News in Review

COMMENTARY AND PERSPECTIVE

RETINA

Time to Rethink Glycemic Targets for Diabetes?

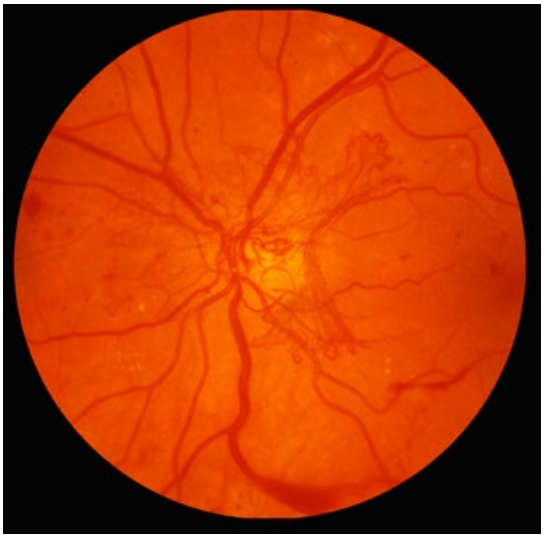
THE GLYCEMIC THRESHOLD ABOVE which diabetic retinopathy (DR) can be predicted to develop is lower for whites than it is for blacks and Hispanics, researchers have found.

In a retrospective study, a team of researchers at the University of Miami used data from 5,338 participants in the 2005-2008 National Health and Nutrition Examination Survey (NHANES). All had diabetes and had undergone digital retinal imaging to determine their retinopathy status. The analysis showed that the hemoglobin A_{1c} (HbA_{1c}) predictive threshold for the incidence of DR among white participants was 6.0%.[1] In contrast, the predictive thresholds for DR in Hispanics and blacks were 6.4% and 6.5%, respectively.

Adequate—but inadequate? "Importantly, all three race/ethnicity–specific glycemic thresholds are less than the recommended 7.0% [for optimal HbA_{1c} control] for people with diabetes," the authors wrote. "This finding suggests that adequate glycemic control does not guarantee protection from diabetic complications, such as DR."

Indeed, the researchers calculated that above these thresholds the risk of a diabetic patient developing retinopathy was approximately 4 to 6 times as high as it would be below them, said lead author Kevin J. Moore, MD, MPH, now at the University of Central Florida in Orlando.

Advising patients. Dr. Moore said the researchers hope their results will help physicians offer more individualized advice to their patients who have diabetes. "This shows that you can have individuals that are considered well-controlled for diabetes but who, based on their race or ethnicity, are still at risk for diabetic retinopathy," Dr. Moore said. "We would hope that our paper would inspire ophthalmologists and primary care providers to emphasize to patients that it's still important to follow up, regardless of how well their diabetes is controlled."



GLYCEMIC CONTROL. *Tight glycemic control in patients with diabetes is recommended as a way to prevent complications, such as the proliferative DR seen here. But should the thresholds be revisited?*

A look at the guidelines. Racial differences in mean HbA_{1c} levels have been discussed in the diabetes literature, but the reasons for these differences are poorly understood, and their potential clinical significance is unknown.[2] The American Diabetes Association (ADA) makes no recommendations that glycemic targets be modified based on race or ethnicity.[3]

Large, prospective treatment trials have demonstrated that retinopathy and other microvascular complications decrease at HbA_{1c} levels below 7.0%, and this is the appropriate target for most patients, according to the ADA's 2019 recommended standards of care.[3] However, the ADA report acknowledged, the lower complication rates achieved in studies have been accompanied by increases in the incidence of serious hypoglycemia.

Because of this risk, it would be "reasonable" for physicians to recommend a lower glycemic target of 6.5% for certain patients, if it can be met without hypoglycemia or other adverse effects, the ADA report said. This includes patients with a short duration of diabetes, long life expectancy, type 2 disease being treated with lifestyle or metformin only, or no significant cardiovascular disease.

By comparison, the Japan Diabetes Society adopted practice guidelines[4] in 2013 that endorse setting the HbA_{1c} target at 6.0% or less when the physician judges that glycemic control can be achieved through diet, exercise, or medication. The guidelines set 7.0% as the ceiling for most other patients, with the goal of preventing complications.

—Linda Roach

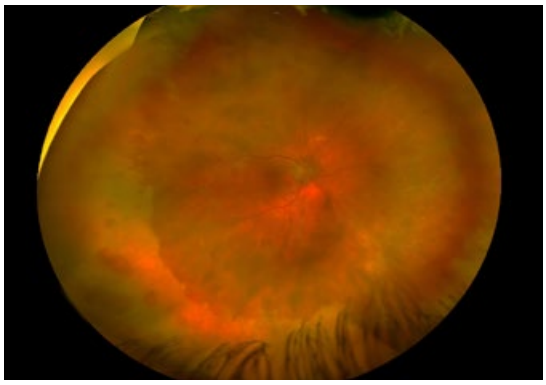
1 Moore KJ et al. *JAMA Ophthalmol.* Published online Feb. 21, 2019.
2 Selvin E. *Diabetes Care.* 2016;39(8):1462-1467.
3 American Diabetes Association. *Diabetes Care.* 2019;42(Suppl 1):S61-S70.
4 Araki E et al. *Diabetol Int.* 2016;7(4):327-330.
Relevant financial disclosures—Dr. Moore: None.

PUBLIC HEALTH

Update on Shingles Vaccine Safety

PUBLIC HEALTH OFFICIALS AND cornea specialists heralded the release of recombinant zoster vaccine (Shingrix, GlaxoSmithKline), given its ability to prevent herpes zoster (shingles) and ward off one of the disease's most serious complications, herpes zoster ophthalmicus (HZO).

The second-generation vaccine for the prevention of shingles was licensed by the FDA for adults age 50 and older in October 2017. Since then, however, the vaccine supply has been plagued with shortages, and some patients have reported side effects that prevented them from following through with the two-dose protocol.



SHINGLES RISK. *This 40-year-old woman presented with acute retinal necrosis due to HZO.*

Although the shortages are expected to persist throughout this year,[1] there is good news: According to the CDC, safety data for the eight months following FDA approval of Shingrix are consistent with comparable data from prelicensure clinical trials.[2] "Systemic and local reactions were most commonly reported, but [they] tended to be nonserious and self-limited," said lead author Elisabeth

IMAGING

Emergencies After Hours: OCT in the Eye-Only ER

OPTICAL COHERENCE TOMOGRAPHY (OCT) HAS COME out of the workday setting and into the night. Doctors at New York Eye & Ear Infirmary (NYEE) of Mount Sinai Hospital in New York report that access to OCT in the hospital's after-hours emergency eye clinic has led to timely diagnoses and vision-saving treatment. Other benefits included improved patient satisfaction and reduced physician stress.[1]

The OCT system used in this study (iScan, Optovue) is described by the manufacturer as automated; it uses computerized voice directives in multiple languages to direct patient positioning and fixation. The technical training of the NYEE ophthalmology residents took less than 30 minutes, the authors said. "Automated OCT minimizes user training, allowing the technology to slip into this acute setting seamlessly," said coauthor Richard B. Rosen, MD, at NYEE.

Review of records. Over a period of 15 months, 202 patients (359 eyes) underwent automated OCT scanning in the hospital's resident-run urgent eye care clinic. The most common complaint that prompted imaging was decreased vision (120, 59%), followed by flashes/floaters (32, 16%), then metamorphopsia, scotoma, and pain.

Impact on patient care. The imaging system proved its worth in furthering rapid triage in appropriate cases, Dr. Rosen said. For example, OCT can be helpful in diagnosing subtle cases of CRAO without characteristic fundus findings and decreased vision. One patient had increased reflectivity of the inner retinal layers and a loss of definition on OCT, confirming a suspected diagnosis of reperfused CRAO. She was transferred to Mount Sinai's main ER for a cardiovascular workup.

Impact on providers. Eighteen residents and seven fellows completed a survey about after-hours access to the imaging modality. Of the 25 participants, 21 felt that use of the automated OCT system improved patient satisfaction and reduced delayed or missed diagnoses, and 19 reported feeling less stress while using the system, as it reduced their uncertainty over subtle pathologies. "Both patients and physicians benefited by the reassurance that the correct diagnosis and appropriate triage plan could be confidently implemented in such a setting," Dr. Rosen said.

Critical caveat. This system was not effective in patients with a visual acuity of 20/400 or worse, as the device's minimum vision requirement stipulates that patients should be able to find fixation cues without operator redirection.

Bottom line. Further study may reveal the utility of automated OCT in sight-threatening conditions such as an unusual presentation of acute retinal arterial occlusion requiring interventional radiology, Dr. Rosen said. Automated OCT "in an urgent care setting can be a powerful tool for triaging a variety of sight-threatening conditions that require immediate attention," he said. The use of such a system "reduces the need to relegate this important diagnostic technology to workday settings where skilled operators are available."

—Miriam Karmel

1 Kaplan RI et al. *BMJ Open Ophthalmol.* 2019;4:e000187.
Relevant financial disclosures—Dr. Rosen: Optovue: C.

M. Hesse, MD, at the CDC in Atlanta.

Safety data. The postlicensure safety profile is based on reports to the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system. VAERS received 4,381 reports of adverse events, including reports from health care providers and the public, between October and June 2018. During that time, some 3.2 million doses of Shingrix were distributed.

Adverse reactions. Signs and symptoms included the following:

- Chills, headache, fatigue, and myalgia were commonly reported, along with injection site reactions.
- Most common signs and symptoms included fever (23.6%), injection site pain (22.5%), and injection site erythema (20.1%).
- All told, 130 (3%) of events were classified as serious.
- People between the ages of 50 and 69 reported a high percentage of systemic signs and symptoms (e.g., chills and headache). In contrast, those age 70 and older reported a high frequency of local symptoms (e.g., injection site pain).

Reassurance. Overall, Dr. Hesse said, the CDC team was "reassured" by the findings. She added that providers should expect that some patients will experience reactions to the vaccine—but that most reactions will be self-limited and should resolve in a few days. The CDC and FDA will continue to monitor the vaccine's safety profile, as the vaccine is still in the early uptake period.

Cornea risk reminder. Kathryn A. Colby, MD, PhD, at the University of Chicago, urged ophthalmologists to continue to educate patients that the vaccine is safe, effective, and can prevent HZO. "Herpes zoster ophthalmicus can cause serious cornea complications that can lead to permanent vision loss and chronic pain that impacts quality of life," she said. "It's good for ophthalmologists to educate patients on the benefit—because we're the ones who will end up managing the complications. We need to get the word out."

—Miriam Karmel

1 CDC. Current vaccine shortages & delays. www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html. Updated November 2018. Accessed March 20, 2019.

2 Hesse EM et al. *MMWR Morb Mortal Wkly Rep.* 2019;68(4):91-94.

Relevant financial disclosures—Drs. Colby and Hesse: None.

CORNEA

Lymphatic Vessels Detected in Failed Corneal Transplants

CANADIAN RESEARCHERS HAVE shown that lymphatic vessels are implicated in corneal transplant graft failure with neovascularization.[1] "Our study proves for the first time the presence of lymphatics in failed vascular corneal grafts and [shows] that they are distinct from blood vessels," said Neeru Gupta, MD, PhD, MBA, at the University of Toronto. "This work highlights the role of lymphatics in corneal transplant failure and points to a need to develop novel treatments that target lymphatic vessels to help manage the failing graft," she added.

Tissue collection. For this study, failed corneal transplant cases were selected from the Toronto Ophthalmic Pathology database. Of 273 cases, 39 contained documented neovascularization. Of these, nine cases (six men, three women) also contained suspected lymphatics. The researchers then obtained conjunctival tissue from six patients (three men, three women) with healthy corneas. These control cases were acquired from the Human Eye Biobank for Research, also located in Toronto.

Methods. The researchers selected the nine failed grafts based on results of immunohistochemistry (IHC), immunofluorescence (IF), H&E staining, and immunoperoxidase staining for CD31, a blood vessel marker. In addition, for two of these cases, they used fluorescence in situ hybridization (FISH) to detect lymphatic mRNAs, including podoplanin. All IF and FISH samples were compared with positive and negative controls and visualized by confocal microscopy.

Results. Podoplanin-immunoreactive lymphatics were detected in all nine failed grafts by IHC; of these, seven also were positive by IF. Moreover, two of the cases were positive for at least two lymphatic markers simultaneously.

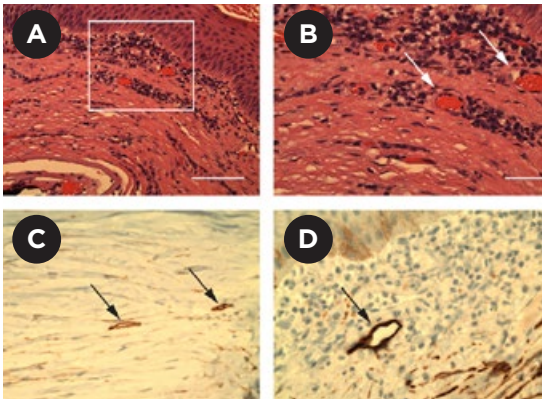
H&E stained sections of failed grafts showed mononuclear inflammatory cells at both low and high power, and neovascularization was confirmed in every case of corneal graft failure by detection of CD31-positive profiles. Varying lymphatic sizes and morphologies were seen both among separate cases and within a single case, and myriad unique lymphatic morphologies were seen.

Next steps. The researchers emphasized that their findings stress the importance of developing new tools, therapies, and imaging modalities to bring about improvements in graft survival.

—Arthur Stone

1 Diamond MA et al. *Br J Ophthalmol.* 2019; 103(3):421-427.

Relevant financial disclosures—Dr. Gupta: None.



FAILED GRAFTS. *These images show neovascularization and suspected lymphatics within failed corneal grafts. Blood vessels shown at 20× magnification (rectangular area, A) and at 40× magnification (arrows, B). Immunoperoxidase images show podoplanin-antibody staining lymphatics (arrows, C and D).*

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.