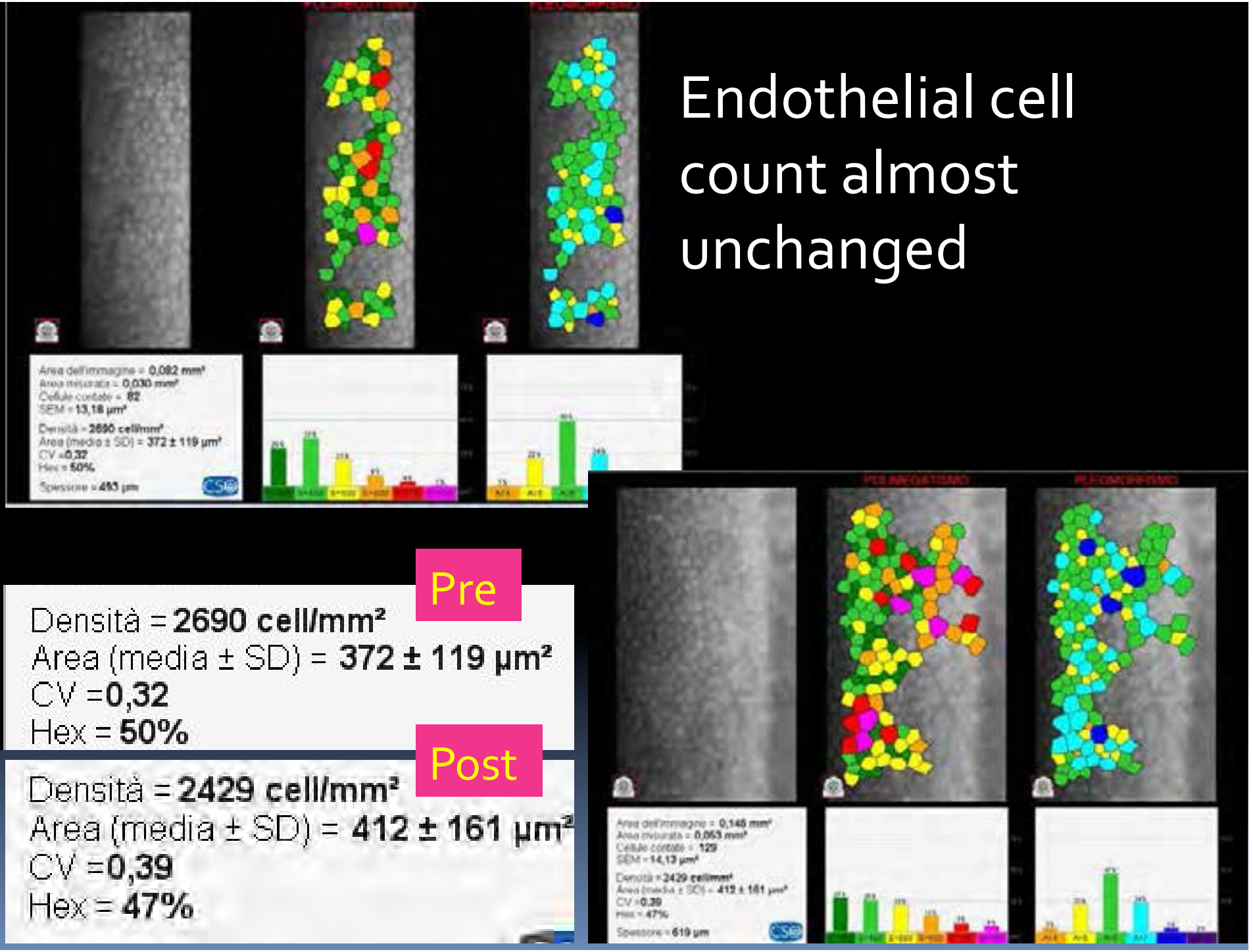
Posterior elevation map

Differential posterior elevation map



Elevation back reduced

Endothelial cell count almost unchanged



Pre

Densità = **2690 cell/mm²**
Area (media ± SD) = **372 ± 119 µm²**
CV = **0,32**
Hex = **50%**

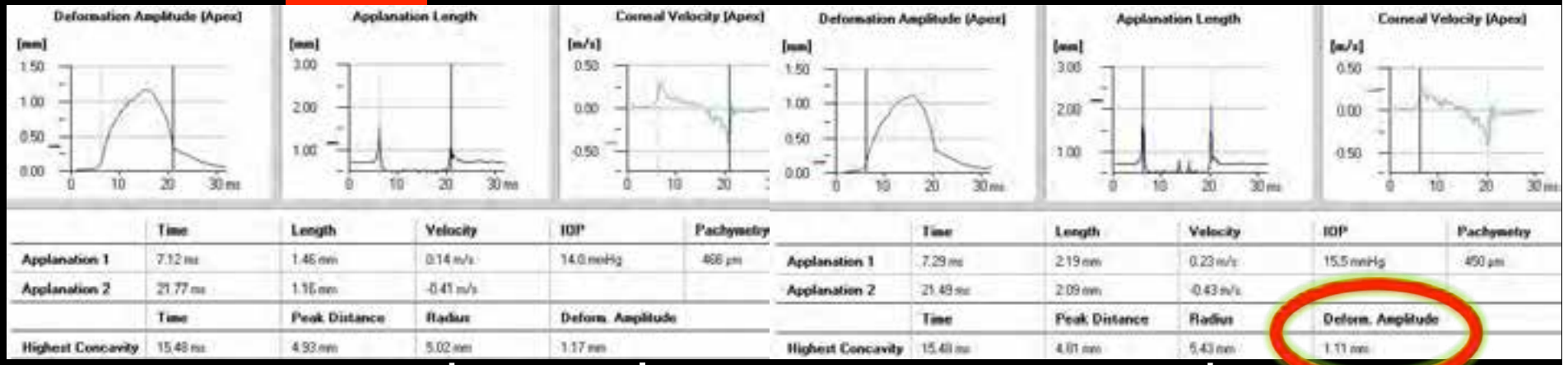
Post

Densità = **2429 cell/mm²**
Area (media ± SD) = **412 ± 161 µm²**
CV = **0,39**
Hex = **47%**

Pre cxl

CORVIS

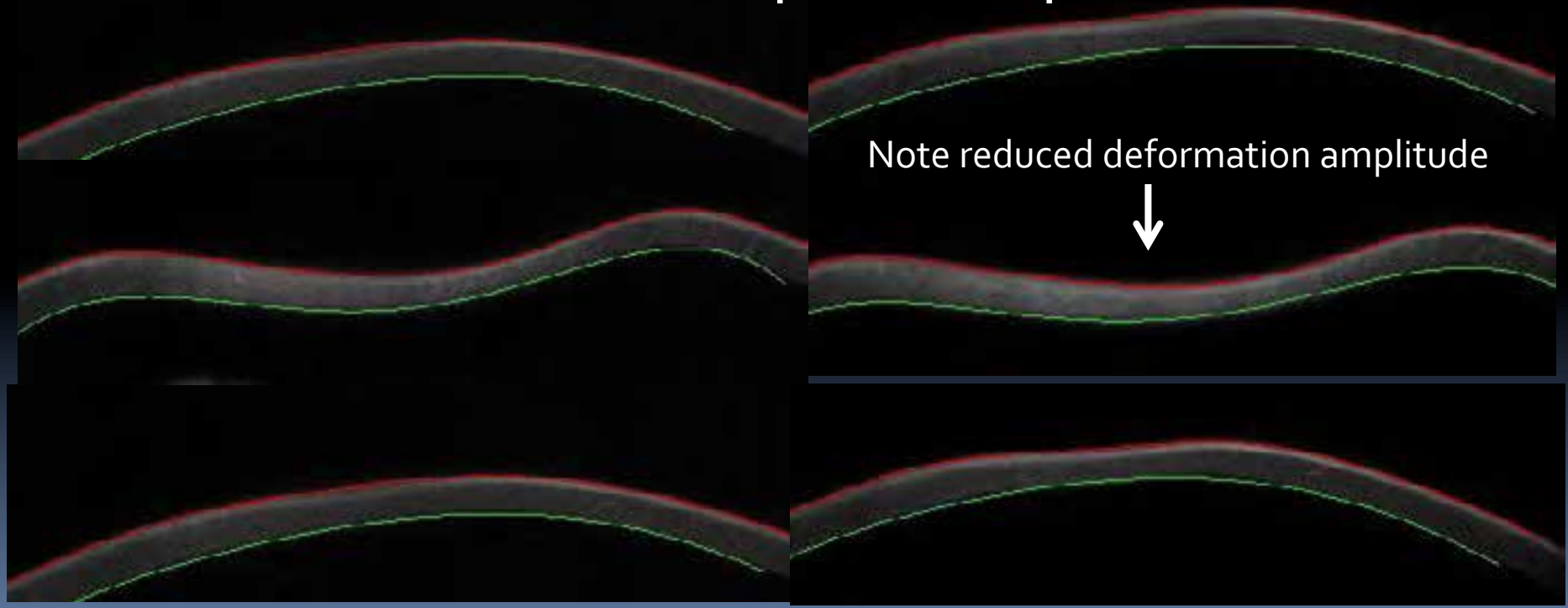
1 mos post cxl ionto



	Time	Length	Velocity	IOP	Pachymetry
Applanation 1	7.12 ms	1.46 mm	0.14 m/s	14.0 mmHg	466 µm
Applanation 2	21.77 ms	1.16 mm	-0.41 m/s		
	Time	Peak Distance	Radius	Deform. Amplitude	
Highest Concavity	15.48 ms	4.93 mm	5.02 mm	1.17 mm	

	Time	Length	Velocity	IOP	Pachymetry
Applanation 1	7.29 ms	2.19 mm	0.23 m/s	15.5 mmHg	450 µm
Applanation 2	21.49 ms	2.09 mm	-0.43 m/s		
	Time	Peak Distance	Radius	Deform. Amplitude	
Highest Concavity	15.48 ms	4.81 mm	5.43 mm	1.11 mm	

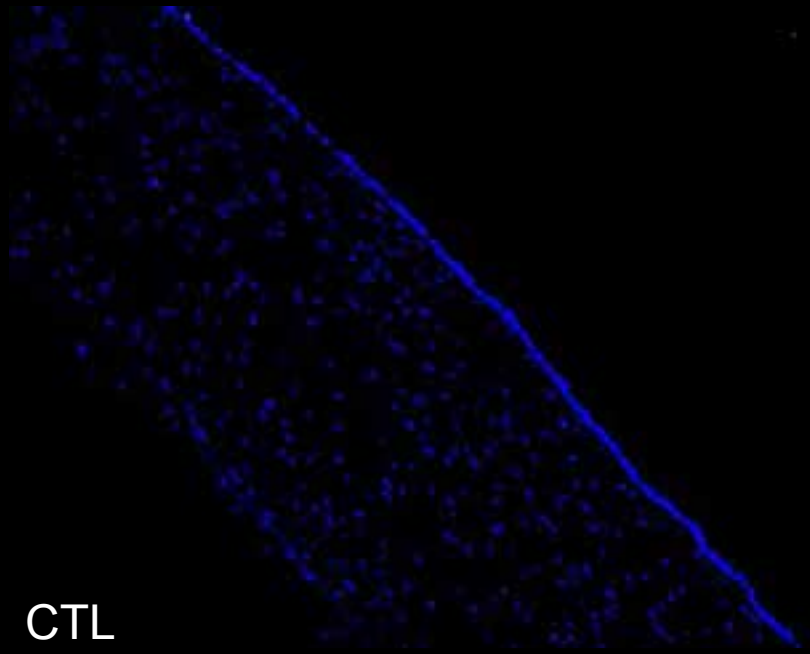
Biomechanical response improved



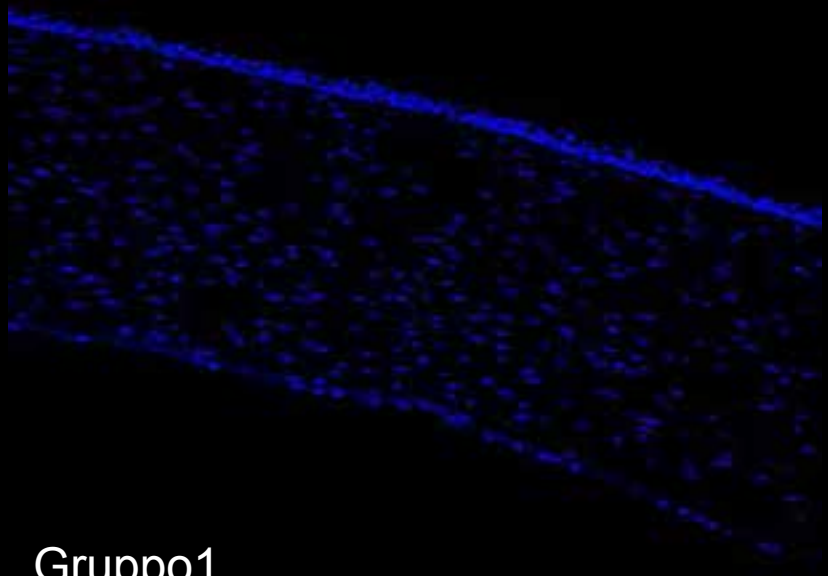
Note reduced deformation amplitude

↓

DAPI: nuclear staining (indice indiretto apoptosi)

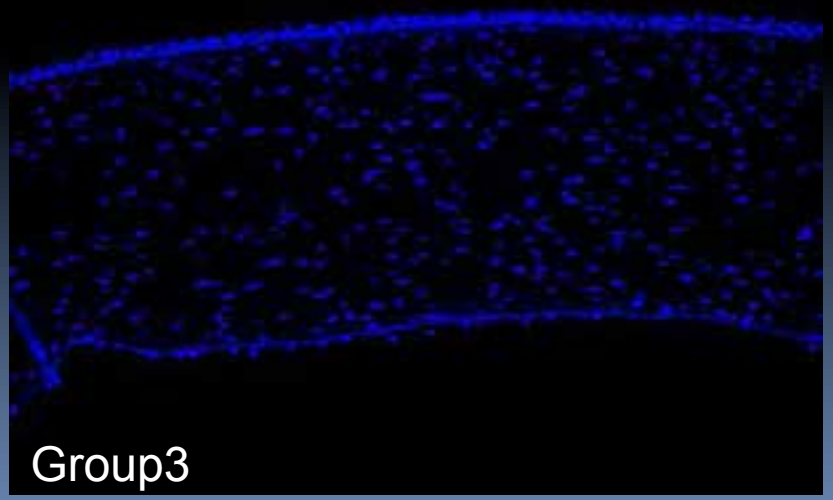


CTL



Gruppo1

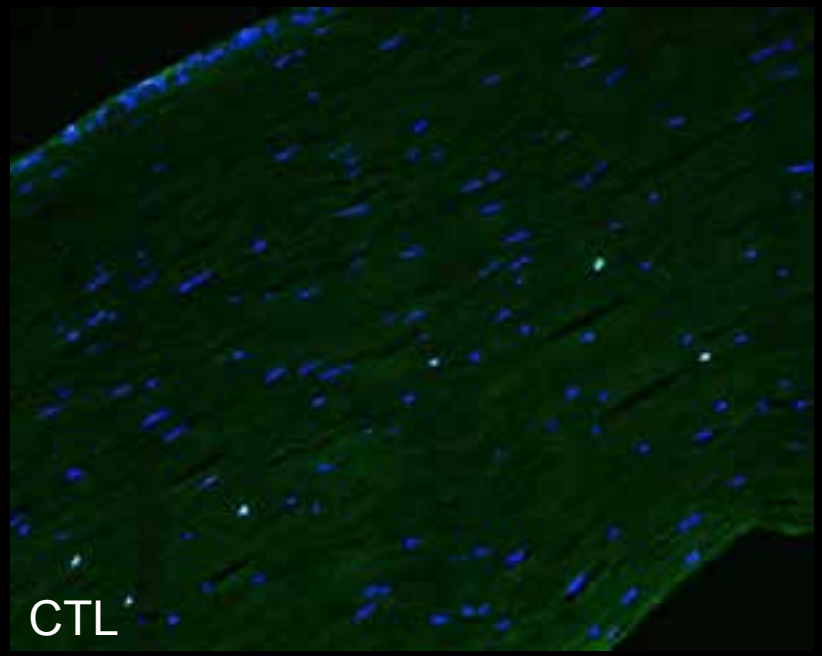
Gruppo2

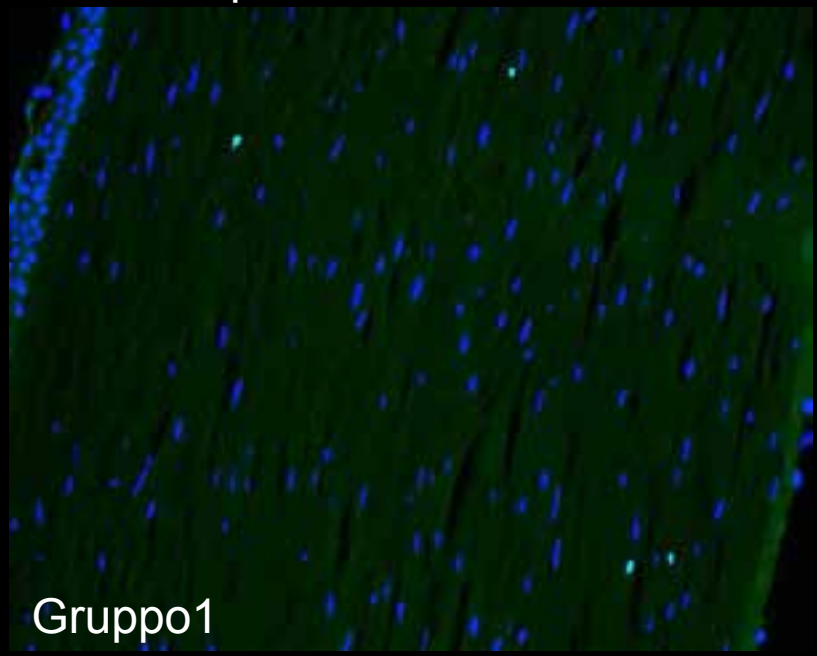


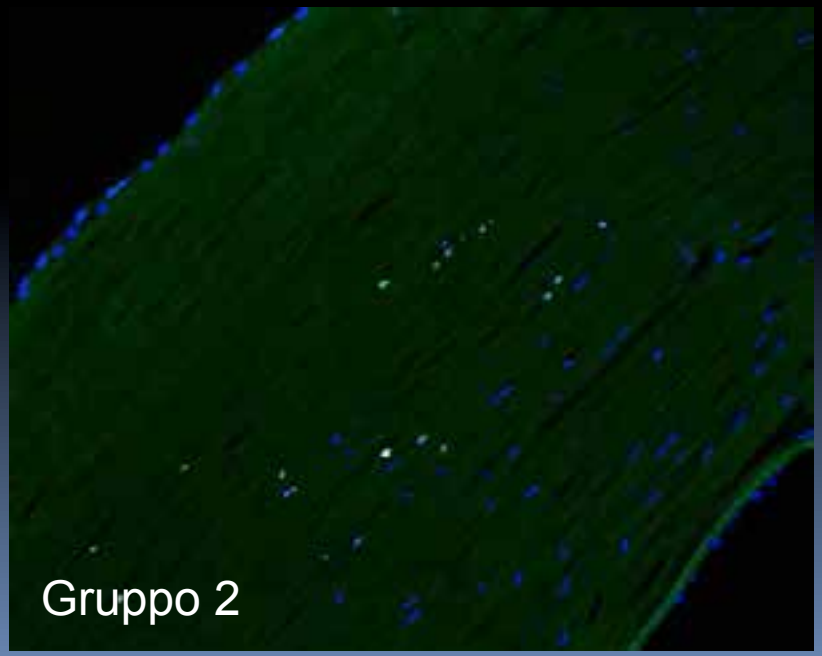
Group3

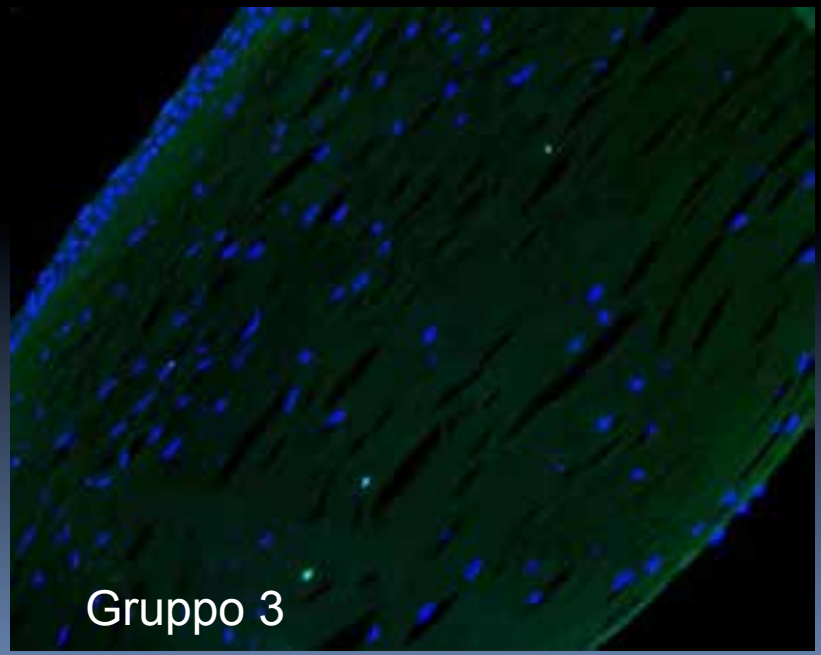
x5

TUNEL: indice apotosi



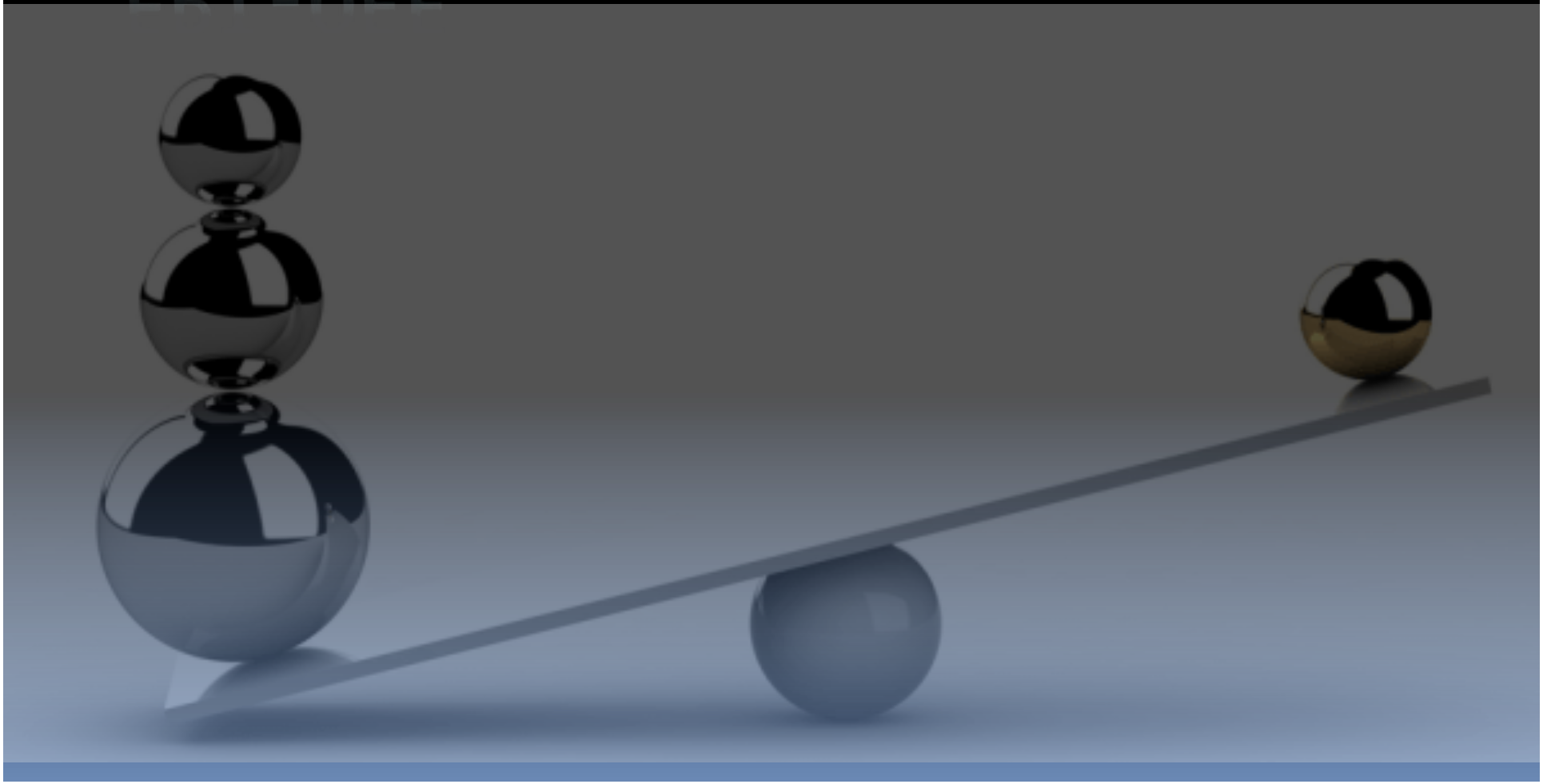






x10

WHAT'S NEW?
COMPARISON WITH STANDARD EPI-OFF



JRS 2016

ORIGINAL ARTICLE

Transepithelial Iontophoresis Versus Standard Corneal Collagen Cross-linking: 1-Year Results of a Prospective Clinical Study

Paolo Vinciguerra, MD; Vito Romano, MD; Pietro Rosetta, MD; Emanuela F. Legrottaglie, MD; Raffaele Piscopo, MD; Claudia Fabiani, MD; Claudio Azzolini, MD; Riccardo Vinciguerra, MD

ABSTRACT

PURPOSE: To compare 1-year transepithelial corneal collagen cross-linking with iontophoresis (I-CXL) outcomes with standard CXL (S-CXL) epithelium-off for progressive keratoconus.

METHODS: Forty eyes of 40 patients with progressive keratoconus were included in this comparative, prospective clinical study. Corrected distance visual acuity (CDVA), spherical equivalent, cylinder refraction, corneal topography, Scheimpflug tomography, aberrometry, and endothelial cell count were assessed at baseline and at 1, 3, 6, and 12 months of follow-up.

RESULTS: Patients received either I-CXL (20 eyes) or S-CXL (20 eyes). Functional parameters (visual acuity and aberrometry) showed a significant improvement ($P < .05$) after 6 and 12 months of follow-up in both groups. In the I-CXL group, the CDVA showed a rapid recovery of vision after 3 months ($P = .01$).**AQ1** Morphological parameters showed a significant reduction of maximum keratometry in the S-CXL group by -1.05 ± 1.51 D after 12 months, whereas the I-CXL group curvature was stable (-0.31 ± 1.87 D). Minimum pachymetry values were stable even after 12 months of follow-up in the I-CXL group, whereas a significant corneal thinning 12 months following treatment was recorded in the S-CXL group ($P < .001$). None of the patients had continuous progression of keratoconus or had to repeat CXL procedures. Endothelial cell counts did not change significantly ($P > .05$).

CONCLUSIONS: The 1-year outcomes suggest that I-CXL might be comparable to S-CXL in stabilizing the progression of the degenerative ectatic disease. Additionally, quicker improvement of functional parameters was reported in the I-CXL group.

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Corneal collagen cross-linking (CXL) is currently the only treatment able to slow or halt the progression of ectatic disease.[1-4] Long-term follow-up studies on CXL refer to the standard technique (S-CXL), which entails epithelial debridement to allow riboflavin (hydrophilic) penetration in the corneal stroma; otherwise the corneal epithelium (lipophilic) reduces its permeability.[5] Nevertheless, epithelial removal causes postoperative pain,[6] delayed visual recovery,[1,7,8] and increased risks of infection. Transepithelial cross-linking (TE-CXL) was introduced to avoid these threats. The original dextran-containing solutions have been reported to be ineffective for TE-CXL,[9-11] but other formulations of riboflavin (with chemical enhancers)[12] showed equivocal results in clinical studies.[13-15] Conversely, preliminary results have shown that transepithelial cross-linking with iontophoresis (I-CXL) is able to increase the riboflavin concentration inside the stroma compared to other TE-CXL techniques together with histological changes.[16-18] Pilot clinical findings using I-CXL have also reported encouraging results.[19] In this study, we compared 1-year results of two groups of patients with keratoconus who were treated with I-CXL and S-CXL (epithelium-off Dresden protocol).

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Dr. Paolo Vinciguerra is a consultant for Nidek and Oculus Optikgeräte, GmbH. The remaining authors have no financial or proprietary interest in the materials presented herein.

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Aim

- To compare 1-year transepithelial corneal collagen cross-linking with iontophoresis (I-CXL) outcomes with standard CXL (S-CXL) epithelium-off for progressive keratoconus.

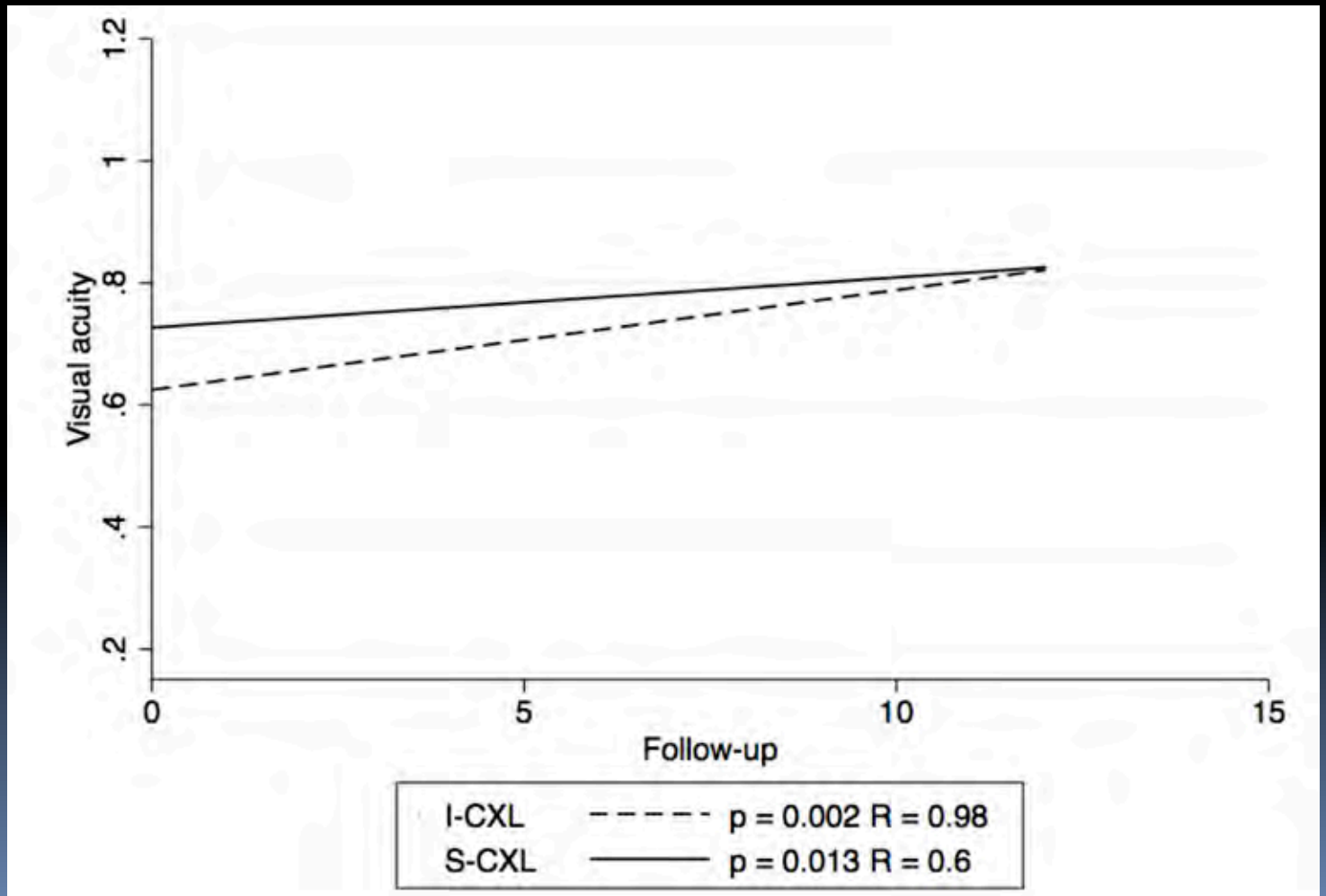
Study design

- Prospective comparative
  - 20 eyes of 20 patients Ionto (I-CXL)
  - 20 eyes of 20 patients Stadard 3 mW (S-CXL)
- 12 months of follow up
- Corrected distance visual acuity (CDVA), spherical equivalent, cylinder refraction, corneal topography, Scheimpflug tomography, aberrometry, and endothelial cell count were assessed.

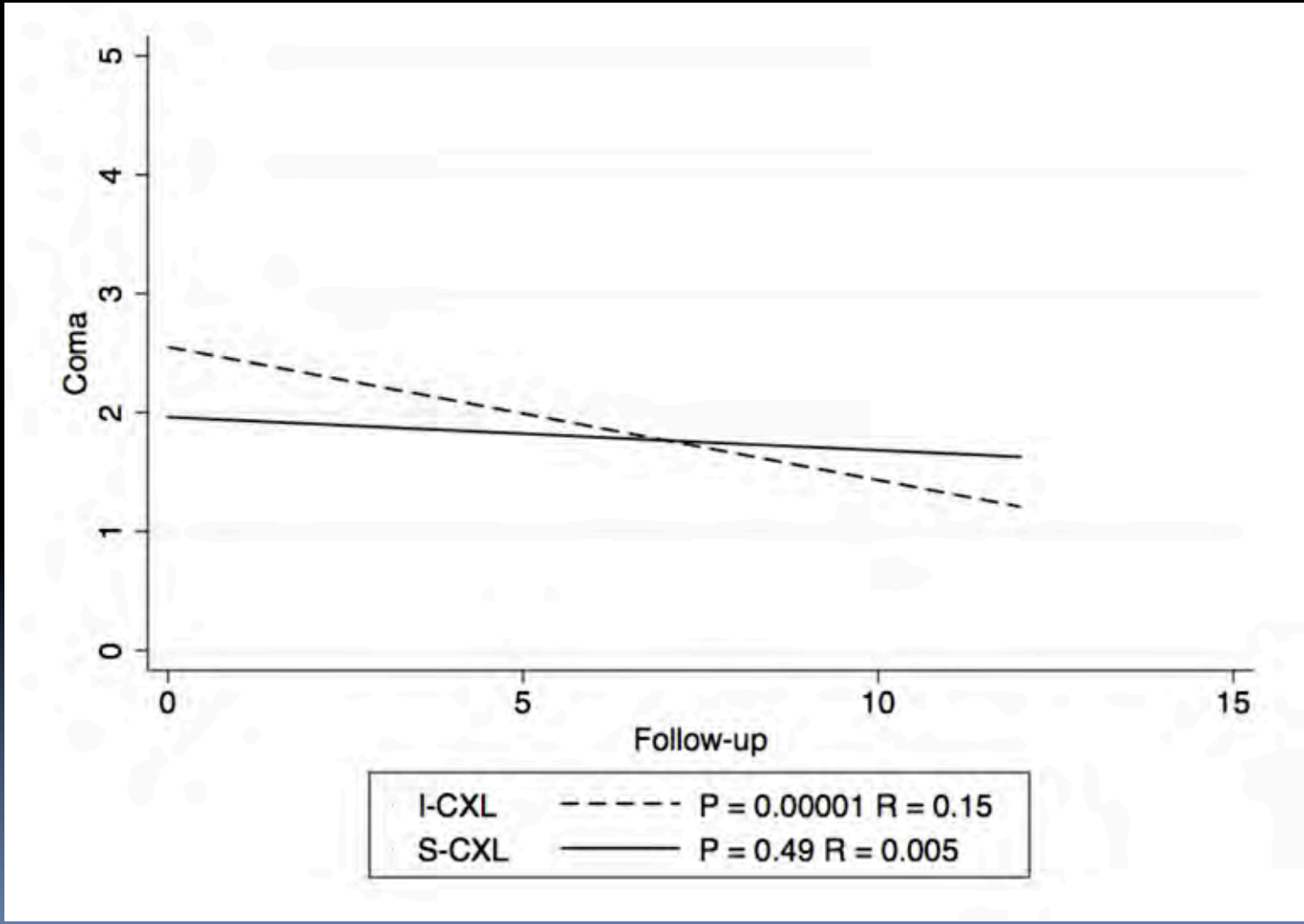
Results

- BCVA
  - I-CXL e S-CXL were comparable, both inducing a significant increase in BCAV
  - I-CXL induces a faster recovery (already at month 3)
- HOA
  - I-CXL is able to significantly reduce HOA and Coma (month 6 and 12)
  - S-CXL group showed an improvement only in coma after 6 and 12 months

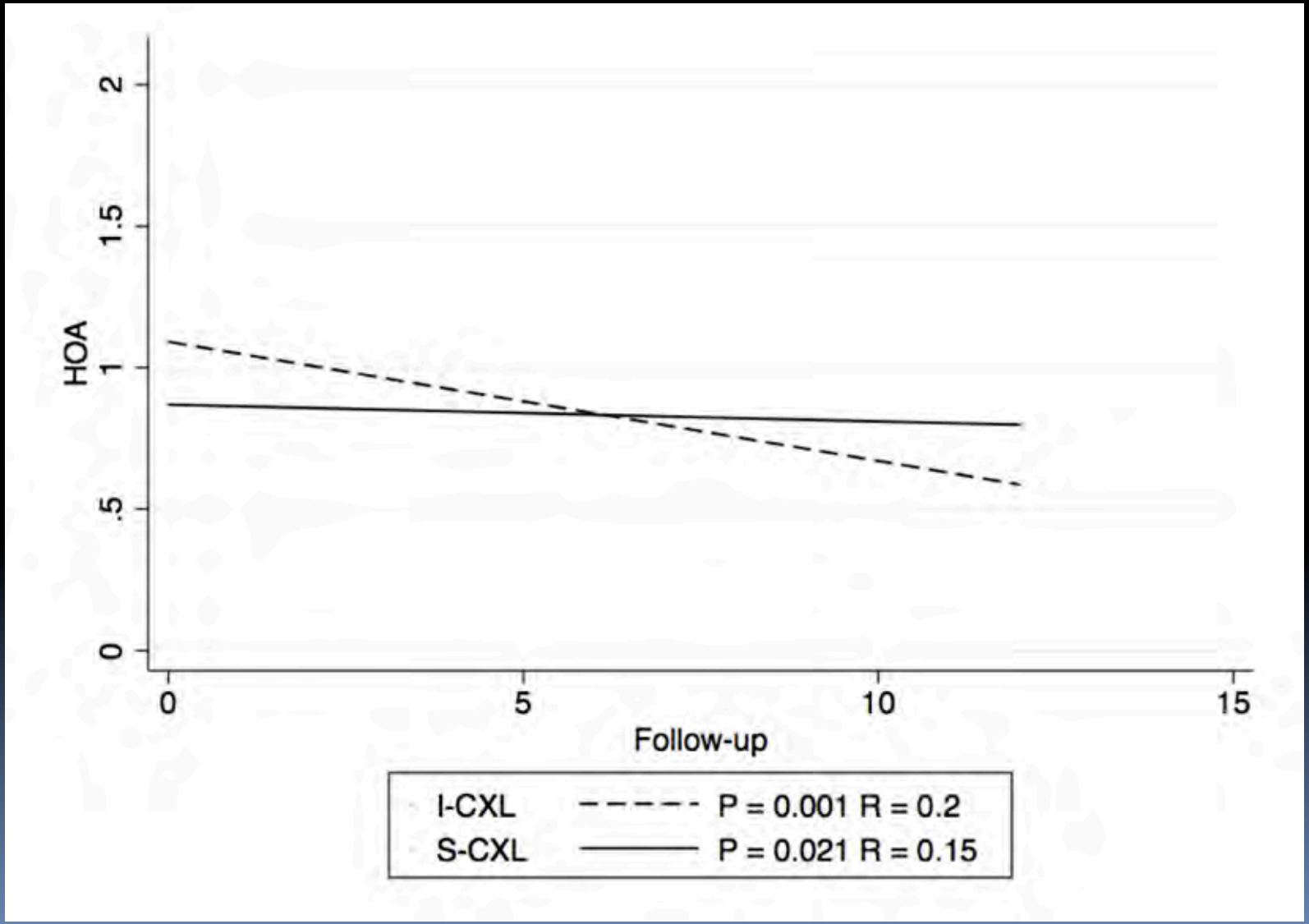
Visual acuity linear regression



Coma linear regression



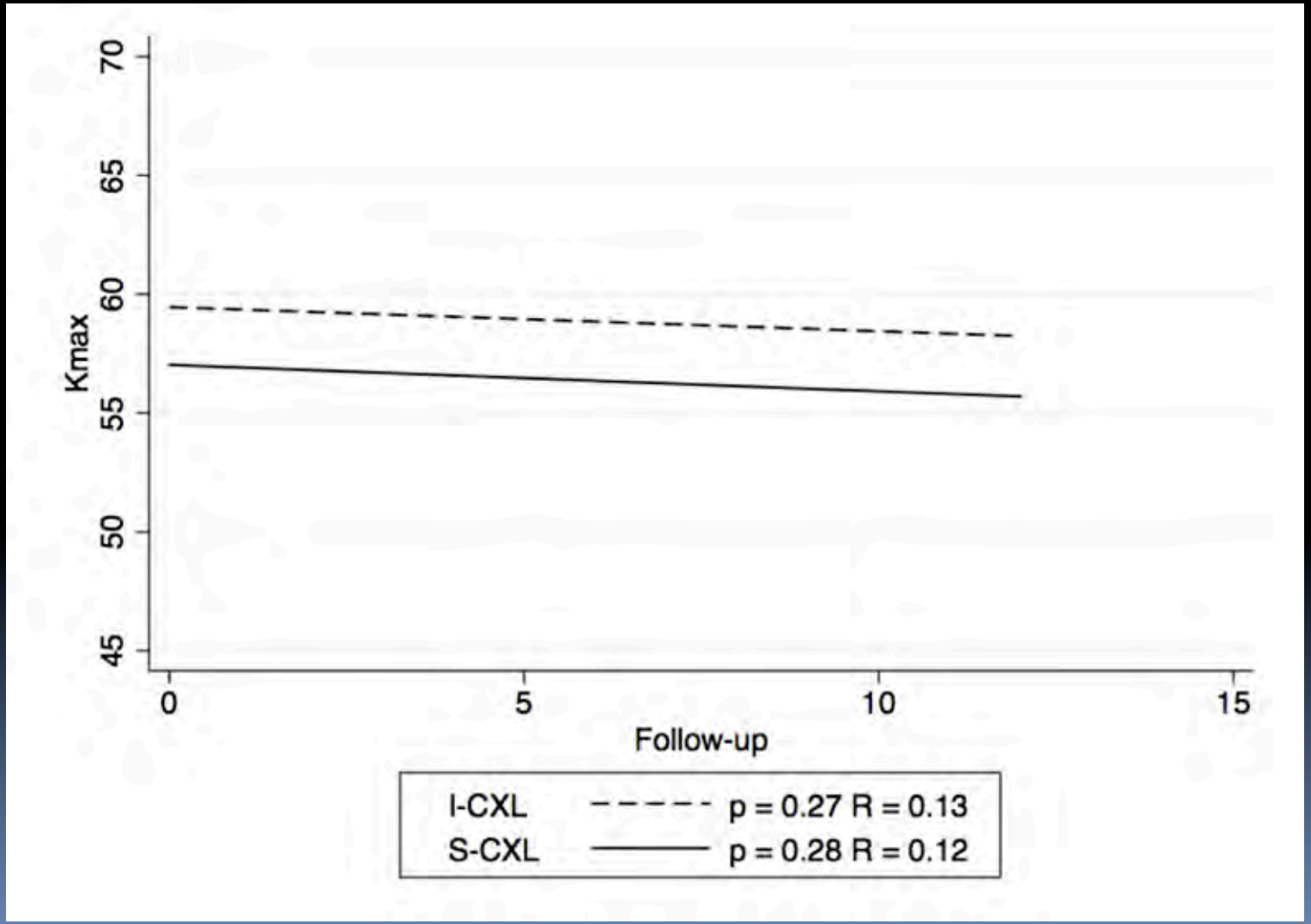
HOA linear regression



Results

- Kmax
  - S-CXL induced a significant improvement of numerous topographic indices during the follow-up (such as CKI)
  - Kmax was reduced significantly by -1.05 ± 1.51 D after 12 months after S-CXL.
  - I-CXL only showed a significant improvement of corneal symmetry index after 12 months of follow-up.
  - The reduction of -0.31 ± 1.87 of Kmax did not reach statistical significance in I-CXL group.

However, linear regression analysis for Kmax was not significant in either group



Results

- Pachymetry
  - The main result of this analysis is that there is a statistically significant thinning of the minimum corneal thickness in the S-CXL group (*P* = .0001), whereas this did not occur after I-CXL.
  - Even after 12 months of follow- up; this difference was statistically significant

Discussion

- These results highlight the clinical efficacy of I-CXL to overcome the problems of TE-CXL: the penetration of riboflavin through the epithelium.
- It is known from preclinical reports that the biomechanical effect, riboflavin penetration, and distribution of I-CXL are higher than in TE-CXL but lower when compared to S-CXL.
- We will continue the follow-up of the patients to determine whether this stiffening effect, even if reduced, will be enough to halt the ectatic disease in the long term.

Conclusions

- At 12 months follow up
  - I-CXL is not inferior to S-CXL
  - Faster recovery of BCVA
  - More reduction of HOA and Coma
  - Does not induce thinning

- Only 12 months! Follow up continues!

Conclusions

- Iontophoresis is a safe technique
- It appears effective in arresting the progression of the disease
- Significant imrpovements of functional parameters
- Reduction of pain