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Multimodal Characterization of Proliferative Diabetic Retinopathy Reveals Alterations in Outer Retinal Function and Structure

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Purpose: To identify changes in retinal function and structure in persons with proliferative diabetic retinopathy (PDR), including the effects of panretinal photocoagulation (PRP).

Design: Cross-sectional study.

Participants: Thirty adults who underwent PRP for PDR, 15 adults with untreated PDR, and 15 age-matched controls.

Methods: Contrast sensitivity, frequency doubling perimetry (FDP), Humphrey visual fields, photostress recovery, and dark adaptation were assessed. Fundus photography and macular spectral-domain optical coherence tomography (SD OCT) were performed. To quantify retinal layer thicknesses, SD OCT scans were segmented semiautomatically.

Main Outcome Measures: Visual function measures were compared among patients with PDR and PRP, untreated patients with PDR, and controls. Mean retinal layer thicknesses were compared between groups. Correlation analyses were performed to evaluate associations between visual function measures and retinal layer thicknesses.

Results: A significant reduction of FDP mean deviation (MD) was exhibited in PRP-treated patients with PDR (MD ± standard deviation, −8.20±5.76 dB; $P < 0.0001$) and untreated patients (−5.48±4.48 dB; $P < 0.0001$) relative to controls (1.07±2.50 dB). Reduced log contrast sensitivity compared with controls (1.80±0.14) also was observed in both PRP-treated patients (1.42±0.17; $P < 0.0001$) and untreated patients (1.56±0.20; $P = 0.001$) with PDR. Compared with controls, patients treated with PRP demonstrated increased photostress recovery time (151.02±104.43 vs. 70.64±47.14 seconds; $P = 0.001$) and dark adaptation speed (12.80±5.15 vs. 9.74±2.56 minutes; $P = 0.022$). Patients who underwent PRP had diffusely thickened nerve fiber layers ($P = 0.024$) and diffusely thinned retinal pigment epithelium (RPE) layers ($P = 0.009$) versus controls. Untreated patients with PDR also had diffusely thinned RPE layers ($P = 0.031$) compared with controls.

Conclusions: Patients with untreated PDR exhibited inner retinal dysfunction, as evidenced by reduced contrast sensitivity and FDP performance, accompanied by alterations in inner and outer retinal structure. Patients who underwent PRP had more profound changes in outer retinal structure and function. Distinguishing the effects of PDR and PRP may guide the development of restorative vision therapies for patients with advanced diabetic retinopathy. *Ophthalmology 2015;122:957-967 © 2015 by the American Academy of Ophthalmology.*

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The International Diabetes Federation estimated that the prevalence of diabetes in 2013 was 382 million people worldwide, and it is expected to reach 592 million people by 2035.[1] Diabetic retinopathy (DR) affects approximately 35% of persons with diabetes, and proliferative DR (PDR) affects approximately 7% of persons with DR.[2] Therefore, PDR and its consequences continue to be a major public health challenge.

Meyer-Schwickerath[3] developed retinal laser photocoagulation for the treatment of PDR in the 1950s, and panretinal photocoagulation (PRP) remains the most widespread treatment for PDR nearly 60 years later. Panretinal photocoagulation induces regression of neovascularization within several weeks of treatment, presumably because of reduction of metabolic demand.[4] Traditionally, it has been assumed that PRP kills poorly perfused cells in the neurosensory retina, the retinal pigment epithelium (RPE), and the photoreceptor layers of the peripheral retina, reducing angiogenic signaling and oxidative stress.

However successful at preventing blindness, PRP invariably causes retinal damage and unwanted visual side effects, including constricted visual fields, reduced visual acuity, altered color vision, impaired dark adaptation, and

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decreased contrast sensitivity.[5–11] Panretinal photocoagulation also compromises retinal structure, with thinning of the nerve fiber layer (NFL), focal retinochoroidal atrophy at burn locations, and scar formation with progressive expansion.[12–16] Thus, PRP superimposes thermal injury-induced retinal degeneration onto the intrinsic neurodegeneration of DR, leaving patients with reduced abilities to drive and read, particularly under low light conditions.[17]

The cellular mechanisms by which persons with PDR lose vision remain unclear, so this study was conducted to test the hypothesis that PRP induces outer retinal dysfunction in patients with PDR. By evaluating retinal structure and function within the same patients, this study additionally aimed to correlate changes in retinal structure with specific visual deficits in PDR. Improved understanding of the pathogenesis of visual dysfunction in individuals with PDR and in those who have undergone PRP could lead to the identification of therapeutic targets for these patients.

Methods

This study was conducted at the University of Michigan W. K. Kellogg Eye Center after approval by the University of Michigan Medical School Institutional Review Board. Participants were recruited from the clinics and through the University of Michigan Clinical Studies website from August 2012 through October 2013. Informed consent was obtained from all subjects before participation in the study. This research adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

Patient Enrollment and Baseline Evaluation

Three groups of patients were enrolled: adults with type 1 or type 2 diabetes who had undergone PRP for PDR (post-PRP group), adults with type 1 or type 2 diabetes with PDR and no history of PRP (treatment-naïve group), and healthy adults (control group).

Inclusion criteria for the post-PRP group were (1) diabetes mellitus as defined by the American Diabetes Association diagnostic criteria[18]; (2) age 18 years or older; (3) best-corrected visual acuity (BCVA) of 20/400 or better in the study eye; and (4) PRP administered 6 months or more before enrollment. Inclusion criteria for the treatment-naïve group were (1) diabetes mellitus; (2) age 18 years or older; (3) BCVA of 20/400 or better in study eye; and (4) evidence of active PDR on dilated fundus examination or fundus photography. Inclusion criteria for the control group were (1) age 18 years or older; (2) BCVA of 20/30 or better in study eye; and (3) no diabetes mellitus.

Exclusion criteria for the post-PRP group and treatment-naïve groups were (1) any eye disease other than PDR; (2) history of drug or alcohol abuse; (3) neurologic or systemic disease that could impair vision; (4) hospitalization within 1 month before enrollment; (5) difference in 2 recent consecutive hemoglobin A_{1c} (HbA_{1c}) measurements of 5% or more; (6) inability to give informed consent or to complete testing; (7) spherical equivalent of more than ±6.00 diopters; (8) pregnant or nursing; and (9) blood pressure of 180/100 mmHg or more. Exclusion criteria for control subjects were (1) spherical equivalent of more than ±6.00 diopters; (2) pregnant or nursing; (3) ocular, neurologic, or systemic disease that could impair vision; and (4) inability to give informed consent or to complete testing.

One study eye was chosen from each patient, and if both eyes met the eligibility criteria, the eye with the better visual acuity was examined. All subjects underwent ophthalmologic examination including refraction and measurement of BCVA using the electronic visual acuity tester with E-ETDRS protocol, applanation tonometry, slit-lamp examination, and dilated fundus examination. A blood sample was obtained from each participant to measure HbA_{1c}.

After refraction and measurement of BCVA, all patients underwent a series of functional visual tests in the study eye: contrast sensitivity, frequency doubling perimetry (FDP), Humphrey visual fields (Humphrey Field Analyzer [HFA] II-750; Carl Zeiss Meditec, Dublin, CA), color vision, Minnesota reading acuity, photostress recovery, and dark adaptation. Contrast sensitivity was measured monocularly using the Pelli-Robson contrast sensitivity chart (Haag-Streit USA, Mason, OH), read at 1 m under standard overhead lighting conditions. Patients were asked to read through each line on the chart until 2 or 3 letters in a triplet were read incorrectly. The logarithmic contrast sensitivity value of the previous triplet of letters determined the patient's contrast sensitivity score. Frequency doubling perimetry was performed with the 24-2 full-threshold testing strategy using the Matrix perimeter (Carl Zeiss Meditec) as described by Jackson et al.[19] Photopic central 10-2 Swedish interactive threshold algorithm standard and peripheral 60-4 threshold visual fields were determined with an HFA. For both FDP and standard Humphrey perimetry, the reliability criteria used were less than 33% fixation errors, less than 33% false-positive errors, and less than 33% false-negative errors. The Farnsworth D15 test was administered to all study participants, and a fail on the Farnsworth D15 was defined as 2 or more diametrical crossings on the test. The test was performed monocularly under a Macbeth lamp providing 270-lux illumination. The Minnesota Reading test was administered to assess reading acuity. The Minnesota Reading test acuity chart contains continuous text phrases in 19 different font sizes, and subjects are timed as they read progressively smaller lines of text. Photostress recovery time was determined by exposing the undilated study eye to a penlight (5000–8000 lux) for 45 seconds and measuring the time until the subject could read 1 Early Treatment Diabetic Retinopathy Study (ETDRS) line above his or her BCVA. Dark adaptation speed was assessed using the AdaptDx dark adaptometer (MacuLogix, Hummelstown, PA) that measures the sensitivity and recovery of rod photoreceptors after bleaching with a 5.8×10^4 cd/m^2 scotopic second flash.[19] The rod intercept value was used to characterize dark adaptation speed. This method provides information about the area of the retina that was not damaged by PRP.

Fundus photography and spectral-domain optical coherence tomography (SD OCT) were performed on all study eyes. A 135° 2-wavelength scanning laser ophthalmoscope image centered on the macula was obtained of each study eye using an Optos camera (Optos, Dunfermline, United Kingdom). Diabetic retinopathy was graded as no DR, mild or moderate nonproliferative DR, or PDR by 2 independent graders (T.W.G. and M.S.S.). Additionally, a 20°×20° SD OCT cube scan (97 sections, 512 A-scans in each B-scan, and 3.87-μm axial resolution) of the macula of the dilated study eye was obtained with a Spectralis SD OCT (Heidelberg Engineering, Heidelberg, Germany). Retinal layer thicknesses in macular cube scans were analyzed in 9 Early Treatment Diabetic Retinopathy Study areas: a 1-mm central circle at the fovea, surrounded by a 3-mm inner ring and a 6-mm outer ring. Both the 3- and 6-mm rings were sectioned further into superior, nasal, inferior, and temporal quadrants. In each retinal B-scan, we measured the thicknesses of the NFL, ganglion cell layer (GCL) plus inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer plus outer nuclear layer (OPL+ONL), the inner segment/outer segment (IS/OS) photoreceptor layer, and the RPE.