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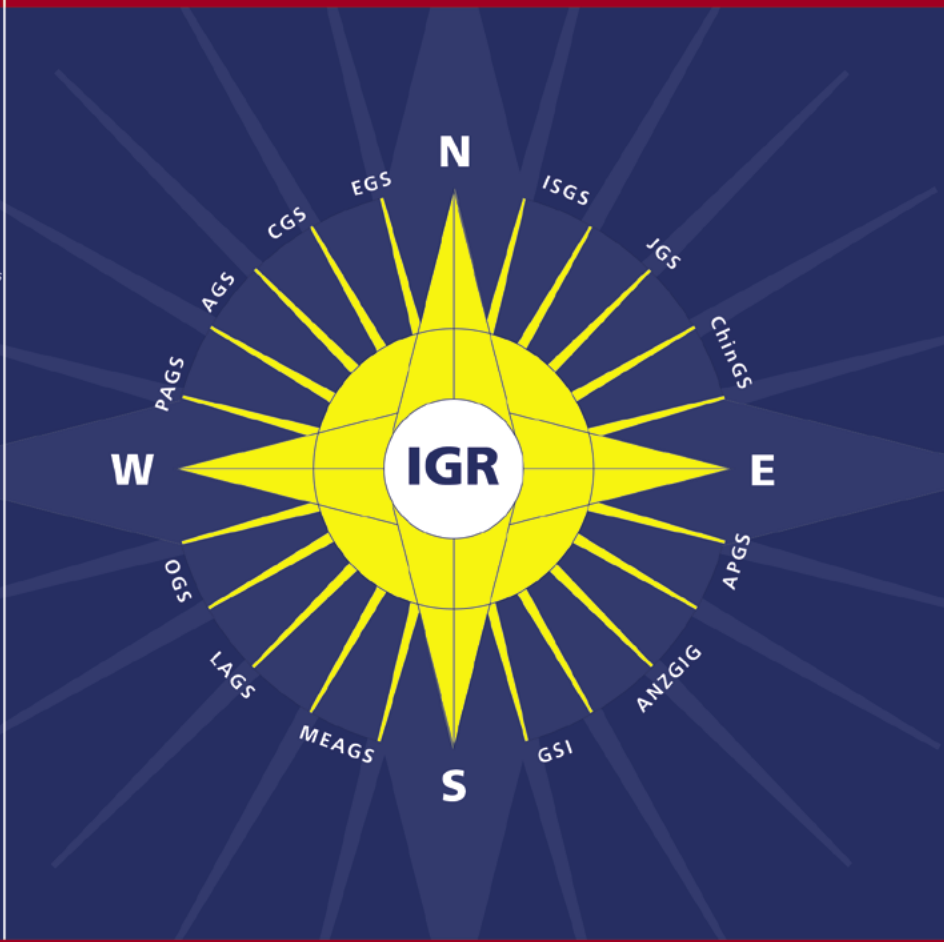

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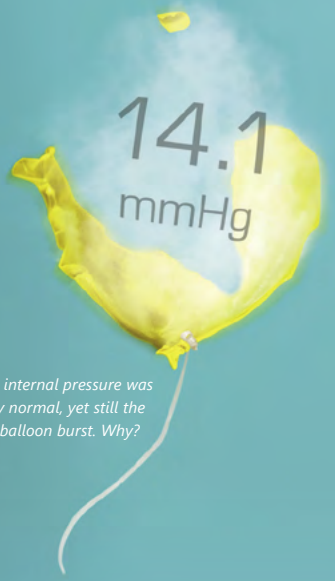

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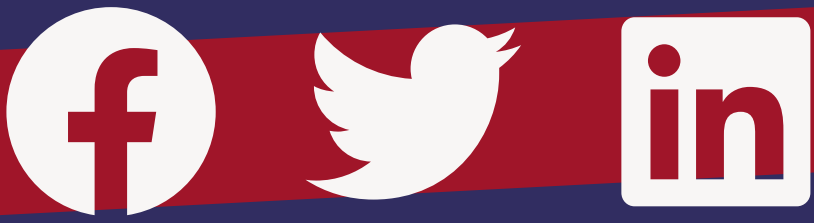

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From the WGA Executive Office

Dear IGR readers,

We hope to see you online at the upcoming 9th World Glaucoma E-Congress which will take place June 30-July 3, 2021. You can still register for our all-virtual congress up to and during the meeting. This year our regional partner is the Japanese Glaucoma Society and there will be a Japanese theme to the scientific program as well as the social activities.

The Program Planning Committee, chaired by Drs. Tina Wong and Arthur Sit, has created a terrific schedule of symposia and courses which will update you on the latest developments in our field as you learn from the leading glaucoma experts around the globe (Discover the program here). You will be able to participate in and access all of the sessions including our Presidential Symposium, 3 Plenary Symposia, 15 Parallel Symposia, 14 Courses, 2 Rapid Fire sessions, 34 regional Glaucoma Society sessions, Film Festival, Posters, and Grand Rounds sessions.

The topic of our Presidential Symposium is *Normal Tension Glaucoma*. It is the most common form of open-angle glaucoma in Japan as well as many other regions in the Asia-Pacific. The latest on risk factors and therapy will be discussed. Other symposia and courses will cover angle-closure glaucoma, artificial intelligence, medical therapy, surgical treatments including MIGS, laser and cyclodestructive procedures, new diagnostics, the basic science of glaucoma pathophysiology, and the post-COVID-19 office.

It has been challenging to get the latest update in glaucoma diagnostic technologies and treatments during the pandemic, and we are glad to offer an interactive platform using innovative technology and sessions for participating in the question/answer sessions, rapid fire sessions, and grand round sessions. You will have the opportunity to ask questions, connect with friends and colleagues who are participating in the congress, and vote on diagnostic dilemmas and treatment approaches for case presentations. We also have numerous opportunities to interact virtually with our supporting industry members who have their own symposia, company pages, and question/answer programs after select courses.

If you have not already, we welcome you to register for the WGC-2021 at www.worldglaucomacongress.org/registration. If you miss any live broadcasts, no need to worry. You will be able to enjoy all content on-demand on the virtual congress platform up to and including December 2021.

See you at the meeting!

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GET TO KNOW US!

Tin Aung

It is hard to believe that it has been almost 15 years since I first joined the WGA as an Associate Advisory Board member back in 2006. Since then, I have taken on a multitude of roles and thoroughly enjoyed every step of the way; from becoming Associate Executive Vice President from 2008 to 2012, joining the Board of Governors in 2013, to having the honor of serving as WGA president from 2016 to 2017.

I strongly believe in the educational focus of the WGA. Some of my personal highlights over the years have been helping organize and participating in several World Glaucoma Congresses, especially as I enjoy meeting and collaborating with people from all over the world. Indeed, I cannot wait for us to be able to connect in person once more at a future WGC event!

I have also been an active participant in many other WGA activities over the years, including the Consensus meetings and serving on the Editorial Board of the International Glaucoma Review. More recently, I am proud to have helped in some of our latest educational initiatives, such as the Angle Closure course under the education committee. It has been wonderful to see the expansion of WGA activities over the years, such as the World Glaucoma Day/Week, the new fellowships for African trainees, improved social media communications and increased engagement with patient support groups. With more and more member glaucoma societies being formed every year, I am confident WGA will only go from strength to strength!

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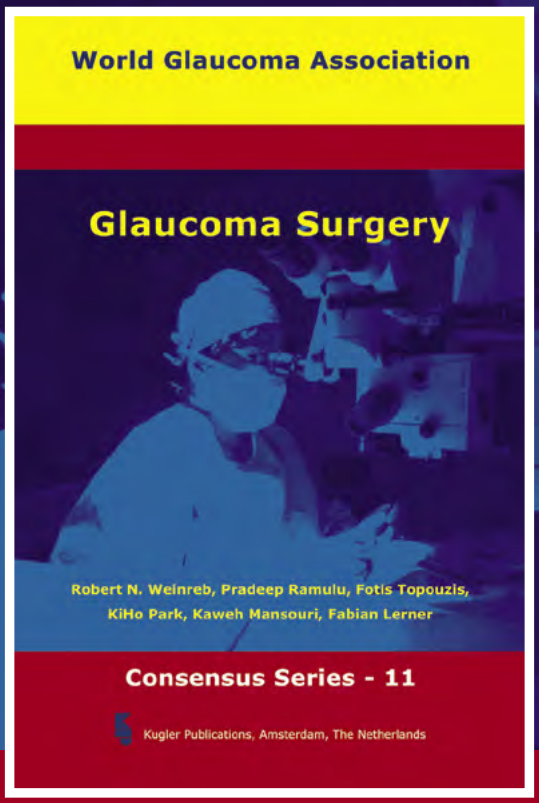

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Editor's Selection

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

Robert N. Weinreb, Chief Editor

Epidemiology

Is Glaucoma Prevalence Linked to Refractive Surgery?

Comment by Cedric Schweitzer, Bordeaux, France

91001 Association between corneal refractive surgery and the prevalence of glaucoma: Korea National Health and Nutrition Examination Survey 2010-2012; Song JS, Lee YB, Kim JA, Lee EJ, Kim H; British Journal of Ophthalmology 2020; 0:

The authors report the association between corneal refractive surgery and the prevalence of glaucoma in a Korean cross-sectional population-based study (KNHANES: Korea National Health And Nutrition Examination Survey). The case group (n = 604) was composed of participants with a previous history of myopic corneal refractive surgery and the control group (n = 3389) was composed of participants with a refractive error between -3 diopters and -12 diopters. Only the right eye of each participant was analyzed and eyes with a previous history of any other ocular surgery were excluded. Noteworthy, preoperative refractive status of the case group was not collected in the database.

After adjustment with age, sex, spherical equivalent and intraocular pressure (IOP), **the authors observed a 9.14 higher risk to develop glaucoma** after a myopic corneal refractive surgery compared to a group of myopic participants without surgery. **Increasing age, male, increasing IOP and decreasing spherical equivalent were also associated to a higher prevalence of glaucoma**.

The authors pointed out that corneal refractive surgery could induce transient IOP spikes during the suction ring step of the LASIK procedure as well as an ocular hypertension induced by a postoperative prescription of topical corticosteroids.

However, despite authors' findings in a large population sample, the association between a previous history of myopic corneal refractive surgery and a higher prevalence of glaucoma still remains uncertain.

Indeed, there are some concerns about the matching and the comparability of the case and the control group with a much higher number of female participants (69.3% vs 48.6% respectively) and the absence of preoperative refractive status in the case group. **Then, while PRK procedure does not require a suction ring and is less likely to induce transient IOP spikes, the surgical procedure was not provided.** Additionally, despite a study based on a large population sample, the analysis may lack of statistical power. Indeed, glaucoma prevalence was 3% in the case group (18 eyes) and confidence interval of the association between the prevalence of glaucoma and corneal refractive surgery was quite large (OR: 9.14 (95%CI:2.22;37.69)).

In conclusion, myopic corneal refractive surgery may lead to a higher prevalence of glaucoma. However, **this association would need to be confirmed in other prospective cohort studies before providing robust recommendations for a refractive surgery procedure in myopic patients.**

Quality of Life

Patterns of Damage Associated with Visual Disability in Glaucoma I

Comment by Deanna Taylor and David Crabb, London, UK

91802 Association of patterns of glaucomatous macular damage with contrast sensitivity and facial recognition in patients with glaucoma; Hirji SH, Hood DC, Liebmann JM, Blumberg DM; JAMA ophthalmology 2021; 139: 27-32

The importance of facial recognition, crucial to social interactions and relationships, cannot be underestimated. Indeed, long-term face recognition problems can lead to chronic anxiety, social isolation and employment difficulties.[1] Whilst it is evidenced in the literature that individuals with advanced glaucoma are likely to experience difficulties recognizing faces,[2-4] the study by Hirji and colleagues is first to investigate the association between patterns of macular damage and face recognition performance.

Hirji *et al.* recruited 72 patients with either focal or diffuse glaucomatous macular damage to perform the Freiburg Visual Acuity and Contrast Test (FrACT) and the Cambridge Face Memory Test (CFMT). The CFMT, originally designed for use in prosopagnosia, is a widely used and recognized face recognition test, used in previous eye research including our lab's work in glaucoma and age-related macular degeneration,[2,5] Hirji *et al.* found diffuse macular damage to be associated with worse contrast threshold and face recognition performance compared with eyes with focal macular damage.

> Diffuse macular damage is associated with worse contrast threshold and face recognition performance compared with eyes with focal macular damage

This has important clinical implications. Clinicians should use these findings to tailor counselling and educate patients as to what their specific pattern of visual field loss might mean in their day-to-day lives. **Moreover, as the authors suggest, where diffuse macular damage is suspected, 'early and aggressive intervention' should be considered.**

One limitation of the CFMT is its reliance on memory. In this study, participants were required to pass the Short Test of Mental Status in order to take part. However, this was designed as a dementia screening tool and it is possible that participants may have passed the test with mild cognitive impairment, perhaps affecting their performance on the CFMT. Future research should consider including face recognition tests that eliminate the recall

aspect of the task, such as the Caledonian Face Test[6] or similar.[7] Nevertheless, this work adds important evidence to an under-researched area in the field, with clear implications for both patients and clinicians.

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Patterns of Damage Associated with Visual Disability in Glaucoma II

Comment by Anders Heijl, Malmo, Sweden

91639 Assessing functional disability in glaucoma: the relative importance of central versus far peripheral visual fields; Odden JL, Mihailovic A, Boland MV, Friedman DS, West SK, Ramulu PY; Investigative Ophthalmology and Visual Science 2020; 61: 23

Maintaining quality of life is a central goal in glaucoma management, as, for example, expressed in the most recent Guidelines of the European Glaucoma Society: 'The goal of care for people with, or at risk of, glaucoma is to promote their well-being and quality of life within a sustainable health care system.' Odden and co-workers' paper is an ambitious addition to the literature on QoL and functional disabilities in glaucoma. This paper summarizes and extends several separate investigations on this subject that have previously been published by the authors during a period of several years.

The authors have studied the effects of central versus peripheral visual field loss on many functional domains including quality of life (QOL), fear of falling, instrumental activities of daily life, driving, reading speed and gait in 231 patients with glaucoma, or suspected glaucoma associated with ocular hypertension, positive family history, or presence of exfoliation syndrome.

Central threshold visual field testing was performed with the 24-2 SITA Standard test, while the peripheral field was tested with a suprathreshold test including 60 test point locations 30°-60° from fixation. Binocular fields were created and test points were dichotomized as being normal/abnormal.

Data were analyzed using multivariable regression models that were created separately for each disability outcome. Age, gender race, and comorbidities were included as covariates in all models. Disabilities were also evaluated both with either central or peripheral damage only as independent variables, and with central or peripheral damage simultaneously included in the model. Thus, **analyses assessed a very large number of relationships.**

Central damage was more strongly associated with most disabilities

The results demonstrated that most study participants had mild disease, with a median MD of only -2.31 dB in the better eye and -5.16 dB in the worse eye. Similarly, the mean percentages of abnormal test point locations were only 1.9% in the central field and 5.4% in the peripheral field.

Despite this material being composed of mostly patients with mild disease, the authors found many statistically significant relationships. Most importantly the relative importance of central and peripheral field loss differed across functional domains. **Central damage was more strongly associated with most disabilities such as fear of falling, QoL, and difficulties with independent activities of daily living**. **Peripheral field loss, but not central, was associated with gait measures: shorter steps and strides and greater variability in step length**. In this cohort, both central and peripheral damage were not significantly associated with maximum reading speed, driving cessation or self-reported driving limitations.

Perhaps importantly, the authors commented that while both peripheral and central regions were important in assessing function, neither contributed a statistically significant amount of additional information when added to original main analyses, and that r^2 values were generally low, and not substantially higher for models including both central and peripheral damage.

We commend the authors for their extensive work in this area, extending over many years. This paper is a valuable addition to the sparse literature on the influence of peripheral visual field damage on functional disabilities. Yet, as the authors state, one should be cautious about generalizing their findings to patients having severe glaucomatous damage, since most patients in the authors studies had mild disease.

It seems that some of the weak relationships and lack of statistical significance might have been due to the fact that the glaucoma/suspect glaucoma population examined was a rather healthy one. Repeating some of the authors' studies in a patient population having moderate to severe glaucomatous field loss might be more revealing.

Repeating some of the authors' studies in a patient population having moderate to severe glaucomatous field loss might be more revealing

Relationships between functional disability and glaucomatous field loss would be expected to be stronger, with higher r^2-values and findings that are clear-cut. And, perhaps the number of patients material needed might be considerably smaller than that reported in the present paper. The areas researched, and at least partially pioneered by the authors are important, and deserve further study.

Basic Science

Endoplasmic Reticulum Protein Load and Glaucoma

Comment by Katie Bollinger and Barbara Mysona, Augusta, GA, USA

90872 ATF4 leads to glaucoma by promoting protein synthesis and ER client protein load; Kasetti RB, Patel PD, Maddineni P, Patil S, Kiehlbauch C, Millar JC, Searby CC, Raghunathan V, Sheffield VC, Zode GS; Nature communications 2020; 11: 5594

Recent studies indicate that chronic ER stress, which develops upon intracellular accumulation of unfolded and misfolded proteins, plays a significant role in the pathophysiology of glaucoma. However, the molecular mechanisms that underlie ER stress-mediated trabecular meshwork (TM) dysfunction and lead to increased intraocular pressure are not well understood. Activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP) are factors known to play a role in several ER stress-associated diseases. ATF4 and CHOP induce the growth arrest and DNA damage-inducible protein (GADD34), which promotes dephosphorylation of eIF2α, leading to increased protein synthesis. Recent studies also indicate that ATF4, CHOP and GADD34 are induced in post-mortem TM tissues from POAG donor eyes.

This work uses a thorough and multifaceted approach to examine the role of ATF4 in the chronic ER stress induced ATF4-CHOP-GADD34 pathway within the TM in human and mouse glaucoma. The authors begin by demonstrating that ATF4, CHOP, and GADD34 are elevated in primary TM cells and tissue from glaucomatous donor eyes. They also show that ATF4 and CHOP are elevated in a mouse model of dexamethasone-induced ocular hypertension. Next, the authors use adenoviral and lentiviral-mediated expression of ATF4 in mouse (C57BL6J) eyes, in GTM3 cell lines, and in primary human TM cells to dissect the molecular mechanisms by which ATF4 leads to glaucoma. **They find that increased expression of ATF4 in murine TM leads to significant and sustained IOP elevation that results in glaucomatous neurodegeneration.** They use CHOP-/- mice to show that CHOP is required for ATF4-induced IOP elevation. To further assess how ATF4 leads to IOP elevation and TM damage, the authors examine ER stress markers, protein synthesis levels, and ER client protein load in Ad.ATF4-transduced GTM3 cells, primary human TM cells and mouse TM tissues. Results indicated that ATF4 increases protein synthesis and ER client protein load in trabecular meshwork. Further experiments also show that ATF4 expression leads to ER-stress-induced cell death within the TM. A particularly exciting aspect of this work shows that suppression of the ATF4-CHOP pathway using either pharmacological or genetic inhibition reduces elevated IOP in Dexamethasone-treated or mutant myocilin ocular hypertensive mice.

The authors have done an excellent job of using a variety of techniques, models and approaches to demonstrate the important role of the ATF4-CHOP-GADD34 pathway in the TM, particularly the role of ATF4 expression in promoting protein synthesis and ER client protein load. One intriguing observation from this work is that ATF4-CHOP interactions may be cell-type specific; TM tissue may require ATF4-CHOP interactions to regulate ER protein client load, whereas other tissues may not.

ATF4-CHOP-GADD34 signaling pathway plays a key pathological role in TM dysfunction and IOP elevation

An interesting question is whether ATF4-CHOP mechanisms are important at the optic nerve head, another region critically affected in glaucoma. In summary these studies indicate that the ATF4-CHOP-GADD34 signaling pathway plays a key pathological role in TM dysfunction and IOP elevation. Inhibition of this pathway offers a potential therapeutic target for slowing glaucomatous progression.

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Energy Metabolism and Neuroprotection

Comment by Adriana DiPolo, Montreal, Quebec, Canada

90934 Disturbed glucose and pyruvate metabolism in glaucoma with neuroprotection by pyruvate or rapamycin; Harder JM, Guymer C, Wood JPM, Daskalaki E, Chidlow G, Zhang C, Balasubramanian R, Cardozo BH, Foxworth NE, Deering KE, Ouellette TB, Montgomery C, Wheelock CE, Casson RJ, Williams PA, John SWM; Proceedings of the National Academy of Sciences of the United States of America 2020; 117: 33619-33627

Harder and colleagues report significant changes in pathways that regulate the metabolism of glucose and pyruvate in glaucomatous mice (DBA/2J strain) using multiple techniques including RNA sequencing and metabolomics. Their findings are consistent with a decline in retinal pyruvate levels and altered glucose metabolism prior to detectable optic nerve degeneration. Oral supplementation of pyruvate or rapamycin, an mTOR inhibitor, provided strong neuroprotection against glaucomatous degeneration using a number of *in vitro* and *in vivo* paradigms. Functional outcome measures included enhanced retinal function in DBA/2J mice, measured by pattern electroretinogram recordings, and anterograde axonal transport visualized by cholera toxin B subunit accumulation in brain targets. **Collectively, these findings suggest that dysfunctional metabolism underlies retinal ganglion cell vulnerability and have promising clinical implications for the use of pyruvate or rapamycin oral supplementation as neuroprotective therapy for glaucoma**. This study is important and adds new knowledge to our current understanding of metabolic deficits in retinal ganglion cells as an important contributing factor to vision loss in glaucoma.

Dysfunctional metabolism underlies retinal ganglion cell vulnerability

An issue that needs careful consideration, however, is the clinical use of rapamycin as neuroprotectant. Other groups have demonstrated that rapamycin-mediated inhibition of mTOR is detrimental for retinal ganglion cell survival and regeneration.[1-3] **The inconsistency in outcomes with rapamycin treatment, often paradoxical, has been well documented not only in the context of neurobiology but also in cancer and metabolic research.** This disparity has been attributed to non-specific effects depending on the time-course of rapamycin administration.[4,5] Specifically, chronic rapamycin treatment can lead to off target effects and activation of compensatory pathways unrelated to mTOR inhibition.[6-8] For example, prolonged rapamycin treatment in mice increases longevity by

reducing mTOR, but leads to glucose intolerance and insulin resistance through disruption of other signaling pathways.[8] **Therefore, caution should be exercised regarding the use of chronic rapamycin as neuroprotective treatment for glaucoma.**

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Protecting RGCs from Oxidative Stress

Comment by Toru Nakazawa, Sendai, Japan

91864 Effect of ubiquinol on glaucomatous neurodegeneration and oxidative stress: studies for retinal ganglion cell survival and/or visual function; Edwards G, Lee Y, Kim M, Bhanvadia S, Kim KY, Ju WK; Antioxidants (Basel, Switzerland) 2020; 9:

Lowering IOP does not completely halt progression of glaucoma. Thus, it is important to identify neuroprotective therapies aimed at reducing RGC death. Although the pathogenesis underlying glaucomatous RGC damage remains unclear, mitochondrial dysfunction induced by IOP elevation and oxidative stress is considered as one of major causal factors in glaucomatous neurodegeneration.

Coenzyme Q10 (CoQ10) is an essential electron carrier in mitochondrial respiratory chain complexes and involved in antioxidant mechanisms. It has been reported that ubiquinol, the reduced and active form of CoQ10, is a neuroprotectant in several neuro-degenerative diseases including Alzheimer's disease, traumatic brain injury, and multiple system atrophy.

In the present study, authors investigated whether ubiquinol supplementation promoted RGC survival as well as preserved visual function against oxidative stress using a chronic mouse model of glaucoma, DBA/2J mice. **As a result, a diet supplementation with ubiquinol significantly enhanced RGC survival.** Authors also demonstrated that ubiquinol significantly blocked BAX activation and increased expression of transcription factor A (TFAM) and activation of oxidative phosphorylation (OXPHOS) complex. TFAM is associated with endogenous repair mechanisms of damaged retinal neurons. OXPHOS complex II is considered to promote cell survival.

Ubiquinol protects RGCs

Therefore, these findings demonstrate that ubiquinol protects RGCs by modulating the BAX-mediated apoptotic pathway and by increasing TFAM expression and OXPHOS complex II activity in glaucomatous neurodegeneration. Additionally, ubiquinol ameliorated RGC death and visual dysfunction in mice against oxidative stress.

Taken together, authors provide us encouraging results indicating that ubiquinol has a therapeutic potential for treating oxidative stress-associated glaucomatous neurodegeneration.

Stem Cells and RGC Replacement

Comment by Keith Martin, Melbourne, Australia

91650 Role of the internal limiting membrane in structural engraftment and topographic spacing of transplanted human stem cell-derived retinal ganglion cells; Zhang KY, Tuffy C, Mertz JL, Quillen S, Wechsler L, Quigley HA, Zack DJ, Johnson TV; Stem cell reports 2021; 16: 149-167

The ability to restore vision in degenerative optic nerve diseases such as glaucoma by transplantation of retinal ganglion cells (RGC) would be transformative, but many challenges remain. A key challenge is to achieve effective integration of transplanted cells into the host retina, with the inner limiting membrane the first barrier that must be overcome.

In an elegant series of experiments published in *Stem Cell Reports,* Zhang *et al.* cultured human embryonic stem cell (hES) derived RGC on mouse retinal explants and explored their survival and integration. The researchers showed that the inner limiting membrane is a significant barrier to integration of cultured cells.

The inner limiting membrane is a significant barrier to integration of cultured cells

Extracellular matrix digestion using a variety of proteolytic enzymes achieved ILM disruption, but some of the protocols caused more widespread retinal damage. **However, the authors nicely demonstrated that using a low dose of pronase E preserved glial reactivity and retinal architecture whilst facilitating neurite outgrowth into the host retina.**

They were also careful to provide evidence that fluorescently labelled cells extending neurites in the host retina were actually transplanted cells, and not host cells that had taken up labels released by transplanted cells – a major issue in some previous studies. They did this by transplanting red labelled RGC onto retinas from animals where all cells express green fluorescent protein. Thus, a cell which fluoresces red but not green is proven to be a transplanted cell.

The authors appropriately discuss the pros and cons of using explant models compared to *in-vivo* experiments, and they caution that surgical peeling of the ILM may be an alternative solution in human eyes prior to cell transplantation. However, they should be congratulated on a study which demonstrates a thoughtful and practical approach to a problem of considerable translational relevance, advancing our understanding in the process.

Models of Glaucoma

Optimizing Bleb Survival in a Rabbit Model

Comment by Benjamin Xu, Los Angeles, CA, USA

91713 Injected versus sponge-applied Mitomycin C (MMC) during modified trabeculectomy in New Zealand white rabbit model; Swogger J, Conner IP, Rosano M, Kemmerer M, Happ-Smith C, Wells A, Schuman JS, Yates CC; Translational vision science & technology 2020; 9: 23

Mitomycin C is routinely administered during trabeculectomy surgery to reduce conjunctival scarring and improve bleb survival. Mitomycin C is a potent alkylating agent that permanently changes exposed ocular tissues. The two most common MMC application methods are placing MMC-soaked cellulose sponges in the sub-Tenon space or injecting a lower concentration of MMC into the intra-Tenon space. While both methods are widely accepted and practiced, differences between the two approaches have only recently been studied.

This study by Swogger and colleagues compares clinical and histological outcomes after glaucoma filtering surgery in rabbits receiving either preoperative intra-Tenon injection (0.2 mL of 0.1 mg/mL) of MMC or intraoperative MMC application by sponge (0.4 mg/mL for four minutes). Ten rabbits total were randomized to the two MMC application methods during modified trabeculectomy surgery. Animals were followed for four weeks after surgery, at which point histopathology was performed. **The authors observed a small but significant benefit in intraocular pressure (IOP) reduction in the injection compared to the sponge group.** They also observed less goblet cell loss (beneficial in eyes with pre-existing ocular surface disease), less loss of vascularity (theoretically less prone to late surgical complications, including endophthalmitis), and lower collagen content (less scarring) in eyes receiving injection compared to sponge.

This study provides unique insight into the histological sequelae of both application methods, which favor injection over sponge. These findings are important as glaucoma surgeons may want to consider other effects of their surgeries outside of IOP lowering. However, the study is limited by its short follow-up duration and small sample size. Longer and better powered studies in human eyes did not find a significant difference in clinical outcomes between injection and sponge groups (Do *et al.*, *AJO*, 2020). Therefore, longer-term animal studies would be beneficial to elucidate chronic outcome differences between injection and sponge.

Clinical Examination Methods

Seasonal IOP Fluctuations I

Comment by Kaweh Mansouri, Lausanne, Switzerland

91626 Seasonal fluctuation in intraocular pressure and retinal nerve fiber layer thinning in primary open-angle glaucoma; Terauchi R, Ogawa S, Noro T, Ito K, Kato T, Tatemichi M, Nakano T; Ophthalmology. Glaucoma 2020; 0:

Terauchi *et al.* are to be congratulated for conducting a large-scale study to evaluate seasonal changes of IOP in healthy subjects and glaucoma patients and their effects on glaucomatous RNFL-thinning. Based on the monthly air temperature in Tokyo, winter period was defined as December through February and summer as July through September. Goldmann applanation tonometry was used for all measurements in the glaucoma group and RNFL thickness was measured using Cirrus OCT.

Including a total of 12 686 healthy eyes and 179 eyes of 179 POAG patients, the authors found a significantly higher IOP in winter than in summer in both subject groups. **In glaucoma patients, winter IOP was significantly higher than summer IOP (13.0±2.3 mmHg vs. 11.9 ± 2.0 mmHg, in the progression vs the non-progression groups; P < 0.001).** The progression group showed a higher summer IOP, lower seasonal fluctuation, and a lower seasonal fluctuation rate than the non-progression group. In healthy eyes too, winter IOP was significantly higher than summer IOP (13.2 ± 3.0 mmHg vs. 12.5 ± 2.9 mmHg; P < 0.001).

> The progression group showed a higher summer IOP, lower seasonal fluctuation, and a lower seasonal fluctuation rate than the non-progression group

Interestingly, the authors found that in eyes with POAG, seasonal IOP fluctuation had a significant impact on the progression of RNFL thinning. **They posited that a temporary IOP decline in summer, rather than a constant IOP throughout the year, may prevent glaucoma progression**.

Several factors may preclude generalizability of this studies results: (1) Most glaucoma patients were classified as NTG (81.6%), reflecting the particular epidemiological situation in Japan; (2) Patients presented a slow rate of visual field and RNFL progression. This may be due to the high proportion of NTG patients and also to the fact that patients with rapid glaucoma progression requiring laser or surgery were excluded; (3) Tokyo has a humid

subtropical climate with intense seasonal fluctuation in air temperature. It would be interesting to know whether glaucoma patients in regions with more stable seasonal temperatures (*e.g.*, San Diego, Beirut, Lisbon) present similar IOP fluctuations; (4) Although only office-hour IOP readings were available, a recent study by our group using an intraocular IOP sensor found similar seasonal 24-h IOP effects and confirmed their findings.[1]

At present, the mechanism underlying seasonal IOP fluctuation remain unknown.

It would be interesting to know whether glaucoma patients in regions with more stable seasonal temperatures (*e.g.*, San Diego, Beirut, Lisbon) present similar IOP fluctuations

In addition to external climate-related factors such as temperature and sun light, intrinsic biological factors may also be involved. For instance, higher endogenous cortisol may be one of the factors to explain the higher winter IOP. **It is likely that a central mechanism and multiple factors including individual acclimatization may be involved that also explain why patients in warmer geographical locations do not seem to have lower IOPs than those in higher ones.**

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Seasonal IOP Fluctuations II

Comment by Tony Realini, Morgantown, WV, USA

91375 Seasonal fluctuation in intraocular pressure and its associated factors in primary open-angle glaucoma; Terauchi R, Ogawa S, Sotozono A, Noro T, Tatemichi M, Nakano T; Eye 2021; 0:

Terauchi and colleagues have conducted a prospective study in which 204 eyes of 204 subjects with medically treated open-angle glaucoma underwent IOP measurement in both the summer and the winter to assess possible seasonal variation in IOP. Mean IOP was higher in the winter than in the summer by about 1 mmHg ($p < 0.001$). Factors associated with seasonal IOP variability included glaucoma type (POAG more so than NTG), family history of glaucoma, and the use of topical beta-blockers.

The significance of this finding is unclear, and as with all interesting research, this study raises more questions than it answers. Is true IOP higher in winter? Why might this be? How might this affect our assessment and management of patients throughout the year? Further study is warranted to more fully explore this finding, as it may shed light on the factors that regulate IOP variability, which in turn may be a risk factor for glaucoma progression.

Risk Factors

Sleep Apnea and Risk of Glaucoma

Comment by Tony Realini, Morgantown, WV, USA

91094 Obstructive sleep apnea as a risk factor for primary open angle glaucoma and ocular hypertension in a monocentric pilot study; Bahr K, Bopp M, Kewader W, Dootz H, Döge J, Huppertz T, Simon P, Prokosch-Willing V, Matthias C, Gouveris H; Respiratory research 2020; 21: 258

Bahr and colleagues have prospectively evaluated the relationship between various glaucoma phenotypes (primary open-angle, normal tension, ocular hypertension and healthy controls) and obstructive sleep apnea (OSA). Over 100 subjects underwent home sleep apnea testing. Among the full cohort, no significant correlation was seen between glaucoma parameters (such as IOP or visual field mean deviation) and apnea parameters (such as the apnea hypoxia index). Interestingly, mean values of all apnea parameters differed significantly between patients with POAG and NTG, with more severe apnea indicators in POAG than in NTG. For instance, the AHI (which is the number of apneic/hypoxic episodes per hour) was much higher in POAG than NTG patients. Similar results were obtained in comparing OHT patients to NTG patients. Their observation that AHI was higher in eyes with high IOP but that AHI did not correlate with IOP suggests a possible different pathophysiology of glaucoma in high- and low-IOP eyes. Perhaps, the authors speculate, **OSA (particularly in its severe form) may raise IOP and may thus play a meaningful role in the pathophysiology of high-IOP glaucoma but not low-IOP glaucoma.** They further speculate that systemic inflammation – which has been reported in both OSA and high-IOP glaucoma – may be part of the link between these two conditions. Further study is needed to better clarify the relationship between glaucoma and OSA.

OSA (particularly in its severe form) may raise IOP and may thus play a meaningful role in the pathophysiology of high-IOP glaucoma but not low-IOP glaucoma

African Genetic Ancestry as a Risk Factor for Glaucoma

Comment by Chiea Chuen Khor, Singapore

91769 Time lag between functional change and loss of retinal nerve fiber layer in glaucoma; Gardiner SK, Mansberger SL, Fortune B; Investigative Ophthalmology and Visual Science 2020; 61: 5

The authors assessed the contribution of African ancestry and potential risk of primary open-angle glaucoma (POAG) using a two-stage study design. This study comprised discovery (1783 participants with POAG and 2047 unaffected control participants) and replication stages (755 participants with POAG and 1380 unaffected control participants), both of which recruited participants who self-reported African American ancestry from Pennsylvania, USA. Consistently in both stages, the authors reported that participants with **POAG had a significantly higher component of African ancestry (as determined using genetically derived ancestry scores from genome-wide genotyping of representative genetic markers) compared to participants without POAG** (Odds Ratio of between 1.14 to 1.27 for every standard deviation increase in ancestry scores).

The authors also performed secondary analysis by constructing a polygenic risk score based on 23 genetic variants previously reported to be associated with POAG risk in (mostly) European ancestry studies. They assessed the utility and performance of this polygenic risk score in their study on African American ancestry participants and observed that each point increase in polygenic risk score was associated with an Odds Ratio of 1.08 increased risk of POAG in African American ancestry participants.

> Although there are shared genetic loci between African ancestry participants and European ancestry participants,[3] significant differences in terms of genetic architecture could exist

I found this large, well-powered and well-controlled study to be very timely, as the genetic architecture of POAG in persons of African ancestry remain understudied, despite the population-wide disease prevalence being significantly higher in African ancestry participants compared to European- or Asian ancestry participants.[1,2] Emerging studies in this area have suggested that although there are shared genetic loci between African ancestry participants and European ancestry participants,[3] significant differences in terms of genetic architecture could exist.[4-6] Most notably, the Odds Ratio per-unit increase in terms of polygenic risk score was modest (OR = 1.08) compared to well known risk factors of

POAG such as age (OR between 1.70 to 2.18 for every ten years increase in age) and sex (OR between 1.35 to 2.61 for male sex). This could be due to the risk score being based on European ancestry studies.

In conclusion, there is an increasing need to evaluate the genetic architecture of glaucoma and other blinding disorders in understudied and underserved populations, such as in participants of African ancestry. Such studies often yield unexpected and extremely helpful insights that illuminate disease biology and open up new approaches to therapy.[7]

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Predicting the Genetic Risk of IOP Spikes by a Genome-Wide Score

Comment by Anthony Khawaja and Stuart Kelsey, London, UK

91808 A polygenic risk score predicts intraocular pressure readings outside office hours and early morning spikes as measured by home tonometry; Qassim A, Mullany S, Awadalla MS, Hassall MM, Nguyen T, Marshall H, Kolovos A, Schulz AM, Han X, Gharahkhani P, Galanopoulos A, Agar A, Healey PR, Hewitt AW, Landers J, Casson RJ, Graham SL, MacGregor S, Souzeau E, Siggs OM, Craig JE; Ophthalmology. Glaucoma 2020; 0:

Intraocular pressure (IOP) monitoring plays a critical role in the management of glaucoma, but traditionally relies on isolated measurements obtained during office hours. These measurements are a poor representation of dynamic IOP fluctuations occurring over a 24-hour period[1] and this unrecognized variability may contribute to progressive glaucomatous neurodegeneration.[2] Recent intraocular sensor device studies have demonstrated substantial long-term IOP variability in addition to short-term fluctuations.[3]

In this cross-sectional study, Qassim *et al.* used mixed-effects linear regression modeling to explore the association between a validated, weighted IOP polygenic risk score (PRS),[4] derived from 146 statistically independent IOP-associated single nucleotide

polymorphisms, and a variety of ambulatory diurnal IOP measurements, using the Icare HOME (Icare Oy, Vanda, Finland) rebound tonometer, to determine whether genetic markers of high IOP provide useful predictive information about out-of-office IOP measurements.

Eyes from participants in the highest IOP PRS quintile had significantly higher maximum early morning IOP (+4.3 mmHg) and mean out-of-office IOP (+2.7 mmHg) compared to those in the lowest quintile and after adjustment for central corneal thickness (CCT) and age. Additionally, **the IOP PRS was able to identify individuals with early morning IOP spikes not otherwise detected during in-office hours.**

There have been huge recent advances in our understanding of the genetic causes of IOP variation and glaucoma risk. Qassim *et al.* are to be commended for examining the potential clinical utility of these genetic findings. Genome-wide association studies are frequently criticized for their lack of translational impact and more studies like this are needed.

Genetic risk stratification may prove to be a useful tool in the identification of susceptibility to out-of-office IOP elevation and could guide additional interventions and aid IOP control in high-risk patients. However, the findings from this study require validation in non-European populations and replication in additional cohorts. Additionally, prospective studies will be needed to determine whether knowledge of an individual's PRS meaningfully impacts their disease trajectory using hard endpoints. It has previously been demonstrated that knowledge of a key IOP-influencing genetic variant in *TMCO1* can improve prediction of which patients with ocular hypertension convert to glaucoma.[5] This current study adds to the evidence supporting a role for more personalized glaucoma care being enabled by genomic prediction.

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Predicting the Genetic Risk of IOP Spikes by a Genome-Wide Score

Comment by Janey Wiggs, Boston, MA, USA

91808 A polygenic risk score predicts intraocular pressure readings outside office hours and early morning spikes as measured by home tonometry; Qassim A, Mullany S, Awadalla MS, Hassall MM, Nguyen T, Marshall H, Kolovos A, Schulz AM, Han X, Gharahkhani P, Galanopoulos A, Agar A, Healey PR, Hewitt AW, Landers J, Casson RJ, Graham SL, MacGregor S, Souzeau E, Siggs OM, Craig JE; Ophthalmology. Glaucoma 2020; 0:

Polygenic risk scores (PRS) are a recently developed genomic tool that determines personal disease risk by aggregating individual genetic effects to create an overall score based on the total number of risk alleles. PRSs have been used to identify individuals at high risk for inherited common diseases including coronary artery disease, obesity, atrial fibrillation, type II diabetes, as well as primary open-angle glaucoma (POAG) and glaucoma-related traits including IOP. Interestingly, POAG and IOP PRSs are associated with important disease features such as age of diagnosis, need for surgical intervention and penetrance of the early-onset glaucoma gene *MYOC*.[1,2] In this study, Qassim *et al.* used a validated PRS comprised of genetic risk factors derived from an IOP genome-wide association study (GWAS) to investigate the relationship between PRS quintiles and IOP levels measured using Icare HOME tonometry. Two hundred thirty-nine individuals had IOP measurements four times daily for five days and reliable measurements were obtained in 176 of these people. People in the highest PRS quintile had a mean increase in IOP (2.7 mmHg, 95%CI 0.61-4.7, P = 0.013) outside of office hours compared with those in the lowest PRS quintile. In particular, people with the highest PRS score had increased early morning IOP (4.3 mmHg 95% CI 1.4-7.3; P = 0.005) and people in the highest PRS quintile were 5.4 times more likely to shown early morning IOP spikes compared to the lowest quintile (odds ratio 95% CI, 1.3-23.6; P = 0.023). These results suggest that **people with higher genetic risk as defined by an IOP PRS are more likely to have higher IOP pressure measurements outside of clinic hours** and especially to have higher IOP in the early morning including IOP spikes. This information could inform therapeutic decisions and may be particularly relevant in people who show evidence of progression despite stable IOP measured in the clinic. There are limitations to the current study including a relatively small number of people studied, however further study and confirmation of these intriguing results is warranted.

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Coffee Consumption and POAG

Comment by Shan Lin, San Francisco, CA, USA

90298 Effects of consumption of coffee, tea, or soft drinks on open-angle glaucoma: Korea National Health and Nutrition Examination Survey 2010 to 2011; Bae JH, Kim JM, Lee JM, Song JE, Lee MY, Chung PW, Park KH; PLoS ONE 2020; 15: e0236152

Bae *et al.* evaluated the effects of coffee, tea, and soft drinks on open-angle glaucoma (OAG) prevalence using the Korea National Health and Nutrition Examination Survey (KNHANES) from 2010-2011. The KNHANES is a population-based survey to represent the health-related status of South Koreans. Exclusion criteria for this analysis included age less than 19 years, pseudo- or aphakia, and retinal and neurological disease which may affect visual field test results. Participants were asked about beverage consumption – specifically coffee, tea, and soft drinks – during the previous 12 months. OAG was defined according to the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) criteria. Visual-field testing was performed using frequency doubling technology (FDT). Beverage consumption over the past 12 months was assessed by questionnaire. There were 6,681 subjects who met the inclusion/exclusion criteria. The authors found that coffee consumption was significantly associated with OAG with an odds ratio of 2.06 (95% CI, 1.11-3.82). There was no association of tea or soft drink consumption with OAG. After stratification by gender, the correlation of OAG with coffee was significant in men (OR, 3.32; 95% CI, 1.53-7.20) but not in women (OR, 1.48; 95% CI, 0.61-3.54). The authors did not find a significant association of any beverage consumption with intraocular pressure.

The unique findings of the study relate to the association of coffee consumption with glaucoma in men but not in women. However, the reason for the different gender results is not clear. Additionally, as acknowledged by the authors, there are limitations to population studies including the inability to discern the detailed caffeine content ingested. Of course, such association studies do not prove causality so further studies would be helpful to discern the potential mechanisms by which coffee drinking can be linked to glaucoma development. In the final analysis, this study may be helpful to guide the Korean public in understanding yet another risk factor (coffee consumption) to perhaps avoid for those at risk for glaucoma, in particular, in men.

Clinical Forms of Glaucoma

Perfusion and Microvascular Changes in NTG I

Comment by Min Hee Suh, Busan, South Korea

90999 Global assessment of arteriolar, venular and capillary changes in normal tension glaucoma; Lin TPH, Wang YM, Ho K, Wong CYK, Chan PP, Wong MOM, Chan NCY, Tang F, Lam A, Leung DYL, Wong TY, Cheng CY, Cheung CY, Tham CC; Scientific reports 2020; 10: 19222

It has long been a debate whether vascular mechanism plays a role in the pathogenesis of glaucoma. As OCT angiography (OCTA) has facilitated the in-vivo assessment of the ocular perfusion, the interest in the compromise of the retinal vasculature in glaucoma has been boosted. A recent study by Lin TPH *et al.* adds to the literature that generalized microvascular attenuations were observed in normal-tension glaucoma (NTG) patients by using both fundus photography and OCTA. Moreover, OCTA-derived retinal capillary metrics attenuations were more strongly associated with NTG than fundus photography.

> Degeneration of the retinal capillary vasculature is a potential surrogate marker of RGC axonal loss in glaucoma

These findings support the notion that **compromised retinal perfusion may play a role in the pathogenic process of NTG**. **Also, this study highlights the clinical utility of OCTA in assessing retinal vasculature.**

Meanwhile, it is still unclear whether vascular compromise is the result or cause of the glaucomatous damage. Theoretically, optic nerve head degeneration can be derived from reduced ocular perfusion.[1] On the other hand, there is an increasing number of studies utilizing OCTA that support the hypothesis that reduced retinal perfusion is rather a consequence of retinal ganglion cell (RGC) degeneration.[2,3] Given that an area of retinal capillary attenuation coincides with that of RNFL defect, microcirculatory insufficiency is rather a consequence of metabolic demand driven by the loss of RGC axon. If vascular compromise is a primary change, it should have followed the retinal arterial territory.[2] Also, OCTA-derived macula vessel density percent loss was significantly less than that for ganglion cell complex (GCC) thickness in early glaucoma eyes.[3]

Either way, degeneration of the retinal capillary vasculature is a potential surrogate marker of RGC axonal loss in glaucoma.

Further work is needed to elucidate the pathogenic role of the optic disc vascular perfusion on the pathogenesis of glaucomatous optic neuropathy.

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Perfusion and Microvascular Changes in NTG II

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

91824 Nocturnal blood pressure dip and parapapillary choroidal microvasculature dropout in normal-tension glaucoma; Shin JW, Jo YH, Song MK, Won HJ, Kook MS; Scientific reports 2021; 11: 206

The choroidal microvascular dropout (CMvD) is a newly described phenomenon using optical coherence tomography angiography (OCTA). The CMvD is preferentially or exclusively found in the area of beta-zone parapapillary atrophy (PPA) either with (conventional beta-zone) or without Bruch's membrane (gamma-zone). The perfusion is impaired in the area of CMvD as assessed by indocyanine green angiography (ICG), which indicates that CMvD is a true perfusion defect rather than an imaging artifact. Much is unveiled regarding this newly described phenomenon. Particularly the pathogenesis of CMvD remains to be elucidated. **Shin *et al*., described that NTG eyes with CMvD had nighttime diastolic BP (DBP) dip of greater magnitude and longer duration than eyes without CMvD**. This finding is in line with previous observations that the presence of CMvD is associated with diastolic BP or mean arterial pressure. Shin *et al*'s study has a strength in that they used 24-h ambulatory BP monitoring data.

The development of CMvD is probably associated with many factors. One thing to be considered is that CMvD is mostly found in the area of PPA and its inner border is adjacent to the disc margin. This preferential location indicates that localized factors in the parapapillary region may also play an important role as well as systemic factors. In addition, it has been recently demonstrated that CMvD is also found in patients with compressive optic neuropathy (CON). This finding indicates that CMvD may occur as a secondary phenomenon to retinal nerve fiber layer loss. The possibility of secondar development of

MvD does not necessarily understate the importance of CMvD. The presence of CMvD in patients with CON indicates that prefusion to the prelaminar and laminar tissue is directly connected or related to the juxtapapillary perfusion. Under this condition, the decrease of metabolic demand in the prelaminar tissue may trigger or induce the development of CMvD. Taking this into account, the primary development of CMvD by a certain mechanism (vessel wall damage due to mechanical stress, or occlusion of capillaries due to vascular stasis or whatever) may promote the damage of axons passing the nearby prelaminar and laminar tissue.

Shin *et al.* nicely demonstrated that the development of CMvD may be associated with systemic vascular factors but there is still a long way to go before the pathogenesis of CMvD is fully understood. Given its potential importance in the pathogenesis of glaucomatous optic nerve damage, understanding how CMvD develops may contribute to improving the management of glaucoma patients which is solely dependent on the IOP lowering.

Corneal Biomechanics in Pseudoexfoliation and Open-Angle Glaucoma

Comment by Cynthia Roberts, Columbus, OH, USA

91065 A comparison of the corneal biomechanics in pseudoexfoliation glaucoma, primary open-angle glaucoma and healthy controls using Corvis ST; Pradhan ZS, Deshmukh S, Dixit S, Sreenivasaiah S, Shroff S, Devi S, Webers CAB, Rao HL; PLoS ONE 2020; 15: e0241296

Although it is important to study potential biomechanical differences between pseudoexfoliation glaucoma (PXG), primary open-angle glaucoma (POAG), and healthy controls, this study fails to determine whether these differences exist or do not exist, due to an incomplete study design and lack of reporting of essential information to be able to draw meaningful conclusions.

It is well known that intraocular pressure (IOP) is the strongest predictor of deformation amplitude (DA), with multiple studies cited by the authors, and yet this was the parameter chosen for a sample size calculation. Therefore, the reported sample size would be appropriate to detect a difference in IOP between groups, but not stiffness. The dynamic response parameters strongly associated with stiffness are those describing the shape of the deformation, including deformation amplitude ratio (DARatio) and Integrated Inverse Radius (IR), neither of which were reported in this study. Stiffness Parameter at first applanation (SP-A1) has recently been shown to predict progression in glaucoma suspects,[1] but this parameter was also not included in the current study. Radius of concave curvature

and peak distance can be considered shape parameters and were reported by the authors. One of these would have been more appropriate for a sample size calculation to detect a difference in stiffness. It is likely that a much greater sample size would have resulted.

The calculated sample size of 40 eyes assumed independence of the parameter on which the calculation is based. Since eyes are not independent, and the authors even state they may be correlated, at a minimum this should be 40 subjects per group for a total of 120 subjects. Yet, there were only 82 subjects enrolled, which means the study is underpowered.

The authors recognize that IOP is a confounding factor when evaluating biomechanical response, and they appropriately incorporate IOP as a co-variate in their analysis. However, they did not identify whether Goldmann Applanation Tonometry (GAT) or Corvis IOP was used as the co-variate. Also, the Corvis ST reports two IOP values, one is uncorrected, and one is biomechanically corrected (bIOP). Again, which Corvis IOP value used is not specified so one must assume the uncorrected IOP value was used. The concern is evidenced in Table 2, which shows the mean Corvs IOP is greater by about 1 mmHg in Controls, but GAT is greater by about 1 mmHg in POAG and GAT is also greater by more than 1 mmHg in PXG. The shift in the sign of the GAT-Corvis IOP error function between healthy controls and both forms of glaucoma generates suspicion that biomechanical response has been altered with disease, especially without a difference in central corneal thickness between groups.

The authors make multiple references that the lower corneal hysteresis (CH) in glaucoma that is reported in the literature is indicative of a 'weaker' cornea, which is not accurate. CH is a viscoelastic term that indicates ability to dissipate energy.[2] It does NOT indicate stiffness. For example, increased IOP is correlated with lower CH due to the reduced ability of the eye to dissipate energy. Higher IOP is also associated with a stiffer response due to the nonlinear properties of the cornea and sclera. In this example, lower CH is associated with a stiffer eye. Lower CH in glaucoma indicates that the glaucomatous eye is less able to dissipate energy than the healthy eye. Therefore, CH and stiffness are both important in the discussion of biomechanics in glaucoma with different interpretations.

Lower CH in glaucoma indicates that the glaucomatous eye is less able to dissipate energy than the healthy eye

Ultimately, the current study does not add to our understanding of the biomechanics in glaucoma. A larger study and inclusion of additional biomechanical parameters related to stiffness are needed in order to be conclusive.

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Medical Treatment

Netarsudil for Glaucoma

Comment by Andrew Tatham, Edinburgh, UK

90997 Pooled efficacy and safety profile of netarsudil ophthalmic solution 0.02% in patients with open-angle glaucoma or ocular hypertension; Singh IP, Fechtner RD, Myers JS, Kim T, Usner DW, McKee H, Sheng H, Lewis RA, Heah T, Kopczynski CC; Journal of Glaucoma 2020; 29: 878-884

The Rho kinase (ROCK) inhibitor, netarsudil 0.02%, was approved by the United States Food and Drug Administration (FDA) in December 2017 and by the European Medicines Agency (EMA) in November 2019. Netarsudil lowers intraocular pressure (IOP) by reducing actin-myosin contraction in the trabecular meshwork to decrease outflow resistance, but it also lowers episcleral venous pressure.[1,2]

Singh and colleagues examined pooled data from the ROCKET series of phase III clinical trials, which evaluated the efficacy and safety of once-daily netarsudil, with study durations ranging from three to 12 months.[3-5] The pooled efficacy analysis included 494 participants randomized to once-daily netarsudil and 510 participants to twice-daily timolol, with baseline IOP less than 25 mmHg. Three months of study treatment were completed by 86.6% (428/494) of participants in the netarsudil group and 94.5% (482/510) in the timolol group. Once daily netarsudil met the criteria for non-inferiority at all nine time points measured (8 am, 10 am and 4 pm at weeks two and six, and month three). Mean IOP on treatment ranged from 16.4 to 18.1 mmHg in the netarsudil group, with a mean IOP reduction of 4.8 mmHg.

A secondary analysis, including 666 patients treated with once-daily netarsudil and 768 with twice-daily timolol, with baseline IOP < 30 mmHg, also showed non-inferiority of netarsudil to twice-daily timolol. Whereas the IOP-lowering effect of timolol depended on baseline IOP, the effect of netarsudil was stable across the range of IOPs. A higher proportion of patients with low baseline IOP (< 23 mmHg) achieved a ≥ 20% reduction in IOP with netarsudil than timolol (57.2% versus 45.6%), whereas timolol performed better in patients with high baseline IOP.

The pooled safety analysis included 1,678 patients, half treated with netarsudil and half with timolol. Treatment was discontinued before cessation of the studies in 31.5% (264/839) of netarsudil and 12.6% (106/839) of timolol patients. The most common ocular adverse events were conjunctival hyperemia (54.4% versus 10.4% for netarsudil and timolol respectively), cornea verticillata (20.9% versus 0.2%), instillation site pain (19.9% versus 21.6%) and conjunctival hemorrhage (17.2% versus 1.8%). Most ocular adverse

events were mild and did not increase with continued dosing. Once daily netarsudil was associated with a similar pattern of systemic adverse events as timolol, but unlike timolol had no effect on heart rate.

Netarsudil was effective across IOP levels

In summary, this pooled analysis showed once-daily netarsudil had an IOP-lowering efficacy non-inferior to twice-daily timolol and that netarsudil was generally well tolerated. Whereas the efficacy of timolol varied with baseline IOP, netarsudil was effective across IOP levels. ROCK inhibitors are the first new class of glaucoma medical treatment for over two decades and provide a novel pharmacological method for IOP reduction. The ROCKET studies offer strong evidence of efficacy and safety, although the discontinuation rate may indicate problems with tolerability in some individuals.

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Bimatoprost Implant for Glaucoma

Comment by Esther Hoffman, Mainz, Germany

90873 Phase 3, randomized, 20-month study of bimatoprost implant in open-angle glaucoma and ocular hypertension (ARTEMIS 1); Medeiros FA, Walters TR, Kolko M, Coote M, Bejanian M, Goodkin ML, Guo Q, Zhang J, Robinson MR, Weinreb RN; Ophthalmology 2020; 127: 1627-1641

In this randomized phase 3 clinical trial, Medeiros and colleagues evaluated the IOP lowering efficacy and safety of a 10 and 15 microgram bimatoprost intracameral implant in open angle glaucoma and ocular hypertension patients.

First-line therapy in glaucoma is commonly topical ocular hypotensive medication. However, less than 50% of all patients take their medication regularly. Patients who do not use their prescribed medication have more severe visual field loss and progression of their disease in general. Therefore, poor adherence is a critical barrier to achieving better outcomes in glaucoma patients. While several studies on teaching, education, counseling and motivation to increase adherence have reported short-term improvement, long term effect on adherence is unknown.

The Bimatoprost implant is an intracameral biodegradable implant designed for sustained-release of bimatoprost. After implantation via a paracentesis, the implant releases bimatoprost continuously into the anterio chamber over a 90-120 day period. In this study, after a medication washout phase, patients were randomized into three groups: 10 micrograms bimatoprost, 15 micrograms bimatoprost, and timolol eye drops. Primary outcome measures were mean IOP and change over a 12-month period.

Both dose strengths of bimatoprost implant were non-inferior to timolol in IOP reduction. As well, most patients were controlled without additional medication 12 months after three administrations of bimatoprost implants. However, some patients (7 in the 10 µg bimatoprost group and 16 in the 15 µg bimatoprost group) showed corneal decompensation requiring removal of the implant.

Further investigations are needed to prove whether or not intracameral bimatoprost can be a successful option to increase adherence to glaucoma therapy long-term.

Some patients showed corneal decompensation requiring removal of the implant

Surgical Treatment

Goniosurgery is not effective in the presence of Sturge-Weber syndrome

Comment by Elena Bitrian and Consuelo Gajardo, Miami, FL, USA

90993 Failure of goniosurgery for glaucoma associated with Sturge-Weber Syndrome; Yeung HH, Kane SA, Turlapati N, Nzuna JS, Walton DS; Journal of Pediatric Ophthalmology & Strabismus 2020; 57: 384-387

Glaucoma associated with Sturge-Weber syndrome (SWS) is one of the most challenging types of childhood glaucoma due to limited response to certain topical medications and surgical treatments and higher risk of surgical complications.

Angle surgery is the procedure of choice for the treatment of most types of pediatric glaucoma. It achieves success rates of 85-90 % in primary open angle glaucoma, but in SWS the success rate is lower.[1]

In this paper, **Yeung *et al*. report their results of angle surgery as a primary treatment for glaucoma associated with SWS in 46 eyes**. They found a failure rate of 98% and interval of failure of four months (range 1-48 months). However, the average age of patients at time of surgery was 1.5 years (with a wide range, 1 month-23 years). There are two peaks of incidence of glaucoma in SWS: congenital and juvenile onset. The congenital type is commonly associated with angle dysgenesis and it is preferably treated with angle surgery because of the angle anomalies and because of the risks associated with more invasive surgery. In the juvenile form, elevation of episcleral venous pressure can be the cause of glaucoma.[2]

The authors state that goniosurgery is not an effective treatment of pediatric glaucoma. However, although the rate of success was not as high as in primary open-angle glaucoma, some patients can achieve long periods of controlled pressure with angle surgery and coadjuvant eyedrops. As well, it can be a temporizing measure allowing their eye to grow and increase the success and predictability of a later filtrating surgery, while decreasing the risk of surgical complications.[3]

In conclusion, even if angle surgery in SWS does not achieve success rates as high as in other types of childhood glaucoma, it delays the need for more invasive filtration surgery (trabeculectomy of tube shunt). Surgeons caring for SWS patients should be proficient at performing surgery in pediatric glaucoma and postoperative care for the patient.

Even if angle surgery in SWS does not achieve success rates as high as in other types of childhood glaucoma, it delays the need for more invasive filtration surgery

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Clinical Outcomes with the Free-Plate Ahmed Valve Implantation

Comment by Jonathan Myers and Daniel Lee, Philadelphia, PA, USA

91088 Clinical outcomes of Ahmed glaucoma valve implantation without fixation of a plate: The free plate technique; Lee HM, Park KS, Jeon YY, Kim WJ, Lee NH, Kim KN, Kim CS; PLoS ONE 2020; 15: e0241886

The notion of omitting tube shunt plate fixation has been circulating for more than a decade.[1] This study by Lee and colleagues is an important addition to the growing body of evidence that what they term the free plate AGV (FPAGV) technique has comparable safety and efficacy vs sutured plates. **The authors' retrospective series thoroughly examines pressure outcomes and a variety of complications and the results of the FPAGV are at least equivalent to sutured plates**. An intriguing aspect of the technique was the anterior anchoring suture passed *through* the silicone tube. This is in distinction to our group's comparative retrospective series on a similar technique where the suture was looped and cinched around the tube.[2] Their penetrating suture may have acted as a venting wick[3] as described in non-valved tube techniques and contributed to the relatively blunted hypertensive phase in the FPAGV group compared to the conventional group in Lee's series.

The study was performed in South Korea, and as the authors discussed, FPAGV has significantly facilitated tube placement in smaller inter-palpebral fissures where exposure and visualization are often challenging. This technique may also be of particular utility in allowing plates to be dropped behind high buckles and in avoiding suturing in areas of

scleral thinning. Some cases may be potentially less well suited, such as shallow orbits or very large globes that might be more predisposed to anterior migration as the orbital rim and positioning behind the equator help maintain posterior plate position in our experience.

Although it is the preferred technique of many surgeons and there is mounting evidence for the safety of FPAGV, it has not been widely adopted among glaucoma surgeons. For those who implant tube shunts regularly, the risk of scleral perforation is low and the slight improvement in efficiency may not be thought to justify the perceived risks of forgoing plate sutures. However, FPAGV may be a helpful technique to turn to in scenarios where plate fixation is inherently challenging.

FPAGV may be a helpful technique to turn to in scenarios where plate fixation is inherently challenging

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Combining Mitomycin C with a Drainage Device

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

91208 Subconjunctival injections of mitomycin C are associated with a lower incidence of hypertensive phase in eyes with Ahmed glaucoma valve; Perez CI, Verdaguer S, Khaliliyeh D, Maul EA, Ou Y, Han Y; Ophthalmology. Glaucoma 2020; 0:

Perez *et al*. examined the efficacy of mitomycin-C (MMC) on the challenging hypertensive phase (HP) of drainage implants. The investigators demonstrated that subconjunctival MMC, injected over the FP7 Ahmed plate, 25 micrograms for three doses, decreased the incidence of the HP from 55% to 17.6% (P = 0.04). At the one- and two-month

postoperative visits, the IOP was significantly lower in the MMC group, but there was no significant difference at six months. However, the need for greater medication burden persisted in the no MMC group.

The main conclusion of the study was the effect of MMC on the HP, but two other important factors include length of time and height of IOP prior to initiating aqueous suppressants.[1,2] For example, it is unclear whether the MMC group had aqueous suppressants started sooner as they were likely seen more frequently when they came in for their MMC injections. It is assumed the eyes had similar types of previous glaucoma surgery, but this is not noted in the paper. Considering the nature of wound healing following drainage implants, especially with percentage differences in the neovascular groups, a one-year follow-up would be more desirable.

Subconjunctival injections of MMC seem to be the current trend that most likely represents a way station on the antimetabolite journey.[3] It is unknown whether subconjunctival injections are better than the time-honored sponge to deliver the MMC. Moreover, the increasing trend of using low energy CPC/Diode following elevated IOP after a tube shunt may potentially reduce the risk of attendant MMC with tube shunts.(4) In spite of all these factors, this subject deserves a prospective study for it potentially is a game changer for IOP control following drainage implant surgery in valved devices. The authors have highlighted the need for further investigation of MMC with tube shunts and should be congratulated for studying these difficult clinical questions.

This subject deserves a prospective study

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Combining Mitomycin C with a Drainage Device

Comment by Vital Costa, Sao Paulo, Brazil

91208 Subconjunctival injections of mitomycin C are associated with a lower incidence of hypertensive phase in eyes with Ahmed glaucoma valve; Perez CI, Verdaguer S, Khaliliyeh D, Maul EA, Ou Y, Han Y; Ophthalmology. Glaucoma 2020; 0:

Perez *et al.* investigated the effects of subconjunctival mitomycin C (MMC) on the rates of hypertensive phase (HP) after the implantation of Ahmed Glaucoma Valves (AGV). Their **retrospective, comparative, single-surgeon study** indicates that intra and postoperative injections of MMC may reduce the occurrence of HP in these eyes. **Their protocol included one injection (0.1 ml of 0.25 mg/ml MMC) over the plate intraoperatively, followed by injections one and four weeks postoperatively. A total of 20 eyes underwent AGV implantation without MMC and 17 eyes underwent AGV implantation with MMC. All eyes had a minimum follow-up of 6 months**. HP, defined as IOP > 21 mmHg during the first three postoperative months, occurred in 17.6% (3/17) of the MMC-treated eyes and 55% (11/20) of the control group ($p = 0.04$). There was no significant difference in mean IOPs at six months (14.0 ± 0.8 mmHg and 14.7 ± 0.9 mmHg for the MMC and control groups, respectively; p=0.6)), but the MMC group required significantly less medications (1.2 ± 0.2 vs. 2.2 ± 0.3 in the control group; $p = 0.007$). Few complications were reported, including one case of punctate keratitis and one eye with lid swelling.

Although previous RCTs have not been able to demonstrate a benefit of intraoperative MMC in eyes undergoing AGV implantation, some retrospective case series have suggested that 5FU/MMC injections may promote better IOP control postoperatively. As suggested by the authors, limitations of this study include its retrospective nature, the small sample size and the short-term follow-up. The design of a double-masked, prospective, randomized trial would avoid selection bias, illustrated in this series, for example, by a different proportion of NVG eyes in the MMC group (60%) and the control group (35%).

In a previous study,[1] we hypothesized that the unsuccessful use of MMC may be explained by the presence of a foreign body, a constant stimulus for fibroblastic proliferation, which may overcome the antiproliferative properties of MMC. A minimum follow-up of one year would be required in order to confirm that this will not happen with this treatment protocol. Furthermore, the authors did not compare success rates of both groups using predefined criteria and Kaplan-Meyer survival curves. In conclusion, as mentioned by the authors, RCTs with a greater number of eyes and longer follow up are needed to evaluate if MMC injections improve the success rates of AGV implantation.

RCTs with a greater number of eyes and longer follow up are needed to evaluate if MMC injections improve the success rates of AGV implantation

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Phaco and IOP in Eyes Previously Implanted with Drainage Devices

Comment by Robert Feldman, Houston, TX, USA

91083 The effect of phacoemulsification on intraocular pressure in eyes with preexisting glaucoma drainage implants; Wong SH, Radell JE, Dangda S, Mavrommatis M, Yook E, Vinod K, Sidoti PA, Panarelli JF; Ophthalmology. Glaucoma 2020; 0:

In this study, **Wang *et al*. retrospectively reviewed patients who underwent phacoemulsification in eyes with preexisting glaucoma drainage implants (GDI). They present results of 51 eyes of 45 patients to evaluate the effect on IOP control.** This is important because many patients who are phakic and undergo GDI will develop cataracts requiring extraction during the first 5 years.[1] The authors were unable to demonstrate any effect on IOP of cataract extraction in this setting and although underpowered were unable to detect a difference between various implant types.

These results are different than cataract surgery in previously unoperated eyes where IOP is expected to decrease about 3 mmHg and different than lens extraction after trabeculectomy which in most reports results in an increased failure rate.[2,3]

The results suggest that the mechanism of failure of a GDI may be different than a trabeculectomy and that postoperative inflammation does not lead to decreased permeability of the implant capsule. In any case the results confirm that phacoemulsification may be safely performed in eyes with a pre-existing GDI without risking loss of control of the glaucoma.

Phacoemulsification may be safely performed in eyes with a pre-existing GDI

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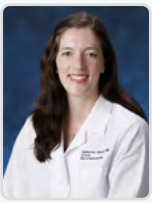
Clinical Outcomes with the XEN45 Gel Stent



Comment by Catherine R. Sheils and Sameh Mosaed, Irvine, CA, USA

91073 Comparison of clinical outcomes with open versus closed conjunctiva implantation of the XEN45 Gel Stent; Do A, McGlumphy E, Shukla A, Dangda S, Schuman JS, Boland MV, Yohannan J, Panarelli JF, Craven ER; Ophthalmology. Glaucoma 2020; 0:

Do and colleagues report the results of **a retrospective multicenter study comparing two surgical approaches for the placement of the XEN45 gel stent**. The analysis includes outcomes from three academic centers, and examined change in IOP from baseline, rates of revision, and rates of treatment failure, comparing an open to a closed approach to stent placement in a group of 137 eyes. In both the open or closed procedures, an *ab interno* or *ab externo* approach was allowed. However, **surgeons who utilized an open approach created a peritomy with dissection of underlying Tenons to bare sclera prior to injection of the stent, whereas in the closed approach, the stent was deployed into the subconjunctival space without prior dissection**. A variable dose of mitomycin C was also injected in the subconjunctival space prior to stent insertion in both groups.

After controlling for factors such as surgeon and dose of mitomycin C utilized, the study found that percentage change in IOP from baseline was higher in the open group compared to the closed group (43.1% vs. 24.8%, respectively).

The study had several other notable findings; rates of operative revision and bleb needling, as well as rates of tube erosion and iris plugging, were significantly lower in the open group compared to the closed group.

The most significant limitation of the study is that the IOP at baseline significantly differed between the open and closed groups, with the open group having a higher pre-intervention IOP. It may be easier to achieve a higher percentage decrease in IOP compared to a lower starting IOP resulting in greater treatment efficacy. Also, eyes in the open group were significantly more likely to have undergone previous glaucoma filtration surgeries which affect the quality of the conjunctiva and Tenons, and may impact postoperative filtration success and complication rates.[1] In short, the two study groups were not comparably matched across these two important features; future studies may benefit from more closely matched open versus closed groups. Another consideration is that only 55 patients were followed out to 12 months postoperatively. As subconjunctival filtration procedures often have variable outcomes in the first year after surgery, it would be of interest to follow the entire cohort for at least one year postoperatively.[2,3]

Do *et al.*'s findings suggest that XEN 45 Gel Stent placement through an open approach, while being more invasive, decreases complications and the need for post-operative bleb needling, and overall may have greater IOP- lowering efficacy.

XEN 45 Gel Stent placement through an open approach, while being more invasive, decreases complications and the need for post-operative bleb needling, and overall may have greater IOP-lowering efficacy

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Prognostic factors

IOP guidelines and Glaucoma Progression

Comment by Luciano Quaranta, Pavia, Italy

91539 Relationship between mean follow-up intraocular pressure, rates of visual field progression and current target intraocular pressure guidelines; Melchior B, De Moraes CG, Paula JS, A Cioffi G, Girkin CA, Fazio MA, N Weinreb R, M Zangwill L, M Liebmann J; British Journal of Ophthalmology 2020; 0:

This paper aims to investigate if treated glaucomatous eyes with intraocular pressure (IOP) within the limits of current guideline-driven target IOPs indeed experience slow rates of glaucomatous visual field (VF) progression at levels close to those occurring due to age-related decay in sensitivity, and if the impact is the same among patients of African descent (AD) and European descent (ED). The dataset was from the multi-site African Descent and Glaucoma Evaluation Study (ADAGES) collaboration[1], an observational, prospective cohort study aimed at identifying factors that account for differences in glaucoma onset and rate of progression between AD and ED glaucoma suspects or patients. For the present report, the authors included only subjects with 'manifest glaucoma' that they defined as participants with glaucomatous optic neuropathy and abnormal baseline VF tests (pattern standard deviation (PSD) with p < 5% or Glaucoma Hemifield Test result 'outside normal limits[1]), with at least five visits and more than two years of follow-up and only reliable VFs. **A total of 8598 24–2 VF tests from 603 eyes of 407 patients (144 AD and 263 ED) were included, split into three groups based on baseline VF mean deviation (MD): G1 (better than −5.0 dB), G2 (−5.0 to −10 dB) and G3 (worse than −10 dB). An eye was defined as clinically stable if its VF change rate shows a MD slope higher ('more positive') than −0.1 dB/year, based on previous estimates of the age-related decay in VF sensitivity in subjects older than 50 years2**. For stable eyes, the medians and IQR of the mean follow-up IOP were G1 = 15.0 mmHg (IQR: 13.1 to 17.7), G2 = 13.2 mmHg (IQR: 11.6 to 14.3) and G3 = 11.9 mmHg (IQR: 10.1 to 13.8) (p<0.01). With the goal of unraveling the relationship between existing guidelines on target IOP vs. MD progression rates, a linear least squares regression was used to calculate median MD slopes as: −0.20 dB/y (IQR: −0.43 to −0.02) for G1 < 21 mmHg, −0.19 dB/y (IQR: −0.51 to −0.01) for G2 < 18 mmHg and −0.15 dB/y (IQR: −0.47 to 0.05) for G3 < 15 mmHg (p=0.63), with no significant differences between racial groups. The authors concluded that in their sample adherence to treatment guidelines helped slow global VF progression rates at various disease stages.

The main goal of the authors was to investigate whether follow-up IOP within the limits proposed by some versions of the current guidelines could help minimize glaucoma VF progression. A relevant byproduct of these results (although its importance has not

adequately been pointed out by the authors, in our opinion) is that the MD slopes were not only close to the age-related decay in sensitivity (−0.1 dB/y), but also close to MD rates (−0.17 ± 0.6 dB/y) found in patients with treated ocular hypertension that did not progress to glaucoma during follow-up. The slow decline in the study population (in which treatment targets were determined for each patient at the ophthalmologist's discretion, not according to any specific guidelines) is a clear piece of evidence demonstrating that, when dealing with any patient, target IOP should be individualized and continuously readjusted according to disease progression, patient age, and other individual conditions and/or risk factors.

The authors claim that the usually observed worse glaucoma prognosis among AD patients may have been largely due to healthcare access, diagnosis, and therapy adherence issues, but also may have been due to problems with statistical treatment. Another limitation is the use of a global-scale parameter such as MD as a proxy for VF progression instead of local-level parameters such as pointwise event-based endpoints. The authors also assumed linearity of MD changes over the entire follow-up period, which may hide changes in progression rates. Another possible issue is that all IOP measurements were carried out during office-hours, which does not capture possible effects of IOP variability on progression rates.

The authors have been themselves adamantly honest in acknowledging the limitations of the present study. They could have also pointed out that the obtained results were exactly as expected, since in the framework they built no other results could be realistically obtained: in the ideal IOP target ranges the disease is controlled, in an apparent tautology. However, despite these limitations, the authors were able for the first time to quantitatively estimate the VF progression rate(s) associated with these average target IOPs for patients with different severity. They also show target IOP should be individualized and continuously adjusted especially dealing with advanced disease progression. We congratulate the authors for their paper and their valuable contribution.

Target IOP should be individualized and continuously adjusted especially dealing with advanced disease progression

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Miscellaneous

Genes, Diet and Caffeine

Comment by Stefano Gandolfi, Parma, Italy

91433 Intraocular pressure, glaucoma, and dietary caffeine consumption: A gene-diet interaction study from the UK Biobank; Kim J, Aschard H, Kang JH, Lentjes MAH, Do R, Wiggs JL, Khawaja AP, Pasquale LR; Ophthalmology 2020; 0:

In this study, **the authors used data from the UK Biobank to examine the association of caffeine intake with intraocular pressure (IOP) and glaucoma, and whether genetic predisposition to higher IOP modified these associations**. The authors reported that coffee, tea and caffeine consumption were associated weakly with lower IOP, and the

association between these exposures and glaucoma were null. However, once exposed to correction for an IOP Polygenic Risk Score, the data support a positive association between caffeine intake and both IOP and glaucoma prevalence, but only among those with the highest genetic susceptibility to elevated IOP.

Once exposed to correction for an IOP Polygenic Risk Score, the data support a positive association between caffeine intake and both IOP and glaucoma prevalence, but only among those with the highest genetic susceptibility to elevated IOP

The strengths of study include (a) a very large sample size of 121,374 participants; and (b) an objective accurate estimate of the IOP (the authors adopted the Ocular Response Analyzer technology, thereby offsetting the measurements for cornea-induced confounders). Weaknesses include a rather weak definition of glaucoma (based upon either patient's reported 'doctor's opinion' or ICD-labelling in medical records) that is exposed to the risk of overestimation (e.g., an ocular hypertensive patient might have being mistaken for an actual glaucoma patient). As well, no data on the severity of the disease are available. However, the appropriate and aided by the large sample size, the outcomes are well-defined and the results are well-supported by the data analysis.

The study's results are consistent with the concepts of personalized medicine. While confirming the available literature on the inconclusive results of generalized analyses on the relationship between caffeine consumption and elevated IOP/glaucoma, they offer a potential path for a better understanding by correcting the data for genetic susceptibility. This study is strategic in promoting a less generalized epidemiology, and thereby offering the clinician more precise tools to understanding the risk to individual patients encountered in everyday practice.

Last, but not least, the data on caffeine consumption have been collected from a large sample of individuals living in the UK. Since the British habits, in terms of caffeine consumption, might not be comparable to what has been observed in other parts of the world. Albeit showing valid results , extending them to the general world population needs further studies.

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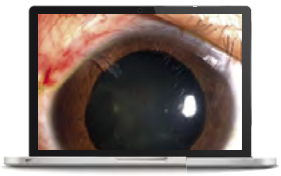

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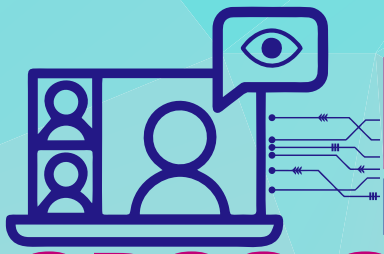

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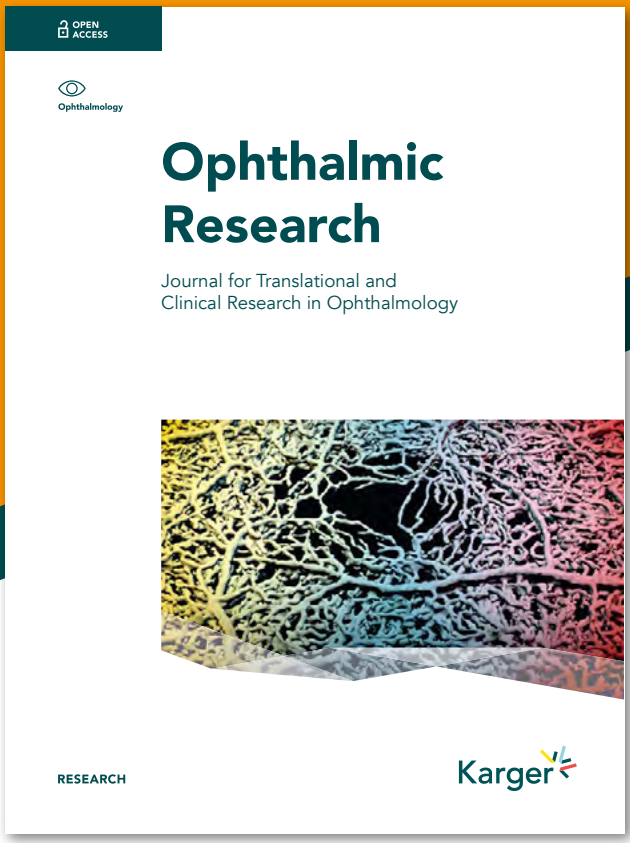

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