Surgery

1. Prospective Randomized Study Comparing ExPRESS to Trabeculectomy: 1 Year Results

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**Purpose:** To compare the efficacy and safety of the ExPRESS shunt to standard trabeculectomy.

**Methods:** Consenting patients with open-angle glaucoma scheduled for filtration surgery were prospectively randomized to trabeculectomy or ExPRESS both with MMC. Exclusion criteria included any previous ocular incisional surgery with the exception of clear cornea phaco or one previous trab, uveitis and vitreous in the anterior chamber. The main outcome was IOP. Secondary outcomes included visual acuity (VA), number of glaucoma medications, complications, corneal pachymetry (CCT), endothelial cell counts (ECC), bleb morphology and additional procedures. Standardized data collection sheets were completed at baseline and day 1, weeks 1 & 2 and months 1, 2, 3, 6 and 12 post-op. A sample size calculation determined that 52 eyes were required to detect a 2 mmHg difference with a power of 80%.

**Results:** 61 of 64 enrolled patients completed 1-year follow-up (31 ExPRESS and 30 Trab). There were no differences in baseline characteristics. The mean baseline IOP decreased from 22.6±10.2 and 22.0±6.8 to 11.0±5.5 and 10.0±4.5 at 1-yr in the ExPRESS and Trab groups respectively (p<0.0001). There was no significant difference in IOP between ExPRESS and Trab groups at any time point. Complete success (IOP 5-18 and 20% reduction from baseline without medication) was obtained in 71% ExPRESS and 57% Trab (p=0.24) and qualified success (+ meds) in 87% ExPRESS and 93% Trab (p=0.67). 8 (26%) of the ExPRESS and 10 (33%) of the Trab patients were using glaucoma medications at 1-yr (p=0.58). Of the secondary outcomes the only significant difference was visual recovery which was faster in the ExPRESS group.

**Discussion:** There are 2 previously published RCTs comparing ExPRESS to Trab1-3. De Jong’s study of 80 eyes reported better IOP control at one year1, however after 3 years there was no longer a difference between the groups.2 Dahan randomized fellow eyes of 15 patients and after a mean follow-up of 23.6 months found no difference in IOP but reported better success with ExPRESS.3 Both studies found no statistically significant difference in glaucoma medications or complications.

**Conclusions:** At 1-year we found no statistically significant difference between ExPRESS and Trab groups regarding IOP, success rates, number of glaucoma medications, final VA, CCT, ECC, bleb morphology, complications and additional procedures. However, postoperative VA recovery was faster in the ExPRESS group.

**References:**
2. Long Term Results from a Prospective, Multicenter Study of a Schlemm's Canal Microstent for IOP Reduction in Open Angle Glaucoma in Phakic and Pseudophakic Eyes

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Purpose: To evaluate the safety and effectiveness of a new implantable device for the treatment of mild to moderate open angle glaucoma.

Methods: This is a prospective, multicenter, single arm clinical evaluation of a Schlemm’s canal microstent (Hydrus™, Ivantis Inc., Irvine, CA) in phakic and pseudophakic eyes with mild to moderate open angle glaucoma. Major inclusion criteria were washed out IOP between 21 and 32 mmHg, a glaucomatous disc, and mean deviation (MD) no worse than -12 dB on automated perimetry. The study device was placed into Schlemm’s canal via an ab interno approach under gonioscopic guidance. Follow up visits were on days 1 and 7 as well as 1, 3, 6, 12, and 18 months postoperatively. Study eyes were assessed regarding IOP, medication usage, and changes in visual status on all follow up visits.

Results: Forty eyes from 40 patients were recruited into the study. Mean (±s.d.) age was 65.5 ± 10.8 years and MD on perimetry was -3.8 ± 5.2 dB. Baseline mean IOP was 21.6 ± 4.11 mmHg on 1.7 ± 1.4 glaucoma medications. There were no serious operative or postoperative complications. At 1, 3, 6, and 12 months follow up, IOP (N) was 19.2 ± 6.4 (40), 16.8 ± 4.1 (40), 16.8 ± 4.0 (38), and 17.9 ± 5.1 (37) mmHg on a mean of 0.3 ± 0.8, 0.6 ± 1.0, 0.7 ± 1.1, and 0.2 ± 0.6 glaucoma medications, respectively. Further follow up at 18 months (N= 33/40 patients) showed that mean IOP remained at 17.8 ± 0.3 mmHg with 0.4 mean medications per patient.

Discussion: Hydrus microstent implantation is associated with both IOP and medication reduction in the first postoperative year. At 18 months, with over 80% of patients completing 18 month follow up, the treatment effect is consistent with findings from 1-12 months.

Conclusions: A permanent implant that provides continuous, durable IOP control could offer an alternative to hypotensive medications for glaucoma patients. Long-term follow up suggests the treatment is safe and the effect is durable for 18 months.

3. Safety and Clinical Effect of Suprachoroidal Micro-stent Implantation in Conjunction with Phacoemulsification Cataract Surgery in Open-angle Glaucoma Patients on One or Two Intraocular Pressure-lowering Medications

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Purpose: This study is designed to determine the safety and clinical effect of the suprachoroidal CyPass Micro-Stent (Transcend Medical, Inc. Menlo Park, CA) implanted in conjunction with cataract surgery in patients with open-angle glaucoma (OAG).

Methods: Subjects on 1 or 2 intraocular pressure (IOP)-lowering medications underwent standard phacoemulsification cataract surgery. After the completion of IOL implantation, a suprachoroidal micro-stent was inserted through the phaco incision and implanted into the suprachriary space under gonioscopic guidance. Inclusion criteria were Schaeffer grade 3 or 4 open-angle glaucoma being treated with 1 or 2 IOP-lowering medications, medicated IOP less than 33 mmHg and operable cataract in the study eye. Subjects were followed for up to 12 months. There were two cohorts, cohort 1 (uncontrolled IOP with baseline IOP ≥ 21 mmHg) and cohort 2 (controlled IOP with baseline IOP < 21 mmHg). Outcome measures included adverse events, complications, IOP, and use of IOP-lowering medications.

Results: 145 patients were enrolled and successfully implanted with the micro-stent after uneventful phaco cataract surgery. No major adverse events such as choroidal hemorrhage, hypotony maculopathy or endophthalmitis were reported. The most common complication was transient hypotony (11%) with all cases resolved within 1 month postoperative. Mean IOP at baseline for cohort 1 (n=51) was 25.9 ± 5.5 mmHg. To date, 22 patients have reached the 12 month visit with a mean IOP of 15.7 ± 2.6 mmHg. Mean baseline medication use for cohort 1 was 1.6 ± 0.5 and the mean medications used for the 12 month patients was 0.9 ± 0.9. For cohort 2 (n=94), mean baseline medications was 1.5 ± 0.5 To date, 43 patients have reached the 12 month visit with mean medications of 0.6 ± 0.8 and continued maintenance of IOP control.

Discussion: In patients on 1 and 2 medications with uncontrolled IOP, suprachoroidal micro-stent implantation in conjunction with cataract surgery can safely reduce both IOP and medication use. In patients with controlled IOP on 1 and 2 medications, combined intervention can reduce topical medication use.

Conclusions: The suprachoroidal CyPass Micro-Stent provides a useful addition to the surgical armamentarium for the reduction of IOP in patients with OAG.
4. IOP and Medication Reduction After Micro-Invasive Glaucoma Surgery with Two Trabecular Micro-Bypass Stents in OAG

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Wills Eye Institute, Philadelphia, PA

**Purpose:** Safe and effective outcomes through two years postoperative have been shown following implantation of a single trabecular micro-bypass stent during cataract surgery in subjects with OAG and cataract. [1][2][3] This prospective study by the micro-invasive glaucoma surgery (MIGS) study group evaluated IOP reduction and safety of two stents in phakic or pseudophakic subjects with OAG not controlled on one ocular hypotensive medication.

**Methods:** Enrollment criteria included OAG not controlled on one medication, CD ratio $\leq 0.9$, medicated IOP $>18$ to $\leq 30$ mmHg, and IOP following medication washout $\geq 22$ to $\leq 38$ mmHg in either phakic or pseudophakic eyes. Forty qualified subjects were implanted with two stents (Glaukos) through a 1-mm clear corneal incision. Ocular hypotensive medication was prescribed if IOP exceeded 21 mmHg. Efficacy assessments were one-year unmedicated IOP reduction $\geq 20\%$, unmedicated IOP $\leq 18$ mmHg, and mean change in IOP. Safety assessment included fundus exam/optic nerve evaluation, slit-lamp findings, BCVA, and complications/adverse events through two years.

**Results:** Mean preoperative medicated IOP was 20.7 mmHg (SD 2.1), and unmedicated (baseline) IOP was 24.2 mmHg (SD 1.5). Twenty-eight subjects have been followed through one year. IOP decreased to 14.0 mmHg (SD 3.3) at 1 month, 13.8 mmHg (SD 3.2) at 3 months, 13.4 mmHg (SD 1.5) at 6 months and 13.6 (SD 2.0) at 12 months. At 12 months, 25 of 28 subjects were on no medications, two subjects were on one medication each, and one subject was on two medications. A small hyphema in one subject at one week resolved by one month.

**Discussion:** Implantation of two stents resulted in significant reduction of IOP and medication burden through 12 months and a favorable safety profile.

**Conclusions:** Phakic/pseudophakic eyes with OAG not controlled on medication may achieve IOP control with reduced medication burden after MIGS implantation of two trabecular micro-bypass stents.

**References**
6. Comparing the Rate of Rim Area Change in Eyes with Visual Field and Optic Disc Endpoints: The Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study

**LINDA M. ZANGWILL, Sonia Jain, Keri Dirkes, Feng He, Robert N. Weinreb, Felipe A. Medeiros, Gary L. Trick, James D. Brandt, George A. Cioffi, Anne L. Coleman, Jeffrey M. Liebmann, Jody R. Piltz-Seymour, Mae O. Gordon, Michael A. Kass.**

UCSD, La Jolla, CA, Henry Ford Health System, Detroit, MI, UC Davis, Sacramento, CA, Columbia University Medical Center, New York, NY, Jules Stein Institute, Los Angeles, CA, New York Eye and Ear Infirmary, New York, NY, University of Pennsylvania Health System, Bristol, PA, Washington University School of Medicine, St Louis, MO

**Purpose:** To compare the rate of rim area loss in ocular hypertensive eyes that developed visual field (VF) primary open angle glaucoma (POAG) endpoints to eyes that developed optic disc POAG endpoints, and to eyes with repeatable optic disc change identified by the OHTS Optic Disc Reading Center (ODRC).

**Methods:** 441 participants (832 eyes) enrolled in the CSLO Ancillary Study to the OHTS were included. POAG endpoint was defined as confirmed VF abnormality or a clinically significant ODRC optic disc deterioration attributed to POAG by the endpoint committee. The rate of HRT rim area loss was measured using multivariable mixed effects models.

**Results:** See Table comparing the rate of rim area loss in eyes 1) that developed POAG by VFs, 2) that developed POAG by optic disc alone, 3) with ODRC optic disc deterioration not yet clinically significant by the endpoint committee, and 4) with no change.

**Discussion:** The mean rate of rim area loss was approximately twice as fast in optic disc POAG endpoint eyes compared to VF POAG endpoint eyes and to eyes with ODRC optic disc changes not considered clinically significant.

**Conclusions:** These results suggest that measuring the rate of structural change provides important information, but should not replace VF testing for the clinical management of ocular hypertensive patients.

### Rim Area Loss in Eyes

<table>
<thead>
<tr>
<th>Initial VF and Optic Disc Change Criteria</th>
<th>N (eyes)</th>
<th>Rim Area Slope (95% CI) (mm2/yr)</th>
<th>P-Value compared to VF POAG Endpoint</th>
<th>P-Value compared to No Change</th>
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<td>VF POAG Endpoint</td>
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<td>0.1655</td>
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<tr>
<td>Optic Disc Reading Center Change Only not yet clinically significant</td>
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<td>-0.0094 (-0.0161, -0.0027)</td>
<td>0.54</td>
<td>0.0012</td>
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<tr>
<td>No Change</td>
<td>731</td>
<td>-0.0021 (-0.0031, -0.0011)</td>
<td>0.1655</td>
<td>NA</td>
</tr>
</tbody>
</table>
7. The Ocular Hypertension Treatment Study: Difference in the Effect of Long Term IOP Variability on the Risk of Developing POAG

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Purpose: To determine if the risk of developing POAG is increased by higher long-term IOP variability as measured by standard deviation (SD), maximum IOP, range, coefficient of variation (CV) and percent change.

Methods: Analysis of baseline and follow-up IOP in 717 participants randomized to observation (OBS) and 720 participants to topical ocular hypotensive medication (MED). Incident POAG was defined as confirmed visual field abnormality or optic disc deterioration of clinically significant magnitude attributed to POAG by an Endpoint Committee. Univariate and multivariate (MV) time dependent Cox proportional hazards models were used to estimate hazard ratios. Serial landmark models were used to estimate the C-index averaged over time. Covariates in MV models were baseline age, CCT, PSD, VCD and follow-up IOP.

Results: IOP variability had statistically significantly greater effect in the medication group than in the observation group. Thus, we report results separately by randomization group. In the OBS group, 102 eyes of 717 participants developed POAG in OHTS I (median f/up 6.9 yrs.). None of the measures of IOP variability independently increased the risk of POAG. In the MED group, 111 eyes of 720 participants developed POAG in OHTS I and II (median f/up 13.0 yrs.); SD (HR 1.21, p=0.024) and CV (HR. 1.19, p=0.045) independently increased the risk of developing POAG. In the MED group, the C-statistic for the “basic” multivariate model with covariates only was 0.755. After adding SD to these covariates, the C-statistic increased to 0.766. After adding CV to these covariates, the C-statistic increased to 0.765.

Discussion: Higher long term IOP variability in the observation group did not independently increase the risk for developing POAG i.e., natural history of POAG. However, in the medication group, higher long-term IOP variability, specifically SD and CV, increased the risk of developing POAG. The addition of either SD or CV did little to improve the predictive accuracy of the MV model.

Conclusions: Long-term variability of IOP was found to be a risk factor for POAG only among treated patients. Factors contributing to IOP variability among treated patients include inherent patient-specific biologic variability and medication consistency among other factors.
8. Nerve Fiber Layer and Ganglion Cell Complex Measurements by OCT as Risk Factors for Visual Field Progression in Glaucoma

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Purpose: The purpose of the study is to determine whether optical coherence tomography (OCT) anatomic measurements are useful in predicting the development of glaucomatous visual field (VF) defects.

Methods: We analyzed the data from perimetric glaucoma (PG) patients enrolled in the multi-center longitudinal Advanced Imaging for Glaucoma Study (www.AIGStudy.net). Both time-domain (TD) and Fourier-domain (FD) OCT were used to measure thickness profiles of nerve fiber layer (NFL). Ganglion cell complex (GCC) thickness maps were measured with FD-OCT. Standard automated perimetry was used to assess VF. Subjects were followed every 6 months. VF glaucoma progression was defined as three consecutive follow-up VF’s that show consistent focal worsening of defects (three completely filled black triangles) by Humphrey Glaucoma Progression Analysis (GPA) software. The Cox proportional hazard model was used to calculate the hazard ratios (HR) for the risk factors; the results were adjusted for correlation between the eyes from the same individual. A multivariate model was fitted for each of the OCT parameters with age and VF pattern standard deviation (PSD).

Results: The analysis included 340 eyes (222 participants) with average age of 61.8, among which 127 (57%) are female and 24 (11%) are African Americans. The average PSD at baseline was 5.6 while the average mean deviation (MD) was -4.8. The average follow-up time was 36 months. In the cohort, 35 eyes had VF progression. The most significant risk factor for visual field progression is GCC Focal Loss Volume (FLV) from FD-OCT (HR = 1.16, per 1% higher, p =0.004). The figure shows the Kaplan-Meier survival curves for patients with high GCC FLV (> 5%) and low GCC FLV (<=5%), the progression probability is 8 times as high after 6 years of follow-up.

Discussion: Glaucoma patients with thinner GCC, NFL, or with higher FLV are more likely to have worsening of visual field defects, even after controlling for age and disease severity (VF PSD) in multivariate analysis.

Conclusions: GCC and NFL measurements using OCT can provide glaucoma patients in care with a better prediction in glaucoma progression.
9. Treatment-to-Outcome Gap in Glaucomatous Eyes Undergoing Trabeculectomy

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Purpose: We hypothesized that intraocular pressure (IOP) lowering interventions in glaucoma may not lead to immediate changes in rates of visual field (VF) progression given what we called a 'treatment-to-outcome gap'. In other words, once the IOP is lowered at a specific time-point, VFs may still progress due to the detrimental effects of pre-existing injury to retinal ganglion cells (RGC) during the period they were exposed to higher IOP. We tested this hypothesis in eyes undergoing trabeculectomy and estimated the average time between IOP reduction and reduction of the slope of VF progression.

Methods: Data from glaucoma patients who underwent a single trabeculectomy were collected retrospectively. We included only eyes with ≥5 SITA-SAP VFs before and after surgery, and excluded those who had repeat surgery during the time period of the analysis. Variables analyzed were VF mean deviation (VFMD), IOP at the date of each VF test, age at time of surgery, and central corneal thickness CCT. Longitudinal data from each eye were analyzed using a ‘spline smoothing’ statistical technique which generates fitted curves of VFMD and IOP over time. First derivatives at each time-point were calculated for these curves allowing a comparison between changes in IOP and VFMD slopes. Mixed linear models were used to test the relationship between fitted IOP, fitted VFMD slopes, and ‘lag slopes’ (the effect of IOP at one visit on the VFMD slopes on following visits).

Results: 56 eyes of 56 patients (mean age, 63.4±13.3 years) were included. Figure 1 depicts the fitted VFMD and fitted IOP change over time. At each time point, for each 1 mmHg IOP increase, the VFMD slopes became 0.050 dB/yr more negative (95% CI = -0.075 to -0.025 dB/yr; P<0.001). For the ‘lag slopes’ analysis, for each 1 mmHg IOP increase at one visit, the VFMD slopes became 0.056 dB/yr more negative at the following visit (95% CI = -0.080 to -0.032 dB/yr; P<0.001). A comparison between the fitted IOP slope and the fitted VFMD slope suggests an average of 40 months interval between the maximum rate of IOP decline (post-surgery) and flattening of the VFMD slopes to zero (Figure 2).

Conclusions: Current IOP measurements determine not only current rates, but also future rates of VF progression, even after substantial IOP reduction has been accomplished surgically. A lag time exists between IOP reduction and VF stabilization. This implies continued RGC death from antecedent injury.

Support: By the Edith C. Blum Foundation, New York, NY; the Sheila Evers Research Fund of the New York Glaucoma Research Institute, New York, NY.

Figure 1. Fitted MD vs. Fitted Time (top) and Fitted IOP vs. Fitted Time (bottom).

Figure 2. Fitted VFMD slopes vs. Time in months (top) and Fitted IOP slopes vs. Time in months (bottom). In the top figure, note that its takes on average 70 months after surgery for the VFMD slopes to become more positive and reach ‘zero’. In the bottom figure, note that the maximum IOP reduction occurs between surgery date (‘zero’) and 30 months, when the rate of IOP reduction starts to increase (despite still being negative). The difference (70-30=40 months) is the estimate of the ‘treatment-to-outcome gap’.
10. Large and Sustained Blood Pressure Dips Are Associated with Visual Field Progression in Normal-Tension Glaucoma

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New York University School of Medicine, New York, NY, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, Cornell University, Ithaca, NY, New York Eye and Ear Infirmary, New York, NY

**Purpose:** Cross-sectional studies suggest that nocturnal systemic hypotension is more common among normal-tension glaucoma (NTG) patients with sustained progressive visual field (VF) loss. However, most studies relied on a single blood pressure (BP) recording and did not consider the patients' nocturnal BP in relation to their usual systemic BP.[1,2] The concept of the 'autoregulatory range' provides an important framework to evaluate nocturnal BP and glaucomatous loss. Autoregulation normally keeps ocular perfusion constant while systemic BP varies. We tested the hypothesis that progressive VF loss in NTG occurs at least in part due to systemic BP falls below the lower limit of autoregulation, resulting in ischemia and optic nerve injury, and that the extent and duration of the nocturnal fall in mean arterial pressure (MAP) below the lower autoregulatory limit may be predictors of progression.

**Methods:** Patients from a referral glaucoma practice diagnosed with NTG and who had reproducible VF defects were screened for potential eligibility. All included patients had a history of IOP 24 mmHg) prior to glaucoma treatment. Patients with a VF defect not attributable to glaucoma were excluded. A complete ophthalmologic examination was performed at baseline and follow-up visits. The baseline evaluation included basic demographic and clinical characteristics, including systemic comorbid conditions. All systemic medications were recorded, with an emphasis on anti-hypertensive medications. Patients had their BP monitored every 30 minutes for 48 hours with an ambulatory recording device at 6-month intervals. All included patients had a minimum of 8 VF tests and progression was defined based on the EMGT criteria and rates of MD change (dB/yr).

**Results:** 166 eyes of 85 NTG patients were included (mean age of 65 years; 67% were women. 24% of patients progressed over a mean follow-up period of 5 years based on the EMGT criteria. Multivariate analysis revealed that the total time that the MAP during sleep was below the daytime mean was a significant predictor of subsequent VF progression (p=0.022). In addition, the total area under curve, that is taking into account the magnitude and duration the BP fell below daytime MAP, was also a predictor of progression (p=0.020). When looking at rates of MD change (dB/yr), there was a significant association with the total time the BP was below MAP (p=0.006), asthma (p<0.001), and use of beta blockers (p<0.001).

**Discussion:** Our data suggests that nocturnal BP dips below the daytime mean MAP, as well as the magnitude and duration of these dips, are predictors of progression in NTG. It is plausible that physiologic low nocturnal BP and/or overtreatment of systemic hypertension may aggravate functional outcomes of NTG patients.

**Conclusions:** 24-hour BP monitoring in NTG patients may be warranted.

**References**
Anterior and Posterior Segment Imaging

II. Deformation of the Non-Human Primate (NHP) Optic Nerve Head (ONH) Connective Tissues within 3-D Histomorphometric Reconstructions of Moderate and Severe Experimental Glaucoma (EG) Eyes

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Purpose: To characterize ONH connective tissue (CT) deformation within 3D histomorphometric reconstructions of 12 moderate to severe (M/S) EG NHP eyes relative to 9 previously reported early EG (EEG) eyes.

Methods: Trephinated ONH and peripapillary sclera from both eyes of 12 adult NHPs, (9 - 21 years old) that had been perfusion fixed at IOP 10 mmHg with one normal, and one M/S EG eye (qualitatively determined by the magnitude of longitudinal change in confocal scanning laser tomography) were serial sectioned, 3D reconstructed, 3D delineated and parameterized using our existing techniques. Significant between eye differences for each parameter, for each M/S EG eye (compared to its contralateral control), exceeded previously reported maximum physiologic inter-eye differences (PIDmax) and were compared to the range of EEG eye change.

Results: M/S EG eyes were ordered by overall ONH CT deformation as characterized by Post-BMO Total Prelaminar Volume, which increased from 40 to 578% vs 36 to 188% in the EEG eyes. Lamina posterior deformation ranged from -37 to -437 µm in the M/S EG eyes vs -29 to -184 µm in the EEG eyes. Lamina thickness increased 30 to 113 µm in 3 M/S EG eyes, was unchanged in 6 M/S EG eyes and was thinned 23 to 31 µm in 3 M/S EG eyes compared to increases ranging from 20 to 61 µm in 8 of 9 EEG eyes. Posterior scleral canal opening (PSCO) offset expansion (range, 25 - 33 µm) was less than that in the EEG eyes (range, 30 - 85 µm) with 1 M/S EG eye demonstrating PSCO contraction (64 µm). Anterior laminar insertion (ALI) and Posterior laminar insertion (PLI) depth (relative to BMO reference plane) was consistently greater in M/S EG compared to EEG eyes.

Conclusions: Global posterior deformation and thickening of the lamina cribrosa continues throughout NHP M/S EG. However, as previously described in humans and monkeys, the lamina is thinned in the most severely deformed eyes. Taken together, our EEG and M/S EG eye data suggest the lamina thickens in most NHP eyes early in the neuropathy then thins as the neuropathy progresses. However, the hypothesis that the lamina cribrosa thins primarily within some eyes is under study using longitudinal SDOCT imaging.

References
12. Reduced Schlemm’s Canal Size in Glaucoma Observed by Spectral Domain Optical Coherence Tomography

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Purpose: Non-invasive imaging of the primary aqueous outflow system may now be made with spectral domain optical coherence tomography (SD-OCT).

Methods: One random eye in 10 healthy (41 ± 17 years) and 9 POAG (64 ± 9 years) subjects were imaged by SD-OCT (Cirrus, Carl Zeiss Meditec, Dublin CA) using the anterior segment 512 x 128 cube scan pattern. SC-CSA was measured in 31 samples per scan volume, traversing a 1mm length of canal centered on a collector channel ostium, by two independent masked observers by manual tracing in ImageJ. Visual field was assessed in the POAG subjects (Humphrey Field Analyzer, Carl Zeiss Meditic, Dublin CA). Mean and quartile SC-CSA's were compared by analysis of variance.

Results: All morphometric parameters were statistically significantly smaller in glaucoma (table, mean ± standard deviation). Mean deviation in the glaucoma cohort was -3.5 ± 3.3 dB.

Discussion: There was a difference in age between the two cohorts, and some difference in SC-SCA may have been due to age. Despite early to moderate disease in the glaucoma subjects, the distribution of SC-CSAs was significantly smaller in glaucomatous eyes. Observed in histological sections and implied in pilot data in living eyes, the present study confirms morphometric changes in structures of the primary aqueous humor outflow pathway visualized non-invasively in human eyes.

Conclusions: On average, SC CSA was 60% smaller in glaucomatous eyes. Some of this difference may have been due to age. This significant difference may be observed non-invasively by SD-OCT.

Support: R01-EY013178, P30-EY008098; Eye and Ear Foundation (Pittsburgh, PA); Research to Prevent Blindness

References

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<tr>
<th>Parameter</th>
<th>Healthy ($\mu^2$)</th>
<th>Glaucoma ($\mu^2$)</th>
<th>% Difference</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Mean</td>
<td>3,262.6 ± 1,875.7</td>
<td>1,396.4 ± 1,096.8</td>
<td>-57.1%</td>
<td>P &lt; 0.001</td>
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<td>25th Percentile</td>
<td>2,273.1 ± 1,550.6</td>
<td>705.9 ± 706.9</td>
<td>-68.9%</td>
<td>P &lt; 0.001</td>
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<td>50th Percentile</td>
<td>3,103.5 ± 1,885.1</td>
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<td>P &lt; 0.001</td>
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<td>75th Percentile</td>
<td>4,072.4 ± 2,226.7</td>
<td>1,939.8 ± 1,553.1</td>
<td>-52.3%</td>
<td>P &lt; 0.001</td>
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13. Identification and Classification of the Collector Channel System with in-vivo High Definition Anterior Segment OCT

ALFREDO R. CASTILLEJOS, Carlos G. De Moraes, Sung Chul Park, Jeffrey Liebmann, Robert Ritch

Einhorn Clinical Research Center, New York Eye and Ear Infirmary, New York, NY, New York University, New York, NY

Purpose: To describe, evaluate and classify in vivo the areas of junction between Schlemm’s canal (SC) and the collector channels (CCs) in normal adult human eyes using a novel technique of serial high definition anterior segment Fourier-domain OCT imaging (FDASOCT).

Methods: 20 normal subjects (mean age: 25±4.0 years) were imaged using FDASOCT scans over the right temporal limbus. First, the area was inspected for CCs; when a clearly visible SC-CC junction was identified, a standardized protocol of serial radial and tangential scans was performed. The highest quality image of each set capturing the ostium of the same CC in both scan orientations was selected for quantitative assessment. The serial scans were used to create composite images which were qualitatively evaluated.

Results: In the radial scans, we evaluated SC cross sectional area (9,248±2,500 µm²), maximum width (28±10 µm) and length (365±46 µm) as well as CCs maximum lumen diameter (12±4 µm). The ostium diameter (18±8 µm) and SC maximum (28±9 µm) and minimum width (12±6 µm) in a 500 µm long section around the junction were evaluated in the tangential scans. Based on their morphometry, CCs were classified into small or large; based on their course, they were divided in anterior and posterior CCs.

Conclusions: The anatomy of the SC-CCs junctions can be objectively measured with real-time, high resolution ASFD OCT and is enhanced by the use of serial radial and tangential imaging. We propose a classification of the CC based on their in vivo anatomy.
14. Retinal Blood Flow in Glaucomatous Eyes with Single Hemifield Damage

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Purpose: To examine the hypotheses that retinal blood flow (RBF) is significantly reduced in the abnormal visual hemifield of glaucomatous eyes with single-hemifield damage; and that there are significant associations between reduced retinal sensitivity (RS) in abnormal hemifield, and RBF; retinal nerve fiber layer thickness (RNFL) and ganglion cell complex thickness (GCC) in the corresponding abnormal hemisphere.

Methods: Glaucomatous eyes with visual field loss confined to a single hemifield underwent Spectral-domain optical coherence tomography (SDOCT), Doppler SDOCT and standard automated perimetry (SAP). Using Dual Angle Protocol, a double-circle scanning pattern was applied to measure the venous BF. Disc photos were registered with Doppler images to identify the veins. RBF was derived from the recorded Doppler frequency shift and the calculated angle between the beam and the vessel. Total and hemispheric RBF values were calculated. Average, superior and inferior RNFL and GCC were measured. Shapiro-Wilk Test, ANOVA with Tukey HSD and regression analyses were performed.

Results: 30 eyes (age 61.5±9.2 yrs) were included. Mean RS was reduced in abnormal hemifield compared with the normal hemifield (22.5±7.1 vs 28.5±2.0dB, p<0.001). Mean RBF was reduced in retinal hemisphere associated with abnormal hemifield vs the opposite hemisphere (15.3±5.4 vs 19.3±8.4 µL/min, p=0.03). The RNFL was thinner in corresponding abnormal hemisphere vs the opposite hemisphere (87.0±20.2 vs 103.7±20.6µm, p=0.002). The GCC was thinner in corresponding abnormal hemisphere vs the opposite hemisphere (80.6±10.3 vs 83.6±10.1µm, p=0.04). The RBF was associated with RNFL (r=0.41, p=0.02) and GCC (r=0.43, p=0.02), but not with the RS in 1/foambert or dB (r=0.31, p=0.09; r=0.30, p=0.10 respectively) in corresponding abnormal hemisphere and abnormal hemifield.

Discussion: Reduced RBF associated with thinner RNFL and GCC in the corresponding abnormal hemisphere, indicates that retinal blood flow is involved in the pathogenesis of glaucoma.

Conclusions: In glaucomatous eyes with single-hemifield damage, retinal blood flow is significantly reduced in the hemisphere associated with abnormal hemifield.

15. Measurement of Optic Nerve Head Blood Flow in Glaucoma by OCT Angiography

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Purpose: To detect changes in optic nerve head (ONH) circulation in glaucoma patients using optical coherence tomography (OCT) angiography.

Methods: One eye of each subject was scanned by a high-speed (100,000 A-scans/sec) 1050 nm wavelength swept-source OCT. The ONH angiography scan spans 3x3 mm and comprises 200x200x8 A-scans acquired in 3.4 sec. Flow was detected using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. Motion artifacts were removed by 3D orthogonal registration and merging of 4 scans. In the merged scan volume, en face maximum projection was used to obtain 2D disc angiograms, from which average decorrelation values (flow indices) were computed from the segmented disc areas. Visual field (VF), disc photography, and confocal scanning laser ophthalmoscopy (cSLO, HRT II) were used to provide standard glaucoma diagnostic evaluation. Comparisons between glaucoma and normal groups were analyzed by Wilcoxon rank sum test. Correlations between SSADA flow index and other measures of function and structure were assessed by linear regression.

Results: Ten glaucoma subjects (6 perimetric, 3 preperimetric, and 1 ocular hypertensive) and twenty normal human subjects were compared. In normal discs, a dense microvascular network was visible on OCT angiography (Fig. 1B). This network was visibly attenuated in all glaucoma subjects (Fig. 1E). The intra-visit repeatability, inter-visit reproducibility, and normal population variability of SSADA-based whole disc flow index were 1.1%, 6.6%, and 4.8% CV respectively. In the glaucoma group, the flow index was reduced by 19% for the whole disc, and by 24% for the temporal ellipse (Fig. 2). These reductions were significant even after accounting for age, cup/disc ratio (photograph), and rim area (cSLO). Both flow indices were significantly (P<0.01) and highly correlated (R < -0.8) with VF pattern standard deviation.

Discussion: OCT angiography, generated by the new SSADA algorithm, is a highly reproducible method for the measurement of ONH perfusion.

Conclusions: OCT angiography could be useful in the evaluation of glaucoma and glaucoma progression.

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**Glaucoma Management and Therapy**

16. A Prospective Randomized, Multicenter, Single-masked, Parallel, Dose Ranging (VOYAGER) Study to Compare the Safety and Efficacy of BOL-303259-X to Latanoprost in Subjects with Open Angle Glaucoma or Ocular Hypertension

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**Purpose:** To determine the most effective drug concentration of BOL-303259-X in the reduction of intraocular pressure (IOP) and assess the safety and efficacy of BOL-303259-X compared to latanoprost 0.005% ophthalmic solution.

**Methods:** Eligible subjects with a diagnosis of open-angle glaucoma or ocular hypertension with IOP ≥ 26 mmHg at least one time point and ≤ 32 mmHg at all time points were offered enrollment. Following randomization, 413 subjects were assigned to one of five treatment groups: BOL-303259-X 0.006%, 0.012%, 0.024%, 0.040% or latanoprost 0.005% ophthalmic solutions. Subjects were seen for 7 study visits over the course of 29 days. Doses were administered once daily in the evening for 28 consecutive days. The primary and secondary efficacy endpoints were a reduction in mean diurnal IOP at Day 28 and sustained IOP reduction on Day 29 respectively. Safety assessments included measurement of adverse events, best-corrected visual acuity, ocular signs and symptoms as well as vital signs. An ANCOVA model with fixed-effect terms was used; for the change from baseline IOP, 1-sample t-tests were performed.

**Results:** Subjects in the intent-to-treat population had a mean age of 61.0 years, were predominantly white (74.1%), and female (61.7%) with 43.6% being naïve to treatment at time of enrollment. Demographic and baseline characteristics were similar across treatment groups. At Day 28, mean diurnal IOP reduction in the BOL-303259-X 0.024% (9.0 mmHg; p = 0.0051) and 0.040% (8.9 mmHg; p = 0.0089) treatment groups was greater than in the latanoprost group (7.8 mmHg); on Day 29, a greater mean diurnal IOP reduction was still observed in the BOL-303259-X 0.024% group (7.20 versus 6.25 mmHg, p = 0.0505) compared to latanoprost. All ocular treatment-emergent adverse events were mild or moderate in severity. Overall, the percentages of subjects with conjunctival hyperemia were similar across treatment groups.

**Conclusions:** BOL-303259-X is a safe and effective IOP-lowering agent at multiple concentrations, reducing IOP in a dose-dependent manner. BOL-303259-X 0.024% QD statistically significantly reduced IOP greater than latanoprost with a similar side effect profile.

17. The Cost of Glaucoma Care Provided to a Sample of Medicare Beneficiaries from 2002–2009

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**Purpose:** To estimate payments for glaucoma care among Medicare beneficiaries from 2002 to 2009.

**Methods:** Data from a 5% random subsample of Medicare billing information from the years 2002, 2006 and 2009 were collected from the carrier, outpatient hospital, inpatient hospital and beneficiary summary files. Medicare beneficiaries with both Parts A and B, fee for service enrollment for > 1 month during the year, who had one of a defined set of glaucoma diagnostic codes were included if they had one glaucoma visit, glaucoma diagnostic test, or glaucoma laser/surgical procedure. Groups coded as open angle, angle closure, or other glaucoma were categorized separately. Claims were classified into glaucoma care, other eye care and other medical care.

**Results:** In 2009, overall glaucoma payments were $73.4 million for the 5% sample, for an overall estimated cost of $748.3 million, or 0.4% of all Medicare payments. Office visits comprised nearly one-half of glaucoma-related costs, diagnostic testing was about one-third, and surgical and laser procedures were about 10% of costs each. Coded OAG and OAG suspects accounted for 87.5% of glaucoma costs, while cost per person was highest in other glaucoma, followed by ACG, then OAG. Fewer than 3% of OAG patients were estimated to undergo surgery and about 7% had laser trabeculectomy in 2009. Laser iridotomy accounted for the highest costs among ACG (35.4% of their total). Other glaucoma patients had the highest proportion of costs devoted to surgery (26.4%), particularly tube-shunt surgeries. The non-glaucoma eye care for glaucoma patients was 67% higher than that for glaucoma care, chiefly related to cataract surgery and diagnosis/treatment of retinal diseases. From 2002 to 2009, glaucoma care costs rose 30%, related to cataract surgery and about 10% of costs each. Coded OAG and OAG suspects for > 1 month during the year, who had one of a defined set of glaucoma diagnostic codes were included if they had one glaucoma visit, glaucoma diagnostic test, or glaucoma laser/surgical procedure. Groups coded as open angle, angle closure, or other glaucoma were categorized separately. Claims were classified into glaucoma care, other eye care and other medical care.

**Conclusions:** Payments for glaucoma were less than 1/200th of all Medicare payments, increasing from 2002 to 2009 at less than the rate of general or medical inflation. Cataract and retinal eye care for glaucoma patients substantially exceeded the cost of their glaucoma care. Visit charges represent the largest category of costs.
I8. Evaluating IOP Reduction Resulting from Sustained Delivery via Travoprost-Eluting Hydrogel Punctum Plugs

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Purpose: To assess mean IOP reduction from baseline over 30 days and 60 days in glaucoma or ocular hypertensive patients treated with the Travoprost Punctum Plugs (TPP)

Methods: Polyethylene glycol hydrogel punctum plugs designed to deliver travoprost for 30 and 60 days were evaluated in a series of 2 prospective studies. 17 and 30 patients with glaucoma or ocular hypertension were enrolled at two institutions in Singapore and South Africa, respectively. In both, naïve and previously treated patients (after undergoing washout) were enrolled and had a TPP inserted in either the upper or lower puncta. Patients with a baseline IOP of < 22 and > 34mm Hg were excluded. At baseline and approximately every two weeks after insertion, the IOP was measured at 8AM, 10AM, and 4PM through 30 and 60 days for Study 1 and 2, respectively.

Results: A clear and sustained IOP reduction from baseline was observed in patients treated with TPP. Mean IOP reduction was greater than 5mm Hg at 30 days in Study 1 across all 3 timepoints. Only 1 from 17 subjects required removal of the plugs because of persistent epiphora. In Study 2 No unanticipated adverse events or serious adverse events occurred, and at 60 days post-insertion, the mean IOP reduction was also greater than 7mm Hg. Overall, plugs were retained well (based on visualization and/or IOP reduction criteria) and were considered straightforward to insert. Hyperemia was not noted to be prominent compared to baseline levels.

Discussion: Initial safety and efficacy was demonstrated for TPP. Therapeutic levels of travoprost were maintained when extending the duration of therapy from 30 days to 60 days.

Conclusions: Extending the duration of the therapeutic effect of the TPP is viable and may be advantageous in overcoming patient non-compliance to topical therapy.
19. A Comparison of Trabeculectomy Surgery Outcomes with Mitomycin-C Applied by Intra-Tenon Injection Versus Sponge Method

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Purpose: The ideal trabeculectomy bleb is described as diffuse with normal vascularity while focal, cystic blebs may be associated with leaks. Intra-Tenon injection of MMC may offer advantages such as creating a more diffuse bleb and providing faster application times during surgery. We investigate the outcomes of trabeculectomy surgery with Mitomycin-C (MMC) applied by intra-Tenon injection versus sponge method.

Methods: We performed a retrospective review of trabeculectomy performed with MMC applied by either intra-Tenon injection prior to the initial incision or by sponge under the conjunctival flap. Main outcome measures compared between groups were intraocular pressure (IOP), medication use and complications. Treatment success was defined as IOP ≤ 21 mmHg or IOP reduced by 20% or greater from baseline with or without the use of glaucoma medications, without additional glaucoma surgery and without a devastating complication (NLP vision, endophthalmitis).

Results: A total of 231 eyes that had received trabeculectomy surgery with MMC with at least 1 month of follow up were included in this study. Lower IOP was noted in the MMC injection group through 36 months post-operatively (Figure). Overall treatment success was 80% in the MMC injection and 70% in the MMC sponge group at post-operative year 3 but this difference did not reach statistical significance. Medication use was significantly lower in the MMC injection group (0.49 vs 0.94 meds) at 3 years (p=0.0328). The late (> 1 month) complication of a tense or vascularized bleb was noted more often in the MMC sponge group (p = 0.009). Other complications (e.g., bleb leaks, choroidal effusions) were not statistically different between groups.

Discussion: In our retrospective study, Mitomycin-C applied by injection resulted in lower IOP, and the need for fewer glaucoma medications. Direct and diffuse application of MMC by injection may promote less scarring and vascularization of the bleb.

Conclusions: Intra-Tenon injection of MMC may provide the advantage of lower IOP and the need for few glaucoma medications.
20. Using Filtered Forecasting Techniques to Determine Personalized Monitoring Schedules for Patients with Open Angle Glaucoma

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Purpose: To determine whether dynamic and personalized schedules of visual field (VF) tests and intraocular pressure (IOP) measurements for patients with open angle glaucoma (OAG) result in an improvement in disease progression detection compared to fixed interval schedules for these evaluations.

Methods: Data from perimetry, tonometry, and relevant sociodemographic factors were obtained from a subset of participants with moderate or advanced OAG who had been enrolled in the Collaborative Initial Glaucoma Treatment Study (CIGTS) or the Advanced Glaucoma Intervention Study (AGIS). These data were used to parameterize a Kalman filter and logistic regression in order to identify personalized indicators of glaucoma progression and to assess when glaucoma patients should next be tested. The Kalman filter is used to dynamically update our knowledge about each patient’s disease dynamics as additional VF and IOP measurements are obtained. We then forecast each patient’s dynamics into the future while incorporating the uncertainty associated with those forecasts. Logistic regression is used to model the relationship between the current and future disease dynamics and glaucoma progression. We developed a dynamic algorithm which combines the Kalman filter updating capabilities and the logistic regression predictive power to determine personalized schedules of VF and IOP testing. Our algorithm was compared against fixed interval schedules of obtaining VFs and IOP measurements from the trials.

Results: 571 patients met the inclusion criteria with a mean length of follow-up of 5.6 years. With over 27% increase of accuracy (p<0.0001), our scheduling algorithm leads to detecting glaucoma progression 63% sooner (i.e. reduced diagnostic delay) than following a yearly schedule (p<0.0001) without increasing the number of follow-up tests performed.

Discussion: Our algorithm for scheduling VF and IOP tests learns about each patient’s unique disease progression dynamics over time using a Kalman filter, thereby enabling adjustment of decisions to the prognostic scenario of each patient.

Conclusions: Dynamic and personalized testing schedules improve the likelihood of detecting disease progression and lead to identification of progression earlier than fixed yearly intervals.
New Concepts

21. Episcleral Venous Pressure in Untreated Open Angle Glaucoma


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Purpose: The contribution of episcleral venous pressure (EVP) to the elevation of intraocular pressure (IOP) in open angle glaucoma (OAG) is unknown. Previous studies of EVP in OAG have been contradictory. In this study, we used a new automated venomanometer, to investigate any difference in EVP between untreated OAG and normal individuals.

Methods: EVP was measured by using a computer controlled venomanometer in one eye each of 101 subjects with untreated OAG (mean age, 64 years; range 24 to 83 years) and 191 eyes of 100 healthy subjects (mean age, 48 years; range 19 to 81 years). The collapse of an episcleral vein during inflation of a transparent chamber applied to the vein was monitored in video images, and the pressure that just began to collapse the vein was assumed to be equal to the venous pressure. Descriptive statistics were calculated for IOP and EVP and differences between groups were examined by using generalized estimating equation models.

Results: IOP of normal eyes and eyes with OAG was 13.7 ± 3.0 mmHg (mean ± SD) and 27.4 ± 8.0 mmHg respectively (p<0.001). EVP of normal eyes and eyes with OAG was 6.9 ±1.9 mmHg and 7.7 ± 2.0 mmHg respectively (p=0.003). EVP was not correlated with age and IOP in either of the groups (p=0.24).

Discussion: In OAG, mean IOP was about 14 mmHg greater than it was in normal subjects, although EVP was less than 1 mmHg greater. This elevation in EVP could contribute in a small part to the elevation of IOP but it is not likely to be a dominant determinant.

Conclusions: EVP in OAG patients is elevated compared with normal subjects. However, elevation of EVP is not a primary cause of IOP elevation in OAG.

References

22. Association between Myopia and Glaucoma in a United States Population

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Purpose: To investigate the association between myopia and the prevalence of glaucoma.

Methods: This cross-sectional study included 5277 participants from the 2005-2008 National Health and Nutrition Examination Survey, ≥40 years old, without history of cataract or refractive surgery, who underwent auto-refraction measurement. The predictor was refractive status; emmetropia (-0.99 to +0.99D), mild myopia (-1.00 to -2.99D), moderate myopia (-3.00 to -5.99D), severe myopia (>6.00D), and hyperopia (>1.00D). The outcomes were self-reported glaucoma, vertical cup-to-disc ratio and visual field defects.

Results: Odds of self-reported glaucoma were not significantly increased in mild (OR 0.90, CI 0.56-1.45), moderate (OR 1.40, CI 0.62-3.16), or severe (OR 0.26, CI 0.09-0.72) myopes compared to emmetropes. Odds of vertical cup-to-disc ratio ≥0.7 were not significantly increased in mild (OR 0.84, CI 0.31-2.25), moderate (OR 0.37, CI 0.04-3.57), or severe (OR 0.85, CI 0.09-8.42) myopes compared to emmetropes. Odds of any visual field defects were significantly increased in mild (OR 2.02, CI 1.28-3.19), moderate (OR 3.09, CI 1.42-6.72) and severe (OR 14.43, CI 5.13-40.61) myopes compared to emmetropes. The χ² test indicated a significant difference (p=0.001) in the distribution of subjects with each category of visual field status across subjects with each refractive status; the proportion of subjects with worse visual field defects increased with worsening myopia severity.

Discussion: This study found an association between myopia and visual field defects, but failed to find an association between myopia and self-reported glaucoma or vertical cup-to-disc ratio. In subjects with mild, moderate, and severe myopia, the odds of having any visual field defect were increased approximately two-fold, three-fold, and thirteen-fold, respectively, compared to subjects with emmetropia.

Conclusions: The association between myopia and visual field defects may represent an increased risk of glaucoma among myopes, and the lack of association with self-reported glaucoma may suggest a need for greater glaucoma surveillance in this population.
24. Changes in Ocular Biometric Parameters over a 24 Hour Period in Ocular Hypertensive

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Purpose: The overall refractive status of the eye is determined by the corneal power, anterior chamber depth, lens thickness and axial length. Intraocular pressure has the potential to affect some of these parameters. Over a 24 hour period the changes in these parameters need to be complimentary to each other to keep the overall refractive error stable throughout the day. To determine the extent of the physical changes and whether they correlate with intraocular pressure (IOP), this study evaluates biometric parameters throughout a day and night in patients with ocular hypertension (OHT) treated with brimonidine or vehicle.

Methods: Thirty patients with OHT (58.6±9.2 years of age) were enrolled in this randomized, double-masked, crossover study. Participants self-administered 0.2% brimonidine or vehicle three times daily for 6 weeks. At the end of each 6 week period, measurements of habitual (seated during the day and supine at night) intraocular pressure (IOP), central cornea thickness (CCT), anterior chamber depth (ACD), axial length (AXL) and lens thickness were made at 8 AM, 3 PM, 8 PM and 3 AM. The results were compared by two-way ANOVA followed by one-way ANOVA and post hoc testing when appropriate. P values<0.05 were considered statistically significant.

Results: In the two-way ANOVA model, time of measurement had a significant effect on IOP, CCT, ACD and AXL. In vehicle-treated eyes, CCT was thicker at 3 AM than any other time (p<0.01), ACD and AXL were larger at 3 AM and 8 PM than 3 PM (p<0.01) and lens thickness did not change (p=0.40). Supine IOP at 3 AM was greater than seated IOP during the day (p<0.01). Brimonidine, with a mean habitual IOP decrease of 1.09 ± 3.72 mmHg during the day and 0.33 ± 4.33 mmHg during the night, did not alter any of these patterns. The shortest AXL and ACD were temporally close to the lowest IOP during the day.

Discussion: The increase in axial length at night (approximately 75 µ) can be attributed to an increase in anterior chamber depth (approximately 90-100 µ). The increase in anterior chamber depth is independent of any change in lens thickness. Brimonidine use does not alter the normal diurnal rhythm of ocular biometric parameters. A more potent ocular hypotensive drug may affect these rhythms and should be evaluated.

Conclusions: Numerous ocular biometric measurements exhibit 24 hour rhythms in patients with OHT. At night the supine IOP increases, the cornea becomes thicker, the anterior chamber depth increases and the axial length increases. These potentially IOP-mediated changes appear complimentary towards maintenance of refractive status of the eye, demonstrating inherent homeostatic mechanisms despite significant changes in the IOP throughout a 24 hour period.
25. A Nested Case Control Study of Plasma ICAM-1, E-selectin and TNF Receptor 2 Levels and Incident Primary Open-angle Glaucoma

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Purpose: An inverse association between body mass index (BMI) and primary open-angle glaucoma (POAG) among women but not men has been described in Nurses’ Health Study (NHS) and Health Professional Follow-up Study (HPFS) participants and confirmed in the Rotterdam Study. We hypothesize that this association is mediated by tumor necrosis factor alpha (TNF-α), which shows differential relationships to BMI by gender.

Methods: We collected blood samples in 1989-1990 (NHS: all women) and 1993-1995 (HPFS: all men). We identified POAG cases occurring after blood draw (NHS: n=229; HPFS: n=116). Controls (NHS: n=461; HPFS: n=228) were matched on age, race, ethnicity, cancer status, and date of blood collection. Plasma concentrations of ICAM-1, E-selectin and sTNF-R2 were measured by an ELISA assay. Cohort-specific multivariable conditional logistic regression model results were pooled using meta-analytic methods.

Results: We observed no associations between ICAM-1 and E-selectin; however, we observed associations with sTNF-R2. Mean (SD) plasma levels (pg/mL) of sTNF-R2 in cases and controls were 2888 (997) and 2986 (912), respectively, in women and 2622 (664) and 2568 (688), respectively, in men. Pooled multivariable results showed no overall relation between sTNF-R2 levels and POAG. However, the results were significantly (p=0.01) heterogeneous between men and women: compared to the lowest tertile of sTNF-R2, the highest tertile showed a significant 43% decreased risk of POAG in women (multivariable odds ratio [OR]=0.58, 95% CI=0.36-0.94; p for trend=0.03) but not in men (OR=1.39; 95% CI=0.74-2.60; p for trend=0.21).

Discussion: Women with low BMI may have low intracranial pressure that disrupts the trans-lamina cribrosa pressure gradient in a manner similar to elevated IOP, triggering ocular production of TNF-α and retinal ganglion cell (RGC) loss. Serum levels sTNF-R2 may cross into the eye to bind TNF-α and thereby prevent glaucomatous optic neuropathy. Interestingly, subcutaneous etanercept, a biologic agent that binds TNF-α, rescues RGCs in an experiment glaucoma model via this mechanism.

Conclusions: Women with POAG may benefit from therapy that modifies intraocular TNF-α levels.