Published in final edited form as:

Asia Pac J Ophthalmol (Phila). 2015 ; 4(4): 228–235. doi:10.1097/APO.0000000000000133.

One Year of Glaucoma Research in Review: 2013 to 2014

Sarah H. Van Tassel, MD¹, Nathan M. Radcliffe, MD², and Anna M. Demetriades, MD, PhD¹

¹Department of Ophthalmology, Weill Cornell Medical College, New York, USA

²Department of Ophthalmology, NYU School of Medicine, New York, USA

Abstract

Purpose—The purpose of this study was to provide the practicing clinical ophthalmologist with an update of relevant glaucoma literature published from 2013 to 2014.

Design—Literature review.

Methods—The authors conducted a 1-year (October 1, 2013, to September 30, 2014) English-language glaucoma literature search on PubMed of articles containing “glaucoma” or “glaucomatous” with title/abstract as a filter. Medical Subject Headings (MeSH) filtered searching was not performed because of the newness of the reviewed material.

Results—Literature review yielded 2,314 articles, after which we excluded reviews and letters to the editor. We highlighted articles featuring new or updated approaches to the pathophysiology, diagnosis, or treatment of glaucoma and gave preference to human research.

Conclusions—This review features literature that is of interest to ophthalmologists in practice and also highlights studies that may provide insight to future developments applicable to clinical ophthalmology.

Keywords

glaucoma; review; optical coherence tomography; intraocular pressure; glaucoma medications; neuroprotection; glaucoma surgery; glaucoma genetics

Introduction

Over the past calendar year, a multitude of studies investigated the pathogenesis, diagnosis, and treatment of glaucoma. Many of these studies aimed to enhance the value of automated perimetry modalities and retinal nerve fiber layer (RNFL) analysis to identify early glaucoma. In addition, authors investigated novel compounds and new laser and surgical techniques for intraocular pressure (IOP) lowering and continued to explore the role of genetics in the development of elevated IOP and glaucoma.

This review highlights a selection of articles that appeared in the English-language literature over the past year. The authors conducted a 1-year (October 1, 2013, to September 30, 2014)

English-language glaucoma literature search on PubMed of articles containing “glaucoma” or “glaucomatous” with title/abstract as a filter, which yielded 2,314 articles. Titles and abstracts were read before determining inclusion, and selected articles were reviewed in full. We excluded reviews and letters to the editor. Large, prospective, randomized trials in humans were given preference for inclusion. The overriding consideration in the selection of specific articles was the desire to include new or updated approaches to the pathophysiology, diagnosis, or treatment of glaucoma that are relevant to the clinical ophthalmologist. Seventy-two articles were chosen for inclusion.

Articles were grouped in sections based on the following major categories: automated perimetry, optic nerve head and imaging, structure and function, intraocular pressure, pharmacologic intraocular pressure lowering, corneal thickness and biomechanics, neuroprotection, glaucoma laser therapy, glaucoma surgery: trabeculectomy, glaucoma surgery: implants, minimally invasive glaucoma surgery, secondary glaucoma, glaucoma genetics, and glaucoma morbidity (Table 1).

Automated perimetry

To evaluate the role of visual field reliability indices in ruling out glaucoma, Rao et al¹ analyzed the pattern of reliability indices in 291 eyes of 291 participants deemed to have normal eyes following glaucoma expert review but initially referred as glaucoma suspects due to cupping by comprehensive ophthalmologists. Authors found that the probability of a visual field (VF) being falsely classified as glaucomatous by the Swedish interactive threshold algorithm (SITA) was associated with false negative (FN) response rates (odds ratio, 1.36; 95% confidence interval [CI], 1.25-1.48, $P < 0.001$), which are not considered when flagging a test as unreliable in SITA. Authors caution that even small FN response rates can lead to visual fields being falsely classified as glaucomatous.¹

Can patients' visual fields improve? In their prospective study of 607 subjects in the Collaborative Initial Glaucoma Treatment Study with newly diagnosed open angle glaucoma (OAG), Musch and associates² found that the number of participants demonstrating substantial VF improvement after treatment initiation was similar to that showing VF loss over time through 5 years, after which time visual field loss became more frequent. Improved IOP control was a predictor for visual field improvement, suggesting that the observed improvement probably was real since at low peak IOP apparent improvement exceeded apparent worsening by three to one. Improvement was more common in females and less common in subjects with cardiovascular disease. Overall, however, the finding of nearly equal cases improving and worsening suggests that most cases of change in mean deviation may be due to fluctuation and require confirmation.²

Frequency-doubling technology perimetry (FDTP) was a popular topic in this year's literature, and many authors explored the role of FDTP in clinical practice. Liu and colleagues³ prospectively followed 179 glaucomatous eyes and 38 normal eyes with standard automated perimetry (SAP) and FDTP testing at 4-month intervals for 36 or more months. Criteria for test location progression was a rate of change of visual sensitivity of -1 decibel (dB) per year for nonedge and -2 dB/year for edge locations. FDTP detected a greater number of progressing locations than SAP ($P < 0.001$). Additionally, the mean

deviation (MD) rate of change was significantly faster for FDTP ($P < 0.001$).³ Similarly, Meira-Freitas et al⁴ prospectively observed a cohort of 587 eyes with suspected glaucoma. In 63 eyes that developed SAP VF loss during average follow up of 73 months, the mean rate of FDTP PSD change was 0.07 dB/year compared with 0.02 dB/year in eyes that did not develop SAP VF loss.⁴

In their prospective study of 51 non-glaucomatous controls and 40 patients with early glaucomatous nerve fiber loss, Prokosch and Eter⁵ found that while sensitivity was highest for flicker-defined form perimetry (87 %) and FDTP matrix (62.5 %), the specificity was highest for SAP (69.2 %). Authors suggest there may be a role for multiple types of perimetry in the assessment of early glaucoma.⁵

Optic nerve head and imaging

To determine whether quantitative optic nerve parameters could effectively distinguish compressive from glaucomatous optic neuropathy, Hata et al.⁶ prospectively assessed 34 patients with compressive optic neuropathy (CON), 34 age-matched patients with moderate or severe glaucomatous optic neuropathy (GON), and 34 age-matched controls. Measured using the Heidelberg Retina Tomograph (HRT) II and Spectralis optical coherence tomography (OCT) instrument, mean and maximum cup depths were significantly smaller with CON than GON (both $P < 0.001$). Compared to glaucomatous eyes, the distance between Bruch's membrane opening and the anterior surface of the lamina cribrosa (BMO-anterior LC) was also significantly smaller in CON ($P < 0.001$). Although the cup to disc (C:D) ratio of CON eyes with a glaucoma-like disc did not differ significantly from cases of GON ($P = 0.16$), the BMO-anterior LC and mean and maximum cup depths of CON with a glaucoma-like discs were smaller than those with GON ($P = 0.005$, $P = 0.003$, $P = 0.001$, respectively).⁶

In similar work by Danesh-Meyer and colleagues⁷ to differentiate CON from OAG, multivariate analysis of OCT measurements demonstrated that OCT temporal sectors are thinner in CON, and average C:D ratio, vertical C:D ratio, and cup volume measurements are larger in OAG. HRT measurements did not distinguish between CON and normal discs.⁷

Akkaya and associates⁸ amassed a cohort of 60 primary open angle glaucoma (POAG) patients with type 2 diabetes mellitus and 41 POAG patients without diabetes to determine the effect of metabolic control on optic nerve head parameters. Duration of diabetes was not significantly correlated with rim area and volume ($P = 0.81$ and $P = 0.79$, respectively). There were weak but statistically significant associations between hemoglobin A1c levels and some HRT 3 parameters including disc area ($r=0.35$, $P = 0.006$), cup area ($r=0.35$, $P = 0.006$), cup volume ($r=0.32$, $P = 0.01$), and cup shape measure ($r=0.32$, $P = 0.01$), implying a protective effect of diabetes over glaucomatous optic nerve insult that warrants further investigation.⁸

Xu and colleagues⁹ investigated the temporal relationship between optic nerve head (ONH) surface depression as measured by confocal scanning laser ophthalmoscopy (CSLO) and RNFL thinning as measured by spectral domain OCT (SD-OCT) in 3238 OCT and 3238 CSLO images obtained from 146 glaucomatous eyes and 70 normal eyes over an average of

5.4 years. Of 23 glaucomatous eyes with both ONH surface depression and RNFL thinning, 19 (82.6%) had ONH surface depression prior to RNFL thinning with a median lag of 15.8 months. In the glaucoma group, only 7% of eyes (4/57) had RNFL thinning at the onset of ONH surface depression, but 45.7% of eyes (21/46) had ONH surface depression at the onset of RNFL thinning. A significantly worse survival probability was observed in eyes with ONH surface depression compared to eyes with RNFL thinning ($p=0.002$). Although agreement with visual field progression was poor for RNFL thinning and ONH surface depression, in eyes with all three findings, ONH surface depression preceded visual field progression in all eyes (6 eyes).⁹

Shin et al¹⁰ investigated the effect of myopic optic disc tilt on SD-OCT parameters and found the temporal RNFL was significantly thicker in the tilted disc compared to non-tilted disc groups. No significant differences were observed in ganglion cell-inner plexiform thickness (GCIPL) between the two groups, leading authors to recommend using caution when interpreting temporal RNFL thickness in glaucomatous eyes with tilted optic discs.¹⁰ Similar findings were reported by Mayama and colleagues¹¹ in their study using measurements obtained by HRT II.

Although the ISNT rule (Inferior > Superior > Nasal > Temporal) for evaluating the neuroretinal rim is commonly used in clinical assessment of the optic disc, multiple researchers cautioned that the ISNT rule with measurements obtained by SD-OCT¹² (RTVue), Cirrus high-definition OCT¹³ (HD-OCT), and HRT¹⁴ does not permit robust differentiation between glaucomatous and non-glaucomatous discs.

Field and colleagues¹⁵ sought to determine whether intereye RNFL asymmetry is suggestive of glaucoma. In 66 OAG eyes and 40 age-matched controls, intereye RNFL asymmetry for global average, all quadrants, and all sectors were significantly greater in OAG eyes compared to controls. Global average asymmetry showed the greatest statistical difference between OAG and normal eyes ($P < 0.001$), with a sensitivity of 74.24% and specificity of 90% when the global asymmetry cutoff was set at 6.0 micrometers (μm).

Given the paucity of normative data on RNFL thickness in children, the role of OCT in congenital and juvenile glaucoma is unclear. Srinivasan and associates¹⁶ performed a case-control study of 45 eyes of 37 children who underwent glaucoma surgery for primary congenital glaucoma (PCG) and 72 eyes of 41 normal children and found that all global SD-OCT parameters including rim area, average RNFL thickness, and ganglion cell complex (GCC) thickness were significantly different in children who underwent surgery for PCG compared with normal children. They are the first to report the GCC values of normal and glaucomatous eyes of children. Authors note that future work is needed to evaluate the role of following RNFL change in children unable to complete reliable visual field testing.¹⁶

Imaging of the optic nerve can occur outside of the ophthalmic imaging suite. Ramli and colleagues¹⁷ used 3 Tesla magnetic resonance imaging (MRI) to evaluate optic nerve head volume and found significantly lower nerve volume in both eyes of patients with severe and mild glaucoma groups compared to controls. Optic nerve volume less than 236 mm³ was 96 % sensitive and 80% specific for severe glaucoma by visual field criteria. MRI research

conducted by Chen et al¹⁸ revealed that morphologic changes in the lateral geniculate nucleus (LGN), particularly LGN height, were significantly correlated with damage to the optic disc in POAG patients, while morphologic changes to the LGN were not related to optic disc parameters in non-glaucomatous control subjects.

Structure and function

Rao and associates¹⁹ compared the ability of SAP and SD-OCT to diagnose glaucoma in 280 eyes of 175 subjects referred by general ophthalmologists for glaucoma evaluation. Based on SD-OCT and at least 2 reliable and repeatable SAP, eyes were classified by experts as having glaucoma (179 eyes) or not (101 eyes). RNFL and GCC parameters of SD-OCT had better sensitivities and negative likelihood ratios (LRs) to diagnose glaucoma. However, the specificities and positive LR of most SDOCT parameters were inferior to SAP.¹⁹

Suh et al²⁰ investigated the relationship between structural damage as measured by RNFL thickness and area of RNFL defect and function as measured by VF indices. A logarithmic scale of RNFL thickness had a negative linear relationship with VF indices. Correlation between the RNFL defect area and MD was significantly greater in the severe stage of VF loss compared with earlier stages (partial Spearman correlation coefficient, -0.66, $P = 0.02$).²⁰ In similar work, Alasil and colleagues²¹ found that the RNFL thickness at which VF loss initially becomes detectable was 100 μm superiorly (inferior VF loss) and 73 μm inferiorly (superior VF loss).

Recognizing the value of identifying glaucoma suspects who will progress to perimetric glaucoma, Miki and colleagues²² prospectively analyzed 454 eyes of 294 glaucoma suspects with SD-OCT and VF examinations and observed that the rate of global RNFL loss was more than twice as fast in suspect eyes that developed visual field defects (VFD) compared to suspect eyes that did not (-2.02 $\mu\text{m}/\text{year}$ and -0.82 $\mu\text{m}/\text{year}$, respectively; $P < 0.001$). Authors suggest that measuring the rate of SD-OCT loss may be useful in the clinical assessment of glaucoma suspects.²²

Selbach et al²³ used Dynamic Vessel Analysis, a noninvasive device that obtains video images of the fundus under green monochromatic light to measure retinal vessel parameters, to measure responses of the retinal vessels to flickering light provocation and evaluate the effects of surgical IOP reduction on retinal blood flow parameters in glaucomatous eyes. In eyes that demonstrated inadequate arterial dilation compared with nonglaucomatous eyes in response to flicking light stimulation preoperatively, the maximum dilation of arteries following the flicker provocation improved from 1.4% before to 3.8% following trabeculectomy ($P < 0.01$), suggesting a possible improvement in retinal perfusion following successful IOP reduction.²³

Using SD-OCT to evaluate the in vivo changes in Schlemm's canal (SC) in patients with primary angle-closure glaucoma after trabeculectomy, Hong and associates²⁴ observed a significant increase in the diameter and area of SC at the follow-up examination compared with the baseline value (SC diameter $\pm$ standard deviation [SD]: $34.2 \pm 6.2 \mu\text{m}$ and $28.4 \pm 6.1 \mu\text{m}$, respectively; SC area: $8117 \pm 1942 \mu\text{m}^2$ and $5200 \pm 996 \mu\text{m}^2$, respectively; all P

< 0.001). Change in IOP was the only variable related to changes in SC after multivariate analysis (SC diameter, $P = 0.002$; SC area, $P < 0.001$).²⁴

Hirneiß and colleagues²⁵ assessed the relationship between structure and function by examining the effect of RNFL thickness obtained by SD-OCT on VF loss and patient-reported visual functioning in 176 eyes of 88 glaucoma patients. In multivariate regression analysis, visual acuity in the better eye (as judged by MD) and MD of the worse eye ($R(2) = 0.334$) were the best predictors of patient-reported visual functioning. Inclusion of structural parameters did not improve the prediction of patient-reported visual functioning scores.²⁵

Marvasti et al²⁶ evaluated the relationship between visual field index (VFI) and retinal ganglion cell count as estimated using time-domain OCT (TD-OCT) measurements and observed that the relationship is nonlinear. VFI underestimated the amount of neural loss early in perimetric glaucoma, which authors caution may affect interpretation of the rate of VFI change over time.²⁶

In a group of 492 eyes of 328 glaucoma suspects, Medeiros and associates²⁷ calculated the mean rate of rim area change in eyes that developed visual field loss compared with those that did not and found the difference to be $-0.011 \text{ mm}(2)/\text{year}$ versus $-0.003 \text{ mm}(2)/\text{year}$, respectively ($P < 0.001$). In multivariate analysis, every $0.01 \text{ mm}(2)/\text{year}$ faster rate of rim area loss was associated with a 2.94 higher risk of visual field damage (hazard ratio, 2.94; 95% CI, 1.38-6.23; $P = 0.005$).²⁷

Intraocular pressure

Given the wide diurnal fluctuations in IOP, a contact lens or implantable device that measures continuous IOP has been sought. Araci and associates²⁸ used microfluidics principles to develop an implantable pressure sensor. The device was embedded into an IOL and implanted in pig eyes during cataract surgery. When enucleated porcine eyes were tested in a pressure chamber, high sensitivity and low measurement variability resulted in a pressure limit of detection of 1 mm Hg.²⁸ Chen and associates²⁹ developed a chipless contact lens that senses corneal curvature deformation to monitor IOP. Tested on a silicone cornea, the lens accurately tracked the curvature change as a function of IOP.²⁹

In a longitudinal cohort study of aging Swedes, Åström et al³⁰ found a small but statistically significant increase in IOP of $0.05 \text{ mmHg}/\text{year}$ ($P < 0.001$) between ages 66 to 87 in eyes not having undergone cataract extraction. The estimated contribution of cataract surgery was -2.13 mmHg ($P < 0.001$), and pseudoexfoliation (PEX) contributed an estimated $+2.05 \text{ mmHg}$ to IOP ($P < 0.001$). Women in the study had a 1.22 mmHg higher IOP than men ($P = 0.001$).³⁰

Kim and associates³¹ investigated the long-term effects of multiple intravitreal antivascular endothelial growth factor (VEGF) injections on intraocular pressure in 629 eyes with neovascular age related macular degeneration and 95 eyes with prior retinal vein occlusion (RVO. In the Cox proportional hazard analysis, prior RVO (3.424 , $P = 0.005$), diagnosis of glaucoma (8.441 , $P = 0.001$), and low baseline IOP (0.865 , $P = 0.040$) were significant risk factors for IOP elevation, but a history of multiple intravitreal anti-VEGF injections alone

was not a significant risk factor for IOP elevation, defined as an increase of 5mmHg over the baseline measurement on 2 consecutive visits. Similar conclusions were reached by other groups in work published this year.^{32,33}

Pharmacologic intraocular pressure lowering

Rho kinase (ROCK) inhibitors are a potential new class of ocular hypotensive agents currently undergoing Phase II and III United States Food and Drug Administration trials.³⁴ Preclinical studies this year demonstrated the ability of novel ROCK inhibitors to lower IOP in rabbits³⁵ and monkeys.^{35,36} Animal models suggest that ROCK inhibitors reduce IOP by changing the cellular behavior of trabecular meshwork cells and increasing aqueous humor drainage via the trabecular meshwork.^{37,38}

The Phase 1 trial of ROCK inhibitor candidate drug K-115 demonstrated its efficacy for lowering intraocular pressure from baseline at 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% concentrations with ocular hyperemia occurring in more than half of participants following instillation.³⁹ In the Phase 2 dose-response study, K-115 0.04% was selected as the optimal dose; 65.3% of patients developed conjunctival hyperemia at this dose.⁴⁰

AR-13324 is both a ROCK inhibitor and an inhibitor of the norepinephrine transporter.⁴¹ In a double-masked, randomized study of 213 patients with OAG or ocular hypertension, Bacharach et al⁴¹ compared the safety and efficacy of two concentrations of AR-13324 with latanoprost. Mean diurnal IOP was 20.1, 20.0, and 18.7 mmHg in the AR-13324 0.01%, 0.02%, and latanoprost groups, respectively, a significant difference in all groups compared with the non-treated baseline IOP ($P < 0.001$). The standard for establishing noninferiority of AR-13324 to latanoprost was an upper 95% confidence limit of $< 1.5\text{mmHg}$ for the difference between the two therapies. Because the upper confidence limits were 2.3 and 2.2 mmHg at day 28 for the AR-13324 0.01% and 0.02% groups, respectively, the criterion for noninferiority to latanoprost was not met. Ocular hyperemia, the most frequently reported adverse event, was more common for both concentrations of AR-13324 compared with latanoprost.⁴¹

Fixed combinations of ocular hypotensives may help improve ease of use and compliance. Ozyol and Ozyol⁴² investigated the efficacy of a latanoprost/timolol fixed combination dosed nightly versus an unfixed combination of timolol gel-forming solution dosed once in the morning and latanoprost dosed in the evening. Although mean IOP reduction from baseline was significant in both groups ($P < 0.01$), the mean IOP reduction at week 8 was significantly greater in the unfixed combination group compared with the fixed combination ($\pm$ SD; $5.7 \pm 3.2\text{ mmHg}$ and $3.2 \pm 2.1\text{ mmHg}$, respectively; $P = 0.001$). A decrease in daytime IOP fluctuation was also observed in both groups, and the difference between the fixed and unfixed combination groups was not statistically significant.⁴²

In a population-based cross-sectional study of 7093 older British men and women to determine the association between systemic medication use and IOP, Khawaja et al⁴³ found that use of systemic β -blockers (-0.92 mmHg ; 95% CI, $-1.19, -0.65$; $P < 0.001$) and nitrates (-0.63 mmHg ; 95% CI, $-1.12, -0.14$; $P = 0.011$) were independently associated with lower IOP but use of statins or aspirin were not statistically associated with IOP after adjustment

for β -blocker use. Authors report their study is the first population-based study to demonstrate and quantify the differences in IOP among users of β -blockers and nitrates.⁴³

Seeking to reduce the burden of topical IOP lowering medication administration, Fedorchak and associates⁴⁴ performed proof-of-principle testing of a controlled release brimonidine tartrate formulation encapsulated in poly(lactic-co-glycolic) acid microspheres. Rabbits treated with with a single sunconjunctival injection of loaded microspheres and those treated with topical brimonidine demonstrated significantly lower IOP measurements compared with rabbits that received blank unmedicated microspheres with no evidence of migration or foreign body response at 4 weeks.⁴⁴

Corneal thickness and biomechanics

To evaluate the role of corneal biomechanical properties on IOP reduction following SLT, Hirneiß and colleagues⁴⁵ examined a group of 68 eyes of 68 medically uncontrolled OAG patients and found in linear regression analysis that corneal hysteresis (CH), corneal resistance factor (CRF), and baseline IOP together explain the IOP reduction with an R^2 of 64%. Patients' baseline IOP significantly correlated with the IOP lowering effect of SLT (maximum Spearman's correlation $r = 0.75$, $P < 0.001$).⁴⁵

Pakravan and associates⁴⁶ investigated the changes in corneal biomechanics after trabeculectomy (23 eyes, group 1), phacotrabeculectomy (23 eyes, group 2), Ahmed valve implantation (17 eyes, group 3), and phacoemulsification (26 non-glaucomatous eyes, group 4). Preoperative CH was lower in glaucomatous eyes (5.4, 5.3, 5.2, and 8.1 mmHg in groups 1, 2, 3, and 4, respectively, $P < 0.001$), and mean CH three months following surgery was significantly increased in glaucomatous eyes (mean CH increased by 2.16, 2.29, and 2.30 mmHg in groups 1, 2, and 3, respectively, $P < 0.001$), a finding that was not observed in the nonglaucomatous phacoemulsification eyes (CH increased by 0.11 mmHg, $P = 0.704$).⁴⁶ CH has been previously reported to partially recover follow successful IOP reduction^{47,48} and leaves open the possibility that CH at high IOP is reduced due to a mechanical aspect of ORA measurement rather than inherent corneal properties.⁴⁷

In their study of corneal biomechanical differences between pseudoexfoliation glaucoma (PEXG) and POAG eyes, Ozkok *et al.*⁴⁹ found mean CH and mean CRF to be significantly lower in eyes with PEXG than those with POAG ($P = 0.0007$ and $P = 0.0001$, respectively), but corneal-compensated IOP was not significantly different between the two groups ($P = 0.72$).⁴⁹

Neuroprotection

Several promising preclinical studies sought to identify novel compounds and mechanisms of neuroprotection. Cheng and colleagues⁵⁰ identified a novel cyclopeptide (C*HSDGIC*) that inhibited ultraviolet B irradiation induced apoptotic cell death in a retinal ganglion cell line. Additionally, pretreatment of rats with the novel cyclopeptide resulted in significantly preserved electroretinogram amplitudes of the a-wave, b-wave, and photopic negative response following induction of in vivo retinal ganglion cell apoptosis compared to untreated rats.⁵⁰

In adult Sprague-Dawley rats, You and associates⁵¹ induced unilateral hypertensive glaucoma and found that rats to which fingolimod (an immunomodulatory drug approved for treating multiple sclerosis) was administered intraperitoneally had reduced loss of scotopic threshold response and significant preservation of ganglion cells and optic nerve axons.

Oncostatin M, a member of the IL-6 family of cytokines, was injected intravitreally in mice immediately following optic crush injury in research conducted by Xia and colleagues.⁵² Significantly higher retinal ganglion cell survival ($P < 0.001$) and electrophysiological activity as measured by pattern ERG amplitude ($P = 0.003$) were observed in treated mice compared to control mice.⁵²

Studies continue to seek possible neuroprotective mechanisms in well-established IOP lowering agents. Pretreatment of pilocarpine to a rat retinal cell culture attenuated glutamate-induced neurotoxicity, a finding from Tan et al⁵³ that was dose-dependent and eliminated by application of atropine and pirenzepine, nonselective and M1-selective muscarinic receptor antagonists, respectively. In their in vivo rat model, inner retinal degeneration was significantly reduced by the application of topical 2% pilocarpine, and a cholinergic cell marker ChAT was found to be upregulated. Authors highlight the potential neuroprotective action of pilocarpine and posit that muscarinic receptors are potential therapeutic targets in glaucoma that might afford a neuroprotective effect.⁵³

Glaucoma laser therapy

To investigate the effects of adjuvant selective laser trabeculoplasty (SLT) versus medication alone on IOP control, medication use, and quality of life in POAG patients, Lee and associates⁵⁴ prospectively randomized 41 consecutive POAG patients to receive a single 360-degree SLT treatment or to continue their usual medication regimen. In both groups, IOP lowering therapies were titrated to the lower of either a 25% reduction from baseline IOP without medication or <18 mmHg. At six months, the SLT group had a lower IOP ($P = 0.03$) and required fewer medications compared with baseline and the medication only group ($P < 0.001$ and $P = 0.02$, respectively) with no statistically significant difference in quality of life indicators as measured by the Glaucoma Quality of Life-15 and Comparison of Ophthalmic Medications for Tolerability survey scores.⁵⁴ In a prospective evaluation of NTG eyes, Lee et al⁵⁵ found a 19.7% reduction in prestudy IOP, a 29.6% reduction from baseline IOP, and a 26.7% reduction in IOP lowering therapy six months following SLT (all $P < 0.05$).

Do topical anti-inflammatory medications after SLT influence its IOP lowering effect? Jinapriya and colleagues⁵⁶ randomized patients with POAG and PEXG to receive placebo (artificial tears), prednisolone acetate 1%, or ketorolac tromethamine 0.5% eye drops four times per day for five days immediately following SLT. Neither mean change in IOP at all times measured nor treatment failure rates were significantly different among groups. At one year following SLT, the percentage of patients maintaining a 20% IOP reduction was 18% to 23%.⁵⁶

Susanna et al⁵⁷ investigated the safety and efficacy of ND:YAG laser goniopuncture for IOP lowering in eyes with late bleb failure and patent internal ostia after trabeculectomy with mitomycin C (MMC) and found the mean IOP decreased from 20.9 mmHg pre-laser to 11.9 mmHg post-laser ($P < 0.001$) with concomitant decrease in IOP lowering agents per eye from 0.7 pre-laser to 0.3 post-laser with mean follow-up of 6 months following laser, suggesting a promising method by which to prolong trabeculectomy success.

Glaucoma surgery: Trabeculectomy

The Tube Versus Trabeculectomy (TVT) Study was a randomized multicenter study of 212 patients with medically uncontrolled glaucoma who underwent cataract and/or glaucoma surgery prior to enrollment and were randomized to tube shunt or trabeculectomy with MMC. Previously reported 5 year results found similar IOP and use of IOP lowering therapy in both groups.⁵⁸ Until now, patients who underwent additional glaucoma surgery were censored from analysis. The new data reveal the rate of subsequent glaucoma surgery was higher following trabeculectomy (29%) than tube shunt (9%, $P = 0.025$).⁵⁹ IOP, number of glaucoma medications, and cumulative probability of failure following additional glaucoma surgery were not significantly different between the groups.⁵⁹

Yamada and colleagues⁶⁰ used data from two prospective multicenter studies to estimate the risk of blindness following bleb-related infection after trabeculectomy. Using data from the Collaborative Bleb-related Infection Incidence and Treatment Study, the calculated cumulative incidence of bleb-related infection at 5 years was $2.6 \pm 0.7\%$ ($\pm$ standard error); the incidence of endophthalmitis was $0.9 \pm 0.4\%$. Following, they used the Japan Glaucoma Society Survey of Bleb-related Infection to calculate rates of blindness (using World Health Organization criteria of 0.04 or less): 14% following bleb-related infection and 30% following endophthalmitis. Overall, they estimated the rate of blindness due to infection developing within 5 years of trabeculectomy to be 0.24-0.36%.⁶⁰

Recognizing the challenge of treating glaucomatous eyes that demonstrate progression despite low IOP, Schultz et al⁶¹ examined the safety and efficacy of trabeculectomy with MMC in NTG patients with preoperative IOP ≥ 15 mmHg during the 12 months prior to surgery. Thirty eyes of 28 patients were enrolled. The mean postoperative IOP ($\pm$ SD; 8.6 ± 2.9 mmHg) and number of glaucoma medications (0.6 ± 1.0) at final follow up (mean 50 ± 31 months) were significantly lower than prior to surgery (13.2 ± 1.4 mmHg and 2.5 ± 1.2 , respectively; $P < 0.001$). At 4 years follow up, the probability of having achieved an IOP goal ≤ 10 mmHg was 68%. The cumulative probability of IOP reduction $< 20\%$ below baseline was 32% during 5 years of follow up.⁶¹

Glaucoma surgery: implants

The Ahmed Versus Baerveldt (AVB) Study is a prospective, multicenter, randomized trial to compare longterm efficacy of the Ahmed valve with the Baerveldt implant in patients with refractory or high-risk glaucoma, and three-year results were recently released.⁶² Both devices were effective in reducing IOP and glaucoma medications. At 3 years, mean IOP ($\pm$ SD) was 15.7 ± 4.8 mmHg in the Ahmed group (49% reduction from baseline, $P < 0.001$) and 14.4 ± 5.1 mmHg in the Baerveldt group (55% reduction from baseline, $P < 0.001$;

comparison between groups, $P = 0.09$). Although the Ahmed group required fewer glaucoma medications at the 1-day, 1-week, and 2-week follow-up visits ($P < 0.05$), the Baerveldt group required fewer medications from 2 months onward with 25% of the Ahmed group and 50% of the Baerveldt group medication free at 3 years ($P < 0.001$). The most common long-term complication was cornea edema, affecting 7% of the Ahmed group and 14% of the Baerveldt group at 3 years ($P = 0.08$).⁶²

Two meta-analyses^{63,64} examined the efficacy and safety of EX-PRESS implantation compared with trabeculectomy for uncontrolled POAG (3 of the 4 randomized controlled trials included in each analysis were the same) and found the two interventions to have similar efficacy in IOP reduction. EX-PRESS implantation was associated with higher rates of complete operative success and fewer hyphemas compared with trabeculectomy.^{63,64} Patel et al⁶⁵ also observed no significant difference in success rates between the two operations but found the overall 1-year cost was significantly greater for EX-PRESS implantation, and the incremental cost-effectiveness ratio was \$9625 (95% confidence interval, \$2435-548,084).

Minimally invasive glaucoma surgery

Grover and associates⁶⁶ reported preliminary results and safety data for gonioscopy-assisted transluminal trabeculectomy (GATT), a minimally invasive circumferential trabeculectomy that improves upon conventional ab externo trabeculectomy by avoiding conjunctival and scleral incisions to identify the canal. In the POAG group, IOP decreased by 11.1 mmHg (SD, 6.1 mmHg; 39.8% [SD, 16.0%]) with an average of 1.1 fewer glaucoma medications at 12 months. In the secondary glaucoma group, IOP decreased by 19.9 mmHg (SD, 10.2 mmHg, 52.7% [SD, 17.4%]) with an average of 1.9 fewer glaucoma medications at 12 months. Treatment was considered a failure in 9% of patients who required further glaucoma surgery. Lens status or concurrent cataract extraction did not significantly effect IOP at 6 or 12 months ($P > 0.35$), and transient hyphema, seen in about 30% of patients at the one week visit, was the most common side effect.⁶⁶ These preliminary results are promising, and GATT may become part of the arsenal with which specialists approach uncontrolled glaucoma.

Ahuja and colleagues⁶⁷ retrospectively collected data from 246 patients undergoing ab interno trabeculectomy with ($n=158$) or without phacoemulsification ($n=88$), including 23 patient with prior failed trabeculectomy or tube shunt. Mean IOP was reduced 29% ($P < 0.001$) and glaucoma medications reduced 38% ($P < 0.001$) at 24 months post-operatively compared with preoperative values. Statistically significant reductions in IOP lasted up to 36 months and medications up to 42 months. At 24 months, 62% of patients achieved postoperative IOP ≤ 21 mmHg or IOP reduction $\geq 20\%$; 22% of patients achieved the authors' most conservative success criteria of IOP ≤ 18 mmHg and $\geq 20\%$ reduction in IOP.⁶⁷

In a comparison of direct costs of treating glaucoma patients within the Ontario Health Insurance Plan (OHIP, Canada), Iordanous and associates⁶⁸ found that the Trabectome, iStent, and endocyclophotocoagulation may all offer modest savings to OHIP compared to the cost of glaucoma medications over a projected period of six years.

Secondary glaucoma

To investigate the causes of glaucoma following open globe injuries, Osman et al⁶⁹ retrospectively analyzed 41 repaired open globe injuries over a 14 year period that developed traumatic glaucoma. They observed that the causes of elevated IOP varied depending on the length of time following repair. IOP elevation within 1 month of repair was attributed to retained lens fragments (26.8%), inflammation (14.6%), and hyphema (7.3%). Elevated IOP in the 2 to 6 month period was the result of synechial angle closure (21.9%) and ghost cells (7.3%). After 6 months, high IOP was due to retained lens fragments (4.8%), angle recession (9.7%), and synechial angle closure (7.3%). The authors emphasize the importance of identifying the cause of elevated IOP in order to achieve appropriate and successful treatment.⁶⁹

Recognizing that eyes often develop glaucoma following Boston type I keratoprosthesis (KPro) surgery, Qian and associates⁷⁰ evaluated the role of anterior segment OCT as a method of visualizing iris and angle structures following KPro surgery. Although anterior segment OCT revealed anatomical changes that could not be detected on clinical examination, authors were unable to demonstrate a relationship between anatomical features and clinical glaucomatous progression.⁷⁰

In the Fluocinolone Acetonide for Diabetic Macular Edema (FAME) studies demonstrating the visual benefit of fluocinolone acetonide (FAc) implants in patients with diabetic macular edema, elevated IOP was a common adverse event.⁷¹ In the FAc 0.2 µg/day group, IOP lowering medications were required in 35.9% to 41.8% of patients compared with 12.5% to 15.2% of patients in the sham group. IOP-related surgery including trabeculectomy, glaucoma surgery, or vitrectomy for elevated IOP was required in 4.4% to 5.2% (8 and 10 eyes, respectively) of treatment (FAc 0.2 µg/day) group eyes compared with 0 to 1.2% (1 eye) of eyes in the sham group.⁷¹

Glaucoma Genetics

Nature Genetics published three studies that together significantly add to the volume of literature on the genetic basis of glaucoma. Chen and associates⁷² conducted a genome-wide association study for POAG in 1,007 high-pressure glaucoma patients and 1,009 controls. They observed a significant association at multiple single-nucleotide polymorphisms (SNP) near ABCA1 at 9q31.1 and suggestive evidence of an association in PMM2 at 16p13.2, findings that were replicated in two additional large sets of cases and controls. ABCA1 and PMM2 are expressed in the trabecular meshwork, optic nerve, and other ocular tissues, and ABCA1 is highly expressed in the retinal ganglion cell layer.⁷²

Gharahkhani and colleagues⁷³ evaluated 1,155 patients with POAG and 1,992 controls as well as four additional replication cohorts totaling 3,548 POAG patients and 9,486 controls in a genome-wide association study and identified three new common variants located upstream of ABCA1, within AFAP1, and within GMDS that confer an increased risk of POAG. As noted above, ABCA1 is expressed in retina, trabecular meshwork, and optic nerve, and AFAP1 is expressed in retinal ganglion cells.⁷³

Finally, Hysi et al.⁷⁴ described the results of a meta-analysis of 18 population cohorts from the International Glaucoma Genetics Consortium, comprising 35,296 multi-ancestry patients, which confirmed genetic association of known loci for IOP and POAG. Additionally, authors identified four new loci associated with IOP, two of which are on chromosome 9 near ABCA1. A separate meta-analysis totaling 4,284 cases and 95,560 controls revealed that three of the loci for IOP were also associated with POAG.⁷⁴

Researchers in the Thessaloniki Eye Study⁷⁵ found that the G153D SNP of LOXL1 gene was strongly associated with PEX and PEXG, but gene variants of the LOXL1 did not help identify PEX subjects at increased risk for glaucoma.

Glaucoma morbidity

Malihi and associates⁷⁶ investigated trends in blindness due to glaucoma in a longitudinal study of all residents of Olmsted County, Minnesota aged 40 years who were diagnosed with open angle glaucoma between January 1, 1965, and December 31, 2000. Blindness was defined as visual acuity 20/200 or visual field constriction to 20°. The probability of progression to glaucoma-related blindness in at least 1 eye at 20 years following diagnosis was significantly lower for subjects diagnosed from 1981 to 2000 compared with those diagnosed between 1965 and 1980 (13.5%, 95% CI, 8.8-17.9 and 25.8%, 95% CI, 18.5-32.5, respectively, $P = 0.01$).⁷⁶

In a study of 18,240 participants who underwent health evaluations including glaucoma screening and subsequent glaucoma evaluation, when indicated, the metabolic syndrome components hypertension and impaired glucose tolerance were associated with an increased risk of NTG.⁷⁷ Kim et al⁷⁷ suggest that metabolic syndrome components may play a role in the pathogenesis of NTG.

Charts of 43 eyes of 36 patients who underwent combined cataract extraction and glaucoma surgery (either trabeculectomy or glaucoma drainage device) were reviewed retrospectively to evaluate refractive outcomes.⁷⁸ Spherical equivalent between -1.00 and +0.50 D was achieved in 74% of eyes 3 to 6 months following surgery. Tzu and associates⁷⁸ judged these outcomes to be favorable given the potential alteration of measurements and introduction of error in a combined approach.

Conclusion

The studies described above are only a minority of the many interesting contributions to the glaucoma literature in the past year. While some of these studies provided answers to questions regarding the pathophysiology, diagnosis, and management of glaucoma that can be implemented by clinicians at present, many others laid the foundation for future research inquiries. The years ahead are certain to disclose insights in the genetic basis of glaucoma, neuroprotection, improved early diagnostic methods, and new treatment modalities.

Acknowledgments

Dr. Demetriades receives funding from a Research to Prevent Blindness Career Development Award and a BrightFocus Foundation National Glaucoma Research Grant.

References

1. Rao HL, Yadav RK, Begum VU, et al. Role of visual field reliability indices in ruling out glaucoma. *JAMA Ophthalmol.* 2015; 133(1):40–44. [PubMed: 25256758]
2. Musch DC, Gillespie BW, Palmberg PF, et al. Visual field improvement in the collaborative initial glaucoma treatment study. *Am J Ophthalmol.* 2014; 158(1):96–104.e2. [PubMed: 24727262]
3. Liu S, Yu M, Weinreb RN, et al. Frequency doubling technology perimetry for detection of visual field progression in glaucoma: a pointwise linear regression analysis. *Invest Ophthalmol Vis Sci.* 2014; 55(5):2862–2869. [PubMed: 24595388]
4. Meira-Freitas D, Tatham AJ, Lisboa R, et al. Predicting progression of glaucoma from rates of frequency doubling technology perimetry change. *Ophthalmology.* 2014; 121(2):498–507. [PubMed: 24289917]
5. Prokosch V, Eter N. Correlation between early retinal nerve fiber layer loss and visual field loss determined by three different perimetric strategies: white-on-white, frequency-doubling, or flicker-defined form perimetry. *Graefes Arch Clin Exp Ophthalmol.* 2014; 252(10):1599–1606. [PubMed: 25074041]
6. Hata M, Miyamoto K, Oishi A, et al. Comparison of Optic Disc Morphology of Optic Nerve Atrophy between Compressive Optic Neuropathy and Glaucomatous Optic Neuropathy. *PloS One.* 2014; 9(11):e112403. [PubMed: 25375855]
7. Danesh-Meyer HV, Yap J, Frampton C, Savino PJ. Differentiation of compressive from glaucomatous optic neuropathy with spectral-domain optical coherence tomography. *Ophthalmology.* 2014; 121(8):1516–1523. [PubMed: 24725827]
8. Akkaya S, Can E, Oztürk F. Comparison of Optic Nerve Head Topographic Parameters in Patients With Primary Open-Angle Glaucoma With and Without Diabetes Mellitus. *J Glaucoma.* 2014
9. Xu G, Weinreb RN, Leung KKS. Optic Nerve Head Deformation in Glaucoma: The Temporal Relationship between Optic Nerve Head Surface Depression and Retinal Nerve Fiber Layer Thinning. *Ophthalmology.* 2014; 121(12):2362–2370. [PubMed: 25108319]
10. Shin HY, Park HYL, Park CK. The effect of myopic optic disc tilt on measurement of spectral-domain optical coherence tomography parameters. *Br J Ophthalmol.* 2015; 99(1):69–74. [PubMed: 25091955]
11. Mayama C, Tsutsumi T, Saito H, et al. Glaucoma-induced optic disc morphometric changes and glaucoma diagnostic ability of Heidelberg Retina Tomograph II in highly myopic eyes. *PloS One.* 2014; 9(1):e86417. [PubMed: 24475117]
12. Rao HL, Yadav RK, Addepalli UK, et al. The ISNT rule in glaucoma: revisiting with spectral domain optical coherence tomography. *Acta Ophthalmol (Copenh).* 2014
13. Hwang YH, Kim YY. Application of the ISNT Rule to Neuroretinal Rim Thickness Determined Using Cirrus HD Optical Coherence Tomography. *J Glaucoma.* 2013
14. Pradhan ZS, Braganza A, Abraham LM. Does the ISNT Rule Apply to the Retinal Nerve Fiber Layer? *J Glaucoma.* 2014
15. Field MG, Alasil T, Baniyadi N, et al. Facilitating Glaucoma Diagnosis With Intereye Retinal Nerve Fiber Layer Asymmetry Using Spectral-Domain Optical Coherence Tomography. *J Glaucoma.* 2014
16. Srinivasan S, Addepalli UK, Rao HL, Garudadri CS, Mandal AK. Spectral domain optical coherence tomography in children operated for primary congenital glaucoma. *Br J Ophthalmol.* 2014; 98(2):162–165. [PubMed: 23740961]
17. Ramli NM, Sidek S, Rahman FA, et al. Novel use of 3T MRI in assessment of optic nerve volume in glaucoma. *Graefes Arch Clin Exp Ophthalmol.* 2014; 252(6):995–1000. [PubMed: 24770532]
18. Chen Z, Wang J, Lin F, et al. Correlation between lateral geniculate nucleus atrophy and damage to the optic disc in glaucoma. *J Neuroradiol.* 2013; 40(4):281–287. [PubMed: 23433902]
19. Rao HL, Yadav RK, Addepalli UK, et al. Comparing Spectral-Domain Optical Coherence Tomography and Standard Automated Perimetry to Diagnose Glaucomatous Optic Neuropathy. *J Glaucoma.* 2014
20. Suh W, Lee JM, Kee C. Depth and area of retinal nerve fiber layer damage and visual field correlation analysis. *Korean J Ophthalmol.* 2014; 28(4):323–329. [PubMed: 25120341]

21. Alasil T, Wang K, Yu F, et al. Correlation of retinal nerve fiber layer thickness and visual fields in glaucoma: a broken stick model. *Am J Ophthalmol*. 2014; 157(5):953–959. [PubMed: 24487047]
22. Miki A, Medeiros FA, Weinreb RN, et al. Rates of retinal nerve fiber layer thinning in glaucoma suspect eyes. *Ophthalmology*. 2014; 121(7):1350–1358. [PubMed: 24629619]
23. Selbach JM, Schallenberg M, Kramer S, et al. Trabeculectomy Improves Vessel Response Measured by Dynamic Vessel Analysis (DVA) in Glaucoma Patients. *Open Ophthalmol J*. 2014; 8:75–81. [PubMed: 25352934]
24. Hong J, Yang Y, Wei A, et al. Schlemm's canal expands after trabeculectomy in patients with primary angle-closure glaucoma. *Invest Ophthalmol Vis Sci*. 2014; 55(9):5637–5642. [PubMed: 25118266]
25. Hirneiß C, Reznicek L, Vogel M, Pesudovs K. The impact of structural and functional parameters in glaucoma patients on patient-reported visual functioning. *PloS One*. 2013; 8(12):e80757. [PubMed: 24312500]
26. Marvasti AH, Tatham AJ, Zangwill LM, et al. The relationship between visual field index and estimated number of retinal ganglion cells in glaucoma. *PloS One*. 2013; 8(10):e76590. [PubMed: 24146895]
27. Medeiros FA, Lisboa R, Zangwill LM, et al. Evaluation of progressive neuroretinal rim loss as a surrogate end point for development of visual field loss in glaucoma. *Ophthalmology*. 2014; 121(1):100–109. [PubMed: 23948465]
28. Araci IE, Su B, Quake SR, Mandel Y. An implantable microfluidic device for self-monitoring of intraocular pressure. *Nat Med*. 2014; 20(9):1074–1078. [PubMed: 25150497]
29. Chen GZ, Chan IS, Leung LKK, Lam DCC. Soft wearable contact lens sensor for continuous intraocular pressure monitoring. *Med Eng Phys*. 2014; 36(9):1134–1139. [PubMed: 25034639]
30. Åström S, Stenlund H, Lindén C. Intraocular pressure changes over 21 years - a longitudinal age-cohort study in northern Sweden. *Acta Ophthalmol (Copenh)*. 2014; 92(5):417–420.
31. Kim YJ, Sung KR, Lee KS, et al. Long-term effects of multiple intravitreal antivascular endothelial growth factor injections on intraocular pressure. *Am J Ophthalmol*. 2014; 157(6):1266–1271.e1. [PubMed: 24561173]
32. Bakri SJ, Moshfeghi DM, Francom S, et al. Intraocular pressure in eyes receiving monthly ranibizumab in 2 pivotal age-related macular degeneration clinical trials. *Ophthalmology*. 2014; 121(5):1102–1108. [PubMed: 24393349]
33. Kim D, Nam WH, Kim HK, Yi K. Does intravitreal injections of bevacizumab for age-related macular degeneration affect long-term intraocular pressure? *J Glaucoma*. 2014; 23(7):446–448. [PubMed: 23632401]
34. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthalmol Auckl NZ*. 2014; 8:883–890.
35. Isobe T, Mizuno K, Kaneko Y, et al. Effects of K-115, a rho-kinase inhibitor, on aqueous humor dynamics in rabbits. *Curr Eye Res*. 2014; 39(8):813–822. [PubMed: 24502505]
36. Sumi K, Inoue Y, Nishio M, et al. IOP-lowering effect of isoquinoline-5-sulfonamide compounds in ocular normotensive monkeys. *Bioorg Med Chem Lett*. 2014; 24(3):831–834. [PubMed: 24412071]
37. Honjo M, Tanihara H, Inatani M, et al. Effects of rho-associated protein kinase inhibitor Y-27632 on intraocular pressure and outflow facility. *Invest Ophthalmol Vis Sci*. 2001; 42(1):137–144. [PubMed: 11133858]
38. Koga T, Koga T, Awai M, et al. Rho-associated protein kinase inhibitor, Y-27632, induces alterations in adhesion, contraction and motility in cultured human trabecular meshwork cells. *Exp Eye Res*. 2006; 82(3):362–370. [PubMed: 16125171]
39. Tanihara H, Inoue T, Yamamoto T, et al. Phase 1 clinical trials of a selective Rho kinase inhibitor, K-115. *JAMA Ophthalmol*. 2013; 131(10):1288–1295. [PubMed: 23787820]
40. Tanihara H, Inoue T, Yamamoto T, et al. Phase 2 randomized clinical study of a Rho kinase inhibitor, K-115, in primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol*. 2013; 156(4):731–736. [PubMed: 23831221]

41. Bacharach J, Dubiner HB, Levy B, et al. Double-masked, Randomized, Dose-Response Study of AR-13324 versus Latanoprost in Patients with Elevated Intraocular Pressure. *Ophthalmology*. 2015; 122(2):302–307. [PubMed: 25270273]
42. Ozyol E, Ozyol P. The Efficacy of a Latanoprost/Timolol Fixed Combination Versus Latanoprost and Timolol Gel-forming Solution Unfixed Combination on Daytime Intraocular Pressure. *J Glaucoma*. 2014
43. Khawaja AP, Chan MPY, Broadway DC, et al. Systemic medication and intraocular pressure in a British population: the EPIC-Norfolk Eye Study. *Ophthalmology*. 2014; 121(8):1501–1507. [PubMed: 24702754]
44. Fedorchak MV, Conner IP, Medina CA, et al. 28-day intraocular pressure reduction with a single dose of brimonidine tartrate-loaded microspheres. *Exp Eye Res*. 2014; 125:210–216. [PubMed: 24983144]
45. Hirneiß C, Sekura K, Brandlhuber U, Kampik A, Kernt M. Corneal biomechanics predict the outcome of selective laser trabeculoplasty in medically uncontrolled glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2013; 251(10):2383–2388. [PubMed: 23835756]
46. Pakravan M, Afroozifar M, Yazdani S. Corneal Biomechanical Changes Following Trabeculectomy, Phaco-trabeculectomy, Ahmed Glaucoma Valve Implantation and Phacoemulsification. *J Ophthalmic Vis Res*. 2014; 9(1):7–13. [PubMed: 24982726]
47. Shimmyo M. Recovery of corneal hysteresis after reduction of intraocular pressure in chronic primary angle-closure glaucoma. *Am J Ophthalmol*. 2009; 148(4):623. author reply 623. [PubMed: 19782799]
48. Sun L, Shen M, Wang J, et al. Recovery of corneal hysteresis after reduction of intraocular pressure in chronic primary angle-closure glaucoma. *Am J Ophthalmol*. 2009; 147(6):1061–1066. 1066.e1–2. [PubMed: 19327738]
49. Ozkok A, Tamcelik N, Ozdamar A, Sarici AM, Cicik E. Corneal viscoelastic differences between pseudoexfoliative glaucoma and primary open-angle glaucoma. *J Glaucoma*. 2013; 22(9):740–745. [PubMed: 24299728]
50. Cheng H, Ding Y, Yu R, Chen J, Wu C. Neuroprotection of a novel cyclopeptide C*HSDGIC* from the cyclization of PACAP (1-5) in cellular and rodent models of retinal ganglion cell apoptosis. *PloS One*. 2014; 9(10):e108090. [PubMed: 25286089]
51. You Y, Gupta VK, Li JC, et al. FTY720 protects retinal ganglion cells in experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2014; 55(5):3060–3066. [PubMed: 24744204]
52. Xia X, Wen R, Chou TH, et al. Protection of pattern electroretinogram and retinal ganglion cells by oncostatin M after optic nerve injury. *PloS One*. 2014; 9(9):e108524. [PubMed: 25243471]
53. Tan PP, Yuan HH, Zhu X, et al. Activation of muscarinic receptors protects against retinal neurons damage and optic nerve degeneration in vitro and in vivo models. *CNS Neurosci Ther*. 2014; 20(3):227–236. [PubMed: 24279639]
54. Lee JW, Chan CW, Wong MO, et al. A randomized control trial to evaluate the effect of adjuvant selective laser trabeculoplasty versus medication alone in primary open-angle glaucoma: preliminary results. *Clin Ophthalmol Auckl NZ*. 2014; 8:1987–1992.
55. Lee JWY, Gangwani RA, Chan JCH, Lai JSM. Prospective Study on the Efficacy of Treating Normal Tension Glaucoma With a Single Session of Selective Laser Trabeculoplasty. *J Glaucoma*. 2014
56. Jinapriya D, D'Souza M, Hollands H, et al. Anti-inflammatory Therapy after Selective Laser Trabeculoplasty: A Randomized, Double-Masked, Placebo-Controlled Clinical Trial. *Ophthalmology*. 2014; 121(12):2356–2361. [PubMed: 25234015]
57. Susanna R, De Moraes CG, Alencar LM, Ritch R. Nd:YAG laser goniopuncture for late bleb failure after trabeculectomy with adjunctive mitomycin C. *JAMA Ophthalmol*. 2014; 132(3):286–290. [PubMed: 24370879]
58. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. *Am J Ophthalmol*. 2012; 153(5):789–803.e2. [PubMed: 22245458]

59. Saheb H, Gedde SJ, Schiffman JC, Feuer WJ, Tube Versus Trabeculectomy Study Group. Outcomes of glaucoma reoperations in the Tube Versus Trabeculectomy (TVT) Study. *Am J Ophthalmol*. 2014; 157(6):1179–1189.e2. [PubMed: 24531027]
60. Yamada H, Sawada A, Kuwayama Y, Yamamoto T. Blindness following bleb-related infection in open angle glaucoma. *Jpn J Ophthalmol*. 2014; 58(6):490–495. [PubMed: 25249179]
61. Schultz SK, Iverson SM, Shi W, Greenfield DS. Safety And Efficacy Of Achieving Single-Digit Intraocular Pressure Targets With Filtration Surgery In Eyes With Progressive Normal-Tension Glaucoma. *J Glaucoma*. 2014
62. Christakis PG, Tsai JC, Kalenak JW, et al. The Ahmed versus Baerveldt study: three-year treatment outcomes. *Ophthalmology*. 2013; 120(11):2232–2240. [PubMed: 23796764]
63. Chen G, Li W, Jiang F, Mao S, Tong Y. Ex-PRESS implantation versus trabeculectomy in open-angle glaucoma: a meta-analysis of randomized controlled clinical trials. *PLoS One*. 2014; 9(1):e86045. [PubMed: 24465860]
64. Wang W, Zhang X. Meta-analysis of randomized controlled trials comparing EX-PRESS implantation with trabeculectomy for open-angle glaucoma. *PLoS One*. 2014; 9(6):e100578. [PubMed: 24972022]
65. Patel HY, Wagschal LD, Trope GE, Buys YM. Economic analysis of the Ex-PRESS miniature glaucoma device versus trabeculectomy. *J Glaucoma*. 2014; 23(6):385–390. [PubMed: 25079306]
66. Grover DS, Godfrey DG, Smith O, et al. Gonioscopy-assisted transluminal trabeculectomy, ab interno trabeculectomy: technique report and preliminary results. *Ophthalmology*. 2014; 121(4):855–861. [PubMed: 24412282]
67. Ahuja Y, Ma Khin Pyi S, Malihi M, Hodge DO, Sit AJ. Clinical results of ab interno trabeculectomy using the trabectome for open-angle glaucoma: the Mayo Clinic series in Rochester, Minnesota. *Am J Ophthalmol*. 2013; 156(5):927–935.e2. [PubMed: 23954209]
68. Iordanous Y, Kent JS, Hutnik CML, Malvankar-Mehta MS. Projected cost comparison of Trabectome, iStent, and endoscopic cyclophotocoagulation versus glaucoma medication in the Ontario Health Insurance Plan. *J Glaucoma*. 2014; 23(2):e112–118. [PubMed: 23807348]
69. Osman EA, Mousa A, Al-Mansouri SM, Al-Mezaine HS. Glaucoma After Open-Globe Injury at a Tertiary Care University Hospital: Cumulative Causes and Management. *J Glaucoma*. 2014
70. Qian CX, Hassanaly S, Harissi-Dagher M. Anterior Segment Optical Coherence Tomography in the Long-Term Follow-up and Detection of Glaucoma in Boston Type I Keratoprosthesis. *Ophthalmology*. 2015; 122(2):317–325. [PubMed: 25264027]
71. Cunha-Vaz J, Ashton P, Iezzi R, et al. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology*. 2014; 121(10):1892–1903. [PubMed: 24935282]
72. Chen Y, Lin Y, Vithana EN, et al. Common variants near ABCA1 and in PMM2 are associated with primary open-angle glaucoma. *Nat Genet*. 2014; 46(10):1115–1119. [PubMed: 25173107]
73. Gharahkhani P, Burdon KP, Fogarty R, et al. Common variants near ABCA1, AFAP1 and GMDS confer risk of primary open-angle glaucoma. *Nat Genet*. 2014; 46(10):1120–1125. [PubMed: 25173105]
74. Hysi PG, Cheng CY, Springelkamp H, et al. Genome-wide analysis of multi-ancestry cohorts identifies new loci influencing intraocular pressure and susceptibility to glaucoma. *Nat Genet*. 2014; 46(10):1126–1130. [PubMed: 25173106]
75. Anastasopoulos E, Coleman AL, Wilson MR, et al. Association of LOXL1 polymorphisms with pseudoexfoliation, glaucoma, intraocular pressure, and systemic diseases in a Greek population. The Thessaloniki eye study. *Invest Ophthalmol Vis Sci*. 2014; 55(7):4238–4243. [PubMed: 24917141]
76. Malihi M, Moura Filho ER, Hodge DO, Sit AJ. Long-term trends in glaucoma-related blindness in Olmsted County, Minnesota. *Ophthalmology*. 2014; 121(1):134–141. [PubMed: 24823760]
77. Kim M, Jeoung JW, Park KH, et al. Metabolic syndrome as a risk factor in normal-tension glaucoma. *Acta Ophthalmol (Copenh)*. 2014; 92(8):e637–643.
78. Tzu JH, Shah CT, Galor A, et al. Refractive Outcomes of Combined Cataract and Glaucoma Surgery. *J Glaucoma*. 2013

Table 1

Reviewed articles by category.

Category	Authors	Title	Journal Name
Automated perimetry	Rao HL, Yadav RK, Begum VU, et al.	Role of visual field reliability indices in ruling out glaucoma.	JAMA Ophthalmol.
	Musch DC, Gillespie BW, Palmberg PF, et al.	Visual field improvement in the collaborative initial glaucoma treatment study.	Am. J. Ophthalmol.
	Liu S, Yu M, Weinreb RN, et al.	Frequency doubling technology perimetry for detection of visual field progression in glaucoma: a pointwise linear regression analysis.	Invest. Ophthalmol. Vis. Sci.
	Meira-Freitas D, Tatham AJ, Lisboa R, et al.	Predicting progression of glaucoma from rates of frequency doubling technology perimetry change.	Ophthalmology.
	Prokosch V, Eter N.	Correlation between early retinal nerve fiber layer loss and visual field loss determined by three different perimetric strategies: white-on-white, frequency-doubling, or flicker-defined form perimetry.	Graefes Arch Clin Exp Ophthalmol.
Optic nerve head and imaging	Hata M, Miyamoto K, Oishi A, et al.	Comparison of Optic Disc Morphology of Optic Nerve Atrophy between Compressive Optic Neuropathy and Glaucomatous Optic Neuropathy.	PloS One.
	Danesh-Meyer HV, Yap J, Frampton C, Savino PJ.	Differentiation of compressive from glaucomatous optic neuropathy with spectral-domain optical coherence tomography.	Ophthalmology.
	Akkaya S, Can E, Oztürk F.	Comparison of Optic Nerve Head Topographic Parameters in Patients With Primary Open-Angle Glaucoma With and Without Diabetes Mellitus.	J. Glaucoma.
	Xu G, Weinreb RN, Leung CKS.	Optic Nerve Head Deformation in Glaucoma: The Temporal Relationship between Optic Nerve Head Surface Depression and Retinal Nerve Fiber Layer Thinning.	Ophthalmology.
	Shin H-Y, Park H-YL, Park CK.	The effect of myopic optic disc tilt on measurement of spectral-domain optical coherence tomography parameters.	Br. J. Ophthalmol.
	Mayama C, Tsutsumi T, Saito H, et al.	Glaucoma-induced optic disc morphometric changes and glaucoma diagnostic ability of Heidelberg Retina Tomograph II in highly myopic eyes.	PloS One.
	Rao HL, Yadav RK, Addepalli UK, et al.	The ISNT rule in glaucoma: revisiting with spectral domain optical coherence tomography.	Acta Ophthalmol. (Copenh.).
	Hwang YH, Kim YY.	Application of the ISNT Rule to Neuroretinal Rim Thickness Determined Using Cirrus HD Optical Coherence Tomography.	J. Glaucoma.
	Pradhan ZS, Braganza A, Abraham LM.	Does the ISNT Rule Apply to the Retinal Nerve Fiber Layer?	J. Glaucoma.
	Field MG, Alasil T, Baniasadi N, et al.	Facilitating Glaucoma Diagnosis With Intereye Retinal Nerve Fiber Layer	J. Glaucoma.

Category	Authors	Title	Journal Name
Structure and function		Asymmetry Using Spectral-Domain Optical Coherence Tomography.	
	Srinivasan S, Addepalli UK, Rao HL, Garudadri CS, Mandal AK.	Spectral domain optical coherence tomography in children operated for primary congenital glaucoma.	Br. J. Ophthalmol.
	Ramli NM, Sidek S, Rahman FA, et al.	Novel use of 3T MRI in assessment of optic nerve volume in glaucoma.	Graefes Arch Clin Exp Ophthalmol.
	Chen Z, Wang J, Lin F, et al.	Correlation between lateral geniculate nucleus atrophy and damage to the optic disc in glaucoma.	J. Neuroradiol.
	Rao HL, Yadav RK, Addepalli UK, et al.	Comparing Spectral-Domain Optical Coherence Tomography and Standard Automated Perimetry to Diagnose Glaucomatous Optic Neuropathy.	J. Glaucoma.
	Suh W, Lee JM, Kee C.	Depth and area of retinal nerve fiber layer damage and visual field correlation analysis.	Korean J. Ophthalmol.
	Alasil T, Wang K, Yu F, et al.	Correlation of retinal nerve fiber layer thickness and visual fields in glaucoma: a broken stick model.	Am. J. Ophthalmol.
	Miki A, Medeiros FA, Weinreb RN, et al.	Rates of retinal nerve fiber layer thinning in glaucoma suspect eyes.	Ophthalmology.
	Selbach JM, Schallenberg M, Kramer S, et al.	Trabeculectomy Improves Vessel Response Measured by Dynamic Vessel Analysis (DVA) in Glaucoma Patients.	Open Ophthalmol. J.
	Hong J, Yang Y, Wei A, et al.	Schlemm's canal expands after trabeculectomy in patients with primary angle-closure glaucoma.	Invest. Ophthalmol. Vis. Sci.
Intraocular pressure	Hirneiß C, Reznicek L, Vogel M, Pesudovs K.	The impact of structural and functional parameters in glaucoma patients on patient-reported visual functioning.	PloS One.
	Marvasti AH, Tatham AJ, Zangwill LM, et al.	The relationship between visual field index and estimated number of retinal ganglion cells in glaucoma.	PloS One.
	Medeiros FA, Lisboa R, Zangwill LM, et al.	Evaluation of progressive neuroretinal rim loss as a surrogate end point for development of visual field loss in glaucoma.	Ophthalmology.
	Araci IE, Su B, Quake SR, Mandel Y.	An implantable microfluidic device for self-monitoring of intraocular pressure.	Nat. Med.
	Chen G-Z, Chan I-S, Leung LKK, Lam DCC.	Soft wearable contact lens sensor for continuous intraocular pressure monitoring.	Med. Eng. Phys.
	Åström S, Stenlund H, Lindén C.	Intraocular pressure changes over 21 years - a longitudinal age-cohort study in northern Sweden.	Acta Ophthalmol. (Copenh.).
	Kim YJ, Sung KR, Lee KS, et al.	Long-term effects of multiple intravitreal anti-vascular endothelial growth factor injections on intraocular pressure.	Am. J. Ophthalmol.
	Bakri SJ, Moshfeghi DM, Francom S, et al.	Intraocular pressure in eyes receiving monthly ranibizumab in 2 pivotal age-related macular degeneration clinical trials.	Ophthalmology.
	Kim D, Nam WH, Kim HK, Yi K.	Does intravitreal injections of bevacizumab for age-related macular	J. Glaucoma.

Category	Authors	Title	Journal Name
Pharmacologic intraocular pressure lowering		degeneration affect long-term intraocular pressure?	
	Isobe T, Mizuno K, Kaneko Y, et al.	Effects of K-115, a rho-kinase inhibitor, on aqueous humor dynamics in rabbits.	Curr. Eye Res.
	Sumi K, Inoue Y, Nishio M, et al.	IOP-lowering effect of isoquinoline-5-sulfonamide compounds in ocular normotensive monkeys.	Bioorg. Med. Chem. Lett.
	Tanihara H, Inoue T, Yamamoto T, et al.	Phase 1 clinical trials of a selective Rho kinase inhibitor, K-115.	JAMA Ophthalmol.
	Tanihara H, Inoue T, Yamamoto T, et al.	Phase 2 randomized clinical study of a Rho kinase inhibitor, K-115, in primary open-angle glaucoma and ocular hypertension.	Am. J. Ophthalmol.
	Bacharach J, Dubiner HB, Levy B, et al.	Double-masked, Randomized, Dose-Response Study of AR-13324 versus Latanoprost in Patients with Elevated Intraocular Pressure.	Ophthalmology.
	Ozyol E, Ozyol P.	The Efficacy of a Latanoprost/Timolol Fixed Combination Versus Latanoprost and Timolol Gel-forming Solution Unfixed Combination on Daytime Intraocular Pressure.	J. Glaucoma.
	Khawaja AP, Chan MPY, Broadway DC, et al.	Systemic medication and intraocular pressure in a British population: the EPIC-Norfolk Eye Study.	Ophthalmology.
Corneal thickness and biomechanics	Fedorchak MV, Conner IP, Medina CA, et al.	28-day intraocular pressure reduction with a single dose of brimonidine tartrate-loaded microspheres.	Exp. Eye Res.
	Hirneiß C, Sekura K, Brandlhuber U, Kampik A, Kernt M.	Corneal biomechanics predict the outcome of selective laser trabeculoplasty in medically uncontrolled glaucoma.	Graefes Arch Clin Exp Ophthalmol.
	Pakravan M, Afroozifar M, Yazdani S.	Corneal Biomechanical Changes Following Trabeculectomy, Phaco-trabeculectomy, Ahmed Glaucoma Valve Implantation and Phacoemulsification.	J. Ophthalmic Vis. Res.
Neuroprotection	Ozkok A, Tamcelik N, Ozdamar A, Sarici AM, Cicik E.	Corneal viscoelastic differences between pseudoexfoliative glaucoma and primary open-angle glaucoma.	J. Glaucoma.
	Cheng H, Ding Y, Yu R, Chen J, Wu C.	Neuroprotection of a novel cyclopeptide C*HSDGIC* from the cyclization of PACAP (1-5) in cellular and rodent models of retinal ganglion cell apoptosis.	PloS One.
	You Y, Gupta VK, Li JC, et al.	FTY720 protects retinal ganglion cells in experimental glaucoma.	Invest. Ophthalmol. Vis. Sci.
	Xia X, Wen R, Chou T-H, et al.	Protection of pattern electroretinogram and retinal ganglion cells by oncostatin M after optic nerve injury.	PloS One.
	Tan P-P, Yuan H-H, Zhu X, et al.	Activation of muscarinic receptors protects against retinal neurons damage and optic nerve degeneration in vitro and in vivo models.	CNS Neurosci. Ther.

Category	Authors	Title	Journal Name
Glaucoma laser therapy	Lee JW, Chan CW, Wong MO, et al.	A randomized control trial to evaluate the effect of adjuvant selective laser trabeculoplasty versus medication alone in primary open-angle glaucoma: preliminary results.	Clin. Ophthalmol. Auckland. NZ.
	Lee JWY, Gangwani RA, Chan JCH, Lai JSM.	Prospective Study on the Efficacy of Treating Normal Tension Glaucoma With a Single Session of Selective Laser Trabeculoplasty.	J. Glaucoma.
	Jinapriya D, D'Souza M, Hollands H, et al.	Anti-inflammatory Therapy after Selective Laser Trabeculoplasty: A Randomized, Double-Masked, Placebo-Controlled Clinical Trial.	Ophthalmology.
	Susanna R, De Moraes CG, Alencar LM, Ritch R.	Nd:YAG laser goniopuncture for late bleb failure after trabeculectomy with adjunctive mitomycin C.	JAMA Ophthalmol.
Glaucoma surgery: Trabeculectomy	Saheb H, Gedde SJ, Schiffman JC, Feuer WJ, Tube Versus Trabeculectomy Study Group.	Outcomes of glaucoma reoperations in the Tube Versus Trabeculectomy (TVT) Study.	Am. J. Ophthalmol.
	Yamada H, Sawada A, Kuwayama Y, Yamamoto T.	Blindness following bleb-related infection in open angle glaucoma.	Jpn. J. Ophthalmol.
	Schultz SK, Iverson SM, Shi W, Greenfield DS.	Safety And Efficacy Of Achieving Single-Digit Intraocular Pressure Targets With Filtration Surgery In Eyes With Progressive Normal-Tension Glaucoma.	J. Glaucoma.
Glaucoma surgery: Implants	Christakis PG, Tsai JC, Kalenak JW, et al.	The Ahmed versus Baerveldt study: three-year treatment outcomes.	Ophthalmology.
	Chen G, Li W, Jiang F, Mao S, Tong Y.	Ex-PRESS implantation versus trabeculectomy in open-angle glaucoma: a meta-analysis of randomized controlled clinical trials.	PloS One.
	Wang W, Zhang X.	Meta-analysis of randomized controlled trials comparing EX-PRESS implantation with trabeculectomy for open-angle glaucoma.	PloS One.
	Patel HY, Wagschal LD, Trope GE, Buys YM.	Economic analysis of the Ex-PRESS miniature glaucoma device versus trabeculectomy.	J. Glaucoma.
Minimally invasive glaucoma surgery	Grover DS, Godfrey DG, Smith O, et al.	Gonioscopy-assisted transluminal trabeculotomy, ab interno trabeculotomy: technique report and preliminary results.	Ophthalmology.
	Ahuja Y, Ma Khin Pyi S, Malihi M, Hodge DO, Sit AJ.	Clinical results of ab interno trabeculotomy using the trabectome for open-angle glaucoma: the Mayo Clinic series in Rochester, Minnesota.	Am. J. Ophthalmol.
	Iordanous Y, Kent JS, Hutnik CML, Malvankar-Mehta MS.	Projected cost comparison of Trabectome, iStent, and endoscopic cyclophotocoagulation versus glaucoma medication in the Ontario Health Insurance Plan.	J. Glaucoma.

Category	Authors	Title	Journal Name
Secondary glaucoma	Osman EA, Mousa A, Al-Mansouri SM, Al-Mezaine HS.	Glaucoma After Open-Globe Injury at a Tertiary Care University Hospital: Cumulative Causes and Management.	J. Glaucoma.
	Qian CX, Hassanaly S, Harissi-Dagher M.	Anterior Segment Optical Coherence Tomography in the Long-Term Follow-up and Detection of Glaucoma in Boston Type I Keratoprosthesis.	Ophthalmology.
	Cunha-Vaz J, Ashton P, Iezzi R, et al.	Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema.	Ophthalmology.
Glaucoma Genetics	Chen Y, Lin Y, Vithana EN, et al.	Common variants near ABCA1 and in PMM2 are associated with primary open-angle glaucoma.	Nat. Genet.
	Gharahkhani P, Burdon KP, Fogarty R, et al.	Common variants near ABCA1, AFAP1 and GMD5 confer risk of primary open-angle glaucoma.	Nat. Genet.
	Hysi PG, Cheng C-Y, Springelkamp H, et al.	Genome-wide analysis of multi-ancestry cohorts identifies new loci influencing intraocular pressure and susceptibility to glaucoma.	Nat. Genet.
	Anastasopoulos E, Coleman AL, Wilson MR, et al.	Association of LOXL1 polymorphisms with pseudoexfoliation, glaucoma, intraocular pressure, and systemic diseases in a Greek population. The Thessaloniki eye study.	Invest. Ophthalmol. Vis. Sci.
Glaucoma morbidity	Malihi M, Moura Filho ER, Hodge DO, Sit AJ.	Long-term trends in glaucoma-related blindness in Olmsted County, Minnesota.	Ophthalmology.
	Kim M, Jeoung JW, Park KH, et al.	Metabolic syndrome as a risk factor in normal-tension glaucoma.	Acta Ophthalmol. (Copenh.).
	Tzu JH, Shah CT, Galor A, et al.	Refractive Outcomes of Combined Cataract and Glaucoma Surgery.	J. Glaucoma.