

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Immunologic Rejection Episodes After Stopping Topical Corticosteroids in DMEK

June 2016

Price et al. evaluated the risk of immunologic rejection episodes when topical corticosteroids are discontinued 1 year after Descemet's membrane endothelial keratoplasty (DMEK) compared with ongoing once-daily use of topical steroids. They found that patients who discontinued steroids had a higher risk of rejection episodes.

In this prospective longitudinal parallel-group study, 400 eyes from 259 DMEK recipients (aged 23-90) were enrolled 1 year after their transplant. To maximize adherence, the researchers allowed the participants to choose whether to stop or to continue the once-daily topical corticosteroid they were already taking. Steroids were discontinued in 277 eyes (no-steroid group) and continued in 123 eyes (steroid group). In the latter group, 100 eyes continued with fluorometholone 0.1%, 21 with prednisolone 1.0%, and 2 with loteprednol etabonate 0.5%.

Study demographics were well balanced between the steroid and no-steroid groups: 99% of the subjects were white, and 95% of the grafts were performed to treat Fuchs dystrophy. Participants were examined at 1, 3, 6,

and 12 months during the second year after their DMEK procedure. Results were evaluated with Kaplan-Meier survival analysis, and the main outcome measure was the incidence of immunologic rejection episodes.

The cumulative incidence of rejection episodes was significantly greater in the no-steroid group (6% vs. 0% in the steroid group; $p = .013$). Thirteen of 14 rejection episodes (all of which were in the no-steroid group) resolved when topical corticosteroids were resumed.

The authors stated that 1 of 277 grafts (0.4%) failed in the no-steroid group, and none failed in the steroid group during the study. Endothe-

lial cell loss between 1 and 2 years was not significantly different between the no-steroid and steroid groups ($6.4\% \pm 12\%$ vs. $5.6\% \pm 14\%$ percent, respectively; $p = .67$).

The authors concluded that continuing once-daily use of even a weak topical corticosteroid was protective against rejection episodes during the second year after DMEK. Based on these findings, they prefer to maintain their DMEK patients on a low-strength steroid. They noted, however, that some patients experience steroid-related intraocular pressure elevation and may

require antiglaucoma drugs; physicians must balance the risks of different strategies for individual patients.

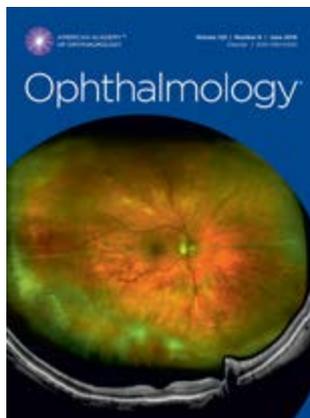
Genetic and Dietary Factors in Progression of Nuclear Cataracts

June 2016

Yonova-Doing et al. examined the heritability of nuclear cataract and prospectively explored the effect of dietary micronutrients on progression of these cataracts. They found that genetics explained 35% of the variation in progression over 10 years, while environmental factors, including diet, accounted for the balance.

The investigators relied on the TwinsUK prospective cohort study. Cross-sectional nuclear cataract and dietary data were available for 2,054 white female twins from the study, and follow-up cataract measurements were available for 324 of the twins (151 monozygotic and 173 dizygotic). The study's main outcome measure was nuclear cataract progression, which was assessed through digital Scheimpflug imaging. The mean interval between baseline and follow-up examination was 9.4 years.

Dietary data were obtained from food-frequency questionnaires, and heritability was modeled through a method that estimates additive genetic effects, shared/family environmental effects, and individual environmental effects in twins. Association between nuclear cataract change and micronutrients was investigated via linear and multinomial regression analysis.



The best-fitting model estimated that the heritability of nuclear cataract progression was 35% and that environmental factors explained the remaining 65% of variance. The study evaluated the effect of a large number of micronutrients. Among micronutrients consumed in the diet, only vitamin C and manganese had significant effect. Vitamin C was protective against both nuclear cataract presence at baseline and nuclear cataract progression, while manganese reduced the rate of nuclear cataract at baseline. Combined micronutrient supplements were protective against nuclear cataract at baseline only.

Geographic Variation in Anti-VEGF Injection Rates and Medicare Payments

June 2016

Erie et al. used Medicare claims data to evaluate geographic variation among intravitreal injection rates and anti-VEGF drug payments per injection across the United States. They found that rates of injection varied 7-fold, and payments 6.2-fold, between the highest and lowest states.

This observational cohort study was based on Medicare Provider Utilization and Payment Data from CMS covering all 50 states and Washington, D.C. The data identified 539,660 unique Part B fee-for-service (FFS) beneficiaries for whom approximately 2,199,199 anti-VEGF drug claims were submitted to Medicare in 2013. The number of FFS Medicare beneficiaries who received intravitreal injections and the mean Medicare-allowed drug payment per anti-VEGF injection (aflibercept, bevacizumab, or ranibizumab) were calculated nationally and for each state. Geographic variations were evaluated by using the extremal quotient, coefficient of variation, and systematic component of variance (SCV).

In 2013, the number of FFS Medicare beneficiaries who received intravitreal injections ranged from 4 per 1,000 beneficiaries in Wyoming to 28 per 1,000 in Utah; the national average was 19 per 1,000. In 2013, the mean SCV was 8.5, confirming high nonrandom geographic variation. The mean

national Medicare drug payment per anti-VEGF ranged from \$242 in South Carolina to \$1,509 in Maine; the average was \$1,078 per injection. Nationally, 94% of injections were office based, and 6% were facility based.

American Journal of Ophthalmology

Driving Performance of Patients With Bilateral Glaucoma

June 2016

To assess the effect of glaucoma on driving performance, Bhorade et al. conducted a case-control study comparing patients with glaucoma against normal controls. They found that glaucoma patients had a significantly higher rate of unsafe on-road driving and required more interventions from the accompanying driving instructor.

This study included 21 patients with bilateral moderate or advanced glaucoma and 38 controls with no ocular disease; all participants were between ages 55 and 90. Participants underwent a variety of baseline assessments, including visual acuity (VA) and visual field (VF), tests of psychological and cognitive status, hand grip strength, neck range of motion, and ability to read and understand road signs. Each participant then took a driving test on a defined 13-mile course on city streets, accompanied by a driving instructor in the front passenger seat and a driving evaluator in the backseat. The evaluator did not know the driver's visual status, although—for safety reasons—the instructor did. The same instructor and evaluator accompanied all participants, and the same car (with dual brake controls) was used in all tests. Overall driving performance of pass versus marginal/fail and the number of wheel or brake interventions were recorded.

The researchers found that the glaucoma group had a significantly higher percentage of marginal/fail performance than the controls (52% vs. 21%, respectively; odds ratio [OR] 4.1) as well as a higher risk of wheel interventions (OR, 4.67). Paradoxically, among the glaucoma patients, there were no significant differences in VA,

VF, contrast sensitivity, or glare testing between those who passed and those who scored marginal/fail. However, the glaucoma patients in the marginal/fail group had worse scores on several psychometric and physical measures such as Trail Making Tests A and B, sign reading, grip strength, rapid walking, and brake response time.

The authors commented that the 48% of glaucoma patients who passed the driving test were most likely using strategies such as saccadic eye movements and head movements to compensate for their visual impairment. The researchers concluded that approximately half of patients with moderate or advanced glaucoma are at risk for unsafe driving—particularly those with worse performance on psychometric and mobility tests—while the other half may be safe drivers.

Photodynamic Therapy to Inhibit MRSA Keratitis Isolates

June 2016

In this in vitro study, Halil et al. examined the effect of photodynamic therapy (PDT) using 2 different photosensitizers—riboflavin or rose bengal—on multidrug-resistant isolates of methicillin-resistant *Staphylococcus aureus* (MRSA). Although both PDT regimens inhibited MRSA, the researchers found that rose bengal was more effective.

Bacterial inocula were obtained from the corneas of 2 patients with chronic exposure keratitis that did not respond adequately to treatment with multiple antibiotics. The inocula were cultured on agar plates and exposed for 30 minutes to different regimens of PDT: UV-A light with 0.1% riboflavin photosensitizer (as used in corneal cross-linking) or green light with 0.03% or 0.1% rose bengal photosensitizer. All 3 preparations were also tested in darkness and ambient light conditions; in addition, irradiation with UV-A or green light alone (no photosensitizer) was evaluated. The agar plates were photographed 72 hours after exposure, and custom software was used to measure bacterial inhibition.

Complete growth inhibition of both MRSA strains was demonstrated (1) for

both rose bengal concentrations under ambient and green LED irradiation, and (2) for the 0.1% rose bengal in the dark. The 0.03% rose bengal in dark conditions showed complete inhibition of strain 2 but incomplete inhibition of strain 1. Riboflavin showed almost complete inhibition with UV-A irradiation, but it had minimal effect in dark and ambient light conditions. In irradiation-only exposure, UV-A achieved 79% inhibition for MRSA-1 and 81% inhibition for MRSA-2. For green light, the inhibition percentages were 50% and 28%, respectively.

The researchers concluded that, compared with topical antibiotics, PDT could prove advantageous in treating bacterial keratitis; moreover, rose bengal—approved for use on the ocular surface as a staining agent—was effective across a wide range of light conditions.

JAMA Ophthalmology

Ocular Findings in Infants With Presumed Zika Virus Infection

May 2016

The Zika virus has quickly reached epidemic proportions, especially in northeastern Brazil, and it has rapidly spread to other parts of the Americas. A recent increase in the prevalence of microcephaly in newborn infants and vision-threatening findings in these infants is likely associated with the rapid spread of the virus. As such, **de Paula Freitas et al.** evaluated the ocular findings in infants with microcephaly associated with presumed intrauterine Zika virus infection in the state of Bahia, Brazil.

This case series was conducted at the Roberto Santos General Hospital, a tertiary hospital in Salvador, Brazil. Twenty-nine infants (58 eyes) with microcephaly (defined by a cephalic circumference of ≤ 32 cm) and a presumed diagnosis of congenital Zika virus were recruited through an active search and referrals from other hospitals and health institutions.

The study was conducted between Dec. 1 and Dec. 21, 2015. All of the infants and their mothers underwent

systemic and ophthalmic examinations. Anterior segment and retinal, choroidal, and optic nerve abnormalities were documented using a wide-field digital imaging system. The differential diagnosis included cytomegalovirus, herpes simplex virus, human immunodeficiency virus, rubella, syphilis, and toxoplasmosis, which were ruled out through serologic and clinical examinations.

Results showed that 23 of the 29 mothers (79.3%) reported suspected Zika virus infection signs and symptoms during pregnancy—18 in the first trimester, 4 in the second trimester, and 1 in the third trimester. Ocular abnormalities were present in 17 eyes (29.3%) of 10 children (34.5%). Bilateral findings were observed in 7 of 10 infants presenting with ocular lesions, the most common of which were focal pigment mottling of the retina and chorioretinal atrophy in 11 of the 17 eyes with abnormalities (64.7%), followed by optic nerve abnormalities in 8 eyes (47.1%), bilateral iris coloboma in 1 patient (2 eyes [11.8%]), and lens subluxation in 1 eye (5.9%).

The authors concluded that congenital infection due to presumed Zika virus exposure is associated with vision-threatening findings, which include bilateral macular and perimacular lesions as well as optic nerve abnormalities in most cases.

Outdoor Ozone Air Pollution and Dry Eye Disease in South Korea

May 2016

The ocular surface is continuously exposed to pollutants in outdoor air, and ocular surface abnormalities related to air pollution are thought to be a subtype of dry eye disease (DED). In the first large-scale study to evaluate the association between various outdoor air pollutants and DED, **Hwang et al.** found that higher ozone levels and lower humidity levels were associated with DED in a Korean population.

For this population-based cross-sectional study, the researchers used data from the fifth Korea National Health and Nutrition Examination Survey, which was conducted from Jan. 1, 2010, to Dec. 31, 2012. Outdoor

air pollution measurements—mean annual humidity, particulate matter with aerodynamic diameter less than 10 μm (PM_{10}), ozone, and nitrogen dioxide levels—were collected from 283 national monitoring stations in South Korea.

Among 16,824 participants (7,104 men and 9,720 women), higher ozone levels and lower humidity levels were associated with symptoms and diagnosis of DED. In one analytic model, the researchers found that an increase in ozone levels of 0.003 parts per million (ppm) was significantly associated with symptoms and diagnosis of DED, while a 5% increase in humidity levels was associated with decreased symptoms and diagnosis of DED. In a second analytic model, an increase in nitrogen dioxide of 0.003 ppm was also associated with a diagnosis of DED. Levels of sulfur dioxide and PM_{10} were not associated with symptoms or diagnoses of DED in either model.

The authors noted that their findings on ozone, humidity, and DED demonstrate associations, not definitive cause and effect.

OTHER JOURNALS

Clinical Disc Margin and Bruch's Membrane Opening in Normal and Glaucoma Subjects

Investigative Ophthalmology and Visual Science

2016;57(3):1468-1475

Amini et al. tested the hypothesis that a mismatch between the clinical disc margin (CDM) and Bruch's membrane opening (BMO) is a function of BMO area (BMOA) and is affected by the presence of glaucoma.

The investigators studied 45 normal eyes (45 subjects) and 53 glaucomatous eyes (53 subjects) that underwent radial optic nerve head imaging with spectral-domain optical coherence tomography. The inner tip of Bruch's membrane and the CDM were marked on radial scans and optic disc photographs, which were then coregistered by means of custom software.

The study's main outcome measure was the difference between the clinical disc area (CDA) and BMOA (i.e., a

CDA-BMOA mismatch) as a function of BMOA and glaucoma diagnosis. Multivariate regression analyses were used to explore and document the influence of glaucoma and BMOA on the mismatch.

The researchers found that global CDA was larger than BMOA in both the normal and glaucoma study groups; however, the difference was statistically significant only in the normal group (1.98 ± 0.37 vs. 1.85 ± 0.45 mm², $p = .02$ in the normal group; 1.96 ± 0.38 vs. 1.89 ± 0.56 mm², $p = .08$ in the glaucoma group). The sectoral CDA-BMOA mismatch was smaller in the superotemporal ($p = .04$) and superonasal ($p = .05$) sectors in the glaucoma group. The normalized CDA-BMOA difference decreased with increasing BMOA in both groups ($p < .001$), and the presence or severity of glaucoma did not affect the CDA-BMOA difference ($p > .14$).

The investigators concluded that the CDA was larger than BMOA in normal and glaucomatous eyes and that this finding was more pronounced in normal eyes than in eyes with glaucoma. The CDA-BMOA mismatch diminished with increasing BMOA, but it was not affected by the presence of glaucoma.

Modified Canaloplasty: A New Option for Patients With a Disrupted Schlemm Canal Wall

Journal of Glaucoma

Published online March 29, 2016

Xin et al. describe a modified canaloplasty technique and report its short-term efficacy in primary open-angle glaucoma (POAG) among patients who had a disruption of the Schlemm canal (SC) wall as a result of prior glaucoma surgery. They found that the technique was safe and effective in this setting.

In this single-surgeon, prospective cohort study, POAG patients who were scheduled for canaloplasty were divided into 2 groups. Group 1 included POAG patients who had not undergone glaucoma surgery; group 2 comprised patients who had failed glaucoma filtering surgery and had a disrupted SC wall.

The status of the SC wall was determined by gonioscopy and ultrasound biomicroscopy. Standard canaloplasty

procedures were performed in group 1; group 2 received a modified canaloplasty technique. Primary outcome measures included intraocular pressure (IOP) and use of glaucoma medication at various follow-up points.

The modified technique was performed with a relay suture guided by an illuminated trocar. Unlike a standard 360-degree canaloplasty, the modified surgery avoided the site of the earlier trabeculectomy; the suture entered and exited on either side of the scleral flap, leaving a tissue bridge.

Seventeen patients were enrolled in group 1, and 9 in group 2. At the 12-month follow-up, no significant differences were noted between groups 1 and 2 in IOP (17.8 ± 2.7 mm Hg vs. 16.7 ± 2.4 mm Hg, respectively) or in the mean number of medications (0.9 ± 1.2 versus 0.3 ± 0.5).

In both groups and at all follow-up points, IOP and mean glaucoma medication usage had decreased significantly compared with baseline measurements ($p < .001$). The rate of successful circumferential catheterization was not significantly different between the 2 groups (88.2% vs. 77.8%, $p = .063$).

The researchers concluded that modified canaloplasty is a feasible, safe, and potentially effective option for patients with POAG who have regions of SC disruption as a result of previous glaucoma filtering surgery.

Retinal Thickness and Risk of Worsening Disability in MS

The Lancet Neurology

2016;15(6):574-578

Most patients with multiple sclerosis (MS) but no previous optic neuritis (ON) have thinner retinal layers than healthy controls. Martinez-Lapiscina et al. conducted a multicenter cohort study of eyes without ON or a history of ON in MS patients to assess the feasibility of using the peripapillary retinal nerve fiber layer (pRNFL) thickness and macular volume as a biomarker for worsening disability in MS.

Investigators in the multicenter cohort study collected data from 879 patients age 16 or older; 74 of them had clinically isolated syndrome, 664 had

relapsing-remitting MS, and 141 had progressive MS.

The investigators assessed worsening disability with the Expanded Disability Status Scale (EDSS). In addition, pRNFL thickness and macular volume were measured once at baseline by optical coherence tomography (OCT). In patients without ON, the baseline OCT values were calculated as the mean value of both eyes without ON; and in those with unilateral ON, the baseline OCT values of the normal eye were recorded.

The investigators who performed OCT at baseline were masked to the EDSS results, and those who assessed disability with EDSS were masked to the OCT results. The risk of worsening disability was identified through proportional hazard models that included OCT metrics and age, disease duration, disability, presence of previous unilateral ON, and use of disease-modifying therapies as covariates.

The authors found that worsening of disability occurred in 252 (29%) of the 879 patients with MS after a median follow-up of 2 years (range, 0.5-5 years). Patients with a baseline pRNFL ≤ 87 μ m or ≤ 88 μ m (as measured by Spectralis or Cirrus OCT devices, respectively) had double the risk of worsening disability at any time after the first and up to the third years of follow-up (hazard ratio [HR], 2.06). The risk increased nearly 4-fold after the third and up to the fifth year of follow-up (HR, 3.81). The authors did not identify any meaningful associations for macular volume. They concluded that baseline pRNFL is a useful predictor of disability in patients with MS and could help in guiding treatment decisions.

Ophthalmology summaries are written by Marianne Doran and edited by Susan M. MacDonald, MD. *American Journal of Ophthalmology* summaries are written by Peggy Denny and edited by Richard K. Parrish II, MD. *JAMA Ophthalmology* summaries are based on authors' abstracts, as edited by senior editor(s). *Other Journals* summaries are written by Marianne Doran and edited by Deepak P. Edward, MD.



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