

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

### High-Dose Vitamin D Does Not Lower Cataract Risk

March 2023

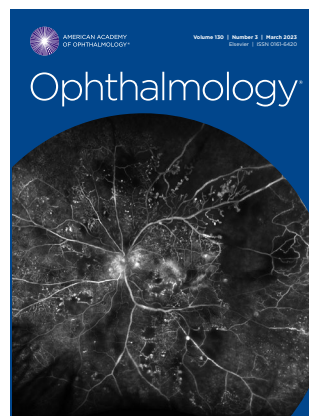
The presence of vitamin D receptors in the lens of the eye raises the possibility that high intake of this vitamin may influence cataract development. However, findings of previous studies have been inconsistent, and randomized controlled trials are lacking. **Rahman et al.** conducted an ancillary study among participants of a nationwide Australian trial of the effects of vitamin D on all-cause mortality (the D-Health Trial) as well as recruited volunteers. Their goal was to determine whether high-dose vitamin D3 could reduce the incidence of cataract in older adults—and they found that it did not.

The D-Health Trial was a seven-year, randomized, double-masked, placebo-controlled study of the Australian general population, which concluded in 2020. In that study, enrollees were assigned randomly to receive 60,000 IU of vitamin D or placebo per month, each taken orally for up to five years. For this ancillary research, **Rahman et al.** invited study participants and volunteers of similar age. They excluded people with hypercalcemia, hyperparathyroidism, kidney stones, osteomalacia, or sarcoidosis, as well as anyone who was taking more than 500 IU per day of vitamin D. The primary outcome measure was the first surgery for cataract. Data were obtained from universal health insur-

ance records and hospital data.

Altogether, 19,925 individuals met the inclusion criteria. The participants' mean age was 69.3 years (range, 60 to 84 years), and 46% were women. The rate of cataract surgery during follow-up (median, five years) was 18.5% in the vitamin D group and 18.3% in the placebo group, and the incidence rates per 1,000 person years were 41.6 in the vitamin D group and 41.1 in the placebo group (hazard ratio, 1.02). Prespecified subgroup analyses by age, sex, body mass index, predicted serum level of 25(OH)D, and level of exposure to ambient UV radiation did not reveal significant differences between the study groups.

In their discussion, the authors wrote, "although the results of the D-Health Trial are likely to be generalizable broadly to the Australian setting and other communities with a similar prevalence of vitamin D deficiency, they are largely uninformative about the effect on cataract of treating vitamin D deficiency or of population-wide supplementation in areas where a much higher proportion of people is vitamin D deficient." As vitamin D deficiency has been linked to elevated inflammation and oxidative stress, supplementation may be helpful



for conditions other than cataract, they acknowledged.

### Surgery for Infantile Nystagmus Confers Modest VA Benefit

March 2023

For an *Ophthalmic Technology Assessment*, **Chang et al.** reviewed published literature to assess the effectiveness of surgery for improving VA in patients with infantile nystagmus syndrome (INS).

Evidence from the qualifying studies indicates that surgical treatments for INS produce moderate improvement in VA.

For this review, the PubMed database was searched for all relevant English-language studies published at any time. The final search was conducted in January 2022. Of 46 studies that warranted full-text review, 23 were appropriate for inclusion. An evidence rating was assigned to each study. One was a randomized trial (level 2), and the others were case series (level 3). Study participants were children and/or adults with INS, and sample sizes ranged from 10 to 100. The proportion of patients with anomalous head position (AHP), strabismus, and sensory diagnoses varied by study. An outcome measure in all studies was BCVA at distance in the null zone (or central gaze if there was no null zone), and most of the studies included data on monocular and binocular BCVA. All patients had at least one month of follow-up.

Surgical interventions for INS included large recession, tenotomy and reattachment (TAR), myectomy (with or without pulley fixation), and anterior extirpation of horizontal rectus muscles, plus a variety of procedures to correct AHP. The randomized study was a comparison of retro-equatorial recession and TAR of all four horizontal recti. Nine case series involved a single procedure aimed at improving VA. In five others, the objective was AHP correction. In eight studies, at least two procedures were performed to address strabismus or AHP.

VA outcomes were mixed. Changes in BCVA ranged from no improvement to .3 logMAR. Most studies found logMAR improvement of .05 to .2. Statistically significant VA improvement occurred in 12 (75%) of the 16 studies in which statistical analyses were performed. No single procedure appeared to be more beneficial than the others. The rates of complications and reoperation were lowest for patients who underwent TAR and were highest for those who received myectomy or anterior extirpation.

Despite the statistical significance of BCVA improvement in many studies, the clinical significance of this improvement was marginal for most patients.

Given the relatively low level of evidence of the studies in this review, the authors recommend further research, particularly to determine the best procedures to dampen the nystagmus. Well-designed comparisons of individual or combination procedures “may lead to important insights on the management of INS,” said the authors.

### **Nanodropper Versus Standard Eyedropper for Pupillary Dilation**

March 2023

Concerns about standard eyedroppers include product waste, potential over-medication, and patient discomfort. For instance, evidence suggests that for every drop instilled successfully, seven drops are wasted. In a randomized noninferiority study in children, Hoppe et al. compared efficacy for a standard-of-care (SOC) eyedropper

(50- $\mu$ L dispersion) and smaller-volume administration (10.4- $\mu$ L dispersion) via the Nanodropper adapter. For pupillary dilation, they found that the Nanodropper was not inferior to SOC.

Participants of the study were children (mean age, 9 years) scheduled for routine pupillary dilation at a pediatric ophthalmology clinic in San Francisco. Each received SOC in one eye and Nanodropper delivery in the other eye. SOC eyes served as the controls. The eye selected for each treatment was determined randomly for each patient. Pupillary dilation was performed with one drop of 1% cyclopentolate, followed by one drop of 1% tropicamide, then one drop of 2.5% phenylephrine. The right eye of each patient was the first to receive drops, regardless of its treatment assignment. Refraction and pupillometry were conducted before instillation of the drops and 30 minutes afterward. The main outcomes were changes from baseline (before drop instillation) in spherical equivalent, pupil constriction percentage, and maximum pupil diameter.

Fifty patients (100 eyes) were included. After controlling for baseline variables, the spherical equivalent 30 minutes after drop instillation was .05 D greater in the Nanodropper group, which did not meet criteria for noninferiority.

The maximum pupil diameter achieved from dilation was lower in the Nanodropper group, but the difference was small enough to denote noninferiority. The constriction percentage achieved from dilation was .57 percentage points higher in the Nanodropper group, which did not represent noninferiority. When accounting for multiplicity, statistical significance was not achieved for any outcome measure.

Although strict noninferiority was achieved for pupillary dilation but not for cycloplegia or constriction percentage, the between-group difference in any outcome was not clinically significant, said the authors. Even so, they concluded, replacing SOC with small-volume eyedroppers should decrease medical waste and reduce the risk of local and systemic toxicity.

—Summaries by Lynda Seminara

## **Ophthalmology Retina**

Selected by Andrew P. Schachar, MD

### **Late Complications in Eyes With Posterior Vitreous Detachment**

March 2023

Patel et al. set out to examine the incidence of delayed complications of posterior vitreous detachment (PVD) and to identify any patient-specific risk factors. They found that the rate of any complication was 25% and that the rates of isolated vitreous hemorrhage, retinal breaks without detachment, and retinal detachments (RDs) were 13.1%, 16%, and 4.2%, respectively. However, while the majority of complications were noted at presentation, a significant proportion of each type was first noted within the six-month follow-up period.

For this retrospective observational study, the researchers used the Vestrum Health database to identify eyes with acute PVDs that occurred between 2015 and 2019. All told, 9,635 eyes were included; of these, 3,990 were phakic, 2,225 were pseudophakic, and 1,252 had documented lattice/peripheral retinal degeneration. (Of note, some charts did not list whether an eye was phakic or pseudophakic.) The patients' mean age was 63 years, and a majority (51.4%) were female. Outcomes measured included the rate of complications at initial presentation and at six months as well as the days to presentation with a complication.

The average time to any complication was 39.4 days. Diagnosis at presentation and complications noted during follow-up were as follows:

- **Isolated vitreous hemorrhage.**

Of 1,261 eyes with an isolated vitreous hemorrhage, 652 (51.7%) were diagnosed at presentation. During follow-up, an additional 101 eyes (8%) developed this complication.

- **Retinal breaks without detachment.** Of 1,539 eyes that had retinal breaks without detachment, 1,172 (76.2%) were diagnosed at presentation. By six months of follow-up, another 295 (19.2%) had developed this complication.

- **RD.** Of 403 eyes with an RD, 299

(74.2%) were noted at presentation. During follow-up, another 104 (25.8%) developed an RD.

With regard to patient-specific risk factors, men were more likely to experience delayed complications than were women (30% vs. 21.7%, respectively;  $p < .001$ ). The rate of any complication among pseudophakic eyes was 25% and 20.7% in phakic eyes ( $p < .001$ ). Among eyes with lattice/peripheral retinal degeneration, 44.2% experienced complications during follow-up. Similarly, a history of retinal breaks or RDs in the fellow eye was associated with a greater rate of complications ( $p < .0001$  for retinal breaks;  $p < .02$  for RDs) in the eye with a PVD.

Not all eyes had isolated pathology; for instance, 401 eyes with a vitreous hemorrhage at presentation also had a retinal break without RD at this point, while another 107 had a vitreous hemorrhage and an RD at presentation.

Given these findings, the authors recommend follow-up at the four- to six-week mark in all patients, counseling regarding symptoms of progression, and extended follow-up around the three-month mark in male patients and in those eyes found to be at greater risk of delayed complications in this study. —*Summary by Jean Shaw*

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Spectacles With Highly Aspherical Lenslets Slow Myopia

March 2023

Slowing myopia progression is crucial to reduce the global burden of this disorder. Optical strategies that not only correct refractive error at the fovea but also modulate defocus at the peripheral retina can slow the progression of myopia. Various types of spectacle lenses have been designed for this purpose. Sankaridurg et al. conducted a randomized, controlled, double-masked, crossover study to compare the progression-slowing capability of lenses equipped with highly aspherical lenslets (HAL) with that of standard single-vision devices (SV;

controls). The results showed that HAL is superior to SV.

Altogether, 119 Vietnamese children participated in this study (age range, 7–13 years). Their spherical equivalent (SE) refractive error ranged from  $-0.75$  to  $-4.75$  D. The participants were assigned randomly to wear HAL or SV initially. After six months (stage 1), they were switched to the other device for the next six months (stage 2). At the end of stage 2, both groups wore HAL for six additional months (stage 3). The groups were identified by the sequence of lens wear. Group 1 was designated as HSH (HAL-SV-HAL) and group 2 as SHH (SV-HAL-HAL). The main outcome measures were 1) the differences between HAL and SV in change ( $\Delta$ ) for SE and axial length (AL) during each stage and 2) the comparison of  $\Delta$ SE/AL with SV between the HSH and SHH groups to explore the possibility of myopia rebound after the switch.

During stages 1 and 2, the progression of myopia was significantly slower with HAL than with SV (stage 1 SE $\Delta$ :  $-0.21$  vs.  $-0.27$  D,  $p = .317$ ; stage 2 SE $\Delta$ :  $-0.05$  vs.  $-0.32$  D,  $p < .001$ ; stage 1 AL $\Delta$ :  $0.07$  vs.  $0.14$  mm,  $p = .004$ ; stage 2 AL $\Delta$ :  $0.04$  vs.  $0.17$  mm,  $p < .001$ ). For  $\Delta$ SE/AL with SV, there was no significant difference between the study groups. The average daily wear time was 14 hours for both types of lenses. The children were compliant with lens wear, and there was no indication of rebound after the switch from HAL to SV. No lens-related adverse event occurred with either lens at any stage of the study.

“The strength of the study was the double-blind, crossover nature,” said the authors, which allowed all participants to experience each type of lens for at least six months. They acknowledged that longer studies are needed to determine the risk of rebound.

### AI Retinal Vasculature Analysis May Predict Risk of NTG Progression

March 2023

The pathogenesis of normal-tension glaucoma (NTG) is unknown, and the condition can be challenging to manage. The mounting evidence

in support of a “vascular theory” of glaucoma comes from cross-sectional studies, which limits the utility of findings. Lin et al. used a deep learning system (DLS) to assess the relationship between DLS-computed baseline measurements of retinal vessel calibers and the risk of subsequent glaucoma progression in patients with NTG. They found, as hypothesized, that narrow retinal vessel calibers are an independent prognostic factor for NTG progression.

For this prospective study, the authors included 390 eyes with NTG that received follow-up for at least 24 months. The authors’ previously validated DLS was used to compute central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) from baseline fundus photographs. The visual field (VF) and retinal nerve fiber layer (RNFL) were evaluated semiannually, and the Cox proportional-hazards model was used to explore the potential relationship between baseline retinal calibers and the risk of NTG progression.

During the mean follow-up period of 34.36 months, progressive RNFL thinning developed in 69 study eyes, while VF deteriorated in 22. According to multivariable Cox regression analysis (adjusted for demographics, IOP, ocular perfusion pressure, systolic blood pressure, axial length, standard automated perimetry mean deviation, and RNFL thickness), narrower baseline CRAE and CRVE were each linked to progressive RNFL thinning (hazard ratio [HR] per SD decrease, 1.36 and 1.35, respectively). Narrower CRAE also was associated with VF deterioration (HR, 1.98).

Each SD decline from baseline in CRAE or CRVE raised the risk of RNFL thinning by more than 30% and the likelihood of VF deterioration by more than 90% during the two years of follow-up. Therefore, “high-throughput deep-learning-based retinal vasculature analysis demonstrated its clinical utility for NTG risk assessment,” said the authors. They added that this research corroborates the vascular theory of glaucoma.

—*Summaries by Lynda Seminara*

### Impact of Dietary Nitrate on AMD

February 2023

Does a high intake of dietary nitrate have an impact on the progression of age-related macular degeneration (AMD)? Broadhead et al. addressed this question in an analysis of data from the Age-Related Eye Disease Study (AREDS) and AREDS2. They found that higher nitrate intake was associated with a lower overall risk of progression to late AMD, including both late AMD subtypes: neovascular AMD and geographic atrophy (GA). However, much of this association was confounded by participants' plant-based dietary patterns. Such patterns tend to be rich in foods that supply nitrates, such as leafy greens.

In AREDS and AREDS2, validated food frequency questionnaires were administered to all participants (N = 7,788). For this post hoc analysis, the researchers performed regression analyses for the outcomes of progression to late AMD or large drusen. They also explored potential interactions with other dietary components, including lutein and zeaxanthin, and performed a genetic risk analysis. The combined AREDS/AREDS2 cohort comprised 4,396 women and 3,392 men. All self-identified as White, and their mean age was 71.1 years. There were 13,511 eligible eyes at baseline—and by final follow-up, 4,575 eyes (33.9%) had progressed to late AMD.

In the AREDS/AREDS2 cohort, those with the highest dietary intake of nitrate (quartile 4) had the lowest risk of progression to AMD (hazard ratio [HR], .77 (95% CI, .69-.86 for quartile 4 vs. quartile 1). These HRs were .71 (95% CI, .61-.83) and .85 (95% CI, .73-.99) for GA and neovascular AMD, respectively. However, when the studies were considered separately, nuances emerged: in AREDS, increased nitrate intake was associated with a decreased risk of GA but not neovascular AMD—and in AREDS2, there was no associ-

ation between nitrate intake and late AMD.

With regard to genetic interactions with nitrate intake, associations were not statistically significant by genotype; however, this analysis was conducted in only a subset of participants. As for other dietary components, high intake of a number of vitamins, minerals, and healthy fats were positively correlated with nitrate intake, and it was not possible to disentangle their individual impact on AMD outcomes.

In their discussion, the authors cautioned that the results of this study do not support recommending nitrate supplementation. However, as they point out, “Much of the outcome associated with nitrate intake can be attributed to plant-based dietary patterns in general, such as a Mediterranean diet.” (Also see related commentary by Michael Larsen, MD, DMSc, in the same issue.)

### Choroidal Changes During Spaceflight

February 2023

Ferguson et al. aimed to objectively document and quantify the prevalence and progression of choroidal folds, retinal folds, and peripapillary wrinkles in crew members flying long-duration missions to the International Space Station (ISS). They found that choroidal folds were the most common fold type to develop.

For this retrospective cohort study, the researchers obtained OCT scans of 36 crew members (72 eyes). The participants' mean age was 46 years, and they had taken part in space missions with a mean duration of 189 days onboard the ISS. The OCT scans were taken before, during, and after spaceflight. A panel of experts examined the scans for the presence of chorioretinal folds. Optic disc edema was identified via calculating peripapillary total retinal thickness, and choroidal folds were quantified based on surface roughness within macular and peripapillary regions of interest. The main outcome measures included fold incidence, peripapillary total retinal thickness, and Bruch membrane surface roughness.

Of the 36 crew members, six (12 eyes) demonstrated at least one type of fold during spaceflight. All 12 eyes had bilateral choroidal folds; two had both choroidal and inner retinal folds, and two had choroidal folds, inner retinal folds, and peripapillary wrinkles. Optic disc edema was observed in 25 of the 36 crew members (42 of 72 eyes). Of these, two eyes also had peripapillary wrinkles, four had inner retinal folds, and 10 had choroidal folds.

Of note, macular and peripapillary choroidal folds developed as early as flight day 26 and as late as flight day 266 and continued to worsen throughout mission duration. In four crew members (six eyes), the macular folds extended into the fovea. Fortunately, each of these four astronauts demonstrated a BCVA of 20/15 or better with normal visual fields and Amsler grid findings within four days after returning from their missions. Even so, as the authors pointed out, “disruption of the foveal photoreceptor layer could pose a vision concern for future extended-duration missions.” (Also see related commentary by Prem S. Subramanian, MD, PhD, in the same issue.)

### Vision Impairment in Older U.S. Adults

February 2023

Killeen et al. updated national epidemiological estimates of vision impairment and blindness in older U.S. adults. According to their analysis, more than 1 in 4 U.S. adults 71 years and older were visually impaired in 2021.

For this study, the authors analyzed data from the National Health and Aging Trends Study (NHATS), a population-based, nationally representative study of Medicare beneficiaries. In 2021, NHATS incorporated tablet-based tests of VA and contrast sensitivity. Data were collected from June to November 2021 and analyzed in August 2022. For this assessment, main outcomes were national prevalence of impairment in distance VA, near VA, and contrast sensitivity.

All told, there were 3,817 respondents in the 2021 NHATS sample; of these, 3,026 were eligible for this anal-



ysis. The prevalence of visual impairment in this group was 27.8% (95% CI, 27.3% to 31.8%). Impairments in distance VA, near VA, and contrast sensitivity were prevalent in 10.3%, 22.3%, and 10% of the participants, respectively. All types of visual impairment were associated with older age, less education, and lower income levels. In addition, impairments in near VA and contrast sensitivity were associated with non-White race and Hispanic ethnicity.

The authors noted that NHATS underwent sample replenishment in 2022 and is expected to provide visual function data on a larger cohort of adults 65 years and older. Overall, they said, the results of this analysis are “vital for informing surveillance of vision health in the United States and may enable public health programs to target individuals at highest risk of poor vision.” (Also see related commentary by Anne L. Coleman, MD, PhD, in the same issue.)

—Summaries by Jean Shaw

## Other Journals

Selected by Prem S. Subramanian, MD, PhD

### Anatomic Failure of MH Surgery Is Common in Blacks

*Graefes Archive for Clinical and Experimental Ophthalmology*

Published online Jan. 5, 2023

Laviers et al. explored the relationship between race and outcomes of macular hole (MH) surgery. They found that the rate of anatomic failure was significantly higher for Black patients than in those from other racial groups.

The study was conducted retrospectively at five hospitals of the U.K. National Health Service and included patients with documented ethnicity who underwent vitrectomy, internal limiting membrane peel, and gas/oil tamponade for any stage of primary full-thickness macular hole (FTMH). The main outcome measure was anatomic success, defined as FTMH closure in one operation. Hole closure was determined by spectral-domain OCT and defined as the absence of any full-thickness foveal neurosensory retinal defect. The key secondary outcome

was change in BCVA from baseline (pre-op status).

Overall, 334 operations for MH were performed. Of these, 78.7% took place in White patients, 11.7% in Black patients, 8.1% in Asian patients, and 1.5% in patients of mixed or other race. The mean age of the study population was 69.7 years, and 68.5% were women. Anatomic success was achieved in 280 (83.8%). Anatomic failure occurred in 38.5% of Black patients and 12.6% of White patients (relative risk, 1.788;  $p = .045$ ). For Asians, the rate of anatomic failure was 18.5%. In regard to BCVA, baseline logMAR improved by a mean of .35 in White patients, .37 in Black patients, .23 in Asian patients, and .38 in those of mixed or other race ( $p = .689$ ). Greater minimum linear diameter boosted the risk of anatomic failure (relative risk, 1.004;  $p < .0001$ ), whereas better pre-op BCVA and anatomic success (both  $p < .0001$ ) conferred greater BCVA improvement.

Although this research indicates that the rate of anatomic failure after FTMH surgery is much higher for Black patients, the reasons for this are unclear, said the authors. They did find that socioeconomic status did not appear to be related and recommend further investigations to understand the vast racial differences in anatomic outcomes.

### High Blood and Pulse Pressures Raise Risk of POAG

*Investigative Ophthalmology & Visual Science*

2022;63(13):3

IOP remains the only modifiable factor to slow progression of primary open-angle glaucoma (POAG), but the relationship between blood pressure (BP) and POAG is not well understood. Most evidence of a possible link between BP and POAG is from cross-sectional research, but only a few studies demonstrated a significant correlation. Mean arterial pressure (MAP) was included in some investigations, but the formulas differed. Pulse pressure (PP) is rarely examined, despite its link to cardiovascular disease and death. Macri et al. looked at the strength and shape

of associations between incident POAG and systolic BP, diastolic BP, MAP, and PP. They found that high systolic BP and PP raised the risk of POAG.

This prospective study involved 484,268 people listed in the U.K. Biobank who did not have glaucoma at the time of enrollment. Incident POAG events were documented at assessment visits, during in-patient hospital admissions, and from primary care data. Repeated measurements of systolic and diastolic BP, MAP, and PP were analyzed as time-varying covariables. All parameters were modeled as both categorical and continuous nonlinear variables. Both univariate and multivariate assessments were conducted. The primary outcome measure was the relative hazard ratio (HR) for incident POAG.

During the 5,715,480 person-years of follow-up (median, 12.08 years), there were 2,390 incident POAG events. Multivariable analyses demonstrated that relative to normal systolic BP and PP (systolic BP, 120-130 mm Hg; PP, 40-50 mm Hg), higher levels of each increased the likelihood of incident POAG (linear trends:  $p = .038$  for systolic BP,  $p < .001$  for PP). The HR for incident POAG was 1.16 points higher for systolic BP in the range of 130 to 150 mm Hg. The ratio was 1.13 points higher when PP exceeded 70 mm Hg. In multivariable models, there was no significant relationship between incident glaucoma and diastolic BP or MAP. The findings were similar for univariate analyses and for BP modeled as continuous variables.

These results suggest that among the BP parameters explored in this study, systolic BP and PP appear to be the most relevant to glaucoma risk. “The varied prognostic significance of these differing BP parameters appears to mirror that seen for systemic cardiovascular risk in older patients,” said the authors; this lends support to a potential role for systemic vascular dysfunction in the pathogenesis of POAG. Although the findings warrant further investigation, the authors noted that systolic hypertension may have potential as a modifiable risk factor for POAG.

—Summaries by Lynda Seminara