Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

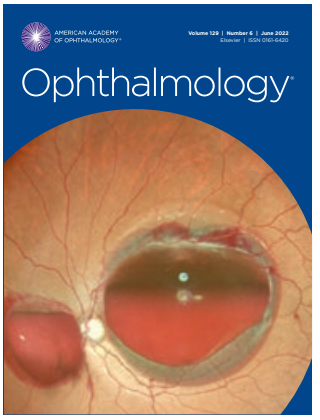
Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

Effects of Alcohol on IOP and Glaucoma

June 2022

The acute effects of alcohol on human eyes include a transient, seemingly dose-dependent reduction of IOP and an increase in blood flow to the optic nerve head, which theoretically may protect against glaucoma. However, heavy use of alcohol is linked to neurodegenerative and cardiovascular disorders as well as systemic biochemical and physiologic changes, which could play a role in glaucoma development. Moreover, epidemiologic studies have found that alcohol use raises the risk of ocular hypertension. To better understand the relationship, **Stuart et al.** conducted a systematic review and meta-analysis of alcohol's effect on glaucoma. Their findings suggest a link between open-angle glaucoma (OAG) and any degree of alcohol consumption.



The authors searched PubMed, Embase, and Scopus for relevant case-control, cross-sectional, and cohort studies that included a quantitative effect estimate and 95% confidence interval (CI) for the relationship between alcohol use and either IOP or OAG. They qualitatively summarized the evidence for any associations detected, and they pooled the effect estimates for alcohol/OAG associations using random effects meta-analysis. Evidence certainty was assessed with GRADE framework.

All told, 34 studies qualified for the systematic review. Of these, 10 demonstrated an association between habitual alcohol use and high IOP as well as ocular hypertension (IOP >21 mm Hg), but the absolute effect sizes were small. Eleven studies (representing 173,058 participants) of the relationship between alcohol and OAG met the inclusion criteria for meta-analysis. The pooled effect estimate (1.18; 95% CI, 1.02-1.36) showed a link between any use of alcohol and OAG ($p = 0.03$). The overall GRADE certainty of evidence was very low.

Although the results suggest that alcohol use is linked to OAG, the authors recommend interpreting their findings with caution, given the heterogeneity of the evidence base, the small absolute effect size, and the minimal statistical significance.

Favorable Findings for the Artificial Iris

June 2022

In an FDA-sanctioned multicenter prospective study, **Ayres et al.** looked at the safety and efficacy of the CustomFlex Artificial Iris for managing partial or full defects of the iris in adults. The device met all key endpoints for efficacy and surpassed its main safety endpoints.

Included in the study were adults with a congenital or acquired iris defect (partial or complete) that caused photophobia and/or glare sensitivity. All patients underwent implantation of the foldable artificial iris during a four-year period (ending Dec. 1, 2017). The devices were implanted with forceps or an IOL injector. The fixation method was determined preoperatively by anatomic features of the anterior segment. The chosen technique could be passive fixation within the capsular bag; passive fixation within the ciliary sulcus; or active fixation to residual iris tissue, the sclera, or an IOL that was then sutured to the sclera. Partial iris-segment implantation was not used in this study. In no case was the device placed in the anterior chamber angle or in a phakic eye.

After implantation, patients were evaluated on day 1, week 1, and months 1, 3, 6, and 12. At each assessment, slit-lamp findings, IOP, implant position, visual symptoms (subjective), and complications were documented. Additional safety measures were corrected distance visual acuity (CDVA) and endothelial cell density (ECD) at months 3, 6, or 12. Patients completed the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) to assess their quality of life and rated their cosmetic results using the Global Aesthetic Improvement Scale. Main

outcomes were photosensitivity and glare results, visual symptoms, NEI VFQ-25 scores, global improvement ratings, and adverse events associated with the prosthesis, the IOL, and the surgery itself.

By 12 months post-op, marked to severe daytime and nighttime light sensitivity were reduced by 59.7% and 41.5%, respectively (both $p < .0001$). Severe daytime and nighttime glare were reduced by 53.1% and 48.5%, respectively (both $p < .0001$). The mean NEI VFQ-25 total score improved 15.4 points, and 93.8% of patients reported improvement in cosmesis. No patient lost more than 2 lines of CDVA, and the median ECD loss was 5.3% at six months and 7.2% at 12 months.

Despite these outcomes, the authors noted that residual iris retraction syndrome can occur with this procedure, which may lead to elevated IOP and recurrent hyphema. However, this was not observed in the present study.

Cuticular Drusen and the Risk of Late AMD

June 2022

Drusen are hallmarks of early age-related macular degeneration (AMD). The subtype known as cuticular drusen was first described in 1977 as numerous small, round, yellow nodules scattered throughout the fundus that showed a hyperfluorescent "stars-in-the-sky" pattern by fluorescein angiography. The morphologic and clinical features of cuticular drusen have led some experts to believe that their presence may infer generalized retinal pigment epithelium (RPE) dysfunction, which could signal greater impairment of visual function. **Goh et al.** aimed to determine if the presence of cuticular drusen in patients with bilateral large drusen affects the rate of progression to late AMD or is linked to faster decline of visual sensitivity before the onset of late AMD. They found that the risk of late AMD and the rate of visual sensitivity decline were similar for eyes with cuticular drusen and conventional drusen.

For this longitudinal study, the researchers enrolled 140 adults aged 50 years and older who exhibited bilateral large conventional drusen without late AMD. Participants were required to have at least one large conventional druse (>125 µm) within 1,500 µm of each fovea, meeting the definition of intermediate AMD. Multimodal imaging (MMI) and microperimetry were performed at baseline and semiannually for up to three years. MMI-based presence or absence of cuticular drusen was determined at baseline. OCT was performed to calculate drusen volume. The associations between cuticular drusen and progression to MMI-defined late AMD and the effect on visual sensitivity were assessed before and after adjusting for confounders such as age, pigmentary abnormalities, and drusen volume. Main outcome measures were the time to MMI-defined late AMD and the change in mean visual sensitivity.

Altogether, 280 eyes were included. Of these, 70 eyes (25%) had cuticular drusen at baseline. Before and after adjustment for confounding factors, there was no significant association between cuticular drusen and the progression rate to late AMD during the three years of follow-up. Similarly, an adjusted model showed no link between cuticular drusen and lower baseline visual sensitivity or quicker visual sensitivity decline.

Based on these findings, the current monitoring strategies for cuticular drusen and conventional drusen should be similar, said the authors.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Cost-Effectiveness of Two MIGS Stents

May/June 2022

Minimally invasive glaucoma surgery (MIGS) is increasingly used to reduce IOP in glaucoma patients and is often performed concurrently with cataract surgery. **Sood et al.** set out to investigate the costs and effects of implanting either the Hydrus Microstent or the iStent inject during cataract surgery in the United States. They found that implanting either device is cost-effective.

For this cost-utility analysis, the researchers used data from published pivotal randomized controlled trials of the two devices. All study participants were 65 years and older and had mild to moderate primary open-angle glaucoma (POAG) with or without visually significant cataract. The researchers then used Markov models to simulate glaucoma progression, over a 35-year period, through four glaucoma states (mild, moderate, advanced, severe/blind) and death in patients with a visually significant cataract. They also included a medication-only reference group to calculate total lifetime costs and outcomes for patients with mild to moderate POAG and no cataract. Main outcome measures included total costs and quality-adjusted life year (QALY). Direct medical costs were estimated at a U.S. Medicare reimbursement rate. Indirect costs included transportation and were derived from the published literature. In addition, the researchers weighted the costs to account for brand-name versus generic medication prices.

Over 35 years in the base case, the Hydrus Microstent plus cataract surgery arm cost $48,026.13 and gained 12.26 QALYs; the iStent inject plus cataract surgery cost $49,599.86 and gained 12.21 QALYs; cataract surgery alone cost $54,409.25 and gained 12.04 QALYs; and initial nonsurgical management cost $57,931.22 and gained 11.74 QALYs. The device arms dominated or were cost-effective when compared with cataract surgery alone within five years and throughout sensitivity analysis, the researchers said. In probabilistic sensitivity analyses, the iStent inject arm was cost-effective in 94.19% of iterations, while the Hydrus Microstent arm was cost-effective in 94.69% of iterations.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Acute Endophthalmitis After Intraocular Procedures

June 2022

Baudin et al. set out to describe the causes of postoperative acute endoph-

thalmitis in France from 2009 to 2018. They found that the raw number of endophthalmitis cases dropped following cataract surgery during this time frame—but increased among patients who received intravitreal injections.

For this cohort study, the researchers used the French national medical-administrative database. Procedures and cases of endophthalmitis were identified based on billing codes in French hospitals and private practices. From Jan. 1, 2009, to Oct. 31, 2018, 14,438,854 intraocular procedures were performed, and 7,522 cases of endophthalmitis occurred. The mean age of affected patients was 71.7 years, and slightly over half (51.12%) were women.

Overall, the incidence of endophthalmitis was low, at .0521 per 100 cases—that is, one case per every 2,000 procedures.

However, this varied by type of procedure:

- **Cataract surgery.** A total of 4,808 cases of endophthalmitis occurred, for an incidence of one case per 1,522 procedures. The case count dropped from 719 in 2009 to 469 in 2017, despite an increase in the number of cataract surgeries (from 584,188 to 847,320) during this same time period. (Of note, 2018 was a truncated year with regard to data collection.)
- **Intravitreal injections.** The number of endophthalmitis cases following intravitreal injections rose from 61 in 2009 to 184 in 2017, for a total of 1,296 during the study period and one case per 4,210 procedures. During the same time frame, the number of intravitreal injections rose from 188,330 in 2009 to 869,575 in 2017.
- **Vitreoretinal surgery.** A total of 698 cases of endophthalmitis occurred following 442,263 vitreoretinal surgeries, for one case per 634 procedures.
- **Other procedures.** These include corneal, filtering, and anterior segment surgeries. Overall, the greatest number of postprocedural endophthalmitis cases occurred following anterior segment surgeries—after 274,995 anterior segment surgeries, 245 cases of endophthalmitis occurred, for one case per 1,122 procedures.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Predicting Strabismus Reoperations in TED

June 2022

To better understand the risk factors and frequency of strabismus reoperation in patients with thyroid eye disease (TED), **Hwang et al.** explored a national claims database in which the average time since the first strabismus surgery was five years. They noted that many patients had a reoperation within a year. The number of muscles involved in the first surgery was the strongest predictor of reoperation and the interval to reoperation: More muscles raised the reoperation risk and shortened the time between surgeries. Patients who required surgery on vertical and horizontal muscles had the highest reoperation rate (30.8%).

For this population-based review, the authors searched the Clinformatics Data Mart to identify adults with newly diagnosed TED who had at least one strabismus surgery between 2003 and 2019. They collected detailed information, including demographics, time from TED diagnosis to initial strabismus surgery, fixation method, time until reoperation, and the muscles involved in the original surgery.

Altogether, 448 cases were assessed. Most patients were white (78%) and female (68%). The mean age at initial surgery was 62.7 for those with reoperation and 63.3 for those without. The mean follow-up time was 5.4 years, and approximately 25% of patients needed reoperation during this period. The mean time to first reoperation was 1.04 ± 1.63 years. Reoperation rates were 19.5%, 24.2%, and 30.8% if the original surgery entailed just vertical muscles, just horizontal muscles, or both types of muscles (respectively); the corresponding mean numbers of muscles were 1.82, 1.42, and 3.15. In terms of risk factors, the main analysis showed just one independent predictor of reoperation: higher number of muscles operated on initially (odds ratio, 1.27; $p = .03$). After adjustment for demographic and other variables, more muscles also coincided with shorter times to first reoperation (hazard ratio, 1.22; $p = .03$).

The authors noted that even though reoperation rates were relatively stable during the study timeline, the risk of reoperation rose from about 20% if one or two muscles were affected to more than 40% if at least four muscles were involved, suggesting that disease severity may correlate with risk. They hope the findings for this nationwide sample will facilitate treatment decisions and improve patient education.

Brolucizumab Holds Promise for DME

June 2022

Brolucizumab, a single-chain antibody fragment that offers deep tissue penetration and a long duration of action, has gained interest as a possible treatment option that may be more patient-friendly than traditional regimens for diabetic macular edema (DME). According to work by **Brown et al.**, the 52-week results of two phase 3 randomized trials suggest that the visual gains from brolucizumab 6 mg are noninferior to those of aflibercept 2 mg and that the newer drug is better at reducing central subfield thickness (CST) and resolving retinal fluid. Brolucizumab showed a favorable risk/benefit profile, and more than 50% of patients maintained their 12-week dosing schedule.

The two double-masked multinational trials (KESTREL and KITE) included patients with type 1 or 2 diabetes whose hemoglobin A1c level was ≤10%; their BCVA letter score ranged from 23 to 78. In KESTREL, participants ($N = 566$) were assigned randomly (1:1:1) to receive brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg. In KITE ($N = 360$), the randomization (1:1) was to brolucizumab 6 mg or aflibercept 2 mg. Baseline demographics were similar for all cohorts.

Patients who received brolucizumab started with five loading doses every six weeks, followed by dosing every 12 weeks (q12w) with the option to adjust or stop dosing at eight-week intervals if disease activity was ob-

served. Patients treated with aflibercept initially received five doses every four weeks (loading period), followed by fixed dosing at eight-week intervals. The main outcome for both trials was BCVA change from baseline to week 52. Only one eye per patient was entered into the analyses.

At week 52, brolucizumab 6 mg demonstrated noninferiority to aflibercept. The mean BCVA gains from baseline, respectively, were 9.2 versus 10.5 letters in KESTREL and 10.6 versus 9.4 letters in KITE ($p < .001$). In both studies, the percentage of patients with CST <280 mm was higher with brolucizumab at weeks 32 and 52. Persistent subretinal and/or intraretinal fluid at week 52 was less common with brolucizumab.

The percentage of patients on brolucizumab 6 mg who maintained the q12w dosing regimen through 52 weeks was 55.1% in KESTREL and 50.3% in KITE. In KESTREL, the rate of serious ocular adverse events was 3.7% and 1.1% with brolucizumab 3 mg and 6 mg, respectively, and 2.1% with aflibercept. In KITE, the incidence of such events was 2.2% with brolucizumab 6 mg and 1.7% with aflibercept.

Based on these findings, brolucizumab may be an effective DME treatment that can reduce burdens for patients, clinicians, and health care systems, said the authors. They noted that 100-week data are forthcoming and should provide more insight into the drug's safety and efficacy.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Phosphodiesterase 5 Inhibitors and Ocular Adverse Events

May 2022

Etminian et al. sought to quantify the risk of serous retinal detachment (SRD), retinal vascular occlusion (RVO), and ischemic optic neuropathy (ION) in men taking phosphodiesterase type 5 inhibitors. They found that regular users of these drugs, which are commonly prescribed for erectile dysfunction, might be at increased risk of SRD, RVO, and ION.

The researchers used the PharMetrics Plus database for this cohort study and the nested case-control analysis. Main outcomes included first diagnosis of SRD, RVO, or ION.

The cohort consisted of 213,033 men; of these, 123,347 used sildenafil, 78,609 used tadalafil, 6,604 took vardenafil, and 4,473 took avanafil. The case-control analysis included 4,584 controls and 1,146 cases of SRD (n = 278), RVO (n = 628), and ION (n = 240). The mean age of both groups was 64.6 years. Patients with SRD, RVO, and ION were more likely than those in the control group to have hypertension, diabetes, cardiovascular disease, or sleep apnea.

Further research is needed to elucidate the mechanisms behind these associations, the authors note. In the interim, they emphasize that individuals who regularly take these drugs should be aware of the risk of ocular adverse events and alert their physicians if they experience any visual deficits. *(Also see related commentary by Brian L. VanderBeek, MD, MPH, MSCE, and Maureen G. Maguire, PhD, in the same issue.)*

Social Determinants of Health and ROP Outcomes

May 2022

How are socioeconomic factors, in the context of race and ethnicity, related to outcomes of retinopathy of prematurity (ROP)? **Karmouta et al.** set out to answer this question in a study of 1,234 preterm neonates in the Los Angeles area. They found that gestational age (GA) was the primary driver of disparities in ROP outcomes.

For this retrospective cohort study, the researchers used U.S. Census Bureau income data and electronic medical records from four neonatal ICUs. Infants included in the study were born at a GA of 30 weeks or less or weighed less than 1,500 g at birth. Also included were those whose GA was greater than 30 weeks at birth but who also had an unstable clinical course and thus were deemed at high risk of ROP. The infants were screened for ROP between Jan. 1, 2010, and Dec. 31, 2020.

The researchers collected data on race and ethnicity, GA, demographics, clinical information, household income, and health insurance status. Main outcomes were diagnosis and severity of ROP.

In an unadjusted analysis, Hispanic neonates were more likely to be diagnosed with ROP and to have more severe disease. However, once the researchers adjusted for GA and socioeconomic factors, they found that lower GA was the primary predictor for ROP incidence (odds ratio [OR], .52; 95% CI, .48-.57; $p < .001$). In addition, higher median household income was associated with higher GA (OR, .26; 95% CI, .09-.43; $p = .002$).

Overall, the study's findings emphasize the role of socioeconomic factors in determining maternal health and fetal outcomes, the authors said, and future studies evaluating the impact that these additional risk factors have on ROP risk would be beneficial. *(Also see related commentary by Alejandra G. de Alba Campomanes, MD, MPH, in the same issue.)*

Academic Ophthalmology and the Gender Gap in Salary

May 2022

Emami-Naeini et al. evaluated disparities in compensation among U.S. ophthalmologists and compared compensation across specialties. They found that female academics were paid less than their male counterparts in ophthalmology—and that this trend was present across other specialties.

For this cross-sectional study, the researchers analyzed salaries of full-time academic physicians who practiced in 154 accredited U.S. medical schools, using the Association of American Medical Colleges' Faculty Salary Report for fiscal year 2019-2020. Of the 84,980 faculty members assessed, 1,607 (39.8% female) were in ophthalmology, 16,142 (32.5% female) were in other surgical specialties, and 67,231 (42.8% female) were in nonsurgical specialties.

Across all faculty ranks, female ophthalmologists earned less in total

compensation than their male colleagues, with the absolute difference in median compensation ranging from $6,000 for those at the instructor level to $112,000 for those serving as chief. Results of regression analysis showed that the absolute difference between male and female ophthalmologists' median compensation was $50,000 (95% confidence interval, $4,600-$96,000). These trends were present across all specialties, with women earning a lower salary at all faculty levels. In addition, the researchers found that those specialties with a lower representation of women (including ophthalmology) had higher pay gaps.

The authors noted that they were unable to analyze trends in compensation over time or to adjust for other factors that may have affected salary (i.e., physician age, years in practice, or geographic location).

—Summaries by Jean Shaw

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

COVID-19 Can Damage Retinal Microvasculature

British Journal of Ophthalmology
2022;106(4):559-563

Zapata et al. explored the possible retinal microvascular anomalies that may result from SARS-CoV-2. They found decreased central retinal vascular density (VD) in moderate and severe cases.

For this case control study, 96 adult patients with confirmed SARS-CoV-2 infection in the preceding three months were stratified by severity as follows: group 1, those with mild disease (n = 24); group 2, those with moderate disease requiring hospitalization but no acute respiratory distress (n = 24); and group 3, those with severe disease with acute respiratory distress, admission to the ICU, and a serum interleukin-6 level >40 pg/mL (n = 21). Age-matched volunteers with negative serologic findings served as controls (n = 27).

All participants completed a structured questionnaire that covered comorbidities, concomitant medications, and use of tobacco, alcohol, and recreational drugs. In-hospital data were gathered retrospectively from the hospital's COVID-19 database. Participants underwent macula-centered high-definition OCT imaging, angiography with fovea-centered OCT, and color fundus photography of the retinal posterior pole.

No lesions were detected for any participant by funduscopy or structural OCT. The difference in VD between those in group 1 and controls was nominal. However, VD was lower in those in groups 2 and 3 ($p = .009$ for group 2 vs. controls and $p = .026$ for group 3 vs. controls).

It is possible that the low VD observed in moderate and severe disease could signal similar problems in other organs. Retinal vascular occlusion has been reported in association with COVID-19 infection. Moreover, previous research suggests that low VD in the central retina may be a general vascular marker of systemic conditions or specific diseases such as chronic kidney disease, diabetes, and Alzheimer disease.

Going forward, longitudinal studies are needed to determine the vascular effects of COVID-19, said the authors, who believe their findings will help in designing future investigations. They acknowledged that the reduced VD of the central retina in moderate and severe COVID-19 demonstrates, at the very least, the complex nature of the disease, including its ability to invade multiple organs.

Thinning of Skull Anatomy in IIH

Journal of Neuro-Ophthalmology
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Barke et al. set out to determine if there is an independent relationship between idiopathic intracranial hypertension (IIH) and thinning of the skull base or calvarium. They found that both structures were narrower in patients with IIH and that patients' obesity was unrelated to changes in either area.

In this retrospective case-control study, each of 63 patients with an IIH diagnosis (case) was matched by age, sex, and race to a patient with a headache diagnosis (control). All participants underwent computed tomography of the head, maxillofacial region, or orbits within three months of their diagnosis. Skull-base thickness was determined by the height of the auditory canal in the coronal plane. Calvarial thickness was measured just anterior to the foramen rotundum in the same plane. Zygoma thickness was chosen as the imaging control because it is not affected by intracranial force.

Each study cohort included 61 females and two males. The mean age was 30.7 years in those with IIH and 32.3 years in controls. There were 24 Whites, 23 Blacks, one Asian, and 15 who described their race as "other" in each group. Obesity was more common in patients with IIH (95% vs. 37% of controls).

All participants with IIH and 13 controls underwent lumbar puncture. The average opening pressures were 40.5 ± 15.6 cm H_2O in patients with IIH and 19.5 ± 8.5 cm H_2O in those from the control group. Visual acuity did not differ significantly between patients with IIH (logMAR 0.22 ± 0.45) and controls (logMAR 0.09 ± 0.30). Those with IIH had a thinner skull base (mean, 4.17 ± 0.94 mm vs. 5.05 ± 1.12 mm; $p < .001$) and calvarium (mean, 1.50 ± 0.50 mm vs. 1.71 ± 0.61 mm; $p = .024$). Mean zygoma thickness was similar for the two groups (IIH, 1.18 ± 0.30 mm; control, 1.26 ± 0.35 mm; $p = .105$).

Patients with IIH experienced more headache (97% vs. 74%; $p = .001$), pulsatile tinnitus (48% vs. 7%; $p < .001$), horizontal binocular diplopia (24% vs. 4%; $p = .006$), confrontational visual field deficit (23% vs. 2%; $p = .003$), and papilledema (74% vs. 0%; $p < .001$). A subgroup comparison of obese and nonobese patients showed no significant differences in thickness of the skull base, calvarium, or zygoma—unlike findings of previous research.

The results suggest that IIH is independently associated with thinning of the skull base and calvarium, said the authors. They recommend investigations of the pathogenesis underlying the link between IIH and these structures. *—Summaries by Lynda Seminara*