

# News in Review

COMMENTARY AND PERSPECTIVE

## RETINA

### Prone Positioning After Macular Hole Surgery

**THE NEED FOR FACE-DOWN POSITIONING** following macular hole (MH) surgery has been a focus of debate among retina specialists for a number of years. In a recent meta-analysis of randomized controlled trials comparing the treatment effect of prone positioning with that of seated or other positions, researchers found no significant differences between the two protocols.<sup>1</sup>

“Our study challenges the notion that all patients must do face-down positioning after surgery to optimize the success of macular hole closure,” said lead author Varun Chaudhary, MD, MSc, at McMaster University in Hamilton, Ontario, Canada.

**Assessing magnitude of effect.** To determine the effect of face-down positioning on both anatomic and functional outcomes, the researchers pooled data from eight clinical trials involving 709 eyes randomized to face-down positioning (n = 358) or to no prone positioning (n = 351). Outcomes, in order of importance, were closure rate, improvement in VA, recurrence rates, visual function, patient satisfaction, patient-reported quality of life, and complication rates.

**Results.** Overall, results of the analysis did not show a difference in closure rates between the two approaches. The relative risk of full-thickness MH closure rate was 1.05 (95% CI, .99 to

1.12; p = .09; GRADE rating = low). This was true for holes both smaller and larger than 400  $\mu$ m. With regard to VA, the results showed that the mean difference between the two

approaches was  $-.07$  (95% CI,  $-.12$  to  $-.01$ ; p = .03; GRADE rating = low).

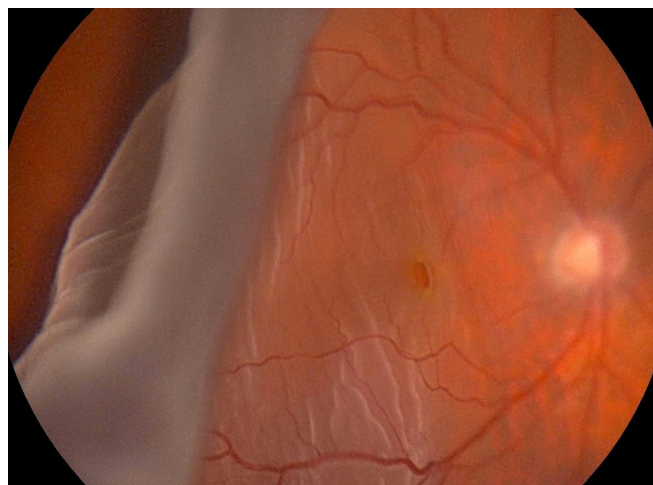
There was also a lack of robust evidence to demonstrate significant differences between the two approaches for adverse events/complication rates, as well as for other outcomes important to patients (e.g., visual function, quality of life, and patient satisfaction).

Similarly, a subgroup analysis showed that hole size (<400  $\mu$ m vs. >400  $\mu$ m), type of gas tamponade, and duration of positioning did not significantly affect outcomes.

#### **Consider patient preferences.**

Because this study could not establish the benefit of face-down positioning with any certainty, surgeons who want to continue the practice might consider reducing its duration, said Dr. Chaudhary. He noted that, because of the study results, he has shortened the length of time he asks patients to lie face down by half.

Dr. Chaudhary stressed that patients who are unable to lie face down should still be considered as surgical candidates and can be expected to achieve high closure rates. And, he said that while there is “a small possibility” that face-



**MACULAR HOLE.** Retinal detachment, giant retinal tear, and macular hole in a 61-year-old patient.

down positioning could increase the chance of closure, it comes at a cost to patient comfort.

“We propose that, given the likelihood that face-down positioning has a very small benefit, this lack of evidence should be shared with patients as part of the informed consent process, and a decision should be made that is in keeping with patient preferences and values.”

**Need for additional research.** Looking ahead, Dr. Chaudhary and his co-authors emphasized the need for ongoing research on the topic. As they wrote, “The lack of precision in determining the true effect of face-down positioning is a topic that would benefit from a large, well-conducted investigation that thoroughly evaluates important outcomes for macular hole surgery.” This would help inform clinical practice and support the development of related practice guidelines, they concluded.

—Miriam Karmel

1 Chaudhary V et al. *Ophthalmol Retina*. 2023; 7(1):33-43.

Relevant financial disclosures: Dr. Chaudhary—None.

## Stress-Induced Aging in Eye Sheds Light on Glaucoma

### RESEARCHERS AT THE UNIVERSITY

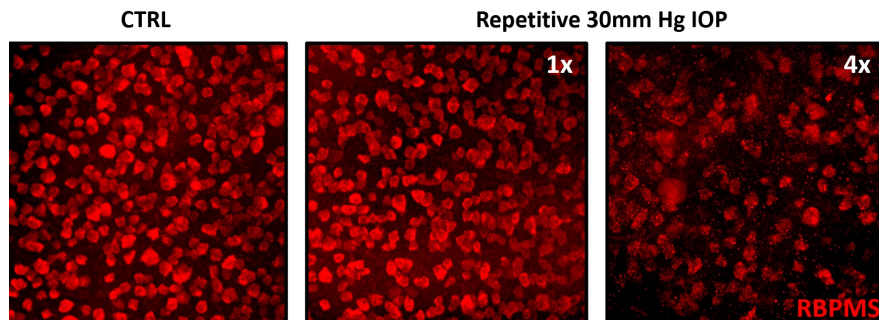
of California, Irvine (UCI) developed a mouse model of ocular hypertension to gain molecular insights into the role of age-related stress in glaucoma. They found that aging increases retinal susceptibility to stress, and that chromatin alterations play an important role in the stress-induced aging of the eye.<sup>1</sup>

“Using a new mouse model to study the molecular mechanisms of retinal aging, we showed that repetitive stress in the retina due to IOP elevation induces molecular changes that are similar to what happens in the aging eye,” said Dorota Skowronska-Krawczyk, PhD, at UCI’s Center for Translational Vision Research. She added, “Understanding the molecular mechanisms of stress-induced aging of the eye can help us develop drugs to prevent or treat the causes of glaucoma and other age-related eye neuropathies, rather than simply managing the symptoms.”

**Study rationale.** The researchers set out to investigate the mechanisms that promote senescence and cell death in retinal ganglion cells (RGCs), as a way of developing new strategies for preventing or treating vision loss in patients with glaucoma, Dr. Skowronska-Krawczyk said. “Based on our previous studies, we hypothesized that stress due to elevated IOP may accelerate aging in glaucomatous retinas.”

**Impact of elevated IOP.** The study’s results support the researchers’ hypothesis. The ocular hypertension-induced stress responses were “driven by senescence and age-related inflammation” (also referred to as inflammaging), Dr. Skowronska-Krawczyk said. Compared with young retinas, aged mouse retinas were more sensitive to IOP elevation and IOP-associated stress.

The researchers also found that elevated IOP promotes age-related epigenetic remodeling, with young murine retinas showing changes typically detected in older retinas. “Our find-



**STRESS-INDUCED RETINAL AGING.** Fluorescence imaging shows significant loss of RGCs (red staining with anti-RBPMS antibody) and aging-like changes in transcriptome and epigenome after repeated mild elevation of IOP.

ings suggest that even mild elevation in IOP in young retinas can accelerate the accumulation of alterations in DNA methylation and histone modification, contributing to eye aging,” Dr. Skowronska-Krawczyk said. These stress-induced epigenetic modifications can result in significant alterations in gene expression, which can ultimately lead to senescence and RGC death, she said.

**Next steps.** The researchers believe that the molecular mechanisms of stress-induced aging in mice are very similar to what happens in the human eye, Dr. Skowronska-Krawczyk said.

Next, the team is planning to perform similar assessments in primates in collaboration with researchers at the University of Alabama at Birmingham School of Medicine. Whether these molecular alterations can be reversed using senolytic or anti-inflammatory drugs to prevent or treat glaucoma remains to be addressed. —*Christos Evangelou, PhD*

1 Xu Q et al. *Aging Cell*. 2022;21(12):e13737.

**Relevant financial disclosures:** Dr. Skowronska-Krawczyk—None.

### CORNEA

## Detecting Keratoconus Progression

### RESEARCHERS HAVE FOUND THAT

corneal epithelial thickness measurements may be useful in detecting actively progressing versus stable keratoconus (KC). This work builds on previous research that showed epithelial analysis can increase the sensitivity for early diagnosis of KC.<sup>1,2</sup>

“With comprehensive mapping

through spectral-domain (SD) OCT, it is possible to reproducibly measure parameters of epithelial thickness,” said Marcony Santhiago, MD, PhD, at the University of São Paulo in Brazil.

**Study details.** The researchers enrolled 50 patients with progressive KC (maximum keratometry [Kmax] increase of 1 D per year), 50 with stable KC, and 50 healthy controls. All individuals underwent SD-OCT imaging to obtain epithelial thickness maps and pachymetry. Minimum and maximum epithelial thicknesses of the map and the difference between the thicknesses (min-max) were compared between the groups. “We aimed to identify measures of corneal epithelium that behave differently in stable keratoconus from those in progression,” Dr. Santhiago said.

**Results.** Epithelium min-max was the only epithelial parameter with a statistically significant difference between the stable and progressive KC groups. Eyes with stable KC presented min-max mean values of  $-18.2 \pm 6.6 \mu\text{m}$ . In contrast, progressing KC eyes presented mean values of  $-23.4 \pm 10.3 \mu\text{m}$  ( $p < .0001$ ).

**Findings assessed.** “We found that epithelial measures are useful to identify eyes with progressing KC and that the variation between the minimum and maximum epithelial points was significantly greater in progressing KC eyes,” said Dr. Santhiago. “A possible explanation for the min-max difference in progression is that the corneal epithelium has rapid cell turnover and is highly reactive to asymmetries in the shape of the underlying stromal surface.”

In addition, he said, “This study confirms that metrics associated with the asymmetric reactive capacity of

the epithelium are capable of detecting subtle differences between groups,” which he described as “more meaningful than values such as epithelial thinnest point.”

A substantial aspect of the research team’s methodology is that “we identified eyes that have progressed based on the limits that would make them candidates for corneal crosslinking (1 D over a year), regardless of their final KC stage,” Dr. Santhiago noted. “Only grouping these eyes in stages, regardless of progression, creates a bias for analyzing any variable role in relevant KC progression.”

**Next steps.** An important part of the group’s research involves the identification of inflammatory biomarkers possibly correlated with structural impairment in eyes with KC, Dr. Santhiago said. Their next step: publishing their latest work, which “showed that progressing KC eyes have a higher concentration of interleukin 6 [IL-6] and cortisol” versus that observed in eyes with stable KC, he said. He added, “There is a significant correlation between increased IL-6 and cortisol with corneal structural change in keratometry and pachymetry.”

**Takeaway for clinicians.** “Combined with the topography of the cornea, the epithelial map helps to understand structural alterations that represent the disease,” Dr. Santhiago said. “It can be a promising complementary tool both in the follow-up of a patient with KC and in the preoperative course of a patient who is a candidate for refractive surgery. In this group, we want to identify KC in its early forms.”

—Patricia Weiser, PharmD

1 Santhiago M et al. *Ophthalmol Science*. 2023;3:100256.

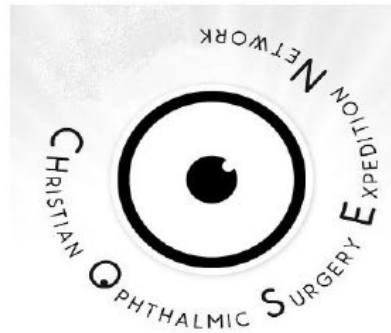
2 Wang Y et al. *J Refrac Surg*. 2018;34(3):201-211.

Relevant financial disclosures: Dr. Santhiago—None.

**MORE ONLINE.** For a map of KC progression, see this article online at [aao.org/eyenet](https://aao.org/eyenet).

See the financial disclosure key, page 8. For full disclosures, including category descriptions, view this News in Review at [aao.org/eyenet](https://aao.org/eyenet).

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