Safety & efficacy of automated Direct Selective Laser Trabeculoplasty: First-in-Human study Results

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Purpose: The Purpose of this study was to evaluate the safety and efficacy of automated Direct Laser Trabeculoplasty (DSLT) applied without a goniolens at various energies to the sclera overlying the trabecular meshwork (TM) in lowering intra-ocular pressure (IOP) in open angle glaucoma (POAG) & ocular hypertension (OHT).
Methods: 15 eyes of 15 patients (1 eye with exfoliative glaucoma 10 with POAG and 4 with OHT)) were treated by the DSLT device. 66% were males, and mean age was 66.2±8.2 years. Pre-medicated patients were washed out from their glaucoma medications. The DSLT treatment included 100-120 sequential non-contact laser shots applied automatically directly on the scleral limbus using image analysis of the limbus location and an eye tracking monitoring. Before the laser was fired multiple safety checks were automatically performed. Laser energy between 0.8 to 1.4 mJ/shot were used. The duration of the irradiation was 1.5 seconds/100 shots.
Results:Mean baseline IOP in patients treated with ≥1 mJ/shot was 26.8±2.5 mmHg (n=13). There was a significant IOP reduction ($p<0.01$).at 1month, 3 months & 6 moths post op. The IOP was 21.5±4.4; 20.7±2.4 and 20.8±3.8 mmHg. In six patients treated with 1.4 mJ/shot 1 month, 3 months & 6 moths follow up showed mean absolute/percentage reduction from baseline of 5.5±3.5 mmHg/19.9 %, 6.8±4.1/24.9% ($p<0.05$) & 7.3±2.5/27.1 % ($p<0.05$) respectively. There was a significant reduction in hypotensive medications from 1.6 ±1.0 to 0.4 ±0.7. One case of transient reduction in visual acuity (resolved in one day) and four cases of transient mild sub-conjunctival hemorrhages occurred (resolved in one day to one-week post-op). All resolved without treatment and with no sequalae. No SAE were observed.
Conclusion: Early experience shows, an automated DSLT is a promising new modality in the treatment of POAG. Higher energy gave better sustained Results. Further studies with more patients are being conducted in order to validate these Results in POAG patients.
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Visual Quality with Hybrid versus Miniscleral Contact Lens Corrections in Subjects with Keratoconus

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Introduction: Hybrid lenses consisting of rigid gas permeable (RGP) center with a soft skirt periphery were created to combine the advantages of RGP and soft lenses. Previous studies report that patients with keratoconus (KC) obtain similar visual quality with hybrid and RGP lenses, but did not compare higher order aberrations (HOA). Therefore, this study compared visual quality and higher order aberrations obtained with miniscleral RGP lenses compared with hybrid lenses.
Methods: Keratoconic patients were fit with both lens types, the first lens being determined randomly, and visual parameters were measured after lens stabilization on the eye. High (100%) and low (10%) contrast LogMAR visual acuity (VA), FACT contrast sensitivity for each spatial frequency, and aberrometry (L80+ wavefront aberrometer, Lenue, FR) was measured with miniscleral (MS) 15 mm lenses (Toplens, Israel), and 14.5 mm hybrid contact lenses (Ultra Health - UH, SynegEyes).
Results: Fourteen eyes (KC is an asymmetric disease) of eight subjects (mean age: 3315.30 ±, range: 18-63, 1 female) with KC were recruited. The 100% VA was significantly improved with UH lenses (0.76±0.16 vs. 0.66±0.17, $p<0.05$) though the 10% VA was not significantly different (MS: 0.20±0.07, UH: 0.17±0.10). The MS provided significantly improved contrast sensitivity (64.33±16.98) compared to the UH (50.75±20.87) for low spatial frequencies (1.5, 3, 6 cpd, $p<0.05$), but not for higher spatial frequencies (8 and 12 cpd). There were no significant differences for HOA corrected with both lens types.
Conclusion: MS lenses provide better visual quality at 100% contrast and low spatial frequencies and should be the preferred modality for KC correction based on visual quality alone.

Does the order of intraocular pressure measurements affect the Results in the left and right eyes?

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Purpose: A comparison of intraocular pressure (IOP) between right and left eyes of a patient is critical to interpretation of Results. Our aim in this study was to determine whether the order of IOP measurement, regardless of whether right or left eye is measured first, affects readings.
Methods: This was a prospective, randomized trial. The study group consisted of 31 healthy and ophthalmologically-normal dogs. In the 1st set of measurements, two IOP readings were recorded in the first (randomly-chosen) eye, followed by two readings in the fellow eye, and two final (repeated) readings in the first eye. After 15 minutes, measurements were repeated in reverse order (2nd measurement set).
Results: There were no significant differences in IOP between left and right eyes, regardless of whether measured first or second ($P>0.05$). In the 1st measurement set, there were significant differences between the 1st and 2nd eyes measured (15.6±0.4 and 14.8±0.5 mm Hg, respectively, $P=0.021$), as well as between the 1st eye measured and the same eye in the repeated measurement (15.6±0.4 and 14.5±0.4 mm Hg, respectively, $P=0.002$). Similarly, in the 2nd measurement set, there were significant differences between the 1st and 2nd eyes measured (14.5±0.4 and 13.7±0.4 mm Hg, respectively, $P=0.02$) as well as between the 1st eye measured and the same eye in the repeated measurement (14.5±0.4 and 13.9±0.4 mm Hg, respectively, $P=0.05$). Finally, there were significant differences between the 1st eye measured in the 1st set and the same eye when measured in the 2nd set (15.6±0.4 and 13.7±0.38 mm Hg, respectively, $P=0.001$), but not between the 2nd eye in the 1st set and the same eye when measured first in the 2nd set. (14.8±0.5 and 14.5±0.4 mm Hg, respectively, $P=0.54$).
Conclusions: IOP measured in the first eye, whether right or left, is higher than the IOP measured in the fellow eye. A small but significant decrease in IOP measurements may occur with repeated measurements in the same visit.

Is it necessary to wait several minutes between applications of different topical ophthalmic drugs?

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Purpose: To determine whether one should wait several minutes between applications of different topical drugs to the same eye.
Methods: Eight dogs were included in the study. The effect of tropicamide on pupillary diameter (PD) was measured over 4 hours when administered alone (baseline), then 1 and 5 minutes prior to, and following, application of saline, with one week washout between the five sessions. The same study design was repeated to study the effect of latanoprost on intraocular pressure (IOP). Data were analyzed using repeated measures ANOVA and Tukey post-hoc test.
Results: At all timepoints in the tropicamide trial, there were no significant differences in PD between baseline readings to those obtained when the drug was administered 1 or 5 minutes prior to, or following, application of saline ($P>0.05$). In all five sessions, maximal PD was reached 30 min after tropicamide application, and maintained for 180 minutes ($P<0.05$). In the latanoprost trial, there were significant differences in just 12/90 multiple comparisons between the five sessions, and in no case was the drug's hypotensive (baseline) effect attenuated by adding a saline drop 1 or 5 min before/after treatment with latanoprost. At 240 minutes, when IOP reached its trough, there were no significant differences between the five sessions ($P>0.05$).
Conclusions: Our Results suggest that waiting one minute between applications of different ophthalmic solutions may be sufficient for maximal drug effect. Care should be taken when extrapolating these Results to other species, different ophthalmic formulations such as oil, or to drugs that may have a synergistic effect.

Retinal and Choroid Thickness Using OCT in individuals with Type-A vs. Type-B behavior patterns

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Purpose: Optical Coherence Tomography (OCT), is a non-invasively imaging device that allows cross-section measurement of eye tissues (e.g. Lemaitre et al., 2016). Studies reports differences in retinal and choroidal thickness in varies pathologies (e.g. Chalam et al.,2012), as Central Serous Chorioretinopathy (CSCR) which is characterized by a thicker retinal and choroidal (Arora et al., 2016). Patients with CSCR show high prevalence of type A behavior pattern (Yannuzi, 1986; Ferrara et al., 2014; Liu et al., 2016). The Purpose of this study is to determine if there is difference in the retinal and choroid thickness among healthy individuals with Type-A vs. Type-B behavior patterns.
Methods: Visual acuity (Snellen, at least 6/12), cover test, autorefractometer (L80, Lenau, France), central retina thickness (3 measurements for each 9 regions) and choroid thickness (OCT, Moptim Ocean; Shenzhen©) was performed on healthy subjects with refractive error between -6.00 to +5.00D. Subjects filled out the Bortner Type-A questionnaire (Cooper, 2013) for behavior pattern classification. Data analysis included T-test and correlation tests. Only the right eye of each participant was included in the analysis.
Results: Fifty-seven subjects (51 female, average age 23.702.85 ±♀ years) participated in the study. Twenty-nine subjects (50.87%) were classified with Type A (50.87%) and the rest with Type B. No statistically significant differences between behavior patterns, were found for choroid ($p=0.45$) and retinal thickness ($p=0.08$). No correlation was found between the questionnaire score (behavioral patterns) and choroid and retinal thickness ($r<0.16$, $p=0.08$).
Conclusions: Contrary to patients with CSCR disease, there was no difference in choroid and retinal thickness between type A and B behavior patterns in healthy subjects.

Effect of contact lens design on objective visual quality metrics in pre-presbyopic patients in photopic and mesopic lighting conditions

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Purpose: To examine the effect of contact lens design (spheric vs. aspheric) on objective parameters of visual quality under mesopic vs. photopic lighting conditions.
Methods: In this prospective, non-dispensing double-blind study, pre-presbyopic patients with visual acuity of 0.7 (decimal) or better were fitted with two types of contact lenses, with spheric and aspheric designs with the optimal refractive correction on glasses. The low contrast (10%) and high contrast (100%) visual acuity (VA) (Snellen chart), amplitude of accommodation (AA) (Push away method, Diopters) and distance contrast sensitivity (CS) (Fact chart, cycles per degree (CPD)) were measured with for both types of contact lenses under mesopic and photopic lighting conditions. The lighting and dim conditions were selected to induce a minimal pupil diameter change of 2 mm. Paired samples t-test, repeated measures ANOVA and Pearson correlation tests were carried out on the outcome measures of the right eyes of the participants.
Results: Thirteen eyes of 13 patients (7 male, mean age: 42.57±2.48; range: 38-45 years) were included in the analysis. Mean CS was significantly better with spherical compared to aspherical lenses for low spatial frequencies (3 CPD: 20.4328.11±81.69 ,±67.62, respectively, $P<0.05$) though there was no significant difference for lower or higher spatial frequencies (1.5, 6, 12, 18 CPDs). The low contrast (10%) and high contrast (100%) VAs were not significantly different between the two lens designs. However, there were significant differences between near VA, distance low contrast VA and AA obtained under dim vs. photopic conditions with the aspheric design correction modality.
Conclusions: Although only marginally preferable, the spherical lens design appears to provide superior visual quality compared with the aspherical lens design for low spatial frequencies. Under dim lighting conditions, where impaired visual function is expected, only the aspheric lens design yielded significant differences in VA and AA parameters.

Anti-VEGF-Aptamer Modified C-Dots A Hybrid Nanocomposite for Topical Treatment of Ocular Vascular Disorders

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Purpose: Pathological angiogenetic ocular diseases, such as Choroidal Neovascularization (CNV), are induced by the vascular endothelial growth factor (VEGF). To date, treatment options are based on repeated intra-vitreal injections of anti-VEGF agents which can be administered only by highly-trained medical personnel and is associated with adverse reactions. We developed hybrid anti-VEGF aptamer modified C-dots, a versatile nanomaterial to topically treat age-related macular degeneration and diabetic retinopathy.

Methods: Toxicity of the hybrid was evaluated both in vitro using fibroblast, adult retinal pigment epithelial (ARPE) and photoreceptor precursor (PRP) cells and in vivo using a rat model. Corneal penetration was studied using both in vivo rat and ex vivo porcine models. The construct efficacy in vitro was evaluated using a rat choroid sprouting assay. Finally, to evaluate the efficacy in vivo, we used a laser-induced choroidal neovascularization (CNV) rat model. Next, RPE choroidal flat mounts prepared two weeks following the laser application were stained to isolectin-IB4 (endothel) and Phalloidin (actin). CNV volume was then calculated using the IMARIS 9.3.1 software on 3D confocal images.

Results: The C-dots showed excellent penetration through the cornea, yielding concentration of up to 54♀ μM upon topical administration, significantly higher than therapeutic levels. The hybrid showed no toxicity for both in vitro and in vivo and further enabled noninvasive intraocular concentration monitoring through the C-dots inherent fluorescence. Furthermore, the hybrid C-dots effectively inhibited VEGF-stimulated angiogenesis in choroidal blood vessels (75% decrease in sprouting area growth compared to control, p=0.007). Finally, in vivo efficacy experiments showed a 30% decrease (p=0.054) in CNV volume in anti-VEGF aptamer injected rats as compared to 60% (p=0.048) in Aflibercept injected rats and compared to a control group.

Conclusions: The hybrid aptamer modified C-dots provide a versatile nanomaterial to treat age-related macular degeneration and diabetic retinopathy by topical application. Further experiments are required to demonstrate CNV inhibition efficacy for this novel topical approach for treatment of CNV.

Time Outdoors, Near Work, and Electronic Device Use in Israeli Children

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Purpose: Outdoor time and near work are risk factors for myopia. There is recent concern that electronic device use may also contribute to myopia. Evidence supporting the contributions of these risk factors is equivocal. Previous studies have reported a high prevalence of myopia in young adult ultra-Orthodox males, possibly attributed to educational demands requiring intense near work from a young age. This study aimed to assess visual activity in three groups of Israeli Jewish children with highly homogenous genetics, but vastly different behaviors.

Methods: Twenty-eight healthy boys, ages 8-10, were recruited from ultra-Orthodox (n=13), religious (n=8), and secular (n=7) backgrounds. A complete eye exam with cycloplegic autorefraction (L80, Luneau, FR) was performed. An Actiwatch was dispensed for children to wear for 7-10 days for objective measures of light exposure and physical activity. Reading, writing, and electronic device use were assessed with a custom questionnaire. Time outdoors was quantified as minutes per day exposed to >1000 lux. Data were analyzed with Kruskal Wallis tests and Bonferroni post hoc comparisons.

Results: Data show that refraction tended to be more myopic in ultra-Orthodox boys (-1.01±1.27 D), although not significantly different than religious (-0.63±1.27D) or secular boys (+0.10±0.32D, P=0.31). Ultra-Orthodox boys learned to read at a significantly younger age (4.38±0.77 years) than religious (5.88±0.35 years, P<0.002) and secular boys (6.14±0.38 years, P<0.001). Ultra-Orthodox boys had significantly less electronic device use than secular boys (0.44±0.62 and 4.52±1.01 hours, respectively, P<0.002), and significantly more reading and writing time than secular boys (2.71±2.10 and 0.78±0.53 hours, respectively, P<0.006). Actigraph data showed that there were no significant differences in daily activity (P=0.64) or time spent outdoors (P=0.51) between groups.

Conclusions: These preliminary findings demonstrate that ultra-Orthodox, religious, and secular boys exhibit distinct behaviors. These behaviors may contribute to previously reported differences in refractive error between groups. Findings suggest that increased near work could be the myopiogenic factor in the ultra-Orthodox population, as opposed to time outdoors or electronic device use. Ongoing data collection to increase sample size will help to confirm this hypothesis.

The effect of decreased near visual acuity on eye movements and reading- using the developmental eye movement test

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Purpose: The Developmental Eye Movement (DEM) test assesses the oculomotor ability of the eyes (Garzia1990,). In order to detect abnormal eye movements the DEM factors out the consequences of automaticity on oculomotor performance (Garzia1990,). The DEM horizontal scanning mode simulates reading and the vertical scanning mode measures automatic retrieval skill (Northway, 2003). In this study we tested the effect of decreased visual acuity (VA) at near on reading and oculomotor ability using the DEM test.

Methods:Healthy subjects between the ages of 18-35, with best corrected VA of at least J3, stereopsis (Randot test) of a minimum 40 SOA, with no strabismus (measured with the cover test), and a minimum of 7cpm on the Binocular Accommodative Facility test were recruited for this study. The DEM test was performed twice, with and without blur in a random order. Blur was performed by adding plus lenses, however number identification (J1) was still possible. DEM Results with and without blur were compared using paired t-test.

Results: Thirty-five subjects (31 women) aged 19-30 years (average age of 23.26±2.86 year) participated in this study. A significant statistical difference was found between horizontal test scores (C), with blur (39.19±9.09) and without blur (32.1±6.24, $p<0.001$) and between the Results of the vertical test (A + B), with blur (37.85±9.91) and without blur (30.98±5.01, $p<0.001$). However, there was no difference between the ratio calculation (with blur R=1.05±0.15 and without blur R=1.04±0.12; $p=0.31$).

Conclusions: Blur does not affect the Results of the ratio calculation (oculomotor ability). It does however affect the vertical (A+B) and horizontal test (C), retrieval and reading ability. Blur causes a slowdown in reading speed and therefore it is very important to give patients their full near correction.

The prevalence of ciliary body detachment in patients with serous choroidal detachment

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Purpose To examine the prevalence, duration and characteristics of ciliary body detachment in glaucoma patients with serous choroidal detachment following filtration surgery.
Methods A prospective case control study. Patients diagnosed with choroidal detachment following glaucoma surgery at a tertiary medical center were recruited. Each patient underwent a complete ophthalmological examination, and an ultrasound biomicroscopy (UBM) scan to evaluate the presence and extent of ciliary body detachment. Follow up examinations including UBM scans were performed at 1 week, 1 month, 3 months and 6 months, or until the choroidal detachment resolved.
Results Nine patients were recruited. Five males and 4 females, ages 60-83 years (mean 71.1). Five underwent trabeculectomy (1 combined with cataract extraction), 2 Ahmed glaucoma valve implantation, and 2 Xen implantation. Mean intraocular pressure (IOP) prior to surgery was 26 mmHg (range 18-38), and following surgery on the day of choroidal detachment diagnosis was 7.3 mmHg (range 3-10). Ciliary body detachment was detected by UBM in all cases, ranging from 90 to 360 degrees. There was no correlation between the degree of pre and post-operative IOP change and the extent of choroidal and ciliary body detachment. All patients were treated with topical and systemic steroids, and topical cycloplegia.
Conclusions To the best of our knowledge this is the first study addressing the prevalence of ciliary body detachments in patients with choroidal detachments. In our series ciliary body detachment accompanied choroidal detachment in all cases. It may be a contributing pathophysiological factor to the post-operative hypotony often seen in patients with choroidal detachment, by having a detrimental effect on aqueous production.

Preoperative Ocular Characteristics Predicting the Development of Intraoperative Floppy Iris Syndrome

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PURPOSE: This study aims to characterize the association between ocular anatomical characteristics on preoperative evaluation and the development of intraoperative floppy iris syndrome (IFIS).

METHODS: In this retrospective study we reviewed medical records of all patients who underwent uncomplicated cataract surgeries by phacoemulsification in Yitzhak Shamir medical center, between September and July 2019. Patients younger than 50 years, with preexisting ocular conditions affecting pupillary size or anterior chamber depth, and who underwent combined procedures were excluded. We collected demographic data, medical history including know risk factors for IFIS, preoperative cataract and pupil measurements and biometric values. IFIS appearance was recorded as well as additional intraoperative and postoperative complications.

RESULTS: 315 eyes of 314 patients were reviewed, of which 300 eyes of 300 patients were found allegeable. Male patients comprised 39.3% (118), and average age was 72.3±8.55 years. Overall 14.3% (43 patients) had been treated prior to surgery with drugs known to cause IFIS, mostly alpha antagonists. IFIS occurred in 15 eyes (5% of surgeries), only 4 of which had received drugs putting them at risk for the condition. The patients in the IFIS group were significantly older than the non-IFIS group with a mean age 77.4±6.9 versus 73.0±8.5 years ($p<0.01$). There was no significant gender difference among the groups. Pupil diameter was significantly smaller among eyes that developed IFIS at 6.13±1.15 mm compared to 7.09±0.95 mm among eyes that did not ($p<0.001$). Adjusting for age, and for concomitant pseudoexfoliation syndrome (PXF) smaller pupil diameter remained predictive of IFIS with an odds ratio of 2.05 (95% confidence interval of 1.24 - 3.39). Anterior chamber depth (ACD) was significantly smaller in the IFIS group on univariate analysis (2.93±0.42 versus 3.13±0.39 mm, $p<0.05$), but after adjusting for age and pupil diameter the difference became nonsignificant. Additional eye dimension values, including axial length (AL) and white-to-white distance (WTW) were not found related to increased risk of IFIS.

CONCLUSIONS: Preoperative pupil diameter after pharmacological mydriasis was the single most significant risk factor for IFIS development on preoperative ocular examination, regardless of alpha-antagonist treatment status.

Face mask worn by patients during intravitreal injections may increase the risk of endophthalmitis

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Purpose: To investigate the usefulness and safety of face mask wear specifically by the patient during intravitreal injection.
Design: A prospective qualitative interventional study on healthy adult volunteers.
Methods: Healthy volunteers were examined with 3 different types of surgical face masks: A) regular surgical face mask with 4 tying strips , B) regular surgical face mask with elastic ear loops, and C) 2200 N95 TB particulate face mask. For each session the periocular area was inspected for air leak during normal respiration, speech and deep respiration. Between sessions the face masks were re-adjusted or switched. Detection of air leak was performed using a thermal camera: FLIR A310 (FLIR systems, Wilsonville, Oregon, US) a very sensitive fixed-mounted thermal imaging camera used to detected very small temperature changes.
Results: The experiment was run 45 times in total: 3 times for 3 mask types on 5 volunteers. Air jets were detected originating from the superior edges of the masks radiating towards the eyelids in 71% of cases (32/45).
Conclusions: Face mask wear by the patient during intravitreal injections may increase the risk of endophthalmitis and must be avoided.

Efficacy and comparison of mini scleral and scleral contact lenses in severe dry eye

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Purpose: To evaluate the efficacy of mini scleral and scleral lenses in the rehabilitation of the cornea in severe dry eye as well as the possible advantage of the scleral versus the mini scleral lens.

Methods: This study included fifteen patients, 29 eyes. The average age of the patients was 45±13 years, 55% women, half with punctal plugs inserted prior to this study, all with severe dry eye. The most common diseases in the study were Sjogren syndrome (4 patients), graft-vs-host disease (3 patients) and Ocular Cicatricial Pemphigoid (2 patients). One patient was fit only unilaterally due to extreme dryness after treatment for Primary Acquired Melanosis (PAM). The patients were divided into two groups, the first group were fit with mini scleral lenses the second group were fit with full scleral lenses. The groups included 8 patients and 7 patients respectively. Visual acuity, corneal staining and conjunctival staining were evaluated at baseline and at 12 months.

Results: There was a statistically significant reduction in corneal staining, improved from 2.361.577 ± to 0.921.222 ± ($P<0.05$) based on Oxford Scheme for grading ocular surface staining. Best-corrected visual acuity improved from 0.47680.3113 ± to 0.71280.349 ± ($P<0.05$). There was not a statistically significant reduction in conjunctival staining from baseline. There does not seem to be a clinically significant advantage to the full-size scleral lens above the mini scleral in both corneal staining and visual acuity. At the 14-18 month follow up 52.6% of the patients reported that they had discontinued wear primarily due to debilitating protein and mucin deposits.

Conclusions: Mini-scleral and scleral lenses are efficacious and well tolerated for use in severe dry eye syndrome up to 14 months. The full scleral contact lens afforded a larger reservoir but also seemed to attract more deposits. The full scleral contact lens was not superior to mini-scleral contact lens.

Infantile high myopia as a presenting sign of retinal dystrophy caused by novel RBP3 nonsense mutation

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Purpose: Three siblings of a consanguineous Bedouin kindred with apparently autosomal-recessive severe myopia since infancy were ascertained in order to characterize their ocular condition and determine its cause.

Methods: Affected individuals underwent thorough ophthalmologic examination including electroretinography (ERG) and ocular coherence tomography (OCT). Genomic DNA was extracted from blood samples of all family members. Using Single nucleotide polymorphism (SNP) microarrays, genome-wide linkage analysis was undertaken. Homozygosity mapping was performed using HomozygosityMapper software. Whole exome sequencing (WES) was performed for one of the patients. Exome data was analyzed using the Ingenuity Variant Analysisג„¢ software and in-house WES data of 300 controls. Next, the mapping and the WES Results were combined to a list of few variants possibly associated with the disease. Sanger sequencing and restriction fragment length polymorphism (RFLP) were used to study the variants found for segregation within the family and healthy ethnically-matched controls.

Results: The three siblings (2 females and a male) presented at age 1-4 years with high myopia (spherical equivalent between -13.00 and -22.50 diopters) and fundus changes compatible with myopia. Through the above process, we identified a duplication in RBP3 (Retinol-binding protein 3) gene (c.1687dupA, p.T563fs*5 (NM_002900.2)) as the most probable disease-causing variant in the family. ERG confirmed retinal dystrophy in all 3 patients with rods more severely affected than cones in two of them. Only one of the patients developed impaired night vision by the age of 10 years.

Conclusions: We report a novel duplication mutation in RBP3 leading to frameshift, premature termination codon (PTC) and possibly Nonsense-Mediated Decay (NMD). Severe myopia associated with RBP3 mutation indicates that the encoded retinol-binding protein 3 plays an important role not only in retinal function, but also in ocular growth and development. Infantile myopia can be an early and only sign of a degenerative ocular disorder which warrants further investigation.

Broad spectrum anti angiogenic therapy for wet AMD

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Age-related macular degeneration (AMD) is a neovascular disease and the leading cause of blindness in people over 65 in the western world. The ›€œwet›€• form of AMD is an angiogenic disease that Results from abnormal choroidal blood vessel growth beneath the retina that can cause hemorrhaging and edema that lead to vision loss. The gold standard treatment for wet AMD is direct intraocular injections of anti-vascular endothelial growth factor (VEGF) therapy, which Results in stabilization of the disease. However, the requirement for repeated intraocular injections and the limitation of targeting VEGF to regress AMD remain major issues. Novel highly potent anti-angiogenic therapies, which can be possibly administered non-invasively, may offer an important alternative to current therapies and improve the clinical outcomes for patients that do not respond to anti-VEGF drugs. Our research focuses on finding new active molecules with anti-angiogenic activity and development of novel nanotechnology based formulation for continuous release of the drug.

We have previously shown that blocking the activity of methionine aminopeptidase 2 (MetAp2), an enzyme that overexpressed in endothelial cells, result in disease regression. Unlike VEGF inhibitors, that stabilizes the CNV lesions we were able to detect regression when using the MetAp2 inhibitor TNP-470. In our current research, using medicinal chemistry we identified novel original MetAp2 inhibitors which has a VEGF-independent mechanism. We predict that such MetAp2 inhibitors may be delivered intraocular or topically and treat AMD by regressing choroid neovascularization, inflammation, and edema. Nanoparticle-based formulations are being also explored to provide better stability, safety and slow release for the drug.

In Vivo Effects of Bimatoprost on Orbital Fat in two different ways of administration

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Purpose: prostaglandin analogues have been used for many years in the treatment of glaucoma.. numerous reports have described eyelid and orbital changes that occur with the use of this medication including hypertrichosis, hyperpigmentation, meibomian gland dysfunction, horizontal eyelid shortening, eyelid retraction, and periorbital lipodystrophy, enophthalmos, and deepening of the superior sulcus deformity. While these effects may have adverse consequences for some patients, this side effect is more noticeable if only one eye is exposed to treatment. the atrophy of the periorbital fat may have a useful role in diseases that lead to orbital and periorbital fat hypertrophy such as thyroid eye disease, in which fat expansion and muscle hypertrophy develop as a consequence of the inflammatory stage of the disease. Currently the solution medicine has to offer are limited to the active stage of the disease. We hypothesized that the adverse effect of PG of PG-associated periorbitopathy (PAP), may be a therapeutic candidate for TED patients. In this study we aim to investigate the effects of bimatoprost (0.03%) administration both in the form of retrobulbar injection and drops on the orbital fat of rats.

Methods: The study included two groups of 10 rat each. First group - Topical bimatoprost (0.03%) drop were administrated to the right eye and saline drops to the left eye. second group - Retrobulbar injection of 0.1ml bimatoprost (0.03%) to the right eye and 0.1 ml saline to the left eye. Three weeks later, all rats were sedated and euthanized. Routine histologic staining was performed and thin sections through the intraconal orbital fat were obtained. Manual adipocyte cell count was preformed

Results: inflammatory response was detected in specimens with retrobulbar injection regardless of the substance injected. specimens treated with bimatoprost demonstrated significant decrease in adipocytes cell count. ($p = 0.005$) when compared with control Fat cells were not detected in nearly half of specimens among eyes treated with topical drops.**Conclusions**: In this study, we demonstrated that bimatoprost application led to significant decrease in adipocyte cells.

PEDF-derived peptide protects against Amyloid-²⁻ toxicity in vitro and prevents retinal dysfunction in rats.

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Purpose: Amyloid-beta) A ,(²⁻a family of aggregation-prone polypeptides, has been found as a significant constituent of drusen, thus implicated in the pathophysiology of age-related macular degeneration (AMD). We have shown that well-defined A ²⁻species possess differential retinal neurotoxicity in rats, where fibrillar and oligomeric assemblies of the A ²42⁻isoform stood as the primary retinotoxic entities. Previous studies showed that A ²⁻binding to the 67kDa laminin receptor (67LR) leads to the internalization and amyloid-related neuronal cell death. Anti-67LR has been used to treat models of Alzheimer™€ıs disease, thus supporting the role of this receptor in A ²⁻pathways. We have found that PEDF335, a pigment epithelium-derived factor (PEDF)-derived peptide, can bind to 67LR. Here, we hypothesized that PEDF335 may limit internalization of A ,²⁻thereby ameliorating its retinal toxicity in vivo.

Methods: Neuroscreen-1 (NS-1) cells were cultured with PEDF335 for 1 h before treatment with oligomeric A ²25-35⁻or A ²42⁻for 24 h. Cell viability was determined by MTT assay. Fluorescent PEDF335 uptake into the cells was assessed. Wild type rats were treated with intravitreal administration10¸ µl (of PEDF335 (3mM) in each eye three days prior to injection of oligomeric or fibrillary A ²42⁻assemblies to the right eye. Retinal function was assessed at baseline and thereafter at 3, 7 and 14 days after the injection. At each time point, electroretinography (ERG) measures were compared between eyes.

Results: PEDF335 treatment blocked amyloid endocytosis and protected NS-1 cells from A-²42⁻induced apoptosis in vitro. We then observed in vivo protection by PEDF335 against A-²42⁻mediated retinal dysfunction. In the presence of PEDF335, ERG responses in rat eyes treated with fibrillary A ²42⁻were intact, whereas those measured in eyes treated with oligomeric A ²42⁻showed marginal attenuation through 14 days. No retinal compromise was recorded in response to PEDF335.

Conclusions: Our Results provide conceptual evidence that PEDF335 protects against oligomeric and fibrillary A ²42⁻retinal toxicity, at least in part, via binding to 67LR through prion protein and inhibition of internalization of the assemblies. Such insights may promote the mechanistic understanding of the pathogenicity of particular A ²⁻species, and may merit further investigation as a potential strategy in AMD.

Activated protein C protective effects on the retina are partly mediated via the Tie2 receptor

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Purpose: Tie2 is a tyrosine kinase receptor for angiopoietins, and is predominantly expressed by the endothelium. The angiopoietins/Tie2 axis plays an integral role in the remodeling, maturation, and stability of developing vasculature, along with the vascular endothelial growth factor pathway. Our recently published data indicate that activated protein C (APC) has protective effects on the retinal blood barrier and can be used to modulate pathological choroidal neovascularization (CNV) in mice.We aimed to study whether the ability of APC to stabilize the blood retinal barrier and to reduce CNV is mediated via the Tie2 receptor.
Methods: In vitro model: human retinal pigmented epithelial (RPE) cells were cultured to achieve a stabilized barrier cell structure. Cell permeability was evaluated in the presence or absence of APC and Tie2 inhibitor, based on monitoring of the transport across the cell layer of labeled dextran. Cellular localization of the tight junction protein Zonula Occludens 1 (ZO1) was studied using immunofluorescence staining and confocal 3D imaging. In vivo model: CNV was induced by laser photocoagulation on C57BL/6J mice. APC was injected intravitreally immediately following injury. For Tie2 blocking experiments, mice were intraperitoneally injected with Tie2 kinase inhibitor, prior to CNV induction. The depth of blood vessel invasion from the choroid into the RPE layer was measured on day 7 following CNV induction on choroidal flatmounts. Cryosections were stained for Tie2 and phosphorylated Tie2.
Results: In vitro: APC reduced dextran leakage through the RPE monolayer in a dose dependent manner in addition to the translocation of ZO1 to the cell borders, forming a typical ZO1 honeycomb pattern, indicating the stabilization of tight junctions. Blocking of the Tie2 receptor reduced APC effects, suggesting that Tie2 receptor is essential for APC-induced barrier stabilization. In vivo: APC treatment significantly reduced the depth of blood vessel invasion from the choroid into the RPE layer, while Tie2 blockade has almost completely abolished APC protective activity. Phosphorylation status of Tie2 in the CNV lesions supported the activation of the Tie2 pathway by APC.
Conclusions: The protective effects of APC in the retina are partly mediated via the Tie2 receptor. The current Results offer an innovative approach that may lead to the development of novel therapeutic strategies targeting CNV.

Protease activated receptor 1 distribution in the neuroretina of mice under physiological conditions and in diabetes

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Purpose: The aim of this study was to characterize the expression pattern of Protease Activated Receptor 1 (PAR1) in the neurorteina, under physiological conditions, and in diabetes .
Methods: Diabetes was induced in C57BL/6J male mice (n=8) at the age of 8 weeks by intraperitoneal injection of Streptozotocin (150 mg/kg). Five weeks following diabetes induction the eyes were removed from diabetic mice and 10 age-similar healthy C57BL/6J male mice and processed for indirect immunofluorescence analysis. PAR1 -/- mice were used as control (n=4 eyes). Paraffin- and frozen retinal sections were stained with an antibody directed against PAR1 (N2-11, Novus, USA) .
Results: A clear PAR1 staining was observed in the nuclei in the ganglion cell layer, inner nuclear layer and outer nuclear layer of diabetic mice. Significantly weaker staining was observed in these layers in the retinas of control non-diabetic mice. No staining was observed in PAR1 -/- mouse retinal sections .
Conclusions: To the best of our knowledge this is the first demonstration of specific PAR1 staining in the nuclei of retinal photoreceptors. The higher expression level of PAR1 was observed in the eyes of diabetic mice may suggest a possible association between PAR1 expression level in the neuro-retina and diabetes .

Migration of mononuclear phagocytes into the subretina contributes to retinal degeneration in the Leber congenital amaurosis RPE65/rd12 mouse model

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"**Purpose**: To assess the role of Mononuclear Phagocytes (MP) in retinal degeneration in the RPE65/rd12 mouse model

Methods: Thirty-nine RPE65/rd12 and ten C57BL/6J wild-type mice were used. RPE65/rd12 mice were treated with minocycline (50 mg/kg) or a similar volume of PBS by daily intraperitoneal injection for 8 weeks starting at age post-natal day 28 (p28). MP density in the sub-retina was determined by choroid-RPE flat-mount analysis and retinal function was determined by electroretinogram (ERG).

Results: MPs in the wild type C57BL/6J retinas at p28 and p84 were exclusively located in the inner retinal layers. In RPE65/rd12 retinas, MPs migrated into the sub-retina as early as p56. By p84 the density of MPs in the sub-retina increased by nearly 3-fold. MP density in the central retina was higher by 2 fold compared with the peripheral retina. Minocycline treatment reduced MP density in the peripheral sub-retina by 59% compared with placebo- treated mice 16.2±1.8) cell/mm^2 vs. 27.2 ±2.4cell/mm^2, p<0.01 .(Maximal ERG b-wave responses were significantly higher in minocycline- vs. placebo- treated mice under light adaptation conditions following 8 weeks of treatment) mean ±SE: 199µv28±µv vs. 129.8µv±9.8µv, p=0.016 .(

Conclusions: MP migration into the subretina contributes to retinal degeneration in RPE65/rd12 mice. These **Results** may provide a rationale for developing treatments that target MP migration for treating LCA and possibly other RP forms associated with retinoid cycle defects.

PRCD interacts with TULP1 and TUB in the mammalian retina

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Purpose: PRCD is a unique photoreceptor disc component, which is involved in outer segment disc formation. The Purpose of this work was to identify PRCD-binding proteins in the retina.
Methods: PRCD protein-protein interactions were identified implementing the Ras Recruitment System (RRS), a cytoplasmic-based yeast two-hybrid system, on a bovine retina cDNA library. Identified interactions were confirmed by co-immunoprecipitation. Immunostaining was used to test the effect of PRCD interactions in the murine retina.
Results: We identified an interaction of PRCD with Tubby-like protein 1 (TULP1). Co-immunoprecipitation in transfected mammalian cells confirmed that PRCD interacts with TULP1, as well as with its homolog, TUB. These interactions were mediated by TULP1 and TUB highly conserved C-terminal tubby domain. PRCD localization was altered in retinas of TULP1-deficient mice.
Conclusions: PRCD is a unique photoreceptor disc component. Our Results show that TULP1, which is involved in the vesicular trafficking of several photoreceptor proteins from the inner segment to the outer segment, is required for PRCD exclusive localization to photoreceptor outer segment discs.

In vivo and histological studies of normal and blind eyes of the Common octopus (Octopus vulgaris)

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Purpose: To study normal and blind eyes of captive Common octopuses (Octopus vulgaris) ante- and post-mortem.
Methods: Eyes of one young (600 gr) normal, and two elderly (2.4-5.5 kg) blind, animals were studied. Slit lamp biomicroscopy was conducted following anesthesia with 55 mM MgCl2 and 1% w/v of 96% ethanol in sea water. Indirect ophthalmoscopy was not conducted, as the pupil did not dilate despite application of topical tropicamide and atropine. Following euthanasia, processing and H&E staining, eyes were studied histopathologically.
Results: Octopuses have no cornea; the eye is protected by fused, transparent eyelids. The ciliary papilla epithelium produces the fibers of the lens and holds the lens in place. The lens is divided into two unequal parts - a small external, and a large internal part, separated by a septum. A muscular ring joins scleral cartilage to the ciliary papilla, allowing for accommodation by lens movement rather than by change in diameter. The retina is inverted, with photoreceptive cells facing the vitreous. Pigment migrates through the retina, changing location as a function of light intensity. Small optic nerve subunits extend through the cartilaginous sclera to the optic lobe of the brain. In the elderly female, severe inflammation and protein changes (analogous to mammalian Morgagnian globules) were seen in the lens, in correlation with the cataract observed biomicroscopically in vivo. Severe inflammation and degeneration was seen in the retinas and ciliary papillas. Clusters of coccoid parasites (Aggregata sp) were seen in many of the blood vessels. In the elderly male, ciliary papilla vacuolation and retinal degeneration were seen. In both tissues, inflammatory changes, characterized by infiltration of hemocytes (analogous to mammalian neutrophils), were mild, as were the lenticular changes.
Conclusions: The eyes of octopuses and mammals are both simple, camera type, eyes, demonstrating convergent evolution in aquatic and terrestrial species. However, there are many anatomic differences. Octopuses can be blinded by cataract, retinitis and retinal degeneration, which may be caused by parasitic infestation in elderly animals.

Protective effects of blue light-blocking cages in the RCS rat model of retinitis pigmentosa

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Purpose: To investigate the effect of housing RCS rats in blue light-blocking cages on retinal degeneration rate.
Methods: RCS rats were born and raised in white opaque cages (n=50) or orange-tinted clear cages (n=43) in the Sheba Medical Center animal facility under dim cyclic light (12 h at < 5 lx, 12 h in the dark). Rats were examined weekly for retinal structure by Spectral Domain Optical Coherence Tomography, blue autofluorescence fundus imaging and histopathology. Retinal function was assessed by Electroretinogram (ERG).
Results: At age of 6 weeks, the SD-OCT thickness of the outer nuclear layer was 2 fold higher in rats raised in the blue light-blocking cages compared with the white cages (mean♀ ± standard error: 33.47um1.88 ±♀ um vs. 14.58um0.99 ±♀um, respectively, p<0.0001). Blue autofluorescence fundus imaging revealed significantly smaller hypofluorescent lesions in rats born and raised in blue light-blocking cages at all ages. At age 10 weeks the hypofluorescent area was 6.3 fold smaller in these rats compared with controls (p=0.035). Significantly higher mean b-wave responses were recorded in rats born and raised in the blue light-blocking cages as early as 4 weeks of age (mean♀± standard error: 316.2 uV32.2 ±♀ uV vs. 194.3uV ±♀ 53.2uV, p=0.024). At age of 8 weeks, rats born and raised in white cages had nearly undetectable b-wave (3.0uV0.78 ±♀uV) whereas rats born and raised in blue light-blocking cages white cages had a significantly higher b-wave (56.75uV10.6 ±♀uV, p<0.001).
Conclusions: Shielding RCS rats from blue light significantly reduced the rate of retinal degeneration and preserved retinal function and structure. Translational implications may include yellow-tinted IOL and glasses for RP patients.

CCR1 Receptor as Therapeutic Target in Atrophic AMD

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Purpose: Development and progression of atrophic age-related macular degeneration (aAMD) was associated with mononuclear cells. In particular, we have previously revealed the deleterious effect of M2a human monocytes-derived macrophages (hmd¸) ex-vivo and in model of photic retinal injury in mice. We have also identified CCR1 receptor as potential key signaling pathway mediating M2a hmd¸ induced retinal injury. Here, we evaluate the role of the CCR1 receptor as a potential therapeutic target for aAMD.
Method: CCR1 antagonist was administrated via subcutaneous injection twice a day starting immediately after light injury (n=10) for 5 days. Visual function and outer nuclear layer thickness were evaluated via electroretinography and histological analysis, respectively. Expression level of CCR1 receptor, microglial and macrophages infiltration, and Muller cells activation were compared between treated and control mice using quantitative real-time PCR (qPCR) and immunohistochemistry (n=6). Expression of CCR1 receptor was also assessed in RD10 mice and in aged (18 months) mice (n=6 and n=3, respectively).
Results: Inhibition of CCR1 receptor showed a protective effect in the light-damaged mice according to ERG (1.36-fold, p=0.02), and histological analysis (1.21-fold, p=0.03). A reduction of the expression of CCR1 receptor as well as the number of activated-microglial cells (0.44-fold, p=0.05) and infiltrated-macrophages (0.41-fold, p=0.005) were found in sections from eyes of treated mice compared with control mice. CCR1 inhibition also ameliorate Muller cell activation with decreased expression of CCL2, CXCL1 and CXCL10 (n=6, 0.10- fold, p=0.01; 0.52-fold, p=0.01; 0.21-fold, p=0.05, respectively). Finally, increased expression of CCR1 receptor was associated with the level of retinal degeneration in RD10 mice and with aged mice.
Conclusion: Inhibition of the CCR1 receptor may serve as a novel therapeutic target in aAMD. Additional investigations are required to determine the underlying mechanism of photoreceptor death in the context of CCR1 receptor activation.

Preschool vision screening and adherence to referrals in ethnic groups in Israel: a prospective study

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Purpose: Studies show that the critical age for vision screening for detection of amblyogenic risk factors is between ages 3-5 though there is little evidence for compliance with screening recommendations. This prospective population-based study determined the compliance of parents with screening recommendations, and examined the relationship between ethnicity, gender, and compliance.

Methods: Preventative care for children 0-6 years of age is given in Israel via Maternal Child Health Clinics (MCHC). Children ages of 3-5 in the Jerusalem District MCHC were invited for vision screening and examined by optometrists between 12/2017-07/2019. Each MCHC serves a homogeneous population that is either ultra-Orthodox (UO) or secular (S) Jewish or Arab (A). Exams included distance visual acuity (Lea chart, decimal units) and retinoscopy. Referral criteria were based on the APPOS guidelines. Parents were surveyed regarding follow-up, diagnoses, and treatments 6 months post screening. Screening failure and compliance rates were reported as proportions with 95% Confidence Intervals (CI). Compliance with referrals was analyzed using logistic regression.

Results: A total of 2893 parents were called to schedule vision screening, and 1512 children were screened (52.3%, 95% CI 50.4-54.1%). Gender and ethnicity were not significantly associated with compliance. A total of 364 children (24.1%, 95%CI 21.9-26.3%) failed the screening and were referred to ophthalmology. The 6 month post screening survey demonstrated that 157 (43.1%) children underwent full eye examination and 35.6% of these had abnormal Results. The average time between screening and full exam was 2.4±2.1 months (0.03±10 range). In contrast, 189 children (54.6%), were not taken for a full exam and three were lost to follow up. There was no difference in adherence between genders (48.9% vs. 40.0%, females and males, respectively, p=0.3). Arabs were more likely to adhere than Jews (60.9% vs. 41.9%, p<0.03) and there was no difference between UO and S Jews (41.7% vs. 42.3%, p=0.9). After adjustment for gender, the odds ratio for adherence between Jews and Arabs was 0.31 95%CI, 0.11-0.80.

Conclusions: Half the parents brought their children in for vision screening. A quarter of children failed vision screening and only 43% were taken to a full eye exam. While adherence to ophthalmic care is low in Israel, the Arab minority may be more likely to comply with screening referrals.

Myopia and childhood migration: a study of 607,862 adolescents

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Purpose: Immigrational studies can shed light on myopia development and reveal high-risk populations. To this end, we investigated the association between immigration, age at immigration, and myopia occurrence at adolescence. Design: Population-based, retrospective, cross-sectional study. Participants: 607,862 adolescents, Israeli-born and immigrants, with origins in the former Union of Soviet Socialist Republics (USSR), Ethiopia or Israeli-natives, assessed for medical fitness for mandatory military service at age 17 years between 1993 and 2016.

Methods: Refraction was determined using subjective visual acuity followed by noncycloplegic autorefraction and subjective validation. Myopia was defined as -0.75 diopters myopia or worse in each principal meridian in the right eye. High myopia was defined as -0.75 diopters myopia or worse in each principal meridian and a spherical equivalent of -6.00 D or worse, in the right eye. Age at immigration was categorized into 0-5, 6-11 and 12-19 years. Univariate and multivariable logistic regression models were made. Myopia odds ratios (ORs) were calculated according to immigrational status, with Israel-natives as controls. Next, myopia ORs were calculated according to age at immigration, with Israeli-born of same origin as controls.

Main Outcome Measures: Myopia prevalence and ORs

Results: Myopia was less prevalent among immigrants than among Israeli-natives. When stratified according to age at immigration, a decrease in myopia prevalence and ORs with increasing age at migration categories was observed, most prominent in immigrants arriving after age 11 years, who also had lower high myopia ORs. USSR and Ethiopian immigrants arriving after age 11 years had myopia OR of 0.65 (95% CI 0.63-0.67; p< 10-205) and 0.52 (95% CI 0.46-0.58; p<10-27) compared to the Israeli-born of same origin. Notably, Ethiopians arriving earlier than age 5 had a two-fold myopia OR than those migrating after age 11.

Conclusion: Immigrants arriving after age 11 years had marked lower ORs for myopia and high myopia relative to the Israeli-born or to those arriving at early childhood, likely due to environmental and lifestyle changes. Differences between immigrants arriving until age 5 to those arriving between 6-11 years were relatively smaller, suggesting exposures at elementary-school age play a greater role in our population.

Lighting and epidemiologic risk factors for myopia in preschool children of the Arab population in Israel

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Purpose: Myopia is known to be associated with genetic and environmental factors such as outdoor activities, near work and night-light sleeping during childhood. In animal models increased levels of lightning were found to be associated with decreased rates of myopia, however not much is known in children regarding indoor light levels and myopia. This research aimed to measure the effect of Kindergarten lightning intensity on refraction of Arab preschool children in Israel.
Methods: A total of 1186 children aged 3-5 years from 27 preschools from the Bakaa-Gat area who had been enrolled there at least 6 months were examined. For each child, the pupil size, corneal reflex and refractive errors were measured by the Plus Optix photoscreener. Children with moderate to high myopia or hyperopia (>+3.00 or >-3.00 D spherical equivalent (SE)) in the photoscreener or other ocular pathology were excluded. Hyperopia and Myopia were classified as SE >+0.25 and >-0.25 D, respectively. The lightning levels were tested by Luxmeter device (Lx) inside the preschools (mean of 4 measured points). Socioeconomic data, medical history and lifestyle were collected from questionnaires of 500 randomly selected parents whose children participated in this study. Data analysis was done by Pearson coefficient and Chi-square tests.
Results: Out of 1073 children that were included, 25 children (2.32%) were found to have myopia and the rest (1048) with emmetropia or hyperopia. Fifty two children who met the inclusion criteria presented with glasses. Mean lightning of all tested preschools was 135.69±508.57 Lx. Mean SE refraction was 0.71±0.68 in right eye (RE) and 0.60±0.69 in the left eye (LE). Correlation between SE of the right (RE) and left (LE) eyes was r=0.81; P<0.001, so only RE was analyzed. Indoor lightning intensity was found to be weekly correlated with refraction (r=0.19; P<0.001). Of the children who presented with glasses, their need for glasses was not found to be correlated with parental smoking, education and glasses wear (P=0.44, P=0.92 and P=0.28, respectively).
Conclusions: Lightning exposure at indoor luminance levels is weakly yet significantly correlated with the degree of myopia. This suggests that exposing children to different light levels only part of the day might play a role in refractive development. None of the parental epidemiologic factors were associated with children need to wear glasses.

Vismodegib for Periocular Locally Advanced Basal Cell Carcinoma

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Purpose: To report the efficacy and safety of vismodegib on a large population of patients with periocular locally advanced basal cell carcinoma (POLA-BCC) based on data from the Safety Events in Vismodegib (STEVIE) trial.
Design and setting: Secondary post hoc subgroup analysis from the STEVIE single-arm, multicenter, open-label study.
Methods: Background, treatment, and outcome data from the STEVIE study database of all patients with POLA and metastatic BCC treated with vismodegib were collected and analyzed.
Results: Ocular or periocular involvement was found in 244 patients after screening all 1215 STEVIE study patients (20%). Locally advanced BCC was diagnosed in 238 of the 244 (97.5%) patients and metastatic BCC in 6 (2.5%) patients. The median duration of exposure to vismodegib was 40 weeks (interquartile range 2078.0“€ƛ): specifically, 39.7 weeks (range 19.976.0“€ƛ) for POLA-BCC and 92.4 weeks (range 53.2163.0“€ƛ) for metastatic BCC. Sixty-nine (28%) patients sustained adverse events (alopecia, muscle spasms, dysgeusia, weight loss, decreased appetite, asthenia, ageusia, nausea, fatigue, and diarrhea). Two-hundred and thirty-two patients (95%) sustained more than one side effect (avg. 5.75). Discontinuation of vismodegib due to an adverse event was recorded in 58 (23.7%) patients. During the study, 22 (9%) of the 244 patients died, 70 (28.7%) achieved complete response, and 94 (38.5%) achieved partial response, yielding an overall response rate of 67.2%.
Conclusions: Vismodegib is well-tolerated by patients with POLA-BCC. Data from the STEVIE trial revealed that it has a safety pro¡¬• le consistent with that reported in previous studies. It is an efficient treatment option that provides a promising prognosis for patients with ocular and periocular BCC.

Retinoblastoma presentation: Africa vs Europe

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Purpose To compare the travel burden and stage of presentation between retinoblastoma (Rb) patients from Africa and Europe.

Methods

A cross-sectional analysis of new Rb patients from Africa and Europe that presented to local Rb centers during a single year. Clinical variables at presentation, including the travel distance from home to Rb center, were compared between patients from each continent. Data on country population size and surface area were retrieved from the World Population Prospects.

Results Overall, 1,024 patients from 43 African countries and 522 patients from 40 European countries were included. Using an average incidence figure of 1/17,000 live births, ג€˜capture ratesג€™ were 42.2% and 109.7% of expected cases from Africa and Europe, respectively. The mean number of Rb centers per country in Africa and Europe, mean country population size and surface area in both continents were comparable (p‰¥0.22ג). To reach an Rb center, patients from Europe traveled on average 421.8 km (95%CI 328.6-537.5) compared to 185.7 km (95%CI 168.0-205.2) for African patients (p<0.001). Mean age at time of diagnosis was 22.0 months (95%CI 19.0-26.0) for European and 30.9 months (95%CI 28.7-32.8) for African patients (p<0.001). Rb cases with positive family history were found in 2.8% vs 8.3% of the African and European samples, respectively (p<0.001). Significantly more patients from Africa compared to Europe had at time of diagnosis advanced Rb (p<0.001).

Conclusions Rb patients in African countries compared to their European counterparts presented older with more advanced disease, and demonstrated a smaller proportion of familial Rb, probably because many do not reach a child-bearing age. Assuming that nearly all Rb centers in the participating African countries were recruited, our findings suggest that these centers serve mainly patients residing in close vicinity, whereas for those residing further away distance is a barrier.

Scleral melting after Ru-106 brachytherapy for uveal melanoma

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Purpose: Scleral melting (SM) is a rare complication among patients treated by brachytherapy for uveal melanoma. Interestingly, the majority of the cases are seen in anteriorly localized tumors, like the ciliary body (CB) melanoma. There are no obvious risks factors that can help predict the development of this complication. The **Purpose** of our study is to determine the prevalence of SM secondary to Ru-106 plaque brachytherapy and assess the associated risks factors.
Methods: A retrospective review and analysis of a cohort of 106 patients with CB melanoma who were treated with RU-106 plaques, in the Ocular Oncology Service of the Hadassah University Hospital from 1991 to 2019. We analyzed whether the following factors are related to SM: age, sex, tumor location, tumor size, radiation dose and time of exposure. Statistical analysis was done with JMP. The inclusion criteria were a diagnosis of ciliary body CB melanoma and information in the medical record. Patients who had metastasis, or undetermined CB tumor were excluded.
Results: Of the 106 cases, 10 develop scleral necrosis or melting. Eight (80%) of the cases of the melting occurred in woman. A CCB Ru-106 plaque was the plaque most used (36.7%), but CIB plaques were seen in most cases of SM (40%). Mean tumor high was 6.32 mm and the most common tumor location was cilio-choroidal in 80% of the SM cases. The mean dose of radiation to the base was 69,037 cGys and to the apex 9,872 cGys. The mean time of exposure was 6.5 days and the median time from radiation exposure to melting was 24 months. The most common treatment was observation only (3) and conjunctivoplasty (3). Contingency analysis was done each of the variables just mentioned. These factors were not statistically related to scleral melting.
Conclusions:Scleral melting in CB melanoma can occur in up to 10% of patients after Ru-plaque treatment. This condition is not related to the extent of the tumor beyond the CB, the dose or time of exposure. In our study, we did not find factors that can predict which patients are at risk of developing scleral melting.

A novel type of corneal epitheliopathy from a new class of antibody-drug conjugate anti-cancer treatments

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Purpose: Antibody-drug conjugates (ADC) is a new class of anti-cancer treatments utilizing monoclonal antibodies conjugated to cytotoxic agents by specialized chemical linkers targeting the chemotherapy to specific cancers, e.g. glioblastoma, multiple myeloma or breast cancer. The **Purpose** of this work is to describe the ocular side effects of this new class of drugs.

Methods: A retrospective analysis of the ocular side effects in patients who received ADC either as part of clinical trials or clinical trial-related companionate use of the same drugs. We describe the phenomenon, its management, and prognosis.

Results: Five patients (2 women) were treated with Depatux M (EGFR IGg1 monoclonal antibody conjugated to the tubulin inhibitor monomethyl auristatin F) for glioblastoma, one man was treated with Belantamab mafodotin (anti-BCMA monoclonal antibody bound to auristatin F) for multiple myeloma, and one woman for metastatic breast cancer with Trastuzumab Deruxtecan. All patients developed corneal subepithelial pseudo-microcysts that started at the limbus and migrated centripetally with only mild superficial punctate keratopathy. We interpreted these changes as a sign of a limbal stem cell (LSC) damage. The pseudo-microcysts could be best seen with retro-illumination, and could barely be noted on anterior OCT scans (Cassia). Visual acuity diminished as the lesions were close to the corneal center. Vasoconstricting drops were recommended immediately prior to treatment and cold compresses during infusion to minimize side effects. Capacious lubrication helped but was insufficient. Bandage contact lenses alleviated symptoms and slightly improved visual acuity. All changes resolved within two weeks of treatment cessation.

Conclusions: We speculate that the findings indicate temporary damage to the limbal stem cells. It is still unclear whether the ADC by themselves damage the LTCs, is it the auristatin, or the antibodies. The release of data from animal studies conducted by the companies may shed light on the mechanism of this side effect. The growing number of ADCs required that clinicians are aware of this side effect and its management.

Adhesion Strength and Rolling Properties of Descemet Membrane Endothelial Keratoplasty Grafts in a Rabbit Eye Model

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PURPOSE. To investigate the optimal time for Descemet membrane endothelial keratoplasty (DMEK) graft peeling, and to analyze the rolling properties of endothelial denuded grafts in a rabbit eye model.

METHODS. The vertical peeling force required to peel 1mm wide Descemet membrane (DM) strips, was measured as the change in weight of the system during force application in a rabbit model. Twenty-one rabbit corneoscleral rims were stored in phosphate-buffered saline (PBS) at 4°C, and force analysis was performed at days 1, 5, or 21 after harvesting. After half of the strips of day 5 corneas were peeled and analyzed, the rims were moved to Optisol GS at 4°C, and the remaining strips were peeled off for force analysis at day 10. Separate DM grafts (n=7) were analyzed by intraoperative optical coherence tomography (OCT) to determine the tissue rolling diameter before and after removal of endothelial cells by a swab. Unpaired t-test was used for statistical analysis.

RESULTS. There was a decrease in DM peeling force (p=0.008) between days 1 and 5 (556.04±111.76 and 324.30±96.4 mg, respectively), and no difference between days 5 and 21 (p=0.53). Peeling force for day 5 corneas placed in Optisol was higher at day 10 (324.30±96.4 to 669.92±166.24 mg, p=0.005). The average rolling diameter of DM grafts was similar before and after the removal of endothelial cells (257.9±131.1 and 249.8±126.6¼m, respectively).

CONCLUSIONS. DMEK Graft procurement could be potentially facilitated by lower DM-stromal adhesion strength at day five after obtaining corneoscleral rims, in a rabbit eye model. Time in storage medium may influence adhesion strength. Endothelial cells do not appear to play a significant role in the rolling diameter of DM grafts.

Femtosecond Laser Assisted In Situ Keratomileusis versus Photorefractive Keratectomy for Correction of Hyperopia

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Purpose: to compare the outcomes of alcohol-assisted or transepithelial PRK with femtosecond LASIK (FS-LASIK) for the correction of hyperopia.
Methods: A retrospective cohort study design was used. The study included patients with hyperopia, with or without concomitant astigmatism, who were treated with either FS-LASIK or alcohol-assisted or transepithelial PRK (PRK group) from January 2013 through December 2014. Procedures were performed with the Amaris 500E excimer laser (Schwind eye-tech-solutions GmbH, Kleinostheim, Germany) using an aberration-neutral profile and a 6.0-7.0 mm optical ablation zone. Background, clinical data and outcomes, including refractive Results, predictability, safety and efficacy, were collected from patients' files. A comparison between eyes treated with FS-LASIK and PRK was performed.
Results: The PRK group was comprised of 23 eyes and the FS-LASIK group of 139 eyes.
At final follow-up, the mean manifest refraction spherical equivalent was -0.4950.709 ±ۦ D in the PRK group and +0.0810.655 ±ۦ D in the FS-LASIK group (P < 0.001). 56.5% and 69.4% of eyes were within±0.50ۦ D of the attempted spherical equivalent correction, respectively (P = 0.231). Efficacy index values were 0.800.26 ±ۦ in the PRK group and 0.920.20 ±ۦ in the FS-LASIK group (P = 0.034). Corresponding safety indices were 0.820.23 ±ۦ and 0.960.16 ±ۦ (P = 0.003). Final uncorrected visual acuity of 20/40 or better was achieved in 78.3% and 89.6% of eyes, respectively (P = 0.162).
Conclusions: Our Results suggest that better predictability, safety and efficacy are achieved with FS-LASIK than PRK surgery when correcting a hyperopic refractive error.

Two novel stem cell populations with distinct cycling properties

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Purpose: To explore limbal stem cell (SC) heterogeneity and pathways
Methods: We used murine K15-GFP transgene that labels the limbus with green fluorescent protein and R26R-Confetti;K14-CreERT2 that allows multi-color cell lineage tracing of limbal SCs with 4 different fluorescent genes. Immunostaining and gene expression study was performed to track cell divisions and active signaling pathways.
Results: Nucleotide incorporation assays and Ki67 staining revealed that K15-GFP positive cells divided frequently. However, a discrete K15-GFP negative cell population was relatively slow cycling. Gene expression study revealed a set of specific markers and pathways expressed exclusively by each cell populations. Moreover, functional study and lineage tracing in vivo revealed the hierarchy and specific signaling pathway that are essential for the transition between quiescent and active SC states.
Conclusions: Altogether, this study reveals two novel SC populations that co-exist in the limbus, and suggests new markers, pathways and proliferative properties for LSCs in the cornea.

A novel quantification system of corneal staining in patients wfluorescein ith dry eyes

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Purpose: to evaluate the correlation between measured corneal fluorescein staining area (CFSA) and symptoms and other clinical measurements of dry eye disease, including NEI.
This was done as part of a large clinical study that evaluated a novel treatment for dry eye.

Methods: Sjogren syndrome dry eye disease patients were followed sequentially with symptoms, artificial tears daily use, Schirmer test result, tear break up time (TBUT) and national eye institute (NEI) score recorded. CFSA was analyzed using a computer software.

Results: 5-7 images from each eye of 12 patients were analyzed (total=156 images). Significant correlation was demonstrated between CFSA and the 10 symptoms score, artificial tears daily use, eye secretion report, TBUT, NEI score ($P < 0.05$).
Conclusion: the **Results** show a correlation between dry eye symptoms and objective validated measures and the corneal fluorescein staining area (CFSA) analyzed with a computer software. CFSA can use as an objective quantitively tool for evaluation of dry eye disease.

Clinical Outcomes of Descemet Membrane Endothelial keratoplasty in Patients Over 85 Years old

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Purpose: Many surgeons are reluctant to perform corneal transplantation in very elderly patients due to expected long rehabilitation, risk of complications and presumed difficulty to adhere to post-operative regime. DMEK, however, provides very rapid visual rehabilitation, lower risk of rejection and less post-operative care than other types of transplantations, thus age may not be a decision-making factor. We present our experience with patients over 85 years of age that underwent DMEK compared to DMEK patients under 70 years.
Methods: The data of all patients undergoing uneventful DMEK surgery between 2016 to 2018 in our institute, with at-least 3 months of follow-up were retrospectively collected. Data collected included patient demographic details, indication for surgery, visual acuity and rate of postoperative complications including graft failure. Clinical outcomes comparison between patients over 85 years old to patients under 70 years old were carried out. Kaplanג€“Meier plot served to assess graft failure rate in both groups.
Result: Forty-eight DMEK cases were included in the study, 27 DMEK in patients over 85 years (mean 87.859% ,±2.7¸female) and 21 DMEK cases in patients under 70 years (mean 59.359.1% ,±7.4¸female). Older patients had higher rate of bullous keratopathy prior to surgery (59.3% vs. 13.6%, p<0.001), lower rate of Fuchs dystrophy (14.87% vs 54.5%, p=0.004) and higher proportion of pre-operative glaucoma (38.8% vs 14.2%, p=0.01). Both groups had a significant vision improvement following surgery. There were no significant differences in rates of graft detachment (p=0.186), number of rebubbling procedures (p=0.1), pupillary block (p=1.0), cystoid macular edema (p=0.62) and infectious keratitis (p=0.24). However, over the entire follow-up period, the >85 years group had higher failure rate (29.6% vs 4.7%, p=0.05), shorter graft survival time (estimated time to failure 29.0±4.8¸ vs 91.6±5.2¸months, p=0.002) and 13.2 times higher relative risk for graft failure (p=0.01), compared to the <70 years group.
Conclusions: DMEK surgery is effective in the elderly population over 85 years with significant improvement in visual acuity without major early postoperative complications. However, incidence of graft failure following DMEK in the older age group is higher.

Repeatability and Reproducibility of Corneal Epithelial Thickness Mapping with Spectral Domain Optical Coherence Tomography

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Purpose: To evaluate the performance of the epithelial thickness mapping (ETM) of the iVue spectral domain optical coherence tomography (SD-OCT) (Optovue Inc., Fremont, CA) in normal and diseased cornea eyes.

Methods: Sixty eyes of 60 subjects were recruited for the study that included normal subjects (n=12) and patients with corneal diseases (12 each with dry eye syndrome (DES), contact lens (CL) wear, post laser refractive surgery (LRS), and keratoconus (KCN)). Three repeated scans were acquired on 3 iVue SD-OCTs with device-designated operators from consented subjects. Each subject was scanned on each device. Repeatability (based on random error of repeated scans) and reproducibility (including the random error and the instrument/operator variability) were assessed based on spatial zones derived from a 6 mm diameter corneal ETM centered on the pupil and compared between the groups.

Results: Fifty-nine eyes qualified for final analysis. Seventy-one of 598 acquired scans (11.9%) were excluded due to scan quality concerns. The percentage of disqualified scans was similar across normal (10.7%) and diseased eyes (12.1%). Of 527 qualified scans, 40 (7.6%) scans required manual edits of the segmentation lines. Repeatability and reproducibility **Results** were similar, indicating minimal device/operator variability for both groups. Repeatability and reproducibility were similar in all sub-groups of cornea patients, excluding the DES group, for which reproducibility was significantly lower (range 3.2-5.5% for DES patients and 1.1-2.9% for normal subjects).

Conclusions: The iVue SD-OCT provides good corneal ETM repeatability and reproducibility in normal and diseased cornea eyes through all map zones.

Automatic detection of complete retinal pigment epithelium and outer retinal atrophy in optical coherence tomography scans using deep learning

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Background/**Purpose** Complete retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA) is an important end stage of retinal degenerations and dystrophies. Objective quantification of cRORA is needed for clinical diagnosis, follow-up, treatment efficacy evaluation, and clinical research. Optical coherence tomography (OCT) has become an essential imaging technology to evaluate the macula. However, the examination of OCT and manual delineation of atrophy for the Purposes of atrophy lesion quantification is tedious, time-consuming and error-prone. Our Purpose is to develop an automatic method for the detection and quantification of complete RPE and cRORA in OCT scans using artificial intelligence based deep learning Methods.

Methods We have developed an automatic method for the classification of retinal atrophy in OCT scans. Our method classifies pixel-wide vertical columns in each OCT slice as showing atrophy or not using a convolutional neural network (CNN). The CNN is trained offline on manually annotated OCT scan slices in which intervals of vertical columns of atrophy have been labelled. The classification of each column is performed on a vertical patch formed by adjacent neighboring columns (three to the left and three to the right of the column). The CNN is then used online to automatically detect atrophy intervals in the slices of a new OCT scan.
The two ophthalmologist co-authors manually annotated 2,941 slices of 56 OCT scans of patients with cRORA. The CNN was trained on 2,049 slices (44 scans), and then validated on 362 slices (6 scans) and tested on 530 slices (6 scans). The correspondence between the manual and the CNN classifications was measured with the mean AUC (area under the receiver operating characteristic curve), and the mean precision, sensitivity and specificity.
Results The AUC on the test set is 0.87. The mean precision, sensitivity, and specificity are 0.86, 0.80, 0.81, respectively. These are Results are close to the measured AUC inter-observer variability of 0.83 on 425 slices.
Conclusion Automated detection and quantification of cRORA using CNN classification in OCT scans achieved expert-level performance. Our method may be a useful clinical decision support and research tool for the diagnosis, follow-up and treatment of retinal degenerations and dystrophies.

Full thickness macular defects in AMD: distinguishing between two clinical entities

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Purpose: Full thickness macular defects (FTMD) in Age-related macular degeneration (AMD) may be an expression of the atrophic nature of the disease, in essence atrophic holes (AH). However, they may sometimes represent full thickness Macular Holes (MH), which are not uncommonly concomitant with AMD, due to the disease's rising prevalence. Since AHs currently have no well-established treatment, whereas MH are potentially treatable by surgical measures, an accurate diagnosis is essential.

This study aims to utilize spectral domain optical coherence tomography (OCT) for investigating morphologic abnormalities of FTMDs in order to differentiate AHs from MHs.

Methods: This study is a multicenter observational chart review. Clinical charts and OCT images of all patients, diagnosed with FTMD with underlying AMD between January 2011 and May 2019, were reviewed. OCT images were analyzed and findings recorded by a retina specialist.

Results: of 83 eyes with FTMD, OCT features enabled a distinction between two entities: AH, diagnosed in 51 eyes, and MH, diagnosed in 32 eyes. MHs were significantly associated with rounded FTMD borders ($p<0.001$), increased perifoveal thickness ($p<0.01$), and presence of intra-retinal fluid ($p<0.01$), or of a free operculum internally to the FTMD ($p<0.01$). AHs featured FTMD bordered by gradually thinning retina ($p<0.001$), a window defect wider than the FTMD ($p<0.001$), and was associated with presence of scar tissue ($p<0.001$), subretinal hyperreflective material ($p<0.05$), and reduced perifoveal thickness ($p<0.05$). The MH inner diameter was smaller than that of AH (mean 882μm and 1199μm, respectively, $p<0.001$), whereas outer diameter was larger in the MH group (893μm and 392μm, respectively, $p>0.01$), making the inner/outer ratio far larger in the AH group (3.5 and 1.2, respectively, $p<0.001$).

Conclusion: An observation of FTMD in AMD patients may present with diagnostic and therapeutic dilemmas. Discerning MH from AH in these patients is possible by using characteristic OCT features as criteria.

Effect of anti-VEGF treatment on choroidal neovascularization flow patterns in age-related macular degeneration assessed by OCTA

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Purpose: Identifying the characteristics of choroidal neovascularization (CNV) is an important key in the diagnosis and treatment of age-related macular degeneration (AMD). Previous studies have described different morphologic patterns of type 1 CNV with OCT Angiography, including "sea fan", "medusa", "tangle" and "dead tree‚€• . The Purpose of this study was to compare morphologic characteristics of CNV flow pattern in treatment-na¯ve versus treated patients suffering from exudative AMD using OCTA.

Methods: Macular OCTA images were acquired using the RTVue XR Avanti with AngioVue. Distinct morphologic patterns and quantifiable features of the neovascular membranes were studied on en face images comparing treatment-na¯ve to treated patients.

Results Sixty-three eyes of 53 patients were included. 22 eyes were treatment-na¯ve, and the mean number of injections in the remaining, treated, eyes was 19.6. Immature lesion was more associated with treatment-na¯ve eyes and hyper-mature lesion was associated with previously treated (p=0.007). Tangle morphology was also associated with treatment-na¯ve eyes (p=0.004), whereas mature core vessels and "sea-fan" morphology were more associated with treated group (p=0.001 and p=0.044, respectively).

Conclusion Treated CNV as opposed to na¯ve CNV develop distinctive morphologic patterns assessed by en face OCTA maps. More work is needed to learn how these features may predict response to treatment.

Long term follow-up of disorganization of the retinal inner layers as a predictor of visual acuity in macular edema secondary to vein occlusion

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Purpose: To investigate disorganization of the retinal inner layers (DRIL), as a long term follow-up biomarker in macular edema (ME) secondary to retinal vein occlusion (RVO).
Methods: Retrospective single-center study of patients with treatment-naïve ME secondary to RVO, treated and followed-up between January 2011 and November 2019. Medical records and spectral-domain optical coherence tomography (SD-OCT) images were collected and analyzed. Key time points: baseline, 4-month and final visits. Main outcome: final best-corrected visual acuity (BCVA).
Results: A total of 110 eyes (104 patients) were included. Mean follow-up time was 4.2 years (range: 1.75-8.3 years). Mean age was 69±11.6, with 50.9% female. Mean BCVA improved significantly from baseline to final visit (p=0.002). In univariate analysis, baseline and final BCVA were significantly correlated to baseline central cross section (CCS) (p<0.0001 & p=0.026), central subfield thickness (CST) (p<0.0001 & p=0.013), central Max (CM) (p<0.0001 & p=0.017), volume (p<0.0001 & p=0.004), DRIL (p=0.001 & p=0.01), external limiting membrane (ELM) disruption (p<0.0001 & p=0.001), visible cone outer segment tips (COST) (p<0.0001 & p=0.004) & Ellipsoid zone (EZ) disruption (p<0.0001 & p=0.003). Baseline epiretinal membrane (ERM) was significantly correlated with final BCVA (p=0.03). Baseline DRIL (p=0.012), CCS (p=0.03) and CST (p=0.01) correlated with final BCVA and remained significant in multivariate analysis. Greater DRIL extent at baseline (700-1000¯¼m) was associated with mean final BCVA logMAR of 0.6, while small extent of DRIL at baseline (<300¯¼m) was associated with mean final BCVA logMAR of 0.35. Four month changes of CCS (p=0.002), CST (p=0.004), CM (p=0.001), ELM disruption (p=0.013) & EZ disruption (p=0.002) correlated with BCVA change from baseline to final visit, with only CST (p=0.04) & CM (p=0.023) remaining significant in multivariate analysis. The mean CST decrease at four months of 150¯¼m and 215¯¼m was associated with BCVA improvement of 1 line and 2 lines respectively at the last visit.
Conclusion: This is the first study to examine long term follow-up of DRIL as a robust biomarker in ME secondary to RVO. Baseline DRIL extent may imply to final BCVA. The initial improvement of CST after first course of treatment could suggest BCVA improvement over a long period of time.

Optimizing the Repeatability of Choriocapillaris Flow Deficit Measurement from Optical Coherence Tomography Angiography

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Purpose: To evaluate the processing technique and slab selection on the repeatability of choriocapillaris (CC) flow deficit (FD) measurements as assessed using optical coherence tomography angiography (OCTA)
Methods: This prospective study included eyes of healthy subjects which were imaged with four foveal-centered 3x3mm consecutive OCTA scans using swept source (SS)-OCTA (PLEX elite 9000, Carl Zeiss Meditec, Dublin, CA). OCTA images were generated using the Max projection, and three 10 -¼m-thick slabs starting 11, 21 and 31 -¼m posterior to the automatically segmented retinal pigment epithelium (RPE) band were exported. Post-imaging processing steps included compensation for signal attenuation, registration and averaging prior to binarization and the CC FD% was computed using the Phansalkarא€™s method with a 43.94 -¼m radius. The intraclass correlation coefficient (ICC) and coefficient of variance (CV) was computed for the four acquisitions to assess the repeatability of the CCFD%. This entire analysis was repeated after separately modulating several parameters: 1) Sum instead of the Max projection, 2) RPE-fit instead of the RPE band as the offset reference, 3) 14.65 and 87.88 -¼m radius values instead of 43.94 -¼m.
Results: Twenty-four healthy eyes of 24 subjects (mean age; 36.4 years old) were enrolled. The CCFD% in the 11-21, 21-31 and 31-41 slabs generated by the Max algorithm and the RPE band showed higher repeatability values (ICC = 0.963, 0.975 and 911; CV = 0.05, 0.05 and 0.05, respectively) than those of the corresponding slabs by the Sum algorithm (ICC = 0.874, 0.916 and 0.776; CV = 0.15, 0.15 and 0.19, respectively) or by the RPE-fit (ICC = 0.865, 0.907 and 0.802; CV = 0.10, 0.06 and 0.06, respectively). Phansalkar radius of 43.94 -¼m was more repeatable than a radius of 14.65 -¼m (ICC = 0.960, 0.960 and 0.912; CV = 0.08, 0.08 and 0.08, respectively) or 87.88 -¼m (ICC = 0.954, 0.958 and 0.894; CV = 0.06, 0.05 and 0.05, respectively). Regardless of which parameter was modulated, the 21-31 micron slab was the most repeatable.
Conclusions: In normal eyes, en face CC SS-OCTA images generated using the Max projection, a 10-¼m thick slab offset of 21 microns below the instrument-generated RPE band, and a Phansalkar radius of 43.94 -¼m, yielded the most repeatable CCFD%. These findings have implications for the design of standardized processing algorithms for quantitative CC assessment.

Choriocapillaris Flow Deficit associated with Intraretinal Hyperreflective Foci in Intermediate Age-Related Macular Degeneration

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Purpose: To evaluate the choriocapillaris (CC) flow deficit (FD) beneath drusen associated with overlying intraretinal-hyperreflective-foci (HRF).

Methods: This retrospective study included patients with intermediate age-related macular degeneration (AMD) who had structural spectral-domain optical coherence tomography (SD-OCT) and OCT-angiography (OCTA) using the Cirrus HD-OCT with Angioplex-software. A 6x6mm volume scan was used for both modalities. Post-imaging processing steps included generation of a drusen map, identification of hyper-reflective dots corresponding to HRF, and generation of a singal-compensated CC slab prior to binarization and CC FD computation. The CC OCTA image was aligned with the drusen+HRF map to define regions-of-interest for CC FD measurement. The CC was quantified below drusen with and without overlying HRF, and within a 150μm-wide ring surrounding the drusen (unaffected by potential HRF-related shadowing), and across the entire 6X6 macular region.

Results: Fifty-three eyes with intermediate AMD were included, 25 eyes with-HRF, and 28 eyes with no-HRF. The mean±SD FD% over the whole 6X6 macular region was 41.1±3.4% in the eyes with-HRF compared to 39.5±3.5% in eyes without-HRF (p=0.001). The mean±SD CC FD% below drusen with-HRF (54.4±9.3%) was significantly greater than below drusen without-HRF (49.6±9.5%; p=0.001). There was a strong positive correlation between the quantity of HRF and the extent of the CC FD (Pearson correlation= 0.81).

Conclusion: Choriocapillaris flow deficits appear to be more severe in eyes with HRF and in particular directly below HRF. As HRF are thought to represent a higher risk or more advanced feature of intermediate AMD, these findings highlight the relationship between the severity of CC FD and overall severity of AMD.

Automatic Detection Of Retinal Disease: Screening and Ophthalmologist Virtual Assistant

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Purpose Development and validation of Artificial Intelligence (AI) Based Technology
For Automatic Assessment of OCT images and clinical decision analysis using decision tree.
Methods A method based on Deep learning tools (Neural networks) and computer aided diagnosis system (CAD), was developed to automatically detect various conditions in 60,000 randomized OCT images.
The objectives of our model were to classify an OCT scan as:
1. Normal, Abnormal or Bad quality.
2. Identifying different biomarkers in each OCT image: Atrophy, Choroidal neovascularization (CNV), Inner distortion, Outer distortion, Drusen, Epiretinal membrane (ERM) , Hyper reflectivity, Inner retinal fluid (IRF), Pigment epithelial detachment (PED), Subretinal fluid (SRF), Tractional retinal detachment (TRD), Vitreomacular traction syndrome (VMTS), Retinal detachment (RD) , Macular hole (MH)/ Macular pseudohole (PMH).
3. Proposed clinical condition: Diabetic retinopathy (DR), Diabetic macular edema (DME), Dry age-related macular degeneration (AMD), Wet AMD, Branch retinal vein occlusion (BRVO), Central Retinal Vein Occlusion (CRVO), Epiretinal membrane (ERM) and Central serous retinopathy (CSC).
4. Classify level of urgency: Checkup, Semi urgent, Urgent.
Main outcome was measured by area under the ROC curve.
Results: The algorithm was trained and evaluated on a longitudinal dataset of 60,000 OCT scans using cross-validation.
Our model achieved an accuracy of 96%±1%ṣd (AUC) on the validation set, after four iterations of training, identifying Normal, Abnormal or Bad quality OCT scan.
A mean of 92%±1%ṣd (AUC) identifying the different biomarkers, a mean of 88%±1%ṣd (AUC) identifying proposed clinical condition and a mean of 92%±1%ṣd (AUC) identifying level of urgency.
In addition, the algorithm offers the clinician a different clinical workup, according to the automated OCT assessment using a decision tree.
Conclusions: The deep learning technique achieves high accuracy in OCT assessment. Our assumption is that our model could surpass this accuracy once trained on a larger dataset and after additional iterations of training.
These findings have important implications in utilizing OCT in both automated screening and in the development of computer-aided diagnosis and management tools in the future that will assist physicians to manage ever-growing workloads, without sacrificing quality of care.

The effect of hemodialysis on individual retinal layers' thickness

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PURPOSE: Retinopathy and nephropathy are characteristic microvascular complications of diabetes mellitus and arterial hypertension. There is disagreement about the effects of hemodialysis on retinal morphology. The aim of this study was to evaluate changes in individual retinal layers' thickness following hemodialysis in patients with end-stage renal disease, using a newly developed advanced image analysis software.
METHODS: A nonrandomized prospective study of patients with end-stage renal disease assessed before and after hemodialysis on the same day. Intraocular pressure and central corneal thickness were analyzed and spectral-domain optical coherence tomography **Results** were automatically segmented using the Orion software and compared.
RESULTS: Thirty-one patients were recruited, seven did not complete all evaluations and 24 were included. The mean age was 66.7±14 years and 62.5% were male. Central corneal thickness did not change following hemodialysis (563.4±30.2μm to 553.1±47.2μm, p=0.247) while intraocular pressure decreased (14.48±2.5 mmHg to 13.16±2.28 mmHg, p=0.028). Individual retinal layers thicknesses showed no significant change including the retinal nerve fiber layer (40.9 ±6.8μm to 40.1 ±5.2μm, p=0.412), ganglion cell and the inner plexiform layer (68.66±8μm to 69.03±7.6μm, p=0.639) and photoreceptor layer (50.26 ±2.8μm to 50.32 ±3.1μm, p=0.869). Total retinal thickness similarly remained constant with 303.7±17.3 μm before and 304.33±18.4μm after hemodialysis (p=0.571).
CONCLUSIONS: In patients with end-stage renal disease hemodialysis does not appear to influence the thickness of retinal layers. These **Results** support the view that hemodialysis does not have a negative impact on the retinal morphology of patients undergoing hemodialysis.

Outcomes of Combined Phaco-Vitrectomy Without Corneal Suturing

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Purpose:To report the outcomes, safety and complications of combined phaco-vitrectomy without preventive suturing of the corneal wounds.
Design:
Retrospective consecutive case series.
Methods:Patients included in this study underwent combined phaco-vitrectomy between January 2018 and June 2019 for various indications including retinal detachment (RD), macular hole (MH), epiretinal membrane (ERM), vitreomacular traction (VMT) and subretinal hemorrhage. The surgery was performed at a single institution by a single retinal surgeon (AH) using 2 different combined anterior and posterior platforms. In all cases the cataract surgery was performed first and vitrectomy followed. In all cased the trocars were inserted after the cataract part. No preventive corneal sutures were planned. Corneal sutures could be used if required.
Results: 23 eyes of 23 patients were included in this study. Suturing of the main corneal incision was necessary in only one case due to a moderate corneal burn. No difficulty was encountered during the trocar insertion despite the absence of prophylactic corneal sutures. Even in intraoperative floppy iris syndrome (IFIS) cases where the iris prolapsed through the corneal incisions during the cataract, the anterior chamber remained firm and stable throughout vitrectomy including trocar insertion and scleral depression. No other complications related to the absence of prophylactic corneal sutures were encountered.
Conclusions: This is the first study to our best knowledge to investigate the outcomes of combined phaco-vitrectomy without preventive corneal suturing. This study proves that preventive corneal suturing are not necessary in combined phaco-vitrectomy. We encountered no complications during surgery or follow-up time related to lack of corneal suturing.

Eye patching after cataract surgery is associated with an increased risk of short-term corneal edema

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Purpose: To evaluate the effect of postoperative eye patching after routine cataract surgery on visual acuity and corneal edema on the first post-operative day.
Setting: Public healthcare center, Shamir Medical Center, Israel.
Methods: This randomized controlled trial included patients undergoing uneventful cataract surgery. Patients were randomized into 2 groups: the surgical eye was patched with a single dose of a local steroid and antibiotic for 24 hours in the first group (patched group), and a plastic shield was used in the second (non-patched group) with local steroid and antibiotic drops used four times daily. The eyes were examined pre-operatively, and on the first post-operative day. Exam included: best corrected visual acuity (BCVA), full slit lamp exam, intra ocular pressure (IOP), anterior chamber depth (ACD), and central corneal thickness (CCT) IOL Master 700 (Zeiss, Germany). Cumulative dissipated energy (CDE) and operation time were recorded for all cases.
Results: One hundred eyes of 100 patients were included in the study, 50 in each group. The average age was 71.9410.39 ±♀, and 48 were female. The two groups did not differ in their pre-operative characteristics. The postoperative increase in CCT 24 hours after surgery was 138♀µm and 70○ µm in the patches group as compared to the non-patched group respectively (p= 0.001). BCVA on the first post-operative day was 0.5±0.45¸LogMAR (Snellen equivalent 6/18) and 0.3±0.3¸LogMAR (Snellen equivalent 6/12) in the patched group and non-patched group respectively (p=0.01). There was no difference in CDE (11.33±9.2¸and 10.22±7.3¸ p= 0.94) between the two groups.
Conclusions: Eye patching after routine cataract surgery is associated with slower visual recovery and an increase in corneal edema on the first post-operative day.

The Effect of Anterior Chamber Depth, Lens Thickness, and White-To-White Measurements on The Barrett Universal II Formula Calculations

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Purpose: To examine the contribution of anterior chamber depth (ACD), lens thickness (LT) and white-to-white (WTW) measurements to intraocular lens (IOL) power calculations using the Barrett Universal II (BUII) formula.

Methods: This is a comparative study. Biometry measurements taken with the IOL Master 700 of consecutive patients undergoing cataract extraction surgery between January and October 2019 were reviewed. IOL power was calculated using the BUII formula, first through inclusion of all measured variables and then by using partial biometry data. For each calculation method, the IOL power targeting emmetropia was recorded and compared for the whole cohort and stratified by axial length (AL).

Results: 376 right eyes were included in the study. The mean IOL power calculated for the entire cohort using all available parameters was 19.84±3.82 diopters (D). When comparing it to the **Results** obtained by partial biometry data, the mean absolute difference ranged from 0.05-0.14D;P<0.0001. When stratifying biometry data by AL, the optional variables (ACD, LT, WTW) had the least amount of effect in long eyes (AL‰¥26ג€mm), with a mean absolute difference ranging from 0.03-0.07D;P<0.001. Short eyes (AL‰₪22ג€mm) demonstrated the highest mean absolute difference (range; 0.11-0.20D;P<0.001). Percentage of eyes with a mean absolute IOL power difference of ‰¥0.25ג€D was the highest (29.6%) among short AL group when using AL and keratometry data only.

Conclusions: Incorporation of LT, ACD and WTW into the BUII formula is of more significance in short eyes. Using the BUII with all biometry data is suggested in short eyes in order to achieve optimal accuracy.

Influence of Spectralis® OCT signal strength on Macular and Retinal Nerve Fiber Layer parameters

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Purpose – To examine the influence of signal strength on macular thickness parameters, macular volume measurement and Retinal Nerve Fiber Layer (RNFL) thickness measured by spectral-domain Optical Coherence Tomography (OCT).
Methods - Macular thickness parameters, macular volume measurement and RNFL thickness around the optic nerve were measured by Spectralis® OCT (Heidelberg Engineering, Vista, California, USA). In each eye, the focusing knob was adjusted to obtain 3 images with different signal strength – Low (below 20), Moderate (20-25) and High (above 25). The relationship between signal strength and the measured data was compared using repeated-measures analysis of variance
Results – Forty eyes of 40 normal subjects were included in the analysis. Significant difference was observed between measurements obtained at different signal strengths. Central macular thickness, macular volume and mean RNFL thickness increased with decreasing signal strength. Other RNFL measurements also increased with decreasing signal strength, but those findings did not reach statistical significance.
Conclusions – Our finding show that thickness measurements taken with Spectralis® OCT increase with decreasing signal strength. These findings come in contrast to previous studies of Cirrus and Stratus OCT, where measurements were shown to decrease with decreasing signal strength. Clinicians must bear in mind that signal strength can somewhat influence OCT Results.

The use of Triamcinolone for hydrodissection and visualization prior to epiretinal injections

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Purpose: In recent years, our group has been evaluating the efficacy of epiretinal injections of viral vectors aimed at transducing photoreceptor cells in sheep. The ovine vitreous poses a mechanical challenge during intravitreal injections, as its dense structure forces some of the fluid injected back out through the port. Although vitrectomy could overcome this problem, this procedure is technically challenging in our animal model and there are cases in which vitrectomy is contraindicated. Therefore, the Purpose of this work was to explore a new technique of hydrodissection between the posterior hyaloid (PH) and the internal limiting membrane (ILM) using triamcinolone, in order to improve the epiretinal delivery of the vector.
Methods: Two eyes of two normal sheep were injected epiretinally with an engineered AAV2 vector suspended in 250♀µL of BSS. The injections were preceded by hydrodissection between the PH and the ILM using triamcinolone acetonide suspension (Triesence, diluted 1:20). Fundus photography was performed immediately after surgery. The effect of triamcinolone on vector infectivity was evaluated by GFP expression in vitro. Serial dilutions of triamcinolone were added to the medium of cultured HEK cells, which were then infected with an AAV2 vector carrying GFP. GFP expression was evaluated using a plate reader and fluorescent microscopy.
Results: Injection of triamcinolone successfully elevated the PH and created an epiretinal bleb. The triamcinolone crystals adhered to the ILM thus enabling improved visualization of the area of injection. Triamcinolone did not have an in vitro effect on virus infectivity.
Conclusions: The use of triamcinolone for hydrodissection between the PH and the ILM enables improved visualization of the epiretinal area. This approach could be useful not only in our ovine model, but also in cases where full vitrectomy is to be avoided, such as in young children.

Discordance between expected and observed prevalence of specific inherited retinal disease (IRD) genotypes

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Purpose: The vast majority of pathogenic recessive mutations are considered fully penetrant. However, recent studies on large cohorts of patients indicated that 26 missense variants are hypomorphic and cause disease only in trans with a severe mutation. Since large sets of both patients and controls of the same ethnicity need to be analyzed, such hypomorphic alleles are difficult to identify. We aimed to compare two values (allele frequency and genetic prevalence) in both Ashkenazi Jewish (ASH) controls and patients, and study variants that show discordant values.
Methods: We selected 187 genes reported to cause an autosomal recessive (AR) inherited retinal disease (IRD). Data of all variants identified in 5185 Ashkenazi Jewish (ASH) individuals were downloaded from gnomAD (version 2). In addition, we added all data reported previously by the Israeli inherited retinal disease consortium (IIRDC), on 269 ASH patients with IRDs. Allele frequency was calculated from gnomAD data and the number of expected affected individuals (genetic prevalence) was calculated based on the Hardy-Weinberg equilibrium. For large deletions that cause IRDs in the ASH population, no gnomAD entries are available, and we therefore used data previously published on a large set of ASH controls in order to calculate genetic prevalence.
Results: Assessment of the gnomAD ASH variants revealed 159 pathogenic alleles and five known ABCA4 hypomorphs. Based on the allele frequencies, we calculated the expected genetic prevalence for each homozygous mutation and each combination of compound heterozygotes. Excluding hypomorphic variants, the most frequent mutations were: ABCA4-p.Gly1961Glu (1829 expected homozygotes), PCDH15- p.Arg245* (547 expected homozygotes), TRPM1- 31355203-31391647del (515 expected homozygotes), MAK Alu insertion (289 expected homozygotes), and CACNA2D4- ex17-26del (279 expected homozygotes). Interestingly, only a single ASH patient in the IIRDC cohort is homozygous for ABCA4-p.Gly1961Glu. A small, but significant ratio, was also observed for the remaining frequent mutations. Two suspected splice-site mutations (in EYS and CNGA3) have relatively high allele frequency but were not observed in patients, indicating that these are not true pathogenic alleles.
Conclusions: Our analysis indicates that IRD prevalence is expected to be higher than previously estimated and that some missense variants, and mainly ABCA4-p.Gly1961Glu, are unlikely to be fully penetrant.

Variable Phenotype of Knobloch Syndrome caused by Biallelic COL18A1 Mutations in Children

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Purpose: Knobloch syndrome is a rare, recessively inherited disorder classically characterized by high myopia, retinal detachment, and occipital encephalocele. Lately, variable phenotypes have been reported. Our aim is to report the clinical and genetic findings of four Israeli children affected by Knobloch syndrome.
Methods: Retrospective study of four patients diagnosed with Knobloch Syndrome, who underwent a full ophthalmic examination, electroretinography and neuroradiologic imaging. Genetic analysis included whole exome sequencing (WES) and Sanger sequencing.
Results: Four Israeli patients (age range at latest follow up: 1-26 years) from three families of various ethnic origins were included in this study. All 4 patients had high myopia (10 D or higher) and nystagmus at presentation. Ocular findings included vitreous syneresis, macular atrophy and coloboma. Two children had retinal detachment. One child had iris transillumination defects and an albinotic fundus, initially leading to an erroneous clinical diagnosis of albinism. Electroretinography performed in all children revealed a marked cone-rod pattern of dysfunction. Brain imaging (performed in 3 of the 4 patients) demonstrated severe occipital encephalocele in 1 patient, minor occipital changes in 1 child, and no abnormalities in another child. Cutaneous scalp changes were present in 3 patients. Systemic associations were identified in 1 patient, including learning difficulties, epilepsy and Dandy Walker malformation. Only 2 patients (siblings) were clinically diagnosed with Knobloch syndrome prior to the genetic analysis. WES analysis, confirmed by Sanger sequencing revealed COL18A1 biallelic null mutations in all affected individuals, consistent with autosomal recessive inheritance.
Conclusions: This report describes variable features in patients with Knobloch syndrome, including marked lack of eye pigment similar to albinism in one child, macular coloboma in 2 children as well as advanced cone-rod dysfunction in all children. One patient had normal neuroradiologic findings, emphasizing that some affected individuals have isolated ocular disease. Since the correct diagnosis was obtained only after genetic analysis, awareness of this syndrome, and especially the unique phenotype may aid early diagnosis, monitoring for potential complications, appropriate genetic counseling and prevention of further affected children in the same family.

OCTA imaging for evaluating graft revascularization post pterygium surgery

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Purpose: To determine the use of OCTA for follow-up of revascularization of conjunctival graft after pterygium excision with conjunctival autograft (PECA) procedure.
Methods: Seven patients, undergoing PECA procedure were imaged with anterior segment OCTA (OPTOVUE) prior to the procedure and during follow up thereafter. Revascularization of the graft was analyzed qualitatively to estimate patterns of blood vessel growth.
Results: While most patients showed no blood flow signal on OCTA one day after surgery, regrowth of blood vessels into the graft were detected starting from post operation day 3-7. The pattern of blood vessel growth was seen as radiating from the center of the graft towards the healthy conjunctiva on the periphery. Grafts demonstrating more extensive zones of flow signal at the beginning of regrowth appeared to have faster later revascularization. Upon one month after the operation all the grafts achieved satisfactory vascularization of the whole graft area.
Conclusions: OCTA is a promising tool for the **Purpose** of evaluating graft revascularization post-surgery. This may help monitor those patients post-operatively, with possible ability to predict or diagnose earlier graft ischemia.

Metallic nanoparticles in tears: Implementation of Ion Beam Analysis to differentiating the rural and urban populations.

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Purpose: To evaluate an individual's exposure to environmental pollutions by measuring metal trace elements in tears. Optimizing high energy ion beam **Methods** to screen tear samples. **Methods**: Two groups of participants, one from Haifa (urban group) and one from Kibbutz Beeri near Gaza (rural group) were enrolled. All study participants were subjected to detailed medical, surgical and environmental history, and signed informed consent according to IRB protocol. Tears from each group were collected using a Schirmer test without application of topic anesthetic. Elemental concentrations in the specimens were extracted in an BINA Accelerator Laboratory, using a Particle Induced X-ray emission (PIXE) analysis. Statistical analyses were performed for demographic, exposure and nanoparticle findings. **Results**: The rural group comprised of 28 participants aged between 31-86, 57% females. The urban group included 28 participants, age 20-59, 69% male. Aluminum (Al) element was detected only in the rural population. Significant differences were also measured in iron (Fe) levels, also reduced in the urban population. The Concentration ratio of Metals/Cl varied notably between the two groups and also within individuals in each group. Concentration of K, which is well-known as part of the tear composition, did not change significantly between all samples. **Conclusions**: We found significance differences in two metal elements: aluminum and iron. These could be due to environmental parameters (forest fire, water content), different diet or industry area surrounding. These preliminary **Results** show that PIXE is a sensitive method for analyzing and quantifying trace metals in the tears, and that tears might be used to personal monitoring of exposure to air pollution.

Therapeutic potential of mitochondrial transplantation in ocular diseases

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Purpose: Mitochondrial dysfunction is associated with various incurable ocular diseases such as acute ischemic insults, age-related diseases like AMD and glaucoma and genetic mitochondrial diseases. Pharmacological therapeutic approaches targeted to the mitochondria have shown promising yet immature **Results**. Here we propose to treat these pathologies by replacing the endogenous damaged mitochondria with exogenous healthy ones, by a novel therapeutic modality known as mitochondrial transplantation (MitoPlant). In this modality, healthy mitochondria are extracted in-vitro, injected into dysfunctional tissue and are spontaneously internalized by the cells. MitoPlant was shown to facilitate functional recovery of tissues in mouse models of ischemic insults of the heart, liver and nervous system, and recently in pediatric patients with congenital heart disease. MitoPlant has never been shown in the eye or has been tested for other than ischemic insults. We hypothesize that MitoPlant in the eye may have a beneficial effect not only in acute ischemia but also in chronic and genetic ocular pathologies.
Methods: Mitochondria were isolated from human ARPE-19 cell-line or from mouse livers, and their purity and function were evaluated. Mitochondrial uptake into several ocular-related cell-lines was examined by flow cytometry, microscopy and PCR. MitoPlant protective effect against oxidative stress was examined in human corneal endothelial cells exposed to H2O2. Cell survival following MitoPlant was evaluated by Neutral Red assay. In-vivo mitochondrial uptake was demonstrated by intravitreal injection of freshly isolated mitochondria into C57BL/6 mice eye. Mitochondrial uptake by Retinal Ganglion Cells (RGCs) was determined 24 hours later by confocal microscopy and PCR. Retinas were assessed by Optical Coherence Tomography imaging system after 3 weeks.
Results: We show that exogenous, functional mitochondria are spontaneously and effectively internalized by ocular cells in-vitro, and protect them from oxidative-stress induced death. Importantly, we show for the first time that injection of isolated mitochondria into the vitreous cavity of mice **Results** in the internalization of functional mitochondria by the RGCs while maintaining normal structure of retinal layers.
Conclusions: Our **Results** suggest that ocular transplantation of mitochondria may serve as a new therapeutic tool that can inhibit cell death in various ocular diseases.

Genetic characterization of Blepharophimosis population in Israel and the relation to ovarian insufficiency

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Aim: The main characteristics of Blepharophimosis syndrome (also called BPES) includes telecanthus, epicanthus inversus and severe ptosis. The inheritance is mainly autosomal dominant, but de novo mutations were also reported. The syndrome is caused by mutations in the FOXL2 gene located on chromosome 3. There are two types of BPES. Both types 1 and 2 involve abnormalities of the eyelids. Only type I is associated with primary ovarian insufficiency.
The aim of the study is to determine the genetics underlying BPES in the Israeli population, and identify women that may show primary ovarian insufficiency.
Methods: Data regarding family history, fertility (primary ovarian insufficiency, pregnancy, sperm donation, in vitro fertilization), mental retardation, lacrimal duct obstruction and other syndromic signs were collected. Genetic analysis of FOXL2 mutation was performed.
Results: Three families with BPES were recruited to the study. Blood samples were collected from 1 affected male, 1 suspected female sibling and 1 healthy mother (family 1) and two symptomatic and healthy subjects were also recruited from family 2. Family tree was drawn for all families. No fertility problems or IVF treatments were reported.
Genetic analysis was performed to locate the mutations associated to infertility.
Discussion: According to scientific literature, FOXL1 is associated with infertility. If so, genetic characterization of patients with BPES is crucial regarding fertility consultant.
Clinical signs and genetic background will be discussed in BPES and primary ovarian insufficiency.

A NOVEL FINDING OF HYPERREFLECTIVE MATERIAL IN THE SILICONE-RETINA INTERFE - AN OPTICAL COHERENCE TOMOGRAPHIC AND HISTOPATHOLOGICAL STUDY

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Purpose: To describe novel findings of hyper reflective material in the silicone-retina interphase on spectral domain optical coherence tomography (SD-OCT) imaging in eyes with silicone oil tamponade.
Methods: Retrospective observational clinical study of consecutive patients who underwent primary pars plana vitrectomy with silicone oil tamponade for rhegmatogenous retinal detachment. Repeat clinical examination and SD-OCT macular imaging performed 3 months after surgery were evaluated to identify any macular pathologies, including formation of epiretinal membranes, intraretinal changes, subretinal fluid, and edema prior to scheduled secondary vitrectomy for silicone oil removal.
Results: Eighty-two patients (mean age 54 years, range 2289“€λ) were included. Twelve eyes (14%) showed discrete preretinal hyper reflective organized coarse material in the silicone-retina interphase on SD-OCT. The material was scattered in the posterior pole, with several foci showing additional hyper reflectivity of the inner retinal layers beneath. These findings did not resemble silicone oil emulsification in size, shape, or reflectivity.
Conclusions: This is the first report on hyper reflective material detected by SD-OCT in the silicone-retina interphase in eyes with silicone oil tamponade. These findings may represent an inflammatory response to silicone oil exposure that may be the initial manifestation of a future proliferative process, warranting a rigorous follow-up protocol for affected patients.

Can we prevent LHON in the next generation?

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Purpose
To discuss family planning options in a family with Leber hereditary optic neuropathy (LHON) with mdDNA mutation at 3460.
Case presentaion
We describe a family with 2 male members diagnosed with reduced vision due to Leber hereditary optic neuropathy and 4 others (not including the carrier mother), 1 male and 4 females, that are known to be carriers of the mtDNA mutation at 3460. Two sisters of the mother also have symptomatic (2, 1 female 1 boy) and asymptomatic family members in each family.
Currently, a female carrier is planning a pregnancy.
Methods
Nowadays mitochondrial manipulation technologies, also known as three-parent baby, are being studied and gaining success. Two techniques are available: spindle transfer and pronuclear transfer. In both techniques the nucleus from the motherג€™s egg and the fatherג€™s sperm are combined with the cytoplasm of a donor egg.
The technology is still raising social and ethical concerns. As of today, the UK is the only country to legalize the technology under restrictions. The technology can also be used in the USA, but every case needs to be individually approved by the FDA.
Conclusions
Mitochondrial replacement therapy may offer healthy baby for carrier mothers New three-person fertilization can target mitochondrial inherited disease. We hereby claim that LHON should be considered for Mitochondrial replacement therapy in order to prevent blindness among offspring.

Case Report: A successful treatment for a child with Cystinosis

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Background: Cystinosis is a rare lysosomal storage disease in which cystine accumulates in organs and tissues throughout the body. Although renal disease predominates in the early forms of cystinosis, all forms of the disease can result in pigmented retinopathy and deposition of cystine crystals in the eye with subsequent photophobia and visual impairment. The early and late forms of ocular disease can both be treated with cysteamine eye drops to halt progression of ocular manifestations and diminish the presence of cystine crystals in the eye. Oral Cysteamine therapy may also decrease the occurrence of retinopathy.
Purpose: 1. Describe a case of successful treatment with Cysteamine eye drops and oral Cysteamine in a child with Cystinosis.
2. Demonstrate the diminishing of Cystine corneal crystals and cystine related retinopathy in Cystinosis caused by a specific gene.
Methods: We describe a case report of a child with Cystinosis, carrying a specific gene, who was admitted to ג€œHaג€™Emekג€• medical center and that was treated with our topical and systemic Cysteamine regimen.
Results: A complete ocular cure was achieved following a complete treatment for a child with Cystinosis with a specific gene. No renal impairment was detected throughout the whole treatment.
Close follow-up demonstrates no return of ocular symptoms. Visual acuity was improved following the treatment and did not deteriorate during the follow-up.
Conclusions: Cysteamine topical and systemic treatment was proved as an efficient treatment for a child with Cystinosis with a specific gene.
Key words: Cystinosis, Cysteamine, gene name, Cystine crystals

Comparison between adhesive properties of a semi-autologous glue composed of cryoprecipitate and commercial thrombin and a commercial biological glue

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Purpose:To compare between adhesive properties of a semiautologous (SA) glue composed of cryoprecipitate and commercial thrombin and a commercial biological glue. Commercial glues are commonly used in Ophthalmology especially during pterygium excision surgery. These biological glues are composed of 2 components; thrombin and fibrinogen- When mixed, create a fibrin network with adhesive properties. In this study we compare (SA) glue composed of human derived cryoprecipitate mixed with commercial thrombin to a commercial glue.
Methods:Cryoprecipitate was obtained from the Israeli blood bank after Helsinki committee approval. Commercial thrombin and fibrinogen ampules (Evicel®) were purchased. Fibrinogen concentration was determined using fibrinogen Clauss assay. We present a comparison of their adhesive bonding strength, microstructure and rheological properties. Designated collagen strips were bonded with different dilutions of the (SA) glue and commercial glue with the same fibrinogen concentration. Bonding strength was assessed through lap shear test using an Instron machine. Scanning electron microscopy was performed to determine microstructure. Rheological properties were analyzed using time sweep test. The gelation time of the glue represents by the time to reach plateau, its storage modulus (G′) which represent the glue stiffness, and its thixotrophic properties were evaluated.
Results:No significant difference in bonding strength between the glues are observed. (SA) fibrinogen concentration was 1-10% of the commercial glue. **Results** are observed also in the diluted fibrinogen glues, where the same fibrinogen concentration of (SA) and commercial were compared. The test was taken in 2 time points,4 hours and 24 hours with similar Results.SEM shows similar microstructure of density, fiber diameter, and element diversity in both glues. Rheological measurements reveal significantly lower storage modulus to the (SA) glue with faster gelation time. Both represent thixotrophic properties with the ability to recover after shear stress.
Conclusion:No significant difference in adhesion strength is observed between commercial and (SA) fibrin glue, even with different fibrinogen concentration. Breaking points of the 2 glues examined were different at each concentration and at each time assessment meaning that the adherence force relies on both these factors. Further assessment of different concentrations & time points is needed to determine the most potent formula

The beneficial effects of aflibercept in treating chemical induced corneal neovascularization

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Purpose: The aim of this study was to evaluate the efficacy of ziv-aflibercept (Zaltrap) or aflibercept (Eylea) in preventing or ameliorating the corneal late phase induced neovascularization following ocular exposure to sulfur mustard (SM) in the rabbit model.
Methods: Chemical SM burn was induced in the right eyes of NZW rabbits by vapor exposure. Zaltrap (2mg) was applied once by subconjunctival injection at 2h, 9 days or at 4 weeks post exposure. Eylea (2mg), the ocular specific preparation, was administered 4 weeks post SM exposure and following an initial one week treatment with 0.1% dexamethasone.
A clinical follow-up was performed for up-to 5-12 weeks following exposure and digital photographs of the cornea were taken for measurement of blood vessel length. Eyes were taken for histological evaluation and extent of NV was determined by using H&E and Masson Trichrome staining.
Results: A single subconjunctival treatment of VEGF-trap 2h or 9 days post exposure presented a slight benefit in reducing the severity of the injury and in postponing the late induced NV growth. However in the group receiving treatment at 4 weeks following exposure, a significant reduced extent of existing NV was already seen at one week following injection, an effect which lasted for at least 8 weeks. The extensive reduction in existing corneal NV in the VEGF-trap treated group was confirmed by histological evaluation. Finally, eyes receiving the steroidal treatment during the first week and the ocular preparation of VEGF-trap following NV detection presented a significant reduction in corneal NV as compared to the steroid only treated group.
Conclusions: Subconjunctival Zaltrap or the combination of dexamethasone followed by Eylea treatment presented a long-term significant benefit in corneal NV reduction following ocular chemical exposure when used against existing NV rather than as a post exposure prophylactic treatment.

Changes in contrast sensitivity after subacute stroke

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Purpose: Contrast Sensitivity (CS) can objectively and non-invasively assess attributes of visual perception but is not often studied in stroke patients. When assessed, CS is reduced in stroke patients especially under poor lighting conditions. However, the time course of this reduction has never been studied. This study aimed to assess CS in post stroke patients one and two months after the injury, compared to healthy controls.
Methods: Patients were recruited from the Rehabilitation unit of the Loewenstein Hospital after subacute stroke and compared to sex and age (±3 years) matched controls, recruited from the patients' escorts. Entrance tests included visual acuity (EDTRS chart, 0.7 decimal and better in each eye), color vision (Ishiara test) and visual fields testing (static confrontation). CS and its time trends were assessed using the Pelli-Robson chart both one and two months after injury. Comparison between stroke patients and controls was done using unpaired samples t-tests, and intra group time trend analysis was done by paired samples t-test.
Results: Twenty six patients were included in each group (mean age for stroke and controls, 61.15±7.87 and 63.19±9.59, respectively, p=0.20, range 45-75 years). The mean log CS was 1.59±0.13 log in the stroke patients one month after the injury and 1.71±0.17 log in the control group (P<0.01). Two months after the stroke, the mean CS was increased to 1.63±0.18 log while it remained steady (1.73±0.18 log) for the healthy individuals (P=0.06)., However, the intra group analysis between the two time points in stroke and control groups were not statisticaly significanct (P=0.5 and P=0.2, respectively).
Conclusions: CS levels decreased after subacute stroke compared to control patients. CS improved over follow up, though not to normal control levels. This study demonstrates that CS is a simple and accessible test providing a basis for initial identification of visual impairment secondary to subacute stroke.

Finite element modelling of corneal paired arcuate relaxing incisions for the treatment of astigmatism

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Purpose: To perform and validate Finite element model (FEM) of corneal paired arcuate relaxing incisions for the treatment of regular astigmatism
Methods: Solidworks CAD software and previous published bio-mechanical models were used to create a theoretical 3D model of the human cornea. Data obtained from Pentacam corneal topography of a healthy patient, was used to create a similar patient-based model. Abaqus FEM software was used to analyze the changes caused by paired arcuate relaxing incisions preformed at different depths, arc lengths and distance from the corneal center. A Python-based code was written to calculate the radii of curvature at the central 1.5mm of the cornea, for the **Purpose** of evaluating the changes in refractive power caused by the arcuate incisions.
Results: The theoretical model demonstrated that, as expected, paired arcuate incisions done on the steepest corneal meridian caused its flattening, with coupled steepening of the perpendicular flat meridian. This effect was increased when the incisions were deeper (300 vs. 400 microns deep) and closer to the central cornea (3 vs 4 mm away from the center). Performing longer incisions, resulted in increased effect but only up to 60 degrees of arc length. Conversely, when tested on the human-based cornea model, 70 degrees incision had a larger effect than 60 degrees incisions.
Conclusion: Our FEM model demonstrated the well-studied effects of paired arcuate corneal incisions on regular corneal astigmatism. Unexpected differences found between the effect of incisions in the theoretical model and the human-based model, demonstrate the complexity of anterior segment bio-mechanics. Further development of this tool can allow us to study the effect of incisions with different geometries on regular and irregular astigmatism.

Automatic segmentation of Descemet's membrane detachment following DMEK surgery

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Purpose: To perform automatic segmentation of Descemet's membrane detachment following Descemet's membrane endothelial keratoplasty (DMEK) surgery
Methods: A standard protocol for acquiring B-Scan anterior segment OCT images from post-DMEK patients was established. B-Scans were processed by various region and boundary extraction Methods combined with several noise reduction filters. Areas of detachment were identified using the novel algorithm.
Results: The process identified successfully areas of detached Descemet's membrane in various images of post-DMEK patients.
Conclusion: Automatic segmentation of Descemet's membrane detachment anterior segment OCT images is possible through the use of image processing algorithms allowing future development of image integration into en-face presentation and volumetric calculations.

Video Recording and Light Intensity Change Analysis during Cataract Surgery Using an Animal Model

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Purpose: To estimate light exposure changes during cataract surgery through intra-operative images simulated from the “patient’s perspective” using an animal model.

Methods: In this experimental study, a 3mm maculostomy was performed through the posterior globe’s surface of 15 porcine eyes. Eyes were fixated to a glass slide and placed over an iPad camera. Video footage of a cataract surgery was obtained through the maculostomy for each eye, keeping light exposure parameters and focus constant. Seventy-five images, five from each eye, were extracted at pre-determined points and mean gray value (MGV), a light intensity measure, was calculated. Differences in MGV between discrete surgical steps were evaluated using multiple one-sample t-tests.

Results: This technique allowed for the capture of a full-length cataract surgery through a 3mm maculostomy. MGV range was 14.21 – 132.51. Light intensity was similar across surgeries and varied greatly through each procedure. A 24% decrease in MGV between post-hydrodissection and post-phacoemulsification stages was noted (difference: -18.36; 95% CI: -30.50 – -6.22; p-value = 0.006). A 22.4% decrease in light intensity was noted after phacoemulsification in comparison to the starting image (MGV difference: -16.78; 95% CI: -32.45 – -1.12; p-value: 0.0375). Light intensity was similar at the start and end of surgery (difference: -7.15; 95% CI: -19.35 – +5.05; p-value: 0.229).

Conclusions: Light intensity changes through different steps of cataract surgery and may be minimal after phacoemulsification completion. This video and data may serve as informational and educational tools for surgeons and patients.

Safety and efficacy of ocular repetitive magnetic stimulation in moderate to severe dry eye disease

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Purpose: To assess the safety and efficacy of ocular repetitive magnetic stimulation (RMS) in the management of patients with moderate to severe dry eye disease (DED).
Methods: Subjects with moderate to severe DED were enrolled into this prospective, interventional, open-label, single-arm pilot study. A novel non-invasive device intended for the application of localized repetitive electromagnetic stimulation to the ocular area was used (Ocular Magnetic Neurostimulation System (OMNS), EpiTech-Mag LTD., Israel). Safety measurements included treatment related Adverse Events (AE), BCVA, and additional secondary assessments for anterior and posterior segment (IOP, Slit lamp biomicroscopy assessment, and SD-OCT). Efficacy signs were measured by the reduction of corneal staining score (NEI scale, 0-15). Efficacy symptoms were assessed by reduced ocular discomfort using PRWL2A questionnaire (Lasik q62-69, scaled to 0-100) and reduced eye lubricant usage. A repeated measures mixed model was used to assess the mean change from baseline Results.
Results: Twenty-nine subjects with moderate to severe DED associated with mixed etiologies were treated in this study: 13 subjects had Sj¶grenâ€™s syndrome, 12 meibomian gland dysfunction (MGD), 4 Aqueous Tear Deficiency (ATD). Treatment was administered in the first 15 subjects to one eye. In the additional 14 subjects both eyes were treated. Safety measurements showed no treatment related AE. BCVA and IOP measurements remained relatively stable. Efficacy measurements showed a statistically significant reduction of corneal staining at 1w (-1.37, p=0.002), 4w (-1.70, p<0.001), 8w (-2.28, p<0.001) and 12w (-1.73, p<0.001). A statistically significant reduction of PRWL2A symptoms was seen at 1w (-9.68, p=0.004), 4w (-13.15, p<0.001), 8w (-13.41, p<0.001), and at 12w (-15.27, p<0.001). 24 subjects using eye lubricants at baseline showed a statistically significant reduction in lubricants consumption at 4w (-2.46, p=0.057), 8w (-2.88, p=0.026) and 12w (-3.82, p=0.005).
Conclusions: The treatment with non-invasive OMNS in subjects with moderate to severe DED was safe, significantly reduced corneal staining score, improved quality of life and reduce the use of eye lubricants. This innovative treatment may serve as an effective adjunct in the management for DED.

Prospective evaluation of naïve PDR cases treated by intravitreal anti-VEGF injections using optical coherence tomography angiography

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Purpose: To compare the detection of retinal neovascularization on fluorescein angiography (FA) and optical coherence tomography angiography (OCTA) in patients with proliferative diabetic retinopathy (PDR) and to assess retinal reperfusion after treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections.
Methods: Treatment naïve eyes, diagnosed with PDR, willing to be started on anti-VEGF treatment without laser were included. We performed an FA Optos 200TX and OCTA-widefield scan (Zeiss Plex Elite 9000) using the montage function at baseline, and upon 6 months of initiation on anti-VEGF, the patients had another OCTA scan. We compared the identification of new vessels on FA versus OCTA. With the help of the Advance Retina Imaging (ARI) network image analysis algorithm software, and Image J, we also looked at changes in the neovascularization size, and changes in both the capillary and perfusion densities in the superficial and deep plexuses over the 6 months.
Results: We included 3 eyes of 3 patients who completed the baseline and follow-up examinations. All the retinal neovascularization identified on FA were equally identified on OCTA. We observed a decrease in the size of neovascularization in all patients, by an average of 65.1%. The capillary density averagely increased by 27.3% in the superficial plexus and by 33.2% in the deep plexus in all eyes. The perfusion density averagely increased by 12.1% in the superficial plexus and by 31.9% in the deep plexus of all eyes.
Conclusion: Our **Results** suggest that OCTA could be used as an effective alternative to FA to actually visualize, measure and monitor the growth or regression of retinal neovascularization. Our **Results** also indicate reperfusion of the retina with anti-VEGF treatment amongst PDR patients, based on measurements of both capillary and perfusion densities in the superficial and deep plexus.

The role of LIM homeodomain 2 (Lhx2) and LIM-domain-binding 1 (Ldb1) in differentiation of the Mammalian Retinal-Pigmented Epithelium (RPE)

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Normal vision depends on the retinal pigmented epithelium (RPE), a metabolic cell layer vital for development and function of the adjacent retinal photoreceptors. However, the transcriptional regulatory program in the course of RPE differentiation and maintenance is still unclear. Lhx2 is currently the only known LIM homeodomain (LIM-HD) member required for the early morphogenesis and patterning of the vertebrate eye. LIM-domain-binding (Ldb) proteins assemble with LIM domains of the LMO/LIM-HD family and stabilize these protein complexes.
My current objective is to uncover the roles of Ldb1/2-Lhx2 complex in mammalian RPE differentiation. I have established Lhx2 and Ldb1/2 conditional mutants in the mouse RPE. Initial immunohistochemical analyses of Lhx2 mutants show reduced expression of early RPE key transcription factors.
To study the role of Lhx2 in human RPE and to further identify direct targets of Lhx2 we utilize RPE generated from human embryonic stem cells (hES-RPE) for chromatin immunoprecipitation followed by sequencing (ChIP-Seq) and for functional studies using lentiviral knockdown approach. Considering the importance of RPE for retinal physiology and the recent advance in using hES-RPE for cell-replacement therapy this study will contribute to uncover gene regulatory networks (GRNs) down stream of Lhx2 and Ldb1/2, involved in RPE fate and function.

Foveal hypoplasia as a cause for unexplained poor visual acuity

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BACKGROUND :
Foveal hypoplasia, often associated with infantile nystagmus and albinism, but can also be an isolated entity. The fundal findings, though quite typical, are very subtle and often difficult to detect, especially in children. Recent studies have shown that Optical Coherence Tomography (OCT) can be used as a diagnostic and prognostic tool in foveal hypoplasia.
PURPOSE:
We present children who were sent for evaluation due to unexplained suboptimal visual acuity, with neither gross ocular or systemic findings.
METHODS:
All children referred to our hospital due to unexplained suboptimal BCVA underwent a full ophthalmic examination as well as SD OCT of the macula. First degree relatives were examined too, whenever possible.
RESULTS:
Eight children 6 to 13.5 years old, 3 males and 5 females were evaluated. Visual acuity ranged from 6/7.5 (0.1 LogMar) to 6/18 (0.48 LogMar). SD OCT revealed some degree of foveal hypoplasia in all of them. On evaluation of family members, foveal hypoplasia was found in 3 families.
CONCLUSIONS
SD- OCT of the macula is a useful tool in the presence of suboptimal visual acuity in children that cannot be explained by ocular examination. It may reveal pathology that cannot be seen by ophthalmoscopy. Macular hypoplasia revealed by OCT can be isolated but can lead to further investigation. With the diagnosis of ocular hypoplasia in these patients, referral of all family members is indicated and whenever similar findings are found, genetic evaluation is justified.

Issues of Multifocal and Bifocal Glasses Compatibility in Parkinsons Disease

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Purpose: To assess the etiology of visual complaints among Parkinson's disease patients who presented to our clinic.
Methods: A retrospective chart review was performed for patients who presented to our neuro-ophthalmology clinic. We identified the charts of patients with Parkinson's disease and recorded information such as age, gender, visual acuity, visual complaints, medical history, exam findings and type of optical correction for each of the patients. The study was performed with the approval of the local ethics review board and conformed with the declaration of Helsinki.
Results: Of 2,950 clinic charts we identified 30 patients with Parkinson's disease. All of the patients had undergone full neuro-ophthalmic examinations. Exam findings included strabismus (46.6%), ocular surface disease (23.3%), color vision abnormalities (20%) and abnormal pursuit and saccadic eye movements (10%). Of the 30 patients with Parkinson's disease, 8 patients (26.6%) used multifocal or bifocal optical correction. Six of them (75%) had visual complaints associated with their optical correction and noted a marked improvement in their visual function with separate distance and reading glasses.
Conclusions: The study findings highlight the many visual difficulties associated with Parkinson's disease and raise a concern regarding the compatibility of multifocal or bifocal optical corrections for patients with Parkinson's disease.

Refractive Surgery in IDF Recruits - a Rising Trend

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Purpose: To determine the prevalence of refractive surgery in recruits for military service in the Israeli Defense Force (IDF) between 2005-2018 and to evaluate the effect of surgery on the recruitsג€™ ability to serve in combat units and accomplish combat training
Materials and **Methods**: A retrospective analysis of medical records of all IDF recruits between 2005-2018. Recruits were categorized as ametropes and those who underwent refractive surgery. Fitness for combat units and completion status of combat training were compared between the two groups.
Results: 5,219 (4,741 male, 478 female) patients underwent refractive surgery during the study period. Refractive surgery prevalence increased from 13/1000 male ametropes in 2005 to 32/1000 males in 2018 ($p<0.001$). Recruits aged 18 and under who underwent surgery increased from 87 in 2005 to 185 in 2018. An average of 65% of operated soldiers who were fit for combat were assigned to a combat unit, significantly higher than the 41% in ametropes ($p<0.001$). Dropout rates from combat training were significantly lower in the refractive surgery group during all study period (1.68% vs. 6.14%, $p<0.001$)
Conclusions: Prevalence of refractive surgery in IDF recruits increased dramatically during the last decade and more of them are applying to combat units. Despite lack of FDA approval for surgery in patients aged 18 and under, we report on an increasing number of procedures in our study population. Both assignment for combat units and completion rates of combat training were higher in soldiers who underwent refractive surgery. Refractive surgery did not harm recruitsג€™ chances of successfully accomplishing combat training, and enabled the possibility of combat service for those who were unfit prior to surgery.

Herpes viral polymerase chain reaction in donor corneas

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PurposeTo discover the occurrence of Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) DNA in transplanted corneas using polymerase chain reaction (PCR).
Unlike other Viruses and microorganisms, HSV and VZV Viruses are not routinely monitored in donorsג€™ corneas or donors blood samples, before or after corneal transplantation.
Methods 75 donorsג€™ corneas were examined by a PCR test before corneal transplantation in search for HSV and VZV DNA. All corneas were morphologically evaluated before surgery by CellChek® wide field microscopy. 31 Corneas were not transplanted after the detection of other infections (HBV, HCV, HIV) or a low cell count (under 2,300). All eyes transplanted with the donorsג€™ cornea were evaluated and followed for corneal transparency, endothelial cells morphology and number by specular microscopy, signs for ocular inflammation, intraocular pressure and anterior segment OCT for graft attachment.
Results Herpes simplex virus type 1 DNA was detected in three transplanted donor corneas out of the 44 that were examined and transplanted (6.8%). All the three HSV positive corneas did not show any morphological difference with wide field microscopy prior to the surgery.
All three eyes transplanted with these HSV positive corneas were used for Descemet Membrane Endothelial Keratoplasty (DMEK). All three corneas cleared, and all grafts were attached until 1 month after surgery and did not show any signs for graft rejection or intraocular inflammation during the follow up period of mean 8 months (range 3-12 months).
Conclusion HSV may be PCR positive in morphologically normal transplanted corneas. Further evaluation with bigger sample size and longer follow up time is needed to establish a clinical correlation to donor graft survival and to recipient ocular infection with HSV.

Ocular toxicity of Belantamab Mafodotin in a compassionate use program to treat patients with relapsed/refractory multiple myeloma

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Purpose: Belantamab mafodotin (BF) is a humanized, anti-B-cell maturation antigen monoclonal antibody conjugated to a cytotoxic moiety (cysя€"mcMMA F) for treatment of relapsed/refractory multiple myeloma (RRMM). Upon binding to plasma cells, cytotoxic moiety is released enhancing immunogenic cell death. In a phase 1 study, BF had a manageable safety profile and demonstrated a rapid, deep, and durable myeloma response as a monotherapy. BF caused reversible ocular, mainly corneal toxicity, which led to treatment delays. We report of the ocular toxicity of BF.
Methods: IRB approval was granted for a retrospective evaluation of patient data. RRMM patients received IV BF at doses up to 3.4 mg/mg q3weeks in Tel Aviv Medical Center, under an expanded access compassionate program. Ocular manifestations were monitored. Treatment was deferred for patients with ocular toxicity until grade‰₪1ג.
Results: Twelve patients with advanced RRMM were treated between July to December 2019, of whom 11 had any follow-up and were included in the report. Patient age♀±S.D. was 65.64±9.53, range 49 to 81. Five of 11 were female. Two patients had 1 treatment cycle, 3 had 2, 3 had 3, 2 had 4 and 1 had 5 cycles. Mean±S.D (range) LogMAR was 0.18±0.16 (0-0.82), IOP was 16.43±3.31 (10-24). On eye examinations, corneal toxicity was absent, grade 1, 2 or 3 in 22.2%, 9.1%, 36.4% and 20.2% respectively, and improved gradually over the course of follow-up. Intraepithelial cysts were very prevalent, with 4.4% having subtle epithelial haze, 35.7% mild microcystic epithelial changes and 22.0% diffuse microcystic changes. Mild (39.6%) and moderate (15.4%) SPK's were also recorded. Conjunctival injection was present in 5.5% of eyes and chemosis in 10.3%. Stromal opacity was rare (1.1%), as was stromal edema (1.1%). No endothelial damage and A/C involvement were recorded. Lens and fundus findings did not progress relative to baseline examinations and are considered normal to the age group of the patients.
Conclusions: The corneal epithelium was the main damage site of ocular toxicity following BF treatment, with 55.0% exhibiting SPK's, and 62.1% having intraepithelial cyst formation. This corneal damage may be reversible and dose dependent, but it reduces visual acuity and exposes the eye to risks of microbial infection and permanent vision loss. These risks should be balanced against durable responses achieved in patients with advanced myeloma.

Ocular surface temperature highlights differences in retinal vascular disease

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Purpose: Diabetic retinopathy (DR) and age-related macular degeneration (AMD) are the two most common disorders encountered by retinal specialists. Though the exact mechanisms that initiate and render DR and AMD are not clear, there is evidence to suggest that both low-grade inflammation and vasculopathy have an imporant role in these conditions. As suggested by previous studies, ocular hemodynamics can be represented indirectly by measuring the ocular surface temperature (OST).We investigated the ocular thermographic profile of patients with AMD and DR to better understand the pathophysiology of these conditions
Methods: Subjects diagnosed with DR or AMD treated at the Goldschleger Eye Institute retinal clinic were recruited. Subjects without any ocular disease were used as controls. Therm-App thermal imaging camera was used for OST acquisition. Room and body temperature were recorded and the mean temperature of the medial cantus, lateral cantus and cornea was calculated using an image processing software.
Results: Thermographic images were obtained from 133 subjects (260 eyes, 97 DR, 163 AMD) and 48 controls (55 eyes). Both room and body temperature correlated significanly ($P<0.01$) with OST measurements, however there were no differences between groups. No significant differences were observed based on sex, lens status or treatment with intravitreal injections). OST was higher in the AMD group and lowest in the DR group ($P<0.001$, adjusted for age, room and body temperature). Subgroup analysis revealed that eyes with diabetic macular edema (DME) had significanly higher OST than DR eye without DME, and very similiar to that in the AMD group. There were no differences in OST between neovascular AMD and non-neovascular AMD eyes.
Conclusions: Although both AMD and DR are considered posterior segment conditions, their effect on OST found here implies that the entire globe is involved. The differences in OST suggest that inflammation has a greater role than ischemia in the pathophysiology of AMD and DME and the opposite in NPDR and PDR. Future longitudinal studies might establish a potential prognostic value for thermographic evaluations in both DR and AMD patients.

Characterization of synaptogenesis in human photoreceptors precursors - In-vitro and ex-vivo model

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Purpose Vision restoration after retinal degeneration is a major challenge in the western world. Using embryonic stem cells (ESC) differentiated photoreceptor cells in cell replacement therapy are holding great hope for retinal treatments. To our knowledge, current studies have shown faint evidence of synaptic connection after cell transplantation in animal models. Our study is concentrated in synaptic formation in differentiated ESC and establishing retinal ex-vivo model to simplify the study of cell integration to recipient retina.
Methods We differentiated ESC towards photoreceptors precursors (PRP) according to our previous protocol (Markus et al., 2019) and we further investigate the influence of various growth factors and small molecules on synapse maturation by adding them from day 30 of differentiation to day 60. We quantified the synapse maturation by RT-PCR for several synaptic genes (RIBEYE, Bassoon, SV2, ELKS).
In order to test the integration ability of our cells, we establish an ex-vivo model for retinal explants. Long Evans and RCS eyes were enucleated, retinas were dissected and the tissue was seeded on tissue culture dish with growth medium. PRP cells were seeded on the retina for 5 days followed by fixation, immunostaining and confocal imaging.
Results Morphology of the cells has not changed due to the different treatments after 60 days of differentiation. DAPT treatment upregulated significantly the synaptic genes (SV2 10.03±5.17 "€λ SEM-fold change, P=.003, P**<0.01 and ELKS 1.97±1.02 "€λ SEM -fold change, P=.035, P*<0.05), BDNF upregulated only the expression of SV2 (4.2±2.75 SEM -fold change, P=0.008, P**<0.01) while the control culture without treatment has not shown any significant changes compared to 30 days culture. PRP cells that were seeded on top of the photoreceptors layer of RCS and long evans retinal explants were detected after 5 days. Cells migrated to the IPL in RCS retinas and survived more than in Long Evans retinas in which cells migrated down to the GCL.
Conclusions DAPT treatment for 30 days enhanced synaptic maturation of PRP. PRP seed on RCS retinal explants survived and migrated to the upper layers of the inner retina, while on Long Evans they migrated to the inner layers of the inner retina. Enhancing synaptic maturation of differentiated ESC and establishing an ex-vivo model for studying of cell integration on retinal explants will facilitate the study of vision restoration by cell replacement therapy.

Soft contact lens wear affects meibomian glands

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Purpose: Multiple studies show that approximately fifty percent of soft contact lens (SCL) wearer dropouts are a result of discomfort due to dry eye. As yet there haven't been clear accounts as to the source or sources of the discomfort. This study's aim was to investigate the relationship between SCL wear and a detrimental effect on meibomian glands (MG).
Methods: Forty three spherical SCL wearers between ages 20-33 were included in this study. Sixty percent of them were female. All were first time wearers instructed to keep SCL on daily between 8-14 hours per day. Each patients' MG were examined before the fitting and at 18 months via slit lamp and meibography. The ocular surface and tear prism were evaluated as well as tear break up time (TBUT), fluorescein and lissamine staining. The study group were subdivided to 14 daily disposable SCL patients, 15 two-week disposable SCL patients and 14 monthly SCL patients. There was a control group that had never worn contact lenses. The data were analyzed by one-way analysis of variance (ANOVA), followed by a Tukey- Kramer test.
Results: Slit lamp changes were manifest in the eyes of every subgroup of SCL type including daily disposable, two week and monthly disposable in comparison to the control group of spectacle wearers, except in the category of tear prism measurement. The statistically significant changes noted included plugged MG orifice ($P<0.05$), meibography ($P<0.05$), TBUT ($P<0.05$), fluorescein staining ($P<0.05$) and lissamine green staining ($P<0.05$).There was no statistical difference in the clinical findings when comparing one subgroup of SCL wearers to another.
Conclusions: Spherical SCL wear causes changes to the MG within 18 months. It is imperative that eye care providers properly instruct SCL wearers to be proactive about proper lid care to maintain health and productivity of glands and maximum tear film quality.This study can lead to further investigations of makeup components, lashes of SCL wearers, perhaps look for higher evidence of demodex, ergonomics and daily habits of SCL wearers

Lens coloboma - Ophthalmic, systemic and genetic manifestations.

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Purpose: Lens coloboma is a rare congenital anomalous development of the
lens, characterized by notching and indentation of the equator of the lens in places where the zonules failed to develop. This condition might be associated with other ocular developmental abnormalities and poor visual function. It can be an isolated incidental finding or a part of other ocular and systemic anomalies.We describe our experience in treating lens coloboma patients and further systematically evaluate them.
METHODS:
A case series. We report 4 cases of lens coloboma, that where examined at Emek Medical Center during the last few years. Demographic data including age, gender, ethnic group, family history, and clinical data: accompanied ocular findings, systemic conditions and genetic evaluation, were collected.
RESULTS:
Four patients aged 2-60 years old at presentation; three were males; one case of incidental finding; three had a family history of a similar condition. On ophthalmic examination: best corrected visual acuity was largely variable (2 meters counting fingers to 6/12); most had significant refractive errors: spherical equivalent ranged from -3.50D to -15.50D and cylinders ranged from 1.25D to 6.00D. Ocular accompanied malformations included lens opacity in three patients, and iris coloboma in one. Systemic malformations included skeletal and cardiac anomalies in one patient, who was found to have Marfans Syndrome on genetic work-up.
CONCLUSIONS:
Lens coloboma may present an isolated, incidentally found sign e.g. on examination prior to cataract surgery, or as a part of other systemic conditions which imply on an underlying systemic disorder with genetic basis. Management should include complete physical and ophthalmic examination of the patient and other family members. Treatment of significant refractive errors and amblyopia prevention. Genetic counseling is highly recommended in selected cases.

Is SCAPER a cell-cycle regulator or a ciliary protein?

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Purpose: To characterize the function of SCAPER, a gene involved in syndromic retinitis pigmentosa.
Methods: SCAPER localization was studies by immunofluorescent staining. A Scaper-mutant strain (named Scaper tm1a(EUCOMM)Hmgu) was available through The European Mouse Mutant Archive (EMMA). Mouse genotyping was performed by a PCR-based assay. Scaper transcripts were analyzed by RT-PCR. Mouse reproductive organs were evaluated by light microscopy of fixed sections.
Results: In ARPE-19 cells SCAPER localizes to both the cytoplasm and the nucleus, as well as to primary cilia. In mouse sperm cells SCAPER is expressed in the head compartment, where it is found both in the nucleus and in the peri-nuclear region, but not in the flagellum. Scaper-mutant male mice are sterile due to the lack of sperm cell production in the testis.
Conclusions: SCAPER was originally identified as a cyclin A associated protein affecting cell-cycle progression. SCAPER's localization to cilia and its effect on cilia length, combined with the similarity of the SCAPER-associated phenotype to other known ciliopathies, raised the option that at least in some tissues SCAPER is a ciliary protein. Therefore, our initial hypothesis regarding the cause for male sterility in Scaper-mutant mice was that SCAPER may localize to the flagellum of spermatozoa and affect sperm motility. However, immunostaining revealed that SCAPER does not localize to the flagellum, but rather to the head of spermatozoa, where it is found in both the nucleus and the peri-nuclear region. Moreover, Scaper-mutant mice produce no spermatozoa. These findings demonstrate that SCAPER is crucial for cell cycle progression and generation of mature spermatozoa in the mouse testis. Further studies will be required to reveal SCAPER's specific function in additional organs, including the retina.

MicroRNAs as biomarkers for ocular involvement in juvenile idiopathic arthritis

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Purpose: Juvenile idiopathic arthritis-associated uveitis (JIA-U) is a silent vision-robing disease. Though early uveitis diagnosis is critical for favorable visual outcome, there are currently no measurable biomarkers to indicate JIA patients at risk. This study was aimed to investigate microRNA (miRNA) expression in JIA-U, and explore their possible role as predictive biomarkers of the disease.
Methods: NanoString miRNA expression assay was performed on peripheral blood mononuclear cells of 23 JIA patients, divided into three groups: patients with active uveitis, patients with inactive uveitis, and a control group of JIA patients who did not develop uveitis. Expression analysis was performed.
Results: miR-582, miR-199b, and miR-365a were downregulated in both the active and the inactive groups compared with the control group (adjusted p-values <0.05). In the active uveitis group miR-197, miR-500, and miR-25 were also downregulated compared with the control group (p-values <0.01), while miR-493 and miR-320e were upregulated (p-values <0.01). miR-450a was downregulated in inactive uveitis (p-values <0.01). Between the active and inactive uveitis groups there was no significant difference in miRNA expression levels. Global miRNA expression analysis revealed a trend discerning all uveitis patients from controls.
Conclusions: miRNA expression profile differs between JIA patients with and without uveitis. Larger studies are needed to repeat, confirm and verify their clinical utility as biomarkers.

A Deep Intronic Substitution in CNGB3 is One of the Major Causes of Achromatopsia among Jewish Patients

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Purpose: Although most (or even all) genes that can cause achromatopsia when mutated are known, many patients are still negative for mutations, even after screening the coding sequence of all known genes. Our aim was to study the prevalence and the associated clinical parameters of a suspected CNGB3 deep intronic substitution.
Methods: We recruited for the study nine patients belonging to six unrelated families. Clinical evaluation included visual acuity testing, refractive error, color vision testing, full-field electroretinography, and retinal imaging. Genetic analysis was performed by Sanger sequencing of PCR products.
Results: We have recently reported, as part of a large European collaboration, that a heterozygous deep intronic CNGB3 single-base substitution (c.1663-1205G>A, IVS14-1205G>A) was found in an Israeli patient with achromatopsia in trans with a known heterozygous splice-site mutation. To understand the prevalence and relevance of this variant, we screened our cohort of patients and identified thus far nine patients of various Jewish ethnicities who belong to six unrelated families. The patients are either homozygous for this mutation or compound heterozygous with another known CNGB3 mutation as a second hit. All patients were diagnosed with a cone-related disease, mainly complete achromatopia. In all cases, the disease had an early congenital onset with typical signs of nystagmus and photophobia and in some cases rod involvement was evident by ERG.
Conclusions: CNGB3 is the most common cause of achromatopsia in patients of European descent, mainly due to a founder panethnic mutation, c.1148del. We reported previously that in the Israeli population, CNGA3 mutations are much more common, as are in China. Here we report of an intronic CNGB3 variant which is almost as frequent as c.1148del in the Jewish population. As gene therapy for CNGB3 is currently under investigation, these patients might benefit from this promising therapy.

Bestrophin1 Mutations Associated with Best Disease and ADVIRC Phenotypes Affect Distinct Biophysical Functions of Bestrophin1

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Purpose: While mutations in Bestrophin1 are classically associated with Best Disease, some mutations were found to be associated with distinct ocular phenotypes, such as Autosomal dominant vitreoretinochoroidopathy (ADVIRC). Previously we have generated stable lines of Retinal Pigment Epithelium (RPE) cells, each expressing different variant of Bestophin1, and shown that Bestrophin1 modulates the phagocytosis process. However, while Best Disease associated mutations lead to enhanced phagocytosis compared to wild-type, ADVIRC line displayed reduced phagocytosis. Given that many biophysical functions have been reported for Bestrophin1, we tested the effect of targeted pharmacological interventions in order to elucidate the biophysical functions of Bestrophin1 that mediate each phenotype.
Methods: ARPE19-based stable lines expressing wild-type, Best Disease, and ADVIRC associated Bestrophin1 were challenged with FITC-labeled photoreceptor outer segments for 3 hours. Control, ATP³⁻S (100µM), DIDS (500µM), and BAPTA-AM (100µM) were added to the reaction to assess the contribution of different biophysical functions of Bestrophin1 to linesâ€™ response.
Results: When ARPE19 stable lines were challenged without pharmacological intervention, we were able to recreate our previous **Results**. Best Disease associated lines (R218S, E300D mutations) displayed enhanced phagocytosis compared to wild-type, and V86M mutation- which is associated with the ADVIRC- displayed reduction in phagocytosis. Addition of ATP enhanced the differences between wild-type and Best Disease lines. In contrast, addition of the chloride channel blocker DIDS reduced the difference between wild-type and Best Disease lines, while the relative response of ADVIRC line was not significantly altered. However, in the presence BAPTA-AM which stabilizes the intracellular calcium levels, ADVIRC line response was reversed, displaying enhanced phagocytosis compared to wild-type, while the relative response of Best Disease lines compared to wild-type was not affected.
Conclusions: Bestrophin1 mutations modulate phagocytosis in a phenotype-dependent manner. Disruption of different biophysical functions appear to mediate the distinct ocular phenotypes resulting from mutations in Bestrophin1. Best Disease mutations probably result in disruption of the chloride conductance moiety, while ADVIRC phenotype appears to result from the disruption of intracellular calcium regulation mediated by Bestrophin1.

Characterization of a new knock-in (KI) Fam161a mouse model for the human pathogenic nonsense mutation p.Arg523*

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Purpose: The FAM161A-p.Arg523* mutation is one of the most common nonsense mutations causing retinitis pigmentosa (RP) in the Israeli Jewish population. This study is focused on the generation of a KI mouse model for this mutation and assessing its effect on retinal function and structure.
Methods: Knock-in (KI) mice with a homozygous p.Arg373* mutation, which corresponds to p.Arg523* in humans, were generated for us by Cyagen Biosciences (www.cyagen.com). RNA was extracted from mice retina and Fam161a expression was studied by RT-PCR. Retinal function and structure were examined at the ages of 1, 3, 4.5, 6 and 8 months using electroretinography (ERG), optical coherence tomography (OCT), fundus autofluorescence (FAF) imaging, and histological analysis.
Results: RT-PCR analysis of KI retinas revealed a normal level of expression of the mutant transcript as compared to WT, indicating that the nonsense-mediated mRNA decay surveillance system does not degrade the Fam161a p.Arg373* mutant transcripts in the mouse retina. Retinal function, examined by ERG, revealed a progressive decrease in amplitudes as compared with WT mice. Retinal structure, examined by OCT, revealed relatively slow loss of outer nuclear layer (ONL) thickness, first evident at 3 months of age. Fundus copy at the age of 3 months revealed narrowing of the blood vessels, and patchy hyperautofluorescent spots were observed on FAF imaging, indicating widespread retinal degeneration. Histological analysis at 6 months of age showed loss of 3-4 rows of photoreceptor nuclei in the ONL as compared to WT controls.
Conclusions: The **Results** indicate that the homozygous p.Arg373* mutation affects retinal function and causes retinal degeneration in the KI mice. Surprisingly, the rate of photoreceptor loss in the KI model is much slower than in the FAM161A KO model we previously characterized. Such a difference in clinical parameters between nonsense and frameshift mutations is not evident in human patients with FAM161A mutations. We intend to use this model to test novel therapeutic approaches for nonsense mutations, including read-through drugs such as Ataluren.

Identification of a Homozygous Fameshift Mutation in SLC4A7 as the Cause of Autosomal Recessive Retinitis Pigmentosa in Jews of Oriental Origin

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Purpose: Mutations in over 250 genes are known to cause inherited retinal diseases (IRDs), yet 25%-40% of cases are unsolved, even after comprehensive next generation sequencing (NGS) analysis. Therefore, our ongoing research focuses on finding novel IRD genes and mutations. In the present study, we identified a homozygous mutation in a novel IRD gene, SLC4A7, previously reported to cause Usher syndrome in knockout (KO) mice.

Methods: We recruited two unrelated Oriental Jewish patients. Clinical evaluation included visual acuity testing, refractive error, full-field electroretinography, Goldmann visual fields, ocular coherence tomography, color, and fundus autofluorescence imaging. Whole exome sequencing (WES) was performed on a DNA sample of MOL1001-1 (Variantyx Inc). Filtering of sequence variants has been performed as we published earlier. Variants were validated by PCR and Sanger sequencing. Allele frequency was analyzed by inspecting the gnomAD database and by screening 187 ethnicity-matched controls. Skin Fibroblasts were collected from a patient and a control via punch biopsy. Protein examination was performed by Western blot using the ab82335 antibody.

Results: Two patients from unrelated consanguineous Oriental Jewish families were diagnosed with IRD, with clinical findings that fall within the spectrum of RP. Aiming to identify the cause of disease, we examined MOL1001-1 for a panel of 109 known IRD genes that was negative, followed by WES analysis that revealed a homozygous frameshift mutation (c.2034dupT, p.Pro679fs) in the SLC4A7 gene, encoding the cotransporter NBC3. The mutation is absent both from the gnomAD database and 187 ethnicity-matched controls. Screening 62 patients of the same origin revealed another patient (MOL0242-1) homozygous for the mutation. We established fibroblast cell-lines from skin biopsies of a patient and a control and verified by RT-PCR that the SLC4A7 transcript is present in both, indicating that nonsense-mediated decay (NMD) surveillance does not act on this transcript. Nonetheless, Western blot analysis showed that the NBC3 protein was absent in patient fibroblasts, while present in control.

Conclusions: Our **Results** indicate that loss of NBC3 function causes photoreceptor degeneration. The SLC4A7 mutation identified either causes loss of the entire protein, or encodes a short dysfunctional one. We suggest screening SLC4A7 in IRD panels, as other mutations in this gene might be identified as disease-causing.

First Steps Towards Gene Therapy of FAM161A: How Can We Overcome Alternative Splicing?

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Purpose: FAM161A mutations are the most common cause of RP in the Israeli population. FAM161A is an excellent candidate for gene therapy since the mRNA is short and all reported mutations are null. However, a major challenge in gene therapy for this gene is an alternatively spliced exon that is important for retinal function. No studies were performed to overcome alternative splicing in gene therapy. We previously reported of a Fam161a KO mouse model showing progressive photoreceptor degeneration. We also demonstrated safe and efficient subretinal or intravitreal injections of AAV-7m8-GFP-hGRK1. Our Purpose was to design, deliver, and study the expression of an AAV vector which contains the coding sequence (CDS) of Fam161a and intronic sequences which surround the alternative exon.

Methods: A plasmid which included the CDS and two introns surrounding the alternative exon 4 was produced. Two non-conserved regions in intron 4 (total of 531bp) were deleted to fit AAV insert size-limits. KO mice were injected subretinally or intravitreally with AAV-7m8-Fam161a with various concentrations of the vector. RT-PCR was performed on retinal RNA to examine the expression pattern. Retinal function was evaluated by ERG and structure by OCT and histological analyses at different ages.

Results: One-month post injection, mice injected with 1E10 viral particles showed some preservation of the ONL in OCT images (mainly at the area of the bleb after SR injection), but no significant difference was noted in ERG examination. The OCT difference was not evident 2 months post injection. At lower concentrations no effect was evident and in higher concentrations accelerated degeneration of the retina was observed.

RT-PCR analysis 1-month post injection revealed that a transcript lacking exon 4 and not the long transcript (including exon 4) was produced. In addition, a minor splice-site within intron 4 was activated to produce a longer transcript including exon 4, part of intron 4 and exon 5. This intronic splice-site is also activated in WT retina as well as in the human orthologue.

Conclusions: To the best of our knowledge, this is the first study which reports Results of AAV injections with the aim of addressing alternative splicing. Our Results indicate that a full-length protein which includes exon 4 is not produced by this construct, and this is probably the reason for the failure of the treatment. Further experiments are needed in order to optimize the treatment.

Photovoltaic restoration of sight in geographic atrophy: one-year follow-up

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Purpose: To evaluate structural integration and functional performance of the photovoltaic subretinal implant in patients with geographic atrophy.
Methods: A prospective study in 5 patients with visual acuity ‰₪20/400ƛ due to geographic atrophy of at least 3 optic discs diameters and no foveal vision. The wireless photovoltaic chip (PRIMA, Pixium Vision) is 2x2mm in size, 30μm in thickness, containing 378 pixels of 100μm in width. Each pixel in the implant converts pulsed near-infrared light (880nm) projected from video glasses into electric current to stimulate inner retinal neurons. Anatomy was assessed with OCT, fundus photography and FA. Prosthetic vision was assessed using Landolt C test and letter recognition.
Results: In all 5 patients, chip implanted under the macula remains stable and functional, with a follow-up exceeding now 12 months in all patients. No decrease in natural eccentric visual acuity was observed in any of the patients. In all 4 patients with the chip placed subretinally, distance to the inner nuclear layer remains in the range of 35-39μm. All 5 patients perceive white-yellow patterns with adjustable brightness, in retinotopically correct locations within previous scotomata. All 4 patients with subretinal placement of the chip achieved letter acuity. Out of them, all 3 patients with central placement of the implant demonstrated acuity in the range of 20/460 - 20/550, which is just 10-30% below the sampling limit of resolution for this pixel size (20/420). Patient with the chip placed off-center demonstrated prosthetic acuity of 20/800. In the second phase of the trial, patients started using transparent augmented-reality glasses, and demonstrated simultaneous perception of the peripheral natural and the central prosthetic vision. Adjustable zoom on new video glasses significantly increased the equivalent prosthetic acuity.
Conclusions: Wireless chip PRIMA implanted under the atrophic macula in patients with geographic atrophy remains stable and functional during the 12 months of follow-up. It did not reduce the natural residual visual acuity in any of the patients. The implant provides central visual perception with acuity close to the single pixel size of the photovoltaic array. Video glasses with optical or electronic zoom provide significantly higher resolution.

Retinotopic to spatiotopic mapping in blind patient implanted with visual cortical neurostimulator

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Purpose: Treating blindness due to diseases that severely compromise the optic nerve will require stimulation at locations in the visual pathway that bypass the eye and the optic nerve. In sighted individuals, due to eye movements, the brain continuously maps visual information acquired at retina-based coordinates to spatial locations in world-based coordinates. Correspondingly, electrical stimulation of visual cortex in blind patients should convey information to the brain that is mapped to the correct spatial location in the world. The Purpose of this study was to verify that electrical stimulation of the visual cortex of a blind patient is correctly mapped based on eye position.
Methods: Electrical stimulation of the visual cortex of a blind subject with bare light perception secondary to Vogt-Koyanagi-Harada syndrome was achieved using the RNS neurostimulator (NeuroPace, Mountain View, CA). Two parallel strips of four electrodes each were implanted over the right medial occipital lobe.
The subject reported the location of the percept from electrical stimulation of a single electrode using a trackable handheld marker. Eye positions were recorded with a timestamp synchronized to the time of stimulation.
Results: The perceived location, resulting from electrical stimulation of the visual cortex, shifted based on the eye position at the time of the stimulation. We were able to remap the measured responses based on measured eye position in order to localize the retinotopic locations associated with each electrode.
Conclusions: Artificial vision generated by electrical stimulation at the occipital lobe creates a percept that is mapped to world-based coordinates based on eye and head positions. The brain of a blind individual has the necessary signals to accurately map visual information necessary to utilize eye movements for visual scanning.

Experimental achromatopsia treatment reveals the extant of cortical recovery in adulthood

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Purpose: CNGA3-achromatopsia is a genetic condition caused by the dysfunction of the retinas cones resulting in photophobia, low visual acuity, and complete color blindness. Lately, three patients were treated under a gene implementation trial repairing the conesג€™ function. The **Purpose** of this study is to investigate the neuroplasticity of the visual cortex following cone input renewal in adulthood.
Methods: Patients underwent fMRI scans using two protocols. The first, a block design experiment mapping high level ventral stream regions such as faces, places and color cortical regions. The second, population receptive field (pRF) paradigm estimating the pRF eccentricities and sizes in early visual cortex (V1, V2 and V3).
Results: We found intact faces and places cortical regions in these patients but no initiation of the ventral stream color regions after treatment. However, we found a striking post-treatment recovery of the pRFs eccentricity and size. Compared with control participants, both characteristics were larger before surgery and decreased after treatment. fMRI Results are with accordance to behavioral Results showing increased acuity with no color vision even a year after surgery.
Conclusion: We suggest adulthood cortical recovery is limited to capabilities which existed prior to surgery: in this case, the improvement in visual acuity with a matching neuronal decrease in pRF size. For color vision, a new capability and concept, there might be a childhood critical period resulting in no initiation of cortical color regions or color perception.

Noninvasive objective diagnosis and monitoring of patients with focal intracranial pathology based on pupil response for focal chromatic light stimuli

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Purpose: To characterize rod-, cone- and melanopsin-mediated pupil light responses (PLR) for small focal chromatic light stimuli presented in peripheral and central retinal locations in patients with brain tumors.
Methods: Eighteen patients with brain tumors and 32 age-similar controls were enrolled. Patients were divided into 2 groups: group I included 10 patients with brain tumors with no apparent contact with the optic apparatus; group II included 8 patients with brain tumors that contacted the optic apparatus. The PLR for small (0.43deg) blue and red light stimuli presented at peripheral (21deg) and central (4.2deg) visual field locations were measured using a chromatic pupilloperimeter under mesopic light adaptation conditions. All subjects underwent a complete ophthalmic exam, standard Humphrey automated perimetry (24-2), color vision test, best-corrected visual acuity, and refraction as well as Spectral-Domain Optical Coherence Tomography (SD-OCT) imaging. All patients underwent brain MRI.
Results: The SD-OCT thicknesses of macular ganglion cell and inner plexiform layers, as well as peripapillary retinal nerve fiber layer, were within normal limits in all patients. The mean normalized pupil size at 3.7sec following blue light offset recorded in patients from both groups was significantly higher compared with controls in central and peripheral locations (all Ps< 0.003). ROC analysis revealed that this PLR parameter had the largest area under the curve (AUC) in the central retina in group I and in the peripheral retina in group II (90.8%, p=0.003 and 89.3%, p=0.003, respectively). In group II, ROC analysis revealed that the maximal contraction velocity recorded in response to the red light stimulus in the peripheral superior test target had the largest AUC (96.4%, p=0.006).
Conclusions: Focal intracranial pathologies may be detected by localized melanopsin-mediated sustained PLR for central blue stimulus. Patients with brain tumors involving the visual pathway had an additional defect in the cone- mediated PLR. Quantification of the PLR for focal central and peripheral chromatic stimuli may serve as a novel noninvasive objective diagnostic tool for focal intracranial pathologies.

A Retrospective Study to Determine the Normal Range of Vascular Compression of the Optic Nerve and Chiasm.

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Purpose: There is literature to suggest that conditions such as normal tension glaucoma and chiasmatic disorders may be caused by mass effect of blood vessels on the optic nerves or chiasm. We sought to determine whether vascular compression of the optic nerve or chiasm can be an anatomic variant.
Methods: We retrospectively reviewed consecutive 3T head MRI studies performed for any Purpose at Hadassah Medical Center. Studies were excluded if there was motion artifact, if they were conducted with a short protocol, or if there was known pathology in the area of the optic nerves, chiasm, or orbit.
Results: Fifty-four studies of separate patients were included in this study. Twenty-two patients demonstrated vascular compression of the optic nerve by the ophthalmic artery. Of these 22 patients, the ophthalmic artery compression was present bilaterally in three patients and three others had vascular compression at the chiasm. One patient had only vascular compression of the chiasm, and another patient only had vascular compression from the internal carotid artery. The presence of vascular compression was not associated with age, gender, or cardiovascular risk factors.
Conclusions: Vascular compression of the optic nerves and chiasm is likely a normal anatomical variant and should not be interpreted as a definitive etiology of vision loss.

Automated Visual Field Abnormalities - a Multi-Phase Survey of Neuro-Ophthalmologists and Consensus Statement

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Introduction: A multitude of terms have been used to describe automated visual field abnormalities. To date, there is no universally accepted system of definitions. Variability among clinicians creates the risk of miscommunication and the compromise of patient care. The Purposes of this study were to 1) assess the degree of consistency among the nationâ€™s neuro-ophthalmologists in the description of visual field abnormalities, and 2) to create a national consensus statement with standardized terminology and definitions.

Methods: In phase one of the study, the countryâ€™s neuro-ophthalmologists were asked to complete a survey requiring free text descriptions of the abnormalities in 10 randomly selected automated visual fields. In phase two of the study, the authors created a national consensus statement on the terminology and definitions for visual field abnormalities using a modified Delphi method. In phase three of the study, the countryâ€™s neuro-ophthalmologists were asked to repeat the initial survey of the 10 visual fields using the consensus statement to formulate their answers.

Results: Twenty-six neuro-ophthalmologists participated in the initial survey. An average of 7.6 distinct terms were used to describe each of the visual field abnormalities (SD 3.5). Twenty-two neuro-ophthalmologists participated in the creation of a consensus statement which included 24 types of abnormalities with specific definitions. Twenty-three neuro-ophthalmologists repeated the survey using the consensus statement. There was a significant decrease in the variability with an average of 5.0 distinct terms per visual field abnormality (SD 1.3, paired t test = 0.02).

Conclusions: The study confirmed a great degree of variability in the use of terminology to describe automated visual field abnormalities. The creation of our consensus statement was associated with improved consistency. Further efforts are warranted to standardize terminology and definitions.

OPTIC NEURITIS MONITORING USING OBJECTIVE VISUAL FIELD TESTING

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Purpose: To objectively asses visual field defects in optic neuritis patients by measuring pupillary light response using a chromatic pupilloperimeter.
Methods: Twelve acute optic neuritis (ON) patients (mean age♀± standard deviation: 339.87 ±♀ years) and 26 age-similar healthy controls (35.412.4 ±♀ years) were enrolled. The pupillary responses for red and blue light stimuli (peak 485 nm and 625 nm, respectively) presented at 54 locations of a 24-2 visual field were recorded. The associations between the percentage of pupil size change (PPC) and the patients' best corrected visual acuity (BCVA) and Humphrey's 24-2 perimetry were determined. In addition, the melanopsin-mediated sustained pupil responses (pupil response recovery, PRP) were evaluated at central and peripheral VF locations.
Results: Substantially lower PPC was recorded in ON eyes in response to blue light stimuli, correlating with low BCVA and Humphrey MD scores. The PPC recorded in response to red light was less affected. PPC recovery was demonstrated in eyes that improved following steroid treatment. PRP in the peripheral VF in response to blue light was significantly faster in ON eyes compared to controls (0.69±0.09♫ vs. 0.833±0.02♪, respectively, p=0.00015). ROC analysis revealed that this pupil response parameter discriminates between ON and healthy eyes with high specificity and sensitivity (area under the curve=0.913, p=0.001).
Conclusions: Chromatic pupilloperimetry can objectively detect damaged areas in the visual field of optic neuritis patients. The pupil response was associated with disease severity and detected improvement correlating with disease recovery following treatment. The melanopsin-mediated pupil response for blue light at the peripheral retina may present a novel noninvasive objective retinal function biomarker for detection of ON.

Cortical responses to prosthetic retinal stimulation are significantly affected by the light-adaptive state of the surrounding natural retina

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Purpose: The retinal prosthesis is a promising approach for vision restoration in age-related macular degeneration (AMD) patients. It is therefore of great importance to investigate the characteristics of the prosthetic response in the presence of a surrounding healthy retina. As sensory adaptation of the natural retina to ambient lighting is vital for functional vision, we investigated the effect of the adaptive state of the natural retina on the cortical responses arising from prosthetic stimulation of the retina.
Methods: Implantation of a photovoltaic subretinal implant in wild-type rats caused localized retinal degeneration above the implant while the surrounding retina remained intact, thus creating a unique model that mimics AMD patients implanted with a subretinal prosthesis. Cortical signals in response to prosthetic retinal stimulation were recorded in dark adapted animals and compared to those recorded following exposure of the surrounding natural retina to bleaching visible light (535nm) at various intensities and durations.
Results: We found that in dark-adapted rats, the prosthetic cortical responses were about 2-fold higher before bleach compared with after bleach, with the dynamics of recovery to the dark-adapted amplitudes remarkably similar to the re-adaptation to dark of the natural retina. Prosthetic signal reduction after bleach was not observed in experiments using retinal degenerate rats, suggesting the involvement of photoreceptors in the observed phenomenon. We hypothesized that the adaptive retinal response to bleaching is mediated by long-range connections in the amacrine cells, as was supported by the absence of the bleaching effect on the prosthetic response following intraocular injection of a GABAa receptor blocker.
Conclusions: These findings have immediate implications for the study of prosthetic vision in patients with retinal degenerations in general, and for study design of sight restoration in AMD patients in particular.

Result of the AssiAnchor Capsule Device in Subluxated Crystalline Lenses

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Purpose: To describe our **Results** with the AssiAnchor capsule device in cases of subluxated crystalline lenses.
Methods: Retrospective evaluation of seven eyes of four patients with subluxated crystalline lenses underwent lensectomy/phacoemulsification with intraocular lens (IOL) implantation using the AssiAnchor capsule device in Kaplan medical center, ophthalmology department. Three patients had Marfan syndrome and one patient had post blunt trauma. Data was collected on the patients demographics, pre- and post-operative distance visual acuity and refraction, intra- and post-operative complications and IOL stability and centration.
Results: Six out of the seven surgeries were uneventful with in-the-bag implantation of the IOL. In the first surgery, a tear of the capsular bag lead to exchanging the IOL and fixating it to the AssiAnchor and to the iris. In the traumatic cataract case, two AssiAnchors were used. Capsular tension ring was implanted in six out of seven surgeries. The average follow up time was 9.5+/-6.8 months. All the IOLs were stable and well centered except for the first IOL that demonstrated slight temporal, not clinically significant, decentration. The distance visual acuity and the refractive parameters improved significantly in all cases.
Conclusion: We found the AssiAnchor capsule device an effective tool with a short learning curve for treating subluxated lenses.

Clinical Outcome of Iris versus Scleral Intraocular Lens Fixation

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Purpose: To compare the safety and efficacy of scleral fixation (SFIOL) and iris fixation of posterior chamber intraocular lenses (IFIOL).

Methods: A retrospective chart review of 112 eyes of 105 patients that underwent SFIOL or IFIOL at the Kaplan Medical Center between 2008 and 2018, seventy three eyes had SFIOL and 39 eyes had IFIOL. The main outcome measures were: operation time, postoperative visual acuity and intra and post-operative complications.

Results: There was no significant difference in the mean operation time between SFIOL and IFIOL. The mean follow-up time was significantly longer for the IFIOL compared with the SFIOL (34±31, vs. 14±20, months, respectively [P>0.001]). Postoperative distance corrected visual acuity (DCVA) at the last follow-up was significantly better than the preoperative DCVA in both groups (SFIOL: 0.52±0.49, vs. 1.20±0.84, [P<0.001], and IFIOL: 0.75±0.88, vs. 1.31±0.81, [P<0.001], respectively [LogMar]). No differences in DCVA were found between the groups. Irregular pupil was found in 59% IFIOL vs. 20.5% of the SFIOL [P<0.001] and corneal edema was found in 10.3% of the IFIOL vs. 1.4%% of the SFIOL [P=0.05]. No other differences in intra and post-operative complications were found between the two groups.

Conclusion: Both IFIOL and SFIOL are effective and safe for the secure of IOL in the absence of adequate capsular support. Both technique resulted in a significant improvement in DCVA. Pupil ovalization and corneal edema were more common in the IFIOL group. Longer follow-up was noticed at the IFIOL group.

Clinical characteristics and outcomes of pediatric posterior lenticonus associated with cataract

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PURPOSE: To analyze the clinical characteristics of children diagnosed with posterior lenticonus associated with cataract who underwent lensectomy.
METHODS: We performed a retrospective study of children with posterior lenticonus associated with cataract who underwent lensectomy at Hadassah University Medical Center between 2007-2017 with a follow up of at least 1 year. Clinical variables and surgical notes were collected.
RESULTS: We reviewed a total of 310 eyes with congenital cataract (135 children with bilateral and 52 with unilateral cases). Only 18 eyes (5.8%) were diagnosed with posterior lenticonus (1 child with bilateral and 16 with unilateral cases). All were healthy without any systemic condition. Eleven children (12 eyes) underwent limbal approach lensectomy and anterior vitrectomy. Eleven eyes had intraocular lens (IOL) implantation at the time of surgery and 1 child was left aphakic. The mean age at the time of surgery was 51.4 (range: 1.5-108) months. The mean time of follow up was 60 (range: 12-90) months. None of the children developed secondary cataract. Secondary glaucoma presented in one child 3.5 years after lensectomy and was managed with topical medication. The mean visual acuity at 1 year of follow-up in 11 eyes was 0.7 LogMAR (range: 1.4-0.2). All children were still with amblyopia at one year follow up, in 90% it was considered deep amblyopia. Strabismus was present in 54.5% of the children, most commonly exotropia.
CONCLUSION: Posterior lenticonus is an unusual unilateral form of childhood cataract. It typically presents at an older age and is associated with resistant amblyopia. Interestingly, post-operative complications are less common than in other types of pediatric cataract

Residual astigmatism predictors by pre-operative modalities in toric intraocular lenses for cataract surgery

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Purpose: With the recent upward trend in toric intraocular lens (IOL) implantation in cataract surgery, preoperative evaluation needs to be optimized in order to minimize residual astigmatism. This study aims to test the correlation between different preoperative assessment instruments and calculators to the post-operative outcomes, and to determine the modality that most accurately predicts the residual astigmatism.
Methods: A retrospective analysis of patients who underwent toric IOL implantation at Hadassah Medical Center between 2017-2019 was performed. Keratoconus patients were excluded. Preoperative assessment included uncorrected visual acuity (UCVA) in logMAR, refraction, corneal topography using Oculus Pentacam, and IOL calculation using Zeiss IOLmaster500, IOLmaster700 and/or Haag-Streit Lenstar900, as well as Barret Toric Calculator (BTC) formula. A comparison was made between the different IOL calculation modalities using Wilcoxon test, Pearson coefficient, and2‡♂ test.
Results: Eighty-four eyes (mean age 65.557.1% ,±14.5¸ female) were included. The preoperative mean UCVA was 0.70±0.5¸logMAR with mean refraction of -1.60±4.7Ḍ sphere and -3.0±1.8Ḍ cylinder (range: -0.50 to -7.00D). Postoperative UCVA was significantly improved to 0.22±0.16¸ logMAR (P<0.001). The refractive cylinder was reduced by 2.19±0.56Ḍ (Range: 0.5-3.25D) postoperatively (P<0.001), yet the magnitude of the residual astigmatism was significantly larger than the one predicted by the IOL calculators (0.970.42±0.8 ,±0.7¸ respectively, P<0.001). Preoperative comparison of the biometry devices to the Pentacam demonstrated a significant deviation in flat K (-0.91±1.72; P=0.05) and steep K (0.74±1.24; P=0.04) values in the case of IOLmaster500, while the Lenstar900 and IOLmaster700 showed similar values with less than 0.50D deviation. This discrepancy, however, had no statistically significant effect on the postoperative UCVA or the residual astigmatism. A higher K-value discrepancy between the IOLmaster700 and the Pentacam was correlated with a non-statistically significant trend towards higher residual astigmatism (r=0.38; P=0.09). No statistically significant association was found between the BTC formula prediction and the residual astigmatism (p=0.74).
Conclusion: None of the modalities tested showed superiority in predicating the residual astigmatism after toric IOL implantation. Improved preoperative tools are needed to optimize toric IOL implantation outcomes.

Alzheimer's disease as a risk factor for a decreased visual outcome after cataract surgery

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Purpose: Neurodegenerative diseases (NDD), including Alzheimer's and Parkinson's diseases, are relatively common among individuals undergoing cataract extraction (CE). Limited data is available on the outcome of CE in NDD patients. This study aims to assess for potential interactions among NDD and the outcome of CE.

Methods: A retrospective analysis of all patients that underwent CE at Hadassah Medical Center between 2013-2018 was performed. Data collected included demographics, pre- and post-operative uncorrected (UCVA) and best corrected by pinhole (BCVA) visual acuity in LogMAR. Patients were then classified into 3 subsets: individual having the diagnosis of Alzheimer's disease (AD) or Parkinson's disease (PD), and ones without the diagnosis of AD or PD (NNDD). Statistical analysis was performed using ANOVA, Pearson Coefficient,2‡ test and multinomial regression models.

Results: From an electronic medical records (EMR) dataset of 11,545 surgeries, 2,684 patients had complete information and were included in the analysis. The mean age was 69.8±14.6 years and 52% were males. The median UCVA of the entire database improved from 0.6 to 0.4 after surgery (P<0.001), while the median BCVA improved from 0.4 to 0.3 after surgery (P<0.001). Twenty-eight AD patients and 33 PD patients were identified in the database. The mean pre-operative logMAR UCVA was similar across the groups (AD 1.38±0.96, PD 0.87±0.67, NNDD 0.98±1.0; P=0.28), as well as the mean pre-operative logMAR BCVA (AD 0.42±0.19, PD 0.43±0.21, NNDD 0.36±0.28; P=0.63). AD patients had poorer post-operative UCVA (1.31±1.1) compared with NNDD (0.67±0.86, P=0.001), with an odds ratio of 1.6 (95% CI: 1.12-2.27, P=0.009) to a worse postoperative UCVA than NNDD patients. On the other hand, PD patients (0.49±0.41) had similar outcome as NNDD (P=0.32). Final BCVA was similar across NNDD (0.33±0.27), AD (0.40±0.22) and PD (0.28±0.22) patients (P=0.76).

Conclusions: Patients with AD and PD enjoy a mean improvement in visual acuity following CE. AD is potentially associated with lower UCVA but similar BCVA compared with PD and NNDD following CE. Technical difficulties in the biometry measurements or the surgical procedure due to poor cooperation of AD patients might underlie the lower final UCVA in AD.

How do non pigmented ciliary epithelium derived exosomes transfer their signals to the trabecular meshwork in the ocular drainage system?

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Purpose: To investigate the internalization mechanisms by which Non-Pigmented Ciliary Epithelium (NPCE) derived exosomes deliver their signals to the Trabecular Meshwork (TM) cells, focusing on endocytosis, phagocytosis and receptor activation.
Methods: Following NPCE exosomes extraction using PEG-8000 precipitation, exosomes size, concentration and membrane integrity were evaluated by Tunable Resistive Pulse Sensing technology, Cryo-TEM and CD81 marker. Proteinase K, diverse temperatures and pharmacological inhibitors (Dynasore/Wortmannin) were used to verify signaling through ligand binding, endocytosis or phagocytosis.
Results: Exosomes membrane remained intact as was seen in Cryo-TEM analysis. SDS-PAGE separation and Ponceau red staining indicated no difference in treated NPCE exosomes protein content compared to untreated ones. Confocal microscopy showed a decrease in the uptake by TM cells of Proteinase K treated exosomes. Incubation of TM cells at low temperature revealed a significant decrease in exosomes internalization. TM cells exposed to pharmacological inhibitors prior to NPCE exosomes addition, demonstrated an inhibitory effect of exosomes uptake mediated through endocytosis and phagocytosis mechanisms, as was analyzed using Flow cytometer. Attenuation of the expression levels of p-GSK3²- and ²-Catenin proteins following drug treatments or exosomes membrane proteins removal was indicated by Western blot analysis for Wnt-TGF²2- proteins levels in TM cells.
Conclusions: Exosomes derived from NPCE cells can be internalized to TM cells in an active manner that involves clathrin/caveolae-dependent routes, involving surface proteins recognition of exosomes by the target cells.

Optical coherence tomography for differentiation between glaucomatous and suprasellar-tumor related optic disc appearance

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Purpose Since both patients with glaucoma and those with suprasellar tumors develop optic disc cupping, we sought to examine the optical coherence tomography (OCT) and OCT angiography (OCTA) optic disc parameters for differentiation between glaucomatous and suprasellar-tumor related optic disc appearance.

Methods A prospective case control study. Patients diagnosed with primary open angle glaucoma or suprasellar tumors were recruited. Each patient underwent a complete ophthalmological examination, spectral domain OCT and OCTA scans, and a visual field examination. Comparison of the clinical, imaging, and visual field **Results** of the glaucoma versus the suprasellar tumor group was made.

Results Thirty-two patients were recruited; 32 with glaucoma (18 males, 5 female) and 9 with suprasellar tumors (3 males, 6 females). The mean age for the glaucoma group was 72.8 years (range 58-90) and for the suprasellar tumors 60.7 years (range 43-73). OCT analysis showed a lower peripapillary retinal nerve fiber layer (RNFL) thickness (p=0.002) and higher rim area (p=0.005) in the glaucoma group. OCTA showed a lower peripapillary vessel density in the glaucoma group (p=0.005). These statistically significant differences between the groups were maintained when stratifying for mean deviation severity.

Conclusions Glaucoma patients have a lower peripapillary RNFL thickness, higher rim area, and a lower peripapillary vessel density as compared to suprasellar tumor patients. These parameters may aid in the initial differentiation between these two optic neuropathies at an ophthalmology clinic setting.

Retinal Displacement Detected with Fundus Autofluorescence following Pneumatic Retinopexy vs. Pars Plana Vitrectomy (INTEGRITY STUDY)

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Purpose-To compare retinal displacement and visual distortion of retinal detachment repair following pneumatic retinopexy (PnR) versus pars plana vitrectomy (PPV). To the best of our knowledge this is the first study to check retina displacement after pneumatic retinopexy.
study design-A retrospective study, comparing two surgical interventions (PnR,PPV) was done. All patients, 18 Years old or older after retinal detachment repair and post operative fundus autofluorescence (FAF) between September 1st 2008 to September 1st 2018 were included. Exclusion criteria were low quality of fundus autofluorescence, Retinal disease with retinal pigment epithelium involvement or lack of proper documentation. The study Primary outcome was retinal displacement determined by retinal vessel printing on FAF imaging. Secondary outcome was visual distortion determined by M chart and Anisokenia test. The study was approved by the institutional ethics committee.
Methods-All FAF photos were analyzed independently by two authors (K.B. and F.C.). The interpreters were blind to the procedure that was done. In case of disagreement between the two analyzers, the FAF was reviewed by both authors together and if there was no consensus a third author analyze the FAF imaging, blind to the first two authors evaluations and the procedure type. When positive displacement was found, the following parameters were analyzed- direction of the displacement, which quadrants are involved in the displacement, macula involvement in the displacement including maximum and minimum values, existence of radial or rotatory displacement, number of RVP lines seen.
Results and **Conclusions**-156 eyes of 150 patients were included in the study of which 48 after PPV, 99 after PnR, and 9 after combined scleral buckle and vitrectomy. Displacement ratio was as follows-50% for PPV group (24/48) 8% for PnR group (8/99), and 78% for S/B+PPV (7/9). For macula off RD's the following Results have been recorded- 57% (20/35) versus 9% (6/66) versus 80% (4/5) for PPV, PnR and PPV+S/B respectively. For macula on RDג€™s 30% (4/13) versus 6% (2/33) versus 100% (1/1) for PPV, PnR and PPV+S/B respectively. A significant statistical difference was noted between PnR and PPV groups (P<0.001).
For conclusion retinal displacement rate after PnR was statistically lower than after PPV. Combined PPV+S/B surgery seems to have a higher rate of retinal displacement.

Minimal treatment for retinal vein occlusion: How low can you go?

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Purpose: Multiple controlled studies have demonstrated the efficacy of intravitreal anti-VEGF and steroid treatment for ME in BRVO with VA 6/12 or worse. Regarding eyes with VA of 6/10 or better, no published data compares intravitreal treatment with observation. Thus, treating physicians are faced with the dilemma of whether to extrapolate from studies on eyes with worse VA and treat these eyes or to take a conservative approach of watch and wait. The Purpose of this study is to describe the clinical course of RVO patients that received no or minimal ocular treatment.
Methods: Medical records of consecutive RVO patients that presented within 4 months of disease onset, with central macular involvement by SD-OCT, with at least 24 months follow-up and that received a maximum of two intravitreal injections, were retrospectively reviewed.
Results: Eight BRVO and 2 CRVO patients were studied. Mean presenting CRT was 433155 ± um (range, 304-825). Two of the eight BRVO patients received 2 bevacizumab injections each, 6 received no ocular treatment. Both CRVO patients received two injections each, one of these was dexamethasone implant and the rest were bevacizumab. Final CRT was 289 41 ± um (range, 217-340). All 10 eyes attained a VA of 6/7.5 or better, 5 attained 6/6.
Conclusions: RVO with center-involving CME and good vision can be managed without ocular treatment or with minimal injections, on condition that the patient is closely monitored. Randomized trials are necessary to establish clear indications for treatment of CME due to RVO presenting with good VA.

Penetrating ocular injuries at Emek medical center between the years 2014 and 2017

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Purpose: Open globe injury is one of the most common causes for irreversible vision loss worldwide, especially at young age . They come at high cost to society and can be prevented . The aim of this study was to describe our experience with penetrating ocular injuries in terms of epidemiology, therapy and outcomes.
Methods: A retrospective chart review of all penetrating ocular injury cases that presented to Emek Medical Center between 01/2014-01/2017. Data collected included demographic (age, gender, ethnic group etc.) as well as clinical (mechanism, extent, treatment, final acuity etc.) information.
Results: 45 charts were included in this study. Incidence was 13 cases per year, with a significant increased incidence (9) in the first two months of 2017. 42% of the patients presented during January, May and August, with a higher incidence in the first half of the week. Male to female ratio 42:3 and right to left eye ratio 15:30. Among the adults (37) the mean age was 39, and among the children (8) it was 8. Only 6 cases involved organic material and their outcome was not different than the inorganic group. 37 (82%) patients underwent surgery during the first 24 hrs and 8 (18%) were treated nonsurgically .In 22% of the patients vitrectomy was needed. All patients were followed up for at least 4 month after discharge. 45% of the patients had improvement in VA at discharge. 24% had VA of 6/18 or better at the final follow up. Complications included: one case of endophthalmitis, 2 cases of retinal detachment, and one evisceration. Conclusion: A poor initial VA does not guarantee a poor final result, especially if there was emergent and appropriate treatment.More effective means are needed to raise the society awareness of this type of injuries and its burden. Protective tools should be mandatory at work. Future National Ocular Trauma Registry would provide better understanding and more confident
Conclusions regarding preventative actions and treatment to ocular penetrating injuries.

Risk Factor for Vision Loss in Anterior Uveitis

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Methods We designed a retrospective observational study. Our data base included all patients diagnosed with AU and treated in Bnai Zionג€™s ophthalmology outpatient clinic between 1985 and 2019. The study population included patients of all ages and all etiologies for AU. The only exclusion criteria were intermediate uveitis, posterior uveitis or panuveitis. We collected data regarding the patientsג€™ demographics, etiology, ophthalmic exam and imaging tests. Statistical analysis was done using SPSS and included Kaplan Meier survival analysis, Pearson2‡ test and Cox Linear regression model

Results 561 Patients met the inclusion criteria (882 eyes). The diagnosis was acute anterior uveitis in 454 eyes, recurrent anterior uveitis in 38 eyes, chronic anterior uveitis in 286 eyes, postoperative anterior uveitis in 20 eyes. Etiology was infectious in 62 eyes, idiopathic in 402 eyes, secondary to a systemic autoimmune disease in 118 eyes and HLA-B27 related in 107 eyes. During the follow up 66 (8.26%) patients were diagnosed with glaucoma, 72 (9.01%) eyes suffered from macular edema, 158 (19.8%) eyes underwent cataract extraction.

In this study 36 (4.5%) eyes had moderate vision loss (MVL) and 71 (8.9%) eyes had severe vision loss (SVL). The risk factor for MVL was chronic anterior uveitis. Risk factors for SVL were infectious uveitis and HLA-B27 uveitis. Causes of vision loss were ERM, CME and corneal opacity.

Patients with chronic anterior uveitis were more likely to suffer from an epiretinal membrane, corneal opacity, CME, glaucoma and had a statistically significant higher rate of cataract extractions.

Conclusions Anterior uveitis is the most common type of uveitis. Based on our large database we found that visual acuity was unchanged during the follow up for most patients, that many patients are first diagnosed at the emergency room and that the highest correlation for MVL and SVL is chronic anterior uveitis. Cataract formation is the most common complication of uveitis and corneal opacity is most common complication to cause MVL and SVL.

Prevalence of Demodex among Chronic Dacryocystitis patients

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Purpose: Proving a causative relationship between DMDX mites and chronic dacryocytitis. Comparing DMDX characterization among patients with different disease severity.
Methods: A case-control study. Patients aged 50-80 with chronic dacryocysitis with scheduled DCR surgery, were asked to give 5-10 eyelashes from infected eye to microscopically detect DMDX mites. A Control group included healthy volunteers participants, with no history of dacryocystitis, local steroid use, roseola, and immunocompetent. In cases where DMDX mites were detected, they would be morphologically classified. General medical and ophthalmological history for each patient were obtained as well. Statistical analyzes were performed using the SAS 9.2 software. Appropriate medical treatment was offered to infected patients prior to their surgery.
Results: 71 eyes of 71 patients participated in the study, 35 were candidates to DCR surgery and 36 eyes were in the control group. Patientsא€™ age ranged from 50 to 73, with an average age of 61 . 28 males and 43 females were included the study, with higher Chronic dacryocystitis and DMDx infection prevalence among women. Among patients with negative DMDX result, women had high prevalence as well. A strong relationship was found between DMDX and dyslipidemia.
Conclusions: No higher prevalence of DMDX among Darcyocysitis patients was found
comparing with the general population. Women suffer more from DMDX infection and
Dacryocystitis, more etiological factors need to be found. A statistically significant association between Dyslipidemia and Demodex inhabitance was found. Further research with larger number of participants is required in the future.

Unjustifiable Abandon of Scleral Buckling Technique: Outcomes of Primary Rhegmatogenous Retinal Detachment Repair among Young Patients

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Purpose: To compare the functional and anatomical outcomes of primary rhegmatogenous retinal detachment (RRD) in eyes operated with scleral buckling (SB) or pars plana vitrectomy (PPV) or combined procedure (SB-PPV).
Methods: A retrospective, comparative case series study. Included were patients under age of 40 who were admitted for surgical management of primary RRD in Ophthalmology department at Hadassah Medical Centre in Jerusalem, Israel, between the years 2006-2014. There were three groups according to the surgical technique; patients who underwent SB surgery (SB group), patients who underwent PPV (PPV group) and patients who underwent a combined surgery (SB-PPV).
Results: Included were 90 patients (57 males, 63%) and 90 eyes. The mean age of the patients was 30.8 years (range, 22-40). In the SB group were included 67 eyes (42 males, 63%). In the PPV group were included 10 eyes (7 males, 70%). In the combined group (SB+PPV) were included 13 eyes (8 males, 62%). Anatomical success was not differed statistically between the three groups (p-value=0.9). Primary anatomical success was 87% in SB group, 90% in the PPV group and 85% in the combined group. Regarding visual acuity (VA) in comparison between the mean VA pre-operatively and post-operatively at last follow up, there was statistically significant increase in the mean VA in SB group (p-value=0.03) but not in PPV (p-value=0.06) or combined groups (p-value=0.9). However, in comparison of the mean VA post-operatively at last follow up between the three groups, there was only significant difference in comparison between SB and combined group (p-value<0.0001) but not between SB and PPV (p-value=0.06) or PPV and combined group (p-value=0.3).
Conclusions: The study did not show significant differences in the functional and anatomical success rates in comparison between SB, PPV and SB-PPV in the treatment of primary RRD. Despite the rising use of PPV for primary RRD, SB is still not inferior than PPV and should be considered in suitable cases.

Multi-Modal Image Analysis to Quantify Elmiron Retinal Toxicity Demonstrates an Dose-Response Curve

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Purpose: To develop a novel multi-modal image analysis to quantify Pentosan Polysulfate Sodium(PPS, Elmiron) retinal toxicity.
Methods: A cross-section, observational study was performed using the Epic record system. The records of all UMass Memorial Healthcare patients were searched for patients using PPS longer than 3 years, with a minimum daily consumption of 100 mg. Imaging modalities included wide field funduscopic color photography, infra-red autofluorescence (IRA), wide field autofluorescence (AF), optical coherence tomography (OCT). Qualitative and quantitative analysis of images were performed. The quantitative analysis included the calculation of the ratio between AF intensity signal in the fovea and in perifovea in all study eyes (AFI ratio), IRA entropy, the ratio between the thickness of the fovea and the thickness of the perifovea area (FT ratio).
Results: Thirty-three eyes of 17 patients (14 females, 3 males) were included. Qualitative analysis showed significant changes only in 3 patients who were exposed to highest doses of PPS, including subtle retinal pigment epithelium changes, central pattern of hypo-autofluorescence accompanied by scattered hyper-AF areas on AF, and a â€˜flying saucerâ€™ macular OCT configuration. AFI ratio and IRA entropy were exponentially correlated with PPS standardized cumulative dose f= 0.3*exp(-0.02*x), (R2=0.95, P<0.05.) FT ratio was significantly correlated with PPS standardized cumulative dose f= 0.3*exp(-0.02*x), (R2=0.089 ,P<0.002).
Conclusion: This study is the first to demonstrate the exponential dose-response correlation between exposure to PPS and retinal toxicity. The novel image analysis techniques that were developed present an opportunity and a tool to further investigate, better understand and quantify the correlations between chronic exposure to systemic medications and retinal toxicity.

Topical interferon alpha 2a for ocular surface tumors

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Purpose: Topical treatment of high grade conjunctival intraepithelial neoplasia (CIN) or primary acquired melanosis (PAM) with atypia with mitomycin C (MMC) is very effective, but some patients have multiple recurrences, and multiple courses MMC result in limbal stem cell deficiency. Alternatives for MMC for CIN include 5-Fluorouracil and interferon-alpha 2b (IFNa2b). Lack of availability of IFNa2b led us to try IFNa2a. The Purpose of this work is to report the first patients treated with IFNa2a for CIN or PAM and compare the Results relative to treatment with IFNa2b or MMC.
Methods: A retrospective analysis of a cohort of patients treated for recurrent PAM/CIN with atypia with IFNa2a (3 milU/0.5ml) that was administered topically from the needleless syringe twice daily for 3-6 months.
Results: Six patients (3 women) were diagnosed with recurrent PAM (4) or recurrent CIN (2). Clinical remission was reached after 2 months irrespective of their diagnosis, but treatment was continued for 6 months in the first 4 patients and 3 months for the last two. Follow-up ranged from 2-12 months. No local recurrence was noted. Side effects included slight irritation and flu-like symptoms (mainly malaise). The first two patients were switched from IFNa2b to IFNa2a and reported that the only difference was slightly more eye irritation with IFNa2a vs. IFNa2b. Clinical remission of pigmentation was faster with IFNa2a than with IFNa2b.
Conclusions: IFNa2b is known to be effective for CIN, to work slower than MMC, but less damaging to the corneal limbal stem cells. IFNa2a appears effective for both CIN and PAM, with minimal tolerable side effects. These initial **Results** indicate that IFNa2a can safely replace IFNa2b in the treatment of CIN and PAM.

Eye-tracking-based prolonged dichoptic amblyopia treatment reduces interocular suppression

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Treatments based on dichoptic perceptual learning tasks and computer games significantly improve visual acuity (VA) in amblyopia. However, these tasks are intensive and repetitive, which often negatively affects treatment compliance and effectiveness.
A prospective pilot study was conducted on 20 children aged 4-16 (8.08±3.2 years, mean±SD) with anisometropic or mixed amblyopia. Passive dichoptic (anaglyph) training included watching 5 movies/week (7.5-hours) for 3 months, followed by 3 movies/week for additional 3 months (4.5-hours). An eye-tracker detected the non-amblyopic-eyeג€™s gaze position and a software blurred its foveal area. The blurring level and diameter was adjusted according to the amblyopic eyeג€™s VA, aiming to reduce the non-amblyopic VA by 2 lines. Best corrected visual acuity (BCVA) at near and distance, stereoacuity, and reading performance were assessed at 4, 8, 12 and 24 weeks.
BCVA improved by 3.1±0.36 LogMAR-lines for near (ETDRS, 95% CI 0.243 to 0.381, p<0.005) and by 2.00±0.34 LogMAR-lines for distance (95% CI 0.132 to 0.262, p<0.0005) at 24 weeks. Binocular VA improved by 1.1±0.25 and 1.1±0.35 LogMAR-lines for near and distance (p<0.005, paired t-test). Mean stereoacuity improved from 285±66 to 68±53 arcseconds (2 octave steps 95% CI 117 to 319, p<0.0005). Reading speed improved by an average of 56% at 12 weeks. No adverse effects were reported; 2 children reported difficulty adhering to the study protocol, with a mean compliance of 95%.
Treatment resulted in significantly improved amblyopic eye BCVA, binocular VA, stereo acuity, and reading speed. Improvement of binocular VA indicated a reduction in interocular suppression. The proposed treatment is thus suitable for mild and moderate amblyopia, is very engaging and tailored to as any video content for high compliance as a home treatment, suitable for toddlers and young children aged 4 years and above.

Subconjunctival Aflibercept for the Treatment of Corneal Neovascularization

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Purpose: To evaluate the effect of a single subconjunctival aflibercept injection on formed corneal neovascularization.
Methods: A prospective clinical trial, conducted at a single tertiary medical center. Included were consecutive patients with corneal pathologies complicated by corneal neovascularization, who were candidates for anti-Vascular Endothelial Growth Factor (VEGF) treatment at the discretion of a cornea specialist. A single subconjunctival injection of 0.08 ml Aflibercept (Eylea25 ®, mg/ml) was administered near the limbus in proximity to the areas of maximal pathological neovascularization. Follow-up visits were scheduled on days 7, 30, 60 and 90 following injection. Best corrected visual acuity (BCVA), intraocular pressure, slit lamp exam, digital cornea photography, specular microscopy and anterior-segment optical coherence tomography (AS-OCT) were documented at each visit. The images were graded by a masked observer for density, extent, and centricity of corneal vascularization.
Results: Six eyes of 6 patients were analyzed. No clinically significant ocular or systemic adverse events were documented. No change was noted in either extent, density or centricity of corneal blood vessels at seven, 30- and 90- days post injection ($p > 0.1$ for all time point comparisons, Friedman test). BCVA fluctuated insignificantly in 5/6 patients during follow-up time, and objective but not subjective improvement of BCVA was noted in one patient with no concurrent change of neovascularization. The recruitment has therefore halted prematurely.
Conclusions: A single subconjunctival aflibercept injection appears to be well tolerated however ineffective for regressing formed corneal neovascularization.

Endophthalmitis Epidemiology Study in the Jerusalem Area

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Purpose To report on the epidemiological, clinical and ophthalmological features of patients diagnosed with endophthalmitis in a tertiary referral center in Jerusalem
Methods Retrospective review of medical charts of patients presenting with endophthalmitis over a 15 year period
Results Included were 73 eyes of 70 patients. Males were affected in 56% of cases. Mean age at presentation was 60 years. Exogenous endophthalmitis accounted for 78% of cases and endogenous endophthalmitis for 22% of cases. Of the exogenous cases, most followed an intraocular surgery (61%), 18% occurred after intravitreal injections, 14% followed infectious keratitis and 7% were post-traumatic. Endogenous cases were predominantly observed in diabetic patients. Bacterial infections was the predominant entity diagnosed in 40 eyes (55%), fungal in 8 eyes (11%) and in the remaining 25 eyes (34%) culture result was non-yielding. Staphylococcus epidermidis was the most commonly isolated microbe in 19% of eyes and Enterococcus faecalis was the second most common detected in 6% of the eyes. Mean logMAR visual acuity (VA) at presentation was 1.6 and it remained unchanged at last follow-up. At presentation, 78% of eyes had poor VA (logMAR ‰¥1ג) and this significantly decreased to 57% by the last follow-up. Systemic antimicrobial therapy was administered to 67% of patients. Intravitreal antibiotics were administered to 99% of eyes with ceftazidime and vancomycin being the most commonly given. Intravitreal dexamethasone was administered concomitantly to 30% of eyes. Pars plana vitrectomy was perfomred in 75% of eyes. Enucleation/evisceration was performed in 5 eyes (7%). There was no evidence of bacterial resistance in the antibiograms for either vancomycin or ceftazidime.
Conclusions Intraocular surgery remains the most common event preceding endophthalmitis with coagulase-negative staphylococci being the most frequently detected microbes. It is a fulminant infection resulting in poor visual outcome despite prompt treatment. Vancomycin and ceftazidime remain an effective combination showing no changes in susceptibility over the years.

The effect of injection volume of ICG into the EVSC on dye distribution and intraocular pressure

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Purpose: To investigate whether the volume of indocyanine green (ICG) injection into the extravascular spaces of the choroid (EVSC) affects dye distribution, intraocular pressure (IOP) and retinal structure.
Methods: ICG was injected into the EVSC of 22 New Zealand rabbit eyes in vivo at three volumes (0.1, 0.2 and 0.3 ml) in the superior-temporal quadrant, 2mm posterior to the limbus. IOP was measured before and after ICG injection. ICG distribution was assessed by multicolor fundus and Spectral Domain Optical Coherence Tomography imaging, and histology analysis.
Results: ICG was detected across the EVSC, reaching the optic nerve head and visual streak following injection of 0.1 ml ICG. No dye was detected in lens, vitreous and anterior segment. Flat-mount analysis revealed that injection of 0.1, 0.2 and 0.3 ml resulted with a coverage area of 58%, 61% and 65% of the posterior segment, respectively within 1 hour following the injection. A mild and transient IOP elevation (‰₪20ג mmHg) was recorded 5 minutes following ICG injection. No hemorrhages or retinal detachment were detected in the injected eyes.
Conclusions: The EVSC injection system enables spreading of ICG from the periphery to the central retina by injection of small volumes. Large volumes can be injected consistently and safely into the EVSC leading to a nearly equal distribution of the dye throughout the posterior segment within 1 hour following the injection.

Does method of delivery influence recurrence of rhegmatogenous retinal detachment.

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Background: Rhegmatogenous retinal detachment is characterized by the presence of a full thickness retinal break. This break is held open by vitreoretinal traction that allows accumulation of liquefied vitreous into the potential space between the retinal pigment epithelium and the neurosensory retina. Although the ophthalmic community is quite unanimous regarding this topic, and despite current evidence suggesting that normal deliveries are not contraindicated in healthy pregnant females with rhegmatogenous retinal detachment risk factors, a common perception among obstetricians is that spontaneous vaginal delivery increases the risk of re-detachment of the retina in women who had been previously treated for rhegmatogenous retinal detachment.
Objective: The aim of this study was to evaluate whether method of delivery has an effect on the incidence rate of recurrent rhegmatogenous retinal detachment in women who have been previously treated surgically for rhegmatogenous retinal detachment.
Study Design: In this retrospective cohort study, data was collected from computerized files on Rabin Medical Center and Clallit Health Services data bases, to create the study group: Women who were surgically treated due to rhegmatogenous retinal detachment and who had given birth after their ocular surgery. Main outcome compared was the incidence rate of recurrent rhegmatogenous retinal detachment following childbirth for every type of delivery; vaginal, assisted delivery and cesarean section.
Results: Fourteen women had given birth after their ocular surgery, all underwent Scleral Buckling. Ten of the women had a normal vaginal delivery, 3 women underwent a cesarean section and one woman had a vacuum-assisted vaginal delivery. No case of recurrent retinal detachment was documented.
Conclusions: Method of delivery does not have an influence on recurrence of rhegmatogenous retinal detachment, thus vaginal delivery is not contraindicated in women with previously treated rhegmatogenous retinal detachment.

The incidence of consecutive exotropia after bi-medial recession for esotropia using non-absorbable or absorbable sutures: retrospective cohort study

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Purpose: To evaluate the incidence of consecutive exotropia following bi-medial rectus recession surgery for esotropia using non-absorbable in comparison to absorbable sutures in children undergoing their first strabismus surgery.
Methods: A retrospective cohort study of all children diagnosed with esotropia who underwent bilateral medial recession (BMR) by a single surgeon between January 2017 to May 2019. As of November 2017, only non-absorbable sutures were used. The patients' medical records were reviewed and demographic, clinical and operative data were collected. Primary outcome was the incidence of consecutive exotropia regarded as more than 8 prism diopters (PD) at distance and near. Surgical success was considered to be an alignment within 8 PD at distance and near.
Results: A total of 93 children were included in the analysis, mean age was 4.32.92 ±♀ years, 39 (41.9%) were female. In 44 children (47.3%) a 5.0 Ethibond suture (Ethibond group) was used and in 49 children (52.7%) a 6.0 Vicryl suture (Vicryl group) was used. Consecutive exotropia occurred in 10 children (20.4%) in the Vicryl group and in 2 children (4.5%) in the Ethibond group (survival analysis= 0.016). Mean follow-up time was 16.53 and 12.48 months in the Vicryl and Ethibond groups, respectively. Two children in the Ethibond group had pyogenic granuloma that resolved after 3 months. In one patient of the Vicryl group suture break necessitated revision under anesthesia 3 days after the original operation.
Discussion: The use of non-absorbable sutures in BMR resulted in significantly less consecutive exotropia.
Conclusion: Routine use of non-absorbable sutures should be considered in medial rectus recession surgery for esotropia.l

Significance of the Time Interval From Diagnosis to First Intravitreal Bevacizumab Injection in Naive Exudative Age-Related Macular Degeneration

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Purpose: To study whether the time interval from diagnosis of naïve exudative Age-Related Macular Degeneration (AMD) to the first intravitreal injection of Bevacizumab, influences the visual and anatomical outcomes, when administered within a month of diagnosis.

Methods: This retrospective study consisted of 134 eyes of 134 consecutive patients diagnosed with naïve exudative AMD in a single tertiary medical center between the years 2013 and 2018. All patients were treated within the first 30 days of their diagnosis, with 3 monthly intravitreal injections of Bevacizumab. followed by a follow up visit one month after the third injection. Patients were divided into three groups; group 1 (n=83) consisted of patients injected with bevacizumab on the day of diagnosis; group 2 (n=22) received treatment 1 to 7 days post diagnosis; and group 3 (n=29) 8 to 30 days after diagnosis. The main outcome parameters in the study were best corrected visual acuity (BCVA) and change in the measured central macular thickness (CMT) using spectral domain optical coherence tomography (OCT) post 3 injections.

Results: Post 3 intravitreal Bevacizumab injections, an improvement in mean CMT was observed in all groups. The mean change in CMT from the first visit to the first follow up visit did not differ with statistical significance between any of the groups, with 133mm, 141mm and 142mm improvement for groups 1,2 and 3, respectively (P=0.960). Mean BCVA improved in all groups after treatment as well, with no statistically significant difference noted between any of the groups either (0.17, 0.079 and 0.113 logmar for groups 1,2 and 3, respectively) (P=0.447).

Conclusions: No correlation was found between the timing of the first Bevacizumab injection, when given within the first month after diagnosis, and the anatomical and clinical Results at the first follow-up visit. Our Results suggest that even if treatment with Bevacizumab is not initiated promptly after diagnosis of naïve exudative AMD, but administered within a month of the primary diagnosis, the visual and anatomical prognosis of the patients may not worsen as a result.

Rapid onset post-operative pre-retinal fibrosis is Macular Proliferative Vitreoretinopathy (PVR) rather than Epiretinal Membrane (ERM) - A case series

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Introduction:Post vitrectomy premacular membranes can cause significant anatomical changes to the macula, leading to functional deficits including decreased visual acuity and metamorphopsia. The traction effect created by these membranes lead to retinal thickening, wrinkling, schesis, detachment and even macular hole. For a very long time, post-operative premacular membranes were considered to be macular pucker, known also as ERM. Recent reports showed that these membranes are a localized presentation of proliferative vitreoretinopathy (PVR). The Purpose of this study was to describe clinical and histological features of macular PVR formed within weeks following pars plana vitrectomy (PPV) surgery.

Methods: In this retrospective observational case series we report 4 cases with severe macular PVR that developed following uneventful PPV and were followed up to 32 months in Hadassah-Hebrew University Medical Center, Jerusalem, between October 2016 and June 2019.

Results: The mean age at presentation was 53 years old. 3 males and 1 female . None of the patients had any previous ocular pathology. All patients underwent PPV for retinal detachment repair. One of them presented with macula-off while the others were macula-on. The mean Best Corrected Visual Acuity (BCVA) at presentation was 0.675 LogMAR. The mean duration of the detachment till the time of the primary surgery was 2.5 days. The mean interval time from last normal post vitrectomy exam to first symptom or diagnosis of PVR was 21 days (range 14-28), but can develop in as fast as 2 weeks. BCVA dropped from a mean of 0.275 LogMAR before the PVR development to a mean of 0.95 LogMAR following its development.

Ocular examination for all the patients showed flat retina and a thick macular PVR membrane, confirmed by optical coherence tomography (OCT) images with a mean central macular thickness (CMT) of 716 microns .

All patients underwent PPV and stripping of membranes. The mean BCVA improved to 0.50 LogMAR and the OCT showed a reduction of mean CMT to 356 microns.

Histological study of the membrane in one patient confirmed the diagnosis of PVR with a proliferation of retinal pigment epithelium cells.

Conclusions: Short-term macular PVR seems to be a different entity from ERM in terms of rapid development, structural distortion, visual compromise and patho-histology. Surgical treatment restores significantly macular function and anatomy.

DYOP Dynamic Visual Acuity Compared with Static LogMAR Visual Acuity

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Introduction: Everyday visual experience involves mobile objects. Surprisingly, standard visual acuity (VA) charts contain stationary optotypes. The DYOP dynamic VA chart (Chart 2020®) measures motion discrimination of a spinning optotype. This study examined the agreement and inter- and intra-test repeatability for VA between the DYOP and the LogMAR tests and compared the test time and subjective experience of the subjects with both tests.

Methods: The monocular VA of the right eye of 103 subjects (82 female, mean age: 29.15±9.77, range: 20-60) was measured three consecutive times with the LogMAR and DYOP charts, in random order. Test duration was recorded, and subjects filled a subjective comparative questionnaire. Inter-test repeatability was assessed by repeating the measurements after 1-2 weeks and analyzing with correlation, paired t-tests and Bland and Altman (B&A) analysis.

Results: Mean LogMAR and DYOP VA (-0.040.02±0.10- ,±0.14, respectively) was highly correlated (R=0.79, p<0.05), but significantly different (p=0.03). B&A analysis showed a small mean difference between tests (0.02±0.08, log units; ~1 optotype), with 0.34 log units limits of agreement (~16 optotypes). The standard deviation of the measurements and intraclass correlation coefficient of the LogMAR (0.03; 0.97 [0.96-0.98]) and DYOP (0.02; 0.98 [0.98-0.99]) were not significantly different. The inter-session repeatability was statistically (p<0.0001) but not clinically (0.03±0.04, log units) significant only for the DYOP. Duration of the LogMAR exam was 13 sec shorter, which was significant statistically (p<0.0001), but not clinically. There were no significant subjective differences between the tests in its understanding, fatigue or frustration, although 23 subjects preferred the LogMAR.

Conclusions: LogMAR and DYOP charts are interchangeable for VA based on the mean difference, with acceptable inter- and intra- test repeatability and lack of clinically significant differences in test time.

Optical Quality And Tear film Change After Reading Electronic Article

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Purpose:♀ To evaluate the influence of smartphone screen reading on optical quality metrics and tear film stability.
Methods: Prospective study was conducted in 40 healthy volunteers that were asked to read an article on a smartphone screen for 20 minutes and the following parameters were evaluated before and after the reading task: Optical quality metrics such as ocular scatter index (OSI), strehl ratio (SR), modulation transfer function (MTF) and visual break up time (VBUT) were measured using a double-pass aberrometer system, non-invasive break-up time (NIBUT) using the Placido rings from corneal topography and fluorescein break up time (FBUT) measured at the slit lamp. Pre and post-task comparisons were made using paired sample T-test.
Results:♀ After the reading, FBUT and NIBUT were both significantly reduced ($p< 0.001$). Visual BUT was also significantly reduced as compared to pre-reading state ($p= 0.018$). OSI increased from 0.53 +/- 0.25 to 0.61 +/- 0.31 after reading but this tendency was not significant ($p=0.06$). The other optical quality metrics, MTF, SR and best focus position did not show any significant difference after the reading.
Conclusions: A short reading session of 20 minutes on smartphone screen in healthy subjects was found enough to affect the tear film stability. Optical quality metrics remains however unaffected.

Low dose atropine as an isolated or as a combination therapy effectively reduces myopia progression

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Purpose: To assess the effects of several types of intervention therapies on the progression of myopia in children.
Methods: This study included 150 eyes of 75 myopic children aged 512“€λ years that underwent intervention for myopia control and were followed over a 4-year period. Additional inclusion criteria was documented myopic progression of at least 0.75D in the 12 months prior to study and astigmatism of less than 2.00D.
The patients were divided into five groups matched for age, gender and spherical equivalent refraction (SER). Fifteen patients applied low-dose atropine (A0.01%), 17 patients were prescribed multifocal ophthalmic lens with a +1.50 ADD in addition to 0.01% atropine treatments (A0.01%+MOL), 12 patients were prescribed soft contact lens with concentric ring up to a +3.5 ADD in addition to A0.01% (A0.01%+SCLCR) atropine and 12 patients were prescribed bifocal glasses with a +2.00 ADD. The control group consist of patients who were prescribed single vision glasses for best corrected distance acuity (n=19). The outcome was SER of both eyes measured by subjective refraction at the end of treatments.
Results: Change in SER at the end of the treatment period was -0.80D ±ָ 0.77 in the A0.01% group, -0.58D0.42 ±ָ in A0.01%+MOL group, -0.47D ±ָ 0.31 in A0.01%+SCLCR group, -1.84D0.76 ±ָ in the bifocal glasses and -2.56D1.07 ±ָ in the single vision control group. There was a rebound effect in all the atropine treatment patients (which was measured one year after the cessation of treatment) -0.19D0.22 ±ָ in A0.01% group, -0.1D0.16 ±ָ in the A0.01%+MOL group and -0.05D0.09 ±ָ in A0.01%+SCLCR group.
Conclusion: The atropine treatment combined with soft contact lenses showed the least rebound effect of all the atropine therapies. There was a significantly reduced myopia progression in all atropine groups in comparison to the other **Methods** over 3 years of treatment and one year after cessation of treatments.

Treatment Results of a novel surgical technique for treating eyelid tumors

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Purpose: Surgical excision is the standard primary treatment option for eyelid tumors. However, in cases with incompletely excised primary tumors, recurrent tumors, or inoperable large primary tumors and elderly patients who cannot tolerate general anesthesia with significant co-morbidities, external beam radiation therapy (EBRT) is considered as an effective alternative/adjuvant treatment modality. However, acute and chronic radiation side-effects (skin reactions, eyelid telangiectasia, eyelid atrophy, eyelash loss (madarosis), epiphora (tearing), ocular surface disorders (dry eyes), cataract, radiation papillopathy, retinopathy & maculopathy and second malignant neoplasms) can lead to significant functional and visual disabilities. We present a novel brachytherapy plaque placement technique for eyelid tumors and the first clinical application.
Methods: A retrospective review and analysis of a cohort of 4 cases with conjunctival melanoma, conjunctival lymphoma, and BCC in the lower eyelid that were treated with sandwich Ru-106 plaque brachytherapy in the Ocular Oncology Service of the Hadassah-Hebrew University Medical Center from 2011 to 2019.
Results: We analyzed data of 4 patients. The median age was 60 years (range, 58-81). The treatment was very well tolerated. Acute reactions consisted of eyelid atrophy and eyelash loss (madarosis). The tumors decreased in size following treatment. The patients tolerated the treatment well. There were no associated adverse events.
Conclusions: Our Results suggest that novel sandwich (Ru-106) plaque brachytherapy is safe, effective and offers very good local control and can be considered for the treatment of eyelid tumors. This therapy provides effective dose distribution, improved surgical maneuverability, and increased tolerability for the patients.

The neural basis of working memory load and emotional expression recognition

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Introduction: Assignments involving working memory and emotion affect subjects' performance in psychophysical experiments and for electrical activity measured in EEG (Kosonogov & Titova, 2018). N170 is a component of electrical voltage measured by ERP in response to a face-viewing stimulus, which peaks negatively and appears 170ms after the onset of stimulation. P300 is a component of electrical voltage that appears in response to decision making and its positive peak and appears ms300 after the onset of stimulation (Leleu et al., 2018). This study examined whether behavioral and memory cerebral differences exist in components of N170 and P300 components at different levels of working memory when viewing faces with different expressions fear, joy, and natural.
Methods: Healthy subjects (ages 20-40) with normal vision (at least 6/9, Snellen chart) participated in the study. The check was made with both eyes The electrical activity was measured by an EEG (EMOTIVE) device when images included 2 (low load) or 6 (high load) faces with 3 types of facial expressions: neutral, fear and joy, all were displayed (30 times for 11 seconds in random order) on a computer screen (screen resolution-1366*768 pixels). Amplitude of N170 and P300 components and the percentages of accuracy in the identification tasks were compares using ANOVA.
Results: Eleven healthy women aged 20-25 (22.45±0.9 years) participated in the study. The N170 amplitude of the O1 electrode was found to be significantly negative at high versus low memory load ($p<0.05$). P300 amplitude at the O2 electrode was found to be more positive at low versus high memory load ($p<0.03$). Low-load accuracy percentages were higher than high-load accuracy ($p<0.0001$). In addition, the facial expressions of joy had the highest percentages of accuracy ($p<0.02$). Amplitude and response times were not different for the three types of facial expressions ($p>0.2$) nor were memory load interaction for the different emotions ($p>0.30$).
Conclusions: Working memory load affects percentages of accuracy and neuronal activity (N170 and P300) related to face processing and divided into categories: neutral, fear and joy. Emotion type affects the percentages of accuracy but does not affect the neural activity (N170 and P300). There is no connection between emotion type and work memory load In neural activity (N170 and P300), In accuracy percentages.

The Importance of vision acuity test, for subjects Older than 40 years for renewal driving license

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Purpose: Retain or renew driving license in Israel requires eye examination with the Titmus Vision Tester (Knesset, 2008), which includes a minimum monocular distance visual acuity of 6/12, binocular fusion which is based on the worth 4 dot test (W4D) and a visual field of 120°̣ (Knesset, 2008). Recently, the law was changed so that only drivers older than 70 years (instead of 40) required to performed the Titmus test. The aim of this study was to examine the incidence of failing in the Titmus (visual acuity, VA less than 6/12 and/or failure in binocular fusion tests only), in subjects over 40 who visit at the Hadassah Academic College (HAC) clinics.
Methods: This retrospective study examines data from driving license eligibility patients (men and women, 16-93 years old) attending the HAC Optometry clinics, from 06/10/2015 to 21/06/2018. The anonymously data includes distance VA and W4D tests. Subjects were divided into 4 different sub-groups age: above 16 years old, above 40,60 and above and 70 years old and above. The prevalence of failure in VA and in W4D test was calculated in each group, and mean and standard deviation was compared between all groups (descriptive study).
Results: Data included 4312 subjects (2494 women): 2032 (47.1%), 937 (21.7%) and 394 (9.1) of the participants were above 40, 60 and 70 respectively.
In VA test, 28.26% of subjects failed in both eyes (29.52%, 39.06% for aged 40 and above 60 respectively) and 11.15% subjects failed in one eye (10.08%,17.25% for aged 40 and above 70 respectively). For binocular fusion test (W4D) 8.44 % had diplopia and failed (5.26%, 10.00%, 0.00% for aged 40, 60 and above 70 respectively) and 32.46% had suppression (29.82%, 23.33%, 23.07% for aged 40, 60 and above 70 respectively)
Conclusions: There is a high incidence of subjects who failed the Titmus Test. These subjects may be drivers who are not aware for their vision lack.

Gadolinium retention in mouse organs following intraperitoneal administration

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Purpose Approximately 0.03% of the patients undergoing neuroimaging with intravenous injection of gadolinium (Gd)-based contrast agent may show Gd deposition disease (GDD). The aim of this study is to detect retention of Gd in tissues following systemic injection, using a combination of Particle Induced X-ray Emission analysis, X-ray fluorescence, and immunohistochemistry.
Methods Five C57Bl6 mice were injected intraperitoneally with 2.5ml of Gd. Two additional C57Bl6 mice were injected intraperitoneally with 2.5ml of saline and served as control.
Three days after injection mice were euthanized and eyes, brain, kidney and spleen tissue were harvested. The samples were analyzed in Particle Induced X-ray Emission analysis, X-ray fluorescence, and immunohistochemistry for metals. The tissues will be stained with metallothionein using monoclonal anti-metallothionein antibody.
Results Brain and eyes were fixated for analysis by Particle Induced X-ray Emission and X-ray fluorescence. Different areas of the brain were screened. Quantification of Gd is being calculated. Immunohistochemistry is under investigation.
Conclusions We present a method for determining and quantifying Gd in tissues using three modalities. The monitoring of Gadolinium in biological samples is important in order to better understand its pharmacokinetics, pharmacodynamics, and metabolism due to its potential cumulative toxic effects.