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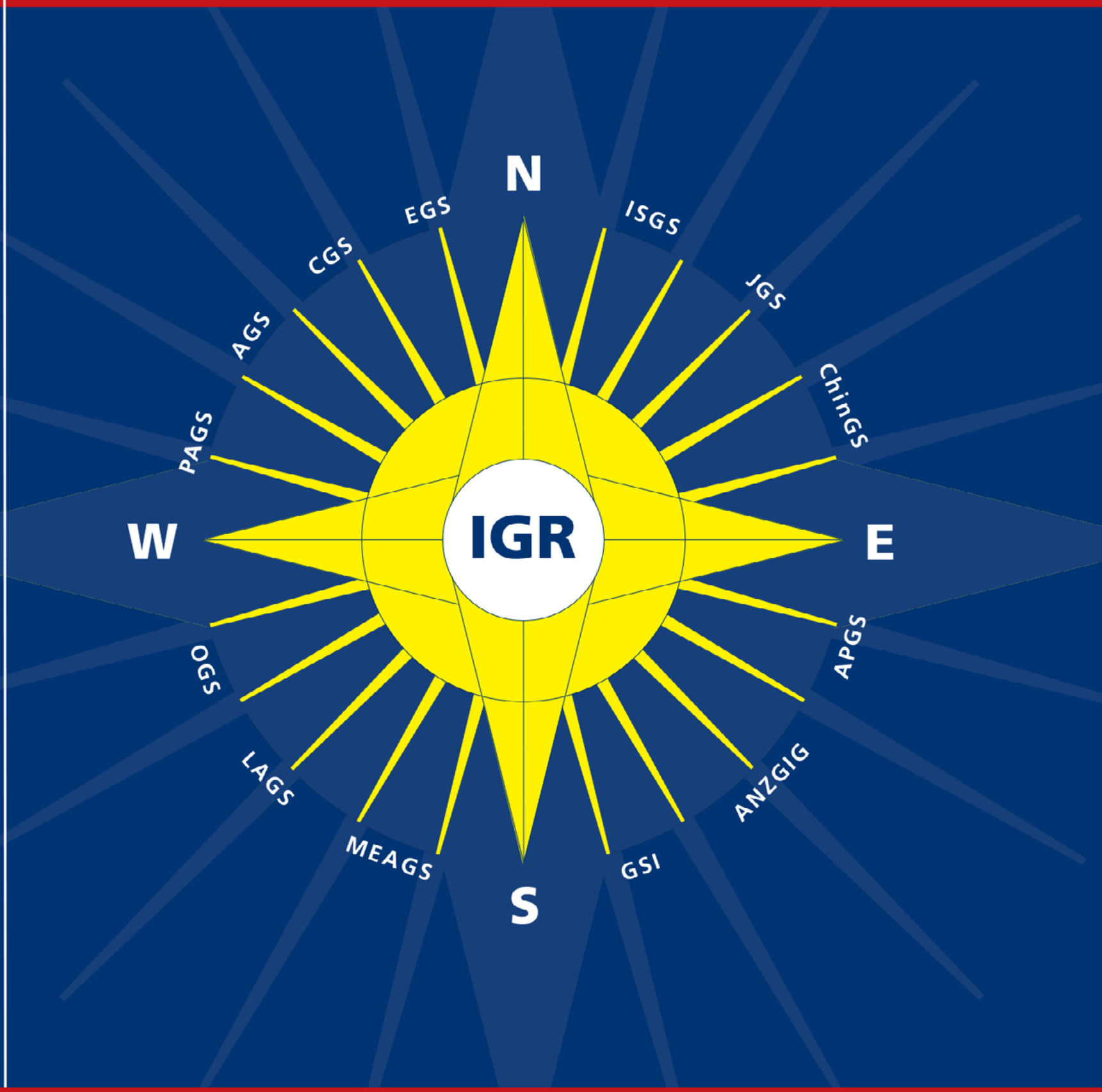

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The Global Glaucoma Network

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Volume 17 no. 3

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The affiliations of the contributors to this issue can be found on www.e-IGR.com.

From the WGA Executive Office

Dear readers,

Once again, we are pleased to present to you the newest issue of *International Glaucoma Review*.

This 17-3 edition is special, as we will be distributing it as a printed copy to participants of the European Glaucoma Society Congress, taking place in Prague from June 19–21, 2016. If you have any chance to meet us onsite, please pay us a visit at the WGA booth #33, located in the exhibitions hall.

The World Glaucoma Association continues to grow. I am delighted to add that we have three new countries in our Glaucoma Community. As per our latest gathering at the ARVO Annual meeting in Seattle, the WGA Board of Governors approved membership of the newly-formed Glaucoma Societies:

- Salvadoran Glaucoma Society
- Glaucoma Interest Group, Myanmar Ophthalmological Society
- Glaucoma Interest Group Vietnam

The organizations are now part of a peer network of over 13,000 glaucoma specialists all over the world. Please refer to the online WGA world map for more information on all affiliated societies.

On April 30, the 10th Consensus meeting was held during ARVO 2016 in Seattle. Over 200 participants and observers from all over the world were present to discuss nearly 100 statements on Diagnosis of Primary Open-Angle Glaucoma. Based on the outcomes of the meeting, the consensus report is now being finalized. We plan to publish the 10th Consensus book right before the start of AAO 2016.

In addition, the WGC-2017 scientific program is nearly complete. We want to recognize the tremendous efforts of the WGC-2017 Program Planning Committee who spent a long day together for a brainstorm session during ARVO 2016. The program overview is now published via the WGA site. Go to www.worldglaucoma.org to preview the program. Registration opens on October 10, 2016!

Please enjoy this IGR and let me know your thoughts regarding our efforts in this and all WGA initiatives. You can reach me at (fechtner@worldglaucoma.com). You can also contact our WGA Executive Office (info@worldglaucoma.org) if you need any information or have questions on IGR- or WGA-related matters.

I look forward to hearing from you.

Professor Dr. Robert D. Fechtner, Executive Vice President

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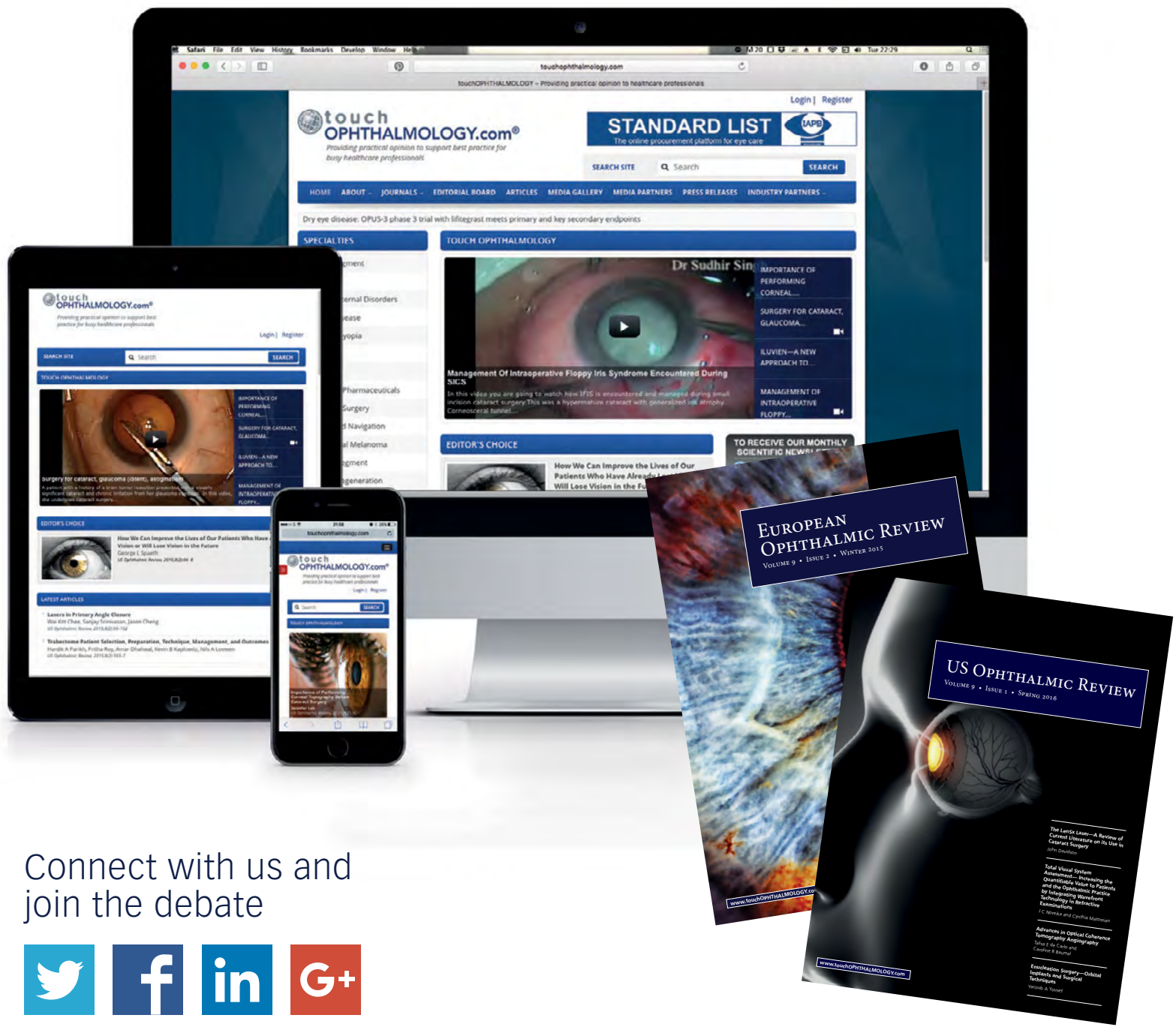

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WGC-2017 Update

Visit our website: www.worldglaucomacongress.org for the latest information.

Program

The Program committee came together at ARVO, in Seattle to finalize the WGC 2017 scientific program. “We are striving to build an exciting, informative and balanced program. We will also feature pseudoexfoliation prominently in the program to commemorate the 100th anniversary of its first description by the Finnish ophthalmologist Lindberg.”—*Jonathan Crowston*.

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Jonathan G. Crowston – Australia

Ringland Anderson Professor of Ophthalmology and Managing Director of the Centre for Eye Research Australia (CERA)

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Päivi Puska
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Anu Vaajanen
Eija Vesti

Program overview

Please find a tentative “Program at a Glance” below. The program at a glance will continue to be updated as topics, speakers and sessions are confirmed, so visit our site regularly to see the latest additions. If you do not want to miss an update, subscribe to the WGA newsletter.

	Wednesday, June 28	Thursday, June 29	Friday, June 30	Saturday, July 1
07:00	Reg. desk open	Reg. desk open	Reg. desk open	Reg. desk open
07:30		Sponsored Breakfast Symposiums, 07:30-08:30	Sponsored Breakfast Symposiums, 07:30-08:30	Sponsored Breakfast Symposiums, 07:30-08:30
07:45				
08:00				
08:15				
08:30		3 x Parallel Symposiums 08:30-10:00	3 x Parallel Symposiums 08:30-10:00	3 x Parallel Symposiums 08:30-10:00
08:45	Business Meetings			
09:00				
09:15				
09:30				
09:45	Symposium for faculty 09:45 - 10:45	30 minute break	30 minute break	30 minute break
10:00				
10:15				
10:30		Plenary Symposium 10:30-12:00	Plenary Symposium 10:30-12:00	Plenary Symposium (Grand Rounds) 10:30-11:30
10:45				
11:00	Society Symposiums 11:00-12:00			15 minute break
11:15				
11:30				
11:45				3 x Parallel Symposiums 11:45 - 13:15
12:00	Global Assembly 12:00-13:00	15 minute break	15 minute break	
12:15				
12:30		Sponsored Lunch Symposium 12:15-13:15	Sponsored Lunch Symposium 12:15-13:15	
12:45				
13:00	Society Symposiums 13:00-14:00			
13:15				
13:30				
13:45		45 minute break	45 minute break	
14:00	Sponsored Symposiums 14:00- 15:00	3 x Parallel Symposiums 14:00-15:00	3 x Parallel Symposiums 14:00-15:00	
14:15				
14:30				
14:45				
15:00				
15:15	30 minute break	30 minute break	30 minute break	
15:30	Opening Ceremony 15:30-16:30	8 Courses 15:30-16:30	8 Courses 15:30-16:30	
15:45				
16:00				
16:15				
16:30	15 minute break	15 minute break	15 minute break	
16:45	Presidential Symposium 16:45-18:15	8 Courses + Rapid Fire Sessions + Poster Walks 16:45-17:45	8 Courses + Rapid Fire Sessions + Poster Walks 16:45-17:45	
17:00				
17:15				
17:30				
17:45				
18:00		15 minute break	15 minute break	
18:15		Sponsored Afternoon Symposiums 18:00 - 19:00	Sponsored Afternoon Symposiums 18:00 - 19:00	
18:30	Welcome Reception 18:30-20:00			
18:45				
19:00				
19:15				
19:30				
19:45				
20:00				

Important dates

OCTOBER 10, 2016

Start abstract submission and congress & hotel registration

JANUARY 30, 2017

Deadline abstract submission

MARCH 31, 2017

Early registration deadline

MAY 15, 2017

Late registration deadline

JUNE 28–JULY 1, 2017

Congress dates

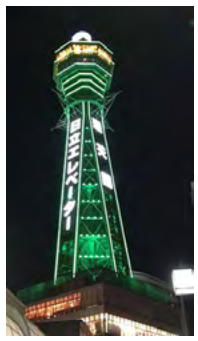
World Glaucoma Week 2016

World Glaucoma Week Committee members about what World Glaucoma Week means to them personally and why is it so important.

The Sixth World Glaucoma Week—celebrated from March 6 to 12, 2016—demonstrated an enthusiastic rally of thousands of volunteers for the awareness and prevention of avoidable vision loss and the suffering caused by this 'sneaky thief of sight'.

In addition to the **431 events** registered in www.worldglaucomaweek.org, many other events, videos, photos and posts have been uploaded throughout the social networks. **More than 3,000 likes on Facebook** (www.facebook.com/WGWeek) demonstrate the value of these awareness campaigns. Social networks move at their own rhythm crossing cultural and linguistic barriers without problems. However, if we hope to send clear and legitimate information to the community, it is crucial that the WGA and WGPA create educational materials about glaucoma using the current content discussed by experts and distribute it using the most contemporary strategies of communication. Another issue is that 'World' Glaucoma week needs to reach everyone. At this point in time, most of the communication by WGA is in English, which is the third most spoken language around the globe after Mandarin and Spanish.

The slogan and logo '**Beat Invisible Glaucoma**' shows the commitment of ophthalmologists, patients and the community around the world in reducing the burden of this disease. Our imagination is infinite and other logos will be adopted according to cultural or linguistic needs.



Like in previous years, WGW participants learned from past experiences to come up with new and creative initiatives. One of the most remarkable activities was **Light Up in Green for Glaucoma** in Japan, where the most famous buildings were illuminated in green during World Glaucoma Week and, in Europe, the Vision Van provided free eye exams and was followed by many people on Twitter. In Latin America, Glaucoma Colombia, a non-profit organization, held more than 50 events all over the country, including a distribution of flyers at a soccer game.

Glaucoma damage never stops and neither will we! As we look forward to **World Glaucoma Week 2017**, it is time to start thinking about how we can contribute and help to raising further glaucoma awareness in the best interests of our patients. We should take into account our three main objectives:

- increase the presence of WGW on social networks;
- create valid up-to-date material for sharing around the world;
- concentrate our effort on people who have an increased risk of suffering glaucoma and are unprivileged for eye care.

We hope you will join us in our initiative!

On behalf of the WGW committee,

Maria Carrasco, Mendoza, Argentina

THANK YOU!
World Glaucoma Week 2016 was a great succes world wide!

WORLD GLAUCOMA WEEK 2017
March 12–18, 2017

www.worldglaucomaweek.org

Your Special Attention For

Device-modified trabeculectomy for glaucoma
Wang X, Khan R, Coleman A
(abstract no. 65863)
Cochrane Database of Systematic Reviews 2015;12:CD010472

Candidate genes involved in the susceptibility of primary open angle glaucoma
Kumar S, Malik MA, Goswami S, Sihota R, Kaur J
(abstract no. 65867)
Gene 2016;577:119-131

Personalizing intraocular pressure: Target intraocular pressure in the setting of 24-hour intraocular pressure monitoring
Sit AJ, Pruet CM
(abstract no. 66216)
Asia-Pacific Journal of Ophthalmology (Philadelphia, PA) 2016;5:17-22

The endocannabinoid system as a therapeutic target in glaucoma
Cairns EA, Baldridge WH, Kelly ME
(abstract no. 66220)
Neural plasticity 2016; 2016: 9364091

Translamina cribrosa pressure difference as potential element in the pathogenesis of glaucomatous optic neuropathy
Jonas JB, Wang N, Yang D
(abstract no. 66289)
Asia-Pacific Journal of Ophthalmology (Philadelphia, PA) 2016;5:5-10

Targeting mitochondrial function to protect against vision loss
Chhetri J, Gueven N
(abstract no. 66577)
Expert Opinion on Therapeutic Targets 2016;20(6):721-736

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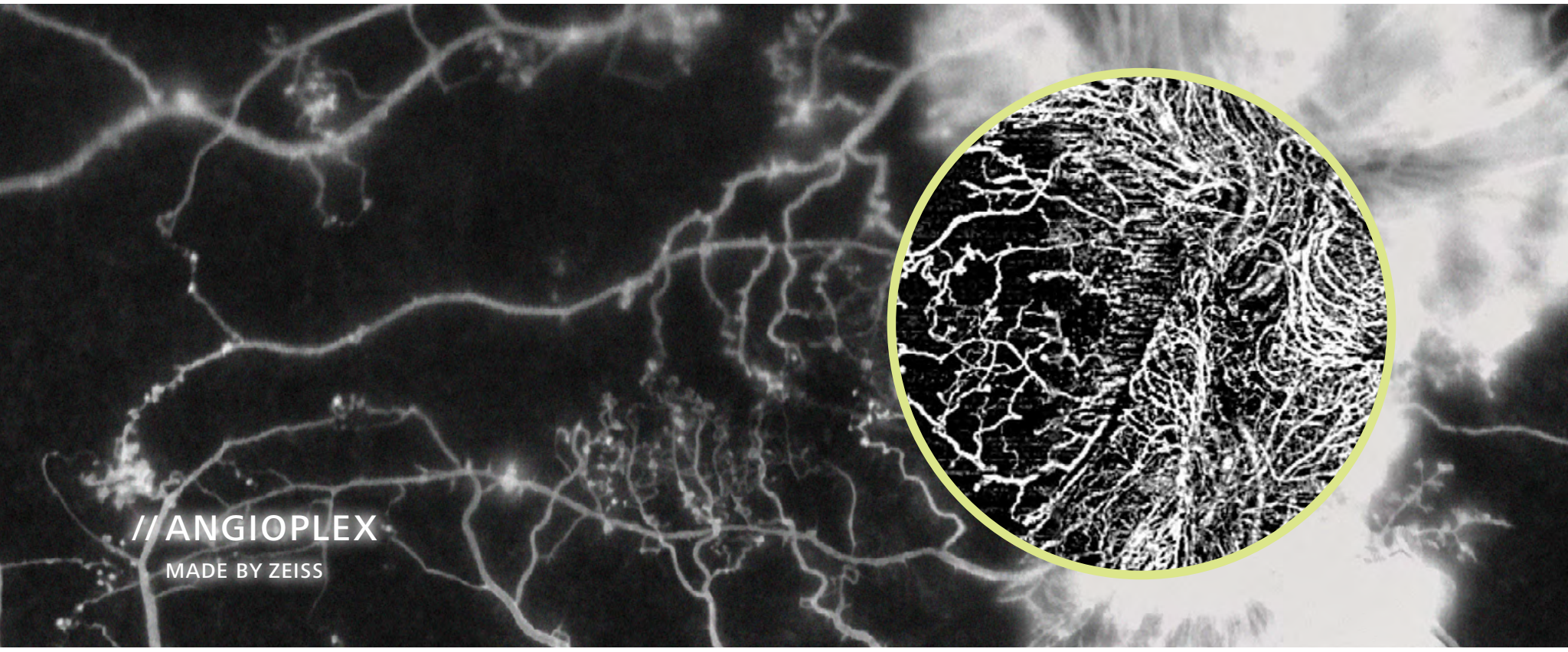

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Glaucoma Dialogue

In this section, a published manuscript of import and potential impact for discussion will be selected. It also provides a forum for manuscripts that some might judge to be controversial or where further discussion of the experimental models or data is warranted. Solicited comments of experts will be sent to the authors of a selected manuscript for a response. Both comments and responses will be published in IGR in their entirety. This should provide interesting information for our readership that is not otherwise available from the published manuscript.

Robert N. Weinreb, Chief Editor

66320 Fast circulation of cerebrospinal fluid: an alternative perspective on the protective role of high intracranial pressure in ocular hypertension, Wostyn P, De Groot V, Van Dam D, Audenaert K, Killer HE, De Deyn PP, Clinical and Experimental Optometry 2019;99:213-218

Comments

Comment by David Fleischman, Chapel Hill, NC, USA

The authors of this hypothesis have contributed considerable work in our understanding of cerebrospinal fluid dynamics and its relationship in glaucoma through many of their prior studies. Further, they have found many convincing pieces of evidence implicating a common pathophysiologic mechanism in Alzheimer's disease and glaucoma. This manuscript offers an interesting theory pertaining to the role of cerebrospinal fluid (CSF) in the pathogenesis of glaucoma. The authors begin by explaining that a reduced cerebrospinal fluid pressure (CSFP) has been associated with glaucoma, as described in retrospective and prospective studies. These same studies also found relatively increased CSFP compared to controls in patients with ocular hypertension (OHT). The concept of the translaminar pressure differential is introduced as the explanation for these findings, whereby a difference between the intraocular pressure (IOP) and CSFP is more important than each variable on its own. The translaminar pressure differential (TLPD) offers a

biomechanical explanation for glaucoma and OHT. The authors, however, point out many flaws with this theory. The CSF within the orbit may not be in direct communication with the rest of the neuraxis, and therefore precluding a transitive relationship in the lumbar opening pressure. Another excellent point questions the protective effect of an increased CSFP since the TLPD in OHT patients was in fact higher than controls in the initial retrospective studies by Berdahl and colleagues.

The authors then present their theory of a fast circulation of CSF as the possible protective factor for glaucoma. Higher CSFP is interpreted as an increased rate of production of CSF compared to clearance through the arachnoid villi. The adequate clearance of CSF is vital for the removal of neurotoxic waste products, such as β-amyloid (Aβ). They reference an animal model of optic neuropathy induced by CSF segregation of an optic nerve (Jaggi GP, *et al*., Br J Ophthalmol 2010). The authors suggest that glaucoma is considered an imbalance between production and clearance of neurotoxins, much like Alzheimer's disease. They present evidence that there is an IOP-sensitive increase in Aβ in glaucoma, and this has been found in the retinal ganglion cells in animal models of glaucoma. As Aβ is an integral component of the senile plaques found in Alzheimer's disease, the authors parlay this into evidence of a pathophysiologic association and mechanistic similarity between the two disorders. The authors conclude this discussion by discussing the overlap of Aβ clearance pathways between the brain and the optic nerve. They briefly mention the plausibility of toxin migration by fluid flow from the vitreous and optic nerve interstitial fluids.

The increased frequency of glaucoma in patients with Alzheimer's disease (AD), and the absence of any cases of ocular hypertension in AD patients implies a susceptibility to IOP-mediated damage, which the authors believe to be due to the reduced rate of metabolite clearance via the CSF.

In summary, the authors present an intriguing alternate hypothesis for the role of cerebrospinal fluid in the pathogenesis of glaucoma, and provide several examples in the pathology of AD to assist their theory. Despite the excellent work by the authors in describing orbital CSF dynamics, there are still many holes in our understanding of CSF movement within the perioptic subarachnoid space. Even more complicated is the relationship of perioptic subarachnoid space pressure to the pressure in the remainder of the neuraxis. This precludes any quantitative discussion pertaining to the TLPD and its role in glaucoma pathogenesis. Similarly, CSFP differences of a few millimeters of mercury, which may or may not be clinically relevant, are difficult to translate over to CSF clearance – in this case the inference that the marginally elevated CSFP in the OHT patients is an indication of fast CSF transport.

That being said, there is as yet insufficient evidence to prove and disprove these theories. However, the theories posed here are not entirely difficult to study – and I look forward to following-up on the work of these investigators. The authors are congratulated for formulating a thoughtful and potentially important theory in the pathogenesis of glaucoma that mirrors the pathogenic mechanisms of Alzheimer's disease.

Comment by Jost Jonas, Heidelberg, Germany

As an anatomical fact, the optic nerve as brain fascicle is surrounded by the optic nerve meninges and imbedded into the cerebrospinal fluid (CSF) with its pressure. Based on this fact, the pressure difference in the lamina cribrosa (as the most likely site of glaucomatous optic nerve fiber damage) is the difference of intraocular pressure minus the tissue pressure of the optic nerve and the orbital CSF pressure. It led to the hypothesis that patients with glaucoma and normal IOP may have a low orbital CSF pressure leading to an increased trans-lamina cribrosa pressure difference. Subsequent clinical and experimental studies suggested that an abnormally low CSF pressure may indeed be associated with glaucomatous optic nerve damage. As a corollary, studies suggested that increased CSF pressure may protect the optic nerve against the development of glaucomatous damage in eyes with ocular hypertension. As a different aspect of the role the CSF pressure may play for the development of glaucomatous optic nerve damage, Peter Wostyn, Hans-Peter Killer and their team proposed that the potentially protective effect of higher CSF pressure could be due to a faster cerebrospinal CSF production leading to increased fluid turnover with enhanced removal of potentially neurotoxic waste products, in particular in the optic nerve CSF space. It could lead to a faster removal of ß-amyloid which accumulates in glaucoma as well as in Alzheimer's disease. This model also refers to the optic nerve compartment syndrome as described by Killer and colleagues, If confirmed, procedures to increase the CSF flow could be helpful against glaucomatous optic neuropathy.

Response by Peter Wostyn, on behalf of the original authors

We would like to acknowledge our appreciation for Prof. Weinreb and the IGR editorial team for paying special attention to our manuscript and for Prof. Fleischman and Prof. Jonas for their thoughtful and generous comments.

In this article, we present a hypothesis according to which the higher cerebrospinal fluid (CSF) pressure reported in ocular hypertension (OHT) patients could protect against glaucoma through its association with a higher rate of CSF formation leading to increased CSF turnover with enhanced removal of potentially neurotoxic waste products that accumulate in the optic nerve. We further postulate that glaucoma may share common ground with Alzheimer's disease, and argue that glaucoma, just like Alzheimer's disease, may occur when there is an imbalance

between production and clearance of neurotoxins, including β-amyloid. Although much more work is required to substantiate this view, further elucidation of a common pathophysiological process linking glaucoma and Alzheimer's disease might offer new perspectives for the development of novel diagnostic and therapeutic strategies for both disorders. We therefore wish to encourage further studies and research in this area.

This personal view suggests that the protective role of high intracranial pressure (ICP) in OHT is not exclusively of a biomechanical nature (lower pressure difference across the lamina cribrosa), but also of a biochemical one (increased neurotoxin clearance). We fully agree with the reviewers that many important issues remain to be resolved before these biomechanical and biochemical theories can ultimately be confirmed or refuted. Killer and Pircher[1] recently challenged the concept of the trans-lamina cribrosa pressure difference (TLCPD). One of their criticisms was that the retrolaminar pressure is measured during lumbar puncture at a site more than 100 cm away from the lamina cribrosa.[1] Indeed, given that it is not possible to measure the retrolaminar pressure clinically, the clinical retrospective[2,3] and prospective[4] studies of CSF pressure in patients with glaucoma took the lumbar CSF pressure measurement as surrogate for pressure in the orbital CSF space. However, from a biomechanical perspective, it must be acknowledged that it is the optic nerve subarachnoid space pressure (ONSP), and not the ICP, that determines the TLCPD since the ONSP represents the true counter-pressure against the intraocular pressure (IOP) across the lamina cribrosa. Given that the imbalance between IOP and ICP may reflect the imbalance between production and clearance of neurotoxins, our group recently presented an alternative viewpoint according to which the TLCPD, calculated as the difference of IOP minus ICP, may be considered as an index for neurotoxic burden in the anterior part of the optic nerve.[5]

All these different aspects in the pathophysiology of glaucoma render primary open-angle glaucoma and normal-tension glaucoma rather a syndrome than a disease and it seems that the time has come to pull together these different aspects and to start a collaborate study including all the groups that work on the same syndrome.

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2. Berdahl JP, Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. Ophthalmology 2008;115:763-768.
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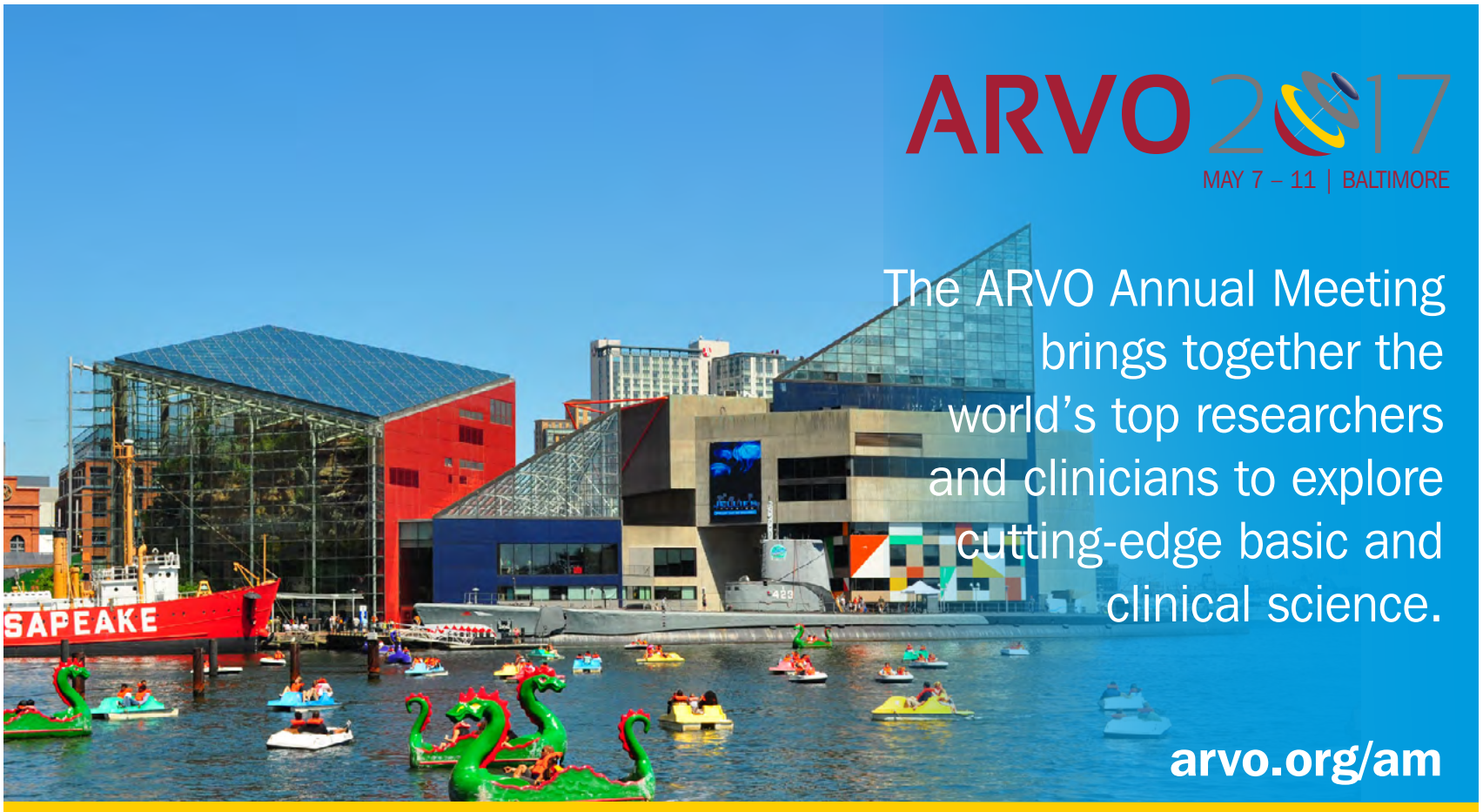

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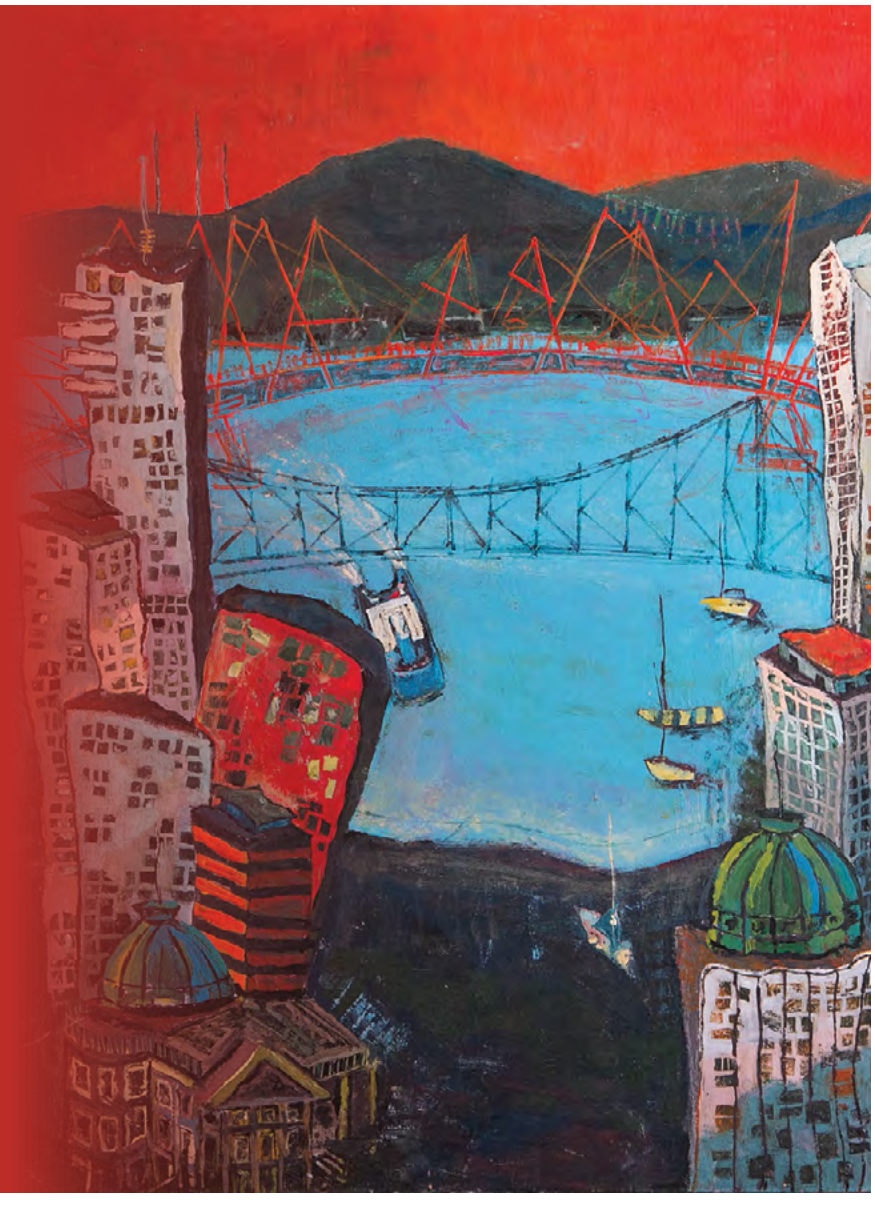

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Meeting Highlights

Top-Three of the XIV Symposium of the Bulgarian Glaucoma Society

Sofia, Bulgaria, March 18–19, 2016

Nataliya Petkova, Sofia, Bulgaria

Congenital glaucoma: pathogenesis, diagnosis, treatment
Pathogenesis ,diagnosis and treatment of primary and secondary congenital glaucoma were reviewed. Congenital glaucoma surgery is a pivotal step in the life of a glaucoma child. Retrospective analyses show equal efficacy of goniotomy and trabeculotomy in many studies, but often more than one or two interventions are needed and the success rate is still unsatisfactory. 360-degree trabeculotomy allows circular visual control of the position of the catheter tip and misdirection can be avoided. Recent own experience with this technique has shown superiority over conventional trabeculotomy and goniotomy. Treatment of congenital glaucoma can be improved by early diagnosis, experienced surgery and consistent follow-up to achieve and preserve lifelong visual functions. (Franz Grehn, Würzburg and Mainz)

OCT update
Identification of structural glaucomatous damage and progression overtime in OCT images is very useful for glaucoma diagnosis and follow-up. During the last 15 years, OCT has evolved significantly and it is now present in most ophthalmic facilities. The evolution of the technique through optical domain, spectral domain, en-face and swept, their advantages, disadvantages and usefulness were described. The information contained in the different print outs and algorithms were reviewed. A methodical interpretation of OCT results were described and recommended. Practical cases were used to explain the different instruments, algorithms and the interpretation of the results. (Alfonso Antón, Barcelona, Spain)

Exfoliation syndrome / Exfoliation Glaucoma: Lessons from the Thessaloniki Eye Study
The Thessaloniki Eye Study (TES) assessed the prevalence of (pseudoexfoliation) PEX and pseudoexfoliative glaucoma (PEXG) and reported on PEX and PEXG characteristics and risk factors. The association of PEX with the level of intraocular pressure (IOP), the degree of optic disc damage and the presence of systemic diseases including cardiovascular disease and the association of IOP with PEX location were specifically studied. In addition, the TES showed that there is increased likelihood of glaucoma at the same screening intraocular pressure in subjects with PEX. Finally, risk factors for PEXG were studied and presented, as well as associations with LOXL1 polymorphisms. (F. Topouzis, Thessaloniki, Greece)

Top-Five of the 8th International Congress on Glaucoma Surgery

Muscat, Oman, February 17–20, 2016

Tanuj Dada, New Delhi, India

The Thom J. Zimmerman Memorial Lecture
Dr George L. Spaeth gave a thought-provoking talk on 'Glaucoma surgery from the point of view that matters – the patient' and emphasized the prime importance of understanding emotional and psychological needs of individual patients and their personal perspective on glaucoma therapy as the guiding force for surgical decision making rather than the target IOP or efficacy of new surgical techniques. (Dr George L. Spaeth, Philadelphia, USA)

The Clive Migdal Appreciation Lecture
Dr Andre Mermoud gave a lecture titled 'Transgress to Progress' introducing a new 'Eye Watch System' to reduce complications of Tube surgery. This is a magnetic system which is implanted between the anterior chamber and the seton tube and can regulate the aqueous flow passing through with the help of an external magnet, and thereby reduce the risk of post-operative hypotony. (Dr Andre Mermoud, Lausanne, Switzerland)

The Doug Johnson Memorial Lecture
Michael Coote spoke on the process of changing the 'goal posts' for interrogating the mechanisms that underpin successful glaucoma surgery. New methods of testing and manipulating the porosity of subconjunctival tissue are the key to designing innovative predictable and more successful glaucoma surgery strategies. (Michael Coote, Melbourne, Australia)

Bioinformatic and chronological analysis of trabeculectomy by utilizing comprehensive functional gene association and cellular event studies: a focus on fibrotic scar formation
Muneeb A. Faiq *et al.* provided a comprehensive event analysis (genetic, epigenetic and cellular) based on the understanding of the process of postsurgical scar formation in trabeculectomy. Two hundred nine genes, 1764 interactions, 24 biochemical processes and 31 cellular functions involved in fibrotic scar formation were identified. Statistical analysis revealed 19 genes that can be targeted to prevent scar formation to improve surgical outcomes. (Muneeb A. Faiq, New Delhi, India)

Trabeculectomy with or without an AC maintainer
This RCT compared the effect of using an anterior chamber maintainer during trabeculectomy on intraocular pressure (IOP) and corneal endothelial cell density (ECD), in a follow-up period of one year. Using an AC maintainer was associated with a greater IOP reduction and less decrease in ECD, giving an additional safety while performing trabeculectomy. (Marilita M. Moschos, Athens, Greece)

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Industry News

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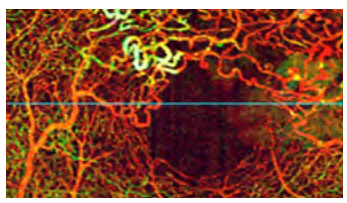

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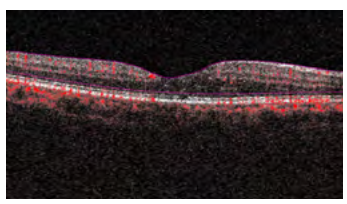

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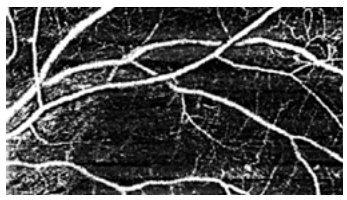

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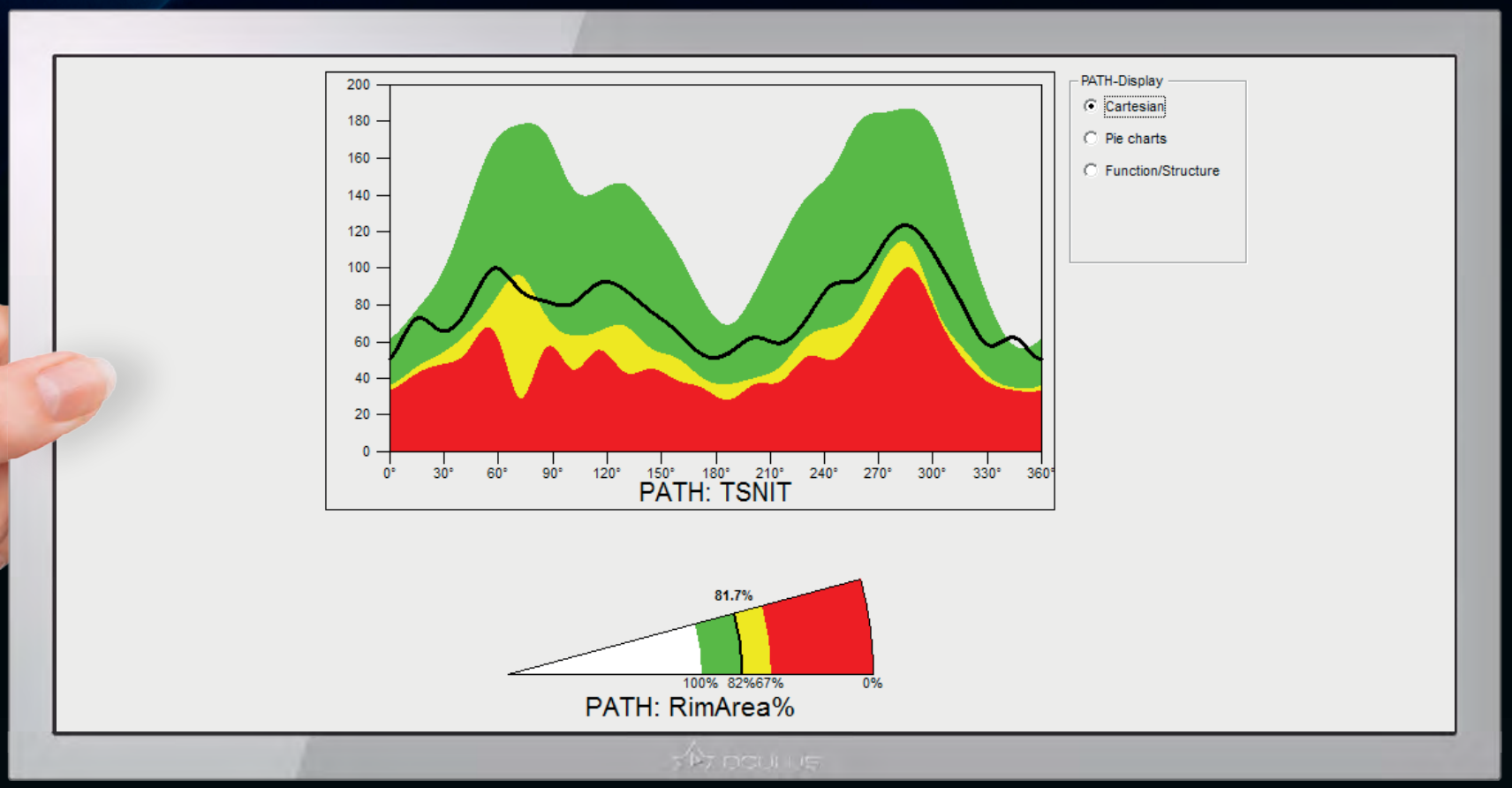

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Editor's Selection

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 Screening

Frequency-Doubling Perimetry for Glaucoma Screening

Comment by Chris Johnson, Iowa City, IA , USA

66389 Evaluation of Frequency-Doubling Technology Perimetry as a Means of Screening for Glaucoma and Other Eye Diseases Using the National Health and Nutrition Examination Survey, Boland MV, Gupta P, Ko F, Zhao D, Guallar E, Friedman DS, JAMA ophthalmology 2016; 134: 57-62

In this publication, the authors evaluated results from 5,746 participants in the National Health and Nutrition Examination Study (NHANES) who had optic disc photographs taken and had performed the N30-5 visual field screening test for frequency doubling technology (FDT) perimetry. The purpose of this assessment was to determine the potential for optic disc photography or FDT perimetry to be used as a population screening test for glaucoma and other ocular and neurologic diseases. Both of these methods have been used previously as diagnostic procedures for ocular and neurologic diseases and for population based screening studies. The optic disc photographs were evaluated by several glaucoma specialists. The authors found that neither procedure had the sensitivity or specificity that was sufficient to justify its use as a rapid and efficient population based screening procedure. Using a best case (benefit of the doubt) approach for FDT, the authors reported a sensitivity of 80% and a specificity of 83%. Somewhat

poorer findings were achieved for optic disc photograph determinations. The authors nicely distinguish between screening (use of a single test) and case finding (more than a single test or a combination of several different tests). Additionally, **the authors also indicate that a single diagnostic test procedure does not provide sufficient information to warrant its use as a population based screening procedure (combinations of test results and additional clinical information is needed), and that a meaningful proportion of the participants were not able to complete the FDT test procedure.**

To be effective, more attention needs to be directed towards the process of vision screening per se, rather than applying clinically based procedures that may not be appropriate for large scale population screening

In addition to these findings, I believe that there are several other factors that are worthy of consideration: (1) Most screening procedures are based on test procedures that have been developed, refined and validated through careful clinical evaluation studies. There are large differences in clinic-based and population-based screening procedures. Development of population screening methods has not been conducted through evaluation of the general population. (2) Screening procedures are performed in a variety of settings that can have different lighting conditions, distractions and other complications that are less frequent in clinical settings. (3) Interpretation of screening procedures by highly-trained specialists is not cost-effective and difficult to maintain. Immediate automatic electronic evaluation of test results would be more beneficial. (5) Glaucoma and other ocular and neurologic diseases are complex and require the accumulation, interpretation and consolidation of many different diagnostic and clinical assessment procedures. To be effective, more attention needs to be directed towards the process of vision screening per se, rather than applying clinically based procedures that may not be appropriate for large scale population screening. Given the large amount of undetected glaucoma and other diseases affecting the visual pathways throughout the world, vision scientists and clinicians should be encouraged to pursue these issues.

Anatomical Structures

Posterior Sclera

Comment by Crawford Downs, Birmingham, AL, USA

66616 Three-Dimensional Strains in Human Posterior Sclera Using Ultrasound Speckle Tracking, Pavlatos E, Perez BC, Morris HJ, Chen H, Palko JR, Pan X, Weber PA, Hart RT, Liu J, Journal of Biomechanical Engineering 2016; 138(2):021015

Scleral biomechanics likely plays an important role in the development and progression of glaucoma, but the contribution of scleral structural stiffness to the disease is not well understood. Experimental and numerical studies indicate that the peripapillary sclera is influential in determining ONH biomechanics because it defines the mechanical boundary condition for the lamina cribrosa at the scleral canal. **Pavlatos, Liu, and colleagues report measurements of 3D peripapillary scleral strains in the nasal quadrant of intact human donor eyes.** They measured through-thickness scleral strain in nine human eyes from donors ranging from 24-72 years old using their novel scanning ultrasound speckle tracking method coupled with posterior globe inflation at pressures from 10 to 19 mmHg. Key findings were that: (1) tensile strain was primarily oriented in-plane with the sclera and perpendicular to the scleral canal, and strains were much lower in the circumpapillary direction, which agrees with previous findings showing that scleral canal expansion is resisted by the circumpapillary ring of collagen fibrils in the peripapillary sclera; (2) through-thickness compressive strains and in-plane tensile strains were similar in magnitude, indicating that the sclera is nearly incompressible and validating a key assumption used in many biomechanical models; (3) there are substantial scleral strain concentrations associated with the penetrating vasculature and Circle of Zinn-Haller in the sclera. Increased scleral strains associated with blood vessels is the most interesting finding of the study, as individual variations in vascular morphology and the vessels' proximity to the scleral canal have the potential to drive large variations in laminar biomechanics. However, the study used human donor eyes in which these vessels were not pressurized with blood, so additional in vivo validation of this interesting result will be required. Testing of additional quadrants in more eyes will provide additional insight into quadrant-dependent and age-related changes in scleral strain.

Lamina Cribrosa and Disc Hemorrhage

Comment by Franz Grehn, Wurzburg, Germany

65998 Lamina cribrosa defects in eyes with glaucomatous disc haemorrhage, Kim YK, Park KH, Acta Ophthalmologica 2015; Nov 2 (e-pub ahead ofprint)

Recent developments in OCT technology such as SS-OCT (swept-source optic coherence tomography) and enhanced depth imaging provide more information on morphology of the various changes of the lamina cribrosa (LC) in glaucomatous eyes during the process of progressive damage. Optic disc haemorrhages (ODH) are typical in glaucoma, in particular in normal tension glaucoma, as frequently present in the authors' country, South Korea.

This paper describes the spatial correlation of LC defects, retinal nerve fiber layer (RNLF) defects and optic disc haemorrhages (ODH). SS-OCT was used for quantifying LC defects. ODH were documented by stereo photography, and RNFL were visualized by SD-OCT. Photographs were electronically superimposed and adjusted to the LC images which allowed to investigate the spatial correlation of DH to LC and RNFL defects.

The two authors were masked to previous information and a consensus was needed to define presence/absence and clock hour (in 1/4 hour steps) position of ODH, RNFL and LC defect. The minimal size of a LC defect was defined as > 100 µm diameter and > 30 µm depth.

Two thirds of disc haemorrhages were infero-temporal, less than 1/3 supero-temporal, a few infero-nasal. Eighty percent of eyes with ODH showed LC defect versus 40% of eyes without ODH. Two thirds (50/75) of the LC defects were located in the infero-nasal quadrant of the optic disc. Eighty-one percent of the eyes with ODH showed a spatial correlation to the RNFL defect, and 60% of the eyes with ODH showed a spatial correlation to the LC defect.

The paper shows that twice as many focal LC defects exist in eyes with ODH than in eyes without ODH. **There was a high spatial correlation between ODH and RNFL defects and a clear spatial correlation between ODH and LC defects.**

This paper also discussed whether DH is a cause or a consequence of LC defects or RNFL defects. If the focal LC defect and DH are spatially correlated, the LC defect can directly trigger ODH by mechanical stress to the capillaries. If focal defect and DH are *not* correlated the following sequence of events could be assumed: (1) LC focal defect; (2) RNFL defect; (3) ODH.

However, we have to consider that the appearance of ODH may follow a dynamic process of increased distensibility of the weakened LC beams and this process cannot be visualized by a cross sectional study. In so far ODH could also be an event before the LC defect becomes visible while the mechanic stress of the LC beams has been already active (such as distensibility, shear stress, etc.) and the build-up of a visible LC defect (as seen as a hole) may only follow during the

subsequent period. This sequence would then explain why some LC defects are not correlated to the present event of ODH, as they date back to an earlier, previously occurring process at a different location while the ODH is a sign of a presently ongoing damage.

In summary, this paper adds very valuable information on the spatial correlation of DH, RNFL defects and LC defects in glaucoma and allows more insight into the mechanism of damage of the RNFL at the optic disc.

Lamina Cribrosa Mechanics in an Animal Model

Comment by Andrew Tatham, Edinburgh, UK

65845 Phase-contrast Micro-computed Tomography Measurements of the Intraocular Pressure-induced Deformation of the Porcine Lamina Cribrosa, Coudrillier B, Geraldes D, Vo N, Atwood R, Reinhard C, Campbell I, Raji Y, Albon J, Abel R, Ethier R, IEEE Transactions on Medical Imaging 2016;35(4):988-999

Intraocular pressure (IOP)-induced deformation of the lamina cribrosa (LC) is believed to be an important mechanism of retinal ganglion cell axonal damage in glaucoma. It is possible to obtain *in-vivo* images of the LC using enhanced depth- or swept-source-OCT, however, the resolution of OCT is limited and it is not always possible to visualize the entire LC due to problems of tissue shadowing and limited light penetration.

X-ray-based imaging provides an alternative method of assessing the LC in the laboratory but also has limitations, particularly as neural tissue and LC collagenous beams have similar X-ray attenuation properties. Researchers have attempted to better differentiate collagen and neural tissue using tissue dyes but application of dyes affects stiffness of the tissue, introducing a potentially important confounding factor in studies of optic nerve head biomechanics.

This paper describes the first use of new imaging technique, known as phase contrast micro-computed tomography (PC µCT), to image the LC. The method allows imaging of soft tissues without the need for contrast agents by taking advantage of the different refractive indices of adjacent tissues, even those of similar density.

The authors demonstrate that PC µCT can be used to image the fine structures of the LC and evaluate structural changes that occur in response to IOP elevation. The study involved mounting porcine eyes in a pressure chamber, with pressure adjusted between 6 mmHg and 37 mmHg. Elevated pressure was shown to result in posterior displacement of the sclera and LC, compressive deformation through the thickness of the LC and sclera, and tensile deformation along the transverse direction of the anterior LC. Certain regions of the LC were subject to considerably more compressive strain than others, being largest in the anterior central LC.

Although the study included only a small number of eyes, and the technique is not suitable *in vivo*, the study shows that PC µCT has the potential to further understanding of optic nerve head biomechanics.

Rim Area Defects

Comment by Tae-Woo Kim, Bundang-gu, Seongnam, Korea

66267 Rate and Pattern of Rim Area Loss in Healthy and Progressing Glaucoma Eyes, Hammel N, Belghith A, Bowd C, Medeiros FA, Sharpsten L, Mendoza N, Tatham AJ, Khachatryan N, Liebmann JM, Girkin CA, Weinreb RN, Zangwill LM, Ophthalmology 2016;123(4):760-770

Glaucomatous optic neuropathy is characterized by the progressive loss of retinal nerve fibers and neuroretinal rim. However, such loss occurs in healthy eyes as well.

Hammel *et al.* characterize the rate and pattern of age-related and glaucomatous neuroretinal rim area changes in subjects of African and European descent who were followed-up for 5.0 years (interquartile range, 2.0-7.4 years) using confocal scanning laser ophthalmoscopy. They found that the **mean rate of global rim area loss was 3.7 times faster (-10.2×10^{-3} vs. -2.8×10^{-3}mm^2/year), and the mean rate of global percentage rim area loss was 5.4 times faster in progressing glaucoma eyes compared to healthy eyes (-1.1% vs. -0.2%/year),** but considerable overlap existed between the two groups; 66% of progressing glaucoma eyes had a rate of rim area change faster than the fastest 5% of healthy eyes, and 38% had a rate of change faster than the fastest 1% of healthy eyes. Rates of change in healthy eyes of patients of African and European descent were very similar (−2.1×10^{-3} and −2.3×10^{-3} mm^2/year, and −0.2% and −0.2%/year).

> Since progressive rim loss is a universal finding with aging, it is important to differentiate glaucomatous rim loss from natural rim loss associated with aging

The rate of rim area loss reported in this study is largely similar with that found in the Ocular Hypertension Treatment Study. In the Ocular Hypertension Treatment Study,[1] mean rates of rim area loss in eyes in which POAG developed and in in which it did not were −13.1×10^{-3} and −2.6×10^{-3} mm^2/year, respectively (or −0.89% and −0.17%/year, respectively).

Since progressive rim loss is a universal finding with aging, it is important to differentiate glaucomatous rim loss from natural rim loss associated with aging. The reported rate in healthy subjects can constitute a reference database of the rate of rim area change which can be used for distinguishing between glaucomatous and age-related rim loss.

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Peripapillary Atrophy and Glaucoma Progression

Comment by Jost Jonas, Heidelberg, Germany

66313 Microstructure of Peripapillary Atrophy and Subsequent Visual Field Progression in Treated Primary Open-Angle Glaucoma, Yamada H, Akagi T, Nakanishi H, Ikeda HO, Kimura Y, Suda K, Hasegawa T, Yoshikawa M, Iida Y, Yoshimura N, Ophthalmology 2016;123(3):542-551

According to recent histological and clinical studies, the parapapillary region can be divided into a peripheral alpha zone characterized by the presence of Bruch's membrane and presence of irregularly structured retinal pigment epithelium (RPE) (appearing upon ophthalmoscopy as irregular hyperpigmentation and hypopigmentation); a beta zone, characterized by the presence of Bruch's membrane and absence of RPE (appearing upon ophthalmoscopy as whitish area with visible large choroidal vessels (the choriocapillaris is closed for most parts of beta zone) and visible sclera); and a gamma zone characterized by the absence of Bruch's membrane (and thus by the absence of RPE and choriocapillaris).

Differentiation between beta and gamma zone may increase the diagnostic value of assessing the parapapillary region in glaucoma

In highly myopic eyes, gamma zone can further be subdivided into a central delta zone covering the region between the optic disc border (defined by the peripapillary ring as the continuation of the optic nerve pia mater and the border tissue of Elschnig and Jacoby) and the merging line of the optic nerve dura mater with the posterior sclera. Delta zone is the equivalent for the elongated and thinned peripapillary scleral flange in highly myopic eyes which is the bridge between the posterior sclera and the lamina cribrosa and which forms the end of the orbital cerebrospinal fluid space. Yamada and colleagues examined in their retrospective cohort study the relationship between the microstructure of the so called parapapillary beta zone and subsequent visual

field progression in 129 patients with primary open-angle glaucoma. They divided their beta zone into a beta zone with Bruch's membrane (i.e. the beta zone as described above) and a beta zone without Bruch's membrane (what is the gamma zone as described above).

In a follow-up of at least two years, eyes with beta zone (with Bruch's membrane) as compared to eyes with gamma zone showed a significantly higher rate of glaucoma progression. In contrast, gamma zone was associated with a slower progression of glaucomatous visual field defects. These results are in agreement with previous histological and clinical studies showing that beta zone is associated with glaucoma (and gamma zone with high axial myopia). Differentiation between beta and gamma zone may increase the diagnostic value of assessing the parapapillary region in glaucoma.

Basic Science

In vitro Trabecular Meshwork Model

Comment by Nils Loewen and Yalong Dang, Pittsburgh, PA, USA

65875 Bioengineered glaucomatous 3D human trabecular meshwork as an in vitro disease model, Torrejon KY, Papke EL, Halman JR, Stolwijk J, Dautriche CN, Bergkvist M, Danias J, Sharfstein ST, Xie Y, Biotechnology and bioengineering 2016;113(6):1357-1368

The trabecular meshwork (TM) is guarding the intake of the outflow system of the eye and traditionally thought of as the primary cause of increased outflow resistance in primary and secondary open angle glaucomas.[1] Establishment of a *TM-based, ex-vivo* model to study outflow and screen drugs has great clinical and experimental value. Based on their previous study,[2] **Torrejon et al. created a bioengineered 3D human TM model which showed behavior similar to human steroid induced glaucoma after several days of treatment with prednisolone acetate.**[3] The expression of myocilin, deposition of extracellular matrix protein, transcellular electrical resistance and cytokines increased, while the expression of MMPs, phagocytic activities of TM cells and outflow facility decreased when compared with untreated controls. To further validate this model, a ROCK inhibitor (Y27632) and an actin disruptor (Lat-B) were also used. This reversed the steroid effect suggesting that this bioengineered 3D TM model can be utilized as a platform to study the pathophysiology of steroid induced glaucoma.

approximately 50% of the outflow resistance is downstream of the TM and similar at different severity stages of glaucoma following ab interno trabeculectomy

Overall, this study is very interesting and will provide a much needed *in-vitro* model to study the complex TM responses without the necessity of an *in-vivo* or *ex-vivo* model. It would be interesting to see if the behavior of this model remains similar when TM cells are nondividing to better reflect their normal *in-situ* behavior.

While this model will help to investigate the TM, the pathogenesis of open-angle glaucoma is still incompletely understood. New evidence indicates that approximately 50% of the outflow resistance is downstream of the TM and similar at different severity stages of glaucoma following ab interno trabeculectomy.[4] This resistance remains even after the destruction of valve-like structures of the collector openings[5,6] and points towards an unidentified outflow resistance in the collector channels or other parts of the aqueous humor drainage system. Organotypical *ex-vivo* models[7,8] might remain the only simplification for now to avoid costly and complex *in-vivo* studies.

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Neurodegeneration and Neuroprotection

Comment by Francesca Cordeiro, London, UK

65944 Tackling Glaucoma from within the Brain: An Unfortunate Interplay of BDNF and TrkB, Dekeyster E, Geeraerts E, Buyens T, Van den Haute C, Baekelandt V, De Groef L, Salinas-Navarro M, Moons L, PLoS ONE 2015; 10: e0142067

One of the most established mechanisms in glaucoma is the induction of retinal ganglion cell (RGC) apoptosis through disruption of retrograde delivery of trophic support - the neurotrophin deprivation hypothesis. However, intraocular and local administration of exogenous neurotrophins to the glaucomatous retina have been met with varying success. The authors speculated that as neuronal response depends where in the pathway signaling is initiated (*i.e.*, in the cell body, in the axon terminals, or on dendrites), delaying or preventing RGC death could be better achieved by interfering with their target areas.

In this new study, Dekeyster *et al.* test the neurotrophin deprivation hypothesis with an alternative approach. **Using rodent models of optic nerve crush and OHT, they assess the induction of retrograde brain-derived neurotrophic factor (BDNF) in the superior colliculus using a viral vector-mediated delivery system. Interestingly, this route was not found to be superior to ocular delivery, with no enhanced display of neuroprotection.**

The study was of a high-quality design, with a detailed temporal characterization of RGC degeneration and expression patterns of BDNF and its receptor TrkB in two mouse models of glaucoma. Intracollicular BDNF overexperssion was definitely achieved, yet no real neuroprotective effect was seen.

The authors carefully consider potential underlying causes for this failure, and put forward reduced neurotrophin responsiveness and impaired retrograde transport in response to BDNF overexpression. It should, however, also be considered that viral vector-mediated overexpression of BDNF in the superior colliculus, whilst being a very elegant apporach, may lead to off-target transduction effects involving different superior colliculus layers, cell types, and BDNF isoforms. Nevertheless, this study advances our knowledge about the pivotal role of neurotrophin signalling in the retina and the brain in glaucoma pathogenesis, and draws attention to the complexity of restoring neurotrophic signalling as a future neuroprotective strategy.

Wound Healing Modulation


Comment by Ingeborg Stalmans and Alix Somers, Leuven, Belgium

66257 Inhibition by a retinoic acid receptor γ agonist of extracellular matrix remodeling mediated by human Tenon fibroblasts, Liu Y, Kimura K, Orita T, Suzuki K, Teranishi S, Mori T, Sonoda KH, Molecular Vision 2015; 21: 1368-1377

Filtration surgery remains the gold standard for the treatment of glaucoma in individuals whose intra-ocular pressure (IOP) is uncontrolled by medication or laser treatment. Excessive subconjunctival scar formation, due to excessive synthesis of new extracellular matrix (ECM) and tissue contraction, may interfere with the long term success of this surgery by obstructing the aqueous outflow with subsequent IOP elevation and bleb failure.

Nowadays the use of antifibrotic agents such as mitomycin C and 5- fluorouracil are encountered in the daily practice to reduce the risk of excessive postoperative fibrosis, but with the known potential severe side effects.

The wound healing response is mediated by matrix metalloproteinases (MMP's), inflammatory mediators and growth factors including the cytokine transforming growth factor (TGF-β), a key mediator.

Retinoic acids, derivates of vitamin A, have several effects on eye development, immunity and tissue repair. The retinoic acid receptor γ agonist R667 in particular, could be a promising alternative antifibrotic stragey.

Liu *et al.* have shown that R667 inhibited TGF-β1-induced collagen gel contraction mediated by human Tenon fibroblasts (HTFs) in a concentration –and time-dependent manner. It inhibited the TGF-β1 induced release of MMP-1 and MMP-3 by HTFs as well as the phosphorylation of FAK, a tyrosine kinase protein that plays an important role in focal adhesions and cell contractility. The production of ECM proteins such as fibronectin and type I collagen was attenuated by R667.

The IOP after experimental glaucoma filtration surgery in rat models was also reduced in the R667 group compared with those that received PBS vehicle. The anti-fibrotic effects may contribute to this finding. Unfortunately, the IOP was only measured up to two weeks after surgery.

This is a valuable and interesting study that opens up for new strategies to inhibit scar formation after glaucoma filtration surgery.

Nevertheless, studies for comparison of surgical outcomes for animals treated with mitomycin C and R667 are needed for further evaluation. Future studies are required to asses the pharmacokinetics and toxicity of ocular administration of this drug. Other limitations of this study are the small sample size (five rat models per treatment group) and the short postoperative follow-up period (two weeks).

Clinical Examination Methods

24-hour IOP and Visual Field Changes

Comment by David Garway-Heath, London, UK and the International Glaucoma Panel*

66229 Visual Field Change and 24-Hour IOP-Related Profile with a Contact Lens Sensor in Treated Glaucoma Patients, De Moraes CG, Jasien JV, Simon-Zoula S, Liebmann JM, Ritch R, Ophthalmology 2015; 0:

Intraocular pressure (IOP) remains the only modifiable risk factor in glaucoma management, highlighting the importance of obtaining accurate IOP measurements in the diagnosis and management of glaucoma patients. A single office IOP may not reflect the true IOP load or range of IOP variation or fluctuations over time. Goldmann applanation tonometry (GAT) remains the reference standard for IOP measurement. However, 24-hour monitoring using GAT is not feasible in routine clinical practice. This has prompted clinicians to search for newer devices which may allow practicable and continuous IOP monitoring in order to supplement, or provide an alternative to, GAT measurements.

Several randomized controlled trials lend credence to the association between mean IOP or IOP fluctuations and visual field (VF) progression, which would support the notion of an association between 24 hour IOP profiling and VF progression in glaucoma patients. The contact lens sensor (CLS, Triggerfish, Sensimed, Sensimed AG, Lausanne, Switzerland) is a device, which allows easy and non-invasive 24-hour monitoring of corneal curvature that may relate to IOP. Its clinical applicability for glaucoma practice depends on the demonstration of a significant association between the CLS 24-hour IOP-related profiles and VF progression.

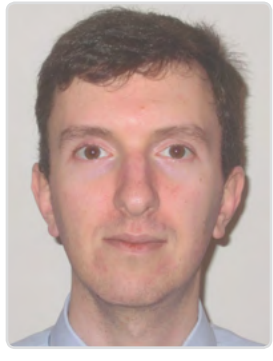
The manuscript by De Moreas *et al.* proposes an association between the 24-hour IOP-related profile based on CLS parameters and VF progression. **The authors have identified CLS parameters that seem to be significantly associated with visual field progression**, using robust statistical measures to smoothen 'noise' and fluctuations in mean deviations (MD), as well as bias due to collinearity among various CLS parameters. Although the paper provides some evidence that the CLS may provide clinically useful data, confirmation of the generalizability

of the results is required. A larger number of parameters was entered into the statistical model and, indeed, the 24-hr CLS model did give a better fit than a GAT-related model. However, this may simply reflect the larger number of parameters in the CLS model compared to the GAT model. The uncertainty regarding which model is best compounded by the lack of information concerning GAT model. Statistical approaches which penalize the estimates of goodness of fit depending on the number of parameters in the model, such as the Akaike Information Criterion, would help interpretation of the data. **Ultimately, the CLS model needs to be validated in an independent dataset to establish whether the data have simply been 'fitted' or whether there is underlying information in the model.**

*Aparna Rao, Luis Pinto, Sergio Mahave, Jin Wook Jeoung, Gokulan Ratnarajan, Rachel Chong, Katarzyna Skonieczna, Antoine Rousseau, Karl Mercieca, Verena Prokosch-Willing

David Garway-Heath is a co-applicant on a grant to develop a contact lens tonometer

IOP and Venous Pulsation Pressure



Comment by Ingeborg Stalmans, Leuven, Belgium and Luís Abegão Pinto, Lisbon, Portugal

66237 Intraocular Pressure Reduction Is Associated with Reduced Venous Pulsation Pressure, Morgan WH, House PH, Hazelton ML, Betz-Stablein BD, Chauhan BC, Viswanathan A, Yu DY, PLoS ONE 2016; 11: e0147915

Increased venous pulse pressure (VPP) has been consistently linked to glaucoma severity and disease progression. As part of a larger, ongoing prospective study, the authors have used an ophthalmodynamometer-based methodology to determine VPP in both glaucoma and glaucoma suspects. Sixty eyes from 31 patients had a baseline VPP measurement followed by an IOP lowering intervention (medical or surgically) and scheduled visits every three to four months before a second VPP measurement performed at the last visit (mean follow-up of 13 months).

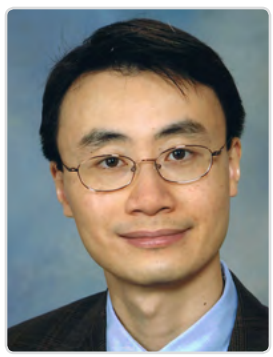
In this sample, decreasing IOP over nearly one year was significantly associated with a decrease in VPP in glaucoma patients (odds ratio of a reduced VPP being 1.60 per mmHg IOP reduction (95% confidence intervals 1.22 to 2.08). **Interestingly, these findings could not be replicated in glaucoma suspects, where no association was found (p = 0.62).**

these preliminary shows promise as they hint IOP-lowering strategies could be used to modulate this increased VPP parameter

Analyzing ophthalmodynamometry data is an inherently challenging task in subjects showing a spontaneous venous pulsation (SVP), which occurs in nearly half of the glaucoma population. With no outside pressure needed to collapse the already pulsating veins, the force needed to apply in the dynamometry is arbitrarily set to 0. Accordingly, this creates a number of data having to be censored as fluctuations in applied pressure cannot be numerically calculated. The authors have tried addressing the issue by analyzing these separately using a binary system, but at the expense of further decreasing their limited sample size.

As we wait the final results of the five-year Vein Pulsation Study Trial in Glaucoma (SPSTG), these preliminary shows promise as they hint IOP-lowering strategies could be used to modulate this increased VPP parameter.

Real-Time Aqueous Outflow Imaging



Comment by Arthur Sit, MN, USA

66251 Aqueous Angiography: Real-Time and Physiologic Aqueous Humor Outflow Imaging, Saraswathy S, Tan JC, Yu F, Francis BA, Hinton DR, Weinreb RN, Huang AS, PLoS ONE 2016; 11: e0147176

Aqueous humor outflow through the conventional outflow system has long been known to be segmental in nature, with higher flow occurring across some regions of the trabecular meshwork.[1] This has significant implications for angle surgeries, including minimally invasive glaucoma surgery (MIGS), since location of the surgery may affect the outcome. Intraoperatively, a fluid wave in the episcleral vessels near the surgery site is a positive prognostic factor, possibly indicating that flow resistance has been reduced in an area of well-functioning distal outflow system.[2] However, success from MIGS is currently unpredictable with highly variable results,[3,4] and there are currently no techniques that can pre-operatively assess the regional variations in the aqueous humor outflow system.

Selecting a single quadrant (*e.g.*, nasal) as the site for angle surgery may not be an ideal strategy, and individualization is required

Saraswathy *et al.*[5] reported on a novel technique (aqueous angiography) for assessing the segmental distribution of aqueous humor outflow using fluorescein angiography. In this study, cadaveric pig and human eyes were perfused with fluorescein solution at constant pressure and the distribution in the aqueous veins was assessed using a Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany).

The authors noted that there was significant variability in the flow distribution of the distal outflow system based on the fluorescein signal. In particular, no single quadrant was consistently identified as having the highest angiographic signal. This suggests that consistently selecting a single quadrant (*e.g.*, nasal) as the site for angle surgery may not be an ideal strategy, and individualization is required. To validate the results from angiography, concurrent OCT was performed, demonstrating open intrascleral lumens where angiography demonstrated flow, and an absence of intrascleral lumens where angiographic signal was absent.

There are a number of potential limitations to this study, which have been acknowledged by the authors. Most importantly, the experiments in this study used cadaver eyes in which the conjunctiva has been removed, and the episcleral veins have been severed. The authors have tried to minimize the potential artifacts by focusing on early fluorescein patterns, which limits the effect of fluorescein accumulation. Other potential confounders are post-mortem cellular changes, clotted blood in the episcleral veins, and tissue swelling. Nevertheless, aqueous angiography appears to be a very promising technique for the assessment of regional variations in the aqueous humor outflow system. If it can be successfully applied in vivo, it may fundamentally alter our approach to performing angle surgeries, and unlock the full potential of MIGS devices.

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Spectral Domain and Swept-Source OCT

Comment by Atusya Miki, Osaka, Japan

65935 Real-time full-depth visualization of posterior ocular structures: Comparison between full-depth imaging spectral domain optical coherence tomography and swept-source optical coherence tomography, Barteselli G, Bartsch DU, Weinreb RN, Camacho N, Nezgoda JT, Marvasti AH, Freeman WR, Retina (Philadelphia, PA) 2016;36(6):1153-1161

Retinal imaging with optical coherence tomography (OCT) plays an integral part in the diagnosis and management of retinal pathologies and glaucoma. Spectral-domain OCT (SD-OCT), which is the most extensively used modality, allows an excellent visualization of retinal pathologies. In addition to retinal imaging, imaging of shallower (the vitreous body and the vitreo-retinal interface) and deeper (the choroid and the lamina cribrosa) structures using enhanced depth imaging (EDI) or swept-source OCT (SS-OCT) has been extensively studied and reported, with the increasing recognition of the importance of these structures in the pathogenesis of various ocular disorders.

In this manuscript, Barteselli and colleagues introduced full depth imaging (FDI), a new OCT imaging technique. FDI is basically a combination of EDI and standard SD-OCT, which takes full advantage of these techniques to visualize both superficial and deep structures. The authors compared the visualization of vitreoretino-choroidal structures between FDI and SS-OCT in 40 healthy eyes, 40 eyes with macular pathologies, and 40 eyes with glaucoma. **FDI offered better visualization of the vitreous body and similar visualization of the retina and the choroid compared with SS-OCT.** FDI has the advantage of offering full depth (from the vitreous body to the choroid) imaging of the posterior pole with a standard SD-OCT device. When compared with SS-OCT, **FDI is potentially disadvantageous in that it is technically more demanding, is unable to produce 3D image, and offers shorter scan length**. Despite these limitations, FDI is a promising alternative. It has been recognized that assessment of preretinal structures in retino-choroidal disorders such as macular degeneration as well as assessment of retino-choroidal structures in preretinal pathologies such as epiretinal membrane (ERM) is important for predicting visual outcome. Therefore, simultaneous visualization of both superficial (vitreous) and deep (choroid) structures by novel FDI SD-OCT technique has a potential of improving our knowledge and clinical practice of various macular disorders.

Reaching for the Brain: Can IOP help estimate Intracranial Pressure?

Comment by John Liu, La Jolla, CA, USA

66262 System for Rapid, Precise Modulation of Intraocular Pressure, toward Minimally-Invasive In Vivo Measurement of Intracranial Pressure, Stockslager MA, Samuels BC, Allingham RR, Klesmith ZA, Schwaner SA, Forest CR, Ethier CR, PLoS ONE 2016; 11: e0147020

Clinical and laboratory evidences have supported the idea that a high translaminar pressure difference, intraocular pressure (IOP) minus intracranial pressure (ICP), is associated with glaucoma pathogenesis. **Accurate but one-time determination of ICP needs a lumbar puncture performed commonly in the lateral decubitus body position, which does not provide dynamic ICP information behind the optic nerve head.** Pulsation of central retinal vein has been proposed as a non-invasive tool to estimate ICP. While the mechanism is not fully understood, the larger magnitude of IOP oscillation compared to the magnitude of ICP oscillation during the cardiovascular cycle is believed to lead to the pulsation. A decrease in IOP or an increase in ICP can change the related magnitude of oscillation and reduce or cease the central retinal venous pulsation. A previous human study using anti-glaucoma medication confirmed that IOP lowering can estimate ICP level. Problems were, however, that this is inaccurate and time-consuming.

> This is an important step for their proof of the concept that monitoring retinal vein parameters during a fast IOP lowering can accurately determine ICP level

In the current study, the authors designed a minimally invasive mechanical system for a rapid and precise IOP lowering. **Using this innovative setup in vivo, a sharp increase in the retinal vein caliber was observed in one tree shrew (*Tupaja glis*) corresponding to a normal ICP level in this species.** This is an important step for their proof of the concept that monitoring retinal vein parameters during a fast IOP lowering can accurately determine ICP level. Such a system is particularly useful for a lower than normal ICP that is associated with glaucoma pathogenesis. There will be much more work to do for the authors. The observation shown in this report needs to be replicated in other tree shrews probably with a range of ICP-controlled experiments. Similar observation has to be verified in other animal species toward eventually a consideration of applications in human patients. In addition, one may question whether the study concept is testable in certain surgical conditions when a rapid IOP fall occurs. Today monitoring changes in retinal vein parameters are not difficult considering advances in non-invasive imaging technology. As a consensus for clinicians and scientists involved in the research

of translaminar pressure difference and glaucoma pathogenesis, a leap forward is to develop a reliable and accurate method for determining ICP behind the optic nerve head. The authors' effort is appreciated. Our task is daunting, but the potential reward is high.

Risk factors

Factors affecting IOP

Comment by Rupert Bourne, Cambridge, UK

66546 Associations with Intraocular Pressure in a Large Cohort: Results from the UK Biobank, Chan MP, Grossi CM, Khawaja AP, Yip JL, Khaw KT, Patel PJ, Khaw PT, Morgan JE, Vernon SA, Foster PJ, Ophthalmology 2016;123(4):771-782

This report by the UK Biobank Eye and Vision Consortium investigated the physical and demographic associations of intraocular pressure (IOP) in a large cohort of approximately 110,573 people aged 40-69 years living in England and Wales. The Ocular Response Analyzer (ORA; Reichert Corp., Philadelphia, PA) was used to take a single measurement of IOP from each eye of participants. The ORA calculates Goldmann-correlated and corneal-compensated IOP estimates (IOPg and IOPcc, respectively). IOPg is analogous to standard noncontact IOP measurements, whereas IOPcc is an IOP estimate that uses a mathematical correction to minimize its corneal dependence.[1-3] Central corneal thickness (CCT) is correlated with IOPg but not IOPcc.

This instrument's outputs for IOPg and IOPcc were statistically tested for associations with sex, age, deprivation index, center of assessment, weight, height, waist circumference, systolic and diastolic blood pressure, body mass index, refractive error, smoking status, diabetes, glaucoma, macular degeneration, and season of IOP measurement using univariable linear regression and then in a multivariable regression model. The analyses confirm many of the known associations between IOP and demographic and systemic risk factors, although it must be cautioned that this is not a population-based study (only 5% the enumerated population were examined), and the age range ends younger than most population-based eye surveys, so direct comparisons are not possible. It is noteworthy that despite incorporating all these risk factors in the model, **the model only explained a small proportion of IOPg and IOPcc variation (adjusted R^2: 5.3% IOPg, 7.4% IOPcc) which is in keeping with low explanatory power reported by other studies**. Of all the variables, self-reported glaucoma had the greatest effect on IOP, equivalent to a five- to ten-fold effect on IOP compared with a decade increase in age.

The relationship of the varying aspects of the ORA signal to their underlying ocular determinants is unknown

Differences in the association of IOPg and IOPcc with self-reported diabetes (positively and significantly associated with IOPg but not with IOPcc), height (positively associated with IOPcc, negatively associated with IOPg), smoking (positively associated with IOPg but negatively associated with IOPcc), and black ethnicity (negatively associated with IOPg, positively associated with IOPcc) are explored in the discussion in relation to possible corneal biomechanical influences. For example, the **thinner CCT found by studies of African populations compared to white populations, supports this report's findings of higher IOPg in whites than blacks, while IOPcc has a converse relationship**. Appropriately, the authors are cautious in being any more than speculative about the significance of these differential associations with IOPg and IOPcc, given that the relationship of the varying aspects of the ORA signal to their underlying ocular determinants is unknown.

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Limbal Changes during Face-down Sleep

Comment by Gustavo de Moraes, New York, NY, USA

66544 Measured Changes in Limbal Strain During Simulated Sleep in Face Down Position Using an Instrumented Contact Lens in Healthy Adults and Adults With Glaucoma, Flatau A, Solano F, Idrees S, Jefferys JL, Volpe P, Damion C, Quigley HA, JAMA Ophthalmology 2016;134(4):375-382

Flatau *et al.* described an interventional trial in which they measured changes in the corneo-scleral junction (herewith called limbal strain changes) in control and glaucoma eyes as a result of mechanical forces applied to the eye when the face of participants rested against a pillow (face-down (FD) position). They used a contact-lens sensor (Triggerfish, Sensimed) that has been previously validated as a tool to indirectly measure volumetric changes in the anterior chamber known to be correlated with intraocular pressure (IOP). The authors also applied a mathematical model derived from experimental studies to determine the relationship between strain change and IOP given pre-defined baseline IOP values. **They found that contact with a pillow in FD position during simulated sleep produced a sustained strain increase in glaucoma eyes but**

not in controls. Of note, the mean FD change in glaucoma eyes was equivalent to strain increase associated with a mean sustained IOP elevation of 2.5 mmHg. More interestingly, a sub-analysis of glaucoma patients with at least five visual field tests prior to the experiment revealed that **these strain changes were more meaningful in eyes with previous progression.**

This is an original study on a clinically-relevant topic and may result in practical applications. Assuming that limbal strain changes indeed reflect IOP elevation (which is supported by the existing literature),[1-3] glaucoma patients may experience detrimental IOP elevation during sleep. Given the amount of time people spend sleeping during their lives, such IOP elevation could lead to a substantial amount of energy applied to the axons in optic nerve head during and individual's lifetime.

Another important conclusion is that the study supports the premise that the biomechanical properties of the eye differ between glaucoma and healthy subjects. This could help explain how different tissues respond to mechanical stress from IOP and why some patients are more susceptible to IOP changes and progressive glaucomatous damage.

The study methodology is clearly described and allow replication of the study. Moreover, the authors should be congratulated for the thorough discussion section, in which they provide supporting literature to explain their findings and speculate – with reasonable basis – on potential clinical implications. In particular, the role of the facial bone structure and the depth of the orbit warrants investigation as to how they could intensify or minimize the present findings. As the authors suggested, preventing mechanisms (such as protective eye shield) should be tested and warrant further investigation.

The study's main limitation is that we cannot assume that the changes reported during the experiment are sustained during the average eight-hour sleep period. The eye is not a closed system. It is possible, for instance, that after some time the eye's outflow facility undergoes changes and the true IOP could return to normal. **Notwithstanding this possibility, studies showing visual field asymmetry associated with preferred sleep position[4,5] support the authors' hypothesis.** Future studies ought to investigate whether interventions with a protective eye shield during sleep can benefit glaucoma patients.

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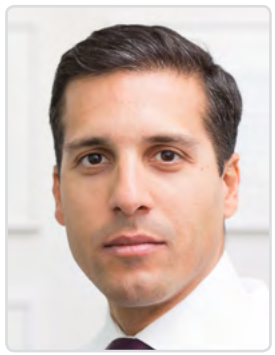
Posture-induced IOP Rise



Comment by Kaweh Mansouri, Geneva, Switzerland

66308 Intraocular Pressure Rise in Subjects with and without Glaucoma during Four Common Yoga Positions, Jasien JV, Jonas JB, de Moraes CG, Ritch R, PLoS ONE 2015; 10: e0144505

The practice of yoga for meditative and recreational purposes has become mainstream in recent decades while elderly people increasingly strive to stay physically active. Therefore, practitioners are regulary confronted with glaucoma patients who inquire about the effect of yoga excercises on their disease status.

IOP is a dynamic parameter and body position is directly related to IOP changes. Previous studies have unequivocally demonstrated that Sirsasana (headstand) produces a temporary increase in IOP by a factor of two.

Jasien *et al.* provide the first data on the effect of four common yoga excercises on IOP: 'downward facing dog', 'standard forward bend', 'plow', and 'legs up the wall'. Ten healthy subjects and ten patients with primary open-angle glaucoma were included and assumed each position for a duration of two minutes. **All four positions produced a statistically significant IOP increase within one minute.** The highest increase occurred in the 'downward facing dog' (17 to 29 mmHg in glaucoma vs. 17 to 27 mmHg in healthy subjects). IOP returned to baseline levels two minutes after returning to a seated position.

> Practitioners are regulary confronted with glaucoma patients who inquire about the effect of yoga excercises on their disease status

The authors applied statistical modeling to account for confounding variables. A limitation was the preponderance of female subjects (90%) and the small sample size, that precluded sub-group analysis by glaucoma types and stages. In reality, many yoga practitioners assume positions for longer than the two minute period studied herein.

Whether the observed acute IOP elevation translates into glaucoma damage and clear practical recommendations cannot be derived from this study. Given the popularity of yoga and the potential for deletrious effects of head-down positions, the glaucoma community is encouraged to conduct a longitudinal study to evaluate this putative relationship. In the mean-time, and based on available evidence, **I cautiously discourage my patients from head-down positions and recommend more frequent follow-up visits**.

Clinical Forms of Glaucoma

Normal Pressure Glaucoma

Comment by Jost Jonas, Heidelberg, Germany

66233 Estimated Trans-Lamina Cribrosa Pressure Differences in Low-Teen and High-Teen Intraocular Pressure Normal Tension Glaucoma: The Korean National Health and Nutrition Examination Survey, Lee SH, Kwak SW, Kang EM, Kim GA, Lee SY, Bae HW, Seong GJ, Kim CY, PLoS ONE 2016; 11: e0148412

The lamina cribrosa in the optic nerve head is the site where the glaucomatous damage to the optic nerve fibers presumably occurs. In the lamina cribrosa, the pressure changes from the level of the intraocular compartment, *i.e.*, the intraocular pressure, to the level of the retrobulbar compartment, *i.e.*, the tissue pressure of the optic nerve and the orbital cerebrospinal fluid pressure (CSFP). Since the orbital CSFP is one of the determinants of the trans-lamina cribrosa pressure difference (TLCPD), the hypothesis was proposed that a low orbital CSFP may play a role in the pathogenesis of glaucomatous optic neuropathy, in particular in patients with normal-(intraocular-)pressure glaucoma.

Since the CSFP cannot be measured directly and non-invasively, attempts have been made to estimate it based on formulas which take into account the dependence of the CSFP on blood pressure, body mass index and age. Using such a formula, Lee and colleagues have calculated the CSFP in a large group of individuals without and with glaucoma. They found that **the calculated TLCPD was significantly higher in patients with normal-pressure glaucoma and IOPs in the high teens compared to normal subjects. In contrast, there was no difference in calculated TLCPD for patients with normal-pressure glaucoma and IOPs in the low teens compared with normal subjects**.

The study partially supports, but also partially may contradict, the concept of low CSFP in the pathogenesis of glaucoma. A major limitation of the study, however, is that the formulas for the estimation of CSFP have not yet been validated. This highlights the importance of developing new techniques for the non-invasive measurement of the CSFP, for ophthalmology as well as for neurology.

Hematologic Markers of Exfoliation Syndrome

Comment by Gábor Holló, Budapest, Hungary

66378 Prediction of Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma by Using Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio, Ozgonul C, Sertoglu E, Mumcuoglu T, Ozge G, Gokce G, Ocular Immunology and Inflammation 2015; Dec 8 (e-pub ahead of print)

It has been previously reported that increased oxidative stress plays a role in the development of cataract and the elevation of intraocular pressure in pseudoexfoliation syndrome (PEX) and pseudoexfoliative glaucoma (PXG). Recently, several studies have also suggested that oxidative stress may be increased systemically in PEX/PXG patients. Ozgonul *et al.* compared the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) between 34 PEX and 29 PXG patients and 42 age and sex-matched healthy control subjects. **They found NLR to be significantly increased in PEX and PXG, and PLR to be significantly increased in PXG compared to controls.** The authors concluded that their findings provide evidence for an association between NLR and PEX/PXG, indicating that inflammation plays a role in PEX/PXG. However, their conclusion is not sufficiently supported by data: the study was retrospective and the patients/groups were not controlled for systemic diseases that are known to significantly increase NLR and PRL (e.g., cardiovascular disease, diabetes and malignancies). Therefore this study can only be considered as one of several small reports which address certain aspects of systemic stress in PEX/PXG, but cannot demonstrate a clear association due to methodological problems.

Cytokines and Exfoliation Glaucoma

Comment by Ursula Schlötzer-Schrehardt, Erlangen, Germany

66368 Proinflammatory Cytokines Induce XFG Development, Sarenac Vulovic TS, Pavlovic SM, Zdravkovic NS, JAMA ophthalmology 2016;134:57-62

Dysregulated expression of proinflammatory cytokines has been implicated in the initiation of various fibrotic disorders and in the pathophysiology of glaucoma. Based on elevated aqueous humor levels of IL-6 and IL-8 in early stages of pseudoexfoliation (PEX) syndrome, previous studies have provided evidence for a stress-induced, spatially, and temporally restricted subclinical inflammation in the onset of the fibrotic PEX process.[1] Subsequent studies confirmed elevated aqueous levels of IL-8[2] and extended the findings to increased concentrations of TNF-α in aqueous humor[3] and of IL-6 in serum[4] samples obtained from PEX patients without or with glaucoma. A positive correlation of aqueous IL-8 (and TGF-ß1) concentrations with IOP led the authors to suggest a critical role for aqueous IL-8 and TGF-ß1 in IOP elevation.[2]

The study by Sarenac Vulovic *et al.* further analyzed the levels of IL-6, IL-17 and TNF-α in aqueous humor and serum of patients with early and late stages of PEX syndrome as well as PEX glaucoma, using cataract patients as control (n = 30 in each group) by ELISA assays. The authors reported **significantly elevated levels of TNF-α and IL-17 in the aqueous humor of all PEX groups** compared to controls, whereas increased IL-6 levels were observed in early PEX and PEX glaucoma only. Serum levels of IL-6 were significantly elevated in early and late PEX syndrome but not in PEX glaucoma. **The authors concluded from their findings that 'local conditions cause chronic inflammation in the eye, subsequently activating fibrotic process with fibrotic tissue deposits in the eye'.**

Apart from the first-time detection of increased levels of IL-17 in aqueous samples of PEX patients, the study unfortunately does not make any significant contribution to the subject

Unfortunately, however, the data presented are difficult to interpret and to compare with previous publications, particularly because aqueous and serum concentrations of IL-6 and TNF-α were considerably higher than those reported from the literature. In particular, the unusually high concentrations of TNF-α (300-500 pg/ml) are in stark contrast to published studies showing undetectable or rather low levels (up to 20 pg/ml depending on disease background) in the aqueous humor of patients. Moreover, an exact definition of early and late stages of PEX syndrome was not provided by the authors further impeding a comparative analysis. Finally, cytokine levels were illogically correlated between different groups, instead of correlating cytokine levels with PEX stage, IOP or other glaucoma parameters. Thus, apart from the first-time

detection of increased levels of IL-17 in aqueous samples of PEX patients, the study unfortunately does not make any significant contribution to the subject and does not give evidence of an 'induction of XFG development by pro-inflammatory cytokines' as indicated in the title.

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Glaucoma and Systemic Diseases

Migraine and Vasospasm

Comment by Ki Ho Park, Seoul, South Korea

65798 Migraine and Vasospasm in Glaucoma: Age-Related Evaluation of 2027 Patients With Glaucoma or Ocular Hypertension, Gramer G, Weber BH, Gramer E, Investigative Ophthalmology and Visual Science 2015; 56: 7999-8007

Gramer *et al.* evaluated the frequency of migraine, vasospasm, family history of migraine, and family history of glaucoma in a group of patients with primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), pigmentary glaucoma, pseudoexfoliation glaucoma (PEX), ocular hypertension (OH), and primary angle-closure glaucoma (PACG). This is the first study to evaluate family history of migraine in glaucoma patients and the association of family history of glaucoma with frequency of migraine.

According to the authors' findings, **migraine was significantly more frequent in NTG (21.4%) than in POAG (13.1%; P = 0.01), PEX (7.8%; P = 0.02), and PACG (10.1%; P = 0.004). Additionally, they reported that patients with a family history of glaucoma had a significantly higher frequency of migraine than did patients without any such history.**

This study supports the idea that ischemia due to vasoconstriction can cause glaucomatous optic nerve damage and that risk factors other than IOP play a relatively larger role in NTG than in POAG

The strength of the paper is that the assessment of family history of glaucoma and other risk factors was performed in different glaucomas in a uniform way, i.e., by one glaucoma specialist using a standardized questionnaire.

The limitation of the study is that the presence or absence of migraine or vasospasm was determined in most cases by patients' questionnaire answer, while only some more recent cases had been diagnosed by neurologists. Even so, this inaugural report on the association of migraine frequency and glaucoma, based on the uniform examination by one glaucomatologist of a large number of subjects, is important and deserves its place in the literature.

Diabetes Mellitus and Glaucoma

Comment by Louis Pasquale, Boston, MA, USA

65884 Diabetes Pathology and Risk of Primary Open-Angle Glaucoma: Evaluating Causal Mechanisms by Using Genetic Information, Shen L, Walter S, Melles RB, Glymour MM, Jorgenson E, American Journal of Epidemiology 2016; 183: 147-155

Considerable epidemiological evidence supports an adverse relation between type-2 diabetes (T2D) and primary open-angle glaucoma (POAG). Appropriately designed genetic studies can avert issues like reverse causation, detection bias and diabetes treatment effects that cast doubt about any relation between T2D and POAG because the genome is inherited from birth.

Appropriately designed genetic studies can avert issues like reverse causation, detection bias and diabetes treatment effects that cast doubt about any relation between T2D and POAG because the genome is inherited from birth

Shen et al. studied 69,685 participants in a large cohort nested in a Northern California health system subjected to high throughout genotyping. The authors used ICD-9 coding to capture POAG, normal tension glaucoma (NTG) and T2D status. Only validation for T2D case identification was performed and given the codes used to define POAG, some of the 3,554 cases captured likely represent individuals with and without reproducible visual field loss. The analysis is limited to Caucasians and it is not clear if the entire cohort was under ophthalmic

surveillance. The authors composed polygenetic risk scores for T2D and confirmed that these panels were robustly associated with T2D. Furthermore, they reproduced the adverse relation between T2D and POAG. Next they showed the T2D genetic risk score was associated with a 2.5-fold increased risk of POAG, although the associations were attenuated and not statistically significant when adjusted for T2D status. Subsequently they stratified the T2D genetic biomarkers into the following categories based on their putative function: adiposity, pancreatic beta cell function, insulin regulation and other metabolic mechanisms. The pancreatic beta cell function genetic subpanel was associated with a 5-fold increased risk of POAG and these results remained significant when adjusted for T2D. No other subset of T2D genetic biomarkers was associated with POAG. Furthermore no association between any of the T2D genetic biomarker panels and NTG was found. While there is no clear biologic hypothesis linking pancreatic beta cell function and glaucoma, these results support a genetic link between T2D and POAG.

Surgical Treatment

Flap Characteristics and Aqueous Flow

Comment by Don Budenz, Chapel Hill, USA

65940 The Influence of Scleral Flap Thickness, Shape, and Sutures on Intraocular Pressure (IOP) and Aqueous Humor Flow Direction in a Trabeculectomy Model, Samsudin A, Eames I, Brocchini S, Khaw PT, Journal of Glaucoma Nov 2015 (e-pub ahead of print)

This study by Samsudin and associates examines the influence of trabeculectomy flap thickness, size, and shape, and suture number and position on fluid flow using a silicone model. This clever experiment showed that thinner and larger flaps result in more flow. Triangular flaps created more resistance to flow than rectangular or square flaps, possibly due to the smaller area of triangular flaps.

> Although many factors contribute to the amount of flow and IOP postoperatively, scleral flap construction and placement and tension on sutures are important things to consider

Not surprisingly, fewer sutures also produced more flow through the flap. The direction of the fluid flow was away from where sutures were placed due to the fluid taking the path of least resistance. Their findings have important implications for trabeculectomy flap creation during surgery.

Although many factors contribute to the amount of flow and IOP postoperatively, scleral flap construction and placement and tension on sutures are important things to consider. **The model created herein suggests that larger, thinner, rectangular flaps result in more flow than smaller, thicker, non-rectangular flaps.** Of course one wants to avoid excess flow in the early postoperative period while having the option of enhancing flow once some healing of the conjunctiva has occurred. The results also suggest that one should avoid sutures on the posterior edge of the flap if one wishes to direct flow posteriorly, generally considered an advantage early or late after trabeculectomy surgery because posterior flow results in posteriorly located and more diffuse blebs.

Ab Interno Trabeculotomy

Comment by Ronald Fellman, Dallas, USA

66510 Transient Ciliochoroidal Detachment After Ab Interno Trabeculotomy for Open-Angle Glaucoma: A Prospective Anterior-Segment Optical Coherence Tomography Study, Akagi T, Nakano E, Nakanishi H, Uji A, Yoshimura N, JAMA Ophthalmology 2016;134(3):304-311

Hypotony induced ciliochoroidal detachment (CCD) is well described after filtration or tube shunt surgery, but is not yet associated with canal-based surgery. Canal surgery only eliminates 50% of the trabecular outflow resistance, so it seems unusual that hypotony would develop, unless there was another mechanism. However, the authors of this study found an inexplicable high rate of CCD (42%), in the immediate postoperative period, after canal-based Trabectome (NeoMedix Corp) surgery. The authors found evidence with anterior segment OCT of direct communication between the AC and the suprachoroidal space, indicating an unintended cyclodialysis cleft. However, they did not mention a shallow chamber nor any gonioscopic documentation that would directly corroborate their findings. This is a very high rate of CCD for an angle procedure. Pilocarpine is well-known to aid in keeping a cyclodialysis cleft open and this drug was used post operatively in all cases. The preoperative use of Pilocarpine was not mentioned.

Although many factors contribute to the amount of flow and IOP postoperatively, scleral flap construction and placement and tension on sutures are important things to consider

Johnstone and Smit reported many years ago that viscodilation of SC with viscocanalostomy created multiple small 'trabeculotomies'. In an analogous manner, it is very feasible that Trabectome may create multiple small nearby cyclodialyses as detected with the high resolution OCT. Simple gonioscopy would have likely revealed a cyclodialysis cleft, but this was not

done. In addition, it is possible the back wall of the canal may be abraded during Trabectome, removing the endothelial barrier allowing the seepage of aqueous into the deep sclera and into the suprachoroidal space. This may be another mechanism, but is purely speculative.

However, we still have to consider other mechanisms of effusion possibly related to the shape of the eye, as CCD was more common in shorter eyes. Is it possible the arc of the trabecular meshwork and canal is more acute in smaller eyes making it more likely to detach the CB or abrade the back wall in certain areas? The most common cause of a CCD after glaucoma surgery is low IOP, but in this case, an unintended cyclodialysis cleft may be the initiating factor that led to low IOP. Surgeons need to start documenting the degree of difficulty of the Trabectome procedure with special reference to the ease of device passage with IOP and potential creation of an unintended cyclodialysis cleft. Careful postoperative gonioscopy will clarify this important imaging observation.

Thus, there are multiple plausible factors that can explain transient CCD including, the creation of an unintended cyclodialysis cleft, choroidal effusion associated with a short eye triggered by transient hypotony, acute lowering of IOP, and seepage of aqueous into the suprachoroidal space from nearby damaged deep sclera. Further studies with combined gonioscopy may better clarify the authors' exciting observation.

Drainage Devices

Comment by Kouros Nouri-Mahdavi, Los Angeles, CA, USA

65891 Risk factors for the hypertensive phase after implantation of a glaucoma drainage device, Jung KI, Park CK, Acta Ophthalmologica 2015; Nov 25 (e-pub ahead of print)

Jung and Park present the results of a prospective study exploring the risk factors for development of hypertensive phase (HTP) after placement of a model FP-7 Ahmed Glaucoma Valve in a group of 128 eyes of 128 patients. They also explored the relationship between the risk factors and bleb wall parameters (thickness and relative density of the bleb wall) on anterior segment OCT (AS-OCT) in 38 eyes.

Longer axial length (> 25 mm) was found to be the strongest predictor of an HTP after surgery. Incidence of HTP was found to be very high in both high myopia and non-high myopia groups (95% vs. 73%, respectively). They reported a thinner capsule on AS-OCT to be associated with high myopia. Eyes with an HTP were found to have similar success rates as compared to those without.

The reported findings are interesting but need to be considered in the context of the study. By defining the HTP as uncontrolled IOP at the three-month point, probably milder degrees of HTP were excluded, in which the IOP was normalized by medical treatment by the third month. The number of prior surgeries was not provided in the two groups. I wonder if highly myopic eyes had a higher rate of prior conjunctival surgeries leading to a more prominent HTP in this group. The success criteria used were lenient overall (IOP ≤ 21 mmHg and 20% reduction of IOP) and the very small number of failures may have led to the lack of a difference between success rates in the two groups (eyes with and without HTN or eyes with and without high myopia) on the Kaplan-Meier curves.

The reported relationship between the AL and development of HTP or bleb wall thickness is new and these findings will need to be confirmed in future studies. Some of the reported relationships might have been driven by outlier points (for example refer to Fig. 5).

The finding of an association between a thicker wall bleb with better IOP control is not consistent with our understanding of bleb remodeling as reported on histological studies by Dr. Molteno's group and other investigators

The authors bring up an interesting theory about why the HTP may be more common in highly myopic eyes. They argue that based on animal studies, myopic sclera (and possibly Tenon's capsule) has less proteoglycans and hence has less water content and therefore, may be less impermeable to water movement. However, the finding of an association between a thicker wall bleb with better IOP control is not consistent with our understanding of bleb remodeling as reported on histological studies by Dr. Molteno's group and other investigators.

In summary, the association between high myopia and the higher incidence of a hypertensive phase is an unexpected finding that needs further exploration. Drs. Jung and Park bring up an interesting hypothesis that will need to be confirmed in future studies. In the meantime, it may be prudent for clinicians to watch for and treat the hypertensive phase more aggressively in patients with high myopia.

1. 2, 3 Stents!

Comment by Steven Gedde, Miami, FL, USA

66286 Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication, Katz LJ, Erb C, Carceller GA, Fea AM, Voskanyan L, Wells JM, Giamporcaro JE, Clinical Ophthalmology 2015; 9: 2313-2320

Katz and associates present an interim report of a prospective randomized study of one, two or three trabecular micro-bypass stents as a stand-alone procedure in patients with open-angle glaucoma. A total of 119 patients (38 with one stent, 41 with two stents, and 40 with three stents) were enrolled at one clinical facility in Armenia and followed for 18 months. **Mean unmedicated IOP at 18 months was 15.9 ± 0.9 mmHg in the one-stent group, 14.1 ± 1.0 mmHg in the two-stent group, and 12.2 ± 1.1 mmHg in the three-stent group.** Unmedicated IOP ≤ 18 mmHg at one year was achieved by 89.2%, 90.2%, and 92.1% in the one-stent, two-stent, and three-stent groups, respectively. **Unmedicated IOP ≤ 15 mmHg was seen in 64.9%, 85.4%, and 92.1% of the respective groups.** No intraoperative ocular adverse events occurred, but specific data about postoperative complications was not provided. The authors only indicate that no patients experienced complications or adverse events commonly associated with conventional glaucoma procedures.

Most previous studies of the trabecular micro-bypass stent have evaluated the procedure in combination with phacoemulsification cataract extraction. The present study investigated stent implantation alone, thus allowing a determination of the IOP-lowering effect of the stent without the confounding influence of cataract surgery. Furthermore, the measurement of IOP at the annual visit after a medication washout period provides a clearer assessment of the efficacy of stent placement. The current study further establishes the benefit of the trabecular micro-bypass stent in reducing IOP, and also demonstrates an incremental enhancement of efficacy with use of multiple stents.

Cost is an important consideration not factored into the study design. Health insurances will generally only reimburse one stent. Additionally, the U.S. Food and Drug Administration approved the trabecular micro-bypass stent in adult patients with mild to moderate open-angle glaucoma in conjunction with cataract extraction, but not as a stand-alone procedure. The authors have acknowledged some weaknesses of their study. It enrolled a homogeneous population of Caucasian patients, involved a single site, did not mask investigators, and had only one baseline IOP measurement. Despite these limitations, the authors are to be congratulated for contributing an important study on the efficacy of the trabecular micro-bypass stent.

Miscellaneous

Dietary Nitrate Intake and Glaucoma


Comment by Marissé Masís and Shan Lin, San Francisco, CA, USA

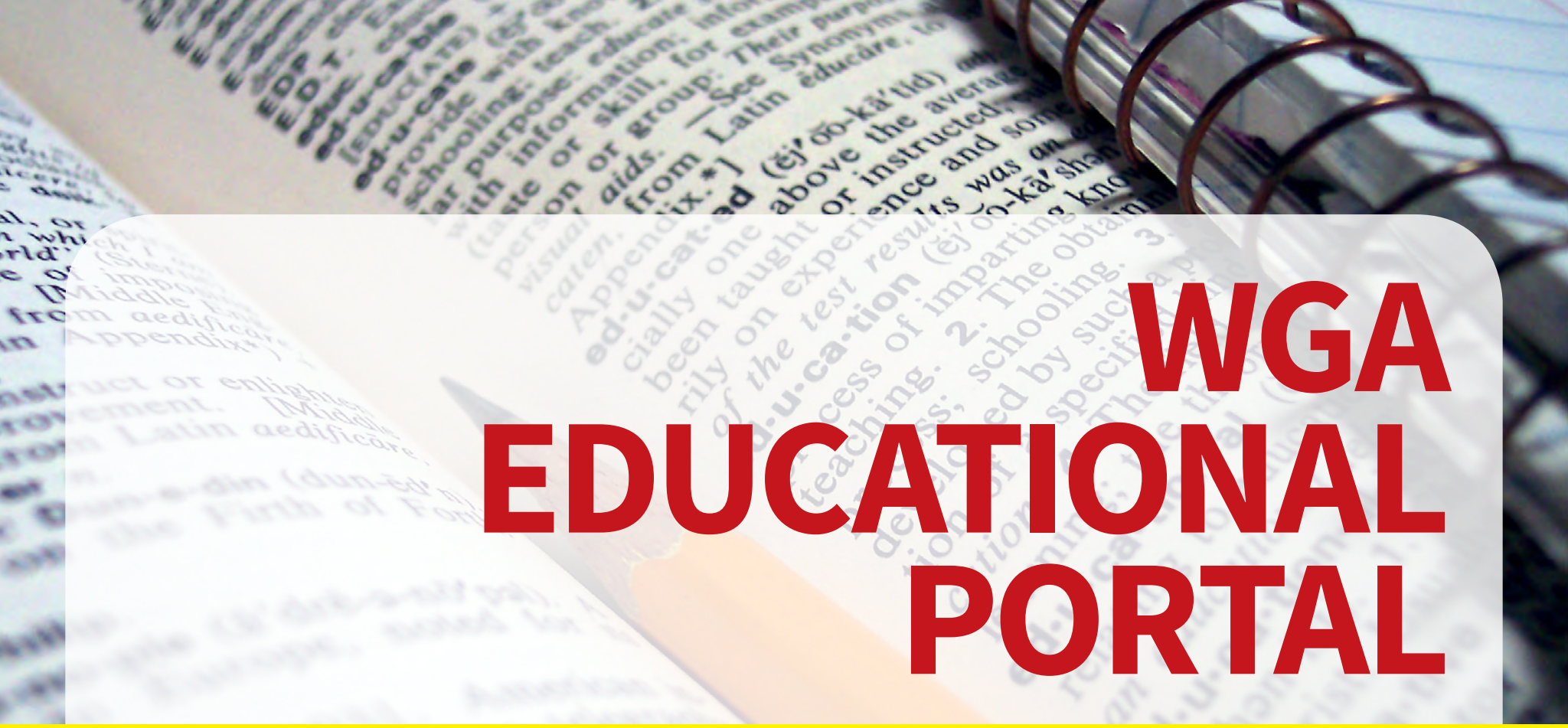
66567 Association of Dietary Nitrate Intake With Primary Open-Angle Glaucoma: A Prospective Analysis From the Nurses' Health Study and Health Professionals Follow-up Study, Kang JH, Willett WC, Rosner BA, Buys E, Wiggs JL, Pasquale LR, JAMA ophthalmology 2016;134(3):294-303

Glaucomatous injury to the retinal ganglion cells has been associated with anatomical damage even to the level of the central nervous system such as the lateral geniculate nucleus and visual cortex. Accelerated apoptosis, oxidative stress, cytokine-related inflammatory processes, and abnormal protein accumulation are some of the proposed cell injury mechanisms which help define glaucoma as a neurodegenerative disease.[1]

Population-based studies are a valuable tool to assess several mechanistic pathways including risk factors that may lead to neurodegeneration. Several papers have been published regarding the effect of diet and nutrients in glaucoma. In 2003, data from the Nurses' Health Study showed no relationship between carotenoids, vitamins C and E, and vegetables and glaucoma risk. Although the relative risk wasn't statistically significant, the trend was in the direction of protection against with antioxidants, and there was no specific analysis of nitrate intake.[2] In 2008 a population based study supported that a higher intake of fruits and vegetables may be associated with a decreased risk of glaucoma in women,[3] and in 2012 similar findings were uncovered in a cohort study of African-American women.[4]

This study by Kang *et al.* adds several promising findings related to dietary intake and glaucoma. It is the first study that assessed eating habits in relation to specific visual field loss patterns (peripheral loss only vs. early paracentral loss). **Dietary nitrate intake, mostly in the form of green leafy vegetables, appeared to have more protective effect against POAG related to early paracentral visual field defects.** In clinical practice, usually these findings are related to normal tension glaucoma, which is the type of glaucoma more susceptible to oxidative stress and vascular dysregulation. **The protective effect of nitrates appears to be dose-dependent and it resulted in a 20-30% lower POAG risk.**

Of course associations found in population studies do not necessarily prove causation or mechanism. Prospective, randomized studies are needed to show causal effects between nutrients and glaucoma development. The evidence for environmental factors in optic nerve damage is growing and a better understanding of these factors may lead us to a more systemic and integrated approach to glaucoma care.



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News flashes

★ Aqueous angiography: real-time and physiologic aqueous humor outflow imaging

★ Toward minimally-invasive in-vivo measurement of intracranial pressure

★ Assuming that limbal strain changes indeed reflect IOP elevation (which is supported by the existing literature), one to three glaucoma patients may experience detrimental IOP elevation during sleep

★ Intraocular pressure rise during four common yoga positions

★ Measured changes in limbal strain during simulated sleep in face-down position using an instrumented contact lens in healthy adults and adults with glaucoma

★ Transient ciliochoroidal detachment after ab-interno trabeculotomy for open-angle glaucoma

★ One, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication

★ Association of dietary nitrate intake with primary open-angle glaucoma

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