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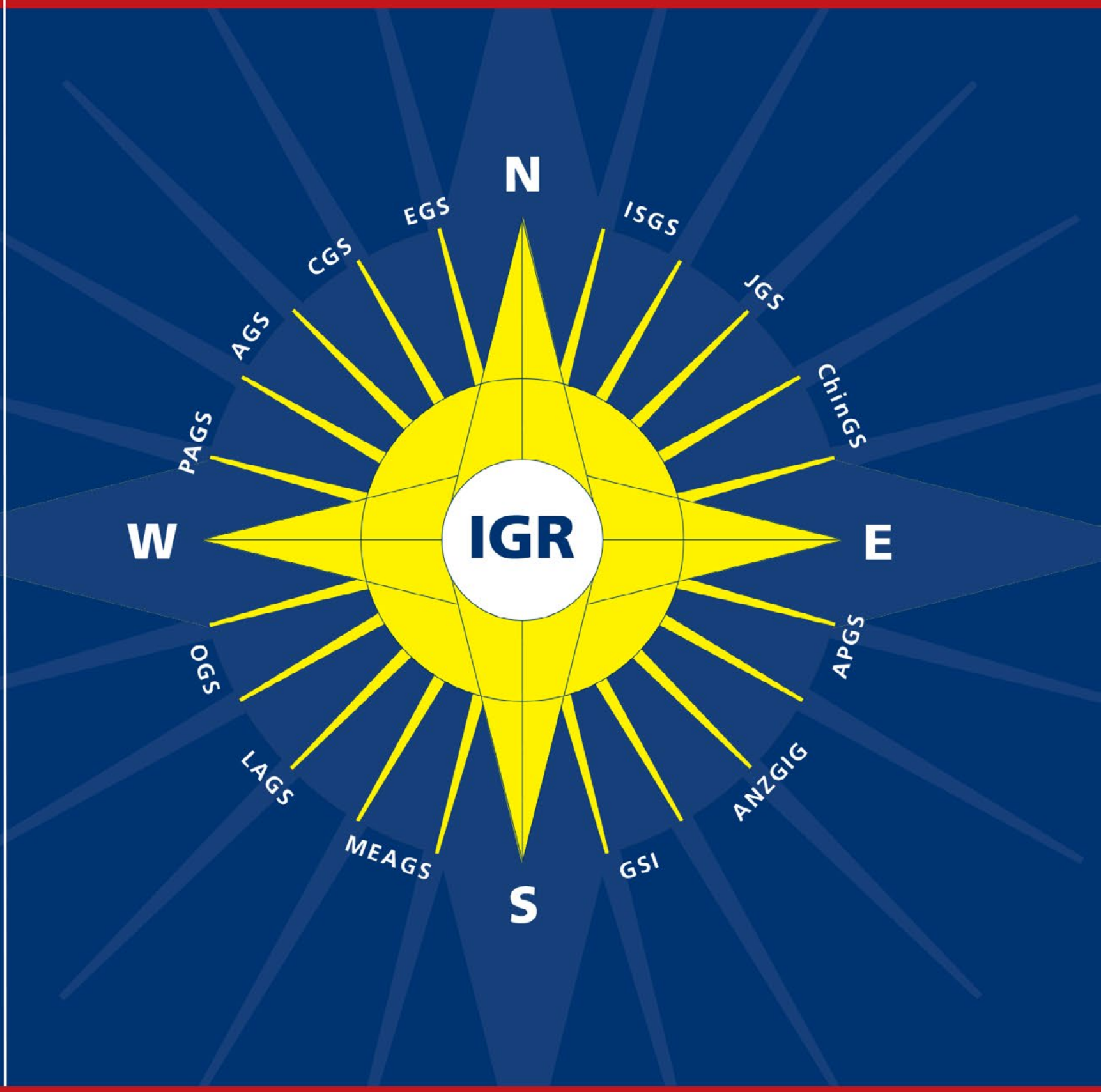

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We are welcoming the start of 2017 with a new IGR Volume, issue 18!

Currently, IGR is distributed via the WGA database and also via our member Glaucoma Societies. Plans are set to make it available via our planned WGA mobile app as well! Be sure we will keep you updated on these developments prior to the start of upcoming World Glaucoma Congress (WGC-2017), taking place in Helsinki, from June 28–July 1. As you may know, all individual members of affiliated WGA Glaucoma Societies are eligible to receive IGR complimentary, four times a year, as well as free access to IGR Online.

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Looking into 2017 and wishing you a year filled with joy, health and success

CELEBRATING 33 YEARS OF THE INTERNATIONAL GLAUCOMA REVIEW

From the WGA Executive Office

Dear readers,

The 7th WGC-2017 will be taking place in less than six months from now. We are grateful to the WGC-2017 Program Planning Committee for setting up a highly interesting program suitable to all interests within the field of Glaucoma. **Click here to view the full program**.

The WGC-2017 program includes the following topics:

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Alongside the official WGC-2017 Congress, the WGA has organized special events, such as the Congress Party at the Kulosaaren Casino – a beautiful restaurant on a private island at Helsinki's seaside, and more spectacular, the Finnish Glaucoma Society's 20th Anniversary Concert! This classical event is being held at the Temppeliaukio Church, 'the Rock Church', one of Helsinki's 'must-see' highlights.

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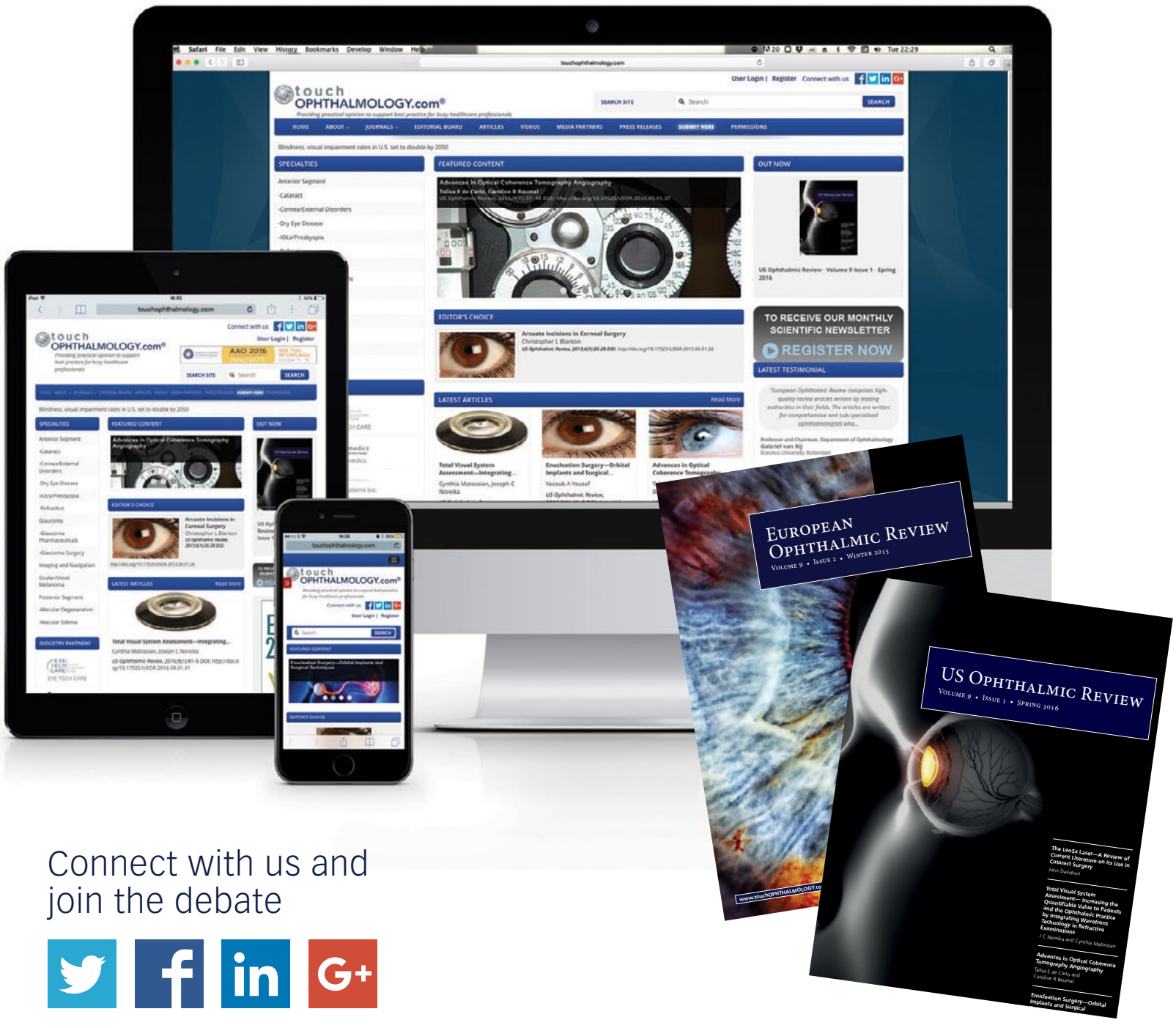

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Glaucoma Overview

Pigment Dispersion Syndrome

Tanuj Dada

The association of ocular pigment dispersion with elevated intraocular pressure (IOP) was first described by Von Hippel[1] in the early years of the nineteenth century and the clinical entity was later termed as pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) by Sugar.[2] PDS is characterized by a triad of increased trabecular meshwork (TM) pigmentation, iris transillumination defects and pigment granules on the corneal endothelium (Krukenberg spindle). It affects nearly 2-3%[3] of the Caucasian population undergoing glaucoma screening and the conversion rate from PDS to PG has been estimated to be 10% after five years and 15% after 15 years.[4] The disease is more common in males, is associated with mild-moderate myopia and nearly one-third of PDS patients eventually develop high ocular hypertension (IOP) or optic nerve damage (glaucoma).

Pathophysiology

PDS eyes are characterized by a deep anterior chamber and a concave iris configuration associated with posteriorly inserted iris, floppy iris stroma or abnormal posterior pigmented epithelium of iris, long anterior zonules, and a relatively mobile lens.[5] On blinking, aqueous is pushed from the posterior to the anterior chamber, thus creating a pressure gradient.[6] During exercise and accommodation,[7,8] the lens moves forward increasing the area of irido-lenticular contact which acts as a flap valve allowing movement of aqueous only in one direction – from posterior to anterior chamber, raising the aqueous pressure in the anterior chamber, causing posterior bowing of the iris and a resulting in ‘reverse pupillary block’. This further aggravates the irido-zonular friction and promotes release of iris pigments into the aqueous. A developmental or a congenital anomaly[9] in pigmented epithelial cells of iris and ciliary body making them more vulnerable to the irido-zonular rubbing has also been advocated as another possible mechanism for pigment dispersion.

The iris pigments thus released, gets deposited in the anterior segment of the eye including the angle structures, and clogs the trabecular meshwork leading to a decrease in the facility of outflow. The uveoscleral outflow is not affected in PDS/PG, unlike in ocular hypertension (OHT)/primary open-angle glaucoma (POAG). In the chronic stages, the TM endothelial cells are overburdened with phagocytosis of melanin granules, eventually leading to cell death. TM beams are then left bare causing collapse and fusion of the TM, increased outflow resistance and chronically raised IOP with consequent optic neuropathy (Fig. 1).[9]

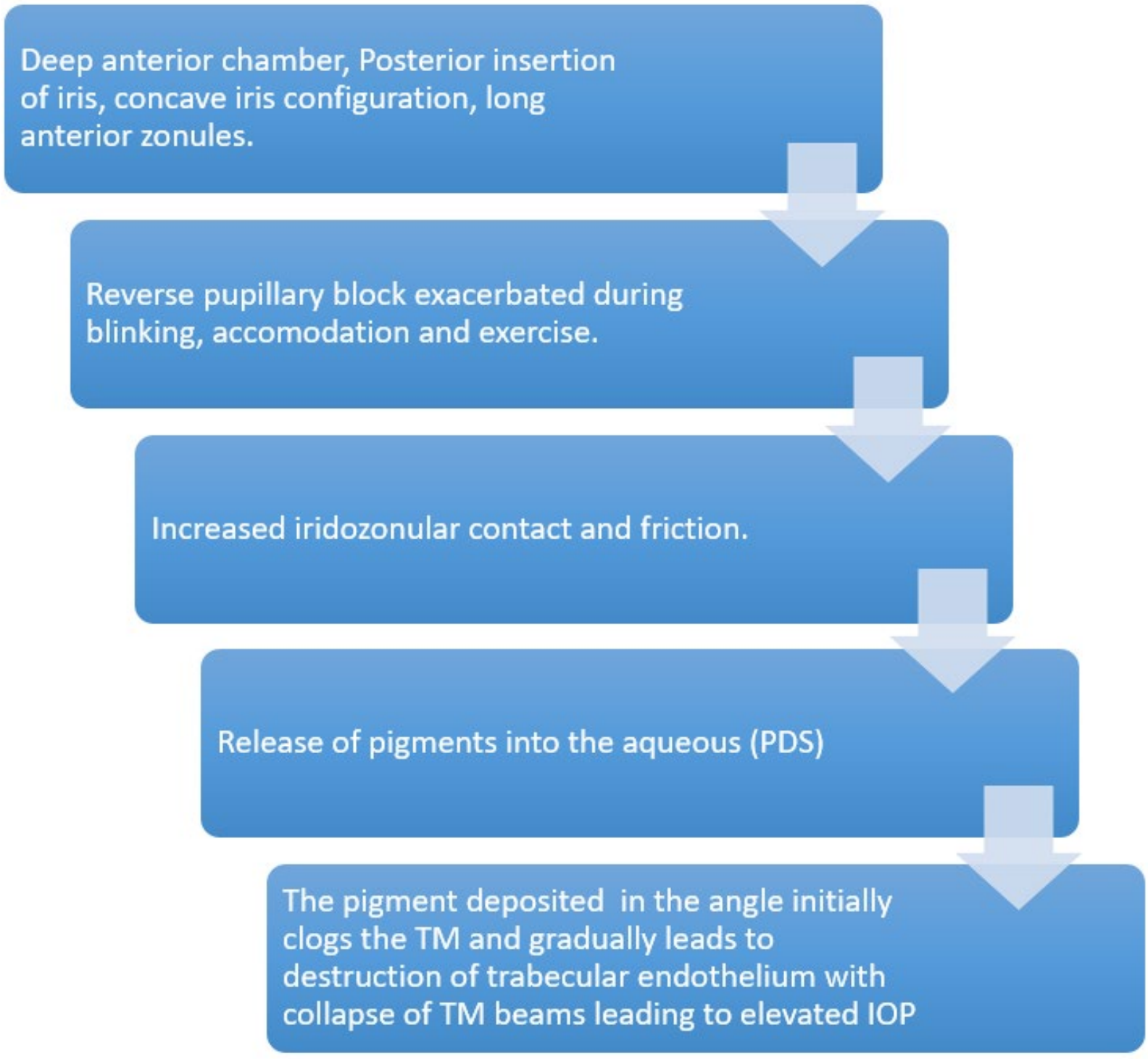

Fig. 1. Flowchart summarizing the pathophysiology of PDS and PG.

Clinical features

PDS is a bilateral disease with age of onset of pigmentary glaucoma usually being in the third to fifth decade of life, while signs of PDS may be visible many years before glaucoma sets in.

Symptoms

Patients with PG may present with a history of colored halos and episodic blurring of vision due to an acute rise in IOP, commonly reported after prolonged accommodative effort, working in dim light or after physical exercise. Many patients may present only in an advanced stage with symptoms similar to POAG. It may be detected an incidental finding during the routine ophthalmic examination, often for associated myopia.

Signs

The pigments released are dispersed by aqueous currents and deposited throughout the anterior segment, giving rise to characteristic clinical features:

- *Krukenberg spindle:* Vertical spindle-shaped deposition of iris pigments on corneal endothelium, infero-central in location corresponding to the convection currents of aqueous. (Fig. 2a)
- *Increased TM pigmentation:* A homogeneous dark brown band of pigmentation, especially in the superior angle with concave iris configuration is visible on gonioscopy. The Schwalbe's line has pigmented deposition and is known as Sampaolesi's line. (Fig. 2b, 2c)
- *Iris transillumination defects:* When the iris is examined in retro-illumination, radial spoke-like transillumination defects are visible in the mid-peripheral iris. (Fig. 2d)
- *Pigment deposition on anterior iris surface:* Pigments get deposited in the iris furrows as concentric rings. This feature again is not easily appreciated in dark-colored irides. In cases with asymmetric presentation, iris heterochromia and anisocoria (due to dilator atrophy) may be evident.
- *Free-floating pigment granules in the aqueous.*
- *Pigment deposition on the anterior and posterior lens capsule.*
- *Zentamayer ring or Scheie strip:* Pigments may be deposited in a ring-like fashion at the level of insertion of zonules into the posterior lens capsule. This is best visualized after pupillary dilation with the patient looking in upgaze.
- *Egger's line:* Refers to the deposition of pigments on the anterior hyaloidocapsular ligament.
- *Posterior segment:* Patients with PDS have an increased frequency of peripheral retinal degenerations like lattice degeneration and retinal breaks. Rhegmatogenous retinal detachment is seen in 6-7% cases of PDS, irrespective of the amount of myopia. A dilated peripheral retinal screening is essential.

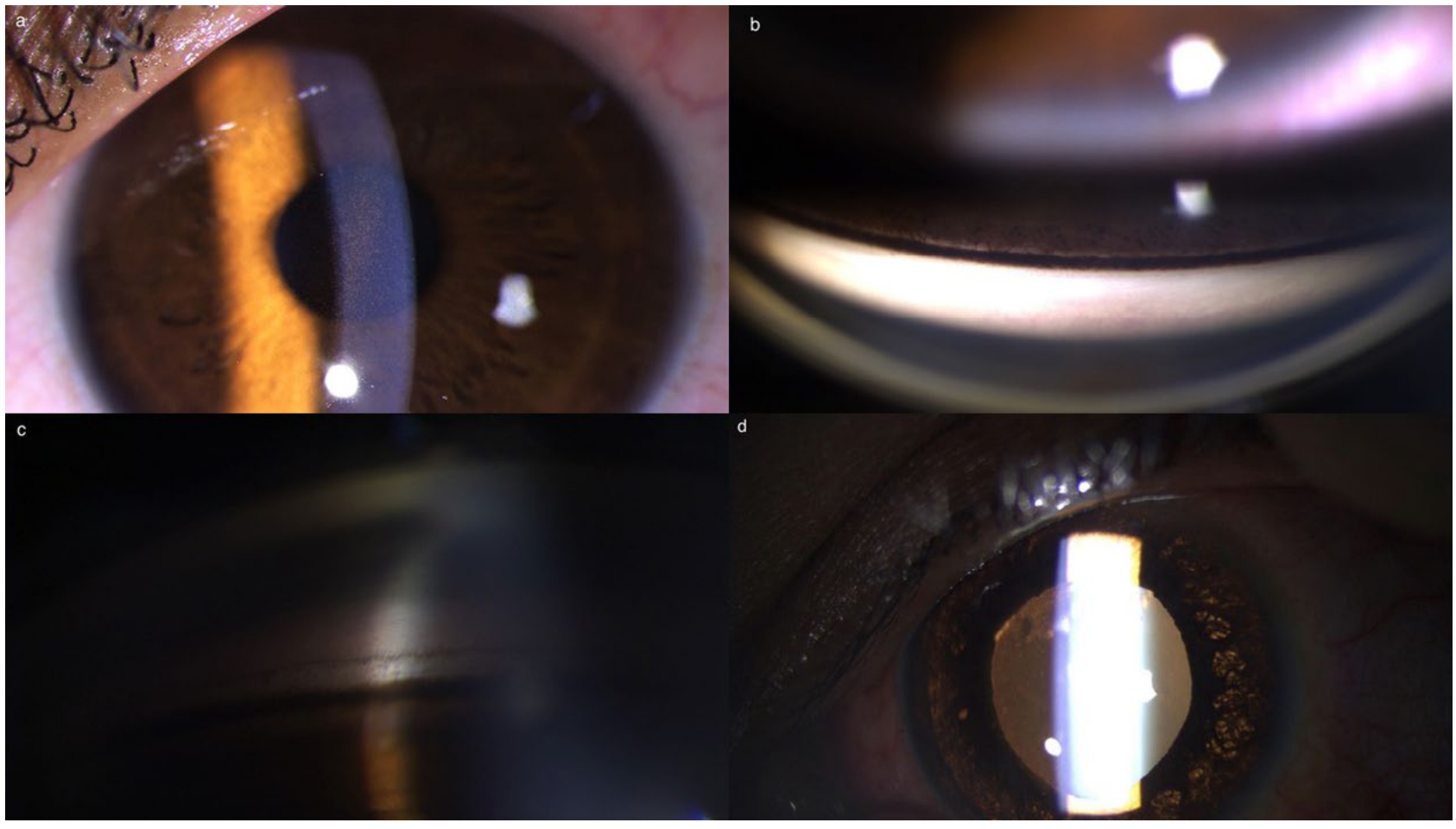

Fig. 2. Clinical features of PDS. **a.** Krukenberg spindle; **b.** Gonioscopy shows dense trabecular meshwork pigmentation in superior angle; **c.** Concave iris with angle pigmentation and Sampaolesi line; **d.** Mid-peripheral iris defects in iris on retro-illumination.

The disease has four distinct clinical phases (Fig. 3). The final 'regression phase' is a less-commonly diagnosed entity. In some patients, the pigment begins to clear up from the anterior segment and IOP may return to normal. However, the glaucomatous optic nerve head changes remain, leading to a misdiagnosis of normal-pressure glaucoma. The increased pigmentation of superior vs. inferior angles visible on gonioscopy, may provide a vital clue to diagnose a regressed PDS.

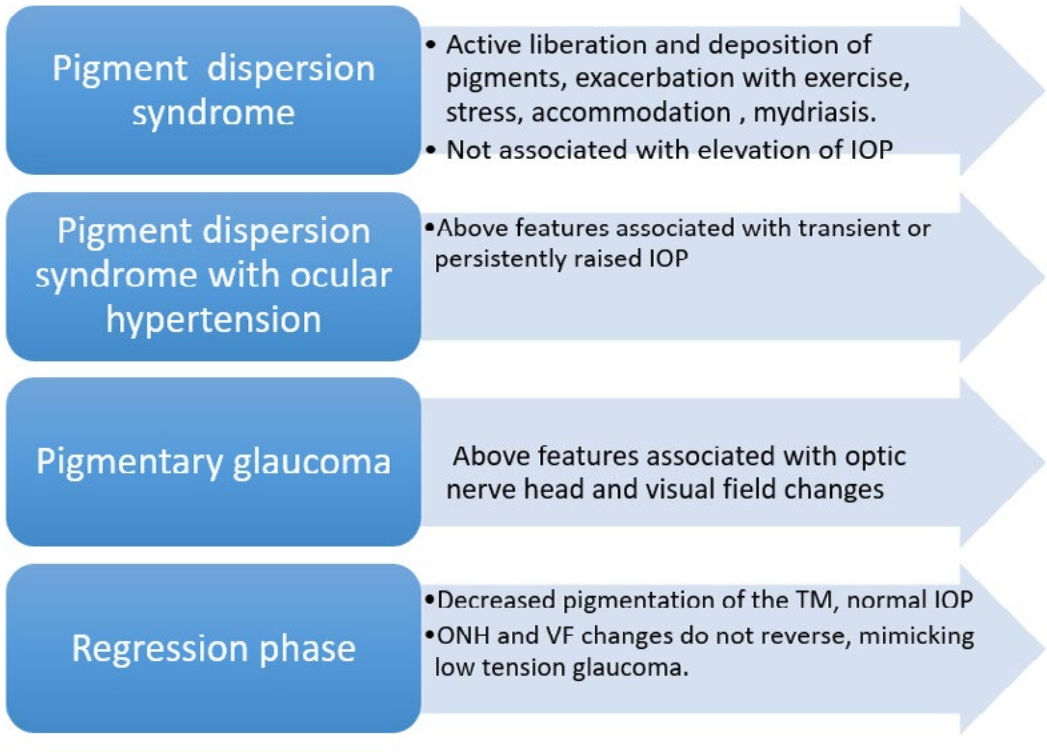

Fig. 3. Clinical phases of the disease.

Diagnosis

Clinical

PDS and PG can be easily diagnosed with careful clinical examination to look for Krukenberg spindle, iris transillumination defects and pigments on lens capsule.

Gonioscopy may show dense pigment deposition and concave iris configuration, thus providing a clinching diagnosis.

Provocative test

Mydriasis with Phenylephrine leading to release of ten or more pigment particles with/without an acute rise in IOP indicates an active phase of pigment dispersion. As the dilator pupillae contracts, the pigmented cells of posterior iris surface rupture releasing large amounts of pigment in the aqueous. This pigment clogs the TM and causes a transient and acute rise in IOP. Although this test can be used to identify patients with active disease and 'high risk' for progression, this test does not have an absolute positive predictive value and may 'miss' high-risk patients.

Imaging

Ultrasound biomicroscopy (UBM) and anterior segment OCT (Fig. 4) may aid the diagnosis of PDS. Characteristic posterior bowing of the iris, amount of irido-lenticular and irido-zonular contact can be seen. It can also be used to study the changes in iris configuration before and after laser iridotomy.

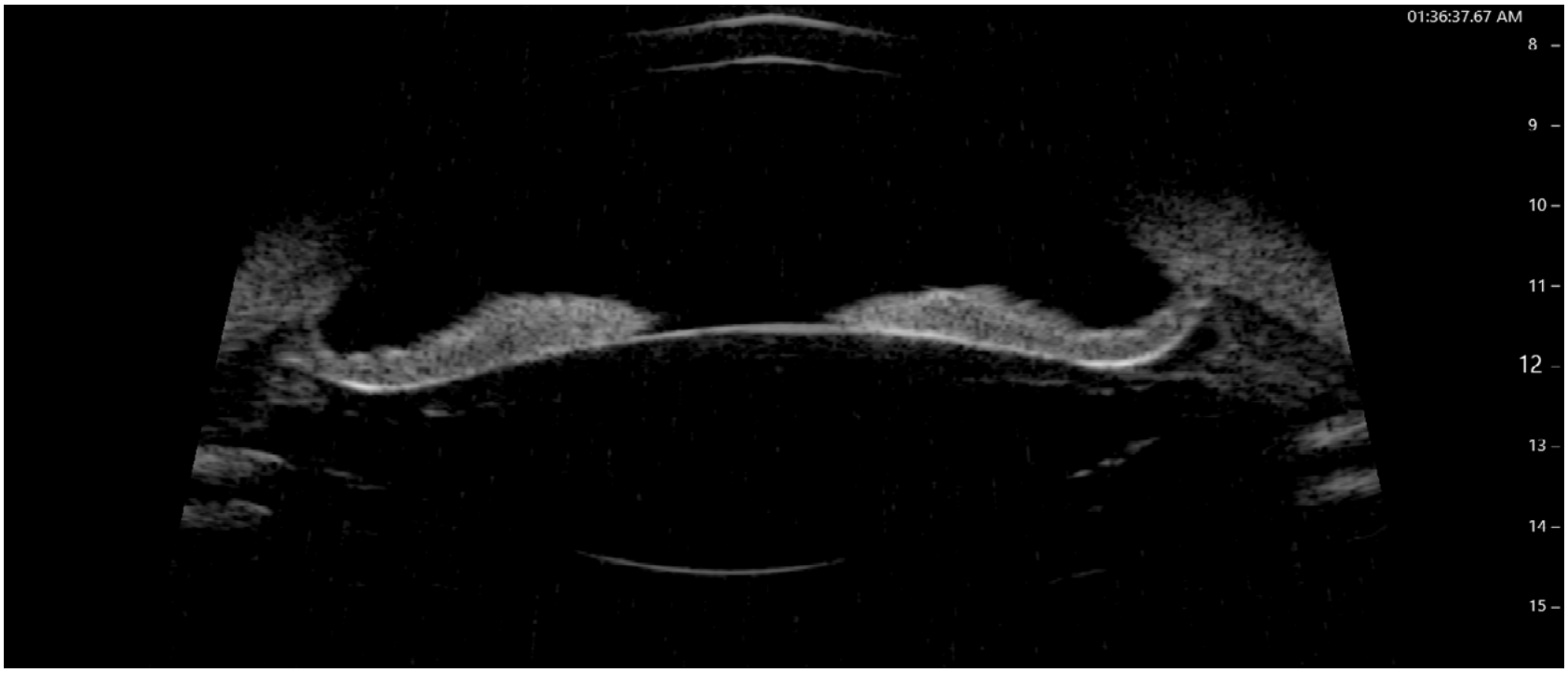

Fig. 4. UBM image showing posterior bowing of mid-peripheral iris.

Differential diagnosis

All conditions that cause liberation of pigments and deposition in various structures of the anterior segment form a differential diagnosis for PDS. Some of these include anterior uveitis (look for cells vs. pigment, keratic precipitates, posterior synechiae), pseudoexfoliation (look for pseudoexfoliative material and peri-pupillary transillumination defects), trauma, malpositioned IOL and neoplasm of the iris/ciliary body (melanoma).

Management

The management protocol of pigmentary glaucoma is essentially same as POAG. Although pilocarpine causes miosis and can reduce irido-zonular contact and increases TM outflow, it is poorly tolerated in the young myopic population of PDS and increases risk of retinal detachment. Prostaglandin analogues which work by enhancing outflow, are the preferred first line agents for lowering of IOP. Other classes of drugs like beta blockers, alpha agonists and carbonic anhydrase inhibitors can be added as second-line therapy, although decreasing aqueous production and inflow may promote pigment accumulation.

Laser peripheral iridotomy

Patients who test positive on phenylephrine mydriatic test are most likely to benefit with an laser peripheral iridotomy (LPI).[10] An iridotomy only relieves the reverse pupillary block, though some patients will continue to have concave iris configuration and IOP spikes after prolonged accommodation or exercise. Even after LPI, the risk of developing PG is not completely mitigated and requires regular long-term follow-up. In a ten-year follow-up study, Gandolfi *et al.* reported that when left untreated, more than 60% of high-risk PDS eyes (positive phenylephrine test) developed ocular hypertension as compared to only 10% of low-risk PDS eyes (negative phenylephrine test). In the high-risk PDS eyes, only 14.3% of LPI treated eyes developed ocular hypertension (> 5 mmHg) as compared to 61.9% of untreated eyes. **Hence LPI significantly lowered the risk of development of ocular hypertension in PDS patients demonstrating active pigment dispersion.** However, LPI is only effective in early phase of the disease and once ocular hypertension/glaucoma has already set in, it will have a limited role. LPI in PDS can be associated with a significant release of pigment and high IOP spikes, with potential of worsening the disease itself. A technique using trans-illumination with reduced requirement of laser energy can be an option to reduce this complication.[11]

Laser trabeculoplasty

Open angles with increased pigmentation makes these patients suitable candidates for laser trabeculoplasty. Caution must be taken to use low levels of energy, and preoperative use of alpha agonists to prevent IOP spikes.

Surgery

If target IOP is not achieved with medical therapy and/or laser trabeculoplasty, filtration surgery is the next course of intervention. Use of adjunctive antifibrotic agents is recommended as the patients undergoing surgery are young, although the risk of hypotonic maculopathy in myopes warrants a cautious use of these agents. There should be a low threshold for cataract surgery if patients present with lenticular opacification, as a lens extraction along with irrigation aspiration may help to decrease the quantum of pigment accumulated in the angle and additionally remove irido-lenticular contact, preventing further disease progression.

Summary

Pigment dispersion can be diagnosed with a careful anterior segment slit lamp biomiscroscopic evaluation including gonioscopy. An early diagnosis of PDS and reduction of active pigment release due to iridozonular friction by performing a laser peripheral iridotomy is recommended. Once PDS is associated with ocular hypertension or optic neuropathy, reduction of IOP using laser trabeculoplasty and prostaglandin analogues is appropriate. An examination of the retinal periphery for lesions predisposing to retinal detachment must be performed in all PDS patients;

other causes of pigment dispersion must be ruled out (especially in case of asymmetric/unilateral disease) and long-term follow-up is required, until disease remission is documented. The research question for the future is the role of lens extraction with or without MIGS in prevention of disease progression in PDS and treatment of pigmentary glaucoma.

References

1. Von Hippel E. Zur pathologischen Anatomie des Glaukom. Arch Ophthalmol 1901;52:498.
2. Sugar HS. Pigmentary glaucoma. A 25-year review. Am J Ophthalmol 1966;62(3):499-507.
3. Ritch R, Steinberger D, Liebmann JM. Prevalence of pigment dispersion syndrome in a population undergoing glaucoma screening. Am J Ophthalmol 1993;115(6):707-710.
4. Siddiqui Y, Ten Hulzen RD, Cameron JD, *et al.* What is the risk of developing pigmentary glaucoma from pigment dispersion syndrome? Am J Ophthalmol 2003;135:794-799.
5. Potash SD, Tello C, Liebmann J, Ritch R. Ultrasound biomicroscopy in pigment dispersion syndrome**.** Ophthalmology 1994;101(2):332-339.
6. Liebmann JM, Tello C, Chew SJ, Cohen H, Ritch R. Prevention of blinking alters iris configuration in pigment dispersion syndrome and in normal eyes. Ophthalmology 1995;102(3):446-455.
7. Pavlin CJ, Macken P, Trope GE, Harasiewicz K, Foster FS. Accommodation and iridotomy in the pigment dispersion syndrome. Ophthalmic Surg Lasers 1996;27(2):113-120.
8. Schenker HI, Luntz MH, Kels B, Podos SM. Exercise-induced increase of intraocular pressure in the pigmentary dispersion syndrome. Am J Ophthalmol 1980;89(4):598-600.
9. Gottanka J, Johnson DH, Grehn F, Lütjen-Drecoll E. Histologic findings in pigment dispersion syndrome and pigmentary glaucoma. J Glaucoma 2006;15(2):142-151.
10. Gandolfi SA, Ungaro N, Tardini MG, *et al.* A 10 year follow up to determine the effect of YAG laser iridotomy on the natural history of PDS: a RCT. JAMA Ophthalmol 2014;132(12):1433-1438.
11. Karickhoff JR. Pigmentary dispersion syndrome and pigmentary glaucoma: a new mechanism concept, a new treatment, and a new technique. Ophthalmic Surg 1992;23(4):269-277.

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(abstract no. 69140)
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MicroRNAs in glaucoma and neurodegenerative diseases
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(abstract no. 69324)
Journal of Human Genetics 14 July 2016; doi:10.1038/jhg.2016.91. [Epub ahead of print]

Targeting mitochondrial function to treat optic neuropathy
Gueven N, Nadikudi M, Daniel A, Chhetri J
(abstract no. 69427)
Mitochondrion 28 July 2016; doi: 10.1016/j.mito.2016.07.013. [Epub ahead of print]

24-h monitoring devices and nyctohemeral rhythms of intraocular pressure
Aptel F, Weinreb RN, Chiquet C, Mansouri K
(abstract no. 69428)
Progress in Retinal and Eye Research 2016; 55: 108-148

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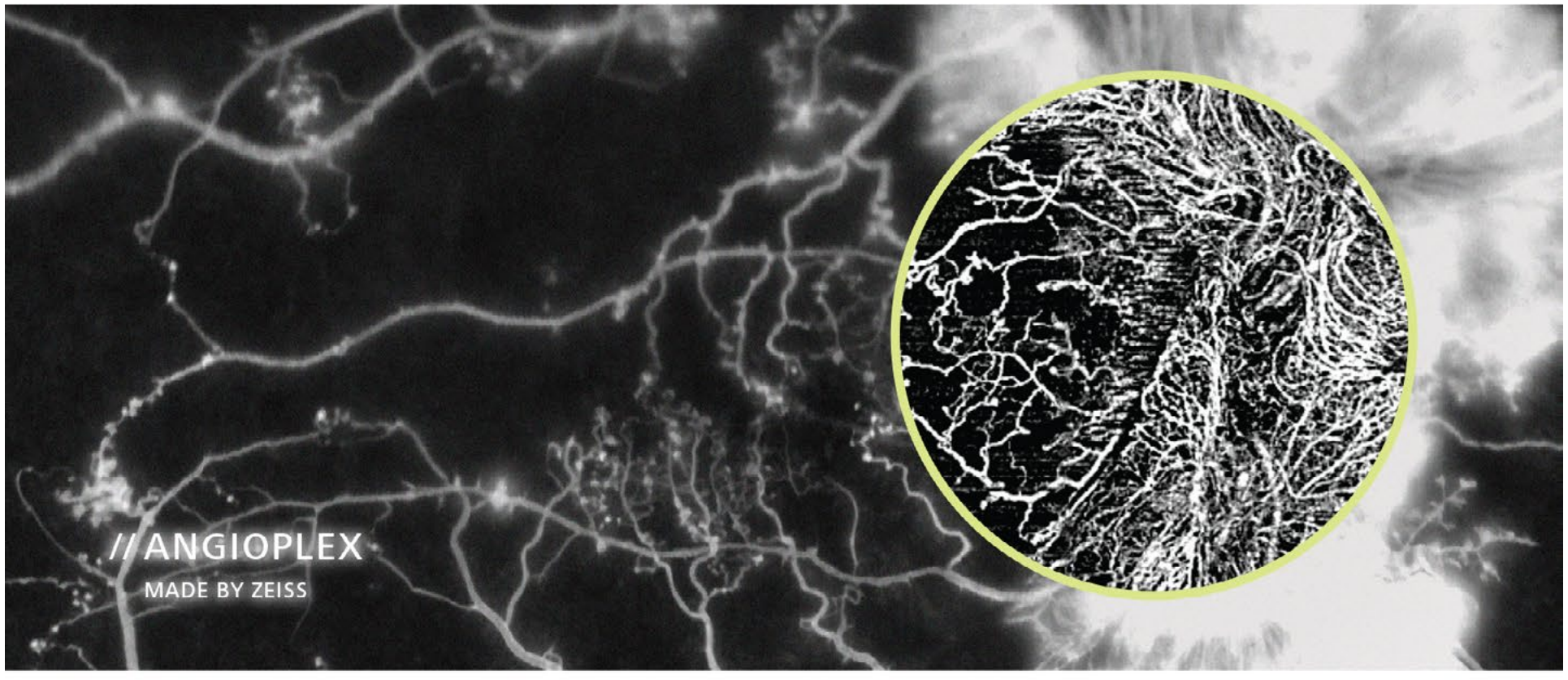

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Glaucoma Dialogue

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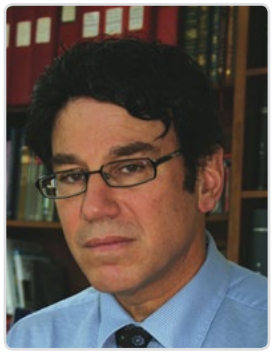

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68907 Validity of the monocular trial of intraocular pressure-lowering at different time points in patients starting topical glaucoma medication; King AJ, Rotchford AP, JAMA ophthalmology 2016; 134: 742-747, http://dx.doi.org/10.1001/jamaophthalmol.2016.0994

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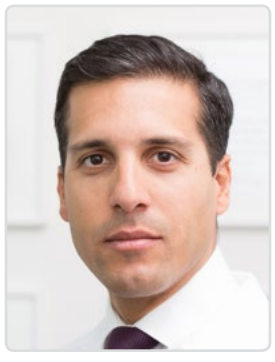

Comment by Kaweh Mansouri, Lausanne, Switzerland

Current tonometry techniques provide single time-point measurements and fail to reflect the true range of an individual's 24-h IOP behavior. This fact is of practical consequence as it impinges on the ability to distinguish between spontaneous IOP changes and the effect of IOP-lowering medications.

The hypothesis that a medication's therapeutic effect can be distinguished from simple IOP fluctuation as the difference between IOP in the treated vs. the fellow eye has been discussed for decades. This so-called monocular trial remains contested and, in recent years, several studies have provided arguments against it.

For the monocular trial to be valid, two basic assumptions need to be fulfilled: 1) IOP patterns should be repeatable and 2) there should be a certain degree of between-eye symmetry. Realini *et al.*[1] found that diurnal IOP was not reproducible from one week to another. However, their

study only used two 12-hour diurnal IOP assessment sessions, one week apart. Studies using continuous 24-h monitoring of IOP-related patterns with a contact lens sensor (CLS) have found good reproducibility from one week to another.[2] Regarding inter-eye symmetry, studies show that IOP may fluctuate moderately in parallel in healthy fellow eyes whereas IOP peaks may not appear at the same time for an individual subject. The concordance of diurnal IOP between fellow eyes with glaucoma was evaluated in one study which found a 68% to 90% probability for the absolute change in IOP between fellow eyes to be within 2 mmHg and 78% to 95% within 3 mmHg. Others, however, previously reported a weaker relationship, with correlations between fellow eyes ranging between 0.65 and 0.73 (mean r = 0.70) under various conditions. Asymmetry of IOP in fellow eyes, however, undermines the validity of inferring IOP changes in one eye based on measurements from the fellow eye. Therefore, and due to conflicting data on inter-eye symmetry, the monocular drug trial has largely fallen out of fashion in recent years. Our group, however, recently conducted a trial using bilateral simultaneous 24-h IOP-monitoring with the CLS and found food inter-eye correlations in glaucoma eyes (r = 0.76). (Unpublished data).

In the present study, King and Rotchford attempted to re-examine the validity of the monocular trial by designing a prospective study with three diurnal IOP measurements and three pre-treatment and three post-treatment visits to overcome the well-known phenomenon of regression to the mean. Their main results can be summarized as:

An important decrease in IOP as a result of regression to the mean was observed and ranged from 2.1 to 4.6 mmHg. They conclude that the normal practice of comparing one baseline visit (instead of three in this study) with one post-treatment visit can overestimate the treatment effect by as much as 36%.

Magnitude of IOP-reduction in fellow eye was similar to the trial eye, meaning that if an effect is observed in the first eye, physicians can expect a similar effect in the second eye.

This is an interesting study and the authors are to be congratulated for addressing this complex question. Whether their results can be extrapolated to other medication classes (travoprost drops were used) and patient populations need to be evaluated. Ultimately, however, clinicians aspire to the routine use of 24-h IOP monitoring technologies in glaucoma patients, obviating shortcomings of current IOP assessment methods.

References

1. Realini T, Weinreb RN, Wisniewski SR. Diurnal intraocular pressure patterns are not repeatable in the short term in healthy individuals. Ophthalmology 2010;117(9):1700-1704. Epub 2010/06/19. doi: S0161-6420(10)00117-X [pii] 10.1016/j.ophtha.2010.01.044. PubMed PMID: 20557945; PubMed Central PMCID: PMC2934877.
2. Mansouri K, Medeiros FA, Tafreshi A, Weinreb RN. Continuous 24-hour monitoring of intraocular pressure patterns with a contact lens sensor: safety, tolerability, and reproducibility in patients with glaucoma. Arch Ophthalmol 2012;130(12):1534-1539. Epub 2012/08/16. doi: 1308384 [pii] 10.1001/archophthalmol.2012.2280. PubMed PMID: 22892888.

Comment by Luciano Quaranta, Brescia, Italy

When medical treatment is initiated in a patient affected by glaucoma, individual response to prescribed agent is extremely important. To better characterize individual response to medications, a monocular trial test (MTT) was first suggested by Drance *et al.*[1] Basically, it consists of administering medical agents unilaterally for a short period, leaving the fellow eye untreated, until a constant hypotensive effect is achieved. MTT rationale is that IOP is not constant, but fluctuates in the short (during the day) and in the long (day-by-day) term. It has been postulated that IOP reduction in the treated eye reflects both therapeutic effect and IOP fluctuations; on the other hand, untreated eye exhibits only spontaneous IOP changes, allowing for a correction of IOP data in the treated eye.

In this study, King *et al.* demonstrated the use of MTT in glaucoma and ocular hypertension naive patients may provide a significantly more accurate estimate of the real therapeutic response to a prostaglandin analogue (travoprost). Moreover, MTT may be effective in estimating therapeutic response also when pre-treatment and post-treatment IOPs are measured at different time-points. According to these results, MTT may not only overwhelm the regression to the mean of IOP values, but also partially correct for short-term and long-term fluctuations.

MTT assumes that diurnal IOP fluctuations are equal, or at least very similar, in both eyes. On this basis, IOP values of the treated eye can be corrected for the measurements of the fellow eye. While a quite similar diurnal IOP rhythm in both eyes of King *et al.*'s cohort can be inferred from the paper, this probably does not apply to all glaucoma patients. Indeed, IOP may vary in an asymmetric fashion, both in healthy and glaucomatous subjects.[2-5] Dinn *et al.* performed diurnal IOP curves on treated and untreated glaucoma patients and found that the probability of having an absolute change < 2 mmHg between fellow eyes was 68% to 90% (untreated subjects) and 72% to 82% (treated subjects) for all time-points.[2] These results indicate that the concordance of diurnal IOP fluctuation between fellow eyes in glaucoma patients is fairly high, but not perfect.

Just like asymmetric IOP fluctuations can be recorded during a diurnal IOP curve, asymmetric IOP fluctuations can be encountered from one visit to another, days or months apart.[6,7] In a retrospective study by Realini *et al.*, 21 of 42 healthy subjects and 24 of 38 glaucoma patients (50% and 63.2%) exhibited an asymmetric IOP fluctuation of at least 3 mmHg from one visit to another, representing a 15% change from baseline.[6] In terms of absolute magnitude, asymmetric IOP fluctuation measured 3.7 ± 1.2 mmHg in healthy subjects and 4.0 ± 1.2 mmHg in glaucoma patients. MTT does not take into account asymmetric fluctuation in the long term, assuming that long-term fluctuation is equal in both eyes. Besides these data, the effect of medical treatment on IOP fluctuation is not completely known,[8] and it cannot be excluded an effect

of medical agents on 24-hour IOP rhythm of the treated eye, both in the short and in the long term. Interestingly, King *et al.* underlined that the treatment in their study did not demonstrate any effect on diurnal IOP pattern, probably as deduced from diurnal IOP curves.

A well-recognized limit of MTT is the assumption there is no contralateral pharmacological effect determined by systemic absorption of the prescribed agent. This assumption limits the use of MTT with several pharmacological classes. While the contralateral effect due to β-blocker agents has been well described,[9,10] little or no effect has been described for prostaglandin analogues.[11]

All these factors should be taken into account when interpreting MTT and the results of this study. MTT could be a useful test in glaucoma practice, when all these assumptions are verified. However, this probably implies as many clinical efforts that overwhelm the advantages of the test.

References

1. Drance SM. The uniocular therapeutic trial in the management of elevated intraocular pressure. Surv Ophthalmol 1980;25:203-205.
2. Dinn RB, Zimmerman MB, Shuba LM, *et al.* Concordance of diurnal intraocular pressure between fellow eyes in primary open-angle glaucoma. Ophthalmology 2007;114:915-920.
3. Sit AJ, Liu JH, Weinreb RN. Asymmetry of right versus left intraocular pressures over 24 hours in glaucoma patients. Ophthalmology 2006;113:425-430.
4. Wilensky JT, Gieser DK, Dietsche ML, *et al.* Individual variability in the diurnal intraocular pressure curve. Ophthalmology 1993;100:940-944.
5. Liu JH, Sit AJ, Weinreb RN. Variation of 24-hour intraocular pressure in healthy individuals: right eye versus left eye. Ophthalmology 2005;112:1670-1675.
6. Realini T, Barber L, Burton D. Frequency of asymmetric intraocular pressure fluctuations among patients with and without glaucoma. Ophthalmology 2002;109:1367-1371.
7. Realini T, Weinreb RN, Wisniewski S. Short-term repeatability of diurnal intraocular pressure patterns in glaucomatous individuals. Ophthalmology 2011;118:47-51.
8. Quaranta L, Katsanos A, Russo A, *et al.* 24-hour intraocular pressure and ocular perfusion pressure in glaucoma. Surv Ophthalmol 2013;58:26-41.
9. Piltz J, Gross R, Shin DH, *et al.* Contralateral effect of topical beta-adrenergic antagonists in initial one-eyed trials in the ocular hypertension treatment study. Am J Ophthalmol 2000;130:441-453.
10. Zimmerman TJ, Kaufman HE. Timolol. A beta-adrenergic blocking agent for the treatment of glaucoma. Arch Ophthalmol 1977;95:601-604.
11. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian Latanoprost Study Group. Ophthalmology 1995;102:1743-1752.

Comment by Tony Realini, Morgantown, WV, USA

King and Rotchford are to be commended for their tenacious defense of the monocular drug trial, a clinical tool that a vast preponderance of studies has established as being generally unhelpful in the clinical management of glaucoma patients.

The monocular drug trial was proposed as a solution to a significant clinical problem: when initiating topical intraocular pressure (IOP)-lowering therapy for glaucoma, how can we distinguish between the therapeutic effect of the medication and the spontaneous IOP changes known to occur in eyes over time? We tend to initiate therapy when IOP is at its peak (*i.e.*, higher than normal and thus deserving of reduction). Assuming that IOP in a given eye fluctuates within some range between a minimum value and a maximum value, any measurement following an extreme measurement (a near-maximum value or a near-minimum value) will likely be less extreme (the so-called regression to the mean). So if we see a patient whose IOP is unusually high (near-maximum), any subsequent IOP measurement is likely to be lower whether or not we initiate therapy. How can we distinguish between therapeutic and spontaneous IOP changes?

Per the monocular trial, we would measure IOP in both eyes, treat one eye, and after a reasonable course of therapy, re-measure IOP in both eyes. In theory, the IOP change in the untreated eye should represent purely spontaneous IOP fluctuation, while the IOP change in the treated eye should represent a mixture of both therapeutic and spontaneous IOP fluctuation. Subtracting the untreated eye's IOP change from the treated eye's IOP change should isolate the therapeutic IOP component.

Clever as it sounds, the monocular trial does not work. It does not work because essentially all of the assumptions underlying the monocular trial are false assumptions. Our group established this in a series of studies that have since all been replicated by independent groups. We also reported (in two separate cohorts of patients) that because of these false assumptions, the monocular trial itself does not work, and this finding has also been confirmed by numerous independent investigators, including the Ocular Hypertension Treatment Study (OHTS) research team which demonstrated the monocular trial's shortcomings in a *post hoc* analysis of the OHTS data set.

So how can King and Rotchford come up with such disparate results? One possibility is a simple Type 2 statistical error: ask the same question over and over again and eventually you will get the wrong answer by chance alone. An alternate explanation is that their data are in fact consistent with the larger body of research on this topic. A closer look at their data suggest this latter explanation as most likely. In their trial, 30 subjects underwent IOP assessment at a series of pretreatment visits, then were treated first in one eye and then both eyes with travoprost, and then underwent IOP assessment at a series of on-treatment visits. As they report, the mean error attributable to the monocular drug trial represented 24-42% of the true IOP reduction observed.

Consequently, their data demonstrate that the monocular trial's estimate of IOP reduction will differ from the true IOP reduction (estimated at 7.0-8.6 mmHg on average) by approximately 2.5 to 4 mmHg or more in half of patients undergoing the trial.

All of us who have studied the monocular trial over the past decade have conceded that the trial almost certainly works well for some people – but unfortunately we have no way of knowing who those people are. Imagine that you have just conducted a monocular trial and observed a 7-mmHg IOP reduction. Was this therapeutic or spontaneous IOP change? Based on the findings of King and Rotchford, there is a 50% chance that the drug really lowered IOP 3.0-4.5 mmHg or less and the remaining IOP change was spontaneous and not therapeutic. The only way you will know for sure how much your treatment lowered IOP is by continuing therapy and reassessing IOP over the next several visits, then comparing these values to those obtained over several prior pre-treatment visits. Given that this is necessary, the monocular drug trial has failed in its goal of isolating therapeutic IOP change and is of little if any real clinical value, and we should simply treat both eyes from the outset.

Response by Anthony J. King and Alan P. Rotchford

We would like to thank Professor Weinreb and the IGR editorial board for selecting our work for discussion. We very much appreciate the reviewers' comments and observations about our paper.

The monocular therapeutic trial (MTT) was introduced to provide a simple, pragmatic and clinically useful method of evaluating the effectiveness of glaucoma drops. However, as the commentators have highlighted its validity has been questioned. To address this gap in the literature we undertook this study, which was designed to address some of the issues raised regarding the validity of MTT and establish whether it was indeed a useful clinical tool.

Although, as mentioned, diurnal variation is an important aspect of IOP measurement, this work is not primarily about **diurnal** behavior of IOP but about **day-to-day** variation. It is the day-to-day variability (which is the cause of mean regression) that impinges on our ability to determine the effectiveness of therapy. However, this day-to-day variability becomes less important if the variability is symmetrical between the eyes – thus allowing one eye to effectively be used as a control when initiating therapy.

Dr. Mansouri's comments regarding the assumptions necessary are important and we can go one step further. There is, in fact, a single combined assumption i.e. that as long as between eye day-to-day repeatability is greater than within eye repeatability, the MTT will provide a more accurate estimate of effectiveness. This (new) table showing within and between eye variances and coefficients of repeatability derived from them illustrates this point (Table 1).

Table 1. Within eye variability compared to between eye variability in day-to-day intraocular pressure values (30 **untreated** right eyes).

	Same eye		**Between fellow eyes**	
	Sa^2	**CR (95%CI)**	Sb^2	**CR (95%CI)**
8am	7.6	7.6 (5.7-9.5)	*3.9*	5.5 (4.1-6.8)
11am	5.1	6.2 (4.7-7.8)	*2.0*	3.9 (2.9-4.9)
4pm	9.4	8.5 (6.3-10.6)	*2.9*	4.7 (3.5-5.9)

Abbreviations: Sa2 (within subject (test-retest) variance comparing (V1-V2)2nd and (V3-V4)2nd (mmHg2)); Sb2 (between subject (test-retest) variance comparing (V11st-V12nd) and (V31st-V32nd) (mmHg2)); CR (coefficient of repeatability (1.96S√2) (mmHg)).

I.e., $Sa^2 > Sb^2$ indicating that repeatability between fellow eyes is greater than within eye repeatability at all time points in our study. The CR can be interpreted as meaning that, for example that at 4 pm, 95% of repeated intra eye measurements on different days would lie within a range of 8.5 mmHg whereas between 95% of fellow eye measurements lie within 4.7 mmHg of each other.

We chose to undertake our study on treatment naïve patients and to use a prostaglandin analogue to minimize the influence of other factors in our evaluation. In addition, this is important and relevant as prostaglandin analogues are normally used as the first line of therapy in treating raised IOP. We accept the limitations of the current study in patients commenced on b-blockers and limits the utility of our findings in this group of patients. We agree with Dr. Quaranta's comments regarding the variability of IOP, however, it is important to remember that the repeatability of GAT is not perfect either. In fact it is around 2 mmHg itself. This 'noise' is obviously not patient-related and represents the absolute limit of repeatability even if there was no variation in subjects' IOP at all. In this context this level of concordance is more than 'fairly high'. And it is unlikely that one would ever be able to identify absolute concordance even if it did exist because of this measurement constraint.

We compliment Dr. Realini on his robust denial of the value of the monocular trial – indeed it is perhaps that we are referring to two very separate interpretations of the monocular trial that leads us to disagree with each other. We consider that the monocular trial is a therapeutic tool used to evaluate the immediate effect of a therapeutic intervention, we do not believe that the value of the trial should be measured on its ability to predict long term IOP control or variability.

Dr. Realini suggests our findings may be attributed to a type-2 statistical error. We assume he means a type-1 error. We feel this is most unlikely, given the strength of the effect at three different time points.

We cannot claim that the MTT will predict a therapeutic effect with 100% accuracy. But it is more accurate than the usual practice of bilateral treatment initiation and comparing a single pre- and post-treatment pair of IOP measurements. In this patient group we previously showed that a single pair of pre- and post-treatment measurements give an estimate of treatment effect with repeatability of ± 73% (± 5.5 mmHg), which we think is not precise enough.[1]

We would agree that it is more accurate to undertake multiple pre- and post-treatment measurements to truly establish the value of a therapeutic intervention. This is indeed what we did for comparison in our study. However, as we have also previously shown, even increasing the number to three pre- and three post-treatment measurements (*i.e.*, six clinic visits) only increased the precision to the same level of precision achieved using the MTT (± 41%) which requires only two visits.[1]

One day we may have an affordable and effective means of continuous IOP monitoring to offer our patients but in the meantime, for those of us who work in healthcare contexts that cannot support the burden of so many additional appointments, the MTT, if used correctly, provides a practical and effective alternative.

Reference

1. Rotchford AP, King AJ. Repeatability of measurements of effectiveness of glaucoma medication. Br J Ophthalmol. 2012;96(12):1494-1497.

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Meeting Highlights

Top-Five of the Russian Glaucoma Society Meeting

Moscow, Russia, December 2-3, 2016

Sergey Petrov

The RGS Annual Congress was held on 2 and 3 December in Moscow (Russia). More than 1,200 physicians from 11 countries and 146 cities came to the Congress.

Professor Andrew Zolotaryev (Samara) reviewed recent data on the anatomy and functions of the uveoscleral outflow. He reported on the results of morphological studies on the uveoscleral outflow and presented clinical data on the efficacy of various modalities for its activation. The author concluded that better uveoscleral outflow preserves vision in glaucoma.

The President of the Russian Glaucoma Society Professor Eugeny Egorov (Moscow) reported on the results of multi-center clinical trial on the efficacy of POAG surgery (*i.e.*, trabeculectomy and NPDS) performed in eight CIS countries (20 clinical centers) on 324 eyes. Sixty-seven percent of patients underwent highly effective trabeculectomy characterized by a later start of hypotensive treatment (15-21 months after the trab). After NPDS, glaucoma therapy was restarted 1.4-1.7 times earlier.

Professor Alexander Kuroyedov (Moscow) reported on the underestimated use of clinical epidemiological findings in clinical practice. In the recent 11 years, 15 multi-center glaucoma trials on its clinical epidemiological characteristics, IOP-lowering therapy, and surgery were performed in Russia. The author concluded that the multi-center trials provide novel insight into the issue of the reliability of the data obtained. Modern clinical epidemiological studies also help to develop recommendations on glaucoma diagnosis, treatment, and monitoring.

The Secretary of Russian Glaucoma Society Sergey Petrov (Moscow) reported on the current international approaches to the initial glaucoma therapy according to the European, Asian, and USA recommendations. Results of the surveys of ophthalmologists from various countries were compared with the results of Russian trials. The trends in the Russian market of glaucoma medications were analyzed as well.

Associate professor of the Department of Criminal Law (Academy of Russian Investigating Committee, Novosibirsk) Nataly Morozova addressed actual issues of patient confidentiality. Her examples referred to the verbal disclosure of health information and medical photos shared

to social media networks as well as the organization of outpatient reception which might be coupled with the violation of law. The key topic of the discussion was the legality of off-label agents use in Russia.

Top-Four of the Annual South African Glaucoma Society Meeting

Cape Town, South Africa, 2016

Ellen Ancker

The Kombo Ombo Primary SLT Study was a RCT Study with 324 patients. They were treated with SLT or beta-blocker for 30 months. The results showed 30% IOP reduction in 76% with timolol versus 58% with SLT. The cost of the SLT was $ 10 versus $ 114 with Timolol treatment. (Tarek Sharaawy, Geneva, Switzerland)

The success rates of a trabeculectomy with a fornix-based or limbus-based conjunctival flap are comparable. The fornix-based blebs are more diffuse, less avascular and have a low incidence of infection. But they experienced more symptomatic hypotony and need earlier cataract surgery. (Catherine Green, Melbourne, Australia)

Why are we operating late? Operating late increases the rate of complications. Glaucoma surgery outcome is correlated to the number of pre-operative BAK. Each additional drop containing BAK increases the risk of early failure by the factor 1.21. (Tarek Sharaawy, Geneva, Switzerland)

The ‘Tipping Point’ of the RNFL thickness is a ~75 micron. Past the tipping point structure and function change together. The floor effect is reached at 45-50 micron when the structure does not change anymore, only the VF. The use of SAP as a sole method of detection of change may result in failure to detect progression. (Catherine Green, Melbourne, Australia)

Top-Seven of the Annual Meeting of the Glaucoma Society of India

Palampur, Himachal Pradesh, India, November 4-6, 2016

R. Krishnadas

Minimum rim width (MRW) as measured by Spectralis OCT offers a novel method of measuring neural rim loss in glaucoma. A study in Central India revealed the greatest rim loss to be in the inferotemporal and superotemporal quadrants of the ONH. MRW requires further evaluation in early diagnosis and estimating progression in persons with glaucoma. (Vinay Nangia, Nagpur, India)

The Hooghly River Glaucoma Study, a population-based study conducted in West Bengal, India revealed the prevalence of glaucoma in the urban population (3.23%, CI 3.5-4.1) was higher than that in the rural counterpart (2.7%, CI 1.09-4.31). The study also observed that PACD is more common in this region of eastern India and recommends inclusion of gonioscopy in the comprehensive eye examination as part of early glaucoma detection and management. (Chandrima Pal, Kolkata, India)

Abnormal anatomical variations in pediatric eyes with shorter axial-length. Morphologic changes in eyes with short axial length following congenital cataract surgery, such as characteristic anterior and ciliary body development anomalies including elongated ciliary processes, abnormal insertion of ciliary body to posterior iris and flat pars plicata, high iris insertion and ill-defined anterior chamber angle structures observed by UBM were positively correlated with elevated intraocular pressures. (Mayuri Khammar, Ahmedabad, India)

Relevance of ocular perfusion dynamics in glaucoma. Ocular perfusion pressure is crucial in maintaining the health of the optic nerve head. A decrease of ocular perfusion pressure below 40 mmHg increases likelihood of progression of glaucoma six-fold. Caution is advised in the use of beta blockers since these drugs can adversely affect nocturnal perfusion pressures with progression of glaucoma despite adequate IOP control. (Pratheep Vyas, Indore, India)

Cerebrospinal fluid pressure – Potential implications for glaucoma. Changes in IOP, Cerebrospinal fluid pressure (CSFP), or trans lamina cribrosa pressure difference (TLCPD) can be associated with a disturbance of homeostasis of the optic nerve head. In particular, glaucomatous optic neuropathy may be due to either an elevated IOP and/or an abnormally low orbital CSFP, or due to a change in the time-dependent relationship between the pulse-synchronous changes in IOP and orbital CSFP. (Jost Jonas, Heidelberg, Germany)

A novel outreach program using a portable fundus camera for glaucoma screening. In community screening employing portable fundus photography as against conventional direct ophthalmoscopy in Southern India, glaucoma referral was observed to be twice as frequent, validating the potential role of low cost portable fundus photography in glaucoma detection in comprehensive eye screening. (Rengaraj Venkatesh, Pondicherry, India)

Aurolab Aqueous Drainage Device, a cost-effective non-valved tube developed for use in lesser developed communities has proved to be safe and effective for use in management of refractory glaucoma and long-term results of the device are awaited. (George V. Puthuran, Madurai, India)

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Editor's Selection

With the multitude and variety of publications it seems almost impossible for the ophthalmologist to intelligently read all the relevant subspecialty literature. Even the dedicated glaucomatologist may have difficulty to absorb 1200+ yearly publications concerning his/her favorite subject. An approach to this confusing situation may be a critical selection and review of the world literature.

Robert N. Weinreb, Chief Editor

Glaucoma as cause of blindness

What are the major risk factors for blindness from POAG?

Comment by David Friedman, Baltimore, MD, USA

69218 Risk Factors Associated with Progression to Blindness from Primary Open-Angle Glaucoma in an African-American Population, Pleet A, Sulewski M, Salowe RJ, Fertig R, Salinas J, Rhodes A, Merritt Iii W, Natesh V, Huang J, Gudiseva HV, Collins DW, Chavali VR, Tapino P, Lehman A, Regina-Gigiliotti M, Miller-Ellis E, Sankar P, Ying GS, O'Brien JM, Ophthalmic Epidemiology 2016; 23: 248-256

The authors present an age- and sex-matched case-control study of African Americans who are older than 35 years of age, with primary open-angle glaucoma being treated in the University of Pennsylvania Health System (UPHS). Cases were blind as defined by visual acuity (VA) of 20/200 or worse using Snellen acuity; no visual field criteria were used to define blindness. Those with any treatment outside UPHS were excluded, resulting in a total of 48 subjects being included; 37 unilaterally blind and 11 bilaterally. Fifty-nine control subjects were age- and sex-matched, had VA better than 20/200 and had received all care at UPHS. Cases and controls were similar in all general health aspects as well as estimated household income. The authors used multiple definitions of non-adherence including missed visits and whether or not the chart included documentation of non-adherence at a clinical visit.

Of note, a third of those blind either presented blind or were blind within a month of diagnosis. **Blind patients were younger at diagnosis (62 versus 67 years of age), had higher mean intraocular pressure (IOP) (29 versus 21 mmHg), and worse baseline vision (median 20/80 versus 20/20)**. Blind patients had higher IOP at follow-up despite more medications and interventions. Doctors questioned adherence more frequently in the charts of those who were blind than in controls, but whether or not this was based on difficulty controlling IOP is not clear. The proportion of missed visits was similar between cases and controls.

Of note, a third of those blind either presented blind or were blind within a month of diagnosis

In multivariable regression analysis, having **vision worse than 20/40 at diagnosis dramatically increased the likelihood of blindness** over follow-up as did having IOP above 21 mmHg at more than 20% of visits and missing more than two visits per year on average. The authors note that those who were blind had more advanced disease at diagnosis with worse vision, higher IOP and a greater likelihood of missing follow-up visits. Despite more treatments to lower IOP among those who ended up blind, IOP was less well controlled over follow-up. While this paper is a case-control study and clinical recommendations cannot be based on these findings alone, **the findings support the recommendation from the Collaborative Initial Treatment in Glaucoma Study for more aggressive treatment in those with more advanced glaucoma at presentation**.

Anatomical structures

What do resilient nerve heads look like?

Comment by Crawford Downs, Birmingham, AL, USA

69210 What is a typical optic nerve head?, Voorhees AP, Grimm JL, Bilonick RA, Kagemann L, Ishikawa H, Schuman JS, Wollstein G, Sigal IA, Experimental Eye Research 2016; 149: 40-47

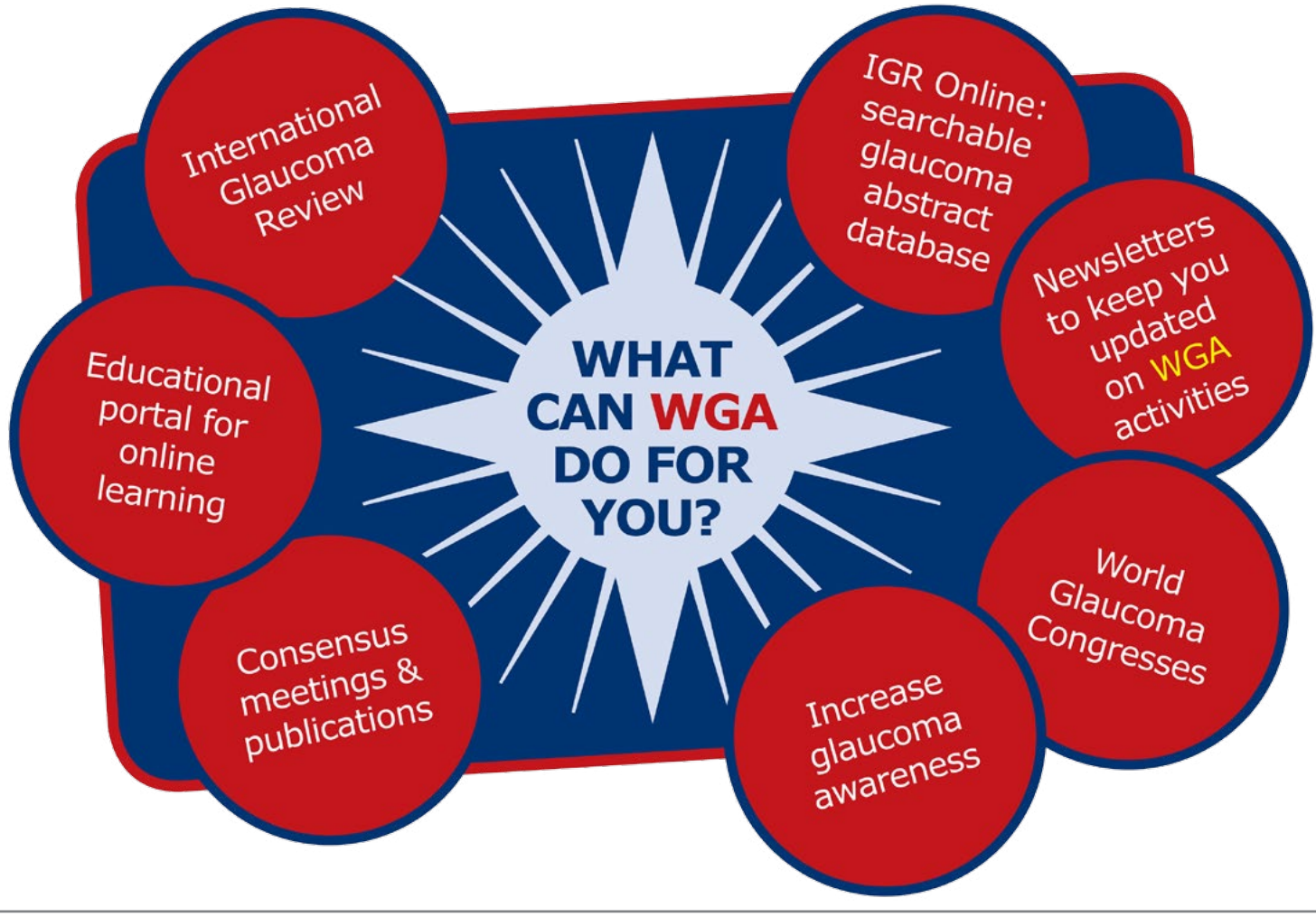
Optic nerve head (ONH) biomechanics has been hypothesized to play an important role in the development and progression of glaucoma, but it is not well understood. The dearth of available data is due to the technical challenges involved in the measurement of ONH tissue mechanical properties (stiffness) and the complexity of the ONH and scleral geometry. Further complicating the study of ONH biomechanics is the biologic variability in the load-bearing structure, which includes geometry (scleral thickness, neural canal shape and size, laminar pore size and beam thickness, *etc.*), and tissue stiffness, which may change with age, pathology, extracellular matrix (ECM) composition, and connective tissue remodeling.

Voorhees, Sigal and coworkers have constructed a series of idealized parametric finite element models of the human eye, within which various geometric and tissue stiffness parameters can be varied to determine which combinations of statistically typical and/or atypical stiffnesses and geometries of the eye, lamina cribrosa, and sclera lead to typical or atypical biomechanical responses of the ONH. Similar to the findings of their previously published work, **results show that the input factors interact in unpredictable ways, and atypical ONHs do not necessarily yield atypical biomechanical responses, and typical ONHs can often exhibit atypical biomechanical responses.** Further, their results suggest that the laminar and scleral stiffness most influence the ONH's biomechanical response to IOP, which supports their previous work.

As the authors acknowledge, these results should be viewed with some caution due to the simplifying assumptions necessary to construct the models. The most important limiting assumptions are the model's inability to consider either regional laminar density or stiffness, or regional differences in laminar and scleral geometry, as well as their limitation to perfectly circular scleral canals. All these remaining factors likely work with the considered parameters in complex ways to contribute to an individual ONH's susceptibility to IOP-related glaucomatous damage, and more work is needed to elucidate these mechanisms.

Results suggest that the laminar and scleral stiffness most influence the ONH's biomechanical response to IOP

This paper is important in that it reminds us that simple biomarkers that aim to predict ONH biomechanical behaviors with only one or two measures may yield an incomplete picture of true ONH biomechanics. Fortunately, recent advances in OCT and other imaging technologies are improving, which may lead to a more comprehensive assessment of ONH biomechanical behavior *in vivo*.



Anatomical structures

Do laminar abnormalities explain disc hemorrhage?

Comment by Ki Ho Park, Seoul, South Korea

69353 Optic Disc Hemorrhages and Laminar Disinsertions in Glaucoma, Sharpe GP, Danthurebandara VM, Vianna JR, Alotaibi N, Hutchison DM, Belliveau AC, Shuba LM, Nicolela MT, Chauhan BC, Ophthalmology 2016; 123: 1949-1956

Previous studies have demonstrated a significant association between disc hemorrhage (DH) and the presence of laminar defects as well as a spatial correlation between the two. The current paper by Sharpe *et al.* is the product of a well-designed and methodologically sound study. They enrolled 52 eyes of 46 open-angle glaucoma patients with DH and 52 eyes of 46 patients without DH matched for age and visual-field mean deviation. The SD-OCT radial cross-sectional images of the optic nerve head were reviewed, by a masked observer, for the presence and location of the laminar disinsertion. **The laminar disinsertion was found in 96% of eyes with DH and in 52% of eyes without DH,** which results are quite similar to a recent SS-OCT-based report:[1] 80.6% (58 of 72 eyes) showing laminar defect in eyes DH; 39.7% (25 of 63 eyes) in eyes without DH.

> We still do not know clearly whether laminar defect is a result of DH and subsequent tissue remodeling or the cause of DH

Thus it seems quite evident that in open-angle glaucoma, DH+ eyes might have about twice the chance of laminar defect as DH- eyes. The strengths of the current study are that the authors used objective grading scores of laminar disinsertion and the subjects were enrolled, for eyes with DH+ or DH-, regardless of the laminar-structural deformity. Further, the results of the current study might partially explain why DH occurs more frequently at the disc margin.

However, we still do not know clearly whether laminar defect is a result of DH and subsequent tissue remodeling or the cause of DH. The lower-pressure subtype tends to support the former hypothesis, and the high-pressure, mechanical-stress-related subtype the latter. Prospective long-term longitudinal studies investigating lamina cribrosa change before and after DH could provide more information regarding the mechanisms associated with DH and laminar defect.

> Laminar disinsertions occurred twice as frequently in eyes with DH

Readers might be curious about whether there was, additionally to the peripheral laminar disinsertion, any non-peripheral laminar defect. As demonstrated by the poor spatial concordance between DHs and laminar disinsertions of the current study, eyes can have DHs that are remote from the laminar disinsertions. In fact, DH does not always occur at the disc margin but, sometimes, in the non-peripheral laminar region or retinal nerve fiber layer outside of the disc. As explained in the paper's Discussion, there are multiple mechanisms of DH, some dependent on laminar disinsertion and others less so.

References

1. Kim YK, Park KH. Lamina cribrosa defects in eyes with glaucomatous disc haemorrhage. Acta Ophthalmol 2016;94(6):e468-473.
2. Kim KE, Park KH. Optic disc hemorrhage in glaucoma: pathophysiology and prognostic significance. Curr Opin Ophthalmol 2016 Nov 4. [Epub ahead of print]
3. Suh MH, Park KH. Pathogenesis and clinical implications of optic disk hemorrhage in glaucoma. Surv Ophthalmol 2014;59(1):19-29.

Basic Science

New susceptibility loci for POAG


Comment by Louis Pasquale and Baojian Fan, Boston, MA, USA

68845 Genome-wide association study identifies five new susceptibility loci for primary angle closure glaucoma, Khor CC, Do T, Jia H, Nakano M, George R, Abu-Amero K, Duvesh R, Chen LJ, Li Z, Nongpiur ME, Perera SA, Qiao C, Wong HT, Sakai H, Barbosa de Melo M, Lee MC, Chan AS, Azhany Y, Dao TL, Ikeda Y, Perez-Grossmann RA, Zarnowski T, Day AC, Jonas JB, Tam PO, Tra, Nature Genetics 2016; 48: 556-562

Ethnicity and a positive family history are strong determinants of primary angle-closure glaucoma (PACG), suggesting that genetic factors play a role in this disease. *Khor CC et al. report the largest genome-wide association study (GWAS) of PACG to date in a sample totaling 10,503 PACG cases and 29,567 controls from 24 countries*. All PACG cases met standardized criteria whose central feature was critical irido-trabecular meshwork apposition without secondary cause. Roughly 40% of cases had a history of acute symptomatology attributable to PACG. In this study, five new genetic loci were significantly associated with PACG: *EPDR1* rs3816415, *CHAT* rs1258267, *GLIS3* rs736893, *FERMT2* rs7494379, and *DPM2–FAM102A* rs3739821. The authors provide convincing evidence for replication of these newly discovered loci. Furthermore, significant associations

at three previously reported loci at *PLEKHA7*, *COL11A1*, and *PCMTD1–ST18* were confirmed. The modest effect sizes for all of these variants (odds ratio ~1.2) underscore the genetic complexity for PACG.

None of the PACG gene variants are found in exons, indicating we do not understand how these variants contribute to PACG pathogenesis

Interestingly, all eight loci for PACG identified by GWAS account for only 1.8% of the overall disease variance, indicating significant missing heritability exists — this is a typical result observed for many complex traits.

While the authors demonstrate that the newly discovered gene products are expressed in ocular tissues, none of the PACG gene variants are found in exons, indicating we do not understand how these variants contribute to PACG pathogenesis. Several of the PACG genes (*EPDR1, FERMT2* and *PLEKHA7*) are involved in cell adhesion while *CHAT* is involved in acetylcholine metabolism. In contrast, known loci for axial length, an endophenotype related to angle closure predisposition, were not associated with PACG in this dataset. We applaud this monumental effort in glaucoma genetics and suspect these findings will open new avenues in exploring glaucoma pathogenesis.

Basic Science

A new potential pathogenic pathway

Comment by Tina Wong, Singapore

69029 Pro-fibrotic pathway activation in trabecular meshwork and lamina cribrosa is the main driving force of glaucoma, Zhavoronkov A, Kanherkar RR, Izumchenko E, Teka M, Cantor C, Manaye K, Sidransky D, West MD, Makarev E, Csoka AB, Cell cycle (Georgetown, Tex.) 2016; 15: 1643-1652

Zhavoronkov *et al.* provides an insightful perspective of the role of signaling pathways governing extracellular matrix regulation on the development and progression of glaucoma. By using bioinformatics to evaluate human trabecular meshwork and lamina cribosa tissue samples, the authors provide a signaling pathway activation profile for glaucoma specifically affecting the extracellular matrix composition in the lamina cribosa and trabecular meshwork outflow facility. The authors report that certain signaling pathways such as p38 act to protect the trabecular meshwork from increases in IOP and ILK activity affects extracellular matrix remodeling following mechanical stretching of the trabecular meshwork from elevated IOP. With regards to the lamina cribrosa, there are signaling pathways identified that can provide a protective effect to withstand increases in IOP, which may provide an explanation to why certain eyes do

not develop glaucoma despite an increase in IOP. **The authors conclude that the connection between fibrosis and glaucoma progression, in relation to trabecular meshwork and lamina cribrosa structural integrity, will enable future research to discover and develop new therapeutics that target the scleral tissue surrounding key structures that play a major role in the development of glaucoma** as a novel approach for the management of disease progression.

Basic Science

Stem cells

Comment by Keith Martin and Tasneem Khatib, Cambridge, UK

69145 Stage-specific differentiation of iPSCs toward retinal ganglion cell lineage, Deng F, Chen M, Liu Y, Hu H, Xiong Y, Xu C, Liu Y, Li K, Zhuang J, Ge J, Molecular Vision 2016; 22: 536-547

Induced pluriplotent stem cells (iPSCs) are a focus of much current interest in regenerative medicine. iPSCs are derived from differentiated cells that are reprogrammed for autologous transplantation as a cell replacement strategy, giving potential benefits over other stem cell strategies in terms of ethical considerations and immune rejection.

In this study, Deng and co-workers described a regime to produce retinal precursors (RPCs) capable of differentiating into retinal ganglion cells (RGCs) from human iPSCs derived from human Tenon's capsule fibroblasts (TiPSCs).

The authors reported an upregulation of eye field transcription factors in DKK1, Noggin and Lefty A (DNL) treated cells relative to controls with 23.14% of all cells immunopositive for the RGC-specific marker Brn3b following additional Atoh7 overexpression. The discrepancy between 80% transfection efficiency of RPCs using the Atoh7 plasmid and 23.14% Brn3b immunopositive cells was noted by the authors and may indicate a need for other factors to optimize RGC differentiation from RPCs.

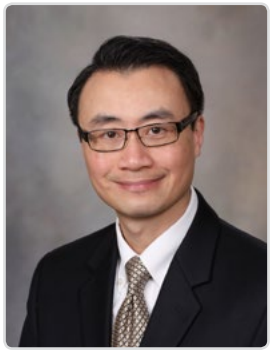
It was of interest that TiPSCs adopted neuro-ectodermal characteristics in the absence of exogenous stimuli. A control group with Atoh overexpression in RPCs that had not been treated with DNL might have helped the clarify contribution this regimen provides to RGC differentiation. Also, the relationship between Ca^{2+} influx and synaptophysin immunofluorescence could perhaps have been strengthened with the demonstration of co-localization with RGC-specific markers.

Despite these reservations, this study adds support to the possible use of human iPSCs as an RGC replacement strategy by demonstrating the potential for functional RGC differentiation *in vitro*. The use of human Tenon's fibroblasts is of particular interest in the context of glaucoma patients due to the ease of access during glaucoma surgery. The need for *in-vivo* studies remains,

optimizing the control of differentiation to minimize tumor formation, integration into the host retinal architecture, axon projection and synapse formation at distant and appropriate targets in the brain.

Basic Science

An implantable device for telemetric IOP monitoring



Comment by Arthur Sit, Rochester, MN, USA

69389 Investigation of a novel implantable suprachoroidal pressure transducer for telemetric intraocular pressure monitoring, Mariacher S, Ebner M, Januschowski K, Hurst J, Schnichels S, Szurman P, Experimental Eye Research 2016; 151: 54-60

Current clinical management of glaucoma patients typically involves measurement of intraocular pressure (IOP) every few months. However, IOP variability has been demonstrated to be a risk factor for glaucoma progression.[1-3] Characterizing IOP variability in individual patients is extremely difficult using traditional tonometers, which are designed for instantaneous ad hoc pressure measurements. Newer technologies, like the Triggerfish contact lens sensor (Sensimed AG, Lausanne, Switzerland), can characterize 24-hour IOP profiles. However, there are no clinically available devices that can potentially provide continuous IOP monitoring.

Mariacher *et al.* reported on a pre-clinical study to evaluate a novel implantable pressure monitoring system developed by Implandata of Hannover, Germany. A previous study in human subjects involved placement of similar devices in the ciliary sulcus.[4] However, sulcus placement had limitations, including the need for concurrent cataract surgery and the risk of iris chafing. In the current study, a modified device was placed in the suprachoroidal space in the eyes of rabbits via a scleral incision. The pressure in the anterior chamber was adjusted using a fluid reservoir, and the readings from the implants were compared with those from an external portable pressure transducer.

It would clearly be impractical to require recalibration every few weeks

The authors reported that **the readings from the telemetric pressure sensor implants closely matched the pressure set by the fluid reservoir (and measured by the external pressure transducer).** While the difference between the implants and the anterior chamber pressure varied with the pressure level, Bland-Altman analysis indicated that the limits of agreement (± 95%) were within 4 mmHg at pressure levels up to 35 mmHg. This comparison was performed five times over 30 weeks post-operatively (one, four, eight, 12 and 30 weeks), with a total of six implants.

However, an important caveat to the results is that the telemetric IOP was recalibrated at each time point by calculating the mean difference between the implant and the external pressure transducer readings at a fluid column level of 20 mmHg. The correction factors seemed to vary by unpredictable amounts, with a change of more than 40 mmHg between time points in one sensor. The reasons for this variability were unclear, and there was much greater variability in some implants. One possibility noted by the authors was that **fibrous tissue forming around the implant could potentially create mechanical stress in the area of the pressure sensors, leading to anomalous readings**. One of the six sensors stopped working entirely after one week.

Another issue is the long-term safety of the implants. The authors noted evidence of device migration in one of the animals. As well, as noted in the paper, potential scarring may negatively impact future glaucoma filtering surgeries as the implant requires a conjunctival dissection and scleral incision.

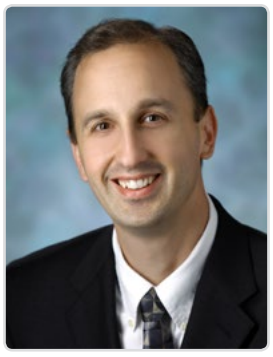
Despite these limitations, this study represents important pioneering work in the field of wireless implantable IOP sensors. However, future work is clearly needed to determine if the correction factors stabilize enough over time to be clinically useful, since it would clearly be impractical to require recalibration every few weeks. As well, the issues of longevity and safety are significant. I look forward to future research that will hopefully address these important issues.

References

1. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. Ophthalmology 2008;115:1123-1129 e1123.
2. Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R. Intraocular pressure control and long-term visual field loss in the Collaborative Initial Glaucoma Treatment Study. Ophthalmology 2011;118:1766-1773.
3. Sit AJ. Intraocular pressure variations: causes and clinical significance. Can J Ophthalmol 2014;49:484-488.
4. Koutsonas A, Walter P, Roessler G, Plange N. Implantation of a novel telemetric intraocular pressure sensor in patients with glaucoma (ARGOS study): 1-year results. Invest Ophthalmol Vis Sci 2015;56:1063-1069.

Basic Science

Neuroprotection *in vivo*



Comment by Derek Welsbie, Baltimore, MD, USA

69373 Topical administration of a Rock/Net inhibitor promotes retinal ganglion cell survival and axon regeneration after optic nerve injury, Shaw PX, Sang A, Wang Y, Ho D, Douglas C, Dia L, Goldberg JL, Experimental Eye Research 2016; 0:

Rho-associated protein kinase (ROCK) 1 and 2 are known to play a role in trabecular meshwork physiology and thus pan-ROCK inhibitors like AR-13324 (Rhopressa/netarsudil) are being developed as clinical intraocular pressure (IOP)-lowering agents. In addition, using multiple rodent models of retinal ganglion cell (RGC) axon injury, ROCK1/ROCK2 have been shown to play a role in promoting RGC cell death and limiting the ability of RGC axons to regenerate.

ROCK-inhibition may have multiple beneficial effects as a glaucoma therapy

In this article, Peter Shaw and colleagues, tested the effect of ROCK1/ROCK2 inhibition, using AR-13324, on RGC survival and axon regeneration in the rat model of optic nerve crush. **Thrice daily administration of 0.6% AR-13324 eye drops (which can penetrate to the posterior segment in mice and rats) led to ~40% rescue of RGC cell death two weeks after injury**. Moreover, unlike vehicle-treated eyes which are devoid of axons extending much beyond the crush site, **AR-13324-treated eye showed clear evidence of short-distance (up to 5 mm) axon regeneration**. Given that ROCKs are known to modulate the phosphorylation status of cofilin and LIM kinase (LIMK), they assayed retinas and optic nerves for these biochemical markers of ROCK activity and found evidence of ROCK inhibition in RGCs and proximal optic nerve glia.

The availability of conditional ROCK1 and ROCK2 knockout mice should make it possible in future to dissect out whether the neuroprotective/neuroregenerative mechanism of ROCK inhibition is RGC-intrinsic or whether there is a role for cell-cell signaling. Of note, the authors found that unilateral optic nerve crush led to an unexpected increase in IOP, even in the uninjured fellow eye. AR-13324 partially blocked the increase so yet another possible mechanism of action in this model involves the role of IOP-lowering. Taken together, ROCK-inhibition may have multiple beneficial effects as a glaucoma therapy and will certainly warrant further investigation.

Clinical examination methods

IOP provocative tests

Comment by Franz Grehn, Wurzburg, Germany

69016 Comparison between intraocular pressure spikes with water loading and postural change, Chong CW, Wang SB, Jain NS, Bank CS, Singh R, Bank A, Francis IC, Agar A, Clinical and Experimental Ophthalmology 2016; 0:

Water loading (water drinking test, WDT) has been a provocative test for intraocular pressure (IOP) spikes since many years. Water loading and other provocative tests try to give diagnostic support whether the aqueous outflow system in the eye can compensate for variations of aqueous flow sufficiently or whether the outflow function is critical. A positive test can also be taken as a surrogate for better or worse IOP control and hence for suspected future functional loss. Provocative IOP peaks may also reflect the fluctuations of IOP outside the routine office measurements.

It is well documented by sleep laboratory research that horizontal body position, in particular the supine position test (ST), increases IOP by 2-4 mmHg in the normal eye. This is usually explained by increase of episcleral venous pressure, but other mechanisms are also considered.

The supine position test may be a safer and more comfortable alternative to the WDT

The paper by Chong *et al.* tested the agreement of the spike IOPs after water drinking test with those of the supine test in 21 primary open-angle glaucoma patients in a consecutive, prospective blinded trial. Patients with other types of glaucoma, previous surgery or laser, or with IOP > 28 were excluded. The water drinking test consisted of drinking 10 ml water/kg body weight within five minutes and IOP measurements at 20 minutes / 40 minutes. The supine test lasted 40 minutes with measurements of IOP at 20 minutes and 40 minutes, while the patient was transiently sitting up for measurement. The I-Care tonometer was used.

In both tests, the IOP was significantly increased at 20 minutes and 40 minutes. **The Bland Altman analysis showed an nearly perfect correlation between the two tests.**

The paper discusses the caveats of water loading for patients with cardiac, renal, prostatic or respiratory disease, while the supine test is less stressful for body functions and the comfort of the patient. Therefore, from the authors' perspective, the ST is easier and safer to perform.

The Discussion section of the paper gives a valuable overview on the various mechanisms behind the two different provocative tests. In the WDT, increase of aqueous inflow, osmotic pressure, peripheral and episcleral venous pressure as well as trabecular resistance are discussed for elevation of IOP. In the ST, the peripheral and episcleral venous pressure are considered the major factor for IOP increase.

In summary, the strong correlation between the IOP increase after the WDT and after ST suggests that similar mechanisms may be responsible for the elevation of IOP. The ST may be a safer and more comfortable alternative to the WDT.

Clinical examination methods

Patterns of field loss in PACG

Comment by Ramanjit Sihota, New Delhi, India

69343 Pattern of Visual Field Loss in Primary Angle-Closure Glaucoma Across Different Severity Levels, Atalay E, Nongpiur ME, Yap SC, Wong TT, Goh D, Husain R, Perera SA, Aung T, Ophthalmology 2016; 123: 1957-1964

In this study, the authors looked at the important subject of visual field defects in different severities of primary angle closure glaucoma (PACG) by using an analysis at each pointwise location, and performing between hemifield and within hemifield evaluations. **They reported the superior hemifield to be more severely affected than the inferior hemifield, with the difference increasing with severity. The nasal area was consistently more affected**.

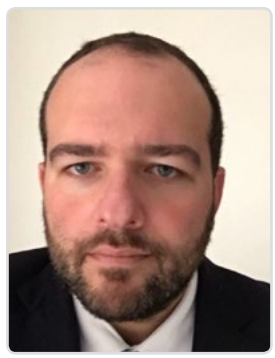
One issue with this study is that the definition of PACG used was only an inability to see the posterior trabecular meshwork on gonioscopy in primary position, without mention of the additional requirement for evidence of iridotrabecular contact, such as synechiae, *etc.* This could have led to the inclusion of patients having primary open angle glaucoma (POAG) with a narrow recess (which is likely in the population studied), or other secondary open-angle glaucomas. Therefore, the conclusions regarding visual field defects seen in these patients may not be definitive for PACG.

As well, patients were excluded if they did not have 'defects typical of glaucoma', which was based on the Ocular Hypertension Treatment Study and representative of POAG. It is possible that PACG patients could present with different defect patterns, which were then not considered, contrary to the aim of the study.

The visual field changes reported in this study are very similar to those seen in POAG, and the results may have been different, and more conclusive, if more stringent criteria for PACG had been used and all defects analyzed.

Clinical examination methods

A new ONH volume change-detection method

Comment by Gadi Wollstein and Fabio Lavinsky, New York, NY, USA

69386 Structural Change Can Be Detected in Advanced-Glaucoma Eyes, Belghith A, Medeiros FA, Bowd C, Liebmann JM, Girkin CA, Weinreb RN, Zangwill LM, Investigative Ophthalmology and Visual Science 2016; 57: OCT511-8

Detection of glaucoma progression in subjects with advanced glaucoma is challenging because the reliability of visual field (VF) testing is reduced in advanced disease,[1] and OCT circumpapillary retinal nerve fiber layer (RNFL) thickness reaches the minimum practical measurement (floor effect) and further thinning cannot be detected.[2,3] Therefore, studying alternative parameters to detect progression in advanced glaucoma is utterly needed.

The present study investigated if OCT's minimal rim width (MRW) and macular ganglion cell inner plexiform layer (GCIPL) can be useful alternatives to detect progression in eyes with advanced glaucoma (VF MD ≤ 21dB). The OCT scans were analyzed using the author's proprietary segmentation algorithm, and the rate of change was computed for each parameter and compared between advanced glaucoma and control eyes. Additionally, eyes were classified as 'progressing' or 'non-progressing' using a Bayesian kernel detection scheme with ONH analysis and an automated machine classifier method with macular analysis.

> Detection of glaucoma progression in subjects with advanced glaucoma is challenging

In advanced glaucoma eyes, the rate of change was non-significant for RNFL and MRW, and significant and steeper than in the control eyes for GCIPL. When eyes were split into progressing and non-progressing groups based on ONH analysis, the rate of change was significantly steeper for GCIPL and not significant for the other structural parameters and VF MD. When progression was defined based on macula analysis, no significant difference was reported for RNFL, MRW and VF MD, but for GCIPL there was a significant thickening reflected in the slope of the progressing group compared with the non-progressing.

These findings demonstrate that GCIPL changed in advanced glaucoma when other structural and VF parameters did not change. However, these results, along with similar longitudinal studies, cannot confirm that these changes truly indicate progression due to the absence of widely accepted gold-standard criteria for progression and the lack of corresponding change with any of the other parameters. Furthermore, the use of customized analysis tools that are not available for clinicians limits the applicability of the findings in clinical practice. Nevertheless,

the results provide an important indication that structural changes vary among locations in the eye, and the best method to detect disease progression in the various stages of disease severity should be further investigated.

References

1. Gardiner SK, Swanson WH, Goren D, Mansberger SL, Demirel S. Assessment of the reliability of standard automated perimetry in regions of glaucomatous damage. Ophthalmology 2014;121:1359-1369.
2. De Moraes CG, Liebmann JM, Medeiros FA, Weinreb RN. Management of advanced glaucoma: characterization and monitoring. Surv Ophthalmol 2016;61:597-615.
3. Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. Prog Retin Eye Res 2007;26:688-710.

Clinical examination methods

Diagnostic accuracy of OCT-A

Comment by Toru Nakazawa, Sendai-shi, Miyagi-ken, Japan

69318 Optical Coherence Tomography Angiography Vessel Density in Healthy, Glaucoma Suspect, and Glaucoma Eyes, Yarmohammadi A, Zangwill LM, Diniz-Filho A, Suh MH, Manalastas PI, Fatehee N, Yousefi S, Belghith A, Saunders LJ, Medeiros FA, Huang D, Weinreb RN, Investigative Ophthalmology and Visual Science 2016; 57: OCT451-9

Previous studies have demonstrated that ocular blood flow (OBF) is reduced in the optic nerve head, retina, choroid, and retrobulbar space in glaucoma. However, these studies were limited by the lack of a reproducible, accurate method to measure OBF, and could not determine whether changes in the microvasculature and in OBF have a causative role in the pathophysiology of glaucoma. Optical coherence tomography angiography (OCT-A) is a recently introduced imaging modality that can characterize the vasculature of each retinal layer and provide a quantitative assessment of microcirculation in the optic nerve head and the peripapillary region.

In this manuscript, the authors used SD-OCT (Avanti; Optovue, Inc.) and OCT-A (AngioVue; Optovue, Inc.) to compare retinal nerve fiber layer (RNFL) thickness in healthy subjects (n = 23), patients with suspected glaucoma (n = 37), and glaucoma patients (n = 104). Two vessel density measurements extracted from the RNFL data were analyzed with the standard AngioVue software: (1) circumpapillary vessel density (cpVD), measured in a 750-µm-wide elliptical annulus around the disc; and (2) whole image vessel density (wiVD), measured over the entire 4.5 x 4.5-mm image field.

The study found that age-adjusted mean vessel density was significantly lower in the OAG eyes than the glaucoma-suspected and healthy eyes (cpVD: 55.1%, 60.3%, and 64.2%, respectively; P < 0.001; and wiVD: 46.2%, 51.3%, and 56.6%, respectively; P < 0.001). The age-adjusted area under the receiver operating characteristic curve (AUROC) for differentiating between glaucoma and healthy eyes was highest for wiVD (0.94), followed by RNFL thickness (0.92) and cpVD (0.83). The AUROC for differentiating between healthy and glaucoma-suspected eyes was highest for wiVD (0.70), followed by cpVD (0.65) and RNFL thickness (0.65). Thus, **OCT-A vessel density had a similar diagnostic accuracy as RNFL thickness measurements for differentiating between healthy and glaucoma eyes.**

Importantly, this is the first report that has used OCT-A to evaluate the microvascular bed of the RNFL, which is the main site of damage in glaucoma. Moreover, the OCT-A measurements were not correlated to disc area, in contrast to other structural measurements, such as RNFL and optic nerve head parameters, which are influenced by optic disc size. While it should be noted that OCT-A does not directly measure blood flow, it should nevertheless provide an excellent imaging target for early glaucoma diagnosis and objective parameters for glaucoma assessment. Furthermore, OCT-A should open new avenues for research into the role of blood flow in the pathophysiology of glaucoma.

Clinical forms of glaucoma

A progression predictor in myopic normal tension glaucoma?

Comment by Tae-Woo Kim, Seongnam, Korea

68923 Optic Disc Rotation as a Clue for Predicting Visual Field Progression in Myopic Normal-Tension Glaucoma, Sung MS, Kang YS, Heo H, Park SW, Ophthalmology 2016; 123: 1484-1493

Although myopia is a well-known risk factor for glaucoma, the underlying mechanism how myopia is related to glaucomatous optic nerve damage remains unclear. Recently, optic disc rotation has become a focus of interest as an important morphologic feature of myopic eyes. It has been reported that the direction of optic disc rotation was a strong predictor of VF defect location in NTG eyes. Sung *et al.* investigated the factors associated with visual field (VF) progression in myopic normal-tension glaucoma (NTG) and determined the relationship between optic disc rotation-VF correspondence and VF progression. Optic disc rotation-VF defect correspondence was defined as eyes showing inferior rotation of the optic disc had an inferior RNFL defect and corresponding VF defect in the superior hemifield and vice versa. **They found that the percentage reduction in IOP from baseline, disc hemorrhage, optic disc rotation-VF defect correspondence were important prognostic factors for patients with myopic NTG.**

The most intriguing finding of this study is the negative association of optic disc rotation-VF defect correspondence with VF progression. Of the eyes with correspondence, more than 70% remained constant without VF progression during a mean follow-up period of six years. This finding suggests that the optic disc rotation has a role in developing RNFL damage and VF defects in myopic eyes, but these structural and functional changes may be static and not progressive.

Optic disc rotation has a role in developing RNFL damage and VF defects in myopic eyes, but these structural and functional changes may be static and not progressive

It remains to be elucidated why and how optic disc rotation is associated with slow VF progression. One possible hypothesis based on the recent observations is that the effect of myopia-related stress on the ONH may be alleviated with time. Some studies suggested that myopia-related tensile stress is a major or predominant insult in eyes with optic disc rotation. It is known that the optic disc changes during early childhood in myopic eyes. Such change would impose stress to the optic nerve head. At some point during life, the stress may overcome the compensatory capability, leading to RNFL damage. Thus, myopic eyes have higher chance to have glaucomatous optic neuropathy. However, since the optic disc change secondary to axial elongation is generally not a life-long process, the tensile stress associated with axial elongation or optic disc change may no longer damage the remaining optic nerve which survived against the existing tensile stress. Taken together, myopia-related tensile stress may be the predominant factor for optic nerve damage in eyes with optic disc rotation-VF defect correspondence. In such eyes, disease progression may be halted or slowed.

Determining the factors associated with faster glaucoma progression is important. At the same time, it is also important to be aware that some patients with glaucomatous optic nerve damage may not progress. Such awareness can save some patients from unnecessary aggressive treatment.

References

1. Park HY, Lee K, Park CK. Optic disc torsion direction predicts the location of glaucomatous damage in normal-tension glaucoma patients with myopia. Ophthalmology 2012;119:1844-1851.
2. Kim TW, Kim M, Weinreb RN, *et al.* Optic disc change with incipient myopia of childhood. Ophthalmology 2012;119:21-6 e1-3.
3. Kim YW, Lee EJ, Kim TW, *et al.* Microstructure of beta-zone parapapillary atrophy and rate of retinal nerve fiber layer thinning in primary open-angle glaucoma. Ophthalmology 2014;121:1341-1349.

Medical treatment

In-vivo histological effects of preservative-free prostaglandins

Comment by Christophe Baudouin, Paris, France

69141 Long-term topical application of preservative-free prostaglandin analogues evokes macrophage infiltration in the ocular adnexa, Trzeciecka A, Paterno JJ, Toropainen E, Koskela A, Podracka L, Korhonen E, Kauppinen A, Kaarniranta K, Smedowski A, European Journal of Pharmacology 2016; 788: 12-20

Preservatives found in most anti-glaucoma preparations have been largely shown clinically or experimentally to induce toxic effects over the long term, with clinical manifestations that include dry eye, allergy, blepharitis, hyperhemia, chronic inflammation of the ocular surface, *etc.* They may impact quality of life, compliance and adherence, and negatively influence surgical outcome. Preservative-free medications are interesting options for avoiding such effects and have particular interest in patients with ocular surface diseases or receiving multiple therapies. However, some prostaglandins due to their own composition require solubilizers to remove the preservative, which can also raise possible tolerance concerns.

Following a first *in-vitro* study, the authors investigated in rabbits three formulations of preservative-free prostaglandins commercially available, namely Macrogol-containing latanoprost, Polysorbat 80-containing tafluprost and bimatoprost free of both preservative and solubilizer. Clinical assessments were performed, completed by complex proteomic and immunohistological techniques in tears, aqueous humor and eyelids. **Overall results favored preservative-free formulations of bimatoprost and tafluprost** and demonstrated a reliable irritative effect of Macrogol-containing latanoprost, consisting of increased conjunctival redness and blinking frequency, more LDH in aqueous humor, significant infiltration of macrophages in the eyelids and possible impact to goblet cells. None of the formulations did induce inflammatory cytokines in the tears. This is an interesting study pointing out the importance of active compounds and their formulations in tolerance issues, beside the major well-known impact of quaternary ammoniums and alternative preservatives. Further studies will be needed to measure clinical relevance of these results, by head-to-head comparisons or meta-analyses of clinical data in large patients populations.

Prostaglandins require solubilizers to remove the preservative, which can also raise possible tolerance concerns

Even if a preservative-free formulation is more irritative, it may remain much less toxic than a preserved one and this question has not been addressed. Indeed we can regret in this study the absence of a control group with a preserved latanoprost formulation, to measure if the solubilizer has similar, higher or lower negative impact to the ocular surface compared to benzalkonium chloride. Clinical benefit of all preservative-free formulations has been shown in clinical studies and clinical practice. It should be determined if such differences between formulations may negatively impact patient outcome and glaucoma care over the long term, especially in fragile and sensitive patients. Nevertheless, though animal models have often been criticized for the lack of relevance toward clinical practice, they have the major advantage of providing arguments to warn clinicians about possible side effects induced in the long run by apparently well tolerated eye drops and to foster innovative formulations and drug developments to limit such effects and improve local tolerance, a more and more recognized component in glaucoma care.

Medical treatment

Latanoprostene Bunod efficacy

Comment by Norbert Pfeiffer, Mainz, Germany

69393 Long-term Safety and Efficacy of Latanoprostene Bunod 0.024% in Japanese Subjects with Open-Angle Glaucoma or Ocular Hypertension: The JUPITER Study, Kawase K, Vittitow JL, Weinreb RN, Araie M, Advances in Therapy 2016; 33: 1612-1627

At last there is hope that we will soon have a new IOP lowering drug for treating elevated IOP in subjects with glaucoma or ocular hypertension. Latanoprostene bunod sounds like the name of another prostaglandin. However, the authors state that "Following ocular instillation, LBN is rapidly metabolized into latanoprost acid, a prostaglandin F2α analog, and butanediol mononitrate, a nitric oxide (NO)-donating moiety, which is subsequently reduced to 1,4 butanediol, an inactive metabolite, and NO." Thus, this may be both a prostaglandine and a nitric oxide donating drug that appears to have mechanism of action which are different from other prostaglandin analogs. Kawasa and colleagues report their results from a single-arm, multi-center, open-label, clinical study in subjects with open-angle glaucoma or ocular hypertension. They observed the usual side-effects typical to prostaglandins with 62% having at least one topical side-effect. IOP lowering was 22% in study eyes and 19.5% in fellow eyes that were also treated after four weeks but also up to one year of follow-up. What does this mean? IOP lowering is in the range of other studies with prostaglandins. But data are from an open-label study. We look forward to a similar study with an active or placebo control. But: good news there is something new on the horizon.

Surgical treatment

Predictors of SLT efficacy

Comment by Albert Khouri, Newark, NJ, USA

69001 Preoperative intraocular pressure as a predictor of selective laser trabeculoplasty efficacy, Pillunat KR, Spoerl E, Elfes G, Pillunat LE, Acta Ophthalmologica 2016; 94: 692-696

Selective laser trabeculoplasty (SLT) is often performed as an adjunct therapy in patients already on medications. In this study, the authors examined the effect of SLT in patients on maximally tolerated therapy. The paper answers a relevant question regarding predictors of SLT efficacy in patients already on multiple medications (mean 2.9 ± 0.9). The cohort included patients with normal pressure glaucoma (NPG, 27% of subjects). Patients with NPG pose a particular challenge as treatment aims to lower an already 'normal' intraocular pressure (IOP).

It was encouraging that SLT worked even in eyes of maximally treated patients

We know from clinical trials that a higher pre-treatment IOP tends to predict a more robust therapeutic response. So, does this concept apply to SLT in patients already on maximal therapy? Pillunat and colleagues answered this question by prospectively enrolling subjects and measuring diurnal IOP (six times/24hr) before and about six months after a single surgeon performed 360 degree SLT. **The only predictor of response was pre-SLT IOP**. In fact, the response to SLT was better with higher baseline IOPs (for each mmHg higher mean diurnal pre-SLT, IOP was reduced by 0.3 mmHg). This is not unexpected and is in line with findings from EMGT. **IOP reduction was observed in 100% of patients with pre-SLT IOP > 18 mmHg**. While patients with pre-SLT IOP < 14 mmHg had less effective results, still 64% experienced some IOP reduction (of note, in this group a third of patients had a slight increase in IOP).

The results of this study are in agreement with the literature – a higher baseline IOP tends to predict a better response. **It was encouraging that SLT worked even in eyes of maximally treated patients**. Perhaps the most promising finding was that **SLT lowered IOP similarly in high- and normal-pressure glaucoma eyes** ($p = 0.887$) as long as pre-SLT IOP was comparable.

Surgical treatment

Repeatability of SLT outcomes

Comment by Tony Realini, Morgantown, WV, USA

69409 Repeatability of selective laser trabeculoplasty for open-angle glaucoma, Francis BA, Loewen N, Hong B, Dustin L, Kaplowitz K, Kinast R, Bacharach J, Radhakrishnan S, Iwach A, Rudavska L, Ichhpujani P, Katz LJ, BMC Ophthalmology 2016; 16: 128

Francis and colleagues have reported the results of a retrospective study evaluating the intraocular pressure (IOP)-lowering efficacy of repeat selective laser trabeculoplasty (SLT) in eyes inadequately controlled with a mean of approximately two topical IOP-lowering medications. The research team found that **when initial SLT's effect waned, repeat SLT (360-degree treatment both times) restored the level of IOP reduction seen after initial SLT both six and 12 months after retreatment.** These results are consistent with a half-dozen other studies documenting the efficacy and safety of repeat SLT. The repeatability of SLT has been controversial in the past. Unlike argon laser trabeculoplasty (ALT), which causes permanent scarring in the trabecular meshwork precluding safe repeatability, SLT causes no such scarring and has been theorized to be repeatable. In fact, the safe and effective repeatability of SLT has now been conclusively established and is no longer controversial at all.

Based on its attributes (efficacy comparable to a prostaglandin, safe, long-lasting, no need for adherence, no exposure to preservatives, and repeatable when its effect wanes), it remains unclear why SLT has not yet supplanted medical therapy as the preferred first-line treatment for POAG

The implication of this important finding is that SLT – repeated as needed – can provide long-term IOP control in patients with open-angle glaucoma. Several studies have established that when used as primary therapy (as was not the case in the Francis study) SLT provides IOP reduction comparable to a prostaglandin analogue. Based on the various studies of repeat SLT, initial SLT seems to last about a year before its effect wanes, and repeat SLT often lasts even longer. Based on its attributes (efficacy comparable to a prostaglandin, safe, long-lasting, no need for adherence, no exposure to preservatives, and repeatable when its effect wanes), it remains unclear why SLT has not yet supplanted medical therapy as the preferred first-line treatment for POAG.

Surgical treatment

Anti-VEGF vs. Valve for neovascular glaucoma

Comment by Sarwat Salim, Milwaukee, WI, USA

69037 Intravitreal ranibizumab injection combined trabeculectomy versus Ahmed valve surgery in the treatment of neovascular glaucoma: assessment of efficacy and complications, Liu L, Xu Y, Huang Z, Wang X, BMC Ophthalmology 2016; 16: 65

Neovascular glaucoma (NVG) is a potentially devastating glaucoma caused by diseases that lead to retinal ischemia and release of vascular endothelial growth factors (VEGF). Recently, anti-VEGF therapy has become a mainstay in treating NVG. Several studies have reported regression of neovascularization, reduced ocular pain, and reduced intraocular pressure (IOP) when using anti-VEFG agents in conjunction with glaucoma surgery.[1-4]

Liu *et al.* prospectively assessed the efficacy and safety of intravitreal ranibizumab (0.5 mg) combined with trabeculectomy (18 eyes) and compared it to FP7 Ahmed valve surgery (19 eyes) at six months for treating neovascular glaucoma. Mitomycin C was used during trabeculectomy (0.4 mg/ml for 1-2 min duration). Panretinal photocoagulation was performed in approximately 90% of the cases in both groups prior to surgery. There was no difference in baseline characteristics, including preoperative IOP. Surgical success was defined as IOP ≥ 6 mm Hg and ≤ 21 mm Hg without any glaucoma medications, additional surgery, or loss of light perception vision. IOP was significantly reduced in both groups with no difference between the two groups at month 6 (P = 0.324). Complete surgical success was 61.1% and 57.9% in the trabeculectomy and Ahmed groups, respectively. Postoperative complications were more commonly encountered in the Ahmed group (42.1% vs. 16.7%). The authors concluded that, **compared to Ahmed surgery, intravitreal ranibizumab combined with trabeculectomy had fewer complications and a higher success ratio**.

This study affirms the use of anti-VEGF therapy in optimizing surgical outcomes and minimizing complications during trabeculectomy

Current literature is limited in comparing different surgical techniques for NVG. The authors are commended for studying the outcomes of two commonly performed procedures for neovascular glaucoma in a prospective interventional series. This study affirms the use of anti-VEGF therapy in optimizing surgical outcomes and minimizing complications during trabeculectomy. Although this is an important clinical study when analyzing outcomes of two procedures separately, one needs to be cautious when interpreting results, comparing two techniques, and drawing conclusions. The study compared two totally different surgeries with lack of

controls. While neovascularization and inflammation were controlled in the trabeculectomy group with prior anti-VEGF injection, Ahmed valve surgery was performed in inflamed eyes with active neovascularization. Because ranibizumab was not used in the Ahmed group, this could have accounted for more complications. The study would have more merit if outcomes were compared of trabeculectomy with and without ranibizumab or Ahmed valve implantation with and without ranibizumab. The study is also limited by a small sample size and short follow-up. It is well known that long-term treatment outcomes are limited in NVG due to progression of underlying disease, irrespective of type of surgical intervention. Therefore, additional research is needed, particularly prospective multicenter trials, with a longer follow-up to understand the efficacy and safety of different surgeries in NVG when augmented with anti-VEGF therapy and pan-retinal photocoagulation.

References

1. How A, Chua JL, Charlton A, *et al.* Combined treatment with bevacizumab and 5-fluorouracil attenuates the post-operative scarring response after experimental glaucoma filtration surgery. Invest Ophthalmol Vis Sci 2010;51:928-932.
2. Jue A. Angiogenesis. Trabeculectomy and bevacizumab. Semin Ophthalmol 2009;24:122-125.
3. Cornish KS, Ramamurthi S, Saidkasimova S, *et al.* Intravitreal bevacizumab and augmented trabeculectomy for neovascular glaucoma in young diabetic patients. Eye 2009;23:979-981.
4. Altintas AG, Arifoglu HB, Tutar E, *et al.* Effect on anterior chamber bevacizumab injection combined with seton implantation in treatment of rubeosis iridis in neovascular glaucoma. Cutan Ocul Toxical 2012;31:124-127.

Miscellaneous

A statistical model to help detect visual field progression

Comment by Andrew Tatham, Edinburgh, UK

69493 A Statistical Model to Analyze Clinician Expert Consensus on Glaucoma Progression using Spatially Correlated Visual Field Data, Warren JL, Mwanza JC, Tanna AP, Budenz DL, Translational vision science & technology 2016; 5: 14

Visual field (VF) progression can be evaluated by direct comparison of VF reports or by using progression software to obtain objective, quantitative data. Progression software performs event- and trend-based analyses, however, these rely either on global indices such as the visual field index (VFI) or on assessing point-by-point change over time, which results in loss of potentially useful information. Clinicians viewing serial VFs can gauge the spatial relationship between potentially progressing points, something that automated software fails to consider but that

may be helpful for improved detection of progression. For example, if there is worsening sensitivity at one VF test location, change at a related location may be more likely to be genuine, whereas change at an isolated location may be more likely to represent noise.

This study examines a new statistical method for detecting VF progression that incorporates spatial information. The model was developed using a dataset of VFs from 191 eyes of 97 patients, with an average of 7.4 VFs per eye obtained over a mean follow up period of 2.6 years. Eyes with 'definite' VF progression were identified by expert clinicians viewing the individual VFs and glaucoma progression analysis (GPA) report. The relationship between rates of change in VF at each test location and the probability of experts deciding an eye was progressing was examined to determine if deterioration at a particular location was more or less predictive of being diagnosed as progressing by experts. The model adjusted the contribution of each test point by accounting for sensitivity of surrounding VF locations, with the spatial locations partially determined using Garway-Heath's map relating VF test locations to regions of the optic nerve head.[1]

When applied to a validation dataset, the new glaucoma progression model provided better predictions of progression compared to competing models. The analysis also revealed that change in sensitivity in regions related to the temporal ONH had a greater influence on probability of progressing compared to change in the nasal sectors. Further validation is needed but it is possible that such a model could be used in clinical practice to improve progression analysis and promisingly there is also the possibility of incorporating information from imaging devices to further improve accuracy.

Reference

1. Garway-Heath DF, Poinoosawmy D, Fitzke FW, Hitchings RA. Mapping the visual field to the optic disc in normal tension glaucoma eyes. Ophthalmology 2000;107:1809-1815.

Miscellaneous

Pathophysiology of glaucoma: Lessons from microgravity

Comment by Hanspeter Killer and Achmed Pircher, Aarau, Switzerland

69227 The pressure difference between eye and brain changes with posture, Eklund A, Johannesson G, Johansson E, Holmlund P, Qvarlander S, Ambarki K, Wahlin A, Koskinen LO, Malm J, Annals of Neurology 2016; 80: 269-276

The relationship between the intracranial and the intraocular pressure and the translaminar pressure difference (TLCPD) has gained interest in the study of glaucoma (particularly normal-tension glaucoma (NTG)), idiopathic intracranial hypertension (IIH) and the visual impairment/intracranial pressure (VIIP) syndrome described in astronauts.

Eklund *et al.* investigated the effect of posture onto the TLCPD in 11 healthy volunteers (age 46 ± 10 years, three males and eight females) by measuring the intracranial pressure (ICP) on lumbar puncture as well as the intraocular pressure simultaneously in supine, sitting and in head-down tilt (HDT) position. The estimated TLCPD at assessed simultaneously measured IOP and ICP was dependent on hydrostatic effects related to body posture.

The pressure behind the lamina cribrosa is virtually not known

The study is nicely conducted, but the results should be interpreted in the light of their limitations.

Firstly, the cohort is small and the age rather young and therefore more representative for IIH patients than patients with NTG.

Secondly, the term intracranial pressure is somehow misleading as it is the lumbar CSF pressure that was measured. Although the CSF pressure at the lumbar site may equal the CSF pressure in the brain[1] it is questionable whether it equals the pressure in the subarachnoid space (SAS) of the optic nerve (ON). Studies applying cysternography demonstrated that in patients with NTG[2] and patients with papilledema[3] CSF does not communicate freely between the intracranial SAS and that of the ON. The SAS of the ON is extremely narrow and due to the mechano-sensitivity of meningothelial cells[4] that cover the meninges (arachnoid and pia layer) as well as the septae and trabeculae, the lumen of the SAS surrounding the ON is highly dynamic. CSF enters into the orbit through the bony optic canal – the static component, which was shown to influence the expression of papilledema (Bidot). In cases of asymmetric papilledema the CSF pathway along the ON might at least at the side of the less affected ON not be patent.

Thirdly, it is still not clear if and how a higher TLCPD might contribute to optic disc cupping as seen in patients with glaucoma. In fact, the calculated TLCPD in the study from Berdahl *et al.*[5] is higher in ocular hypertension compared with that in NTG. The calculated TLCPD in the study from Eklund *et al.* concerning lumbar CSF pressure measurement in supine position in 11 healthy is even higher than the calculated and as pathologic suggested TLCPD in NTG patients published in the studies from Berdahl *et al.*[5] and Ren *et al.*[6] Further, a recent study (Pircher *et al.*) did not show a correlation between the TLCPD and the mean deviation of visual field defects in 38 patients with NTG.

All these questions need to be addressed for further advancement of the TLCPD concept and cannot be eliminated by measuring IOP and CSF-p simultaneously as the pressure behind the lamina cribrosa is virtually not known.

References

1. Lenfeldt N, Koskinen LO, Bergenheim AT, Malm J, Eklund A. CSF pressure assessed by lumbar puncture agrees with intracranial pressure. Neurology 2007;68:155-158.
2. Killer HE, Miller NR, Flammer J, *et al.* Cerebrospinal fluid exchange in the optic nerve in normal-tension glaucoma. Brit J Ophthalmol 2012;96:544-548.
3. Killer HE, Jaggi GP, Miller NR, *et al.* Cerebrospinal fluid dynamics between the basal cisterns and the subarachnoid space of the optic nerve in patients with papilloedema. Brit J Ophthalmol 2011;95:822-827.
4. Xin X, Fan B, Flammer J, *et al.* Meningothelial cells react to elevated pressure and oxidative stress. PloS one 2011;6:e20142.
5. Berdahl JP, Fautsch MP, Stinnett SS, Allingham RR. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case-control study. Invest Ophthalmol Vis Sci 2008;49:5412-5418.
6. Ren R, *et al.* Cerebrospinal fluid pressure in glaucoma: a prospective study. Ophthalmology 2010;117: 259-266.

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Diagnosis of Primary Open Angle Glaucoma

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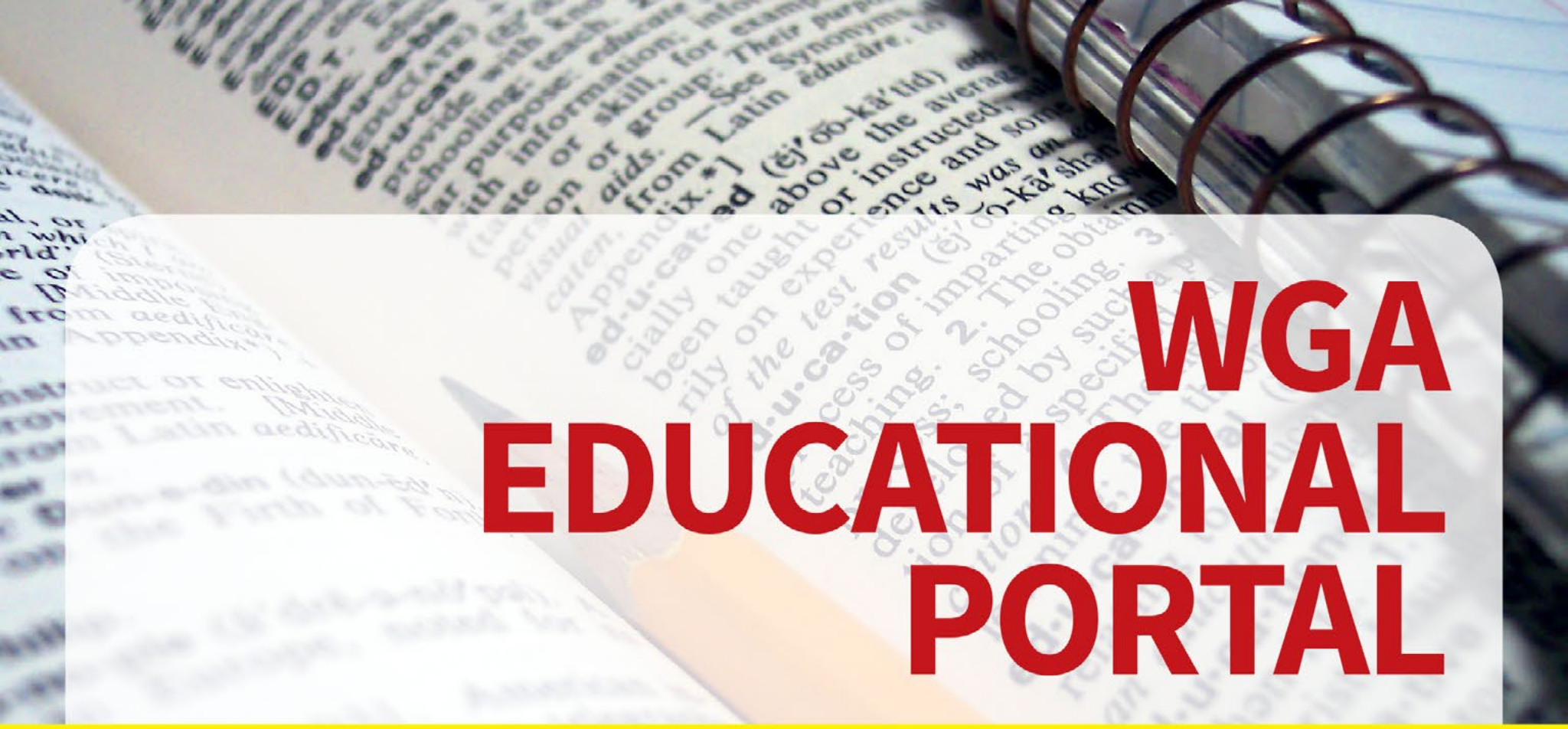

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News flashes

- ★ Results suggest that the laminar and scleral stiffness most influence the ONH's biomechanical response to IOP
- ★ We still do not know clearly whether laminar defect is a result of DH and subsequent tissue remodeling or the cause of DH
- ★ Laminar disinsertions occurred twice as frequently in eyes with DH
- ★ None of the PACG gene variants are found in exons, indicating we do not understand how these variants contribute to PACG pathogenesis
- ★ Is it impractical to require recalibration of a tonometer every few weeks? ROCK-inhibition may have multiple beneficial effects as a glaucoma therapy
- ★ Is the supine position test a safer and more comfortable alternative to the water drinking test
- ★ Why is detection of glaucoma progression in subjects with advanced glaucoma challenging?
- ★ Optic disc rotation has a role in developing RNFL damage and VF defects in myopic eyes, but these structural and functional changes may be static and not progressive
- ★ Prostaglandins require solubilizers to remove the preservative, which can also raise possible tolerance concerns
- ★ SLT is effective even in eyes of maximally treated patients
- ★ It remains unclear why SLT has not yet supplanted medical therapy as the preferred first-line treatment for POAG
- ★ Does anti-VEGF therapy improve surgical outcomes and minimize complications of trabeculectomy?
- ★ Is the pressure posterior to the lamina cribrosa known?

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