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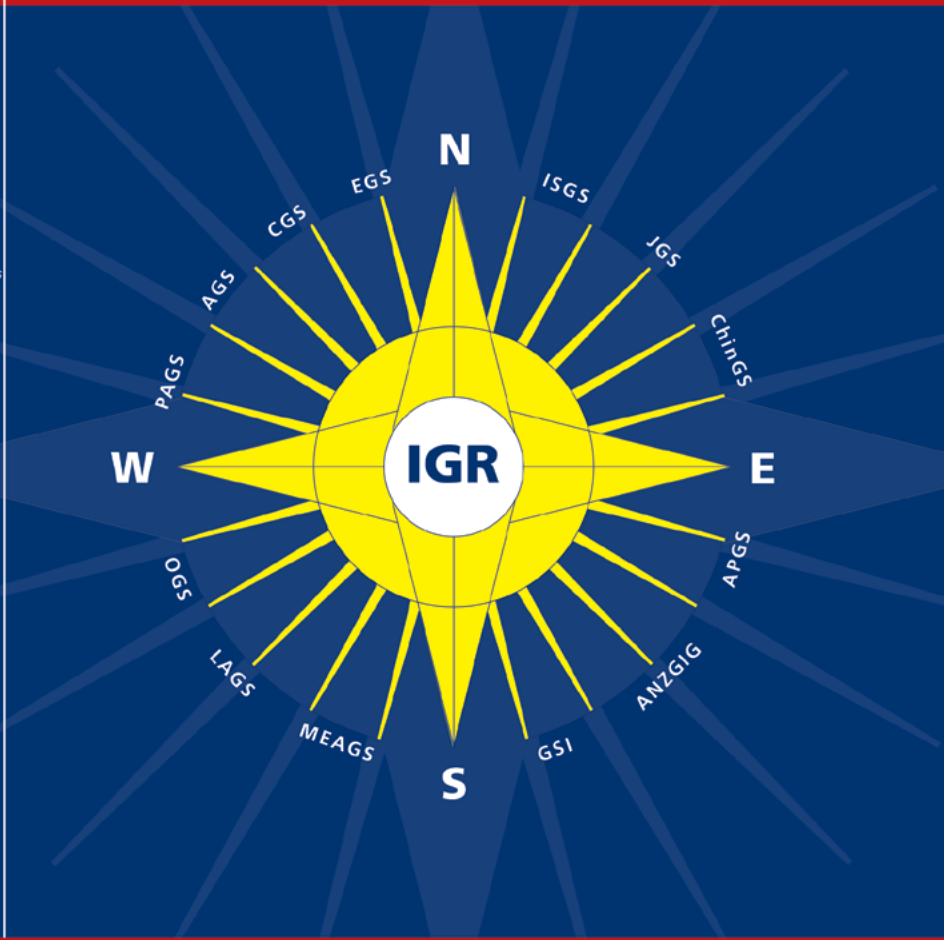

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WGA#One is the name of the World Glaucoma Association's customer relationship management system. With WGA#One we are moving forward towards one platform, and hence one user profile, for all our services.

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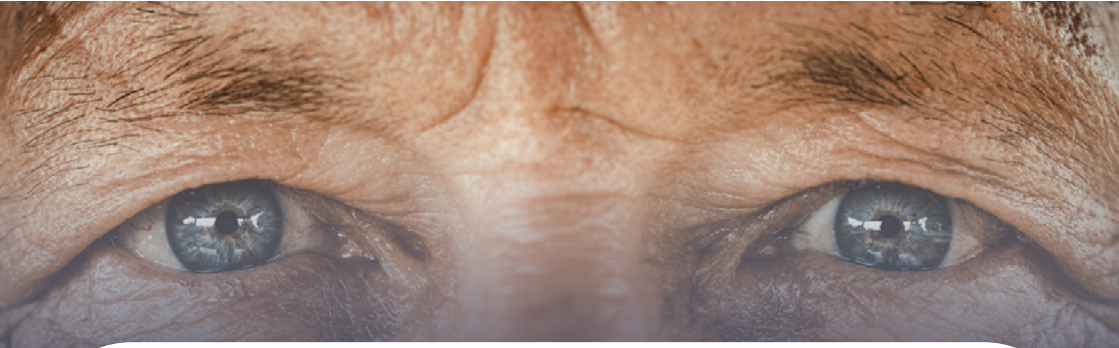

Envisioning a Better Future For Patients With Glaucoma

Glaucoma is one of the leading causes of irreversible blindness worldwide and it is a growing problem, with the number of people affected estimated to reach 111.8 million people by 2040.[1] More than 11 million people are estimated to be bilaterally blind (in both eyes) from glaucoma.[2]

Early diagnosis and treatment initiation is critical to help prevent vision loss from glaucoma, as symptoms may be hard to detect when the condition first develops.[3,4] AbbVie focuses on clinically relevant science to make a meaningful difference for patients and seeks to elevate the standard of care from the front to the back of the eye by addressing areas of unmet needs.

With over two decades of experience researching eye diseases, Jie Shen, Ph.D., AbbVie's Vice President of Local Delivery Translational Sciences, leads a team of scientists responsible for designing and conducting studies, evaluating drug behavior in the eye, and testing promising drug candidates in early-stage clinical trials. Jie and team utilize state-of-the-art imaging modalities found in world-class clinical research institutions, digital technologies, statistical modeling and data science to accelerate the translation of science to new medicines.

It is the people around the world living with eye conditions like glaucoma that motivate AbbVie's eye care scientists to push forward with leading-edge translational research, with the aim to deliver medicines with best-in-class outcomes to patients.

In this quest to meet patient needs, AbbVie is leveraging capabilities at its Genetic Research Center and investing in technology to accelerate and

optimize R&D, for example, identifying biomarkers that can help indicate at an early stage whether a drug may be effective. Jie also highlights the importance of AbbVie's biostatistics support, including machine learning, which can help to derive more benefit from available data in the early discovery phase.

Pursuing these goals is enabled by an eye care journey that began as Allergan over 75 years ago, bolstered today by AbbVie's legacy in complex diseases and global scale.

While eye care may seem simple, with some vision issues being solved by people wearing glasses, contact lenses, or using eye drops, the reality is what works for some does not work for others. With a background in academia and many years as a practicing ophthalmologist, Mike Robinson, M.D., AbbVie's Vice President, Clinical Development, Ophthalmology has seen firsthand the great need to elevate the standard of care and continuously improve existing options. This is why AbbVie is focused on addressing the unmet needs in glaucoma.

"We continue to look for solutions in our clinical trials. Our goal has been and continues to be identifying ways to meet people where they are in their ability to preserve their vision, and our clinical trials are looking at ways to provide glaucoma patients additional options," says Mike.

AbbVie will continue to push the envelope through R&D and collaborations, to accelerate the development and commercialization of better treatment pathways and solutions for patients.

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From the WGA

Dear IGR readers,

We are very proud to share the success of the **10th World Glaucoma Congress** (June 28-July 1, 2023), organized by the World Glaucoma Association (WGA) in Rome, Italy. We welcomed over 3100 ophthalmologists and allied health professionals from more than 100 different countries, positioning it as the second largest glaucoma meeting held anywhere in the world to date.

Much appreciation to those who were able to participate, speak, and moderate this year. Our sincere gratitude to our Program Planning Committee, chaired by Drs. Arthur Sit and Kaweh Mansouri!

For this very special anniversary edition of WGC, participants enjoyed an inspiring and comprehensive program prepared by a globally diverse faculty: 80+ Scientific Sessions, 40 Society Symposia, 16 Industry Symposia, 800+ Accepted Abstracts, 8 Wetlabs, 2 Industry Showcases and much more. To reflect on these and many of the other Congress-highlights such as the Presidential Symposium and the extensive Social Program, please take a look at the Aftermovie.

Mark your calendars and save the date for the 11th World Glaucoma Congress in Honolulu, Hawaii, USA taking place **June 25-28, 2025**!

We are currently planning the next series of the Fundamental Questions in Glaucoma Video Lectures and Surgical Grand Rounds. Keep an eye on our website for more information. The recorded sessions of the previous webinars and talks can be accessed by everyone with a WGA#One account on the WGA Video Library.

Best wishes,

Shan Lin
MD
Executive Vice-President

Kaweh Mansouri
MD MPH
Associate Executive Vice-President

GET TO KNOW US!

Pradeep Ramulu

Many of you reading come from great home institutions/departments, with great colleagues such as (for me at Johns Hopkins) Harry Quigley, Henry Jampel, David Friedman and others who have taught us so much about glaucoma and were role models in their dedication to patients and research. And many of us have participated in first-rate national and regional societies, such as the American Glaucoma Society, that have put on first-rate programs, provided grant funding to answer important questions, and fostered a community of scholarship and clinical excellence.

But there is only one WORLD Glaucoma Association that allows us the opportunity to extend our perspective beyond our Institution, country, and region, and redefine our notions of what glaucoma is and how it should be treated in the context of the best experts from around the globe. For me, I have realized many times over that the truth regarding glaucoma is complex, and that what I have thought to be true may not be 'as true'. Indeed, it has been a singular privilege of my career to tap into the best minds of the world to educate myself, and hopefully to share some of the incredible wisdom we have in our community with others.

I would like to thank the WGA for initially allowing me to participate in the Associate Advisory Board, an organization which has grown in scope and purpose so that we continue to engage the best, most dedicated faculty into our organization and grow them into future leaders. Through the AAB, I was allowed to join the Education Committee under the leadership of then Committee-Chair (and subsequently WGA President) Fabian Lerner, who began the processing of building a first-rate library of educational resources including Basic and Advanced courses to teach the fundamentals of glaucoma. It has

been a real joy to continue Fabian's work as director of this committee, using the committee's innovative ideas and dedication to build further resources including more courses, a series of short peer-reviewed video lectures on fundamental topics (the Fundamental Questions in Glaucoma series), and (following the brilliance of Dr. Tanuj Dada) the WGA Surgical Grand Round series – which has introduced a video-based approach to challenging surgical situations to world-wide audiences of over 1000 doctors.

Finally, it has been a pleasure to work with the great leaders at the WGA on projects including:

- **Dr. Bob Weinreb's consensus series**, particularly the 11th Consensus Meeting focused on Glaucoma Surgery, where I worked with a great group to finalize the 'Guidelines for surgical trials and outcome measures' section.
- **Drs. Winnie Nolan**, **Tina Wong**, and **Arthur Sit/Kaweh Mansouri**, who led the 2019, 2021, and 2023 Congresses, and helped me and the terrific Epidemiology/Genetics committees assemble first-rate sessions with amazing speakers.
- Our *IGR* and *Journal of Glaucoma* teams that have helped with these incredible resources for article reviews and new glaucoma-related literature, respectively.

Lastly, the WGA has been about forging friendships from around the world, bringing me closer to practitioners of great dedication, ethics, and compassion that inspire me to be better with my patients every day. To all my friends reading, and to those I have yet to meet, I look forward to seeing you again soon..

World Glaucoma Association
The Global Glaucoma Network

WGA Award recipients 2023

Laureate Award

The World Glaucoma Association Laureate Award is the highest honor that the Association can bestow. A WGA Laureate has an immense, unique and rare impact on our field through selfless leadership, scientific contribution, education and mentorship and advancement of the WGA goals.

Robert N. Weinreb (United States)

Founders Award

The World Glaucoma Association Founders Award is for an individual with a dedication to advancing the goals of the WGA, whose efforts have contributed significantly to our mission.

Ningli Wang (China)

Special Recoginition Award

The World Glaucoma Association Special Recognition Award is for an individual who has made extraordinary contributions to the WGA organization over a span of several years.

Tanuj Dada (India)

See all WGA award winners here

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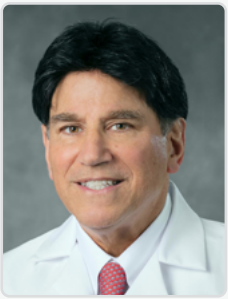
Editor's Selection



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

Basic Science

Modelling the biomechanics of the ONH and cornea

Comment by Arthur Sit, Rochester, MN, USA

107711 The effects of negative periocular pressure on biomechanics of the optic nerve head and cornea: A computational modeling study; Safa BN, Bleeker A, Berdahl JP, Ethier CR; Translational vision science & technology 2023; 12: 5

The Multi-Pressure Dial system (MPD; Equinox Ophthalmic, Inc., Newport Beach, CA) is an investigational device that produces a vacuum in the periocular region as a potential treatment for patients with glaucoma by purportedly reducing intraocular pressure (IOP). Previous research from this group using analytical mathematical models predicted an increase in ocular volume with application of negative periocular pressure (NPP), which would presumably lead to tissue distension (strain) similar to what would occur with elevation of IOP.[1] This leads to important questions about how IOP should be defined. The authors define IOP as the pressure difference between the intraocular environment and the rest of the body. However, this is very different from the conventional definition of IOP as transcorneal pressure, which reflects the difference in pressure between the intraocular environment and the air surrounding the eye. If pressure is decreased uniformly around the eye, tissue strain would be expected to increase throughout the eye, equivalent to an increase in IOP. In this case, transcorneal pressure would be the correct definition of IOP.

However, the current study from Safa *et al.* suggests that the effects of NPP may be more complex, causing different effects on the anterior segment versus the optic nerve head. In this case, the appropriate definition of IOP under NPP becomes more difficult.

This study investigated the effects of NPP on the biomechanics of the anterior segment and optic nerve head. The authors developed a finite element model based on existing models and published values for tissue properties. The model was optimized and validated by comparison with published ocular compliance data. Tensile and compressive strains were analyzed in four regions: lamina cribrosa (LC), prelaminar tissue (PLT), limbus, and corneal apex. A robust range of parameters were analyzed in four different simulations: 1. Normotensive case with IOP of 15.8 mmHg (baseline); 2. Goggle case with -7.9 mmHg NPP applied; 3. Hypertensive case with IOP of 31.6 mmHg; and 4. IOP fixed case with NPP applied but a constant IOP of 15.8 mmHg. They found that the hypertensive case resulted in markedly increased tensile strain in all four regions assessed compared to baseline. In contrast, application of NPP (cases 2 and 4) resulted in increased corneal and limbus tensile strain (although less than the hypertensive case) but decreased tensile strain in the PLT and LC suggesting a beneficial effect in the optic nerve head. The effect of different NPP distributions was also assessed, including vacuum linearly decreasing from the corneal apex to the optic nerve, vacuum only at the anterior segment, and vacuum uniform from the apex to the anterior margin of the peripapillary sclera. None of these resulted in significant differences in outcomes.

The authors are to be commended for this thorough study examining the effects of NPP on ocular tissue biomechanics. Boundary conditions are key determinants of results from finite element analysis and the authors have examined a wide range of conditions. However, **one critical boundary condition that was kept constant in all the simulations was retrolaminar tissue pressure (RLTP)**. In their simulations, LC tensile strain increased when translaminar pressure difference (TLPD) increased (Hypertensive case), decreased when TLPD decreased (Goggle case), and was essentially unchanged when TLPD was unchanged (IOP fixed case). If RLTP was not constant but instead decreases due to NPP, then any potential beneficial effect on PLT and LC strain may be reduced or even adversely affected due to increased TLPD.

One argument for not varying RLTP could be that CSF pressure is determined by intracranial pressure, which would not be affected by NPP. However, the relationship between intracranial pressure and optic nerve CSF pressure is complex, particularly in glaucoma patients. Morgan *et al.* previously demonstrated that the translaminar pressure gradient is no longer dependent on CSF pressure when CSF pressure drops below a threshold.[2] Further, CSF flow in the optic nerve appears to be impaired in normal tension glaucoma patients.[3,4] Another argument could be that NPP does not affect peripapillary pressure. Shafer *et al.* investigated the effect of NPP on retrobulbar pressure in human cadavers.[5] While there was no immediate change in retrobulbar pressure with application of the vacuum, there was a gradual decrease in pressure with extended application in one of the two eyes studied. Further, cadaver models cannot fully replicate the complexity of a living eye with changes in ocular and periocular blood flow resulting from application of vacuum. Regardless of the limitations, the authors have produced a thought-provoking study highlighting the complexity of changes that occur with NPP. Further studies are required to model the changes that occur in eyes with a dynamic retrolaminar tissue pressure under negative periocular pressure and explore the changes that occur in living human eyes.

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Basic Science

Histo-architectural effects of IOP

Comment by Michael Girard, Singapore

108138 Who bears the load? IOP-induced collagen fiber recruitment over the corneo-scleral shell; Foong TY, Hua Y, Amini R, Sigal IA; Experimental Eye Research 2023; 230: 109446

The corneoscleral shell could play a pivotal role in enhancing our comprehension of glaucoma's development and progression. Beyond its crucial role in maintaining the optical integrity of the eye, its posterior part protects the delicate optic nerve head (ONH). This shielding mechanism is thought to be achieved through the precisely organized collagen fibers within the peripapillary and posterior sclera, thus serving as a resilient barrier against mechanical insults stemming from fluctuating intraocular pressure (IOP) and other external loads. Conversely, the anterior segment of the corneoscleral shell has been recognized as a potential biomarker for glaucoma. It has occasionally been proposed

as a surrogate indicator for axonal damage in select, though not all, types of glaucoma. The supposition is that corneal collagen composition might mirror that of the ONH, thus providing a basis for these associations.

Given the potential significance of collagen microstructure in glaucoma, the authors aimed to assess the recruitment of collagen fibers as a function of IOP (at either physiological or elevated levels) and whether such responses were heterogeneous. In this context, a recruited fiber is defined as one that has straightened (due to IOP-induced stretching), consequently assuming load-bearing capabilities, and no longer exhibiting a 'wavy,' 'crimped,' or 'tortuous' configuration. In essence, the authors' **primary objective was to ascertain the proportion of collagen fibers contributing to the load-bearing function under IOP-induced stress in various regions of the corneoscleral shell.**

To this end, the authors developed an elegant strategy to make such measurements using human donor eyes. First, they imaged (using polarization light microscopy) and mapped collagen crimp over the entire corneoscleral shell in nine human donor eyes. Second, they used a computational model to simulate how such fibers would unfold for two levels of IOP, *i.e.* baseline at 15 mmHg, and elevated at 50 mmHg. Using such an approach, the authors successfully established the rate at which collagen fibers transitioned from a crimped to an uncrimped state (*i.e.*, became recruited) and precisely identified their specific locations within the corneoscleral shell.

Overall, the authors found that fiber recruitment was highly heterogeneous. At baseline IOP, fibers were recruited the fastest in the posterior sclera (90% of fibers were recruited) as opposed to ~30% in the cornea and peripapillary sclera. Surprisingly, at an IOP of 50 mmHg, fibers were fully recruited across the shell, except at the equator and in the peripapillary sclera (70% recruitment only).

This study offers a comprehensive view of the intricacies of the eye as a mechanical system. Firstly it tells us that the rate of stiffening with IOP is going to differ considerably in different regions of the corneoscleral shell. Secondly, it reinforces that summarizing eye rigidity with a single parameter is not feasible, as tissue stiffness exhibits heterogeneity, but also changes in tissue stiffness with IOP. Thirdly, it indicates that even at an elevated IOP of 50 mmHg, not all fibers in certain eye regions are fully recruited, suggesting the presence of a reserve capacity to adapt to additional loads.

The proposed work exhibits merit, and there are several aspects worth considering for future enhancements. For instance, the authors might contemplate incorporating experimental validations of recruitment under varying levels of IOP. Additionally, expanding the scope of the research to encompass other crucial loads that could contribute to glaucoma, such as optic nerve traction, cerebrospinal fluid pressure, and others, could offer valuable insights.

Finally, it is worth noting that if fiber recruitment could be measured *in vivo*, it has the potential to inform us about which ONHs are more likely to withstand mechanical stress across a wide spectrum of internal and external biomechanical loads, and which ones might be more susceptible to failure, leading to neural and connective tissue damage.

Basic Science

Learnings from a classic rodent model

Comment by Robert Nickells, Madison, WI, USA

108575 Natural history of glaucoma progression in the DBA/2J Model: Early contribution of Müller cell gliosis; Amato R, Cammalleri M, Melecchi A, Bagnoli P, Porciatti V; Cells 2023; 12: (9):1272.

Progressive degeneration of the optic nerve and retinal ganglion cells (RGCs) is a hallmark of glaucomatous pathology. While there is consensus that an increase in intraocular pressure (IOP) above physiological levels is the major initiator of pathology, principally at the level of the optic nerve head, there is still uncertainty of what the actual pathological mechanisms are that elicit the degenerative response. Enter our limited understanding of the roles that glial cells have in both moderating and exasperating these signals. The retina and optic nerve combined contain at least four different glial cell populations, including astrocytes, Müller cells, microglia/monocytes, and oligodendrocytes. All these cells are likely important actors in this overall process, creating a complex dance that is only slowly being dissected in our quest to understand the link between IOP-induced mechanical stress and RGC pathology.

Amato and colleagues have tackled this dissection by correlating four metrics of (1) IOP change; (2) RGC loss; (3) macroglial (astrocyte and Müller cell) reactivity; and (4) vascular changes over a time course of glaucomatous pathology in the DBA/2J mouse model. Progression of pathology in DBA/2J mice has been studied for over 20 years. These animals exhibit an increase in IOP beginning at seven to eight months of age with optic nerve degeneration and RGC loss quickly following suit. By ten months of age, at least 40% of eyes have reached end-stage disease and by 15 months, most eyes are severely affected.[1,2] The group assessed changes of each of these four metrics in groups of DBA/2J mice at the ages of two, six, ten, and 15 months, thereby bracketing the major period of IOP increase. **They found that ocular hypertension correlates with RGC loss, astrocyte reactivity, and vascular pathology including a breakdown of the blood retinal barrier as a function of ZO-1 decreases**. Importantly, they observed Müller cell reactivity and the production of HIF-1a and VEGF at six months of age, two factors that can contribute to vascular permeability. Collectively, **the authors suggest that non-IOP related factors are contributing to RGC pathology, although the precise role of Müller cells in this process, whether being an early protective event or a pathological event remain to be elucidated**.

This study is compelling, showing a potential contribution of Müller cells changes that precede statistically significant elevations in IOP

There are some caveats associated with this work that should be kept in mind when considering it. Firstly, DBA/2J glaucoma is both highly variable and asymmetric[1,2] and relatively few eyes were actually used for each set of experiments. When making comparisons between two or more metrics, it is important not to use generalized data and instead use stratified comparisons (one eye for two metrics compared, etc.). Secondly, the critical time points of IOP elevation were not included in the study, which may have an impact on interpretation. Thirdly, any evaluation of glial responses in glaucoma should consider reactivity of microglia. In the DBA/2J model, for example, microglial responses have been reported as early as 3 months of age.[3] Fourthly, the authors used GFAP staining as the single marker of glial reactivity. While this often appears in the literature, it does not appreciate the complexity of the reactive response and instead assumes that glial cells respond monolithically and not as a continuum of varying phenotypes.[4] Nevertheless, this study is compelling, showing a potential contribution of Müller cells changes that precede statistically significant elevations in IOP.

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Clinical Examination Methods

24-hour monitoring to detect glaucoma progression

Comment by Arthur Sit, Rochester, MN, USA

107957 24-Hour monitoring of intraocular pressure fluctuations using a contact lens sensor: Diagnostic performance for glaucoma progression; Gaboriau T, Dubois R, Foucque B, Malet F, Schweitzer C; Investigative Ophthalmology and Visual Science 2023; 64: 3

Intraocular pressure (IOP) is highly variable and follows a distinct circadian rhythm with values higher during sleep than while awake when measured in the normal physiologic positions.[1] Secondary analyses of data from large clinical trials clearly show that increased IOP fluctuations between study visits is associated with increased risk of glaucoma progression, at least in some patient populations.[2,3] However, waiting months to years to assess IOP fluctuations is obviously not ideal for glaucoma management. The advent of new technologies for near-continuous IOP monitoring is providing a wealth of data, but how to interpret that data is still an emerging field. Gaboriau *et al.* performed an innovative study that analyzed 24-hour IOP profiles collected using the Triggerfish contact lens sensor (CLS; Sensimed, Etagnières, Switzerland).

This prospective cohort study included 54 eyes of 54 open-angle glaucoma patients with at least two years of follow-up and five reliable visual-field tests using standard automated perimetry. CLS profiles were collected between May 2015 and May 2016, and subjects were divided into fast progressors (MD progression rate more than -0.5 dB/year) and slow progressors (MD progression rate less than or equal to -0.5 dB/year).

The CLS records voltage changes due to deformation of the cornea from IOP changes instead of IOP itself. Although the CLS records measurements every five minutes, each measurement is based on raw data consisting of 300 samples obtained over 30 seconds. Unlike most other CLS studies, this study used the raw data, with 24-hour profiles processed in three stages: (1) Removal of very short-term fluctuations (10 ms time scale) associated with blinks; (2) Adjustment for drift over the 24-hour period; and (3) Wavelet-based analysis to examine fluctuations over multiple different time scales ranging from 10 min to ≥4000 min. IOP profile fluctuations between the two patient groups were compared by examining the absolute area under the receiver operating curve (AUROC) from wavelet-based analysis. **The authors found that fast progressors had higher AUROC for time scales of 24-hours and 60-220 minutes.** There was no difference at a time scale of 120-500 minutes.

This study has significant strengths in the systematic approach provided by wavelet-based analysis. However, there are several potential weaknesses in the study. Most importantly, the two groups were not equivalent: the fast progressors had higher baseline IOP and

more severe VF defects. Whether or not the 24-hour IOP profiles would provide additional predictive power beyond these two parameters was not analyzed. Also, the duration of follow-up or any changes in therapy during follow-up were not reported and are potential confounders. It would also have been valuable if the authors reported the relationship between shorter time scale (30-125 minutes or less) fluctuations and glaucoma progression. Nevertheless, the analysis approach and results of this study provide important information about the predictive value of IOP fluctuations at different time scales for progression of glaucoma and the authors are to be congratulated for their work.

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Clinical Examination Methods

Predicting visual hemifield extension

Comment by Christopher Girkin, Birmingham, AL, USA

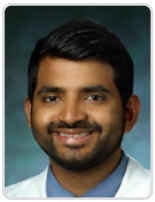
107536 Structural and vascular changes in glaucoma with single-hemifield defect: predictors of opposite hemifield visual field progression; Lee A, Sung KR; Graefe's Archive for Clinical and Experimental Ophthalmology 2023; 261: 1669-1680

Lee and colleagues have recently published the results of a retrospective observational study examining the associations between the rate of change in vascular density and structural parameters of the optic nerve head, macular and retinal nerve fiber layer (RNFL) measured with optical coherence tomography and angiography (OCT/A) in 61 patients with open-angle glaucoma with visual field loss confined to one hemifield to determine if these factors are predictive of the development of a new visual field defect in the unaffected hemifield. These associations were evaluated within separate multivariable cox-proportional hazard models for the OCTA and OCT parameters. These were evaluated separately due to multicollinearity when included in the same model. For structural parameters, they found that a greater rate of change in the RNFL thickness in the normal hemifield, along

with greater rates of change in global macular ganglion cell thickness were associated with the development of a new visual field defect (defined by Early Manifest Glaucoma Trial criteria). In the OCTA model, optic nerve head and macular vessel density in the affected and unaffected hemiretinas were associated with the development of a new visual field defect in the perimetrically normal hemifield. Despite the relatively small sample size, this work is additive to several prior case-control studies showing signs of subtle injury in the hemiretina associated with the perimetrically normal hemifield. These results suggest that changes in the vascular and structural parameters maybe a warning sign to alert the clinician of the potential for continued damage. The authors note that there was collinearity between structural and vascular parameters indicating that these parameters were tightly correlated. Thus, **it remains unclear if the vascular parameters assessed with OCTA are truly independent of the structural parameters assessed with OCT in the prediction of glaucomatous visual field progression in these patients.**

Clinical Examination Methods

Fast progressor prevalence



Comment by Pradeep Ramulu and Jithin Yohannan, Baltimore, MD, USA

107576 Fast progressors in glaucoma: Prevalence based on global and central visual field loss; Jackson AB, Martin KR, Coote MA, Medeiros FA, Girkin CA, Fazio MA, Liebmann JM, De Moraes CG, Weinreb RN, Zangwill LM, Wu Z; Ophthalmology 2023; 130: 462-468

Jackson *et al.* use a multi-institutional longitudinal dataset of treated glaucoma patients to study the prevalence of rapid progressors as defined by global and central visual field (VF) loss. They find that **the prevalence of rapid progression defined by global VF loss (rate of mean deviation [MD] change < -1 dB/year) is approximately 12%, in line with previously published studies**. **They define rapid central VF loss by computing the slope of the total deviation values of the 12 test locations in the central 10 degrees (MTD10 < -1 dB/year) and find a similar rate of rapid progression (11.7%).** Additionally, rather than solely relying on pre-specified cutoffs, they define rapid progression based on normal distribution cutoffs. This approach **found poor overlap between progressing eyes defined by global (MD) and central (MTD10) definitions of rapid progression**. For instance, when defining rapid progression as the bottom 0.5% of the normal distribution of slopes, they found only one in four eyes progressing by central change (MTD10) progressed by global change (MD).

Based on these results, one may ask whether following global VF, central VF, or some other measure of VF worsening is more valuable. Some areas of the VF will progress more dramatically in specific patients (due to disease progression or statistical noise). For this reason, focusing on additional regions of the VF may pick up progression that analysis of the full VF does not. But can one also make a functional argument for the central visual field being most critical? While some papers have suggested central loss is more associated with quality of life, better peripheral vision is more associated with less frequent/notable events (falls, motor vehicle accidents, difficulty searching) that are nonetheless quite important and impactful.

These results highlight the prevalence of treatment failures in routine clinical practice

Additionally, these results highlight the prevalence of treatment failures in routine clinical practice. Future work must seek to reduce the rate of vision loss in the approximately 10% of patients undergoing treatment who progress at an unacceptably fast pace. Recent advances in artificial intelligence models, which forecast eyes at higher risk for rapid progression (PMID: **36944385) with early data, are likely a step in the right direction. Still, much work remains to make these models accessible to the clinician. Further, we need a better understanding of how various treatment decisions impact the rate of visual field progression. While large clinical trials (UKGTS, LIGHT, HORIZON, etc.) allow us to understand the effect of a limited number of treatments on VF change in narrow subpopulations of patients,** we often lack evidence they need to guide clinical decisions in the face of unique combinations of patient characteristics and an ever-growing array of therapeutic options encountered in real-world clinical settings. Again, interpretable and causal models developed using sizeable real-world datasets and trained to assess the impact of various treatments on VF trajectory may help us better understand the impact of our decisions on a patient's risk for rapid progression.

Risk Factors

Is low serum vitamin D related to higher IOP?

Comment by Shan Lin, San Francisco, CA, USA

107559 Inverse relationship between verum 25-hydroxyvitamin D and elevated intraocular pressure; Lee JH, Kwon YJ, Lee HS, Han JH, Joung B, Kim SJ; Nutrients 2023; 15(2):423.

There has been controversy about the relationship of serum vitamin D levels and intraocular pressure (IOP). There is abundant data supporting the role of vitamin D in reducing inflammation as well as in promoting antioxidant pathways. Accordingly, there is good evidence to correlate low serum vitamin D with glaucoma. However, there has not been a previous study utilizing a large database to evaluate the correlation of serum vitamin D with IOP. Lee J-H. *et al.* have utilized the data of a large sample of patients from their Nowon Eulji Health Promotion Center to assess this topic. Data was available from 15,338 participants. Serum vitamin D is measured as 25-hydroxyvitamin D (25(OH)D). Subjects were classified into: 1) 25(OH)D deficiency (< 20 ng/mL); 2) 25(OH)D insufficiency (20-29 ng/mL), and 3) 25(OH)D sufficiency (30 ng/mL or greater). The numbers in each group were 9800, 3685, and 1853, respectively. The outcome was elevated IOP (22 mmHg or greater). The authors found that **the proportions with elevated IOP were greatest in the 25(OH)D deficiency group (3.2%), followed by the 25(OH)D insufficiency group (2.4%), and the 25(OH)D sufficiency group (1.6%) (overall p<0.001)**. In pairwise comparisons, the differences between the deficiency group and either of the other two groups were statistically significant. However, the difference between the insufficiency and sufficiency groups was not ($p = 0.051$). Statistical analysis showed that there was an inverse relationship between 25(OH)D levels and IOP, *i.e.*, lower 25(OH)D levels were associated with a greater IOP ($p < 0.001$). In subgroup analysis, the female and elderly subgroups did not show statistically significant relationships of 25(OH)D status and elevated IOP. The authors speculate that there may be an interaction of vitamin D and sex hormones on the effects on IOP. In males and the young, addressing vitamin D deficiency may be an avenue to prevent glaucoma. The main limitation of this study is that it is cross-sectional and provides evidence for an association but not a causal relationship.

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Risk Factors

Is low serum vitamin D related to higher IOP?

Comment by Anne Coleman, Los Angeles, CA, USA and Ramin Talebi, Philadelphia, PA, USA

107559 Inverse relationship between serum 25-hydroxyvitamin D and elevated intraocular pressure; Lee JH, Kwon YJ, Lee HS, Han JH, Joung B, Kim SJ; Nutrients 2023; 15(2):423.

This cross-sectional study by Lee *et al.* examined the association between vitamin D levels and elevated intraocular pressure (EIOP) using health examination data from a single center. There is a known inverse relationship between serum 25(OH)D levels and glaucoma risk, which has been attributed to the role of vitamin D in reducing oxidative stress on the optic nerve and trabecular meshwork. The authors of the present study extend this association to intraocular pressure by hypothesizing that serum vitamin D levels are inversely related to EIOP. EIOP was determined using a threshold of ≥ 22 mmHg measured by an air puff tonometer. Serum 25(OH)D levels were determined through laboratory measurements of blood samples and categorized into 25(OH)D deficiency (< 20 ng/mL), insufficiency (20-29 ng/mL), and sufficiency (≥ 30 ng/mL). The association between 25(OH)D levels and risk of EIOP was determined using cubic spline analysis and logistic regression modeling, adjusting for several demographic characteristics, social factors, and physical and laboratory measurements.

A total of 15,388 participants ages 19 years and older with IOP and serum 25(OH)D data were included. **Spline analysis demonstrated an inverse non-linear dose-response relationship between serum 25(OH)D and EIOP risk (p < 0.001).** This dose-response relationship was also observed in regression analysis. **In fully adjusted models, the 25(OH)D insufficiency (odds ratio [OR]: 0.72, 95% 95% confidence interval [CI]: 0.56-0.92) and 25(OH)D sufficiency (OR: 0.51, 95% CI: 0.34-0.78) groups had significantly lower odds of EIOP compared to the 25(OH)D deficiency group.**

The study findings significantly lack generalizability as the population was ethnically homogenous and the data lacked information about glaucomatous status or past exposure to IOP lowering pharmacotherapy

The study results suggest an inverse dose-dependent association between serum 25(OH) D levels and EIOP. The use of two distinct statistical methods and several covariates on a large sample provides a robust analysis to support the inverse association. The application of both spline analysis and logistic regression allows readers to examine the relationship continuously and provides useful thresholds to consider for clinical screening. Importantly, the study findings significantly lack generalizability as the population was ethnically homogenous and the data lacked information about glaucomatous status or past exposure to IOP lowering pharmacotherapy. Further studies are needed to examine the effects of serum 25(OH)D and Vitamin D supplementation on IOP, especially among treatment-naïve patients and patients at risk of glaucoma. We congratulate the authors on studying this very important relationship.

Glaucoma and Systemic Diseases

Sleep apnea and glaucoma

Comment by Steve Mansberger and Erick Rivera, Portland, OR USA

107255 Long-term effects of obstructive sleep apnea and its treatment on open-angle glaucoma: a big-data cohort study; Lee TE, Kim JS, Yeom SW, Lee MG, Lee JH, Lee HJ; Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine 2023; 19: 339-346

This study includes over 12,000 subjects from a health services database from Korea to determine whether obstructive sleep apnea (OSA) and incident glaucoma have an association. The Study groups were defined as subjects with an OSA diagnosis within a two-year period and are matched to a Control group based on gender, residential area, economic status and other health conditions. They queried the database over the subsequent ten years for incident glaucoma, and excluded subjects that received a diagnosis of OSA during the follow-up period. **Patients with OSA have 42% increase in risk (Hazard Ratio (HR) of 1.42) for developing OAG compared to non-OSA patients**. In only a two-year period, **treatment of OSA, either OSA surgery or CPAP treatment, decreased the risk of developing OAG (HR 0.71, HR 0.06)**.

Another issue is that the study excluded those that developed OSA, and would be more likely to create attrition from the control group and increase the likelihood of an association in the Study group. This might magnify the treatment of OSA

The study strengths are its large sample size and adjustment for multiple factors associated with glaucoma and sleep apnea. However, there are a number of possible weakness. The CPAP data and treatment was only collected for two years. It is surprising that this had such a large effect when only available for two years and available at the end of the study. Another issue is that the study excluded those that developed OSA, and would be more likely to create attrition from the control group and increase the likelihood of an association in the Study group. This might magnify the treatment of OSA. It would be valuable to understand how including them would influence the results and consider adjustment for follow-up time. The study does not define glaucoma and a selected small chart review to validate the diagnosis of glaucoma would be valuable. Finally, it would be important to state and control for sleep testing since some patients with glaucoma may have been referred for sleep testing and vice versa. Did the patients undergo any other confounding treatment for their sleep apnea such as weight loss?

While the benefits to glaucoma of treating OSA is still controversial, it is important to refer patients with suspected sleep apnea for testing because treatment of sleep apnea has large health benefits for other health conditions

We congratulate the authors on this longitudinal study. While the benefits to glaucoma of treating OSA is still controversial, it is important to refer patients with suspected sleep apnea for testing because treatment of sleep apnea has large health benefits for other health conditions. I refer patients for sleep testing if they are falling asleep during their visual field testing; have snoring and become apneic during their eye surgery; or give a history of sleep disturbances.

Medical Treatment

Neuroprotection

Comment by Keith Martin, Melbourne, Australia

108604 Phase I NT-501 ciliary neurotrophic factor implant trial for primary open-angle glaucoma: Safety, neuroprotection, and neuroenhancement; Goldberg JL, Beykin G, Satterfield KR, Nuñez M, Lam BL, Albini TA; Ophthalmology science 2023; 3: 100298

A significant minority of people with glaucoma continue to lose vision despite therapies that lower intraocular pressure. Thus, there remains an unmet clinical need for treatments that protect or enhance visual function. Ciliary neurotrophic factor (CNTF) has been shown to protect retinal function in multiple pre-clinical models of retinal disease. The NT-501 device is an intravitreal implant that contains encapsulated, immortalized human RPE-derived cells engineered for long-term release of CNTF into the human eye. The device has previously been shown to increase retinal thickness in early phase clinical trials in retinitis pigmentosa and AMD. In the current study by Goldberg *et al.,* the NT-501 device was implanted in 11 eyes of 11 patients with glaucoma in a Phase 1 safety study where participants were followed for 18 months. **The implant was reported to be safe and well-tolerated in eyes with POAG, with no devices having to be removed during the study**.

The investigators reported that some subjects who received the implant demonstrated both structural and functional improvements suggesting biological activity. However, as the investigators point out in their discussion, this was a small, non-randomized study, and the baseline level of disease was significantly worse in the implanted eyes than in the fellow eyes. This might potentially bias the results toward observing improvements or less worsening of structural and functional measures in the study eyes. Thus, it remains to be seen if this strategy can mediate consistent neuroprotection or neuroenhancement in human glaucoma.

It remains to be seen if this strategy can mediate consistent neuroprotection or neuroenhancement in human glaucoma

However, the encouraging safety data has supported the premise for a randomized phase II clinical trial of single and dual NT-501 CNTF implants in patients with POAG, which is now underway. The results are awaited with great interest.

Medical Treatment

Impact of low vision on medical treatment

Comment by Andrew Tatham and Celia Alcalde, Edinburgh, UK

108441 Patients with low-vision struggle with placing eye drops and benefit from an eye drop aid; Grissom N, Gardiner SK, Rees JP, Sanchez FG, Mansberger SL, Cunningham ET, Burgoyne CF, Rice K, Belter C, Kinast RM; Ophthalmology. Glaucoma 2023; 6(5):501-508.

Many patients struggle to correctly instill their eye drops, especially those with low vision.[1] This study examined whether a nose-pivoted delivery device (NPDD) could improve drop instillation in patients with visual acuity worse than 20/60 or with visual fields worse than 20 degrees in the better seeing eye. The NPDD is a silicone alignment aid with a sleeve that fits around the eye drop bottle and an extended portion that rest on the bridge of the nose stabilizing the bottle over the ocular surface during drop instillation.[2]

Thirty participants were recruited, and video recorded self-administering drops of artificial tears in both eyes using their usual technique. A short teaching session was then provided including advice on a traditional eye drop instillation technique and instruction in how to use the NPDD. Participants were then asked to instill eye drops using the traditional technique and using the NPDD, with the order randomized. Videos were graded and primary success defined as an eye drop reaching the eye without the bottle touching the eye or periocular surface.

At baseline a high proportion of participants struggled instilling drops, with an eye drop reaching the ocular surface in only 64%. Forty percent touched the ocular or periocular surface with the bottle tip, and a mean of 2.4 drops were dispensed per instillation attempt. Use of the NPDD improved successful drop delivery from 52% to 76% (P = 0.013) and reduced medication wastage. **Contact between the bottle tip and eye or periocular region decreased to only 14% and contact with the eye decreased from 21% to 0%.** In addition, 73% of participants preferred the NPDD to the traditional method and this figure was 94% among those who reported difficulty using eye drops. There was also an improvement in ease-of-use scores, self-perceived success, and all participants would recommend the device to others.

The proportion of eye drops successfully reaching the eye was actually lower using the nose-pivoted delivery device, though this was not statistically significant (64% versus 59%)

Although the NPDD improved success, improvement was driven by the reduction in contact between the bottle tip and eye. The proportion of eye drops successfully reaching the eye was actually lower using the NPDD, though this was not statistically significant (64% versus 59%). The high proportion of patients with low vision unable to deliver an eye drop to the eye highlights the need of improved methods of drug delivery in this vulnerable population, who are likely at high risk of further functionally significant visual loss if they are not receiving medications as intended.

While the NPDD reduced bottle tip contact, improved patients' perception of ease of use and confidence in eye drop self-administration, the failure to increase the proportion successfully delivering a drop to the ocular surface is disappointing. A bottle tip touching the ocular surface may have no detrimental effect on treatment efficacy but successful drop delivery to the ocular surface is essential. The study importantly highlights difficulties in eye drop administration as a major barrier to effective glaucoma treatment and clinicians should be aware of this common limitation of topical therapy, especially when considering treatment options in those with low vision.

Although in this small study the NPDD did not improve the proportion of patients with low vison able to successfully deliver a drop to the ocular surface, patients were extremely satisfied with the device and preferred it to their traditional drop instillation method. It would be interesting to explore if longer periods of practice using the NPDD improve performance as in the current study participants were only permitted a few minutes with the device.

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Medical Treatment

Gene therapy

Comment by Makoto Aihara, Tokyo, Japan

108419 Matrix metalloproteinase-3 (MMP-3)-mediated gene therapy for glaucoma; O'Callaghan J, Delaney C, O'Connor M, van Batenburg-Sherwood J, Schicht M, Lütjen-Drecoll E, Hudson N, Ni Dhubhghaill S, Humphries P, Stanley C, Keravala A, Chalberg T, Lawrence MS, Campbell M; Science advances 2023; 9: eadf6537

IOP-lowering is indispensable for the treatment of glaucomatous optic nerve damage. The current therapeutic approach mostly depends on eyedrops, which is a big burden for glaucoma patients, especially the elderly. In this respect, gene therapy to lower IOP is an ideal approach to reduce the burden in both patients and medical staffs. O'Callaghan *et al.* developed a new strategy through infecting corneal endothelial cells by AAV-9 induced MMP3 expression. Based on their previous reports using mice, efficacy and safety profile of MMP3 expression by intracameral injection were biologically optimized and confirmed. Their experiments were well-conducted, and these plausible data supported the sustained reduction of outflow resistance leading to IOP reduction in mouse and non-human primates. Their strategy that MMP3 delivery through aqueous humor to outflow tissues from the non-dividing corneal endothelial cells is excellent and appropriate for the sustainable gene therapy and worth to be proceeded to the clinical trial.

> Once the TM cells or Schlemm's canal endothelial cells are damaged and lose their function, the induction of MMP3 may not be effective

Still, there are some challenges for clinical trials. The indication for gene therapy might depend on glaucoma subtype, stage of disease and level of IOP. In glaucoma eyes, many biological factors to increase ECM and tissue scarring such as TGF families or lipid mediators are present in the aqueous humor. It is unknown whether MMP3 induction can overcome the scarring process and recover the function of conventional outflow pathway. Before gene therapy, the function of the outflow pathway should be thoroughly evaluated, although we do not have a useful tool so far. Once the TM cells or Schlemm's canal endothelial cells are damaged and lose their function, the induction of MMP3 may not be effective. Long-term expression of MMP3 may induce unknown adverse events such as chronic inflammation or retino-choroidal changes through the uveoscleral pathway.

However, this study is a big advance for the new treatment for IOP reduction in glaucoma.

Surgical Treatment

Iridotomy for angle-closure prevention: 14-year outcomes

Comment by Alanna James and Benjamin Xu, Los Angeles, CA, USA

108334 Fourteen-year outcome of angle-closure prevention with laser iridotomy in the Zhongshan Angle-Closure Prevention Study: Extended follow-up of a randomized controlled trial; Yuan Y, Wang W, Xiong R, Zhang J, Li C, Yang S, Friedman DS, Foster PJ, He M; Ophthalmology 2023; 130(8):786-794.

This study is a follow-up to the original six-year Zhongshan Angle-Closure Prevention (ZAP) trial and presents 14-year data on progression rates from primary angle-closure suspects (PACS) to primary angle closure (PAC). The ZAP trial, conducted in Guangzhou, China, enrolled 889 participants with bilateral PACS, defined as two or more quadrants of non-visible trabecular meshwork on gonioscopy without peripheral anterior synechiae (PAS) or elevated intraocular pressure (IOP) over 21 mmHg. One eye was randomized to treatment with laser peripheral iridotomy (LPI) and the other eye served as a control. The primary outcome measure was progression to PAC, defined as IOP greater than or equal to 24 mmHg, formation of one or more clock hours of PAS, or an episode of acute primary angle closure (APAC).

The six-year and 14-year ZAP trial findings are largely consistent with a few key differences. The 14-year data was completed in 499 of the treatment eyes (56.13%) and 501 of the control eyes (56.36%). **The 14-year progression risk was three-fold lower among treated than control eyes, which is greater than the two-fold risk reduction reported in the six-year study**. In both studies, the lower progression was lower largely due to lower risk of PAS formation in the treated group. The 14-year progression risk among control eyes remained low (1.4% per eye year), although this was higher than the six-year progression risk (0.8% per eye year). There were no new episodes of APAC between years six and 14 with total of five control eyes and one treated eye ($p = 0.1$). The 14-year number needed to treat to prevent one case of PAC was 12.4 compared to 44 at six years. Only two (0.22%) treated and four (0.45%) control eyes developed primary angle-closure glaucoma (PACG). The 14-year study found that patients with baseline IOP greater than 15 mmHg, Van Herrick grading less than 15%, and IOP increase after DRPPT less than 4 mmHg were two to three times more likely to progress to PAC. **The authors again recommended against widespread LPI for PACS given these findings.**

The 14-year number needed to treat to prevent one case of PAC was 12.4 compared to 44 at six years

The ZAP trial is a well-designed and executed study. By using fellow eyes as controls, confounding and biasing effects were mitigated. The 14-year sample size was robust despite participant attrition, providing sufficient statistical power to draw meaningful conclusions about long-term risk of progression. **While the data shows LPI reduces risk of progression to PAC, this is primarily due to lower risk of PAS formation, which is of questionable clinical significance**. One of the common critiques of the ZAP trial is its potential lack of generalizability due to a relatively homogeneous study population. Nevertheless, this study offers valuable information and provides compelling evidence to shift practice patterns away from widespread LPI treatment of PACS eyes. This approach helps reduce healthcare costs and avoid unnecessary complications in the form of inflammation, IOP spikes, dysphotopsias, and cataract formation. However, it is crucial to remember that a subset of PACS will eventually progress to PAC and PACG without treatment, which can be visually devastating. Therefore, additional clinical methods are needed to identify high-risk PACS patients who would benefit from LPI or other interventions.

Surgical Treatment

Iridotomy for angle-closure prevention: 14-year outcomes

Comment by Sasan Moghimi, La Jolla, CA , USA

108334 Fourteen-year outcome of angle-closure prevention with laser iridotomy in the Zhongshan Angle-Closure Prevention Study: Extended follow-up of a randomized controlled trial; Yuan Y, Wang W, Xiong R, Zhang J, Li C, Yang S, Friedman DS, Foster PJ, He M; Ophthalmology 2023; 130(8):786-794.

Prophylactic laser peripheral iridotomy (LPI) traditionally has been recommended for primary angle-closure suspect (PACS) patients to prevent progression to angle closure. However, mass laser intervention is costly and thus requires substantial evidence to support this as a broad prophylactic strategy.

The landmark Zhongshan Angle Closure Prevention (ZAP) trial[1] was a randomized clinical trial that recruited 889 subjects with bilateral PACS, aged between 50 to 70 years, through community-based screening in Guangzhou, China and explored the benefit of treating PACS eyes with LPI. Bilateral PACS patients were treated with LPI in one randomly selected eye, with the fellow eye serving as an untreated control.

Six-year report of ZAP study and a recent five-year findings from Singapore Asymptomatic Narrow Angles Laser Iridotomy Study (ANA-LIS)[2] LPI achieved a 50% reduction in the six-year risk of progression to primary angle closure (PAC) in PACS. Given the low incidence rate of outcomes that have no immediate threat to vision, these studies did not recommend widespread prophylactic laser peripheral iridotomy for primary angle-closure suspects. The number needed to treat to stop one case of PACS from converting to PAC was 44 at year six (in the ZAP trial) and 22 at year five (in ANA-LIS). **However, these studies lacked the statistical power necessary to make risk assessment and recommendations for clinicians which PACS patients would benefit from LPI.**

In the extended report from the ZAP trial, Yuan *et al.* completed a 14-year follow-up of the study to identify the risk factors related to PACS progression with or without LPI. Three hundred and ninety LPI-treated eyes and 388 control eyes were lost to follow-up. Thirty-three **LPI-treated eyes (4.27 eyes per 1000 eye-years) and 105 control eyes (13.59 eyes per 1000 eye-years) reached the primary endpoint (Hazard ratio:0.31, P < 0.01)**. **We would need to treat 12 PACS to prevent 1 PAC occurrence over 14 years.** Again, the benefit of treatment was achieved mainly by reducing the development of peripheral anterior synechiae (conversion to PAC). Primary angle-closure glaucoma was found in two LPI-treated eyes and four control eyes. Within them, 1 LPI-treated eye and five control eyes progressed to acute angle closure.

The main limitation of the study is the generalizability of the results

They conducted Risk Assessment in treated and untreated PACS eyes. **Higher IOP, shallower limbal anterior chamber depth (LACD), and greater central anterior chamber depth were associated with an increased risk of end points developing in untreated eyes**. **In the treated group, eyes with higher IOP, shallower LACD, or less IOP elevation after the darkroom prone provocative test (DRPPT) were more likely to demonstrate PAC after LPI.**

The main limitation of the study is the generalizability of the results. The study cohort was entirely comprised of Chinese subjects, and therefore, the results may not be fully generalizable to other racial and ethnic groups. This ethnicity is considered a high-risk group for angle-closure disease. Interestingly, only 12% of PACS progressed after 14 years, which is much lower than other reports which ranged from 9-22 % in a five-year follow-up.[2-4] Of note, in the ANALIS study, 9.5% of patients with PACS progressed over five years of follow-up.[2] The only study conducted for > 10 years reported a 35% progression rate of PACS in Inuit patients.[5] These differences may be related to the hospital-based population of some of these studies and more lenient definitions of end-point. Nonetheless, the low incidence rate observed in the ZAP study does not align with the high prevalence of PACG in the Chinese population.

As the annual incidence of PAC was low and AAC and PACG were relatively rare in the community-based population with PACS over the long term, clinicians should assess the risk factors for

progression when treating patients with PACS and prophylactic LPI should be recommended preferentially to those at the highest risk of angle closure

The current report confirms that Laser Peripheral Iridotomy is safe and results in a two-third decrease in PAC occurrence after LPI over 14 years. As the annual incidence of PAC was low and AAC and PACG were relatively rare in the community-based population with PACS over the long term, clinicians should assess the risk factors for progression when treating patients with PACS and prophylactic LPI should be recommended preferentially to those at the highest risk of angle closure.

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Surgical Treatment

Stent vs. hole: Insights from GPS

Comment by Kaweh Mansouri, Lausanne, Switzerland

108212 Gel stent versus trabeculectomy: The randomized, multicenter, Gold-Standard Pathway Study (GPS) of Effectiveness and Safety at 12 months; Sheybani A, Vera V, Grover DS, Vold SD, Cotter F, Bedrood S, Sawhney G, Piette SD, Simonyi S, Gu X, Balaram M, Gallardo MJ; American Journal of Ophthalmology 2023; 252: 306-325

One of the puzzling aspects of glaucoma management is the longevity of its gold standard surgical solution, trabeculectomy. Few other medical specialties, not even mentioning ophthalmic subspecialties, can 'boast' of such an unflattering remedy, one with a safety profile und unpredictability that seem to stem from pre-modern medicine. Therefore, for any new glaucoma surgical technique to compare itself to trabeculectomy seems at once logical and brave nevertheless. Therefore, Sheybani and colleagues are to be congratulated for having conducted this RCT of the XEN gel stent to trabeculectomy.

Designing such a study confronts the investigators with many questions, each with their own limitations and pitfalls. The authors wisely chose a primary end point, which is a composite of efficacy and safety and should avoid biasing the study to either of the studied techniques: the proportion of patients at month 12 achieving ≥20% IOP reduction from baseline without increase in IOP-lowering medications, clinical hypotony, loss of vision to counting fingers, and/or secondary glaucoma surgical intervention. The authors found that **at one year the XEN gel stent was statistically non-inferior to trabeculectomy with 62.1% vs. 68.2% achieving that endpoint**. Notable findings favoring the XEN stent were (1) faster visual recovery; (2) greater six-month improvements in visual function problems; and (3) lower rates of office-based postoperative surgical procedures (34.7% vs. 63.6%), and lower rates of hypotony (23.2% vs. 50.0%). Favoring trabeculectomy was a statistically lower IOP, fewer medications, and fewer surgical failures.

This study's results, if replicated in other populations and other glaucoma types would place the XEN gel stent as a viable less-invasive alternative to trabeculectomy, especially when efficacy, safety, and patients' quality of life are weighted against each other

This well-designed study has few limitations, including a low representation of patients of African ethnicity (< 18% of the total) and with a diagnosis of pseudo-exfoliation glaucoma (< 4% of the total). It is also regrettable that measurements of endothelial cell density were not obtained, given that this newly important parameter could guide surgeons towards their decision.

This study's results, if replicated in other populations and other glaucoma types would place the XEN gel stent as a viable less-invasive alternative to trabeculectomy, especially when efficacy, safety, and patients' quality of life are weighted against each other.

Surgical Treatment

Drainage biostent

Comment by Antonio Fea, Torino, Italy

107434 Biotissue stent for supraciliary outflow in open-angle glaucoma patients: surgical procedure and first clinical results of an aqueous drainage biostent; Ianchulev T, Weinreb RN, Kamthan G, Calvo E, Pamnani R, Ahmed IK; British Journal of Ophthalmology 2023; 2:bjo-2022-322536.

In this study, ten patients underwent combined phacoemulsification cataract surgery with a permanent supraciliary biostent implantation. **The biostent comprised decellularized scleral allograft tissue microtrephined into a polymer tubular implant**. Patients enrolled in the study had been diagnosed with POAG (angle 3+ in all four quadrants) cataracts and did not previously undergo glaucoma surgery. Significant corneal opacities and visual field loss within central 10° were exclusion criteria. Patients were visited at one week, one month, six months, and 12 months after surgery. All patients at 12 months reached a sustained IOP reduction (40% from baseline) and a significative reduction in IOP medication use (62%). Mean IOP at baseline was 24.2 mmHg, at 12 months follow-up 14.6 mmHg. No stent displacement or corneal touch was reported; no significant hyphema, anterior segment inflammation, or peripheral anterior synechiae were observed post-operatory follow-up. Endothelial cell density was 2619 ± 228 (cells/mm^2) at baseline, 2312 ± 210 cells/mm^2 at 12 months follow-up. Mean BCVA was 0,81 logMAR at baseline (20/130) and 0,26 logMAR at 12 months follow-up (20/36).

The authors adequately disclose the limits of this study: the relatively short duration of follow-up and the small number of subjects enrolled. The authors tried to compare the endothelial cell loss of the biostent with other MIGS. However, the follow-up duration in the current study is shorter, and the comparison may be misleading. Furthermore, endothelial cell loss may become evident well after one year, as with the Cypass. The biostent

softness, biocompatibility, and the observation that it did not dislodge nor move during the one-year follow-up are reassuring. The short-term follow-up needs further investigation to answer questions on the biocompatibility and tolerability of the device.

Despite the small number of patients enrolled in this study, this new supraciliary biostent combined cataract surgery results are promising. IOP control, tolerability, safety, and one-year biostent stability of the device are essential and valuable points.

Surgical Treatment

Microhook trabeculotomy vs. dual blade goniotomy

Comment by Ronald Fellman and Davinder Grover, Dallas, TX, USA

107557 Comparison of mid-term outcomes between microhook ab interno trabeculotomy and goniotomy with the Kahook dual blade; Okada N, Hirooka K, Onoe H, Okumichi H, Kiuchi Y; Journal of clinical medicine 2023; 12: (2):558.

Comparing outcomes of two surgical procedures in a retrospective manner remains a formidable task. Propensity score matching is one statistical method to eliminate bias to have a 'best match' when comparing groups. **The authors chose a genetic algorithm of propensity matching to eliminate bias to compare outcomes of microhook trabeculotomy (Tanito) to a goniotomy dual blade (KDB or Kahook dual blade).** The title of the manuscript implies trabeculotomy versus goniotomy, but the nomenclature of canal-based MIGS is confusing, partly due to Current Procedural Terminology coding (CPT). The comparison is actually incise or excise the TM, different methods to reduce outflow resistance. In either event, with the propensity scoring algorithm, the authors found no statistical difference in outcomes or complications between the two groups. However, with the genetic propensity scoring method, the reader is left wondering what happened to the 50% of patients who were evaluated but excluded due to propensity matching.

The average reader may not be a statistician, (including ourselves) and would benefit from a brief explanation of how a random seed value set to 111 and a caliper coefficient set to 0.2 may potentially alter outcomes. An analysis of traditional outcomes to propensity scoring would be valuable to the surgeon.

One additional topic that is pertinent to the entire MIGS space is the health economics of MIGS and cost implications of surgical choices

One additional topic that is pertinent to the entire MIGS space is the health economics of MIGS and cost implications of surgical choices. **The KDB is a disposable instrument and the Tanito blade is re-usable.** This cost factor may play into a surgeon's treatment algorithm, depending on the health care system in which one operates.

Propensity matching should reduce selection bias, but the match is only as good as the variables that were studied. The authors looked at (Table 1) age, gender, type of glaucoma, preoperative IOP, no. of IOP-lowering medications and axial length. These are all very important variables. Another option would be to add two additional factors: (1) the duration of use of the antiglaucoma medication; and (2) the stage of disease. Both factors are implicated in outcome measurements. Including these variables may lead to a stratification match that may reveal valuable clinical pearls for the clinician. Only variables that are measured can be accounted for in a genetic propensity match.

The authors should be congratulated for their work that leads us all to think 'What is the optimal propensity score match for glaucoma surgical studies'? This remains to be explored and would be a meaningful exercise for national and international glaucoma societies. The authors should also be commended for performing a MIGS comparative study with two to three-year outcomes, more of which are greatly needed in this space.

Surgical Treatment

Phaco-endo-cyclo-photocoagulation

Comment by Lisandro Sakata, Paraná, Brazil

108094 The effect of combined phacoemulsification and endo-cyclophotocoagulation on intraocular pressure fluctuation assessed by the water drinking test in patients with primary open-angle glaucoma; Mohammad Razali A, Tang SF, Syed Zakaria SZ, Che-Hamzah J, Aung T, Othman O, Md Din N; Ophthalmic Research 2023; 66(1):854-861.

Razali *et al.* performed a prospective, non-industry sponsored study to evaluate the effect of phacoemulsification and endo-cyclophotocoagulation (Phaco-ECP) on IOP as assessed by the water drinking test (WDT) at least six weeks after the procedure, in 20 eyes of 17 patients with primary open-angle glaucoma (POAG). When compared to the baseline WDT, **there was no difference between the mean and peak IOP, albeit a significant reduction in IOP lowering medications after the intervention (2.2 ± 1.5 vs. 0.35 ± 0.9, p < 0.001)**. Interestingly, the IOP fluctuation was significantly greater postoperative (4 vs. 11 eyes showing IOP fluctuation > 6 mmHg), and the authors hypothesized that procedures aiming to reduce aqueous production may not blunt IOP fluctuation.

IOP fluctuation was significantly greater postoperative (4 vs. 11 eyes showing IOP fluctuation > 6 mmHg), and the authors hypothesized that procedures aiming to reduce aqueous production may not blunt IOP fluctuation

However, as mentioned by the authors, there are some relevant limitations, such as the relatively small sample size; varying glaucoma severity; non-standardized ECP technique; the reduction of glaucoma medications after the procedure – which was guided according to a target IOP of < 18 mmHg, apparently in a non-standardized way; and the varying time of follow-up when WDT was repeated after the procedure (9.4 ± 3.8 weeks). It is unclear if the authors attempted to perform the WDTs at the same time of the day, which could impact IOP fluctuation assessment. Previous studies have observed that the 'IOP peak' showed a better reproducibility than 'IOP fluctuations', as assessed by the WDT.[1] All these factors may influence the interpretation of the current paper's results and future studies should confirm its findings.

Although reducing the burden of multiple medications is desirable, there is a need to assess more clinically meaningful endpoints of the relatively new glaucoma surgical procedures to enable a better decision making process, particularly to properly allocate the limited resources for preventing glaucoma blindness worldwide

The authors are to be congratulated for contributing to the investigation of Phaco-ECP effect on IOP in a more comprehensive way than isolated IOP measurements. They observed that Phaco-ECP allowed the reduction of IOP lowering medications maintaining similar IOP mean and peak at the WDT. Although reducing the burden of multiple medications is desirable, there is a need to assess more clinically meaningful endpoints of the relatively new glaucoma surgical procedures to enable a better decision making process, particularly to properly allocate the limited resources for preventing glaucoma blindness worldwide.[2,3]

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Prognostic Factors

Systemic factors associated with glaucoma progression

Comment by Joo Young Shin and Sally Baxter, La Jolla, CA, USA

107485 Systemic factors associated with 10-year glaucoma progression in South Korean population: a single center study based on electronic medical records; Yoon JS, Kim YE, Lee EJ, Kim H, Kim TW; Scientific reports 2023; 13: 530

In this study, Yoon *et al.* evaluated factors associated with faster retinal nerve fiber layer (RNFL) thinning on optical coherence tomography in primary open-angle glaucoma (POAG) patients using electronic medical record data. They employed decision tree models, random forest models, and models based on permutation methods, interpreted by the Shapley additive explanation (SHAP) method. In addition to detecting previously known ophthalmic risk factors, they also identified several systemic risk factors.

In the decision tree model, a higher lymphocyte ratio (> 34.65%) was the most important systemic variable discriminating faster or slower RNFL thinning, and higher mean corpuscular hemoglobin (> 32.05 pg) and alkaline phosphatase (> 88.0 IU/L) concentrations were distinguishing factors in the eyes with lymphocyte ratios > 34.65% and ≤ 34.65%, respectively. In the random forest model, higher lymphocyte ratio and higher platelet count were the strongest systemic factors associated with faster RNFL thinning. Previous studies have identified altered immunity as POAG risk factors. Song *et al.* recently reported a genetic predisposition of higher lymphocyte count to be associated with glaucoma.[1] However, previous studies investigating neutrophil to lymphocyte ratio in POAG have reported controversial results,[2-5] and no significant difference was found in a recently reported meta-analysis, which also suggested different results among patients of different ethnicities.[6] Further large-scale prospective longitudinal studies with diverse patients will be needed to confirm these findings.

The strength of machine learning models, over conventional linear regression models, is their consideration of potential non-linear relationships and interactions among features. However, one challenge is the limited interpretability of machine learning models. Recently, there have been numerous efforts made for a more explainable artificial intelligence,[7] such as the SHAP method used in this study.[8,9] Overall, this study demonstrated the use of machine learning approaches using large-scale data in detecting risk factors associated with multifactorial diseases such as POAG.

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Artificial Intelligence

Machine-learning-based detection of glaucoma

Comment by Xiulan Zhang and Deming Wang, Guangzhou, P.R. China

107486 Assessing the external validity of machine learning-based detection of glaucoma; Li C, Chua J, Schwarzhans F, Husain R, Girard MJA, Majithia S, Tham YC, Cheng CY, Aung T, Fischer G, Vass C, Bujor I, Kwoh CK, Popa-Cherecheanu A, Schmetterer L, Wong D; Scientific reports 2023; 13: 558

The field of glaucoma detection has advanced through machine learning (ML) approaches, exhibiting high diagnostic accuracies.[1,2] However, a notable challenge arises from the lack of external validation for these models, leading to reduced interpretability and limited clinical applicability.[3,4]

In a prospective study conducted by Li *et al.*, ML models were developed using retinal nerve fiber layer (RNFL) thickness obtained from a compensation model and OCT data in a diverse dataset of Asian and Caucasian glaucoma patients and controls. **The ML models demonstrated superior performance in the Asian dataset (AUC = 0.96) compared to the Caucasian dataset. Notably, the model trained with compensated RNFL thickness (AUC = 0.93) outperformed models trained with original (AUC = 0.83) and measured data (AUC = 0.82).**

> The relatively modest sample size of the European validation set elicits concerns, while the inherent dissimilarity in demographic metrics between the European and Asian datasets further compounds the issue

This study assumes significant importance as it highlights an objective challenge in glaucoma ML models, whereby models trained on a specific dataset manifest reduced performance in other datasets. Nevertheless, the presented methods expose certain limitations. The relatively modest sample size of the European validation set elicits concerns, while the inherent dissimilarity in demographic metrics between the European and Asian datasets further compounds the issue. Consequently, it becomes imperative to investigate whether disparities in structural parameters among subjects across diverse datasets emanate from variations in data distribution or intrinsic disparities among ethnic groups.

However, glaucoma ML research is unequivocally confronted with the pressing challenge of diminishing model performance when applied to external datasets, necessitating urgent resolution. Consideration should be given to the development and implementation of data-sharing and privacy-preserving frameworks, such as federated learning. Furthermore, future research should prioritize compensatory models and the utilization of larger, diverse datasets. **The construction of multicenter public datasets and databases encompassing structural parameters, such as RNFL thickness, across various ethnic populations, is imperative to enhance the generalizability and reliability of ML-based glaucoma detection.**

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Miscellaneous

Do blue-light filtering IOLS affect glaucoma?

Comment by Cedric Schweitzer, Bordeaux cedex, France

108367 The effect of blue-light filtering intraocular lenses on the development and progression of glaucoma; Hecht I, Kanclerz P, Achiron A, Elbaz U, Tuuminen R; Journal of Glaucoma 2023; 32: 451-457

The authors report the result of a retrospective registry-based cohort study of 11028 cataract surgeries (11028 patients) performed over a 11-year period of time (2007-2018) in a single Finnish center. The authors compared the onset and the progression of glaucoma during the follow-up in two parallel groups of intraocular lenses (IOL), the first group received a blue-light filtering IOL (SN60WF, Alcon inc.) (n = 5188 eyes, 47%) and the second group received a non-blue-light filtering IOL (ZA9003 or ZCB00, Johnson & Johnson inc.) (n = 5840 eyes, 53%). During the follow-up, 316 eyes developed glaucoma and 662 eyes

were already followed for glaucoma. A cox regression survival analysis was performed and showed after adjustment for age and gender, a 22.2% lower risk of glaucoma onset for the blue-light filtering IOL group (Hazard ratio (HR): 0.778 95% Confidence Interval (CI):0.621-0.975, P = 0.029), whilst eyes with a diagnosis of glaucoma had a 38.4% lower risk to have a glaucoma procedure during the follow-up again in the blue-light filtering IOL group (HR: 0.616,95%CI:0.406-0.935, P = 0.023). Interestingly, the magnitude of differences between the two groups gradually increased during the follow-up.

Due to its short wavelength, blue-light is not absorbed by the cornea and is supposed to be harmful on the retina pigment epithelium and could be associated with the onset of age-related macular disease. Some experimental studies suggested that blue-light could also be harmful on retinal ganglion cells. Indeed, due to their non-myelinated characteristics, retinal ganglion cell axons have a large mitochondrial activity to enable the transmission of nerve impulses. Some studies showed that short wavelength light (400-460 nm) could be absorbed by the mitochondrial chromophores and could thus impair mitochondrial function.

While the study is likely well-powered with a large sample size and a long duration of follow-up in the two groups, its **retrospective design could be associated with a significant risk of attrition bias that could limit the generalisability of the authors' findings**. Noteworthy, despite intraocular pressure is known to be the main risk factor for glaucoma onset and progression, the authors did not include this parameter in the multivariate analysis. Thus, a potentially significant confounding factor was not taken into account in the survival analysis that could bias the estimate of the exposure of retinal ganglion cells to short wavelength light.

In conclusion, while cataract surgery is a common procedure, the influence of blue-light on the onset and progression of glaucoma would need to be further analyzed in a prospective randomized clinical trial to enable strong recommendation for IOL implantation.

Miscellaneous

Niacin intake and glaucoma

Comment by Anthony Khawaja and Blanca Sanz-Magallon Duque De Estrada, London, UK

108165 Associations between niacin intake and glaucoma in the National Health and Nutrition Examination Survey; Lee SY, Tseng VL, Kitayama K, Avallone TJ, Yu F, Pan D, Caprioli J, Coleman AL; Journal of Glaucoma 2023; 32: 443-450

The potential benefits of niacin (vitamin B3) in glaucoma have been under investigation in recent years. Oral niacin is protective against glaucoma in animal models,[1] and an IOP-independent association between niacin intake and decreased risk of open-angle glaucoma has been observed by Jung *et al.* in a Korean population.[2]

Yee *et al.* build on this work in a cross-sectional study examining the association between dietary niacin intake and glaucoma risk in the 2005-2008 US National Health and Nutrition Examination Survey (NHANES) population. Dietary niacin was measured using two 24-hour recall surveys with post-survey dietary interviews, while glaucoma was ascertained using regraded disc images using the Wilmer criteria. The study also measured and adjusted for a variety of confounding factors.

Each one-mg increase in daily niacin intake was associated with a 6% lower glaucoma odds (OR 0.94, 95% CI: 0.90, 0.98) in the maximally adjusted model. However, a significant association was not observed in the model adjusted only for age, sex, and ethnicity. Moreover, there was not even a trend towards an association when examining niacin in quartiles. **This lack of robustness of the association to different analytical approaches raises the possibility of a chance finding**. It is possible the analysis examining niacin intake as a continuous variable was susceptible to leverage by outliers. While there was a suggestion that the association was only apparent in women, there was no significant interaction with sex, suggesting this may also be due to chance.

Limitations of the study include recall bias and the assumption that niacin intake during the observed period accurately represented long-term intake. Nutritional supplements and dietary tryptophan (which is endogenously converted to an active form of niacin) were not accounted for. Glaucoma diagnosis was limited to disc images. It is notable that the authors only examined 'definite' glaucoma, which had a low prevalence and could therefore result in unstable statistical results. If this association was also apparent for 'probable' glaucoma, it may increase our confidence that this is not a chance finding.

Despite the limitations, this study adds to the growing body of evidence supporting a protective effect of dietary niacin on glaucoma risk

Despite the limitations, this study adds to the growing body of evidence supporting a protective effect of dietary niacin on glaucoma risk. We eagerly await the results of the multiple randomized-control trials examining niacin in glaucoma patients currently in progress. A well-tolerated oral therapy that is complementary to currently available glaucoma therapies would be strongly welcomed.

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Miscellaneous

Niacin intake and glaucoma

Comment by Jost Jonas, Heidelberg, Germany

108165 Associations between niacin intake and glaucoma in the National Health and Nutrition Examination Survey; Lee SY, Tseng VL, Kitayama K, Avallone TJ, Yu F, Pan D, Caprioli J, Coleman AL; Journal of Glaucoma 2023; 32: 443-450

In a large cross-sectional study consisting of more than 5000 adult participants of the 2005-2008 National Health and Nutrition Examination Survey (NHANES) and including 55 (1.0%) patients with glaucoma, Lee and colleagues reported on an inverse relationship between a higher niacin intake and a lower glaucoma prevalence. The NHANES is a survey of the U.S. civilian, noninstitutionalized population and was conducted by the US National Center for Health Statistics. Dietary niacin intake was assessed based on two 24-hour dietary recall

interviews, and glaucoma was defined by regrading optic disc images. The multivariable regression analysis was adjusted for age, sex, ethnic background, education level, income, body mass index, smoking status, alcohol use, cardiovascular disease, diabetes mellitus, daily energy intake, vitamin B2 and B6 consumption, and macular degeneration. Using niacin intake as a continuous variable, each additional one mg of dietary niacin intake was associated with 6% lower odds of glaucoma in adjusted analyses (odds ratio (OR): 0.94; 95%CI: 0.90, 0.98). When analyzed in quartiles, however, the highest quartile of dietary niacin intake did not correlate significantly with the glaucoma risk in partially or fully adjusted models (fully adjusted OR: 0.30, 95%CI: 0.05, 1.93). In a similar manner, when assessed as a binary variable, a higher dietary niacin intake was not significantly associated with the glaucoma risk in partially or fully adjusted models (fully adjusted OR: 0.61; 95%CI: 0.30, 1.23). Stratified by sex, niacin intake as a binary variable was significantly associated with a lower glaucoma risk only in women (OR: 0.35; 95%CI: 0.14, 0.90), but not among men (OR: 1.12: 95%CI: 0.32, 2.31). Besides the limitation in the general statistical significance of the results, other limitations of the study were listed by the authors, such as that the study only assessed dietary niacin intake while supplementary niacin was not recorded; that niacin for the therapy of hyperlipidemia was excluded; that tryptophan, albeit the possibility of its endogenous transformation into niacin, was not included as a variable; that the glaucoma diagnosis might have been inaccurate in some circumstances since only optic disc images were available (e.g., the glaucoma prevalence was relatively low in the present study as compared to previous several population-based studies); that glaucoma was not differentiated into open-angle glaucoma versus angle-closure glaucoma and that intraocular pressure was not included into the analysis; and that the study as a cross-sectional investigation could not assess causality. In conclusion, future studies may further evaluate the potential association between niacin intake and glaucoma to further corroborate the findings and conclusions made in the present study.

Miscellaneous

SARM1 inhibition and traumatic glaucoma

Comment by Dorota Skowronska-Krawczyk and Cezary Rydz, Irvine, CA, USA **108175** Differential effects of SARM1 inhibition in traumatic glaucoma and EAE optic neuropathies; Liu P, Chen W, Jiang H, Huang H, Liu L, Fang F, Li L, Feng X, Liu D, Dalal R, Sun Y, Jafar-Nejad P, Ling K, Rigo F, Ye J, Hu Y; Molecular therapy. Nucleic acids 2023; 32: 13-27

The study by Hu *et al.* examined the effects of SARM1 inhibition in glaucoma and experimental autoimmune encephalomyelitis mouse models. Rapid loss of nicotinamide adenine dinucleotide (NAD+) has been shown to drive axonal degeneration. Continuous production of NAD+ is thus crucial for axon survival.1 SARM1 (sterile α and TIR motif-containing protein1) possesses NAD^+ hydrolase activity, leading to the destruction and lower levels of NAD^+, thereby driving axonal loss. Efforts aimed at blocking SARM1 have been demonstrated to be protective in neurodegenerative disease models.[2]

The authors explored two therapeutic strategies for SARM1 inhibition and compared them with germline SARM1 deletion in three *in-vivo* optic neuropathy models. These therapeutic approaches included antisense oligonucleotide (ASO) delivery and adeno-associated virus (AAV)-mediated RGC-specific knockdown of SARM1. The authors used a series of approaches to assess therapeutic effects in traumatic optic nerve crush (ONC), silicone oil-induced ocular hypertension (SOHU) glaucoma model, and experimental autoimmune encephalomyelitis (EAE)/optic neuritis model. Their methods included therapeutic impact both structurally (by analyzing number of RGCs, axons and thickness of fiber layers) and functionally through RGC function assessment via electrophysiology.

> The study demonstrated that both intravitreal ASO and AAV delivery led to comparable neuroprotective effects on both RGC soma and axons in the SOHU glaucoma model

The study demonstrated that both intravitreal ASO and AAV delivery led to comparable neuroprotective effects on both RGC soma and axons in the SOHU glaucoma model. Strikingly, the effects of these two approaches differed in the ONC model, where a protective effect was observed only in RGC axons and not in RGC soma. Interestingly, neither

of the two intravitreal SARM1 inhibition strategies, nor germline SARM1 knockout (KO), had any impact on RGC or ON survival in the EAE/optic neuritis model suggesting distinct mechanism of pathology and reason for RGC loss in this model.

In summary, the authors have shown that SARM1 inhibition is neuroprotective in glaucomatous and traumatic optic neuropathies but not in the condition characterized by the loss of myelination of ON. Furthermore, **the study has demonstrated the effectiveness of local inhibition of SARM1 via intravitreal injection of ASO and AAV-mediated RGC-specific knockdown, thereby minimizing the risk of systemic side effects associated with gene modulation.**

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Ricardo Abe and Vital Costa

2. Primary angles closure suspect

Jesa Nadine Protasio, Augusto Azuara-Blanco, Tin Aung

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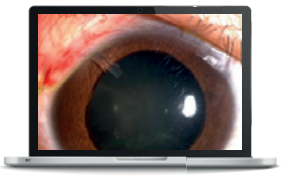

3. Management of PACG

Chang Liu, Monisha Nongpiur, Tin Aung

4. Approach to Exfoliation Syndrome and Exfoliation Glaucoma

Vijaya Lingam, Mona Khurana, Ronnie George

All modules were written by world-renowned experts in the field, and reviewed by members of the WGA Education Committee. They are intended for ophthalmologists and other eye-care providers.

All texts, pictures, and videos were adapted to an online platform by a team of e-learning experts. This will allow you to have a pleasant learning experience. At the end of each module, there is a multiple-choice test that will auto-correct once the exam is completed. You will also be able to download a Certificate of Completion.

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News Flashes

- ★ This study is compelling, showing a potential contribution of Müller cells changes that precede statistically significant elevations in IOP
- ★ These results highlight the prevalence of treatment failures in routine clinical practice
- ★ The main limitation of this study is that it is cross-sectional and provides evidence for an association but not a causal relationship
- ★ The study findings significantly lack generalizability as the population was ethnically homogenous and the data lacked information about glaucomatous status or past exposure to IOP lowering pharmacotherapy
- ★ Another issue is that the study excluded those that developed OSA, and would be more likely to create attrition from the control group and increase the likelihood of an association in the Study group. This might magnify the treatment of OSA
- ★ While the benefits to glaucoma of treating OSA is still controversial, it is important to refer patients with suspected sleep apnea for testing because treatment of sleep apnea has large health benefits for other health conditions
- ★ It remains to be seen if this strategy can mediate consistent neuroprotection or neuroenhancement in human glaucoma
- ★ The proportion of eye drops successfully reaching the eye was actually lower using the nose-pivoted delivery device, though this was not statistically significant (64% versus 59%)
- ★ Once the TM cells or Schlemn's canal endothelial cells are damaged and lose their function, the induction of MMP3 may not be effective
- ★ The 14-year number needed to treat to prevent one case of PAC was 12.4 compared to 44 at 6 years
- ★ The main limitation of the study is the generalizability of the results
- ★ As the annual incidence of PAC was low and AAC and PACG were relatively rare in the community-based population with PACS over the long term, clinicians should assess the risk factors for progression when treating patients with PACS and prophylactic LPI should be recommended preferentially to those at the highest risk of angle closure

- ★ This study's results, if replicated in other populations and other glaucoma types would place the XEN gel stent as a viable less-invasive alternative to trabeculectomy, especially when efficacy, safety, and patients' quality of life are weighted against each other
- ★ One additional topic that is pertinent to the entire MIGS space is the health economics of MIGS and cost implications of surgical choices
- ★ IOP fluctuation was significantly greater postoperative (4 vs. 11 eyes showing IOP fluctuation >6mmHg), and the authors hypothesized that procedures aiming to reduce aqueous production may not blunt IOP fluctuation
- ★ Although reducing the burden of multiple medications is desirable, there is a need to assess more clinically meaningful endpoints of the relatively new glaucoma surgical procedures to enable a better decision making process, particularly to properly allocate the limited resources for preventing glaucoma blindness worldwide
- ★ The relatively modest sample size of the European validation set elicits concerns, while the inherent dissimilarity in demographic metrics between the European and Asian datasets further compounds the issue
- ★ Despite the limitations, this study adds to the growing body of evidence supporting a protective effect of dietary niacin on glaucoma risk

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