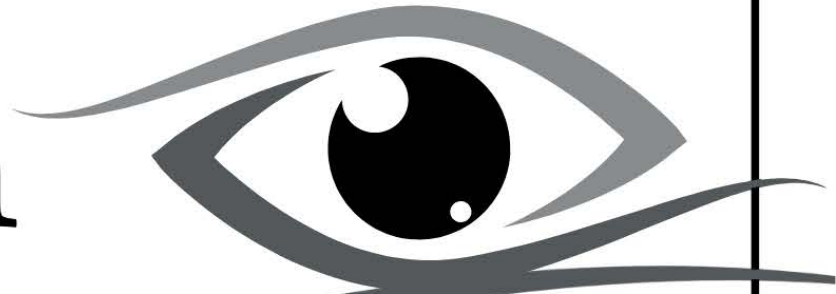




College of Optometry
UNIVERSITY OF HOUSTON

CE in
Austin

October 26-27, 2024



**Saturday
Handouts**

Conference Director

Janet Garza, OD, FAAO

CE in Austin

October 26-27, 2024

Conference Director
Janet Garza, OD, FAAO

Conference Moderator
Pat Segu, OD, FAAO

Program Location
DoubleTree by Hilton Austin
6505 North Interstate 35, Austin, TX 78752

Saturday, October 26, 2024

7:00 am - 8:00 am	Check-In: Badge Pick Up and Seating		
8:00 am - 8:05 am	Announcements & CE Credit Overview		
8:05 am - 9:45 am	Oral Pharmaceuticals in Primary Care Optometry <i>Blair Lonsberry, OD</i>	2 D/T Hours	COPE ID # 88662-PH
9:45 am - 10:15 am	Break		
10:15 am - 12:00 pm	Systemic Diseases and Glaucoma <i>Blair Lonsberry, OD</i>	2 D/T Hours	COPE ID # 94071-GL
12:00 pm - 1:00 pm	Lunch		
1:00 pm - 1:50 pm	Top 10 Medications and Their Ocular Side Effects <i>Blair Lonsberry, OD</i>	1 D/T Hour	COPE ID # 91265-PH
1:50 pm - 2:05 pm	Break		
2:05 pm - 2:55 pm	Xtra, Xtra- Read All About It! Combination of Refractive Surgery with Corneal Crosslinking(CXL) in Borderline Corneas <i>Anuradha Veerappan, OD, MS</i>	1 D/T Hour	COPE ID # 93884-PO
2:55 pm - 3:15 pm	Break		
3:15 pm - 5:00 pm	Cataract Surgery: Pre and Post Op Care <i>Anuradha Veerappan, OD, MS & Justin Simbulan, OD</i>	2 D/T Hours	COPE ID # 93886-PO

Systemic Diseases and Glaucoma

Blair Lonsberry, MS, OD, MEd., FAAO
 Professor of Optometry
 Pacific University College of Optometry
 blonsberry@pacificu.edu

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- ### Disclosures:
- AbbVie: advisory board
 - Sun Pharmaceuticals: speakers bureau,
 - Apellis: speakers bureau,
 - Dompe: advisory board,
 - Thea Pharmaceuticals: advisory board

2

- ### Case
- 55 YO Black male presents for an eye exam with complaint of decreased vision at near
 - Medical history:
 - Hypertension- managed with lisinopril
 - Type 2 diabetes- managed with metformin
 - Cholesterol – takes a statin
 - Ocular history:
 - Mother has advanced glaucoma (he brings her in for her appointments)

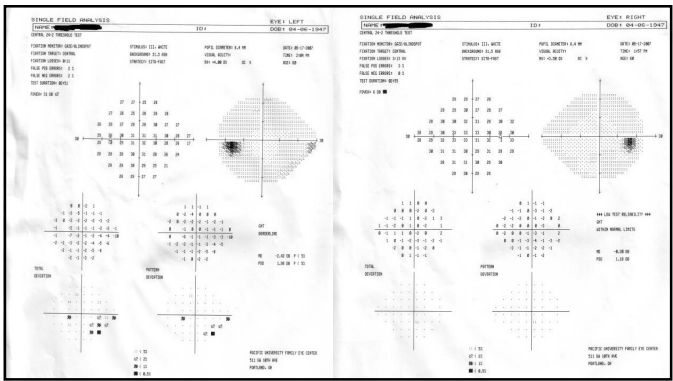
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- ### Case
- VA: 20/20 OD, 20/20 OS
 - PERRL no APD
 - Gonio: ciliary body in all quadrants
 - Pachy: 540, 550 OD, OS
 - IOP: 16, 16
 - Fundus eval: see photos
 - OD: 0.45/0.45
 - OS: 06/0.5
 - HVF: see photos

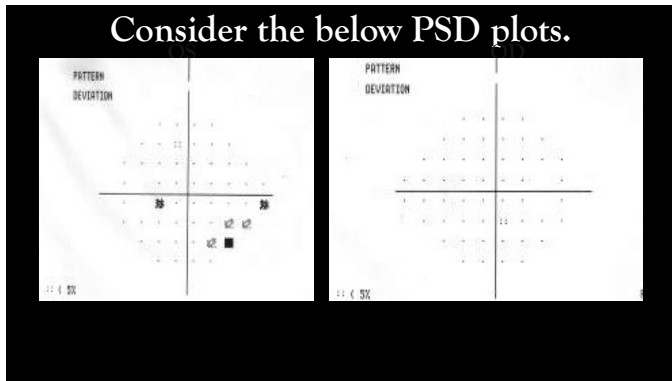
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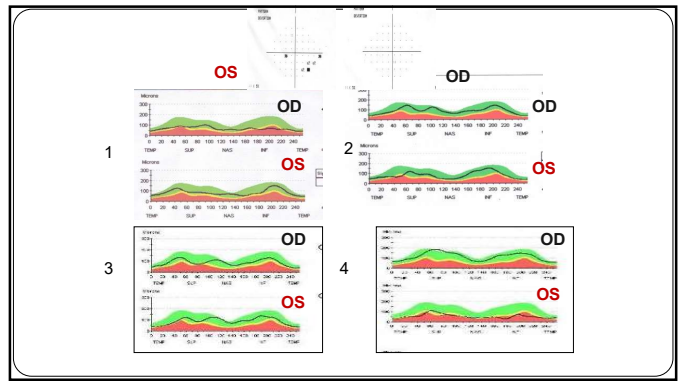
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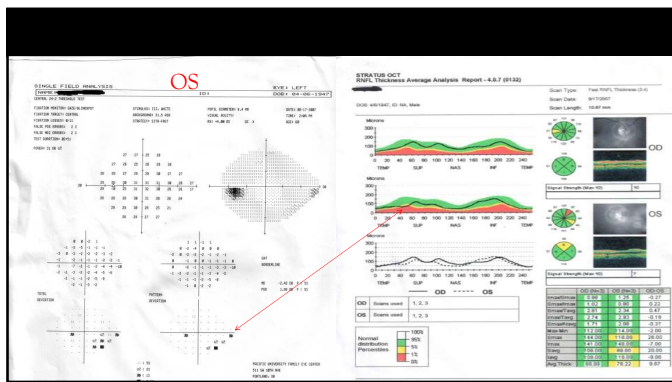
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8



9

What we did.

- We discussed with the patient:
 - appears he has early glaucomatous changes
 - early nasal step OS,
 - reduced NFL OS
 - positive family history
 - Positive for medical history of diabetes, cholesterol and hypertension
 - educated patient that we could monitor him very closely every 3 months and watch for further change, and then begin treatment at that time
 - or he could begin treatment

10

Treatment/Follow Up

- Patient chose to begin treatment
- We started him on Travatan Z qhs in the left eye
 - felt this would be the best medication for lowering his eye pressure without significant side effects related to his hypertension
- Patient returned 2 weeks later for a follow up and his IOP had decreased from 16 to 12 in the left eye.
- Patient asked whether there was potential to have glaucoma in his right eye
 - said it was possible and he decided he wanted to initiate treatment in his right eye as well.

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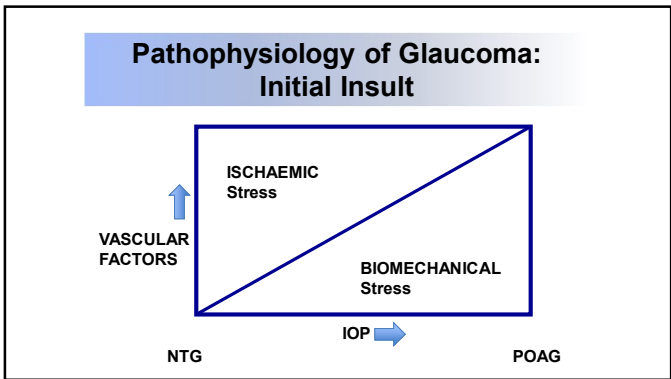
Do systemic diseases play a role in the pathogenesis of glaucoma?

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Glaucoma as a Systemic Disease

- Vascular Theory of Glaucoma – Ischemia
- Mechanical Theory of Glaucoma – Pressure
- Neurodegenerative Disease like Alzheimer’s Dementia (AD)
- Autoimmune Disease
- Systemic medications

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Initial Insult?

- Mechanical Theory
 - suggests that glaucoma may be the result of increased IOP, resulting in high-tension areas that cause displacement and deformation of the cribriform plate, compression of prelaminar tissue, and, as a result, loss of glial cells
 - The reason for an increased IOP is an increase in resistance in the main structures of the eye fluid outflow – in the trabecular reticulum and Schlemm’s canal
 - Elevated IOP directly damages nerve fibers as they pass through the ONH.

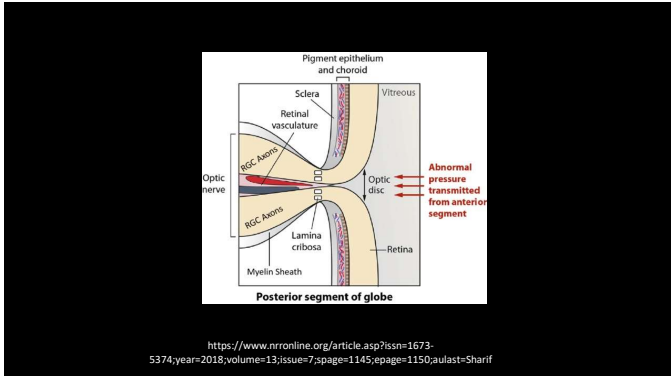
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Pathophysiology of Glaucoma

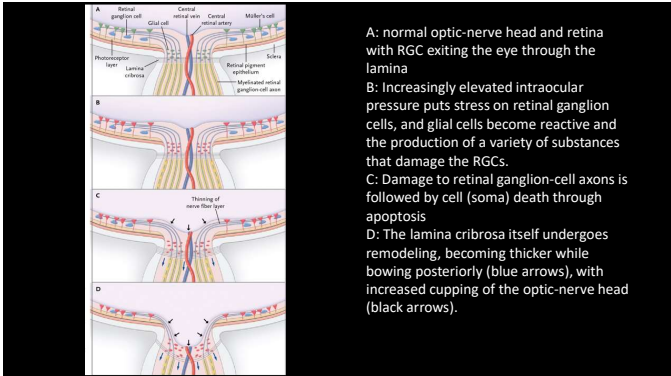
Optic Nerve Head

- Loss of retinal ganglion cells
 - Blockage of axonal transport at the level of the lamina cribrosa
 - Loss of neurotrophic factors induces apoptotic cascade
 - genetically programmed cell suicide, no inflammation
 - Apoptosis may also be caused by excitotoxicity from ischemia
- Remodeling of lamina cribrosa
- Loss of neuroretinal rim

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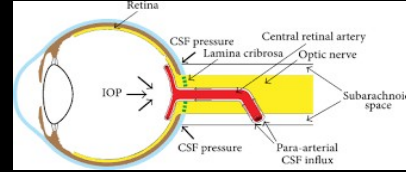


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Initial Insult?

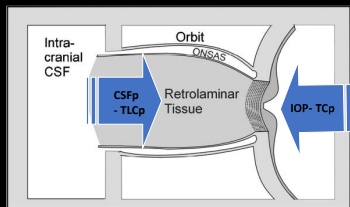
- Vasogenic/Vascular Theory
 - decrease in the hemoperfusion of the eye, which leads to ischemia of the optic disk and retina
 - does not give full account of this theory, since there is evidence of both hypertension as a serious risk factor for the development of glaucoma and hypotension, which strongly affects the development of glaucoma
 - Elevated IOP damages microvasculature of ONH, thus axons die.
 - Difference between IOP and ONH perfusion pressure.

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Trans-LC Pressure Difference



This model could explain why patients with NTG tend to have a low systemic BP and why eyes with normal IOP glaucoma and eyes with high-pressure glaucoma, in contrast to eyes with a direct vascular optic neuropathy, show profound similarities in the appearance of the ONH

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Ocular Blood Flow

- Ocular blood flow (OBF) is a key factor for the health of retinal ganglion cells.
- According to Ohm's law, it depends on ocular perfusion pressure (OPP) and the vascular resistance ratio; the mechanisms of retinal autoregulation can modify the latter.
- Clinical data show that OPP correlates better with the occurrence and progression of glaucomatous lesions compared to blood pressure (BP) or IOP alone

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- Retinal autoregulation is the complex physiological process by which constant blood flow is ensured despite significant variations in the OPP
- Vascular dysregulation is a primary step initiating glaucomatous damage via OBF instability, affecting the optic nerve and retina by the enhancement of ischemic injury and promoting the apoptosis of retinal ganglion cells.
- Changes in arteriolosclerosis additionally bring a vulnerability factor of the optic nerve to small variations in perfusion eye pressure by compromising auto-regulation

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- vascular dysregulation may increase the vulnerability of the optic nerve to slight variations of IOP, BP or metabolic needs of retinal ganglion cells, because in this case, small variations of OPP may cause a significant decrease in OBF, beyond normal limits, resulting in retinal ganglion cell ischemia

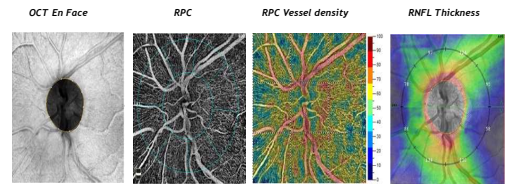
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Ocular Perfusion Pressure

- Mean **ocular perfusion pressure (MOPP)** = $\frac{2}{3}$ (mean arterial **pressure** – IOP)
 - where mean arterial **pressure (MAP)** = $DBP + \frac{1}{3}(SBP - DBP)$
- Probably more clinically relevant:
 - **DPP (diastolic PP):** $DBP - IOP$

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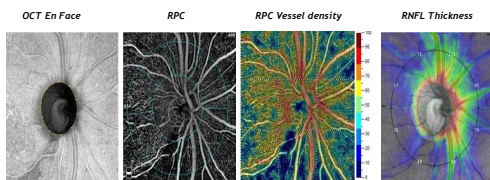
Normal Eye



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

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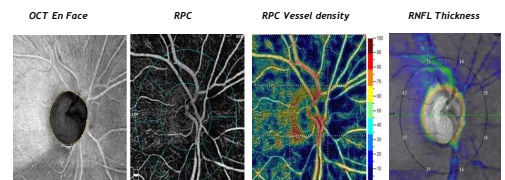
Moderate Glaucoma



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

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Advanced Glaucoma



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

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Blood Pressure

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Systemic HTN and Glaucoma

- Beaver Dam Eye Study (2005)
 - Beaver Dam Eye Study found an increase in IOP of 0.24 mmHg for every 10 mmHg of systolic BP and 0.43 mm Hg increase in IOP/10 mm increase in diastolic BP
 - The pathophysiological mechanisms include an increase in the ultrafiltration of the aqueous humor, an increase in the pressure in the episcleral veins, with secondary reduced trabecular filtration, but also an increase in the general sympathetic tonus with age.
 - Decreasing systolic or diastolic BP > 10 mm Hg over 5 years associated with significant reduction of IOP
- British General Practitioner Data Base (2005)
 - Patients with glaucoma 23%-36% more likely to have systemic HTN than patients without glaucoma

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- extensive clinical studies show, paradoxically, that chronic arterial hypertension may increase the risk of glaucoma, despite the protection that should be associated with increased OPP
- The Baltimore Eye Survey showed a relationship dependent on the age of the subjects:
 - Protective effect for the young and a risk factor for the elderly, probably explained by the associated peripheral vascular changes.
- In clinical practice, in older individuals, glaucoma and arterial hypertension, treated or not coexist frequently.
- Clinical studies support the existence of a clinical paradox:
 - Too aggressive lowering of BP is not beneficial for tissue perfusion, not only at the level of the retina and optic nerve but also in the brain and heart

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The Relationship Between Components of Metabolic Syndrome and Open-Angle Glaucoma

Paula Anne Newman-Casey, MD,¹ Nidhi Tahir, MS,¹ Bin Nan, PhD,² David C. Muech, PhD, MPH,^{1,2} Joshua D. Stein, MD, MS¹

Table 4. Hazard for Open-Angle Glaucoma Among Patients with One or More Components of the Metabolic Syndrome*

Metabolic Syndrome Component	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
Hypertension only	1.26 (1.22-1.31)	<0.001	1.17 (1.13-1.21)	<0.001
Diabetes only	1.47 (1.34-1.61)	<0.001	1.35 (1.21-1.50)	<0.001
Hyperlipidemia only	0.94 (0.91-0.98)	<0.001	0.95 (0.91-0.99)	0.004
Obesity	1.14 (1.11-1.17)	<0.001		
Obesity-x interaction				
Female, obese ^a			1.06 (1.00-1.10)	0.011
Male, obese ^a			0.98 (0.94-1.03)	0.538
Diabetes + hypertension	1.79 (1.69-1.89)	<0.001	1.48 (1.39-1.58)	<0.001
Diabetes + hyperlipidemia	1.28 (1.21-1.36)	<0.001	1.13 (1.05-1.21)	<0.001
Hypertension + hyperlipidemia	1.15 (1.12-1.18)	<0.001	1.09 (1.06-1.12)	<0.001
Diabetes + hypertension + hyperlipidemia	1.51 (1.46-1.57)	<0.001	1.26 (1.22-1.31)	<0.001

Ophthalmology. 2011 Jul;118(7):1318-26. doi: 10.1016/j.ophtha.2010.11.022. Epub 2011 Apr 9.

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- ### Possible Reasons that HTN is a Risk Factor for Glaucoma
- Arteriosclerotic damage to vessels feeding the optic nerve (vascular theory of glaucoma)
 - Increased ciliary body perfusion causing increased aqueous production (elevated IOP)
 - Increased episcleral venous pressure (elevated IOP)
 - Association with Hypotension
 - Blood pressure medications
 - Dys(auto)regulation

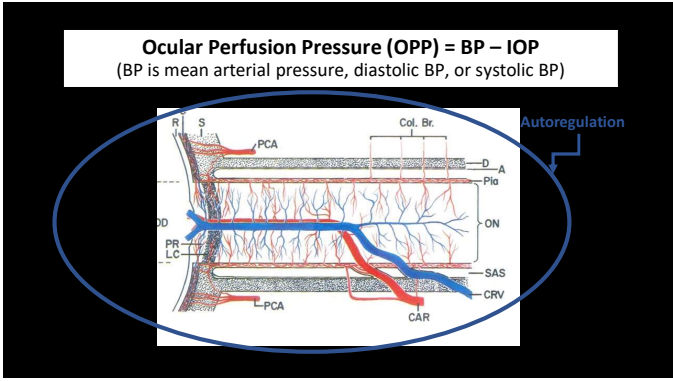
33

- ### Low Blood Pressure
- Low diastolic BP (DBP) has the immediate effect of reducing OPP, with insufficient ocular perfusion.
 - Numerous studies, across large population groups, show a high correlation between low OPP and prevalence, incidence and progression of glaucoma
 - The Egna-Neumarkt Study demonstrated that low diastolic pressure below 50 mmHg is associated with a 4.5-fold prevalence of glaucoma compared to those with a diastolic pressure above 65 mmHg.
 - in the Provector VER study, patients with diastolic pressure below 45 mmHg were found to have a 3-fold risk of developing glaucoma in comparison to subjects with DBP above 65 mmHg.

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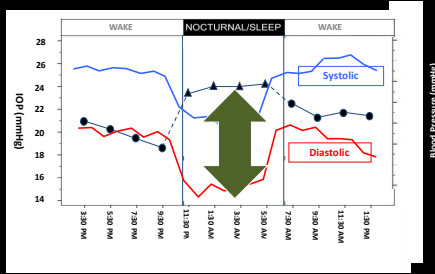
- ### Low Blood Pressure
- The Barbados Eye Study demonstrated a 2-fold risk of glaucoma in individuals with arterial hypotension.
 - Individuals with an SPP < 98 mm Hg had a higher risk of glaucoma progression than those with an SPP > 153 mm Hg, and a DPP < 53 mm Hg was associated with a higher risk of glaucoma progression than was a DPP > 73 mm Hg
 - Nocturnal -dips- of more than 10 mmHg compared to DBP baseline were found to be another documented risk factor for glaucoma progression

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Habitual IOP and Pulse Pressure



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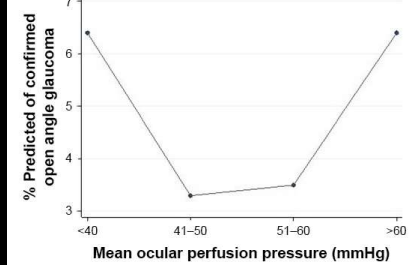


Figure 3 Relationship between OPP and confirmed POAG. Abbreviations: OPP, ocular perfusion pressure; POAG, primary open-angle glaucoma.

Cantor E, Mendez F, Rivera C, Castillo A, Martinez-Blanco A. Blood pressure, ocular perfusion pressure and open angle glaucoma in patients with systemic hypertension. Clin Ophthalmol. 2016;10:1511-1517. <https://doi.org/10.2117/OPH.116747>

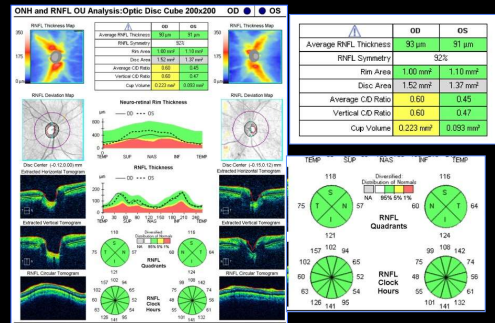
38

Arturo: 50 y/o Russian Male

- RK 1991 -> 20/20 with hyperopic correction: +5.50 -1.50X090
- TA: 32/18
- Pach
 - 544 μ
 - 558 μ
- Gonio -CBB
- - PMHx
- - meds



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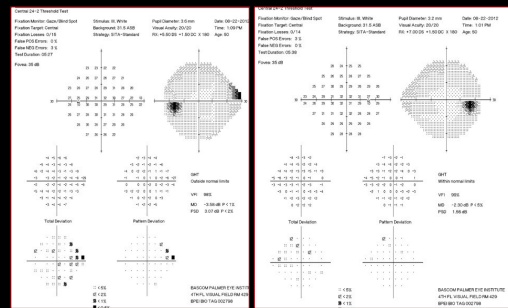


40

1 Mo Later

- TA: 24,25 RE; 18 LE
- (Initial IOP 32/18)
- How do you account for the difference?
- Illustrates the importance of establishing a baseline

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IOP and Glaucoma Progression

- In addition to the absolute IOP level, **IOP fluctuations and, in particular peaks, have been well accepted as an independent risk factor for glaucoma progression.**
- Several studies have previously reported the association between IOP peak and visual-field decline in primary open angle glaucoma (POAG).

Relationship between nocturnal intraocular pressure-related peak recorded by contact lens sensor and disease progression in treated glaucomatous eyes

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- Literature suggests that in a majority of normal subjects and glaucoma patients, the IOP peak is recorded during the nocturnal period during which IOP measurement is not routinely obtained.
- **There is also enough evidence to support that IOP measurements during routine office hours fail to detect IOP peak in up to 62% of glaucoma patients.**
- Nevertheless clinicians judge the therapeutic efficacy of IOP-lowering interventions on measurements obtained during the office hours. Therefore, potentially missing the highest 24 hour IOP reading is responsible for causing progression in treated glaucomatous eyes.

Relationship between nocturnal intraocular pressure-related peak recorded by contact lens sensor and disease progression in treated glaucomatous eyes

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Original Article

Relationship between nocturnal intraocular pressure-related peak recorded by contact lens sensor and disease progression in treated glaucomatous eyes

Suneeta Dubey, Deepthi Mittal, Saptareshi Mukherjee, Madhu Bhoot, Yadunandan P Gupta

- 2020 study found that there exists a definite association between Nocturnal IOP-related spike and disease progression in treated glaucomatous eyes.
- **Patients showing glaucoma progression on Guided Progression Analysis (GPA) of the Humphrey Visual Field (HVF) Analyzer were more prone to develop Nocturnal IOP-related peak than those patients who are clinically stable with no documented progression on visual field analysis.**

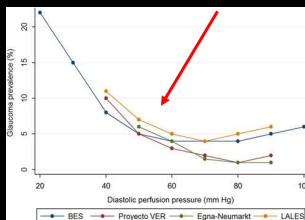
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OPP and Glaucoma Risk: Cross-Sectional Studies

- Baltimore Eye Survey (AA and Caucasian)¹
 - 6x increased incidence of POAG in subjects with lowest category of Ocular Perfusion Pressure (OPP)
- Egna-Numarkt Study (Caucasian)²
 - Lower Diastolic Ocular Perfusion Pressure (DOPP) associated with 2.5 fold increase in glaucoma risk
 - diastolic pressure below 50 mmHg is associated with a 4.5-fold prevalence of glaucoma compared to those with a diastolic pressure above 65 mmHg
- Los Angeles Latino Eye Study (Latino/Hispanic)³
 - 1.9 fold increase in glaucoma risk in those with lower OPP
- Proyecto Ver (Hispanic)⁴
 - Found lower Diastolic Perfusion Pressure (DPP) associated with 4-fold increased risk of POAG
 - patients with diastolic pressure below 45 mmHg were found to have a 3-fold risk of developing glaucoma in comparison to subjects with DPP above 65 mmHg
- **Nocturnal -dips- of more than 10 mmHg compared to DBP baseline were found to be another documented risk factor for glaucoma progression**

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Cross-Sectional Studies



J Glaucoma, 2018

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24-Hour IOP and Blood Pressure

- **therapeutic planning of glaucomatous patients should also include 24-h automated monitoring of BP, especially in those cases with IOP within the limits of the target values but showing progression of VF defects.**
- Moreover, clinical studies show that patients with low OPP or large nocturnal 'dips' in BP frequently present with autoregulation disorders both in the retinal vasculature and in the peripheral circulation in general
 - **Nocturnal -dips- of more than 10 mmHg compared to DBP baseline were found to be another documented risk factor for glaucoma progression**
- Although higher SPPs are observed in POAG patients during the morning, lower DPPs are found during the night (Costa, et al., BJO 2010)
- 48-hour ambulatory BP measurement (Charlson, et al., Ophthalmol 2014) in patients with NTG

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Increased Nighttime Blood Pressure in Patients with Glaucoma

Cross-sectional Analysis of the LIGHT Study

Takamitsu Yoshikawa, MD, PhD,¹ Kenji Ohayashi, MD, PhD,² Kimie Miyata, MD, PhD,¹ Keigo Sasaki, MD, PhD,² Nahoko Ogata, MD, PhD¹

Ophthalmology
Volume 126, Issue 10, October 2019, Pages 1360-1371

- **Conclusions:** "The presence of glaucoma was associated significantly with increased nighttime BP and the nondipper pattern of the BP... Further prospective studies are needed to determine whether the glaucoma severity and progression are associated with the nighttime BP"

LIGHT = Longitudinal Study of Biological Circadian Rhythms in Glaucoma Patients: Home Testing of Circadian Intraocular Pressure and Biological Parameters

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Risk Factors Associated with Structural Progression in Normal-Tension Glaucoma: Intraocular Pressure, Systemic Blood Pressure, and Myopia

Wanhyun Lee, Hyeon Yane, Joo Yeon Kim, Gwne Je Seonae, Chan Yun Kim, Hyoung Won Bae

- **Diabetes, disc hemorrhage, and minimum SBP were found to significantly influence structural progression.**
- Analysis identified 108 mm Hg as the cutoff value for minimum SBP and revealed minimum SBP and DBP to be the most significant variables for progressive peripapillary RNFL thinning and progressive macular GCIPL thinning, respectively.
- proposed cutoff (target) values for minimum SBP and DBP: 107–108 mm Hg and 63 mm Hg, respectively.

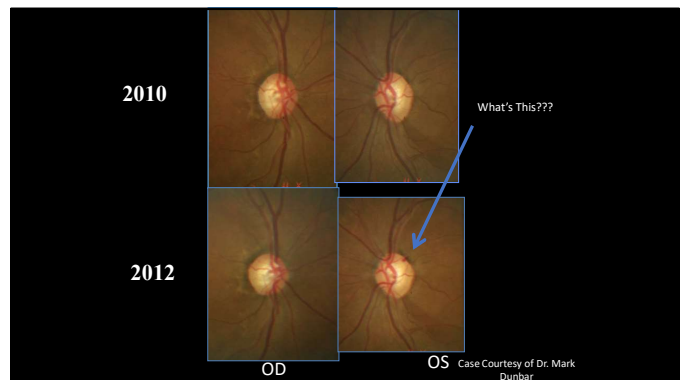
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Vesta: 61 y/o Hatian Female

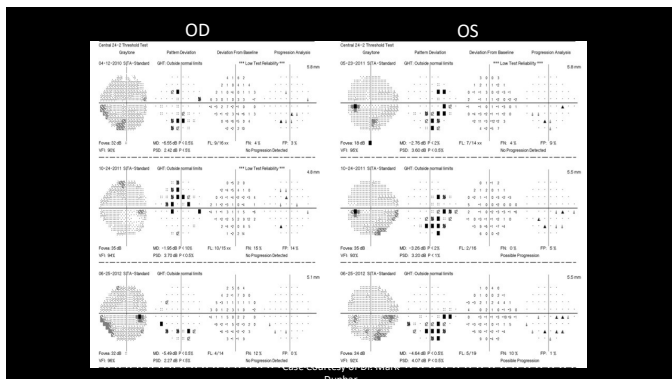
- GL suspect 2001 – suspicious ON's
- NTG since 2006
- Meds: Alphagan P bid OU, latanoprost qhs OU
- Medical Hx: HTN, HIV (+) for > 15 yrs
- VA: 6/6 (20/20)
- TA for the past 3 or 4 yrs: 9-13 mmHg OU
 - Last 2 visits 9 mmHg – today 13
 - Pachs: 450 microns

Case Courtesy of Dr. Mark Dunbar

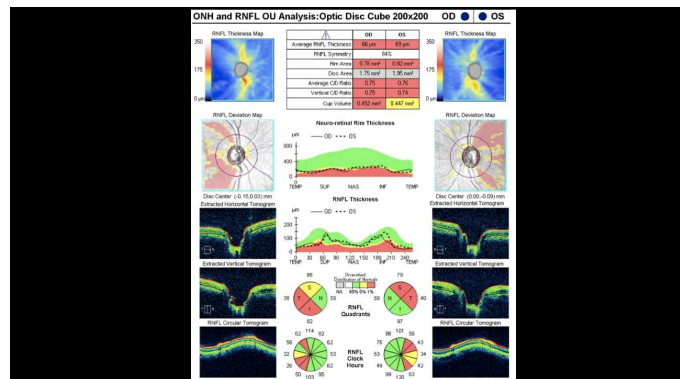
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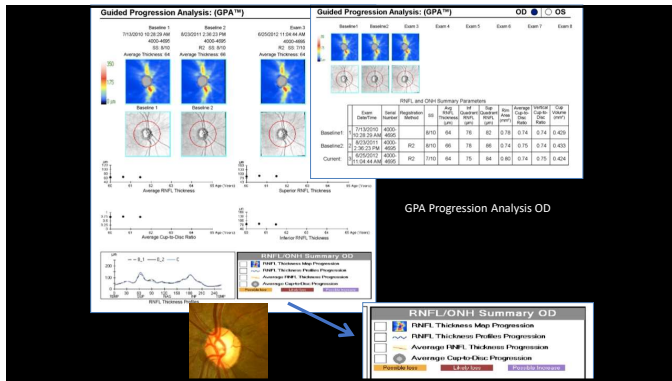
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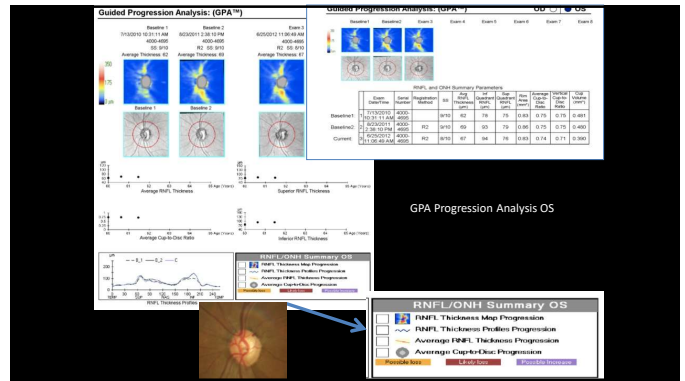
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Vesta: 61 y/o Hatian Female

- NTG OU with thin corneas
- OS:
 - Optic Nerve and HVF show trend towards progression....
- OCT shows no change

Case Courtesy Dr. Mark Dunbar

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Vesta: 61 y/o Hatian Female

- How do you manage this patient?
 - Currently on latanoprost and alphagan OU
- This is what was done....
 - Stopped Alphagan P
 - Switch to Combigan bid OU
 - Continue with latanoprost qhs OU
 - RTC 1 mo

Case Courtesy of Dr. Mark Dunbar

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Optic Disc Hemorrhages

- Quigley et al. suggested that disc hemorrhage occurs due to microvascular damage during posterior bowing of the lamina cribrosa
- In early glaucoma
 - Usually located inferotemporal or superotemporal
- Associated with:
 - Localized RNFL defects
 - Neuroretinal rim notches
 - Visual field loss
- Sign of progressive disease
 - OHTS, NTGS, EMGT

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- Within two months of detection can develop RNFL and visual field defect
- Most often in patients with focal normal-pressure glaucoma
- studies have reported that systemic vascular diseases, such as hypertension, diabetes mellitus, and atherosclerosis, can induce ischemic changes around the optic disc, increasing the incidence of disc hemorrhage
- Similar to systemic hypotension, ischemic changes induced by a disc hemorrhage might therefore affect the structural progression of NTG eyes

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Optometrists Can Impact OPP By:

- Measuring blood pressure
- Ensuring that at-risk patients are not taking their blood pressure meds at bedtime
- Working with PCPs to ensure that OPP is taken into account
- Prescribing glaucoma therapies that work during the nighttime period (PGA, CAI, ROCK inhibitors, SLT, surgery)
- Measuring nighttime IOP???

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Bedtime is the best time to take blood pressure medication

- Largest study finds greater reduction in risk of cardiovascular disease and death from bedtime rather than morning medication
- Date: October 22, 2019
- Source: European Society of Cardiology
- Summary: People with high blood pressure who take all their anti-hypertensive medication in one go at bedtime have better controlled blood pressure and a significantly lower risk of death or illness caused by heart or blood vessel problems, compared to those who take their medication in the morning, according to new research.
- Randomized 19,084 patients to taking their pills on waking or at bedtime, and followed them for the longest length of time -- an average of more than six years -- during which time the patients' ambulatory blood pressure was checked over 48 hours at least once a year.

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Cardiovascular Disease

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Cardiovascular Disease

- Cardiovascular disease (CVD) is a general term for conditions affecting the heart or blood vessels.
- CVD can include:
 - hypercholesterolemia,
 - hypertriglyceridemia,
 - Ischemic heart disease,
 - cerebrovascular disease,
 - transient ischemic attack,
 - valvular heart disease,
 - arrhythmia,
 - heart failure, and
 - vascular disease, including peripheral vascular disease and thromboembolic disease

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Risk Factors for Rapid Glaucoma Disease Progression

THOMAS CHUN-WAI CHAN, CHANDRA BALA, ANNA SRI, TIONA WAN, AND ANDREW WHITE

The risk of having rapidly progressive disease is doubled in those with a cardiovascular history

TABLE 3. Binomial Regression Analysis of All Risk Factor Variables for Rapidly Progressive Glaucoma Disease Within the Framework of Generalized Estimating Equations.

Variable	Odds Ratio (95% Confidence Interval)	P Value
Age (per year)	1.03 (0.99 - 1.06)	.19
Baseline MD (per 1-dB improvement)	0.93 (0.88 - 0.99)	.03
Medication changes (per change)	1.15 (1.02 - 1.30)	.02
IOP-lowering surgery (per surgery)	1.91 (1.50 - 2.44)	<.01
Baseline IOP (per mm Hg)	0.88 (0.81 - 0.96)	<.01
IOP fluctuation (per unit SD)	1.07 (0.67 - 1.71)	.77
Average CCT (per μm)	0.99 (0.98 - 1.00)	.23
PXF (reference no PXF)	2.65 (0.95 - 7.44)	.06
Disc hemorrhage (reference no hemorrhage)	0.93 (0.43 - 2.00)	.84
Hypertension (reference not hypertensive)	1.21 (0.55 - 2.63)	.63
Diabetes (reference no diabetes)	0.64 (0.20 - 2.04)	.45
Hypotension (reference not hypotensive)	2.40 (0.60 - 9.80)	.22
Cardiovascular disease (reference no cardiovascular disease)	2.33 (1.03 - 5.27)	.04

CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; PXF = pseudoexfoliation syndrome.

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Hyperlipidemia, Blood Lipid Level, and the Risk of Glaucoma: A Meta-Analysis

Shiming Wang¹ and Xianyi Bao²

- CONCLUSIONS. The evidence suggests that hyperlipidemia is significantly associated with an increased risk of glaucoma and that hyperlipidemia and the increased blood lipid levels are associated with increased IOP.
- the mechanisms explaining how hyperlipidemia could increase the risk of the progression of glaucoma are unclear.
 - One possible explanation might be that excess blood lipid levels would increase the episcleral venous pressure and blood viscosity, resulting in a consequent decrease in outflow facility.

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Cardiovascular Disease

- Vasospasm
 - **Vasospastic disorders are conditions where small blood vessels near the surface of the skin have spasms that limit blood flow (e.g. Raynaud phenomenon)**
- Vascular dysregulation clearly plays a role in glaucoma
 - The association of glaucoma with peripheral vasospasm was found to be a significant risk factor for progression (Dascalu, et. al. 2020)
 - Clinical studies support evidence that there is an increased incidence of peripheric autoregulation disorders in patients with glaucoma

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Smoking

- **Surprisingly, many studies have not shown a link between smoking and glaucoma and/or results have been confounding**
- However, recent studies have shown an increased risk often associated with heavy smoking
 - The Sun Cohort (2016):
 - results suggest a direct association between current smokers and the incidence of glaucoma. In particular, this association was related to the number of pack-years, which was not found in the case of former smokers nor in the case of passive smokers
 - A 2018 study suggests that heavy smokers (> 1 ppd) have a higher risk as compared to mild or moderate smoking

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Migraines

Pro

- migraine was examined as a potential risk factor in the Collaborative Normal-Tension Glaucoma Study.
 - As expected, most migraine headaches occurred in women, but the syndrome emerged as an independent risk factor for visual field progression.

Con

- The Beaver Dam Eye Study found no relationship between open-angle glaucoma and migraines.
- The Blue Mountains Eye Study also found no overall association but did report a significant odds ratio of 2.5 for glaucoma in people aged 70 to 79 years who had a history of migraines.
- The European Manifest Glaucoma Trial examined the risk associated with a self-reported history of migraine. The investigators found an insignificant univariate hazard ratio of 1.37 and no association in multivariate analyses.
- The Canadian Glaucoma Study is a multicenter, prospective longitudinal study examining a variety of systemic risk factors, including migraine, for the progression of glaucoma. At baseline, 9.2% of the men and 19% of the women in the study have a history of migraine. With a median follow-up of 5.3 years, migraine did not emerge as a risk factor for glaucomatous progression.

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Migraine and increased risk of developing open angle glaucoma: a population-based cohort study

Wen-Yu Huang^{1,2}, Chien-Chia Su^{1,3,4*}, Tsing-Hong Wang^{1,2} and H-Ju Tai⁴

- Results:
 - Migraineurs had more vascular comorbidities than the comparison cohort.
 - The overall incidence of OAG (per 1000 person-years) was 1.29 and 1.02, respectively, for migraineurs and the comparison cohort during the 10-year follow-up period.
 - Age, hyperlipidemia, and diabetes mellitus were three significant risk factors for OAG in migraineurs.
 - After adjusting for patients' age and vascular comorbidities, migraineurs were found to have a 1.68-fold greater risk of developing OAG than the comparison cohort
- **Conclusion: Migraine is associated with a higher risk of OAG for patients with no comorbidity who are aged under 50 years.**

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Diabetes Mellitus

Diabetes: Glaucoma Risk Factor???

- **Diabetes mellitus had been proposed as a risk factor for POAG, but epidemiologic studies on the association between diabetes and glaucoma have been controversial**
 - Original OHTS Study:
 - According to the OHTS predictive model published in 2002, diabetes mellitus appeared protective against progression from ocular hypertension to open-angle glaucoma,
 - The ascertainment method for identifying a history of diabetes involved asking patients whether they ever were told by their doctor that they had diabetes or sugar in their blood.
 - Additionally, patients with diabetes who had diabetic retinopathy were excluded from the study.

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DM Associated with Increased Risk of Glaucoma

- Blue Mountains Eye Study
 - **Glaucoma** prevalence was increased in people with **diabetes**, diagnosed from history or elevated fasting plasma glucose level (5.5%), compared with those without **diabetes** (2.8%; age-gender adjusted odds ratio [OR] 2.12)
- Beaver Dam Eye Study;
 - The presence of open-angle glaucoma is increased in people with older-onset diabetes.
- Framingham Eye Study
- Los Angeles Latino Eye Study
- Numerous Others

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Possible Reasons Diabetes is a Risk Factor for Glaucoma

- **Vascular injuries** would reduce blood flow to the retina and optic nerve, resulting in reduced nutrient and oxygen supply to the RGC axons and increased expression of hypoxia inducible factor-1 in the retinal cells in response to elevated IOP.
 - Likely to induce the degeneration of the RGCs and initiation of glaucomatous damage
- **Hyperglycemia and lipid anomalies induced by diabetes could increase the risk of neuronal injury**, indicating that the RGCs were more likely to be killed in the patients with diabetes.
- hyperglycemia of aqueous humor in the eyes of diabetes patients would stimulate the synthesis and **accumulation of fibronectin in the trabecular meshwork to promote depletion of trabecular meshwork cells**, which could impair the outflow system of the aqueous humor and finally result in POAG
- Patients with diabetes get more eye exams?

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Diabetologia, 2004 Jun;21(6):609-14.

Diabetes mellitus as a risk factor for primary open-angle glaucoma: a meta-analysis.

Borroni S, Foglio V, Filippini S,
Department of General Practice, General Hospital of Athens G. Gennimatas, Athens, Greece. sborroni@med.uoa.gr

Abstract

CONCLUSIONS: Our meta-analysis results suggest that diabetic patients are at significantly increased risk of developing primary open-angle glaucoma. Clinicians should be aware of this possibility.

the random and the fixed-effects model.

RESULTS: Twelve studies published between 1997 and 2001 were included (five case-control studies and seven cross-sectional studies). Significant heterogeneity among the studies was detected ($P = 0.023$). No evidence of publication bias was found ($P = 0.37$). The association of diabetes mellitus with primary open-angle glaucoma was statistically significant assuming either a random effects [OR = 1.50, 95% confidence interval (CI) 1.16, 1.93], or a fixed-effects model (OR = 1.27, 95% CI 1.10, 1.45).

CONCLUSIONS: Our meta-analysis results suggest that diabetic patients are at significantly increased risk of developing primary open-angle glaucoma. Clinicians should be aware of this possibility.

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Progression of Primary Open-Angle Glaucoma in Diabetic and Nondiabetic Patients

HUIYUAN HOU, TAKUHEI SHOJI, LINDA M. ZANGWILL, SASAN MOGHIMI, LUKE J. SAUNDERS, KYLE HASENSTAB, ELHAM GHAHARI, PATRICIA ISABEL C. MANALASTAS, TADAMICHI AKAGI, MARK CHRISTOPHER, RAFAELLA C. PENTEADO, AND ROBERT N. WEINREB

- **CONCLUSIONS:** POAG patients with treated type 2 DM, who had no detectable diabetic retinopathy, had significantly slower rates of RNFL thinning compared to those without diagnosed DM. (Am J Ophthalmol 2018;189:1-9. © 2018 Elsevier Inc. All rights reserved.)

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Obstructive Sleep Apnea

Obstructive sleep apnea

- Most common sleep disorder
- Prevalence depends on how defined
- Most agree that 3-7% of adults have moderate to severe sleep apnea
- Found in up to 1/4 of males over 20 years of age if include mild forms
- Women less commonly affected, more common post-menopausal.
- Often undiagnosed (80%)
- **OSA is significantly associated with several life-threatening cardiovascular diseases, neurovascular and cerebrovascular diseases and endocrine disorders.**

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Obstructive Sleep Apnea (OSA)

- Symptoms
 - Loud snoring
 - Chronically disturbed sleep (patient may not be aware)
 - Excessive daytime sleepiness
 - Irritability, depression, and personality changes
 - Morning headaches
 - Tired upon awakening
 - Cognitive impairment

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OSA pathophysiology

- OSA is due to complete collapse of upper airway* in sleep
- As patient enters deep sleep, upper airway closes
- Thrashes, snorts, partially awakens and reopens airway with a gasp
- Can occur hundreds of time per hour

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OSA contributing factors

- Most patients are obese and have "thick" necks
- May have small or receding jaw
- May have increased size of soft palate and tongue
- Often a history of heavy drinking
- History of asthma

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Normal Tension Glaucoma in Patients With Obstructive Sleep Apnea/Hypopnea Syndrome

Pei-Wen Lin, MD, Michael Friedman, MD, FACS,†‡ Hsin-Ching Lin, MD, FACS,§ Hsueh-Wen Chang, PhD,|| Meghan Wilson, MD,‡ and Meng-Chih Lin, MD**

Conclusions: Patients with OSAHS had a high prevalence of NTG, especially in patients with moderate and severe OSAHS. The severity of OSAHS inversely correlated with retinal nerve fiber layer thickness. Clinicians need to consider the possibility of glaucoma in patients with moderate and severe OSAHS.

(J Glaucoma 2011;20:553–558)

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ORIGINAL STUDY

Meta-Analysis of Association of Obstructive Sleep Apnea With Glaucoma

Shulin Liu, MD, Yu Liu, BS,† and Xin Liu, BS‡*

Conclusion: OSA was a risk factor for glaucoma. A large number of studies is needed to explore the mechanisms that link OSA with glaucoma.

Results: Six primary studies (3 cohort study and 3 case-control studies) were included in this meta-analysis involving 2,263 (101 participants). There was a significant association between OSA and glaucoma (adjusted odds ratio [OR] = 1.45, 95% CI, 1.21–1.69, P = 0.0002). This was no significant publication bias.

Conclusions: OSA was a risk factor for glaucoma. A large number of studies is needed to explore the mechanisms that link OSA with glaucoma.

Key Words: obstructive sleep apnea, glaucoma, meta-analysis
(J Glaucoma 2016;25:1–7)

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OSA and Glaucoma

- **prolonged episodes of hypoxia directly damage the ONH, retinal ganglion cells (RGCs), and its axons.**
 - Hypoxia will cause oxidative stress and inflammation by increasing of reactive oxygen species and inflammatory markers which subsequently leads to mitochondrial dysfunction of RGCs and glaucoma.
- OSA causes definite vascular changes and **vascular dysregulation of ONH**
 - As a result of vascular dysregulation, ischemia and abnormal perfusion pressure optic nerve may be more sensitive even for normal IOP to get damage
 - Supine position increases IOP and obesity is a risk factor for increased IOP

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OSA and Ocular Conditions

- Apart from glaucoma, OSA is associated with several other ocular disorders including:
 - floppy eyelid syndrome (FES),
 - nonarteritic ischemic optic neuropathy,
 - papilledema,
 - optic neuropathy,
 - idiopathic intracranial hypertension,
 - diabetic retinopathy,
 - geographic atrophy,
 - age-related macular degeneration,
 - retinal vein occlusion, and
 - central serous retinopathy

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Neurodegenerative Disorders

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Glaucoma and Neurodegenerative Disorders

- Chronic inflammatory response that activates microglia and astrocytes
 - Triggered by oxidative stress
- Oxidative stress causes mitochondrial dysfunction
 - High oxygen demand of GCs is not met, leading to apoptosis

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Neurodegenerative Diseases

- Alzheimer's disease
- Parkinson's disease
- Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease)
- Many studies showing a relationship between glaucoma and degeneration in these diseases

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Alzheimer Dementia (AD)

- occurs in older adults, typically older than 65 years and with increasing incidence and prevalence over the next two decades
- memory impairment as the most common initial symptom.
- Other common early features are impaired executive function and reduced insight.
- Behavioral and psychologic symptoms, apraxia (inability to perform motor tasks), and sleep disturbance become more common as the disease progresses.
- **Growing evidence linking primary open angle glaucoma and AD**
- May also be a link to certain types of cataracts (e.g. cortical spoking)

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RNFL and GC in Alzheimer Disease

- **Several studies have shown that patients with AD have thinner RNFL and GC**
 - **Considered as a possible biomarker for the suspicion of or diagnosis of AD**
 - **Is this also glaucoma?**

Evaluation of Retinal Nerve Fiber Layer and Ganglion Cell Layer Thickness in Alzheimer's Disease Using Optical Coherence Tomography

The mean RNFL and GCL-IPL thicknesses were thinner in the AD group than in the control group. These findings suggest that RNFL and GCL-IPL thickness may be biological markers for AD.

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Peripapillary Retinal Nerve Fiber Layer Thickness in Patients with Alzheimer's Disease: A Comparison of Eyes of Patients with Alzheimer's Disease, Primary Open-Angle Glaucoma, and Preperimetric Glaucoma and Healthy Controls

12 Przemysław Zabel
12 Jakub J. Kalużyński
14 Monika Wilkoń-Dębczyńska
14 Martyna Gębala-Toloczko
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© Med Sci Monit, 2019; 25: E001-008
DOI: 10.1373/mon.2018.091007

Conclusions: Neuronal damage in the central nervous system (CNS) also affects to retinal axons. A major problem is to distinguish the cause for a moderate decrease in the RNFL thickness. This is particularly true for patients with glaucoma who have not been diagnosed with changes in the visual field. It is not possible to distinguish the cause of a mild decrease in the RNFL thickness based on the SD-OCT. This may result in misdiagnosis of glaucoma, unnecessary use of anti-glaucoma eye drops, and a delayed diagnosis of AD.

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Parkinson disease

- Parkinson disease (PD) is the most common cause of parkinsonism, a syndrome manifested by rest tremor, rigidity, bradykinesia, and postural instability.
- "The shaking palsy"
- A progressive neurodegenerative disease
- Uncommon in patients < 40 years old
- Men > women
- Affects ~1% of elderly patients
 - Family history
 - Having a first degree relative with PD increases the risk by 2.3x

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Parkinson disease pathophysiology

- Dopamine depletion from the basal ganglia results in major disruptions in the connections to the thalamus and motor cortex and leads to parkinsonian signs such as bradykinesia.
 - Basal ganglia is the motor control center of the brain and is crucial for the coordinated and smooth control of motor functions
- Damage to the **substantia nigra**
 - Substantia nigra plays important role in modulating motor movement
- Lewy bodies
 - Abnormal protein clumps in the substantia nigra

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Parkinson disease features

- While PD has traditionally been considered a motor system disorder, it is now recognized to be a complex condition with diverse clinical features that include neuropsychiatric and other nonmotor manifestations in addition to its motor symptomatology
- Clinical features:
 - Bradykinesia* (slowness of movement)
 - Tremor
 - Rigidity
 - Postural instability (late finding)
 - Not diagnostic criteria
 - Occurs later in the disease

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Parkinson Disease and Vision

- The impact of ocular and visual disorders is particularly troublesome for patients with PD, because they typically have problems with internally guided movements and postural control, which they can compensate for by guiding their movements visually
 - over 80% of PD patients who fell within a one-year timeframe were visually impaired, compared with 66% of non-fallers

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Parkinson Disease and Glaucoma

- Epidemiologic data on the association between glaucoma and PD are scarce. Two studies found a prevalence of glaucoma of 16-24% in PD compared with about 7% in controls
 - Retinal degeneration due to progressive retinal dopamine depletion and alpha-synuclein mediated axonal degeneration in both PD and glaucoma
 - angle-closure glaucoma can occur due to blocked aqueous outflow, associated with dopaminergic and anticholinergic medication, especially in patients with a pre-existent narrow chamber

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Exfoliation Syndrome

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PEX

- Characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues
- PXS is reported to be the most common identifiable cause of open-angle glaucoma
 - however, not all participants with PXS develop glaucoma

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Systemic Manifestations

- Pseudoexfoliation material (PXM) deposits around blood vessels connective tissue.
- It has been identified as a generalized disorder of the extracellular matrix, involving the:
 - skin, extraocular muscles, heart, lung, liver, kidney, and meninges in addition to the eye
 - Patients with PEX are prone to present with ischemic heart disease in addition to abdominal aortic aneurysms and homocystinuria. Patients that present with PEX should be screened for these detrimental cardiovascular disorders.
 - patients with Alzheimer's disease have a higher incidence of PXS

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Increases with Age

- In Finland, the incidence rose from 10% for persons aged 60 to 69 years old to 33% in persons 80 to 89 years old.
- Increased incidence with age was also found in populations in Norway, Japan, Australian aborigines, and in the United States.
- Eyes with exfoliation may convert to PXG at a rate of approximately 30% per decade

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PXF/PXG

- Pseudoexfoliation glaucoma (PXG) is a severe type of glaucoma with a higher risk of blindness.
 - PXG is associated with a higher maximum and mean intraocular pressure (IOP) at the time of diagnosis, and a higher 24-hour pressure curve than primary open angle glaucoma (POAG)
 - PXG patients were seen to have significantly greater mean visual field defects at presentation than POAG patients

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PEX/PXG

- Pseudoexfoliation glaucoma (PXG) is a severe type of glaucoma with a higher risk of blindness.
 - the IOP is harder to control in PXG than POAG
 - PXG is more difficult to manage clinically, with a higher incidence of treatment failure than POAG.

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Autoimmune Diseases

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Glaucoma is an Autoimmune Disease??

- Recent article and research has proposed that glaucoma is a form of autoimmune disease
- Both antibodies and CD4 T-cells as well as microbiota take part in the pathogenesis of both glaucoma and rheumatoid arthritis (RA).
- Heat shock proteins (HSPs) which originate in bacteria cross-react with RCG epitopes and were involved in rat model of retinal injury.
 - Enhanced expression of HSPs in the retina was associated with glaucoma-like neuropathology and previous studies have also suggested a pathogenic role for HSPs in RA.
- glaucoma should be included in the spectrum of autoimmune diseases and that proven medications for RA should be adopted as an innovative IOP-independent therapeutic strategy for glaucoma

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JIA Ocular Manifestations

- Classic triad of iridocyclitis, cataract and band keratopathy
- Overall incidence of iridocyclitis is approx 20%.
- Glaucoma affects between 14%-48% of children with JIA-associated uveitis and is a common cause of irreversible visual impairment.
- Elevated IOP in the setting of chronic inflammation is often multifactorial.
 - Trabecular meshwork dysfunction and the formation of synechiae increase resistance through outflow pathways, a process that corticosteroids can exacerbate.
 - Managing the complex balance between the control of IOP and of inflammation can therefore be challenging.

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Systemic Lupus Erythematosus (SLE) and Glaucoma

- it has been reported that patients with SLE have a higher prevalence of both cataracts and glaucoma because of long-term steroid use
- Hsu, et al., 2020 reported after controlling for sex, age, socioeconomic status, and geographic region, the adjusted risk were significantly higher for both cataracts and glaucoma in patients with SLE.
 - In addition, there were some differences in the risk between the sexes
 - While the risk was significantly elevated in both sexes for glaucoma, with a higher risk observed in male patients with SLE.
 - For both cataracts and glaucoma, the risk was highest among patients with SLE in the youngest age group

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Systemic Medications Known to Modulate Risk of Open-Angle Glaucoma

- Several classes of systemic medications are known to or suspected to modulate glaucoma risk, either through their direct effects on IOP or via mechanisms independent of IOP
- The rise of polypharmacy coupled with the increasing burden of glaucoma highlight the need for a better understanding of how systemic medications affect glaucoma risk.

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Summary of systemic medications that may increase or decrease the risk of glaucoma

Open-angle glaucoma			
Medications known to increase the risk of OAG	Medications known to decrease the risk of OAG	Medications that may decrease the risk of OAG	Medications with mixed findings
Corticosteroids	Beta blockers	Metformin Statins Bisphosphonate (TNF- α antagonists) SSRIs Post-menopausal hormones Cannabinoids	Calcium channel blockers
Angle-closure glaucoma			
Medications known to increase the risk of AACG			
Anticholinergics Adrenergics Cholinergics Sulfonamides Anticoagulants			

OAG open-angle glaucoma, AACG acute angle-closure crisis, TNF tumor necrosis factor, SSRIs selective serotonin reuptake inhibitors

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Medications

- Corticosteroids:
- Studies have demonstrated that exposure to corticosteroids causes increased resistance of aqueous outflow through the trabecular meshwork.
 - This may be attributed to accumulation of undigestible glycosaminoglycans in the human trabecular meshwork as a result of inhibition of matrix metalloproteinase inhibitors or through upstream activation of transforming growth factor β signaling

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Medications

- Beta-blockers:
 - Many studies have shown that systemic beta blocker use is associated with IOP reduction.
 - Nonselective beta blockers are thought to be more effective in lowering IOP compared with cardioselective agents given increased activity at beta-2 receptors.
 - In a large population based study conducted in the United Kingdom, patients receiving oral beta blockers were found to have ~1 mmHg lower IOP compared with those not using these medications after controlling for age, sex, and body mass index.
 - Additional evidence suggests that oral beta blockers may be associated with a decreased risk of incident glaucoma

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- Metformin:

- Metformin is a caloric-restriction-mimetic drug whose neuroprotective effects have been shown to delay or reduce risks for a variety of age-associated systemic diseases; recent studies have demonstrated an association between metformin use and decreased risk of OAG in persons with diabetes mellitus

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- Statins:

- Statins are a class of medications used to treat hyperlipidemia;
- In light of evidence showing a protective effect against cerebrovascular disease, interest in a neuroprotective role for statins in glaucoma has grown in recent years.
- Statins have been associated with decreased risk for developing OAG while other cholesterol lowering agents have not, suggesting properties unique to statins (beyond lowering of cholesterol) may be responsible for such a risk reduction

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- SSRI:

- Selective serotonin reuptake inhibitors (SSRIs) are used as line agents in the treatment of depression and other psychiatric conditions, and there is also some suggestion that these medications may reduce the risk of OAG.
- study found that SSRI users had a 30% reduced risk of POAG requiring filtration surgery compared with non-users, an association that was independent of the underlying reason for taking these medications

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- Cannabinoids

- A number of case reports and in vitro studies have found that cannabinoids can effectively lower IOP.
- cannabinoids may be involved in increasing aqueous humor outflow or by reducing aqueous production .
- However, substantial and frequent doses of cannabinoids are required to achieve sustained IOP reduction, and this can predispose patients to cardiovascular and neurologic adverse effects.
- Given their short duration of action and multiple psychotropic and cardiovascular adverse effects along with a lack of evidence supporting an effect on altering the disease course of glaucoma

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Thank You!!!

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Xtra, Xtra- Read All About It!

Combination of Refractive Surgery with Corneal Crosslinking (CXL) in Borderline Corneas

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1

Background

- Service Director, Ambulatory Surgery Center (ASC) at UHCO
- Contact lens & Family Practice Services at UHCO
- Lasik & PRK co-management

2

Financial Disclosures

None

3

Objectives for Today's Webinar

1. PRK, LASIK, SMILE: Comparison of refractive procedures
2. Tomography Corneal Scans Review
3. Keratoconus overview (KCN)
4. Corneal Collagen Crosslinking (CXL): method, indications
5. CXL – Plus: CXL with PRK in the treatment of Keratoconus
6. *Risky Corneas*: Benefits/ risks of combining Refractive Surgery with CXL in "borderline corneas" (PRK Xtra, LASIK Xtra, Smile Xtra)

4

#refrativesurgerygoals

Spectacles and Contact-lens free






- Sports, Occupation, Lifestyle, High Prescriptions

Candidate Profile Key

- Systemic Health
- Meds
- Cycloplegic Refraction
- Pachymetry
- Corneal Integrity

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Corneal-based Refractive Procedures

-  Radial Keratectomy (RK)
-  Photorefractive Keratectomy (PRK)
-  Laser-Assisted In situ Keratomileusis (LASIK)
-  Small Incision Lenticule Extraction (SMILE)
-  Collagen Crosslinking (CXL)

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Limitations of Refractive SX procedures

Procedure	Sphere range	Cylinder range	Limitations
LASIK	-10.00 to +4.00 D	Up to -4.00 D	Thin corneas, small PA, Flat/steep corneas
PRK	-10.00 to +4.00 D	Up to -4.00 D	Pre-op dry eye, post-op haze may occur
SMILE	-1.00 to -10.00 D	Up to -3.00 D	Re-treatments difficult, more edema
ICRS	-1.00 to -4.00 D myopia and KC patients	None	21 years or older, CCT 450 microns, no central scarring
Inlay KAMRA	-0.75 D starting point	None	Presbyopic, Non-dominant eye, haze formation
CXL	None	none	CCT 400 microns, progressive disease
Phakic lenses	-3.00 to -20.00 D	Up to -4.00 D	Myopia only, possible glaucoma
RLE	All ranges	Up to -5.00 D	Not FDA approved, presbyopic considerations

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Photorefractive Keratectomy (PRK)

8

PRK



- Removal of epithelium
- Photoablation of tissue

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PRK

PRK Procedure

Step 1: Alongside numbing drops, an alcohol solution is placed on the eye to help soften the cornea.

Step 2: The surgeon then smooths the surface of the cornea with a special surgical instrument.

Step 3: An excimer laser is then used to precisely reshape the curvature of the cornea's surface.

Step 4: A bandage-like soft contact lens is then placed on the cornea to help protect the eye as it heals.

Clinical advantages of PRK

- PRK treatments on the surface has LESS of a chance to DESTABILIZE abnormal cornea
- Decreases changes of post-laser ectasias
- Eliminates flap complications (that are present c LASIK)
- Better Visual quality?
- Larger RSB left in place post PRK

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PRK Pros

- Removal of Corneal EPITHELIUM, BOWMAN'S LAYER, SUPERFICIAL STROMAL TISSUE
- NO FLAP*
- EXCIMER laser applied directly to:
 - Central corneal stroma (myopia) or
 - Mid peripheral corneal stroma (steepens central cornea to correct hyperopia)
- Residual corneal thickness post Tx: 400 um
- PRK FDA Approval Tx RANGE: -10D to +4D, up to 4D cyl

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PRK Complications

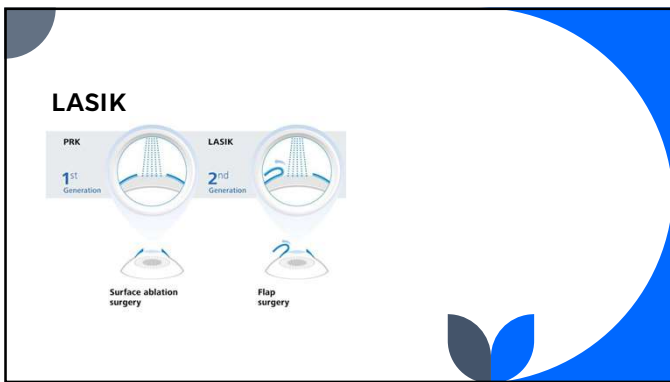
- Corneal defect, healing time c vision fluctuation
- Stromal haze, delayed healing

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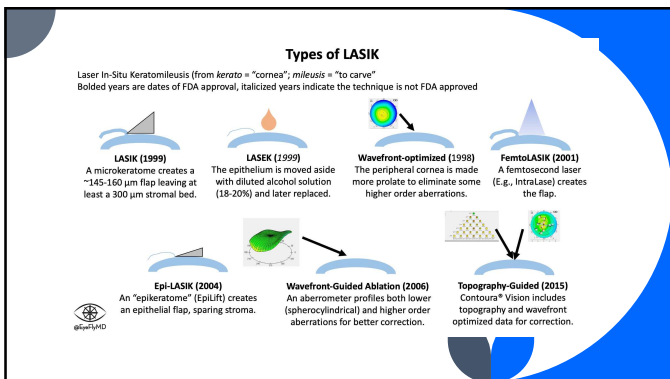
Laser-Assisted In Situ Keratomileusis (LASIK)



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1. Uses femtosecond laser for flap creation

2. More accurate and precise

3. Less complications

4. Less IOP spikes

5. Faster

Lasik Eye Surgery

- Residual corneal thickness post Tx: 250-300 microns
- LASIK FDA Approval Tx RANGE: -10D to +4D

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Lasik Complications

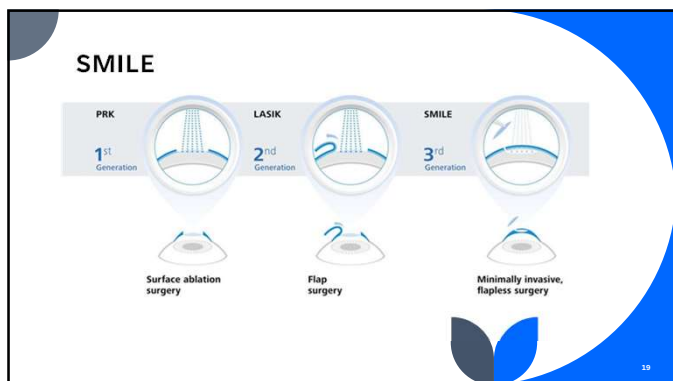
1. Serious Infection	2. Flap complications	3. Ectasia
4. Residual Refractive error	5. Diffuse Lamellar Keratitis (DLK)	6. Epithelial ingrowth
7. Glare	8. Dry eye syndrome (DES)	9. Corneal haze

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Small Incision Lenticule Extraction (SMILE)

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SMILE (FDA 2016)

- Flapless procedure
- 2-3mm incision
- Treats myopia, astigmatism
- Limitations: -1.00 to -10.00, -3D astigmatism – max 10D treatment

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SMILE (FDA 2016)

- Femtosecond laser creates a lenticule of stromal tissue
- Small side incision to remove the stromal tissue
- Thickness of stromal tissue removed depends on patient's RE

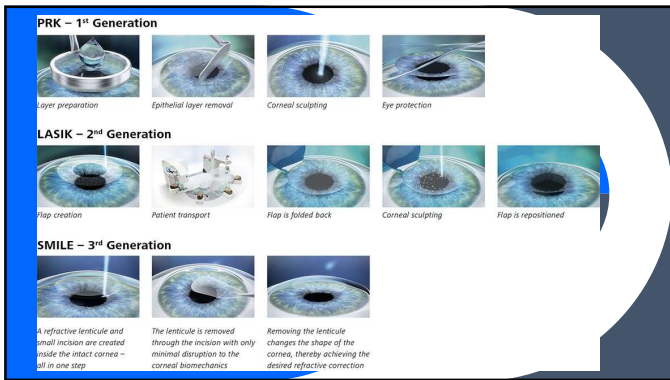
SMILE with femtosecond laser

<https://www.youtube.com/watch?v=1oJFShANMtc>

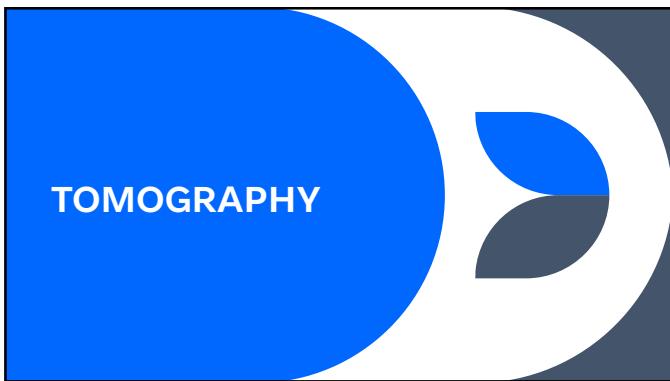
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MAPS & COLOR SCALE

How are "Elevation" Maps Displayed ?

The most common method is to compare the data against a suitable reference surface.

Color Scale: Elevation Map

- high anterior to the reference surface
- low posterior to the reference surface

• Relative elevation measures height difference in microns from a best-fitting reference sphere
 In all elevation maps, green is the reference surface or zero level
 Red is high and positive, Blue is low and negative

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Normal Corneal Scan

Normal topography

- Progressive flattening from center to the periphery by 2-4D
- Nasal area is flatter than the temporal area

Values to record in EMR

- HVID: AKA White to white (W to W), @Cornea
- Flat K @ __deg, Steep K @ __deg
- Type of astigmatism
 - WTR, ATR, Oblique
- Thinnest pachymetry reading

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Tomography: 4 Maps Refractive

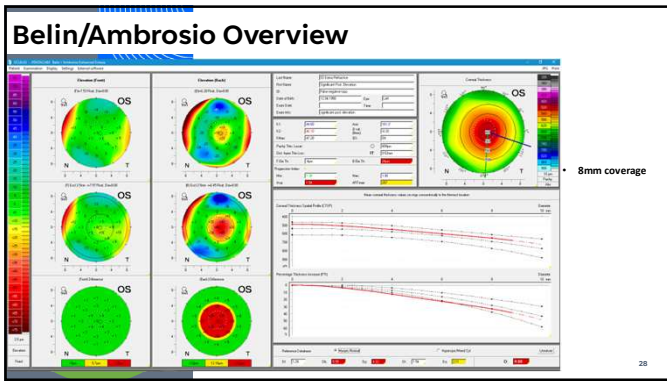
Selectable maps

- Quality inspection
- Axial/sagittal scans
- Tangential map
- Elevation (front)
- Elevation (back)
- Corneal thickness

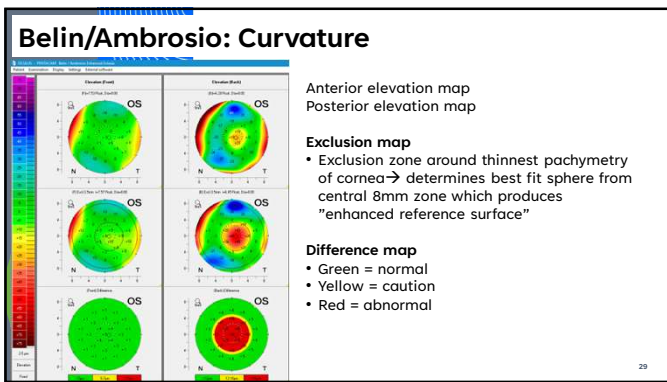
Good references:

- [Corneal Imaging: An Introduction \(uiowa.edu\)](#)
- [Mapping Out Corneal Topography \(reviewofoptometry.com\)](#)

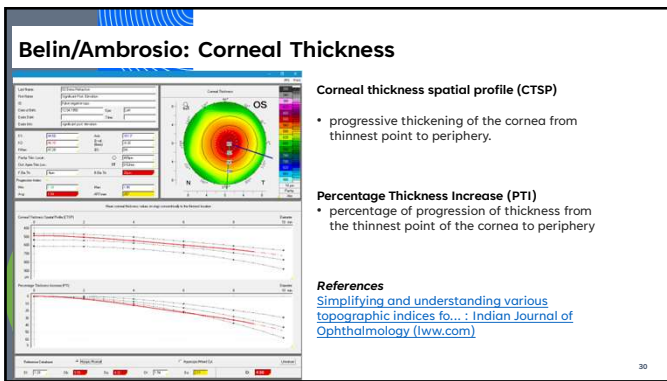
27



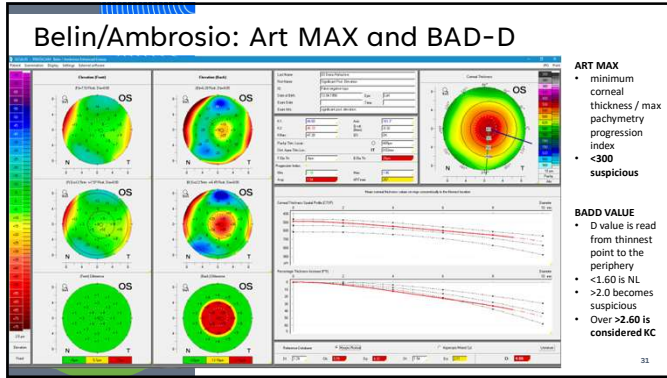
28



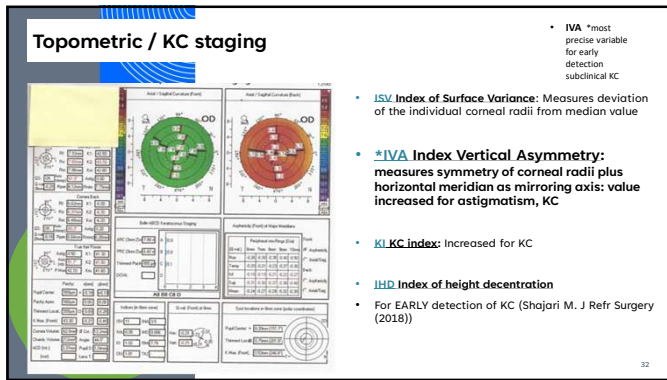
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Keratoconus (KCN)

Bilateral, progressive thinning of the cornea (typically asymmetric)

Corneal stroma: made up of water + collagen
Collagen makes the cornea strong and flexible, and helps keep its regular, round shape.

With KCN, the corneal stroma thins and bulges into an irregular cone shape, resulting in vision loss.

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Risk factors for KCN

01 Genetics +Fam hx KCN or hx systemic conditions (ex Down's Syndrome) have a higher risk of developing KCN	02 Chronic Eye Inflammation Constant inflammation from allergies or irritants can contribute to the destruction of corneal tissue	03 Eye rubbing Chronic eye rubbing is associated with developing keratoconus. May also be a risk factor for disease progression	04 Age KCN begins at puberty and progresses into mid 30s
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Corneal Collagen Crosslinking (CXL)

- Pros/Cons
- FDA approved cases and ages
- Concept of crosslinking
- Management post op care
- Visual recovery
- Pt expectations
- Factors that we use to determine progressive KC

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CORNEAL COLLAGEN CROSSLINKING (CXL)



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CXL

Minimally invasive procedure to SLOW or STOP the progression of corneal ectatic conditions (Ex: **Keratoconus** – Pellucid and Terrein Marginal degeneration), **Post refractive surgery: LASIK, PRK**)

FDA approved 2016 for **progressive KC** and post-refractive ectasias

Approved for Age 14 or older

Components: photosensitizer + UV light source

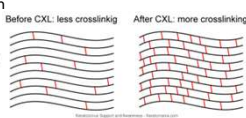



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CXL

- Crosslinking refers to the ability of collagen fibrils to form chemical bonds with adjacent fibrils
- Crosslinking occurs naturally in the cornea with age
 - KC and ectasias rapidly progress in adolescence and early adulthood
- Univ of Dresden est protocol in late 1990s.
 - Porcine and rabbit corneas soaked in Riboflavin exposed to UV to induce corneal crosslinking



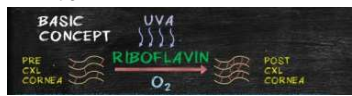



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CXL Concepts

- Riboflavin B2 is a photosensitizer that can be absorbed by the corneal stroma, absorption peak 370nm
- UV light
 - UV-A light using a total fluence of 5.41J/cm²
- Photochemical reaction
 - Riboflavin exposed to UV-A light **generates reactive oxygen species**
 - Induces covalent bonds between collagen molecules and between collagen and proteoglycans
- Oxygen is essential for the induction of free radicals





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BASIC CONCEPT
 PRE CXL CORNEA → UVA + RIBOFLAVIN → POST CXL CORNEA
 O₂

HISTORY
 WOLLENSAK ET AL 2003

ADVANCES

- ✓ PULSED CXL
- ✓ ADAPTED FLUENCE
- ✓ CXL PLUS
- ✓ PHOTOREFRACTIVE INTRASTROMAL CXL
- ✓ SCLERAL CXL
- ✓ LASIK XTRA
- ✓ OTHER CXL METHODS

PROCEDURE
 DRESDEN PROTOCOL

VARIATIONS IN UVA DELIVERY

- ✓ ACCELERATED CXL
- ✓ @ THE SLIT-LAMP

VARIATIONS IN RIBOFLAVIN DELIVERY

- ✓ EPI OFF
- ✓ EPI ON

EFFECTS & SAFETY

- ✓ CXL IN ANTERIOR STROMA - KERATOCYTE APOPTOSIS AND REPLACEMENT
- ✓ LSC SAFE
- ✓ ENDOTHELIUM SAFE

USES

- ✓ KERATOCONUS ★★★
- ✓ FMD ★★★
- ✓ POST LASIK ECTASIA ★★★
- ✓ PAKK CXL ★★★
- ✓ PKC ★

SPECIAL SITUATIONS

- ✓ KIDS - SAFE & STRAIGHT AWAY
- ✓ THIN CORNEAS
- ✓ HYPO-OSMOLAR OR HIGHER CONC. RIBOFLAVIN
- ✓ PREGNANCY OBSERVE / CXL CONTRAINDICATED

COMPLICATIONS

- ✓ HAZE
- ✓ INFECTION
- ✓ PAIN
- ✓ PERSISTENT EPI PERFECT & CORNEAL MELT
- ✓ PROGRESSION

■ AAME

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“Progressive” KC

Every progressive pt needs to have the option of CXL and to be followed closely

Progressive corneal ectasias

- ≥ 1D increase in astigmatism in MR
- ≥ 1D steepening in keratometry
- ≥ -0.50D myopic shift of spherical equivalent refractive error

- Progressive drop in Best spectacle corrected visual acuity (BSCVA)
- Change in CL fit, requiring a re-fit within 1 year

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Contraindications (CI) to CXL

- Corneal thickness < 400 microns
- Prior herpetic infections
- Current infection
- Severe central corneal scarring or opacification
- Hx poor corneal epithelial wound healing
- Severe untreated ocular surface disease
- Autoimmune diseases (relative CI)

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Cross-Linking Procedure

-  FDA approval (April 2016): 14-65 y/o
-  Indication: 1) Progressive KC 2) Corneal ectasia following refractive surgery
-  Drug device combination: KXLUV System
Avedro (Glaukos) Photrexa and Photrexa viscous
-  Epithelium off (epi-off) technique

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FDA approved device by Avedro to treat CXL



- Only approved FDA CXL device
- Exposure: 365 nm
- UVA irradiation: 3.0 mW/cm²
- Laser alignment
- Wireless control for beam alignment
- Fully-integrated stable delivery platform
- Touch screen operation
- Self-calibration UVA intensity

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Photrexa = riboflavin solution

- Photrexa viscous (isotonic)
 - 1.46 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution for topical administration
 - 3.0 mL volume
- Photrexa (hypotonic)
 - 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solutions for topical administration
 - 3.0 mL volume
- 30 min application

Goals of CXL

- Create new corneal collagen cross-links
- Shorten and thicken collagen fibrils
- Stiffen and strengthen the cornea

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Management

- Like PRK post-op care
 - BCL removal once epithelium has healed
- Haze develops in almost all patients unlike PRK
 - Haze does not affect vision
- Watch for infiltrates or ulcers
- Cornea takes longer time to heal in more advanced cases
- Can develop scarring and stromal edema
- Steroids 4-8 weeks
- CL fit once cornea has healed, but may change
 - soft and scleral lenses 4 weeks, RGP and hybrid 3-6 months depending on corneal integrity


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CXL recovery


- Very similar to PRK
 - Days 1-3 vision is okay but comfort is poor
 - Days 4-5 vision is poor but comfort is better
 - Days 5-14+ vision is fluctuating
- Rx and lens type will need to be adjusted weeks and months and potentially years after the procedure
- Corneal Crosslinking occurs slowly
 - First 4-8 weeks Crosslinking begins
 - Studies indicate corneal structure changes as far out as 5+ years


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Patient Expectations for CXL

 Managing pt expectations-SO important!

 These pt's want "Cure for KCN"

 Cross-linking will NOT work like laser vision correction to improve VA without glasses

 Crosslinking will NOT prevent the need for vision correction in form of glasses and contacts

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CXL Plus (+)
Advance Treatment for KC

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CXL + PRK = CXL(+), Study 01/2024

Advances in the Treatment of Keratoconus: Epithelial-On (EPI-On) Corneal-Collagen Cross-Linking (CXL) and CXL-Plus Procedures

Abstract
 Keratoconus (KC) incidence is on the increase. The advent of corneal collagen cross-linking (CXL) has revolutionized the management of KC. This systematic review looks at the efficacy and complications of two recent treatments within CXL: Epithelial-On (EPI-On) CXL and CXL-Plus procedures. Two separate literature searches were carried out for articles in CXL, with only peer-reviewed articles published in the last five years were included. Studies that only the most recent articles were included. A total of 11 articles were selected for this review. There were noted trends regarding the efficacy of EPI-On. The magnitude of difference was not between EPI-On and Standard Epithelial On (SE-CXL). However, it was found that EPI-On was inferior to standard CXL in terms of reducing haze. There was a higher rate of progression in patients treated with EPI-On CXL, with an increased rate of patients requiring re-treatment due to the advancement of their KC. While some studies report CXL plus procedures demonstrating long-term efficacy and safety, a considerable number of studies after revision, reporting a significant deterioration in corrected distance visual acuity (CDVA). Consequently, a positive attitude regarding the safety and visual efficacy prospects, given the fact of almost large randomized controlled trials (RCTs) in the current literature.

Comparing Epi On CXL vs. CXL (+)

CXL-Plus procedure

- stabilization of KC + address refractive issues, including BCVA, and high-order aberrations (HOAs).
- The 10-year outcomes of a CXL-Plus procedure, (aka Athens Protocol) demonstrate that same-day CXL-Plus procedures are safe and exhibit long-term efficacy.
- Of the 144 eyes, 94.4% showed a significant reduction and stabilization of KC over the 10-year period, accompanied by improvements in UDVA and BCVA.

https://assets.cureus.com/uploaas/review_article/pdf/217478/20240103-32597-1q0yvl.pdf

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Xtra, Xtra!
Combining Refractive SX with CXL

"At-Risk" Corneas:
 Combining Refractive surgery with CXL in "borderline corneas"
 (PRK Xtra, LASIK Xtra, Smile Xtra)

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Xtra, Xtra! Combining Refractive SX with CXL

Review Article

Refractive surgery with simultaneous collagen cross-linking for borderline corneas - A review of different techniques, their protocols and clinical outcomes

Bharat Puro, Nigam Gantam, Swetha Sathya, Sri Ganesh

Non-invasive corneal cross-linking (CXL) has been proposed as an adjunct therapy to corneal refractive procedures to prevent future corneal ectasia, especially after performed in borderline corneas. This review compares the currently available techniques (PRK, Xtra, SMILE) for refractive surgery and simultaneous CXL (PRK Xtra, LASIK Xtra, and SMILE Xtra) to evaluate the overall results relating to the safety, efficacy, and postoperative complications associated with these procedures. A comprehensive literature search of various databases including PubMed, Scopus, Cochrane Database, and MEDLINE was performed. Up to May 2020 four relevant studies were found for PRK Xtra, LASIK Xtra, and SMILE Xtra. The studies were categorized into the review and CXL, PRK Xtra, LASIK Xtra, and SMILE Xtra. A PRK Xtra, LASIK Xtra, and SMILE Xtra. CXL was performed in a separate study. The results of the studies were compared to evaluate the safety, efficacy, and postoperative complications associated with these procedures. The results of the studies were compared to evaluate the safety, efficacy, and postoperative complications associated with these procedures. The results of the studies were compared to evaluate the safety, efficacy, and postoperative complications associated with these procedures.

Brar S, Gautam M, Sute SS, Ganesh S. Refractive surgery with simultaneous collagen cross-linking for borderline corneas - A review of different techniques, their protocols and clinical outcomes. Indian J Ophthalmol 2020;68:2744-56
[DOI: 10.4103/0365-3075.301404](https://doi.org/10.4103/0365-3075.301404)

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Refractive Surgery c Simultaneous CXL (Dec 2020)

Methods	1,512 number of eyes
PRK	221
PRK Xtra	294
LASIK	398
LASIK Xtra	446
SMILE	62
SMILE Xtra	91

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Ectasia: Mechanism in LASIK

Lasik associated with highest risk of ectasia, prevalence 0.02% to 0.6%

➔

Mainly attributed to corneal flap- which can weaken corneal structure and decrease corneal rigidity

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Reasons that could lead to Ectasia following Refractive Surgery

Tissue subtraction with creation of vertical cuts (LASIK) for flap creation or delamination cuts in SMILE

Injury to Bowman's membrane (PRK) lead to mechanisms of ECASIA via BIOMECHANICAL weakening

Other risk factors: Pre-op high myopia or hyperopia, Thin corneas, Abnormal topography, Eye rubbing, Pregnancy, Hormonal imbalance, Systemic meds

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BIOMECHANICAL Advantage OF CXL

In refractive surgery: 2 main post-op issues

- Post-op Regression
- Corneal ectasia

Both thought to result from biomechanical changes affecting the strength of the cornea due to tissue removal

CXL already proved to provide corneal stability in KCN

→ applying the same concept: CXL in refractive surgery. CXL may lead to LESS epithelial thickness increase (a possible factor in regression)

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Patients seeking refractive correction for Myopia / Myopic astigmatism

Consider the following criteria:

- Age
- SE ≤ 10.00 D
- Thinnest Pachymetry
- RSBT
- Biomechanical indices: CBI, TBI
- Contributory history: Family history of KCN, allergic eye disorder

PRK/LASIK/SMILE (if no risk factors are present)

PRK/LASIK/SMILE+ Simultaneous Collagen Crosslinking (if risk factors present)

Risk factors present (2 or more):

- Age > 30 years
- SE ≥ 6.00 D
- Suspicious Topography +, but no KCN
- Thinnest pachy < 480 μ
- RSBT: 250-280 μ
- OAD > 1.45
- CBI < 0.5
- TBI < 0.29
- Positive Contributory history

“Xtra”: 2 risk factors or more

CBI and TBI are measurements of biomechanical indices

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Surgical Procedure in this Study Review (Brar, et al Dec 2020): PRK Xtra

4 studies: 2 retrospective studies, 1 prospective comparative study, 1 retrospective cohort study

No common agreement on riboflavin dye, power and duration of UV-A irradiation to be delivered to cornea for any of the combined refractive surgery and CXL procedure

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LASIK Xtra Procedure

12 longterm studies, 1 year follow up. 9 studies were myopia cases, 3 for hyperopia

- ✓ Creation of LASIK flap followed by laser ablation
- ✓ Lifting of flap with with flap open->apply 0.22% riboflavin onto stromal bed and soak for 45-120s
- ✓ Irrigation of stromal bed to rinse off riboflavin solution
- ✓ Corneal flap repositioning
- ✓ UV-A irradiation through corneal flap

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SMILE Xtra

3 relevant studies, follow up: 6 months

- SMILE performed following standard protocol
- 0.25% riboflavin in saline injected into the interface
- Diffuse for 60s, rinsed off with balanced salt solution
- UV-A irradiation performed through cap for 75sec

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Safety with the Xtra Procedures

PRK Xtra	<p>Good safety for myopic cases, 1 pt developed sterile marginal infiltrate (resolved c topical tx). No significant complications (delayed epi healing, corneal ectasia or significant corneal haze)</p> <ul style="list-style-type: none"> • May be associated with highest risk of post op haze • PRK alone can lead to haze, in combination with CXL-increased risk in higher corrections (3/4 studies reported this)
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Safety with LASIK Xtra, SMILE Xtra

LASIK Xtra	<p>Safe procedure. No eye had decrease in CDVA. Complications are minimal, rare and transient. No corneal ectasia</p>
SMILE Xtra	<p>Good safety, without any visually threatening complications</p>
LASIK Xtra & SMILE Xtra	<p>Advantage over PRK Xtra in terms of post op healing/ pt comfort</p> <ul style="list-style-type: none"> • CXL performed through the flap/ cap of intact epithelium-which significantly reduces chance of post op complications (prolonged wound healing, pain, infectious keratitis, excessive haze)

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Conclusions & Future Directions

- Review results: combining refractive surgery and CXL- generally SAFE and effective in stabilizing refractive and keratometric outcomes

Future directions

- Need to optimize UV-A energy level to minimize risk complications
 - Level of UVA energy, lower UVA energy used since indication for CXL is prophylactic instead of therapeutic
- More randomized comparative studies with longer follow-up's suggested to evaluate safety and efficacy of procedures

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