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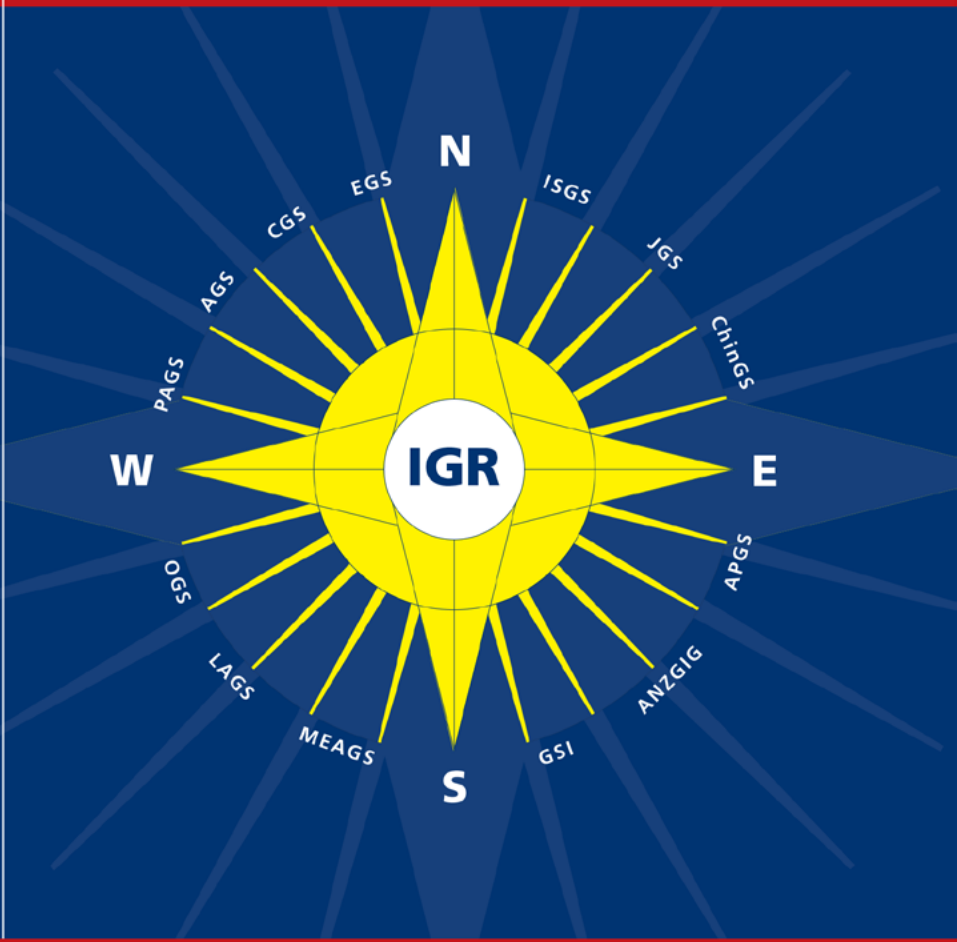

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Editor's Report

I welcome you to the first online only issue of the International Glaucoma Review (IGR). With this issue, we have made the transition from print to electronic distribution.

As usual, the IGR will provide you with high quality glaucoma content including the Comments in the Editor's Selection, the Dialogue, Opinion, and news from the WGA, meeting reports, etc. With this new format, you will be able to quickly navigate the content online and obtain the information that is of interest. If desired, you also will be able to obtain more details via direct links (articles, abstracts, database, etc.).

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Please note a new feature, the bookmark function. Through this item you can save a search for easy access to new abstracts when they are available. Do let us know if there is additional functionality that you would like added to the website!

With the increasing number and variety of publications. it seems almost impossible to read and absorb more than 1200 annual publications. Even just reading those publications that relate to a particular aspect of glaucoma can be a daunting task. The IGR addresses this challenge by critical selection and review with Comments of the relevant glaucoma-related literature. This has resulted in four levels of IGR review:

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Enjoy!

Dr. Robert N. Weinreb, Chief Editor
La Jolla, CA, USA

From the WGA Executive Office

World Glaucoma Congress 2015

Register online now. The next World Glaucoma Congress will be held in Hong Kong from June 6-9, 2015. The Program Committee is developing a program of interesting topics and excellent faculty. We have been in close communication with our local organizing committee about political events in Hong Kong and continue to monitor events. We are reassured that we will find the city peaceful, orderly and welcoming for our Congress in June 2015.

Make your plans to attend WGC 2015 Via the WGA website, www.worldglaucoma.org. The Program at a glance is available to assist you with registration and planning your travel to HK. Within the extensive HK Congress & Exhibition Center, an intimate congress layout will be created, which will allow you to meet your worldwide glaucoma colleagues and friends.

Glaucoma Care in Africa Initiative

The World Glaucoma Association identified “Impact in Developing Countries” as an unmet need and this is a priority in our Strategic Plan. As an initial effort we hosted an African summit meeting to explore the dimensions of the problems there. Under the leadership of our President, Prof. Jeffrey M. Liebmann, the Board of Governors has agreed to launch a continued initiative regarding glaucoma care in Africa. Currently a taskforce is being established, chaired by Prof. Neeru Gupta (CA) and Prof. Franz Grehn (DE).

The aim of the outcome of the project will be to provide recommendations on a network for collaboration, resources for education for African healthcare workers and identify other ways WGA could have an impact on glaucoma education and care in Africa.

Please do get in touch via the WGA Executive Office (info@worldglaucoma.org) if you have a special interest in this topic, would have interesting experiences to share and also if you would be willing to actively participate in the initiative.

IGR Goes Online

This issue is the start of a new era for IGR, as it is the first online only issue. Please see the report from our Editor, Prof. Robert N. Weinreb, that highlights some of the features of our transformation to an electronic publication.

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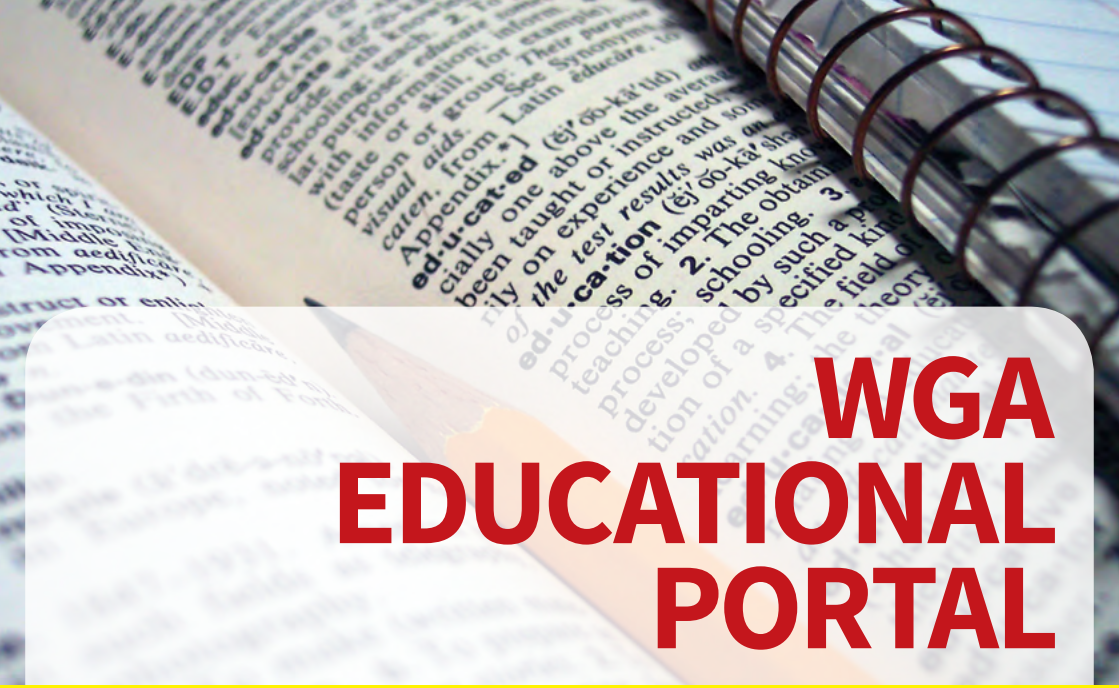
Please enjoy this first “online only” IGR and let me know your thoughts regarding our efforts in this and all WGA initiatives. You can reach me at (Fechtner@worldglaucoma.com). You can also contact our WGA Executive Office (info@worldglaucoma.org) if you need any information or have questions on IGR or WGA related matters. I look forward to hearing from you.

Professor Dr. Robert D. Fechtner, Executive Vice President

Your Special Attention for

Intraocular pressure homeostasis: maintaining balance in a high-pressure environment
Acott TS, Kelley MJ, Keller KE, Vranka JA, Abu-Hassan DW, Li X, Aga M, Bradley JM
(abstract id **56100**)
Journal of Ocular Pharmacology and Therapeutics 2014; 30: 94-101



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Glaucoma Opinion

What is next for genetics and glaucoma?

Janey L. Wiggs

Twenty years ago the first of the glaucoma genetic linkage studies was completed and these have now yielded a handful of genes that cause early-onset familial glaucoma: *MYOC* (juvenile open-angle glaucoma), *PITX2* (Axenfeld-Rieger syndrome), FOXC1 (anterior segment dysplasia and iris atrophy), *PAX6* (Aniridia), *CYP1B1* (primary congenital glaucoma), *LTBP2* (primary congenital glaucoma), *OPTN* and *TBK1* (familial normal-tension glaucoma).[1] In 2007, the first genome-wide association study (GWAS) for common complex forms of glaucoma was completed and subsequently this approach has yielded seven genes/genomic regions: *LOXL1* (pseudoexfoliation syndrome), *CAV1/CAV2* (POAG), *CDKN2BAS* (primary open-angle glaucoma (POAG) and NTG), *SIX6* (POAG), *TMCO1* (POAG), 8q22 (NTG), *PLEKHA7* (angle closure), *COL11A1* (angle closure).[1] Although these discoveries represent great progress, this collection of genes still only accounts for a fraction of glaucoma heritability. Future goals for glaucoma genetic research include finding more genes for early-onset familial glaucoma and adult-onset common glaucoma and using the genetic information to develop clinically meaningful gene-based screening, diagnostic and prognostic tests, as well as novel gene-based therapies.

> Future goals for glaucoma genetic research include finding more genes for early-onset familial glaucoma and adult-onset common glaucoma.

Finding new glaucoma genes

Powerful new DNA sequencing technologies such as whole exome sequencing (WES) can be used to find disease-causing genes in smaller families and even individuals, eliminating the need for the very large families previously required for gene discovery using genetic linkage analysis. Identifying disease-causing genes using these older methods was laborious and time-consuming. WES examines the entire coding sequence (exome) of a patient and through comparison with the exomes from healthy controls or unaffected family members the DNA sequences unique to affected individuals can be identified. Genes with DNA sequence variants found only in affected individuals are likely to be the cause of the inherited disease. As **the current collection of early-onset glaucoma genes**

only accounts for about 20% of affected families, WES is expected to find interesting novel genes in many more families in the near future. Showing that novel gene variants are indeed responsible for disease development remains a challenge. However, animal model systems such as morpholino knock down in zebrafish and disease modeling in iPS (induced pluripotent stem) cells are helpful.

The **current collection of genes contributing to common forms of adult-onset glaucoma with complex inheritance also explains only a fraction of the disease heritability.**[2] Unlike early-onset diseases where a single mutation can be responsible for the disease, in complex disorders each genetic variant has a small incremental effect on disease susceptibility. Aggregates of multiple gene variants, possibly in combination with environmental risk factors, are required for the disease to become fully manifest. Disease genes influencing susceptibility to adult-onset disorders are identified by genome-wide association studies where the frequency of gene variants is compared in cases and controls. Because gene variants contributing to adult onset diseases with complex inheritance have relatively modest biological effects, the difference in variant frequency between cases and controls is usually small. Consequently, gene discovery for adult-onset disease-associated variants requires a large number of cases and controls providing sufficient statistical power to detect significant differences in variant allele frequencies. The current collection of genes known to contribute to adult-onset forms of glaucoma were discovered using thousands of cases and controls and finding new genes will require even larger sample sizes with more statistical power. Assembling the large cohorts required for these studies typically requires collaborative efforts and several consortia have formed to facilitate GWAS studies in glaucoma including the NEIGHBORHOOD (National Eye Institute Glaucoma Human genetics collaboration Heritable Overall Operational Database) and the IGGC (International Glaucoma Genetics Consortium) consortia. Additionally, all the genes and genomic regions discovered so far for adult-onset forms of glaucoma have been in the Caucasian and Asian populations. Genetic studies of African-Americans, the ethnic group most likely to develop glaucoma, are clearly needed.

The GWAS is an initial approach that identifies common variants that contribute to disorders with complex inheritance. Other analyses to consider for complex disorders such as POAG, NTG, pseudoexfoliation syndrome and angle closure glaucoma are gene-gene and gene-environment interactions and biological pathway analyses. Environmental exposures are emerging as important risk factors for pseudoexfoliation syndrome and glaucoma and considering the robust association of pseudoexfoliation syndrome with the *LOXL1* gene, studies of gene-environment interactions involving *LOXL1* will be important. Biological pathway analyses are also proving to be useful in identifying molecules and pathways that contribute to disease and that may be targets for novel therapies.[3]

Genetic testing

Currently, the eight genes known to cause early-onset familial forms of glaucoma can be used for genetic testing. **Genetic testing for these disorders has several benefits: mutation carriers can be identified and treatment can be started before damage to the optic nerve occurs, in families disease surveillance can be targeted to mutation carriers so that family members who do not have the mutation and are not at risk can avoid unnecessary exams, and as gene-based therapies are discovered individuals who are carriers of a specific mutant gene who would benefit from gene-based therapy can be identified.**

Genetic testing should be performed in a CLIA (Clinical Laboratories Improvement Amendments) certified laboratory where quality control can be monitored. Testing requires either a saliva or blood sample from the patient and family members. Most genetic testing uses DNA sequencing to detect disease-causing mutations and this may be done on a gene by gene basis or by screening all the genes that can contribute to the condition in one test using next-generation sequencing techniques.[4] After the test data is analyzed a report is written and returned to the referring physician for discussion with the patient and families and genetic counseling as necessary. Patients and their families who are most likely to benefit from genetic testing using the current collection of genes are those with disease onset before age 40 or with advanced disease before age 50 and a history of glaucoma in a first degree relative.[5]

For adult-onset glaucoma gene-panel tests, allowing for simultaneous testing of multiple risk alleles, are a better measure of adult-onset disease risk. However, to be effective the gene panels need to be comprehensive and the clinical benefit of the test should be evaluated. The genes currently known to contribute to the adult-onset glaucomas represent only a fraction of the overall heritability and panel tests have not yet been studied to determine if testing for this collection of genes has clinical utility. New studies identifying more genes could lead to more comprehensive gene panels that have the potential to accurately identify patients at risk for disease prior to the onset of irreversible damage to the optic nerve.

Gene-based therapies

> An important goal of genetic research is to define the underlying molecular events responsible for the disease and use that information to develop novel gene-based therapies that target the actual disease-causing molecular pathophysiology.

An important goal of genetic research is to define the underlying molecular events responsible for the disease and use that information to develop novel gene-based therapies that target the actual disease-causing molecular pathophysiology.

For some types of early-onset familial glaucoma gene-based therapies may be available in the near future. For example, patients with elevated IOP due to mutations in *MYOC* may benefit from chemical chaperones or other approaches that relieve the misfolded protein response induced by gene mutations.[6] The discovery of more genes responsible for early-onset glaucoma will make it possible to offer gene-based therapies to more patients affected by these devastating forms of glaucoma.

For adult-onset glaucoma there is also the promise of gene-based therapies in the future. Rather than targeting a single gene, for these complex forms of glaucoma it may be preferable to target the biological pathways that include the disease susceptibility genes. The NEIGHOBRHOOD study has identified several pathways associated with POAG and NTG.[3] Developing therapies directed at these pathways may lead to novel and potentially neuro-protective treatments. The discovery of more genes contributing to adult-onset forms of glaucoma will likely identify additional important disease mechanisms that could also be targeted for novel therapeutics.

Over the past decade there has been considerable progress in our understanding of the genes responsible for and contributing to both rare and common forms of glaucoma. An important next step is the discovery of new genes making it possible to gain a better definition of disease-related molecular pathophysiology, improve genetic testing and provide more opportunities for gene-based therapies.

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Meeting Highlights

Highlights of the 2nd Asia-Pacific Glaucoma Congress / 10th International Symposium of Ophthalmology / 26th Annual Scientific Meeting of the Hong Kong Ophthalmological Symposium

Hong Kong, PRC, September 26-28, 2014

Poemen Chan

At this event, the Name lectures session was under the spotlight. The lectures highlighted some interesting and most forthcoming challenges of eight different specialties in ophthalmology. **Robert Ritch** provided us with exciting insight of glaucoma treatment beyond lowering intraocular pressure (IOP); namely, the controversial topics of neuroprotection and 'non-pharmaceutical therapy', how we should interpret the currently available evidence and the problems that we are facing for the development of these alternative therapies.

Another eye-catching feature were the keynote/Plenary/Ward lectures. **Robert Weinreb** discussed about another hot topic – 24-hour IOP measurement. He talked about personalising the management of IOP; how measurement of IOP at different times of the day and 24-hour IOP monitoring might help us to appropriately select personalised therapy for our patients. Gene transfer via viral or non-viral vectors for the treatment of ocular diseases such as Stargardt's disease and wet AMD are already underway for clinical trials. **Paul Kaufman's** lecture took a step further and discussed the strategies for glaucoma gene therapy, which include increasing conventional and/or uveoscleral outflow, decreasing aqueous humour production and neuroprotection. The future is challenging but equally exciting.

There were also numerous Instruction courses and skill transfer sessions. I was very inspired by **Paul Palmberg's** session on Tran-corneal needling at the slit lamp. One would be amazed how much a 30-gauge needle that 'bent like Zorro' could achieve when needling a failing bleb, without upsetting the conjunctiva. Also, the dramatic change one could make out of a needle for patient with acute primary angle closure.

There were also numerous exciting free papers. **Vinay Nangia** shared his study on translamina cribrosa pressure (TLCPD) difference and open-angle glaucoma (OAG). In the Central India Eye and Medical Study that involves more than 4000 subjects, Dr Nangia demonstrated that TLCPD calculation was better associated with glaucoma presence and amount of glaucoma optic neuropathy when compared to IOP measurement. This supports the potential role of low cerebrospinal fluid pressure in the pathogenesis of OAG.

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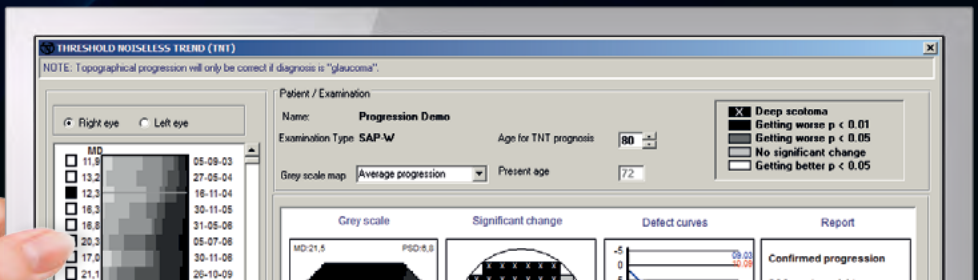

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Glaucoma Dialogue

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

Robert N. Weinreb, Chief Editor

Article

56225 Glucose-induced temporary visual recovery in primary open-angle glaucoma: a double-blind, randomized study, Casson RJ, Han G, Ebneter A, Chidlow G, Glihotra J, Newland H, Wood JP, Ophthalmology 2014; 121: 1203-1211

Comments

Comment by Jonathan Crowston, Melbourne, Australia

This manuscript is of substantial interest, not because it proffers glucose as a potential treatment for glaucoma, but because **it provides evidence in further support of the notion that in glaucoma, there exists a subpopulation of retinal ganglion cells that are metabolically challenged and manifest a reversible reduction in function**. Although a number of cohort studies have shown a degree of improvement in visual function in glaucoma patients following IOP lowering, this study is novel in demonstrating improvement in visual function through a mechanism distinct to IOP lowering.

> This study is novel in demonstrating improvement in visual function through a mechanism distinct to IOP lowering

By giving an intensive regime of glucose drops (50% every five minutes for one hour), Casson and colleagues were able to significantly increase vitreous glucose levels in pseudophakic individuals. This increase in vitreous glucose levels was associated with a significantly improvement of visual acuity and contrast sensitivity in a cohort of glaucoma patients.

In a separate *in-vitro* study published recently in IOVS,[1] the same group also showed that glucose rescues cultured retinal ganglion cells from rotenone, a complex-I inhibitor that blocks ATP production through oxidative phosphorylation. Glucose in these studies protected retinal ganglion cells through restoration of ATP through glycolysis and the pentose phosphate pathway.

> This sweet study provides much food for thought!

It is interesting to speculate whether the recent description of complex I dysfunction in a glaucoma cohort[2] points to the possibility of a parallel scenario in glaucoma, whereby OXPHOS impairment compromises RGC function and that this is overcome by increasing vitreous glucose levels. Further work is clearly needed in order to understand the precise nature of bioenergetics stress in retinal ganglion cells and how this might be overcome to promote neurorecovery. This sweet study provides much food for thought!

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Comment by Jeffrey Goldberg, San Diego, CA, USA

In a series of animal models of optic neuropathies including glaucoma and retinal ischemia models, Casson and colleagues have demonstrated a neuroprotective effect of exogenously supplying glucose, presumably supporting energy-deprived retinal ganglion cells in these disease models. Other studies examining other aspects of energy and metabolic balance have also supported the **premise that retinal ganglion cells may perform**

better if given a 'metabolic booster shot', for example by increasing oxygen tension. Now Casson and colleagues take this research a step forward into the clinic.

In an initial phase on patients about to undergo vitreoretinal surgery they applied a 50% glucose topical solution every five minutes for one hour and found an increase in vitreal glucose in pseudophakic, but not phakic patients.

Using these data to select only pseudophakic POAG patients with moderate to severe optic neuropathy (average MD was -12.1), patients were randomized to a masked cross-over design trial in an initial study of 50% glucose against 0.9% saline drops, and then a follow-up study of 50% glucose against equi-osmolar 8% saline. In both studies the investigators found an improvement in central contrast sensitivity and logMAR visual acuity during the 50% glucose treatment phases, when averaged across participants. Not all participants responded favorably to topical glucose, but the overall results are nevertheless impressive.

Strengths of the study included strong study design with statements of pre-selected endpoints and a rationale for each. A particular highlight is the investigators' willingness to take on a first-in-human trial of this sort, particularly as pre-clinical research has generated many candidate approaches for neuro-enhancement but few that have been translated to human testing.

> Many candidate approaches for neuro-enhancement but few that have been translated to human testing

Limitations of the study were few and were mainly questions that can be addressed in follow-on research. One such question is whether there is any specificity to POAG patients, or would such enhancement be seen in normal subjects. In some ways this is irrelevant as an enhancement for POAG patients that also enhances visual function of non-glaucoma patients is still a significant step forward for the field as specificity to POAG is not a prerequisite for treatment. Although the investigators selected only pseudophakic patients based on the penetration of glucose into the vitreous, a topical application may reach retinal ganglion cells or the optic nerve without a significant elevation of vitreal levels in phakic patients, and given the significant fraction of phakic glaucoma patients, it would clearly be worth looking for an effect on function in this population.

Finally, the duration of effect and its implications for dosing should be assessed in future pilot studies, plausibly in preparation for larger, longer term multicenter trials that could assess long term safety, durability of enhancement, and neuroprotection. This latter point will be particularly interesting as could improving bioenergetics through exogenous glucose supply protect retinal ganglion cells from decline over the long term, in addition to promoting short-term neuro-enhancement? **It is an exciting premise for patients to consider the possibility of offering an inexpensive topical therapy that could enhance function and perhaps provide protection against visual decline.**

Comment by Keith Martin, Cambridge, UK

In their previous work, the authors have explored the relationship between glucose levels and retinal ganglion cell (RGC) survival in models of acute and chronic retinal ischemia as well as in a rodent model of experimental ocular hypertension. They have demonstrated that elevated vitreous glucose levels appear to correlate with improved RGC survival and they have postulated a mechanism by which elevated glucose could improve the function of 'sick' RGC. The laboratory studies have been carefully performed and thoughtfully analyzed. In the current clinical study, an attempt has been made to start to apply these findings to human glaucoma. The authors aim to test the hypothesis that topically delivered glucose could improve some measures of visual function in aphakic glaucoma patients given 50% glucose eye drops every five minutes for one hour. They interpret their results as demonstrating a possible effect of glucose eye drops on visual performance and they discuss carefully several possible explanations, including an effect of elevated vitreous glucose on retinal function as well as a direct effect on the cornea.

The authors are to be commended for this translational approach and for designing a study which, though unavoidably limited by the constraints of human clinical trials to explore mechanism, nevertheless raises many interesting questions. **The possibility that the findings of improved visual function could be due to an osmotic effect on the cornea which differed between the 50% glucose and 0.9% saline drops was addressed by a follow-up study where the drops were matched for osmolarity by using 8% saline. This was a laudable attempt to exclude a corneal explanation for their findings but I do wonder if using 50% L-glucose, a glucose isomer that cannot be metabolized, would have been a better control.** As the authors freely acknowledge, the possibility of a non-retinal explanation for their finding remains even though their demonstration of elevated vitreous glucose levels in pseudophakic patients given glucose drops appears convincing.

A further limitation, pointed out by the authors themselves, is the lack of a non-glaucoma control group. This would have been a very interesting addition to the study because, as things stand, it is unclear whether the effect observed is related purely to glaucoma. It would also be interesting to know if a similar effect is observed in other conditions where retinal function is compromised such as macular degeneration. The authors plan further studies using retinal electrophysiology as an endpoint and these studies will hopefully provide complementary information that will help us understand what is going on here better.

Overall, this is a very interesting study performed by careful researchers which builds on solid laboratory work demonstrating an effect of elevated glucose levels on RGC survival. I think mo**re work is needed to prove conclusively that the effect observed is directly caused by an effect on retinal metabolism** but, like many pioneering studies, the current work has suggested a whole set of new experiments that I hope will be performed to test this idea further.

Response by Robert Casson on behalf of the original authors

We would like to thank the editorial team at *IGR* for selecting our paper for discussion and the reviewers for their generous comments.

About ten years ago, we serendipitously noted that elevated vitreous glucose levels provided a robust neuroprotective effect against ischemic retinal injury.

Based on this finding, and the work of others, particularly Barry Winkler, we have been struck by the retina's unusual energy metabolism. We have pursued the possibility that we might manipulate it to clinical advantage in **diseases where energy failure is part of the problem, a disease set that probably includes primary open-angle glaucoma (POAG), at least in some individuals.**

Our current study aimed to translate laboratory findings to the clinic using a modified outcome paradigm. In the broadest sense, **neuroprotection refers to the relative preservation of neurons against actual or potential threat. This is easy to measure in acute animal models. But for chronic diseases, like POAG, neuroprotection implies a reduction in the rate of neurodegeneration, requiring many months**, if not, years to determine. The statistical test on the primary result of the EMGTS was a basic two-sample test of proportions after at least four years follow-up. Although it is likely that alternative creative study designs including recruitment of rapid progressors and Bayesian rather than frequentist statistical approaches could shorten clinical trial durations, a convincing demonstration of neuroprotection is a high-hanging fruit.

> A convincing demonstration of neuroprotection is a high-hanging fruit

In 1940, at Harvard University, McFarland and Forbes demonstrated recovery of dark adaptation in hypoxic human subjects after inducing hyperglycemia. We believe this finding and our current findings are a manifestation of **'neurorecovery'**. Although not neuroprotection *per se*, the findings imply a **recoverable neuronal state,** and that energy deficiency is producing functional visual deficits. The advantage of neurorecovery as the primary outcome is that it is rapid and inexpensive to measure.

Although we believe it is unlikely that elevating vitreal glucose levels is a viable treatment for chronic glaucoma, similar strategies could conceivably be developed for acute glaucoma and other ocular conditions where energy failure is part of the pathogenesis. Importantly, further research is needed to better understand retinal metabolism. For example, it is unclear whether retinal ganglion cells actually display a Pasteur effect. In fact, the preferred energy substrate of CNS neurons, including retinal neurons, remains controversial. We believe this would be a fruitful area of research for glaucoma and other retinal and optic nerve diseases.

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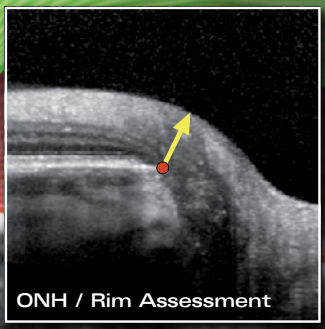

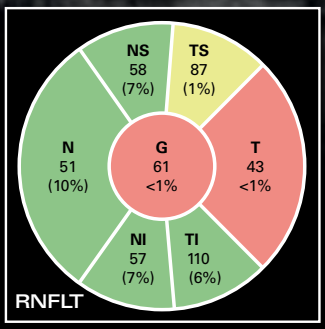

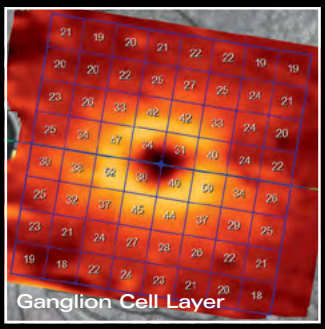

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Editor's Selection

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

Robert N. Weinreb, Chief Editor

Epidemiology

To what extent is IOP heritable?

Comment by Monisha E. Nongpiur and Tin Aung, Singapore

56146 Heritabilities of intraocular pressure in the population of Korea: the Korean National Health and Nutrition Examination Survey 2008-2009, Kim NR, Park HJ, Suh YJ, Chin HS, Kim CY, JAMA ophthalmology 2014; 132: 278-285

Glaucoma is frequently associated with abnormally elevated intraocular pressure (IOP), which results from impaired drainage of aqueous humour through outflow pathways. IOP remains the only major modifiable risk factor for glaucoma to date. Glaucoma is generally considered a complex trait, most likely resulting from the interactions of multiple genetic factors as well as environmental exposures.

In this study, Kim and colleagues investigated the familial correlations and heritability of IOP in an Asian population. The authors found significant correlation coefficient estimates for IOP between parent-offspring pairs (0.19, $P < .001$), sibling pairs (0.31, $P = 0.001$), and also between spouse pairs (0.29, $P < .001$). A heritability estimate of 0.345 (adjusted for age, sex, refractive error, body mass index, systolic blood pressure, and fasting serum glucose

and total cholesterol levels) was obtained and the total variance in IOPs were explained by the additive genetic factor (36% [95% CI, 32%-40%]) and unique environment factors (64% [95% CI, 60%-68%]). The authors additionally evaluated the impact of parents' IOP on offspring's IOP. For this analysis, the subjects were stratified into groups: those with IOP19 mmHg and those with IOP < 19 mmHg, based on the mean plus two standard deviation IOP value of the entire study population. A greater risk of high IOP (*i.e.*, 19 mmHg) in offspring was observed when both parents had high IOP (odds ratio, 9.76 [95% CI, 2.16-44.12]) compared to offspring with no parents having high IOP. This was a well-conducted study, however, the findings of a higher correlation between spouse pairs compared to parent-offspring pairs is rather surprising. The authors proposed shared environmental effects since marriage and time of marriage as the reasons for the findings; however the other likely possibility could be the effect of age, as spouse pairs are more inclined to be of a similar age group. Interestingly, Klein *et al*.[1] in their evaluation in a Caucasian population noted no significant correlation for IOP between spouse pairs.

> A greater risk of high IOP (i.e., ≥ 19 mmHg) in offspring was observed when both parents had high IOP (odds ratio, 9.76 [95% CI, 2.16-44.12]) compared to offspring with no parents having high IOP

The heritability estimates of IOP inferred from this study is consistent with others conducted in Caucasian populations,[1-3] and **supports the rationale for IOP to be considered an endophenotype for glaucoma.** However, when assessing IOP, it is important to keep in mind that it is a variable trait, which is affected by several intrinsic factors such as corneal thickness, physiological diurnal fluctuations, as well as external factors such as the type of instrument for measurement of IOP, examiner experience, and patient posture. **It would be interesting to know if the genes/genetic variants that govern IOP also confer similar susceptibility to glaucoma in different ethnic groups.**

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Glaucoma as cause of blindness

Comment by Chris Johnson, Iowa City, IA, USA

55997 Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime, Saunders LJ, Russell RA, Kirwan JF, McNaught AI, Crabb DP, Investigative Ophthalmology and Visual Science 2014; 55: 102-109

Previous investigations of the likelihood of glaucoma patients developing visual impairment or statutory blindness have been based on relatively small sample sizes (300 patients or less) and manual perimetric testing, which has been reported to be highly variable and dependent on the skills and experience of the examiner. In the present study, the authors evaluated automated visual field findings on more than 3,700 patients, and used computer modeling and linear regression of Mean Deviation (MD) to estimate the prevalence of visual impairment and statutory blindness over the lifetime of these patients. The authors found that 3% of patients demonstrated a progression of greater than -1.5 dB per year, 10.4% reached visual impairment within their lifetime, and 5.2% achieved statutory blindness.

> 3% of patients demonstrated a progression of greater than -1.5 dB per year, 10.4% reached visual impairment within their lifetime, and 5.2% achieved statutory blindness

The results for statutory blindness compare favorably with the small sample longitudinal studies using manual perimetric results. There appear to be advantages and disadvantages associated with this procedure. The advantages are that it is possible to provide a prediction of whether glaucomatous visual field loss will produce changes in the patient's activities of daily living and quality of life. It also provides a means of detecting fast versus slow progressors, to direct potential changes in therapeutic intervention. Additionally, the findings are based on existing technology and analysis procedures. **The disadvantages are that nearly one third of the potential cases were excluded because they did not meet the reliability criteria established for this study,** eliminating a significant portion of the population. **Another disadvantage is that this model assumes that the rate of progression will be linear and that this rate will be constant throughout the patient's lifetime,** whereas it is likely that the rate may reflect a higher rate of progression as glaucomatous damage increases over time. Finally, it is clear that the testing and analysis procedures for perimetry in glaucoma will change considerably over a reasonable time period, so that current assumptions and methods may not be suitable for the future. A dynamic model may be preferable for future purposes.

Anatomical Structures

Iris dynamics and angle-closure risk

Comment by Shan Lin, San Francisco, CA, USA

56333 Comparison of dynamic changes in anterior ocular structures examined with anterior segment optical coherence tomography in a cohort of various origins, Seager FE, Jefferys JL, Quigley HA, Investigative Ophthalmology and Visual Science 2014; 55: 1672-1683

Seager *et al*.[1] reported the results of anterior segment optical coherence tomography imaging among groups with different geographical origin, seen within a clinic setting. Diagnoses ranged from normal to primary open-angle glaucoma to various forms of angle closure (suspects, PAC, AACG and PACG). The total number of subjects was 267, including whites, African-Americans, Chinese, Koreans, Indian (Asian), and others.

The main findings were that whites and African-Americans had a greater iris area at baseline than Chinese and Koreans; however, the Chinese race was the only one in which less loss of iris area per mm of pupil dilation (going from light to dark conditions) was associated with greater risk for an angle closure diagnosis. The authors speculate that this dynamic factor is one of the predisposing reasons that Chinese may be at higher risk for angle closure.

Overall this paper presents interesting findings, which add to the literature on anatomic reasons for angle closure variability among races. There are some aspects worthy of comment and further consideration. For example, in the present paper, 'baseline' for iris parameters is under light conditions. In most studies, the 'baseline' values for iris and angle measurements are in the dark. This makes physiological sense in that dark situations are when angle closure risk is higher. Their use of parameters in the light is likely the reason for discrepancies with prior studies.[2,3]

The findings related to **the dynamic change in the iris going from light conditions to the dark seem to be very relevant to understanding why Chinese have particularly high risk**. Dr. Quigley is to be congratulated in proposing early on that the anatomic conditions leading to angle closure are more related to dynamic rather than static features of the anterior segment. In support of their findings, our group's study comparing ethnic Chinese and whites found that Chinese have greater thickening of the iris at the angle when going from light to dark.[4] Also, Chinese have greater narrowing of the angle than whites in that transition, which was associated with iris thickening only in the Chinese group.[5]

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Optic disc rim and parapapillary zone

Comment by Jost Jonas, Heidelberg, Germany

56348 Microstructure of β-zone parapapillary atrophy and rate of retinal nerve fiber layer thinning in primary open-angle glaucoma, Kim YW, Lee EJ, Kim TW, Kim M, Kim H, Ophthalmology 2014; 121: 1341-1349

Recent histomorphometric and clinical studies have suggested that the conventional parapapillary beta zone which has so far been defined as the area with visible sclera and visible large choroidal vessels can be subdivided.[1] In the new classification, alpha zone in the periphery of the parapapillary region is ophthalmoscopically characterized by irregular pigmentation in the level of the retinal pigment epithelium (RPE). Upon optical coherence tomography (OCT) and upon histology, it is featured by the presence of Bruch's membrane covered with irregularly structured RPE. 'Beta zone' in the new classification is the region following centrally to the alpha zone and is characterized by the presence of Bruch's membrane and absence of RPE; Bruch's membrane is denuded from the RPE.[2,3] Upon ophthalmoscopy, it is characterized by visible large choroidal vessels and visible sclera, since the RPE is absent and thus the view onto the choroidal and scleral structure is facilitated. A new gamma zone (or called peripapillary atrophy minus Bruch's membrane in the article by Kim and colleagues[4]) is located between the new beta zone and the optic

disc border and is characterized by the absence of Bruch's membrane.[2-4] Since there is no Bruch's membrane, there is neither RPE or choriocapillaris. The development of the gamma zone may be due to the myopic enlargement of globe which takes place asymmetrically towards the posterior pole. If at birth, all three layers of the optic nerve head (Bruch's membrane opening; choroidal opening; scleral opening) may be aligned to each other, the myopic stretching taking place predominantly closer to the posterior pole may lead to a shift of the inner opening (*i.e.*, Bruchs' membrane opening) in the direction of the fovea. It leads to a misalignment of Bruch's membrane opening with the scleral opening, so that Bruch's membrane may overhang into the optic nerve head on the nasal side, while at the temporal disc border, a region develops which is no longer covered by Bruch's membrane. This would be the gamma zone (peripapillary atrophy minus Bruch's membrane in Kim's *et al*. study[4]).

> Differentiating the old beta zone into a new beta zone (associated with glaucoma) and a gamma zone (associated with myopia) may increase the precision of the beta zone for the diagnosis of glaucoma

Typically, the gamma zone exists in medium myopic or highly myopic globes. In the study by Kim and colleagues on patients with open-angle glaucoma, the rate of retinal nerve fiber layer thinning was faster for eyes with 'beta zone with intact Bruch's membrane' ('new beta zone', see above) than for eyes without beta zone or eyes with beta zone without Bruch's membrane (new 'gamma zone', see above). It fully agrees with recent histologic and clinical studies, in which the new beta zone (Bruch's membrane present, RPE absent) was associated with glaucoma, while the gamma zone (Bruch's membrane absent, RPE absent) was strongly associated with axial myopia.[2,3] All studies mentioned suggest that differentiating the old beta zone into a new beta zone (associated with glaucoma) and a gamma zone (associated with myopia) may increase the precision of the beta zone for the diagnosis of glaucoma.

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Mechanic factors underlying axonal damage

Comment by Ki Ho Park, Seoul, South Korea

56036 Eye-specific IOP-induced displacements and deformations of human lamina cribrosa, Sigal IA, Grimm JL, Jan NJ, Reid K, Minckler DS, Brown DJ, Investigative Ophthalmology and Visual Science 2014; 55: 1-15

While there have been many reports on the change in the thickness or volume of optic nerve head tissue after intraocular pressure (IOP) change, the study by Sigal *et al*. is quite unique in that it performed high-resolution measurements of displacements and deformations induced within the human lamina cribrosa (LC) microstructure. After an acute increase in the IOP of six donor eyes, the microstructural change was analyzed in terms of displacement, stretch, shear, and compression.

Based on second-harmonic-generated imaging, the microstructural displacement and deformation were determined two-dimensionally at IOP levels varying from 10 to 50 mmHg. The authors found that **IOP elevation induced substantial levels of in-plane LC stretch and compression**. The regions of largest displacement, stretch, compression, and shear were not co-localized. The responses of the contralateral eyes to IOP were not always more similar than were those of the unrelated eyes. The study clearly showed the regions of different kinds of deformation in the LC, which might facilitate understanding of the pathogenesis of mechanical axonal damage in glaucoma.

> The regions of largest displacement, stretch, compression, and shear were not co-localized

The finding that the regions of stretch and compression did not co-localize when analyzed two dimensionally is very interesting. However, it is possible that in the axis vertical to the plane of analysis (z-axis), the stretched region has a compressive z-axis component and the compressed region has a stretched z-axis component.

Even though there are some limitations, such as (1) the lack of blood flow in the system, which might have contributed to the IOP-induced structural LC change; and (2) the two-dimensional analysis, the study represents pioneering research on LC microstructural change induced by IOP elevation. I look forward to the authors' follow-up research based on 3-D analysis of LC change.

IOP-induced laminar changes in POAG and APAC

Comment by Ian Sigal, Pittsburgh, PA, USA

55960 Changes in the lamina and prelamina after intraocular pressure reduction in patients with primary open-angle glaucoma and acute primary angle-closure, Park HY, Shin HY, Jung KI, Park CK, Investigative Ophthalmology and Visual Science 2014; 55: 233-239

Deformations of the optic nerve head (ONH), particularly the lamina cribrosa, in response to IOP elevation are likely to be a major factor on retinal ganglion cell axon insult and thus play a role in the development and progression of glaucoma. Park *et al*. acquired and analyzed SD-OCT images from 20 patients with primary open-angle glaucoma (POAG) who underwent glaucoma surgery and 17 patients with acute primary angle-closure (APAC) who underwent laser peripheral iridoplasty. Eyes were imaged before and one month after the IOP-reducing intervention, and the anterior prelaminar and laminar surfaces delineated manually on several B-scans. The positions of these surfaces relative to Bruch's membrane opening and their changes with IOP treatment were analyzed.

The most important result was that for similar IOP reductions **APAC patients showed significantly more pronounced anterior movement of the laminar and prelaminar tissues and thickening of the prelaminar tissues than POAG patients**. The effects of the IOP reduction on POAG eyes confirm previous findings [1], but the comparison with APAC eyes is novel to the study by Park *et al*. The results are interesting because **if the changes in prelaminar and laminar tissues due to the IOP-reduction treatment are taken as a measure of 'relief' from the insult to the axons due to the elevated IOP, then the smaller changes in POAG eyes could suggest that these eyes benefit less from IOP-lowering treatment than APAC eyes**. The actual 'relief' to the axons may be the result of a complex interaction between the level of IOP, tissue anatomy, biomechanical properties (*e.g*., stiffness) and astrocyte sensitivity among other factors, and not directly captured by lamina or prelaminar displacement. Also, the results show that after a couple of days exposure to elevated IOP (2.5 ± 1.3 days in APAC eyes), there are still significant differences in morphology and sensitivity to IOP reduction with eyes that lived under chronic IOP elevation (at least 78 ± 21 days in POAG eyes). However, as a cross-sectional study, the results cannot tell if the characteristics of the POAG eyes are the result of the chronic IOP elevation, or if they were an existing risk factor.

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Basic Science

Trabecular meshwork cell loss and regeneration

Comment by Terete Borrás, Chapel Hill, NC, USA

56161 Outflow tract ablation using a conditionally cytotoxic feline immunodeficiency viral vector, Zhang Z, Dhaliwal AS, Tseng H, Kim JD, Schuman JS, Weinreb RN, Loewen NA, Investigative Ophthalmology and Visual Science 2014; 55: 935-940

It is well-accepted that trabecular meshwork (TM) cellularity decreases with age and POAG patients have lower TM cellularity than age-matched controls. Since Alvarado's first report in the early 1980s, cell loss mechanisms and their potential association with elevated IOP have been barely studied. The main reason for this lag was the lack of a model able to manipulate the TM cellular system.

Making use of their experience delivering transgenes to the TM using lentiviral vectors, Loewen's group put together a very clever idea to specifically ablate TM cells in living rats. The authors generated a lentiviral vector carrying the Herpes Simplex Virus thymidine kinase gene (HSVtk) and targeted it to the rat's TM. This gene product phosphorylates nucleotide analogs, such ganciclovir (GCV), which compete with normal nucleotides during DNA replication and lead cells to its death. The strategy is being extensively used in cancer to specifically destroy rapidly growing tumors. Its application to manipulate TM cellularity is clever and highly innovative. After showing proof of principle in culture, the authors injected HSVtkiG intracamerally followed by intraperitoneal GCV one week post-infection. IOPs went down one to two days post-GCV and recovered at 30 days. **Histology showed TM cell depletion from two to seven days post-CGV and cell recovery at 30 days.**

> Although some methods need polishing, their strategy and findings open a new research era on the role of TM cellularity

Although some methods need polishing (precise cell counting descriptions), their strategy and findings open a new research era on the role of TM cellularity. Discussion of the unexpected GCV effect on quiescent cells, correlation of TM cell loss with lower pressures rather than with glaucomatous signs, or the remarkable finding of cellular regeneration, would had been desirable. However, it is not expected to have all answers in a first study. What is truly important is that **this innovative approach gives the field a much needed model to study loss/regeneration of TM cells *in vivo*.**

Genetic drivers of aqueous and CSF secretion

Comment by Rand Allingham, Durham, NC, USA

56198 Gene expression-based comparison of the human secretory neuroepithelia of the brain choroid plexus and the ocular ciliary body: potential implications for glaucoma, Janssen SF, Gorgels TG, Ten Brink JB, Jansonius NM, Bergen AA, Fluids and barriers of the CNS 2014; 11: 2

Janssen and co-workers compare gene expression (transcriptomes) of the non-pigmented neuroepithelial lining of the ciliary body (NPE) and choroid plexus (CPE). These cells secrete aqueous humor and cerebrospinal fluid, thus responsible for generating intraocular pressure (IOP) and cerebrospinal fluid pressure (CSFP), respectively. It has been postulated that the pressure difference experienced by the lamina cribrosa may be important in glaucoma pathogenesis. Therefore, it is of interest to examine the gene expression of these two cell types. Substantial similarities and differences in gene expression among the 30,589 uniquely expressed genes were found. Molecular pathways for neurologic function and disease, neurodegenerative disorders like Alzheimer disease, and immunological pathways were implicated. Surprisingly, 1000 genes were more highly expressed in one epithelium versus the other. A large number of genes (31) that code for ion channels involved in AH and CSF production were highly expressed in one or both epithelia. Transcripts for 19 POAG candidate genes were found. TMCO1, associated with IOP level was highly expressed in both epithelia. A gene implicated in normal tension glaucoma, CDKN2B, was more highly expressed in CPE. Another POAG-risk associated gene, SIX6 was expressed more highly in NPE. Genes involved in congenital glaucoma (CYP1B1) and early-onset forms of glaucoma,(MYOC and PAX6) were expressed more highly in NPE.

This is an excellent paper that helps clarify the role of these cells in processes relevant to glaucoma and other related disorders. The presence and expression level of specific genes helps clarify which may be important in carrying out key functions in specific cell types. Actively transcribed genes can help determine potential therapeutic targets, for example, the presence of transcripts for alpha-2 adrenoreceptors. **The authors note that some alpha-2 adrenergic antagonists reduce IOP while increasing CSF pressure making these agents an attractive therapeutic target.** Finally, analyzing specific cells obtained from intact human tissues can provide better understanding and context for what is observed in cell cultures or animal models.

Molecular mechanisms of steroid-induced glaucoma

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

56532 Ocular-specific ER stress reduction rescues glaucoma in murine glucocorticoid-induced glaucoma, Zode GS, Sharma AB, Lin X, Searby CC, Bugge K, Kim GH, Clark AF, Sheffield VC, Journal of Clinical Investigation 2014; 124: 1956-1965

Ocular hypertension and secondary open-angle glaucoma can occur as side effects of glucocorticoid therapy in some patients. However, the molecular mechanisms underlying glucocorticoid-induced glaucoma are poorly understood.

Zode *et al*. established a mouse model of glucocorticoid-induced glaucoma with topical, ocular administration of 0.1% dexamethasone. In this model, intraocular pressure (IOP) rose and ER stress-associated damage occurred in the retinal ganglion cells in the trabecular meshwork (TM). Withdrawing dexamethasone reduced ER stress and IOP elevation, parallel to human glucocorticoid-induced glaucoma. Additionally, reducing ER stress by deleting the *Chop* gene or using chemical chaperone treatment prevented IOP elevation in the model, suggesting that reducing ER stress has potential as a therapeutic strategy for treating glucocorticoid-induced glaucoma.

Importantly, the authors found that the unfolded protein response was activated in a primary culture of human dexamethasone-treated TM cells, suggesting that ER stress is a primary event in the TM in glucocorticoid-induced ocular hypertension. Additionally, dexamethasone-induced ER stress in the TM occurred before IOP elevation in the mice, suggesting that **ER stress induction is a primary event in IOP elevation in glucocorticoid-induced glaucoma**.

These findings suggest important new possibilities for therapeutic strategies. In particular, CHOP may be a therapeutic target for glucocorticoid-induced glaucoma. **CHOP expression/activity inhibitors may have clinical benefit in IOP-lowering treatment**.

Interestingly, the authors found that topical dexamethasone induced the accumulation of myocilin (MYOC) protein in the TM of mouse eyes. The authors previously reported that mutant MYOC can accumulate and promote ER stress in the TM in association with IOP elevation.[1] Although the mechanism of MYOC accumulation is still unknown, MYOC contributes to IOP elevation. Thus, patients with mutations in the MYOC gene may have a higher risk of glucocorticoid-induced glaucoma.

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Astrocytes and capillaries in the ONH of various animal species

Comment by Harry Quigley, Baltimore, MD, USA

56340 Comparative quantitative study of astrocytes and capillary distribution in optic nerve laminar regions, Balaratnasingam C, Kang MH, Yu P, Chan G, Morgan WH, Cringle SJ, Yu DY, Experimental Eye Research 2014; 121: 11-22

In order to improve understanding of the pathogenesis of glaucoma, this investigation quantified the proportion of the optic nerve head (ONH) occupied by astrocytes and capillaries among five species. However, there are a number of limitations with this study.

Unfortunately, the authors did not study monkey and mouse ONH, the two most frequent animal models in experimental glaucoma studies.

The report included only six humans, ranging from 23 to 62 years of age. ONH tissues change dramatically with age, so this is too few to do an age study and too diverse to give information on the eye at the peak age of glaucoma (60-85 years). For the animal eyes, the ages are not given; several studies now show differences in glaucoma susceptibility by age in monkey, rat and mouse.

The authors' data indicate that astrocytes occupy almost 70% of the human lamina cribrosa. An optic disc of 1.5 mm diameter would have an area of 1.76 mm^2. There are ~1 million human ganglion cell axons of 1 micron diameter, occupying 0.78 mm^2 area or ~44% of the tissue. The report's finding is seemingly incompatible with the space needed for axons, connective tissue beams and blood vessels.

There are a number of other methodological issues. First, the investigators studied fixed tissue, thereby giving estimates for cellular density that potentially differ from fresh tissue. They assumed that all nuclei in the ONH and nerve were astrocytes, a choice inconsistent with the presence of endothelium, pericytes, laminar fibroblasts and oligodendrocytes. In the rat, they included some of the unmyelinated optic nerve as lamina cribrosa. In human eyes, they studied only one ONH area, missing the chance to look for regional differences that might underlie regional glaucoma damage.

Overall, the data are specific to the methods used, so that they are more useful as relative than absolute values. It is not clear how the quantification used here would be helpful in understanding glaucoma damage. There are no horse models of glaucoma, and pig and rabbit models have only rarely given quantifiable data. It will be interesting to see if follow-up studies can make these data relevant.

Mitochondrial alterations in glaucoma

Comment by Jonathan Crowston, Melbourne, Australia

56181 Coenzyme Q10 inhibits glutamate excitotoxicity and oxidative stress-mediated mitochondrial alteration in a mouse model of glaucoma, Lee D, Shim MS, Kim KY, Noh YH, Kim H, Kim SY, Weinreb RN, Ju WK, Investigative Ophthalmology and Visual Science 2014; 55: 993-1005

Coenzyme Q10 (CoQ10) is present in the inner mitochondrial membrane and is component of the electron transport chain shuttling electrons from complexes I and II to complex III. This is a key step in ATP production by oxidative phosphorylation (OXPHOS). This interesting study demonstrated a significant increase in RGC survival in DBA/2J mice, with inherited glaucoma, that were fed with a CoQ10 diet for six months compared to control animals not fed a supplemented diet. Increased RGC survival was associated with lower astroglial activation at the optic nerve head as well as lower levels of retinal oxidative stress.

Another interesting observation in this study was that retina of untreated DBA/2J mice had increased mitochondrial DNA copy number, increased complex IV levels and transcription factor profiles indicative of upregulated mitochondrial biogenesis in the retina. This points to a possible compensatory mechanism whereby the retina responds to IOP injury by increasing the number of mitochondria, perhaps in response to increased metabolic demand required to undertake repair processes.

> This points to a possible compensatory mechanism whereby the retina responds to IOP injury by increasing the number of mitochondria

Interestingly, the CoQ10-fed mice had a muted mitochondrial biogenesis in the retina, despite lower rates of RGC death. A potential explanation for this is that by promoting ATP production CoQ10 obviates the need for mitochondrial biogenesis. **The mechanism by which CoQ10 reduced RGC loss in this particular model, however, remains to be determined.**

A number of studies have pointed to systemic mitochondrial DNA mutations and OXPHOS dysfunction in glaucoma patients. In contrast, the mice used in this study would be expected to have a normal complement of mitochondria (for age). How then does an essential co-factor of OXPHOS promote RGC survival? **The authors (indirectly) point to an interesting hypothesis whereby IOP elevation per se might promote mtDNA damage through glutamate excitotoxicity and oxidative stress.** This is an area that clearly requires further work but could provide another piece in the jigsaw of our understanding of the pathogenesis of glaucoma optic neuropathy.

Do statins influence aqueous secretion?

Comment by Nils Loewen, Pittsburgh, PA, USA

56206 Pharmacological regulation of SPARC by lovastatin in human trabecular meshwork cells, Villarreal G, Chatterjee A, Oh SS, Oh DJ, Rhee DJ, Investigative Ophthalmology and Visual Science 2014; 55: 1657-1665

SPARC (Secreted Protein Acidic and Rich in Cysteine) is a micro-RNA is expressed in the trabecular meshwork that has been implicated in IOP regulation and primary open-angle glaucoma (POAG) pathogenesis. Previous work by Villarreal *et al*. demonstrated that SPARC was highly up-regulated following TGF-b2 treatment in human TM cultures.[1] In their current study, the authors reported the effect of lovastatin on SPARC, TGF-b2 and KLF4 in primary human TM cell monolayer cultures. They demonstrated that **lovastatin inhibits SPARC expression, while increasing KLF4 expression**. While the authors measured both mRNA and protein expression levels, the results suggest a much more significant effect on protein expression levels as compared to mRNA expression levels, as acknowledged in the discussion. This may suggest a post-transcriptional regulatory mechanism, or perhaps regulation through microRNA.

> Statins, a class of medications approved for lowering cholesterol, may have utility in the treatment of glaucoma

The clinical significance of these findings is that statins, a class of medications approved for lowering cholesterol, may have utility in the treatment of glaucoma. However, the suggested mechanism for lovastatin regulation of SPARC and the direct effect of SPARC on IOP are not complete. Despite widespread use, initiation of statins has not yet been noticed to have an effect on IOP or the course of glaucoma. **The involvement of both KLF4 and TGF-b2 in the mechanism, and the stronger effect on protein expression**

levels as compared with mRNA suggest that there is more to this mechanism, perhaps two separate pathways that ultimately affect SPARC expression. This work provides further insight into the molecular pathways involved in IOP and outflow regulation at the level of the TM. However, the mechanisms by which IOP are regulated, and the role of SPARC (causative or merely correlated) remains to be seen. The new data in this study is intriguing and perhaps pathway analysis tools[2] could be applied to better understand the context.

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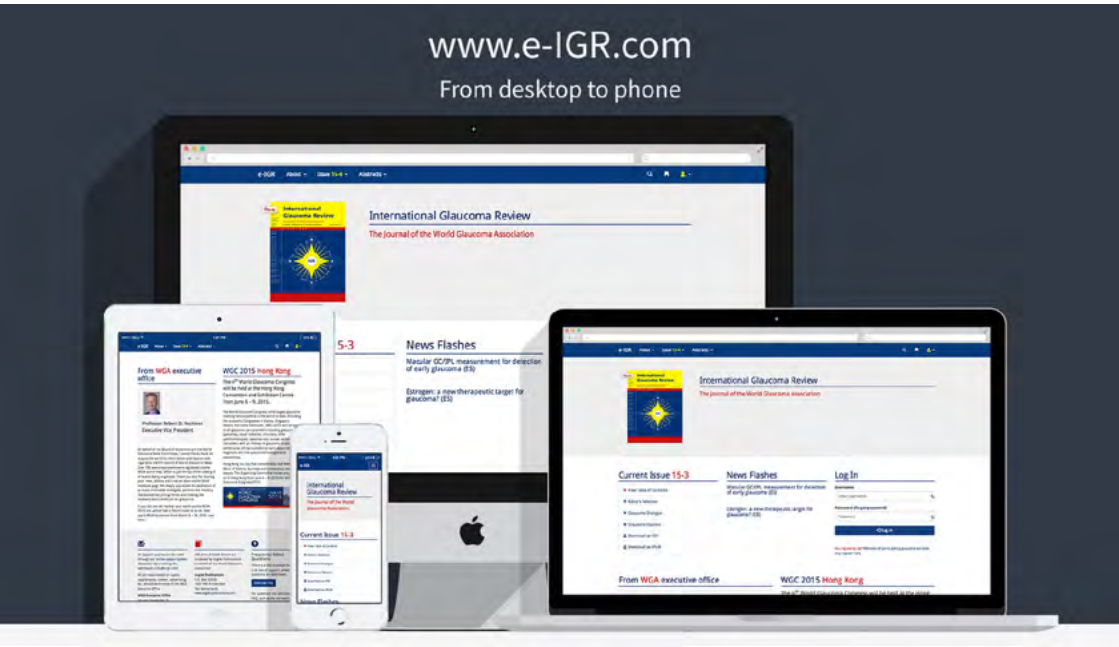

Clinical Examination Methods

Factors affecting IOP

Comment by Minguang He, Guangzhou, P.R. China

56379 Changes in intraocular pressure and associated systemic factors over 10 years in subjects without ocular disease at baseline, Kitamura K, Yokomichi H, Yamagata Z, Tsuji M, Yoda Y, Kashiwagi K, Journal of Glaucoma 2014; 23: 185-189

Kitamura *et al*. investigated the ten-year IOP changes in 3785 Japanese people aged 23 to 80 years and found that the mean IOP reduced significantly by about 0.7 mmHg after ten years. Given the fact that the risk of glaucoma will increase exponentially with IOP, the findings may somehow suggest the risk of glaucoma will decrease with aging. The authors also found an association of IOP changes with the level of BMI, SBP and DBP and further point to the statement that further lowering these systemic factors or perhaps changing lifestyle may help reduce IOP. However, an interpretation of the results and their implications for the prevention of glaucoma should be understood at least in the context of dose-response effect. **For instance, we are not sure how much benefit there is on the risk of glaucoma if the mean IOP decreases with 0.7 mmHg in ten years, similarly, what level of decrease on BMI and blood pressure is required to have clinically meaningful decrease on IOP and risk of glaucoma?** A further analysis on the optic disc and visual field changes among the participants with greatest increase of IOP, such as five mmHg in ten years, will be interesting in terms of understanding the impact of increased IOP among the 'normal' people at baseline. On the other hand, the results should also be interpreted carefully in the scenario of a better understanding of the study methodology. **The study participants were recruited from a group of health checkup people with high dropout, 3845 in ten years among 20700 at baseline.** IOP was measured using the non-contact method where a proper calibration of the tonometer device can be challenging and difficult for a ten-year period of time. These challenges may somehow affect the quality of the results.

Measuring ONH perfusion

Comment by Lin Wang, Portland, OR, USA

56439 Optical Coherence Tomography angiography of optic disc perfusion in glaucoma, Jia Y, Wei E, Wang X, Zhang X, Morrison JC, Parikh M, Lombardi LH, Gattey DM, Armour RL, Edmunds B, Kraus MF, Fujimoto JG, Huang D, Ophthalmology 2014; 121: 1322-1332

Dr. Jia and colleagues have compared optic nerve head (ONH) perfusion between normal and glaucoma subjects, using a high-speed swept-source OCT instrument and a split-spectrum amplitude-decorrelation angiography (SSADA) algorithm developed in their lab. With the technique an exquisite 3-D ONH vascular architecture image is generated to quantify the ONH perfusion with optic disc flow index, a computed arbitrary unit. These results show several important findings. Firstly, in addition to excellent intra- and inter-visit repeatability measured by this technique, it reveals that **the inter-subject variability of the optic disc flow index in the normal population is much lower (5.0%, coefficient of variance) than the other instruments**.

Glaucoma eyes had attenuated flow both in the superficial disc and in the deeper lamina cribrosa

While the ocular perfusion pressure in these same subjects has a large variation, this suggests that the ONH blood flow is well regulated and maintained within a relatively narrow range. With this exceptionally tight inter-subject variability, improved from their previous work by using this latest iteration of the cutting-edge technology**, a 25% lower flow index in the glaucoma group can be effectively discerned** with 100% sensitivity and specificity. Secondly, the 3-D angiography allows the optic nerve head perfusion to be projected onto en face views in 3 layers (retinal, choroidal and scleral/lamina cribrosa). Although each layer was not quantitatively compared between normal and glaucoma, evaluation based on the 3D angiography images suggests that **glaucoma eyes had attenuated flow both in the superficial disc and in the deeper lamina cribrosa**. This finding provides important clinical evidence of insufficient blood flow perfusion deep within the glaucomatous lamina cribrosa, one of the important issues regarding the measurement from all optically-based blood flowmeters. In spite of the limitations that have been thoroughly discussed in the paper, this study represents important progress which increases the toolset we can use to understand the hemodynamic changes in the ONH in glaucoma.

Comment by Yoshiaki Yasuno, Tsukuba, Ibaraki, Japan

56439 Optical Coherence Tomography angiography of optic disc perfusion in glaucoma, Jia Y, Wei E, Wang X, Zhang X, Morrison JC, Parikh M, Lombardi LH, Gattey DM, Armour RL, Edmunds B, Kraus MF, Fujimoto JG, Huang D, Ophthalmology 2014; 121: 1322-1332

The authors developed and applied a new angiographic modality, optical coherence tomography angiography (OCTA), to glaucoma subjects including eight perimetric glaucoma and three pre-perimetric glaucoma subjects together with 24 normal controls. The OCTA is an emerging modality enabling non-invasive angiography of posterior eye. Among several variations of OCTA, the authors utilized their own developed method, split-spectrum amplitude-decorrelation angiography (SSADA), which is minimally suffered by subject motion and provides high contrast en-face and three-dimensional angiographies of a macula and an optic nerve head. The authors first utilized OCTA for quantitative observation of vasculature at the optic nerve head. This observation showed that the **normal discs had denser microvascular network than glaucomatous discs**. **In addition, there appeared to be reduced flow in the lamina region of the glaucomatous disc compared with the normal disc**.

OCTA may become a powerful tool for glaucoma diagnosis and evaluation of glaucoma progression

Although OCTA was originally utilized for qualitative imaging of vasculature, the authors also developed a quantitative metric based on OCTA, so called as a disc flow index, which is expected to be large if the flow is large. The flow index showed high intra-visit repeatability (1.2%) and inter-visit reproducibility (4.2%). **The disc flow index in the glaucoma group was 25% lower than the normal group (p = 0.003). The disc flow index was significantly negatively correlated with visual field pattern standard deviation in the glaucoma group** (R^2 = 0.752, p = 0.001). This suggests that the flow index may be a good indicator of glaucoma severity. This study has shown that OCTA is useful for both qualitative angiographic observation of optic disc as well as quantitative evaluation of the flow in the optic disc. OCTA may become a powerful tool for glaucoma diagnosis and evaluation of glaucoma progression.

Clinical Forms of Glaucoma

Primary angle closure and myopia

Comment by David Friedman, Baltimore, MD, USA

56512 Myopia in Asian subjects with primary angle closure: implications for glaucoma trends in East Asia, Yong KL, Gong T, Nongpiur ME, How AC, Lee HK, Cheng L, Perera SA, Aung T, Ophthalmology 2014; 0:

Yong and colleagues recruited 427 individuals with angle closure from the Singapore National Eye Center clinics to assess the association of primary angle closure (PAC) with refractive errors. The actual recruitment and patient selection process is not stated so it is difficult to know how this subset of angle closure patients compares to the overall population of those with angle closure in Singapore. Furthermore, Singapore overall has very high rates of myopia, so findings from this single site study may not apply to other locations where myopia is less common.

The study population included suspects (PACS), those with primary angle closure (PAC) and those with PAC glaucoma (PACG) as well as individuals who had had an acute primary angle closure attack (APAC). Refractive error was determined by autorefraction. About half of all subjects were hyperopic, and about one out of five subjects was more than 0.50 diopters myopic. 6.6% and 2.6% of subjects had between -2D and -5D of myopia and more than -5D of myopia, respectively.

When assessing differences in biometric parameters comparing myopes to emmetropes and hyperopes, anterior chamber depth, central corneal thickness and lens thickness were all similar across the groups. Myopes had longer axial and vitreous lengths, and borderline larger lens vault.

While the authors state that nearly one in four subjects with angle closure are myopic, the fact is that this population may not be representative, and some of the myopia is almost certainly due to cataract among this older population. Furthermore, the cutoff of -0.5D is low and a alternative cutoffs were not provided.

> The authors strongly recommend (and I agree) that gonioscopy still be performed when assessing individuals with myopia, even high myopes

Previous reports have consistently found that a small proportion (1.5 to 3%) of those with angle closure have myopia of -5D or greater. This appears to continue to be the case in

Singapore and the fact that other factors including anterior chamber depth were similar in myopes and hyperopes with angle closure indicates that vitreous chamber depth elongation likely explains why some myopes can still have angle closure. **Based on the findings the authors strongly recommend (and I agree) that gonioscopy still be performed when assessing individuals with myopia, even high myopes.**

Comment by Catherine Liu, Taipei, Taiwan

56512 Myopia in Asian subjects with primary angle closure: implications for glaucoma trends in East Asia, Yong KL, Gong T, Nongpiur ME, How AC, Lee HK, Cheng L, Perera SA, Aung T, Ophthalmology 2014; 121: 1566-71.

Yong and associates reported that myopia was present in 94 (22%) subjects in a study of 427 subjects with angle closure; 11 (2.6%) among them were high myopia (£ -5.00D), a figure similar to what had been reported by Chakravarti and Spaeth.[1] A new finding of this study is that **myopic angle-closure patients had longer axial length (AL) and vitreous cavity length than their hyperopic and emmetropic counterparts, but had comparable anterior chamber depth (ACD)**. These findings are consistent with our current understanding of risk factors for angle closure and morphology of myopic eyes.

Assessment of ACD during slit-lamp biomicroscopy is useful in screening for angle closure, even for eyes with myopia

What the authors did not demonstrate is the mechanisms for angle closure in these myopic eyes. All subjects had received laser iridotomy, but patients with previous iridoplasty were excluded. Among the 11 high myopic patients listed in Table 3, three aged 70 years or older had AL shorter than the average (21.33 mm, 21.71 mm, and 21.16 mm, respectively), which leads one to reason that these patients actually are hyperopic angle-closure by nature who developed myopia late in life (possibly after iridotomy) due to cataract development. A figure displaying AL distribution of all the myopic eyes would help readers better understand these patients' ocular status. Besides, which eye of each subject was chosen for analysis (the eye with greater myopia? higher presenting IOP? or worse optic nerve?) was not mentioned, which could potentially bias the study results.

Hyperopia is a risk factor for angle closure which is prevalent in elderly Chinese born before 1950,[2] but an increasingly high prevalence of myopia has been shown in China, Singapore, and Taiwan in recent decades.[3-5] Although on average myopic eyes have deeper ACD than hyperopic eyes, the study by Yong and associates suggests that assessment of ACD during slit-lamp biomicroscopy is useful in screening for angle closure, even for eyes with myopia.

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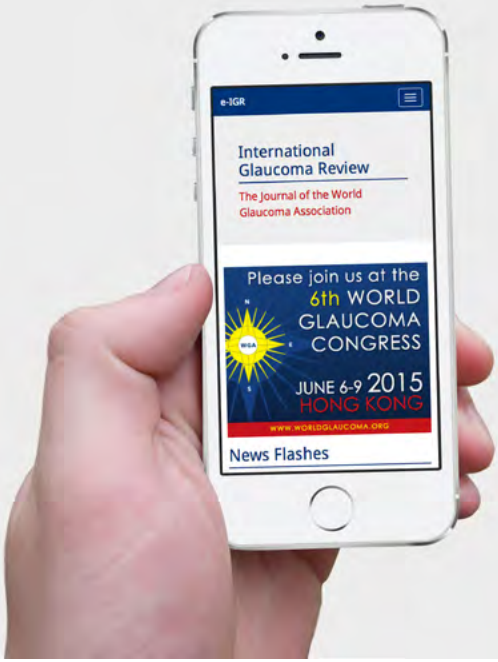

Medical Treatment

Real-life effectiveness and clinical trial efficacy of anti-glaucoma drugs

Comment by Robert Feldman, Houston, TX, USA

56218 Effectiveness of intraocular pressure-lowering medication determined by washout, Jampel HD, Chon BH, Stamper R, Packer M, Han Y, Nguyen QH, Ianchulev T, JAMA Ophthalmology 2014; 132: 390-395

Lowering IOP remains the predominant strategy for treating glaucoma, and medications are an invaluable tool. They are cost-effective, non-invasive, and effective, which results in medications generally being the first-line of treatment. Randomized clinical trials (RCTs) are considered the definitive source of information about a medication's efficacy. However, as Jampel *et al*. point out, while RCTs are invaluable to modern medical research and provide crucial information about a drug's efficacy and safety, certain aspects of an RCT may not be comparable to real world patients. RCTs have a specific population dictated by inclusion and exclusion criteria and dedicated coordinators reminding patients to take their medications, minimizing confounding variables. In the real world, the setting is not as stringent, and patients are often noncompliant, administer drops incorrectly, and have other comorbid conditions.

The goal of Jampel *et al*.'s study was to investigate medication use in a real world setting and compare the IOP-lowering effectiveness in the real world to IOP-lowering efficacy in an RCT setting. They investigated the 'efficacy-effectiveness gap' by analyzing the difference in IOP in 619 primary open-angle glaucoma (POAG) patients before (ON IOP) and after (OFF IOP) the medication washout phase for a large RCT. **They found that when one, two, or three medications were removed, there was a statistically significant increase in IOP, with the biggest change in IOP occurring after removal of one medication.**

When these data were compared to previous RCTs, the effectiveness of removing one medication matched the efficacy of the clinical trials, contrary to the authors' hypothesis. This effectiveness-efficacy relationship also held for 2 and 3 medications. **While this study has the inherent limitations of a retrospective study, the data show that RCTs aren't that far off from approximating real world patients.**

The 'effectiveness-efficacy gap' isn't a very large gap, and RCTs are confirmed as an excellent way to evaluate glaucoma medications.

Comment by Ramanjit Sihota, New Delhi, India

56218 Effectiveness of intraocular pressure-lowering medication determined by washout, Jampel HD, Chon BH, Stamper R, Packer M, Han Y, Nguyen QH, Ianchulev T, JAMA Ophthalmology 2014; 132: 390-395

This is an interesting but retrospective study purportedly looking at a possible 'real-world' scenario of medical therapy in glaucoma. Data of 619 patients having mild or moderate primary open-angle glaucoma, being screened for inclusion in a phase-3 study of CyPass Micro-Stent was analyzed. Patients underwent a screening IOP measurement at one point in time, following which glaucoma medications were discontinued, as per predetermined washout periods – five days for carbonic anhydrase inhibitors, 14 days for alpha agonists and 28 days for all other drugs. Absolute change in IOP by withdrawing one medication was 5.4 ± 3.0 mmHg, after two drugs it was 6.9 ± 3.3 mmHg and after withdrawing three drugs it was 9.0 ± 3.8 mmHg. A calculation of the percentage decrease in IOP was made as: IOP change divided by final IOP, and was 23 ± 12%, 28 ± 11% and 34 ± 11 % respectively for one, two and three topical glaucoma medications. Of patients on a prostaglandin analogue, 67% had a decrease in IOP > 20 %.

There are a few limitations of the study. The washout period as ascertained in the only study by Stewart *et al.*,[1] was 3.3. ± 3.0 weeks for brimonidine and 4.4 ± 3.2 weeks for latanoprost. Therefore, the washout periods used in this study appear inadequate for the ascertaining drug efficacy. There was no analysis of change in homogenous groups, using a particular medication/combination of medications. Instead, for example, in single medication analysis, a prostaglandin analogue was analyzed together with a carbonic anhydrase inhibitor or alpha agonist. The analysis of IOP increase – change in IOP divided by IOP ON medication – does not appear as logical as the analysis of IOP decrease, both differ significantly. One hundred and seven of 619 patients, and more significantly 16% of patients using two drugs, did not show an increase in IOP of more than 20%, implying that patients could have been non-responders.

A targeted analysis could have provided better data on the efficacy of each drug or combination used.

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Surgical Treatment

Morphological changes after deep sclerectomy

Comment by Stefano Gandolfi, Parma, Italy

55564 Visante anterior segment optical coherence tomography analysis of morphologic changes after deep sclerectomy with intraoperative mitomycin-C and no implant use, Pérez-Rico C, Gutiérrez-Ortíz C,Moreno-Salgueiro A, González-Mesa A, Teus MA, Journal of Glaucoma 2014; 23: e86-e90

More than two decades have elapsed since Thom Zimmermann described a new technique he named 'non-penetrating trabeculectomy', leading to external limbal filtration and IOP drop in open-angle glaucomas.[1] However, there still is a significant debate on some presumed landmarks for obtaining successful surgeries, as well as on the ultimate explanation on how and why deep sclerectomy works.

As early as in the year 2001, Marchini and co-workers, by applying UBM on eyes operated with deep sclerectomy + re-absorbable hyaluronic acid implant, suggested three possible mechanisms for IOP reduction, namely: (a) external subconjunctival filtering bleb; (b) increased uveoscleral outflow; and (c) transcleral filtration.[2] The authors were also warning of the dynamic nature of the so-called 'intra-scleral lake', measuring a significant decrease in size as early as six months after surgery. Shortly thereafter, these results were confirmed by Kazakova and co-workers, whose retention of a measurable intrascleral lake was slightly higher.[3] The potential impact of the presence (and, in some cases, the size) of an intrascleral decompression chamber on the long-term success of deep sclerectomy was then investigated with controversial results.[4,5] The work of Perez-Rico and co-workers offers additional food for thoughts. Their data clearly show that (a) a scleral lake can be detected in the vast majority of eyes (in their case series, *in every eye*) operated with DS as long as five years after surgery; (b) the use of an implant is not mandatory to maintain a patent scleral lake in the long term; (c) the biometry of the scleral lake can vary among individual eyes; (d) external effective subconjunctival filtration, as measured by the presence of a low-reflectivity in the bleb tissue, is a main drive to complete post-operative success.

> Unfortunately, while correlating the biometry of the scleral lake with the IOP, the authors merged IOP data with and without topical anti-glaucoma medications

Unfortunately, while correlating the biometry of the scleral lake with the IOP, the authors merged IOP data *with and without* topical anti-glaucoma medications.

Therefore, their data, suggesting a possible inverse relationship between the size of the scleral lake and post-operative long-term IOP, meanwhile extremely interesting, are still not completely conclusive.

In conclusion, the race to fully understand the mechanisms of action of deep sclerectomy is still ongoing but, after the work by Perez-Rico and colleagues, more insights are now available.

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Health Economics

Impact of technological progress and demographic change on eyecare

Comment by Franz Grehn, Wurzburg, Germany

55519 Increase in examinations for cataracts, glaucoma, diabetic retinopathy and age-related macular degeneration: Comparative cross-sectional study between 2010 and 1997 in ophthalmological practices, Bertram B, Gante C, Hilgers RD, Ophthalmologe 2013; 0:

This paper describes frequency of diagnosis of four major ophthalmic diseases in a representative sample of ophthalmic practices in Germany in 1997 versus 2010, taking into account the demographic changes during this period. The four leading diagnoses were: cataract, glaucoma, diabetic retinopathy, and macular degeneration/vitreoretinal disease.

The comparison was made between a previous study of 19,047 patients from 106 ophthalmologists in 1997 versus a representative sample of 15,125 patients of 96 ophthalmologists in 2010. The proportion of patients of age ≥ 70 years treated in these practices increased from 25.3% in 1997 to 40.8% in 2010 (relative increase 61.3%). The proportion of glaucoma care in the 1997 sample was 16.0%, and in the 2010 sample 18.9% of all diagnoses, respectively (cataract 11.9% vs 14.9%, Diabetes 6.2% vs 9.5%, and AMD/vitreoretinal disease 4,3% vs 6.7%).

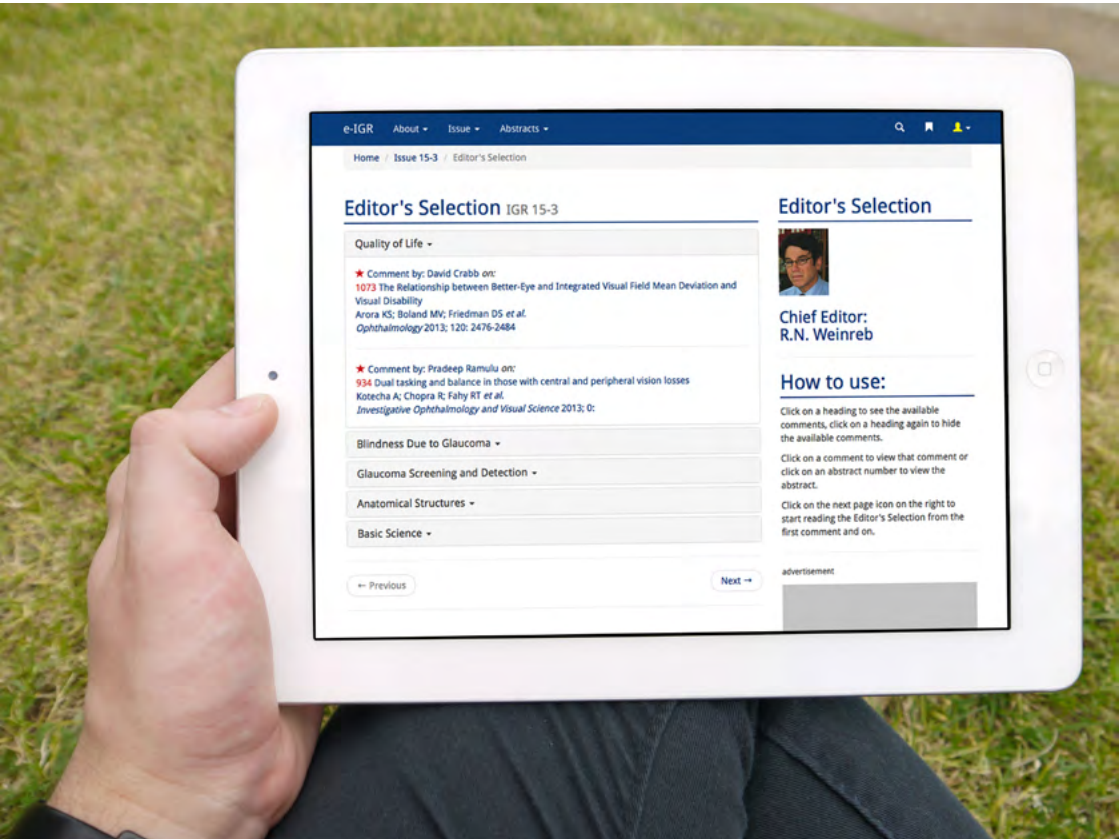
Glaucoma patients of the 2010 sample were seen 5.2 times per year in these ophthalmic practices. Imaging was performed in 7.6% and pachymetry in 3.4% of visits. For screening of glaucoma, 11.2 % of patients were seen.

> This study of German ophthalmic care in 1997 versus 2010 shows that the number of examinations for glaucoma has significantly increased

This study of German ophthalmic care in 1997 versus 2010 shows that the number of examinations for glaucoma has significantly increased. Even when adjusted for demographic change, the increase is considerable. The absolute number of glaucoma patients in Germany is estimated to be 1 Mio (total population 81 Mio). The estimated number of screening examination for glaucoma in 2010 is 4 Mio. The relative increase may have several sources beyond demographic change: (1) The awareness for glaucoma in the population has increased; (2) The decrease of refund for a comprehensive ophthalmic examination has pushed the system towards extra-paid examinations such as screening

packages, imaging, pachymetry etc.; (3) The threshold for following and treating glaucoma patients has been reduced due to several factors (medicolegal, financial, technical etc.); (4) **The use of standard imaging techniques for the diagnosis of glaucoma has increased the number of borderline diagnoses that have to be followed.**

In summary, this overview illustrates the challenge of an increasing need for glaucoma care due to demographic changes as well as an increment of glaucoma follow up due to modern technology and screening.



Miscellaneous

Anti-VEGF injections and IOP

Comment by Malik Kahook, Denver, CO, USA

56090 Intraocular pressure in eyes receiving monthly ranibizumab in 2 pivotal age-related macular degeneration clinical trials, Bakri SJ, Moshfeghi DM, Francom S, Rundle AC, Reshef DS, Lee PP, Schaeffer C, Rubio RG, Lai P, Ophthalmology 2014; 121: 1102-1108

Jalil and colleagues first reported sustained elevation in intraocular pressure (IOP) after injection of the anti-vascular endothelial growth factor (VEGF) agent bevacizumab in 2007.[1] Since this first report, there have been several publications that support or reject the connection between injections of anti-VEGF agents (pegaptanib, bevacizumab and/or ranibizumab) and sustained elevation of IOP in patients with age related macular degeneration (ARMD). The report by Bakri and colleagues leverages phase-III data from the ANCHOR and MARINA studies to complete a post-hoc analysis of IOP trends post repeated injections with ranibizumab. They concluded that more ranibizumab-treated eyes had one or more episodes of IOP elevation from baseline of six mmHg or more or eight mmHg or more, with concurrent highest IOPs of 21 mmHg or more and 25 mmHg or more versus sham or photodynamic therapy (PDT). Based on their findings, they recommend that IOP should be monitored in eyes receiving ranibizumab.

> They recommend that IOP should be monitored in eyes receiving ranibizumab

There are several limitations to this study, including a lack of uniformity for IOP-measuring methods and lack of standardization for when IOP was measured. Since this was an ARMD centric study, we are not provided with data on nerve status, visual field status or gonioscopy. There is little information on subgroup analyses of patients with pre-existing glaucoma who were enrolled into both studies and whether they had an increased risk for IOP spikes during the trial. **Overall, the novelty of this study is centered on the prospective nature of data collection and the presence of a control group (sham injections and PDT) that allows for more objective analyses** compared to previous retrospective studies that lacked a concurrent control group. The mechanisms leading to IOP elevation remain unclear and are not addressed by this study.

Reference

1. Jalil A, Fenerty C, Charles S. Intravitreal bevacizumab (Avastin) causing acute glaucoma: an unreported complication. Eye (Lond) 2007;21(12):1541.

Vision restoration for glaucoma

Comment by Tanuj Dada, New Delhi, India

56237 Vision restoration training for glaucoma: a randomized clinical trial, Sabel BA, Gudlin J, JAMA ophthalmology 2014; 132: 381-389

Sabel & Gudlin report the results of a randomized, double-blinded placebo-controlled clinical trial (completed in 2007!) aimed to determine if behavioral activation of areas of residual vision using daily one-hour (two 30-min sessions) vision restoration training for glaucoma for three months improves detection accuracy compared with placebo. Thirty-four patients with glaucoma (mean age: 61.7 years; range: 39-79 years) were initially randomized, but only 26 patients were included in the final analysis . The primary end point was change in detection accuracy in high-resolution perimetry. In the 'within group' analysis, the authors found that vision restoration training for glaucoma led to significant detection accuracy gains in high-resolution perimetry (P = 0.007) but not with white-on-white or blue-on-yellow perimetry. Furthermore in the 'between group' analysis, the pre-post differences after vision restoration training for glaucoma were greater compared with placebo in all three perimetric tests respectively. An improvement in (faster) reaction time was also noted although vision-related quality of life was unaffected.

The authors propose a new rehabilitation treatment option for partial reversal of visual field defects in glaucoma patients and report that visual field defects caused by glaucoma can be improved by repetitively activating residual vision through training the visual field borders and areas of residual vision, thereby increasing their detection sensitivity.

Although these results are novel, several issues remain unanswered. The extent of improvement was very variable with one-third of patients not showing any improvement. The sample size and power calculation for the RCT has not been detailed with only 13 patients in each arm. **The mean improvement in detection accuracy was within the mean test retest variability of the visual field.** The influence of age, sex, baseline visual field damage, visual acuity, contrast sensitivity, type of glaucoma, etcetera on test results has not been evaluated. How long does the improvement last after cessation of training and would a change in the duration of training session have an impact on the results? The authors mention visual neural plasticity as a causative instrument in vision restoration, but have not included any objective parameter to evaluate this hypothesis. Despite these limitations, this pilot study offers a new hope for glaucoma patients and encourages further research into vision restoration training.

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News flashes

- ★ **IOP should** be monitored in eyes receiving ranibizumab
- ★ **Assessment** of anterior chamber depth during slit-lamp biomicroscopy is useful in screening for angle closure
- ★ **Gonioscopy** should be performed when assessing individuals high myopia
- ★ **Statins** may have utility in the treatment of glaucoma
- ★ **The retina** responds to IOP injury by increasing the number of mitochondria
- ★ **3% of patients** demonstrated a progression of greater than -1.5 dB per year, 10.4%
- ★ A convincing demonstration of neuroprotection is a high-hanging fruit
- ★ **Goals for** glaucoma genetic research include finding more genes for early-onset familial glaucoma and adult-onset common glaucoma

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