Ask The Experts: When You're Treating Your Glaucoma Patients

Ben Gaddie, O.D. FAAO
AND
Eric Schmidt, O.D. FAAO
2-Hour Glaucoma Cope-Pending

1

Ben Gaddie OD Disclosures

Consultant for:

- Tarsus
- Bausch and Lomb
- Abbie Vie
- Harrow
- Sydnexis
- Topcon
- Ocusoft
- Azura
- Mediprint
- Alcon

2

Eric Scmidt, OD Disclosures

Consultant/Speaker Bureau

- Allergan/Abbie Vie
- Bausch and Lomb
- Lumenis
- Ocular Therapeutics
- Tarsus
- Visus
- M&S Technologies
- Avellino
- Topcon
- Apellis
- Sight Sciences

3

Agenda

- Detecting change and/or progression
  - Nuances for determining progression with both VF and OCT
  - Frequency of testing and justification
- Adding Therapy
  - Managing patient expectations
  - Drops vs. SLT
  - Additive MOA
  - Frequency of dosing
  - Generic vs. Branded
- What is Maximal Medical Therapy (MMT)?
- Identifying and managing allergies and sensitivities to glaucoma medications
  - Preservative related allergies
  - Drug related allergies and sensitivities

4

Agenda Continued

- Discussion on presentations of various drug allergies and sensitivities
- How do I make sure my patient gets the medication I want them to have?
  - Specialty pharmacies
  - Prior Authorizations
  - Appeals
  - Compounding
- When is the appropriate time to make a referral?
  - To whom?
  - Co-manage or turn over?

5

Agenda continued

- Questions commonly asked by referring doctors relative to glaucoma
  - What do you think about neuroprotection?
  - Can marijuana be used to treat glaucoma?
  - Can patients take their PGAs every other day?
  - Should we do MRI's on patients with normal pressure and glaucoma findings?
  - Should we do LPI on all narrow angle patients?
  - Can you still have some variants of angle closure if a patient has a patent PI?

6

Progression in Glaucoma

- Very complicated to look at progression of glaucoma as a topic itself
- Must confirm if glaucoma is truly progressing
- Many factors have contributed to higher rates of progression
  - CH at baseline
  - CCT at basline
  - Family History
  - Magnitude of IOP lowering
  - Treatment vs. no treatment
  - Macular ganglion cell layer thickness at baseline
  - IOP at baseline
  - Extent of presenting disease burden

7

Detecting Progression in Glaucoma

- Important to correlate and look at both functional and structural changes to call out progression in glaucoma
- Visual Field testing is both subjective and yields poor reliability requiring multiple repeats to establish progression[1]
- OCT is objective and precise but is thought to be less helpful in advanced glaucoma due to the floor effect[2]

1. Chauhan BC, Garway-Heath DF, Goni FJ, et al. Practical recommendations for measuring rates of visual field change in glaucoma. Br J Ophthalmol. 2008;92(4):569–573.
2. Bussel, Wollstein G, Schuman JS. OCT for glaucoma diagnosis, screening and detection of glaucoma progression. Br J Ophthalmol. 2014;98(Suppl 2):ii15–19.

8

- Most investigators feel OCT is more useful in pre-perimetric or early glaucoma while VF is more useful in moderate to advanced disease progression[3-5]

3. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol. 1991;109(1):77-83.
4. Zhang X, Loewen N, Tan O, et al. Predicting Development of Glaucomatous Visual Field Conversion Using Baseline Fourier-Domain Optical Coherence Tomography. Am J Ophthalmol. 2016;163:29–37.
5. Estimating Lead Time Gained by Optical Coherence Tomography in Detecting Glaucoma before Development of Visual Field Defects. Ophthalmology. 2015;122(10):2002–2009.

9

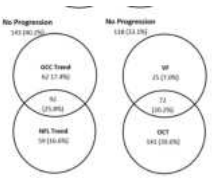
Comparison of Glaucoma Progression Detection by Optical Coherence Tomography and Visual Field

X Zhang et al. Am J Ophthalmol. 2017; 184:63-74

- "OCT is a more sensitive than VF for the detection of progression in early glaucoma. While the value of NFL declines in advanced glaucoma, GCC appears to be a useful progression detector from early to advanced stages."

10

Pre-perimetric progression via various measures



11

Importance of Detecting Early Structural Change

- Evidence that progressive structural changes on OCT often precede functional loss and patients with faster change on OCT are at risk for worsening VF[6]

6. Tatham AJ et al. Detecting Structural Progression in Glaucoma with Optical Coherence Tomography. Ophthalmology 2017 Dec;124(12S):S57-S65.

12

MF

When Should Patients Return?

Managing Glaucoma

13

When Should Patients Return?

- Baseline period – making the diagnosis whether it is OHTN or Glaucoma
  - Important to have good quality visual fields and OCT as therapy is initiated
  - If therapy is initiated, then see 2-6 weeks afterwards
    - Making sure the medication/procedure is tolerated and effective
    - Having only one post therapy IOP measurement can be misleading
    - If not at target IOP, see sooner
  - Follow up period is for first year
  - If the person has mild to moderate glaucoma, examine every three months
    - Fields and imaging done at 6, 12, 18, 24 months
    - If stable and good quality can reduce interval for both doing fields/imaging and when to examine patient
- Stable vs. Uncontrolled

14

When Should Patients Return?

- Is there a need to do visual fields after the initial assessment if the patient is stable?
  - If OCT is stable, why do a field?
- Which fields to do?
  - 24-2 vs. 24-2C vs. 10-2
  - SITA Standard vs. Fast vs. Faster
  - What about bundling fields
    - Do 2 SITA Faster fields at one visit separating by few minutes

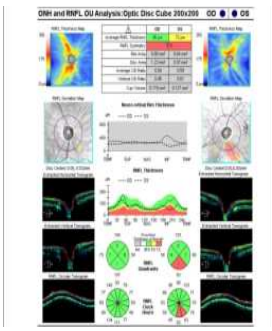
15

Frequency of Glaucoma Testing

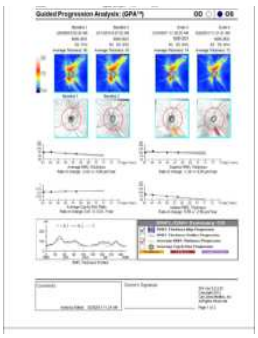
(NOTE: Testing can be performed any time the doctor suspects patient is progressing)

- Ocular Hypertensives under good control
  - Once per year VF/OCT/Gonio/Photo
- Pre-Perimetric or mild glaucoma
  - 2 x per year for first two years
    - If stable, then do annual from there
    - If unstable, continue to utilize functional and structural testing as needed to determine rate of progression resetting target IOPs.
- Moderate, stable glaucoma
  - 2 x per year if stable first two years
  - 1-2 x per year pending patient stability
- Severe glaucoma, stable or unstable
  - 2 x per year
  - 1 x per year VF 10-2

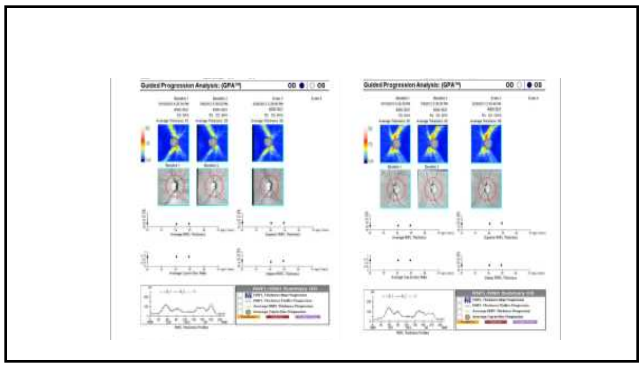
16



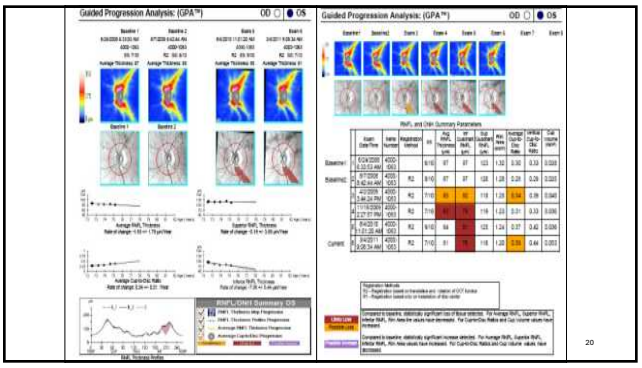
17



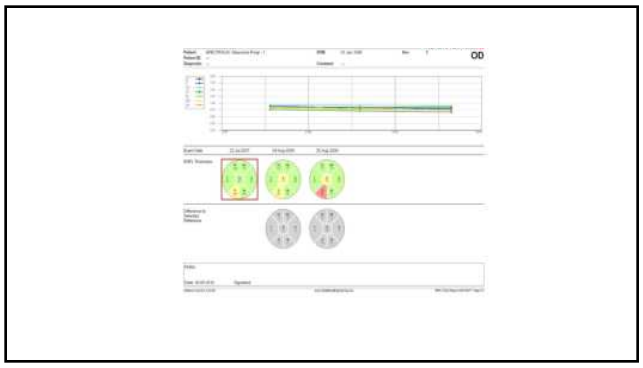
18



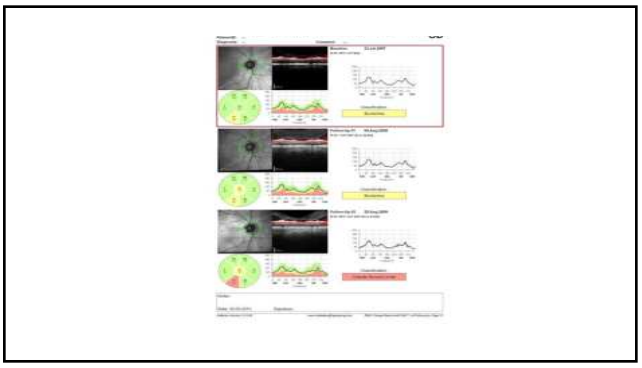
19



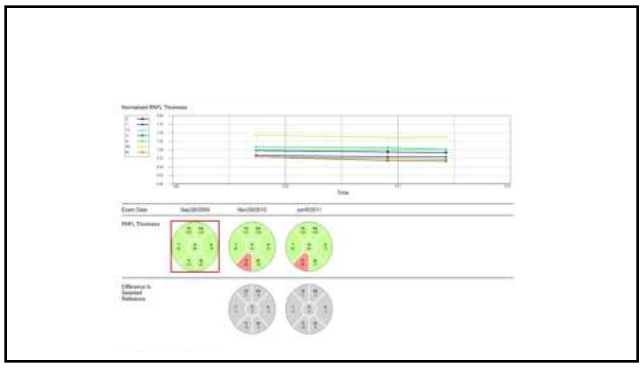
20



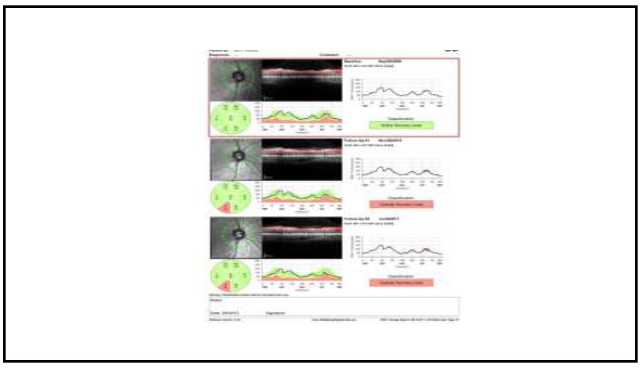
21



22

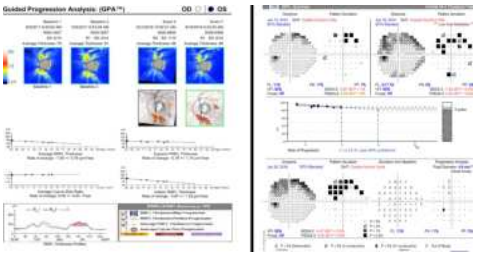


23



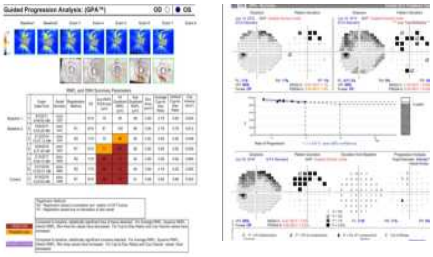
24

Has Progression Occurred Here? OCT vs. Visual Field



25

Has This Glaucoma Progressed?



26

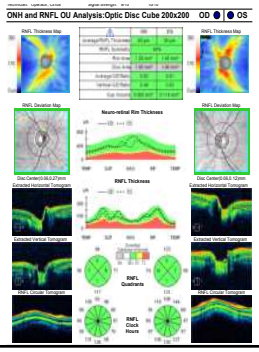
Case Example

- 58 YOWM
- Diagnosed with glaucoma 3 yrs ago
- Suspect prior to that for 4 years
  - IOP always <24
- Then IOP shot up to 30 and treatment began
  - Pretreatment IOP 24 OD and 30 OS
  - Pachymetry 503 OD and 512 OS
  - CH 7.5 OD and 9.6 OS

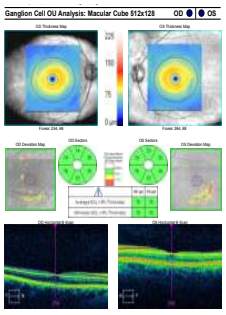
27

- Then IOP shot up to 30 and treatment began
  - Pretreatment IOP 24 OD and 30 OS
  - Pachymetry 503 OD and 512 OS
  - CH 7.5 OD and 9.6 OS
- Treated with latanoprost and IOP 14-15 OU x 3 years
- Why is he progressing? What should we do?

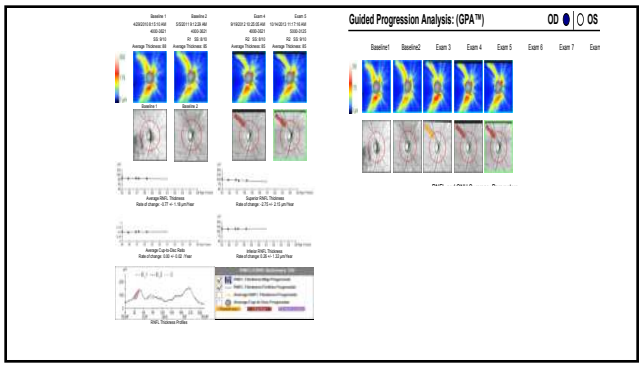
28



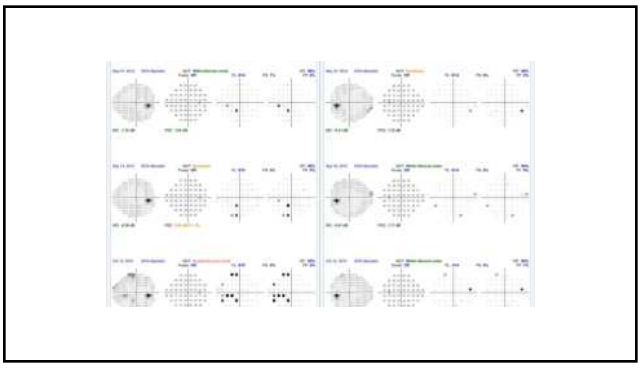
29



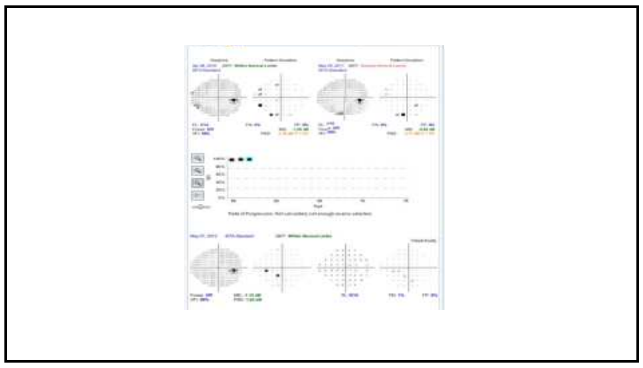
30



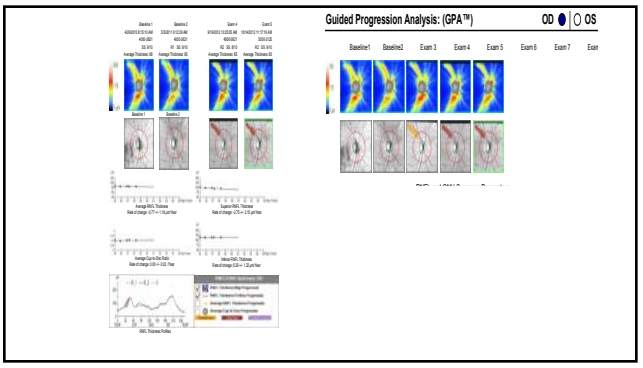
31



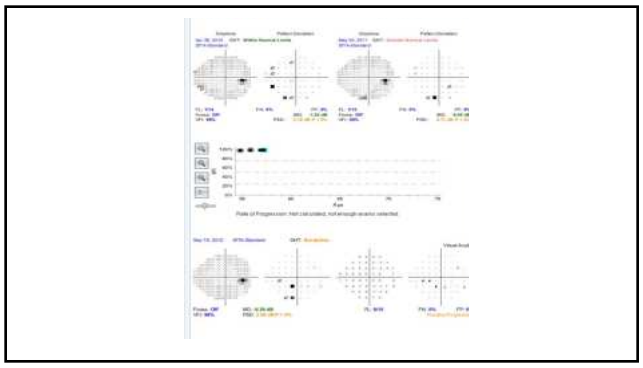
32



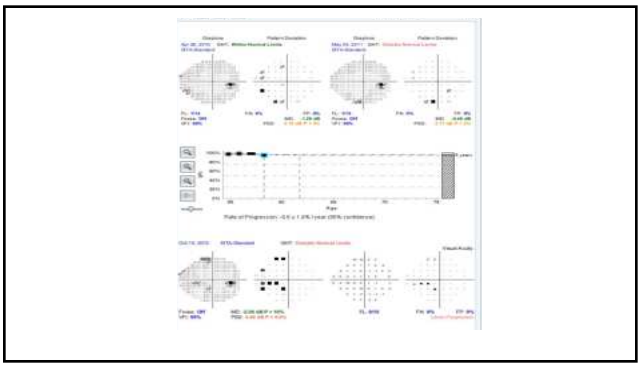
33



34



35



36

- Even though IOP has been lowered by 38 and 50 % respectively, we are still seeing progression
- Is this progression seen from original damage (latency) or new?
- Note CH and CCT as negative prognostic indicators for progression

37

Plan?

- Plan: Given relative youth and quick early progression, SLT performed OU

38

6 week Post OP SLT OU

- IOP 9mm Hg OD and 11 mmHg OS
- Is this low enough?
- How do you know?
  - Re baseline, monitor VF and OCT
- What are future treatment options:
  - Repeat SLT
  - Combo medicine
  - Combined cataract with ECP or Glaukos
  - Incisional glaucoma surgery/MIGS

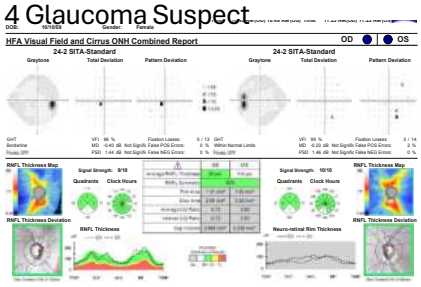
39

Case Example

- 60 YO African American Female
- Presented 2014 as a glaucoma suspect
- IOP in 2014 OD 21 and OS 18
- CH OD 9.2 and OS 6.7
- PACHS 525 OU

40

2014 Glaucoma Suspect

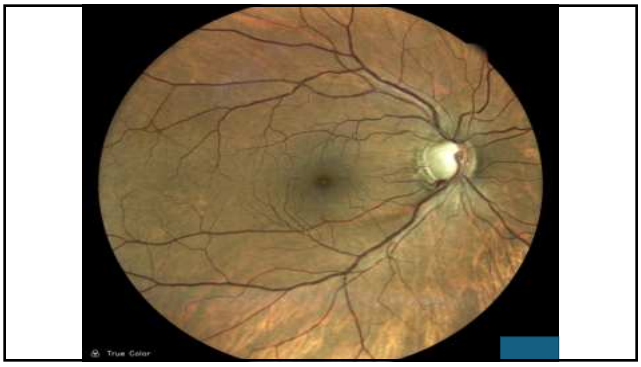


41

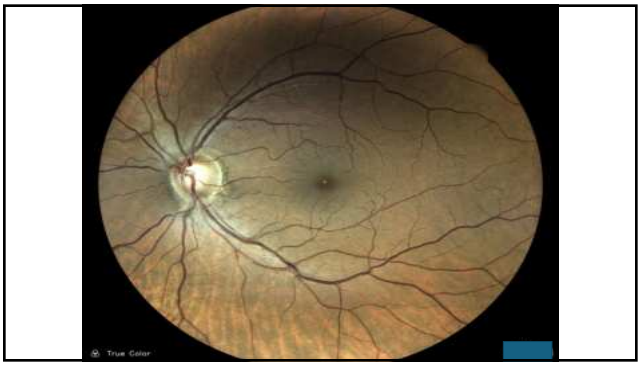
2015-2018

- Patient did not return for follow up
- July 2018 returns for an exam
- IOP 28 OD and 23 OS

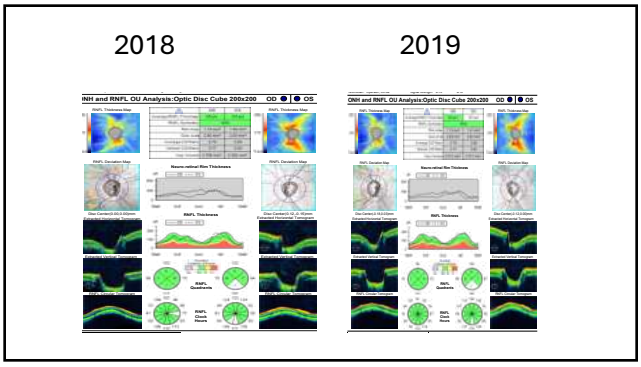
42



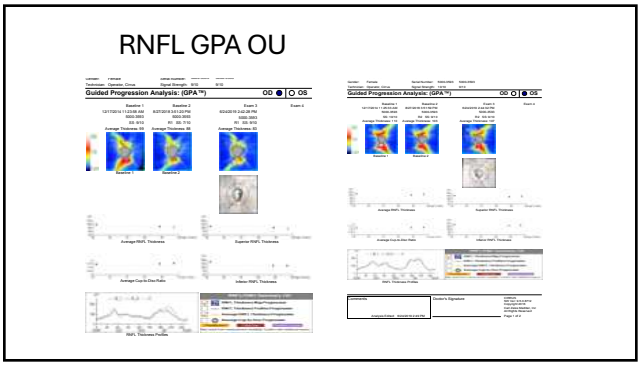
43



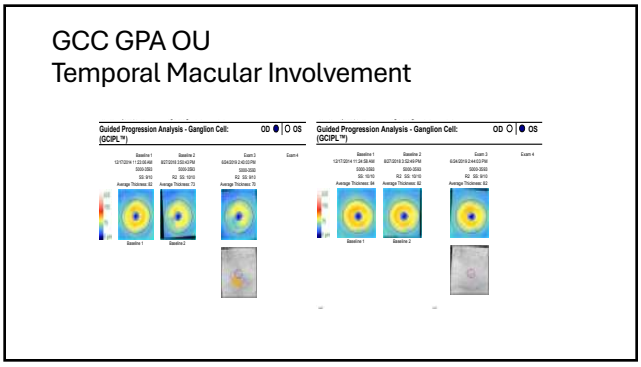
44



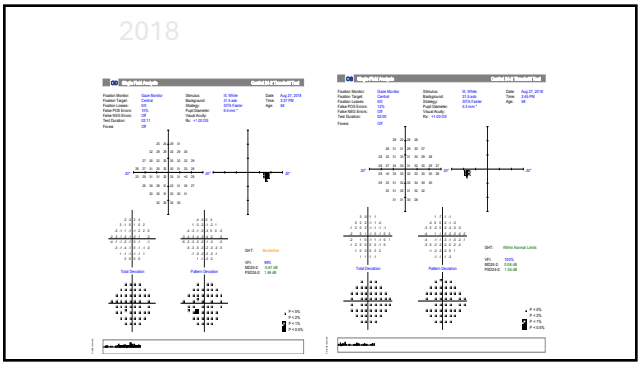
45



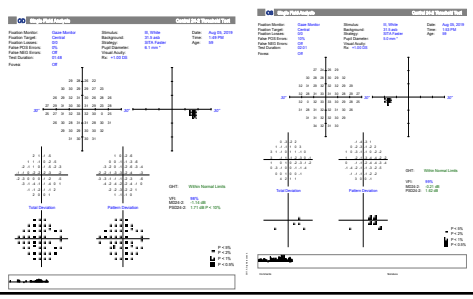
46



47



48

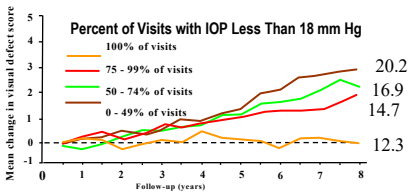


49

AGIS 7

Sustained IOP below 18 mm Hg:

Positive Correlation with Stability of Visual Field



AGIS Investigators. 2000. Am. J. Ophthalmol., 130, 429–440

50

Reassessing Target IOP After Starting Therapy

- How do you know that the target you set is low enough to prevent further damage (VF or OCT)?
  - Imaging and Perimetry
    - Has there been subsequent RNFL loss since starting treatment or development of new or first VF defects?
  - How has the IOP fared against target?
    - Never meets target?
    - Sometimes meets target?
    - Always hits target?

51

Reassessing Target IOP After Starting Therapy

- If target IOP not reached or consistent, what is the next step:
  - Consider replacing within class
    - i.e. Latanoprost for Bimatoprost or Latanoprostene bunod, etc
  - Consider adding a second bottle of IOP lowering medicine
    - Single agent adjunct (to a PGA for example):
      - Beta blocker, TCAI, Alpha agonist, Netarsudil
    - Combination agent*
      - Combigan, Cosopt, Rocklatan, Simbrinza
    - Laser Trabeculoplasty
- Then reassess in same manner as before

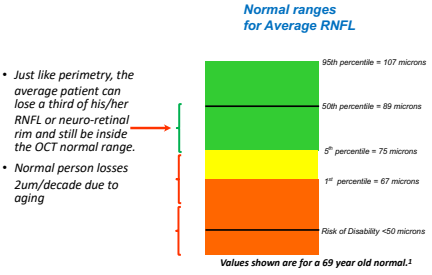
52

2 Groups of Patients to Watch and Treat Aggressively

- Macular Vulnerability Zone patients
- Patients progressing on OCT that are subtle and indicative of fast progressors

53

OCT and Progression Range

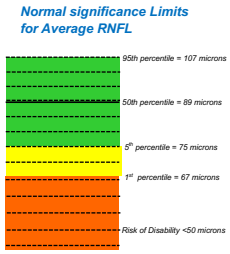


54

SDOCT measurements are highly reproducible.

2-4 Steps in Range

- *We can measure multiple steps of statistically significant change while a glaucoma suspect still is in the green normal range.*



- *Leung et al. Ophthalmology 2009;116:1257*
- *Roh et al. Ophthalmology 2013;120:969*
- *Wong et al.* Optom Vis Sci 2014;92
- Matlatch et al, IOVS Sep 2014 .

55

BG

Advancing Therapy

56

57

SLT and the LIGHT Study

58

Introduction

- SLT reduces IOP by increasing trabecular outflow with a single, painless outpatient procedure with good safety profile and limited recovery time
- Approved by the FDA in 2001
- IOP lowering effect comparable to medication without medication associated side effects
- While not permanent, it is repeatable
- Still not routinely offered as first line treatment

59

Selective Laser Trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma

- United Kingdom study set in 6 hospitals
  - Recruited patients from 2012-2014
  - Observer masked
  - Randomized
  - Treatment naïve patients/newly diagnosed OAG
    - No previous IOP lowering drops, laser or surgery

60

LIGHT Study Design

- 718 patients entered the study (1235 eyes)
- Patients randomized on a 1:1 basis to either:
  - SLT (356 patients, 613 eyes)
  - Drops (362 patients, 622 eyes)

61

Topical Medication Algorithm

- Drug classes for 1st, 2nd, and 3d line treatment were determined by the NICE guidelines[5]
- First line-PGA's
- Second line- Beta Blockers
- Third line- TCAI or Alpha Agonist
- Fixed combinations were allowed
- MMT=Clinician judged max most intensive combination of medicines that could be tolerated

62

Results

- Overall 509 (95%) of 536 SLT treated eyes were at target IOP @ 3 years
- Target IOP achieved without medication in 419 (78.2%) of 536 eyes treated in SLT arm
  - 321 eyes (76.6%) required only one SLT session

63

Results

- 499 (93.1%) of the 526 eyes treated medically were at target IOP @ 3 years
  - 346 (64.6%) were using a single medication
- At 3 years:
  - 93.0% of visits were at target IOP for SLT group
  - 91.3% of visits were at target IOP for med group

64

Treatment Escalations and Progression of Disease During Study

- More treatment escalations occurred in the SLT group (348 eyes) than the Medication group (299 eyes)
- Progression
  - 36 eyes in the Medication group showed algorithm-confirmed progression
    - 3 eyes converted from OHT to OAG
    - 33 eyes with OAG progressed
  - 23 eyes in the SLT group
    - 2 eyes converted from OHT to OAG
    - 21 eyes with OAG progressed
- 11 eyes (1.8%) in the Medication group required incisional glaucoma surgery
  - NO EYES IN SLT GROUP REQUIRED INCISIONAL SURGERY

65

Adverse Events

- SLT Group
  - 6 eyes had an IOP rise of 5mm Hg or more on day of treatment
    - Only 1 eye required treatment
  - 122 eyes (34.4%) had transient discomfort, blurred vision or photophobia not requiring treatment
- Medication Group
  - 150 eyes had aesthetic side effects or allergic reactions

66

Cost of Therapy

- Eye drops were approximately double the cost effect of SLT
- Difficult to extrapolate to US market but general financial math should apply
- Eventual ophthalmic surgery (trab, tube, cataract etc) over the 3 years was significantly less in the SLT group compared to the Medication group

67

Cost and Cost Effectiveness

- SLT as first line resulted in a significant cost savings relative to surgery and medication
  - Approximately 451 dollars/pounds savings in provider related visit costs per patient
  - For every patient given SLT in lieu of drops, the cost savings are greater than the cost of SLT for **2 additional patients!**
  - This is also equal to the cost of five additional office visits

68

Clinical effectiveness of SLT vs. Drops

- IOP Control
  - SLT first approach provided better IOP control over 3 years with more visits at target IOP compared to drops
    - Less intense drop treatment than Medication group
    - NO glaucoma surgeries required compared to Medication group
  - Could be due to adherence with SLT vs. Drops

69

Clinical effectiveness of SLT vs. Drops

- IOP Control
  - SLT provides better diurnal IOP stability[6]
    - Could be due to continuous effect on TM versus episodic administration of medication
  - Primary SLT afforded drop free control of IOP for 3 years in 74.2% of patients
    - This is much higher than in previous studies with less stringent success criteria
    - Prior treatment and more severe disease likely reduce the effect of SLT in those patients[7]
    - Likely the reason for such a robust response in treatment naïve patients in this study

70

Safety of SLT vs. Drops

- This study showed a greater safety profile of SLT than previously reported
  - No systemic side effects reported
  - Only 1 eye had an IOP spike
    - Compared to previously reported rates of 28.8%[8]
    - 2-week IOP checks did not change management for any patient and appears to be unnecessary
      - Avoidance of this could save more $ to the system
  - Lower rate of cataract surgery in SLT arm which supports the existing evidence of drops increasing incidence of cataract and surgery[9]

71

Conclusions

- Selective laser trabeculoplasty provides superior IOP stability to drops, at a lower cost AND
  - 74% or ¾ of patients are successfully controlled without drops for at least 3 years after a single treatment

72

Conclusions

- Selective laser trabeculoplasty as an initial treatment for glaucoma is associated with the following:
  - Lower cost
  - Good clinical outcomes
    - 2-week follow up not necessary
  - Lower symptom scores
  - Drop-freedom for most patients
- SLT should be offered as an alternative to IOP lowering drops as initial therapy on a more widespread basis

73

Identifying and managing allergies and sensitivities to glaucoma medicaitons

74

Alpha Agonists (Alpha-2 selective)

- This sensitivity has been called many things
  - Allergy
  - Follicular Conjunctivitis
  - Atopic reaction
- ~20 % rate of reaction with .2%
  - When on branded .1% it is suspected to be less than 5% rate
  - When combined in branded combigan drops to about 10% but still 1 in 10 will get the allergy, usually 6-12 mos after starting

75

Brimonidine Allergy

76

Latanoprostene Bunod 0.024%(LBN)

- First nitric oxide donating compound investigated for topical ophthalmic use
- Novel nitric oxide donating prostaglandin F2α receptor agonist
- Received FDA approval in 2017
- The data has demonstrated significant IOP lowering and a favorable safety profile
- Dual mechanism of action

Hoy SM. Latanoprostene Bunod Ophthalmic Solution 0.024%: A Review in Open-Angle Glaucoma and Ocular Hypertension [published correction appears in Drugs. 2018;78(8):857]. *Drugs*. 2018;78(7):773-780. Fingeret M, Gaddie IB, Bloomenstein M. Latanoprostene bunod ophthalmic solution 0.024%: a new treatment option for open-angle glaucoma and ocular hypertension. Clin Exp Optom. 2019;102(4):341-510.

77

Most Common Ocular Adverse Reactions in APOLLO and LUNAR*[1,2]

Adverse Reactions	LBN (n=611)	TIMOLOL 0.05% (n=271)
Conjunctival Hyperemia	5.9%	1.1%
Eye Irritation	4.6%	2.6%
Eye Pain	3.6%	2.2%
Ocular Hyperemia	2.0%	0.7%
Instillation Site Pain	2.0%	1.8%

*Pooled data from all tested time points in the APOLLO and LUNAR studies: ocular adverse reactions occurring in ≥2% of study eyes

Less than 1% discontinuation due to ocular adverse reactions[2]

- Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions
- These included ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis, and foreign body sensation

78

Rho Kinase Inhibitors

- **Netarsudil ophthalmic solution 0.02%**
- Rho kinase drug discovery program initiated in 2006
- Goal to identify an effective and well-tolerated ROCK inhibitor with a durable IOP lowering effect.
- Most effective compounds were ROCK/NET inhibitors (norepinephrine transporter)
- In addition to trabecular outflow, animal and donor eye studies showed a decrease in aqueous humor production and episcleral venous pressure
- The decrease in EVP is felt to be related to NET inhibition.

79

Preferred Term (with Incidence ≥5% (Pooled Safety Population)	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Eye Disorders		
Conjunctival Hyperemia	456 (54.4)	87 (10.4)
Cornea Verticillata (corneal deposits/corneal opacity)	175 (20.9)	2 (0.2)
Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
Vision Blurred	62 (7.4)	12 (1.4)
Lacrimation Increased	60 (7.2)	5 (0.6)
Erythema of Eyelid	57 (6.8)	6 (0.7)
Visual Acuity Reduced	44 (5.2)	13 (1.5)

80

- Cornea verticillata (lipid micro-deposits in the corneal epithelial layer)
- Rocklatan (netarsudil .02% + latanoprost .005% FDC)™: ~5%
- Rhopressa (netarsudil .02%)™: ~4%
  - ~5-9% reported in Rocket 1 and Rocket 2
- Asymptomatic
- Only visible via biomicroscopy evaluation
- Benign corneal deposits (phospholipidosis) are a familiar outcome with other drugs such as amiodarone

Cornea Verticillata

81

- Cornea verticillata observed (20.9%)
  - Resolved in 95.6% of patients after treatment ended (OBS01); 2 patients still being followed
  - Not associated with changes in visual function
- Cornea verticillata well-studied in patients on amiodarone therapy[1,2]
  - Approved 1984 USA, observed for decades
  - Present in >98% of patients taking standard oral dosages of amiodarone
  - Rarely interferes with vision

82

83

84

Table 2. Safety summary

	Netarsudil/ Latanoprost FDC (n=238)	Netarsudil 0.02% (n=243)	Latanoprost 0.005% (n=237)
Eye disorders, n (%)			
Conjunctival hyperemia	150 (63.0)	125 (51.4)	52 (21.9)
Conjunctival hemorrhage	31 (13.0)	44 (18.1)	3 (1.3)
Cornea verticillata	42 (17.6)	33 (13.6)	0 (0)
Eye pruritus	27 (11.3)	22 (9.1)	3 (1.3)
Punctate keratitis	12 (5.0)	18 (7.4)	10 (4.2)
Lacrimation increased	17 (7.1)	20 (8.2)	1 (0.4)
Visual acuity reduced	13 (5.5)	13 (5.3)	6 (2.5)
Vision blurred	11 (4.6)	15 (6.2)	3 (1.3)
Blepharitis	14 (5.9)	8 (3.3)	5 (2.1)
Administration site conditions, n (%)			
Instillation site pain	55 (23.1)	60 (24.7)	18 (7.6)

Adverse events occurring in ≥1% of patients in any treatment arm are presented.
Patients with known contraindications or hypersensitivity to latanoprost were ineligible for participation in this study.
FDC, fixed-dose combination.

85

Netarsudil Side Effects: Conjunctival Hemorrhage

- Conjunctival hemorrhage (17.2%)
  - Small
  - Transient
  - Visualized by examiner with slit lamp magnification
- Do not appear to be associated with or cause ocular pathology

86

Rho Kinase "Brimonidine effect"

87

Questions Doctors ASK:

- What do you think about neuroprotection?
- Can marijuana be used to treat glaucoma?
- Can patients take their PGAs every other day?
- Should we do MRI's on patients with normal pressure and glaucoma findings?
- Should we do LPI on all narrow angle patients?
- Can you still have some variants of angle closure if a patient has a patent PI?

88

What is the Role of Estrogen in Glaucoma Age of Menopause in Women

89

The Risk of glaucoma after early bilateral oophorectomy

Abstract

90

Published in final edited form as:
Exp Eye Res. 2019 September ; 186: 107706. doi:10.1016/j.exer.2019.107706.

Menopause exacerbates visual dysfunction in experimental glaucoma

Andrew J. Feola[a,b], Jiaming Fu[a], Rachael Allen[a,b], Victoria Yang[a], Ian C. Campbell[a,b], Amy Ottenheyer[a], C. Ross Ethier[b], Machelle Pardue[a,b]

[a]Center for Visual and Neurocognitive Rehabilitation, Atlanta VA Healthcare System, Atlanta, GA, United States

[b]Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, United States

[c]Emory University School of Medicine, United States

Abstract

Glaucoma is the leading cause of irreversible blindness worldwide. Recently, estrogen deficiencies caused by early menopause, alterations in estrogen signaling via mutations in estrogen receptors, and polymorphisms along estrogen metabolic pathways have all been linked to an increased risk of developing glaucoma. Here, we examined how menopause and age impact visual function and retinal structure in an experimental model of glaucoma. Young (3–4 months) and aged (9–10 months) female Brown Norway rats were divided into pre- and post-menopausal cohorts by surgically inducing menopause via ovariectomy (OVX). After six weeks, ocular hypertension (OHT) was induced unilaterally for a period of eight weeks. Four cohorts were successfully followed to eight weeks: young sham (y = 8), young OVX (n =9), aged sham (n =10), and aged OVX (n =11) animals. Intraocular pressure (IOP) was monitored weekly in all groups. Prior to inducing OHT (baseline) and at four and eight weeks after inducing OHT, we assessed visual acuity via the optomotor response (OMR) and retinal structure using optical coherence tomography (OCT). OHT decreased the OMR in all cohorts. We found that spatial frequency thresholds decreased by 54% in OVX animals after OHT compared to sham animals after OHT, regardless of age (p < 0.001). We also found thinning of the retinal nerve fiber layer (RNFL) and loss of total retinal thickness after induction of OHT. Aged animals had more thinning of the RNFL and loss of total retinal thickness compared to young animals (p < 0.001). Overall, OHT caused significant changes in visual function and retinal structure. Observing that OVX in young and aged animals further decreased spatial frequency thresholds after OHT suggests that an estrogen deficiency may intensify visual impairment after OHT.

91

The Association of Female Reproductive Factors with Glaucoma and Related Traits

A Systematic Review

Kian M. Madjedi, MD,[1,2] Kelsey V. Stuart, MSBCS, MSc,[1] Sharon Y.L. Chua, PhD,[1] Paul J. Foster, PhD, FRCSEdi,[1] Nicholas G. Strouthidis, MD, PhD,[1] Robert N. Luben, PhD,[1,3] Alasdair N. Warwick, MBBS, BSc,[4] Jae H. Kang, ScD,[5] Janey L. Wiggs, MD, PhD,[5] Louis R. Pasquale, MD,[1,6] Anthony P. Khawaja, PhD, FRCOphth[1,3]

Topic: This systematic review summarizes evidence for associations between female reproductive factors (age at menarche, parity, oral contraceptive [OC] use, age at menopause, and postmenopausal hormone [PMH] use) and intraocular pressure (IOP) or open-angle glaucoma (OAG).

Clinical Relevance: Understanding the associations between female reproductive factors and glaucoma may shed light on the disease pathogenesis and aid clinical prediction and personalized treatment strategies. Importantly, some factors are modifiable, which may lead to new therapies.

Methods: Two reviewers independently extracted articles in MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials databases to identify relevant studies. Eligibility criteria included studies with human subjects aged > 18 years, a measured outcome of either IOP or OAG, a cohort, case-control, cross-sectional, or randomized controlled trial design, a reported measure of association, such as the hazard ratio, relative risk, odds ratio, or mean difference, with an associated confidence interval, and a measured exposure of at least 1 of the following variables: age at menarche, parity, OC use, age at menopause, or PMH use.

Results: We included a total of 27 studies. Substantial differences in study designs, exposure and treatment levels, treatment durations, and variable reporting precluded a meaningful quantitative synthesis of the identified studies. Overall, relatively consistent associations between PMH use and a lower IOP were identified. Estrogen-only PMH use may be associated with lower OAG risk, which may be modified by race. No significant associations were found with combined estrogen-and-progesterone PMH use. No strong associations between parity or age at menarche and glaucoma were found, but a younger age at menopause was associated with an increased glaucoma risk, and adverse associations were identified with a longer duration of OC use, though no overall association with OC use was found.

Conclusions: The association between PMH use and lower IOP or OAG risk is a potentially clinically relevant and modifiable risk factor and should be investigated further, although this needs to be interpreted in the context of a high risk of bias across included studies. Future research should examine associations with IOP specifically and how the relationship between genetic factors and OAG risks may be influenced by female reproductive factors. *Ophthalmology Glaucoma 2022;5:628-647* © *2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license* (http://creativecommons.org/licenses/by/4.0/).

92

Age at Menopause

The epidemiologic literature does not consistently support an overall association between age at menopause and POAG; however, several subgroup analyses suggest a higher risk of POAG in those with an earlier age at natural menopause. A lower risk of POAG was also found in a large subgroup analysis of older women (> 65 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the POAG risk.[14] Although no association between the age at menopause and OAG with elevated IOP (specifically, > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigation. Such a study may, however, prove logistically challenging, as it would require measuring IOP values before and after the menopausal transition and adjusting for age.

Menopause can occur naturally or can be induced by surgery or radiation. Each of these types of menopause can influence the age at menopause,[40] but the specific effects of each are not yet fully understood.[42] The number of studies reporting each of these subtypes individually did not make a subanalysis realistic in this review, although an effort was

93

Age at Menarche

A younger age at menarche should theoretically confer greater overall lifetime estrogen exposure, which would lead to a hypothetically lower risk of POAG. Evidence from the included observational studies,[14,19,22–24] however, suggests no clear association between the age at menarche and risks of POAG. This may be owing to the inability to meta-analyze the various studies, leading to this review being underpowered to identify a true association. Although no studies directly examined the association between age at menarche and IOP, a secondary analysis of the NHS found that a later age of menarche was associated with a slightly higher risk of the normal-tension subtype of POAG (IOP < 22 mmHg),[14] suggesting that a potential association between menarche age and glaucoma may occur via non–IOP-mediated mechanisms. The relationship between age at menarche and POAG should be further investigated, more completely accounting for the entire female reproductive and postreproductive history.

94

Lifestyle Factors in Glaucoma;
Drinking, Diet, Exercise, Smoking

95

The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

ARTICLE OPEN

Association between lifestyle habits and glaucoma incidence: a retrospective cohort study

Asahi Fujita[1,2✉], Yohei Hashimoto[1✉], Hiroki Matsui[1], Hideo Yasunaga[1] and Makoto Aihara[1]

BACKGROUND/OBJECTIVES: Although lifestyle habits may represent modifiable risk factors of glaucoma, the association between lifestyle factors and glaucoma is not well understood. The aim of this study was to investigate the association between lifestyle habits and the development of glaucoma.

SUBJECTS/METHODS: Participants who underwent health check-ups from 2005 to 2020 using a large-scale administrative claims database in Japan were included in the study. Cox regression analyses were performed where glaucoma development was regressed on the lifestyle (body mass index, current smoking, frequency and amount of alcohol consumption, eating habits, exercise habits and quality of sleep), age, sex, hypertension, diabetes mellitus and dyslipidaemia.

RESULTS: Among the 3,110,743 eligible individuals, 59,975 developed glaucoma during the mean follow-up of 2058 days. Factors associated with increased risk of glaucoma were overweight/obese (vs. moderate weight: hazard ratio, 1.04 [95% confidence interval, 1.02–1.07]), alcohol consumption of 2.5–4.9 units/day, 5–7.4 units/day, and ≥7.5 units/day (vs. <2.5 units/day: 1.05 [1.02–1.08], 1.03 [1.01–1.06] and 1.06 [1.01–1.12], respectively), skipping breakfast (1.14 [1.10–1.17]), late dinner (1.05 [1.03–1.08]) and daily walking of 1 h (1.14 [1.11–1.18]). Factors associated with decreased risk of glaucoma were daily alcohol consumption (vs. rarely: 0.94 [0.91–0.97]) and regular exercise (0.92 [0.90–0.95]).

CONCLUSIONS: Moderate body mass index, having breakfast, avoiding late dinner, limiting alcohol intake to <2.5 units/day, and regular exercise were associated with a reduced risk of developing glaucoma in the Japanese population. These findings may be useful for promoting glaucoma prophylaxis.

Eye; https://doi.org/10.1038/s41433-023-02535-7

96

Greater Physical Activity Is Associated with Slower Visual Field Loss in Glaucoma

Moon Jeong Lee, BS,[1] Jiangxia Wang, MS,[2] David S. Friedman, MD, PhD,[1] Michael V. Boland, MD, PhD,[1] Carlos G. De Moraes, MD, MPH,[3] Pradeep Y. Ramulu, MD, PhD[1]

Purpose: To determine the association between physical activity levels and the rate of visual field (VF) loss in glaucoma.
Design: Longitudinal, observational study.
Participants: Older adults with suspect or manifest glaucoma.
Methods: Participants wore accelerometers for 1 week to define average steps per day, minutes of moderate-to-vigorous activity, and minutes of nonsedentary activity. All available VF measurements before and after physical activity assessment were retrospectively analyzed to measure rates of VF loss.
Main Outcome Measures: Pointwise changes in VF sensitivity associated with physical activity measures.
Results: A total of 141 participants (mean age, 64.9±5.8 years) were enrolled. Eye mean deviation (MD) at the time of physical activity assessment was −6.6 decibels (dB), and average steps per day were 5613±3158. The unadjusted average rate of VF loss as measured by pointwise VF sensitivity was 0.36 dB/year (95% confidence interval, −0.37 to −0.35). In multivariable models, slower VF loss was observed for patients demonstrating more steps (+0.007 dB/year/1000 daily steps, $P < 0.001$), more moderate-to-vigorous activity (+0.003 dB/year/10 more minutes of moderate-to-vigorous activity per day, $P < 0.001$), and more nonsedentary activity (+0.007 dB/year/30 more minutes of nonsedentary time per day, $P = 0.005$). Factors associated with a faster rate of VF loss included older age, non-white race, glaucoma surgery, cataract surgery, and moderate baseline VF damage (−6 dB ≥ MD >−12 dB) as opposed to mild VF damage (MD >−6 dB). Similar associations between baseline accelerometer-measured physical activity and rates of VF loss were observed over other time periods (e.g., within 1, 3, and 5 years of activity assessment).
Conclusions: Increased walking, greater time spent doing moderate-to-vigorous physical activity, and more time spent in nonsedentary activity were associated with slower rates of VF loss in a treated population of patients with glaucoma, with an additional 5000 daily steps or 2.6 hours of nonsedentary physical activity decreasing the average rate of VF loss by approximately 10%. Future prospective studies are needed to determine if physical activity can slow VF loss in glaucoma or if progressive VF loss results in activity restriction. If the former is confirmed, this would mark physical activity as a novel modifiable risk factor for preventing glaucoma damage. *Ophthalmology 2019;126:958-964 © 2018 by the American Academy of Ophthalmology*

97

Association between Exercise Intensity and Glaucoma in the National Health and Nutrition Examination Survey

Victoria L. Tseng, MD, PhD,[1] Fei Yu, PhD,[1,2] Anne L. Coleman, MD, PhD[1,2]

Purpose: To examine the association between exercise intensity and glaucoma in the National Health and Nutrition Examination Survey (NHANES) population.
Design: Retrospective, cross-sectional study.
Participants: Adult participants of the 2005–2006 NHANES aged 40 years and older.
Methods: Objective exercise intensity was assessed based on measurements from accelerometers worn by participants over 1 week. Subjective exercise intensity was assessed with questionnaire responses. Glaucoma was defined with 2 definitions based on (1) the Rotterdam criteria and (2) ophthalmologist grading of optic disc photographs for characteristic features of glaucoma. Covariates included age, gender, ethnicity, blood pressure, body mass index, and spherical equivalent. Logistic regression was performed to assess associations between objective and subjective exercise intensity and glaucoma while controlling for all covariates. All data were weighted based on the NHANES multistage sampling design.
Main Outcome Measures: Prevalence of glaucoma based on the 2 definitions described.
Results: The study included a sample of 1387 participants, of whom 68 (4.9%) had glaucoma based on Rotterdam criteria and 7 (0.5%) had glaucoma based on disc image grading. This translated to a weighted estimate of 70 246 160 individuals, with an estimated prevalence of glaucoma of 3.1% based on the Rotterdam criteria and 0.3% based on disc image grading. After adjusting for covariates, each 10-count increase in accelerometer intensity was associated with decreased odds of glaucoma using both criteria (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.95–0.99 for Rotterdam; OR, 0.90; 95% CI, 0.85–0.95 using disc image grading). With Rotterdam criteria, participants who spent the day standing or walking versus sitting had 58% decreased odds of glaucoma (OR, 0.42; 95% CI, 0.25–0.70). With disc image grading, participants who performed moderate amounts of vigorous activity had 95% decreased odds of glaucoma compared with those who performed no vigorous activity (OR, 0.05; 95% CI, 0.01–0.56).
Conclusions: In the 2005–2006 NHANES adult population, increased exercise intensity is associated with decreased odds of glaucoma. Further population-based studies are needed to examine associations between additional aspects of exercise and glaucoma. *Ophthalmology Glaucoma 2020;3:393-402 © 2020 by the American Academy of Ophthalmology*

98

Smoking and progressive retinal nerve fibre layer thinning in glaucoma

WHAT IS ALREADY KNOWN ON THIS TOPIC

- The association between smoking and glaucoma progression has not been well known.

WHAT THIS STUDY ADDS

- Greater smoking pack-year index was associated with faster rates of retinal nerve fibre layer thinning over time in patients with glaucoma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Smoking pack-year index might add information to the assessment of risk of glaucoma progression.

99

ABSTRACT

Background/Aims To investigate the relationship between smoking and smoking intensity, and the rate of retinal nerve fibre layer (RNFL) thinning in patients with primary open angle glaucoma (POAG).

Methods In this longitudinal study, patients with POAG who had at least 3 years of follow-up with a minimum of 5 visits of optical coherence tomography (OCT) were enrolled. The smoking intensity was calculated as the pack-year at the baseline OCT. Univariable and multivariable linear mixed models were used to determine the effect of each parameter on the rates of RNFL thinning over time. Non-linear least-squares estimation with piecewise regression model was used to investigate the cut-off point for the relationship between circumpapillary RNFL thinning and smoking intensity.

Results A total of 466 eyes of 314 patients were included over the mean (95% CI) follow-up of 6.6 (6.4 to 6.7) years. Of the 314 patients, 121 (39%) had reported any history of smoking. Greater smoking intensity was associated with faster RNFL thinning (−0.06 (95% CI −0.11 to 0.00) µm/year per 10 pack-year higher; p=0.031) after adjusted for confounding factors. RNFL thinning became significantly faster when smoking intensity was >8 pack-year.

Conclusions Smoking intensity is associated with faster rates of RNFL thinning. Evaluation of smoking intensity might add information to the assessment of risk of glaucoma progression. Future studies are required to explore if withdrawing smoking as a modifiable risk factor can decrease progression in patients with glaucoma.

100

Clinical and Epidemiologic Research

Alcohol Consumption, Genetic Risk, and Intraocular Pressure and Glaucoma: The Canadian Longitudinal Study on Aging

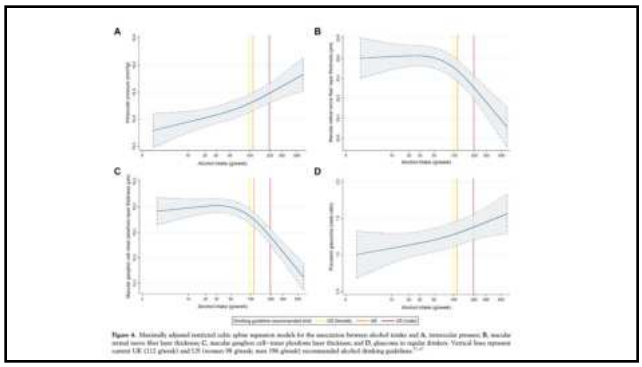
Alyssa Grant,[1] Marie-Hélène Roy-Gagnon,[1] Joseph Bastasic,[1] Akshay Talekar,[1] Mahsa Jessri,[2] Gisele Li,[3] Ralf Buhrmann,[4] and Ellen E. Freeman[1,5,6]

101

The Association of Alcohol Consumption with Glaucoma and Related Traits

Findings from the UK Biobank

102

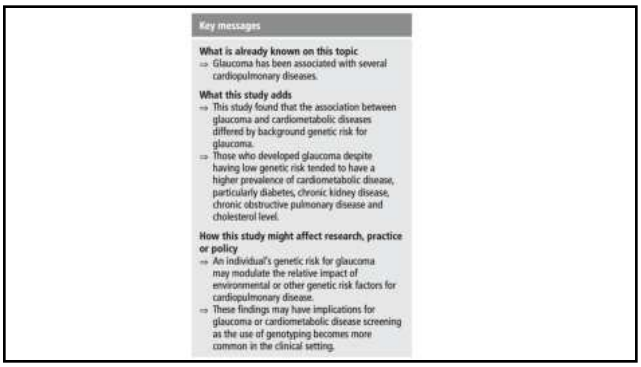


103

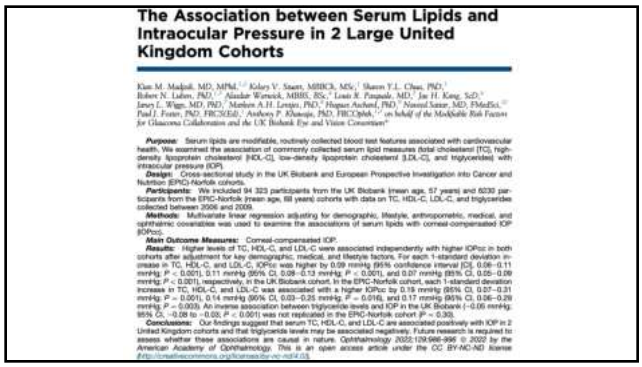
Cardiopulmonary Associations with Glaucoma

104

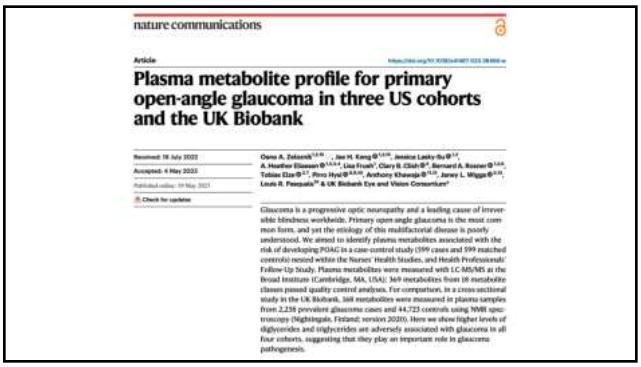
105



106



107



108

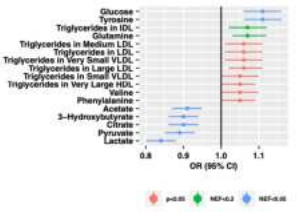
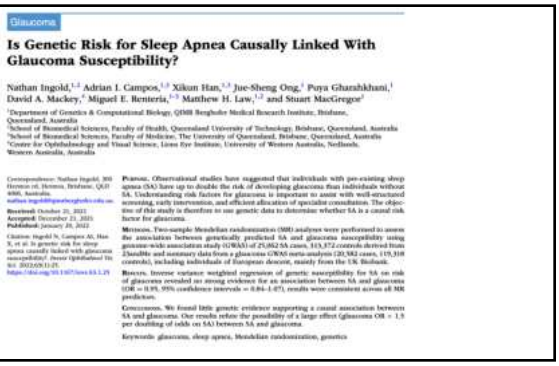


Fig. 4 | Individual metabolites (out of *N* = 168) that were at least nominally significantly associated with prevalent glaucoma in the UK Biobank (2238 cases, 44,723 controls). Data are presented as odds ratios and 95% confidence intervals estimated with logistic regression models. The logistic regression model includes adjustment for age, gender, smoking status, physical activity, BMI, ethnicity, spherical equivalent, coffee consumption, tea consumption, alcohol intake, systolic blood pressure, cholesterol level, diabetes, coronary artery disease, and statin use. All statistical tests are two-sided, and we accounted for multiple comparisons by using p-values based on number of effective tests (NEF). Source data with exact values are provided as a Source Data file.

109

What's the Deal with Sleep Apnea and Glaucoma?

110



Glaucoma

Is Genetic Risk for Sleep Apnea Causally Linked With Glaucoma Susceptibility?

Nathan Ingold,[1,2] Adrian I. Campos,[1,3] Xikun Han,[1,3] Jue-Sheng Ong,[1] Puya Gharahkhani,[1] David A. Mackey,[4] Miguel E. Renteria,[1,5] Matthew H. Law,[1,3] and Stuart MacGregor[1]

[1]Department of Genetics & Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
[2]School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Queensland, Australia
[3]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia
[4]Centre for Ophthalmology and Visual Science, Lions Eye Institute, University of Western Australia, Nedlands, Western Australia, Australia

Correspondence: Nathan Ingold, 300 Herston rd, Herston, Brisbane, QLD 4006, Australia.

Received: October 21, 2021
Accepted: December 23, 2021
Published: January 20, 2022

Citation: Ingold N, Campos AI, Han X, et al. Is genetic risk for sleep apnea causally linked with glaucoma susceptibility? *Invest Ophthalmol Vis Sci.* 2022;63(1):25. https://doi.org/10.1167/iovs.63.1.25

Purpose. Observational studies have suggested that individuals with pre-existing sleep apnea (SA) have up to double the risk of developing glaucoma than individuals without SA. Understanding risk factors for glaucoma is important to assist with well-structured screening, early intervention, and efficient allocation of specialist consultation. The objective of this study is therefore to use genetic data to determine whether SA is a causal risk factor for glaucoma.

Methods. Two-sample Mendelian randomization (MR) analyses were performed to assess the association between genetically predicted SA and glaucoma susceptibility using genome-wide association study (GWAS) of 25,062 SA cases, 313,372 controls derived from 23andMe and summary data from a glaucoma GWAS meta-analysis (20,582 cases, 115,310 controls), including individuals of European descent, mainly from the UK Biobank.

Results. Inverse variance weighted regression of genetic susceptibility for SA on risk of glaucoma revealed no strong evidence for an association between SA and glaucoma (OR = 0.95, 95% confidence intervals = 0.84–1.07), results were consistent across all MR predictors.

Conclusions. We found little genetic evidence supporting a causal association between SA and glaucoma. Our results refute the possibility of a large effect (glaucoma OR > 1.5 per doubling of odds on SA) between SA and glaucoma.

Keywords: glaucoma, sleep apnea, Mendelian randomization, genetics

111

BMJ Open

Association of sleep behaviour and pattern with the risk of glaucoma: a prospective cohort study in the UK Biobank

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Based on the UK Biobank data, this is the first large prospective cohort study to comprehensively assess the association of sleep behaviours and patterns with glaucoma.
- ⇒ The application of cluster analyses (ie, multiple correspondence analysis (MCA) and a k-means clustering algorithm) enabled us to extract the most informative sleep patterns that inherently existed in the study population. Consequently, the exposed and reference groups in our analyses are realistic and mutually exclusive, leading to the most meaningful comparisons.
- ⇒ A wide range of important confounders were considered in the analyses since detailed information was available on sociodemographic factors, lifestyle, and somatic comorbidities.
- ⇒ The data were obtained from the UK Biobank but are not a representative sample of the entire UK population. The generalisation of our findings to the entire UK or other populations needs further assessment.

112

BMC Medicine

RESEARCH ARTICLE Open Access

Associations of sleep apnoea with glaucoma and age-related macular degeneration: an analysis in the United Kingdom Biobank and the Canadian Longitudinal Study on Aging

Xikun Han[1,2*], Samantha Sze-Yee Lee[3], Nathan Ingold[1,2], Nigel McArdle[3,4], Anthony P. Khawaja[5], Stuart MacGregor[1,2] and David A. Mackey[3,6]

Abstract

Background: Sleep apnoea, a common sleep-disordered breathing condition, is characterised by upper airway collapse during sleep resulting in transient hypoxia, hyperperfusion of the optic nerve, and spike in intracranial pressure. Previous studies have reported conflicting findings on the association of sleep apnoea with glaucoma, and there are limited reports on the link between sleep apnoea and age-related macular degeneration (AMD).

Methods: Middle-aged and older participants from the longitudinal United Kingdom (UK) Biobank (*n* = 502,505) and the Canadian Longitudinal Study on Aging (CLSA; *n* = 24,073) were included in this analysis. Participants in the UK Biobank and the CLSA were followed for 8 and 3 years, respectively. Participants with diagnosed glaucoma or AMD at baseline were excluded from the analysis. In the UK Biobank, sleep apnoea and incident cases of glaucoma and AMD were identified through hospital inpatient admission, primary care records, and self-reported data. Multivariable Cox proportional hazards models were used to explore associations of sleep apnoea with incidence of glaucoma or AMD.

Continued on next page

113

(Continued from previous page)

Results: During the 8-year follow-up in the UK Biobank, glaucoma incidence rates per 1000 person-years were 2.46 and 1.59 for participants with and without sleep apnoea, and the AMD incidence rates per 1000 person-years were 2.27 and 1.42 for participants with and without sleep apnoea, respectively. Multivariable adjusted hazard ratios of glaucoma and AMD risk for sleep apnoea were 1.33 (95% confidence interval [CI] 1.10–1.60, $P = 0.003$) and 1.39 (95% CI 1.15–1.68, $P < 0.001$) relative to participants without sleep apnoea. In the CLSA cohort, disease information was collected through in-person interview questionnaires. During the 3-year follow-up, glaucoma incidence rates per 1000 person-years for those with and without sleep apnoea were 9.31 and 6.97, and the AMD incidence rates per 1000 person-years were 8.44 and 6.67, respectively. In the CLSA, similar associations were identified, with glaucoma and AMD odds ratios of 1.43 (95% CI 1.13–1.79) and 1.39 (95% CI 1.08–1.77), respectively, in participants with sleep apnoea compared to those without sleep apnoea (both $P < 0.001$).

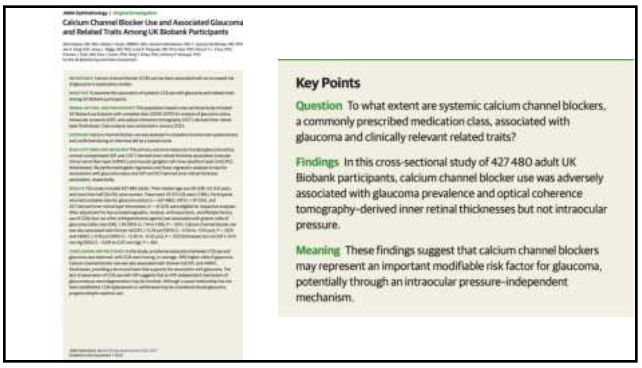
Conclusions: In two large-scale prospective cohort studies, sleep apnoea is associated with a higher risk of both glaucoma and AMD. These findings indicate that patients with sleep apnoea might benefit from regular ophthalmologic examinations.

Keywords: Sleep apnoea, Glaucoma, Age-related macular degeneration, UK Biobank, CLSA, Cohort study

114

Associations Between Niacin Intake and Glaucoma in the National Health and Nutrition Examination Survey

115



Calcium Channel Blocker Use and Associated Glaucoma and Related Traits Among UK Biobank Participants

Key Points

Question To what extent are systemic calcium channel blockers, a commonly prescribed medication class, associated with glaucoma and clinically relevant related traits?

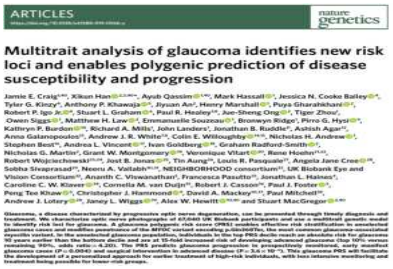
Findings In this cross-sectional study of 427 480 adult UK Biobank participants, calcium channel blocker use was adversely associated with glaucoma prevalence and optical coherence tomography–derived inner retinal thicknesses but not intraocular pressure.

Meaning These findings suggest that calcium channel blockers may represent an important modifiable risk factor for glaucoma, potentially through an intraocular pressure–independent mechanism.

116

How Do Genetics Play into Glaucoma?

117



ARTICLES nature genetics

Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression

118

Glaucoma: Which Genes Do We Already Know

- Genes associated with Adult Onset Glaucoma (Autosomal Dominant/Monogenic)
  - MYOC
    - Autosomal Dominant inherited POAG as well as JOAG
  - LOXYL1
    - Exfoliation syndrome/glaucoma
      - Encodes enzyme that crosslinks elastin and collagen
  - PMEL
    - Premelanosome protein in pigmentary dispersion syndrome/glaucoma
  - OPTN
    - Optineurin, involved in neuroprotection
  - WDR36
  - TBK1
    - Tank binding kinase 1
    - NTG primarily
- **All one of these genes account for less than 5% of all cases of adult onset glaucoma**
  - ***Note-No genetic associations for steroid-induced glaucoma***

119

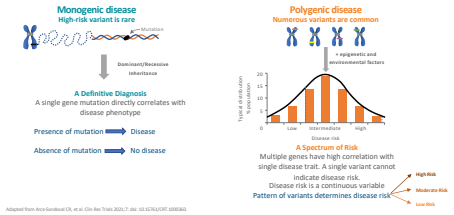
Most Glaucoma is not voiced by monogenic programming

- More commonly, POAG is a complex inherited trait with:
  - Multiple genes with small effect combining to form "risk"
  - Environmental triggers or "turning on" the gene
  - Proximity to a given Loci
- All necessary for "Disease" development
- These genes are not the common ones described on the previous slides
- Over 127 loci have been identified by Genome Wide Association Studies (GWAS)
  - -16 of which are targeted by current existing glaucoma drugs

120

Inheritance of Glaucoma is both Monogenic and Polygenic

Polygenic Disease e.g. POAG has Complex Phenotype and Risk Profiles



Adapted from Arce-Sandoval CA, et al. Clin Rev Trials 2021;7. doi: 10.5761/CRT.1000360.

121

121

Genome Wide Association Studies GWAS

- Several large population based GWAS are in existence and used in this study
  - UKB
    - Population based study in UK of 500,000 participants
    - 7800 POAG vs. 119,000 controls
  - ANZRAG
    - 3100 cases of European ancestry POAG along with 6750 controls
  - Neighborhood GWAS
    - Meta analysis from 8 independent datasets of European Ancestry in US
    - 3900 POAG vs. 35,000 controls
  - BMES
    - Population based cohort study of common ocular diseases in people over 50 in Australia
  - Progressa-prospective longitudinal study of genetic risk factors in 388 patients with early glaucoma

122

GWAS

- Allows pathway analysis for POAG associated risk loci

Some of these genes have been associated with mechanisms for POAG development

Examples:
-Endoplasmic reticulum stress response
-Extracellular matrix
-Cell adhesion
-TGF alpha and beta signaling
-Vascular development
-Lipid metabolism
-Endogenous Nitric Oxide Synthetase)
-Mitochondrial Function

- However none of them on their own would lead to development of disease

123

Methods

- Develop a glaucoma Polygenic Risk Score (PRS)
- Characterize 67,000 Optic Nerve Photographs of UK Biobank participants
  - Used vertical C/D ratio (VCDR) as an endophenotype for glaucoma
  - Also used genetic data from large genetic study using IOP as endophenotype
  - Combined with multitrait analysis of GWAS to identify new genetic loci
    - MTAG

124

Results

- In addition to the already established 127 gene loci, this study identified another 176 loci from VCDR/IOP/GWAS MTAG
- Optimized the prediction of glaucoma risk by combining correlated or associated traits
- Outcome of a Polygenic Risk Score (PRS)
- This PRS had a better prediction ability than any of the input traits alone (IOP, VCDR, GWAS)

125

Main Outcomes

- PRS Prediction
  - Individuals in the top PRS decile reach an absolute risk of glaucoma ***10 years earlier*** than those in the bottom decile **(6.34 x higher likelihood of having POAG)**
  - These same individuals in the top PRS decile are at a ***15-fold increased risk of developing advanced glaucoma***
  - PRS ***predicts glaucoma progression*** in prospectively monitored, early manifest glaucoma cases
  - PRS ***predicts need for surgical intervention*** in advanced glaucoma cases
  - ***PRS will facilitate a personalized approach for earlier treatment of high-risk individuals with less intensive monitoring and treatment for lower-risk patients***

126

Implications For Clinical Care

- Currently, gene based diagnostic tests are available for congenital and juvenile POAG
  - Monogenic or single gene mutation is sufficient to produce the disease phenotype
    - Commercially available monogenic test
- What about for everyone else?

127

Implications For Clinical Care

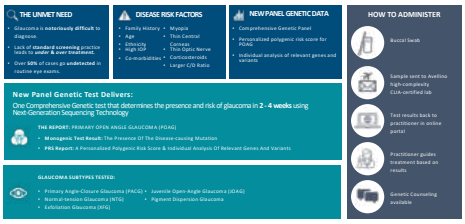
- For adult-onset, complex-inherited forms of glaucoma, polygenic risk scores are being investigated as a potential tool for personalized risk stratifications
- **Genetic Eye Disease Panel For Optic Nerve Disease and Early Manifest Glaucoma (GEDi-O)**
  - Available via Ocular Genomic Institute @ Massachusetts Eye and Ear
    - 22 genes including inherited retinal diseases
    - Glaucoma: 97% sensitivity and 100% specificity

128

Anticipated New Commercial Glaucoma Genetic Polygenic Risk Score

- Expected Q1 2023
- Cheek Swab
- 2-3 week turn around
- Cost unknown
- Insurance unknown

129



130