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Reading deficits in diabetic patients treated with panretinal photocoagulation and good visual acuity

Amro Omari, Leslie M Niziol and Thomas W Gardner

Department of Ophthalmology and Visual Sciences, W. K. Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan, USA

ABSTRACT.

Purpose: **Patients with proliferative diabetic retinopathy (PDR) treated with panretinal photocoagulation (PRP) can have abnormal visual functioning that may be missed by Snellen visual acuity alone. We investigated reading deficits in patients treated with PRP for PDR using the Minnesota reading (MNREAD) test.**

Methods: **Thirty patients treated with PRP and 15 controls underwent best-corrected visual acuity (BCVA), the MNREAD, frequency doubling perimetry (FDP), and fundus photography. Panretinal photocoagulation (PRP)-treated subjects were compared to controls on MNREAD results by two-sample *t*-tests and Wilcoxon tests and Pearson correlations were used to assess the association between performance on MNREAD and other central visual function tests within PRP subjects.**

Results: **Panretinal photocoagulation (PRP)-treated patients had reduced MNREAD acuity ($p < 0.0001$) and increased critical print size ($p = 0.01$) compared to controls but not a significantly reduced maximum reading speed ($p = 0.06$). Logmar MNREAD acuity was strongly positive correlated with logMAR BCVA ($r = 0.58$, $p = 0.0098$) and strongly negatively correlated with FDP foveal threshold ($r = -0.63$, $p = 0.0030$). Maximum reading speed was positively correlated with FDP foveal threshold ($r = 0.57$, $p = 0.0143$) and FDP mean deviation ($r = 0.51$, $p = 0.0432$). Visual acuity did not correlate with the sensitivities on the FDP.**

Conclusion: **The MNREAD test reveals that PRP reduces reading ability and other aspects of macular function, and thus provides new understanding of how vision-related quality of life is impaired. These findings may lead to improved means to evaluate and enhance vision following treatment for PDR.**

Key words: diabetes – diabetic retinopathy – minnesota reading test – panretinal photocoagulation

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Introduction

Proliferative diabetic retinopathy (PDR) is characterized by retinal neovascularization (Duh et al. 2017), and its treatment commonly includes panretinal photocoagulation (PRP) (Martinez-Zapata et al. 2014; Bressler et al. 2017; El Rami et al. 2017). Treatment outcomes are typically evaluated based on central visual acuity (VA) (Stewart 2016), but other measures of visual function (Spreng et al. 2018), including tests of contrast sensitivity, reading ability, visual field sensitivities and vision in dim light conditions provide more comprehensive information about macular function (Boynton et al. 2015). As such, patients often feel their reduced vision negatively impacts their quality of life (QOL), which may be overlooked when vision assessment is based on acuity alone. Recent gene therapy studies have demonstrated the ability to restore central vision in persons with advanced retinal degeneration (Bainbridge et al. 2015; Russell et al. 2017). Eyes treated with PRP exhibit reduced peripheral and macular function and fundus lesions similar to those in eyes with retinitis pigmentosa. Similar future efforts to improve vision in persons who have undergone PRP will require comprehensive measures of visual function and impact on the QOL to determine successful responses to therapy.

Reading charts have been used to quantify central visual function for retinitis pigmentosa, macular degeneration and glaucoma (Virgili et al. 2004; Ishii et al. 2013; Radner 2017; Varadaraj et al. 2018). Unlike Snellen VA charts that use single letter optotypes, reading charts provide more information on visual function by using sentences in a logarithmic scale. In addition to the reading acuity, reading tests provide the maximum reading speed and the critical print size that can assess the ease with which patients can read. Previous studies have also correlated reductions in reading speeds

with reduced sensitivity on microperimetry (Edington et al. 2017), suggesting that reading tests uncover other aspects of visual dysfunction. Moreover, reading is more representative of the impact of vision on the QOL than Snellen VA, because it reflects real world function in patients with macular pathologies (Jackson & Owsley 2003; Kanonidou 2011). It also tests vision at a different distance than standard Snellen VA. To our knowledge, reading ability as measured by the Minnesota reading (MNREAD) test has not been evaluated on persons who have undergone PRP.

Boynton et al. (2015) initially described this cohort's performance on a variety of visual function tests in comparison with non-diabetic controls. Over two-thirds of the patients had a VA of 20/20 or better but severe deficits on photopic visual fields and dark-adaptation testing. Furthermore, many patients at follow-up have admitted that they gave up reading due to their retinopathy. Therefore, it is apparent that Snellen VA does not adequately describe visual function related QOL in this cohort. In this analysis, we investigated both the performance on the MNREAD in the PRP-treated subjects compared to controls and the relationship between results of the MNREAD test with other deficits of macular visual functioning in PRP-treated subjects. Our central hypothesis is that PRP-treated subjects will have a significantly reduced performance on the MNREAD (as manifested by a reduced reading acuity, slower maximum reading speed, and larger critical print size) compared to controls. We also predicted that the reduction in MNREAD parameters would correlate with reductions on other macular function tests such as Snellen VA and sensitivity on the frequency doubling perimetry (FDP).

Materials and Methods

This study was conducted at the University of Michigan W. K. Kellogg Eye Center. The study adhered to the tenets of the Declaration of Helsinki, and was approved by the University of Michigan Medical School Institutional Review Board (HUM 60596). Diabetic patients with PDR treated by PRP and age-matched controls were enrolled into the study after a screening visit in the retina clinic. Signed informed consent was acquired from all participants before research testing.

Patient enrollment and evaluation

Subject enrollment and the eligibility criteria were the same as the study by Boynton et al. (2015). Briefly, the PRP study group enrolled adults with type 1 or 2 diabetes mellitus who had PDR treated with PRP at least 6 months before enrollment into the study. Inclusion criteria for the study group were the following: (1) age ≥18 years old; (2) diabetes mellitus as defined by the American Diabetes Association diagnostic criteria; (3) treatment of PDR by PRP ≥ 6 months prior to enrollment; (4) stable PDR after the PRP treatment; and (5) best-corrected visual acuity (BCVA) of 20/400 or better in the study eye. If both eyes were eligible, the one with the worst BCVA was chosen as the study eye.

Exclusion criteria for the PRP study group were the following: (1) any retinal or ocular disease other than PDR; (2) any significant cystoid macular oedema; (3) any high-risk ocular neovascularization; (4) history of drug or alcohol abuse; (5) any neurologic or systemic disease that could impair vision, other than diabetes; (6) any systemic or ocular medication that could affect vision; (7) hospitalization within 1 month of screening; (8) difference in two recent consecutive haemoglobin A1c measurements ≥5%; (9) unable to give informed consent or unable to complete testing; (10) spherical equivalent > ±6.00 dioptres; (11) pregnant or nursing; (12) blood pressure ≥ 180/100 mmHg.

The study also enrolled 15 age-matched controls enrolled as volunteers. Inclusion and exclusion criteria were the same for controls, except that they had no condition that could affect vision.

All subjects underwent a comprehensive ophthalmologic examination including a slit lamp exam and dilated fundus exam with a 90 D lens (performed by T.W.G). Age and demographic data were taken to allow age matching for comparisons between groups. Medical and ocular histories were taken to ensure that subjects met enrollment criteria and that we knew the type and duration of diabetes in PRP subjects. Optimal refraction was assessed manually using the phoropter, and measurement of BCVA was done using the electronic VA tester with Snellen chart line testing. LogMAR VA was recorded and used for statistical analysis. A blood sample was obtained from each participant to measure glycosylated haemoglobin (HbA_{1c}) levels if they had not been measured within the last 6 months.

If patients were eligible and consent was given, screening was completed and patients returned for a study visit. During this visit, functional vision tests were performed in the same order, which included MNREAD testing and FDP. Phenotyping included fundus photography.

Minnesota reading test

The MNREAD test is performed with a single reading card that contains multiple 10-word text phrases, each in different font sizes, and with the characters and lines equally spaced. The largest font size of a phrase corresponds to a Snellen line of 20/400 and the smallest font size corresponds to a Snellen line of 20/06. Subjects underwent MNREAD testing in a designated room where light intensity was calibrated to standard room light conditions at a luminescence of around 100 cd/m^2. The reading card was placed 40 cm from the subject and vision was corrected to that distance. Subjects read aloud progressively smaller MNREAD text phrases starting at 20/400, and decreasing in logMAR increments of −0.1, using only the study eye. While subjects read a phrase, the other phrases were blocked out so that they could not read ahead. The amount of time to read each phrase was recorded, as well as the number of words read correctly and incorrectly. Different MNREAD cards were used based on whether the study eye was a right or left eye. All the characteristics of the cards were the same, but the letters had a different orientation.

Three variables were calculated from testing results: the MNREAD testing acuity, maximum reading speed, and the critical print size. The MNREAD testing acuity was determined as the phrase with the smallest font size where a patient could read all the words, even if they read some of them incorrectly. If the subject did not read any of the words correctly, then we recorded the MNREAD acuity as the phrase above. The reading speed for a standard 10-

word phrase (600) was calculated using the following formula:

$$\text{Reading speed} = (60 \times (10 - \text{number words read incorrectly})) / \text{time (seconds)}.$$

The maximum reading speed was deduced as the fastest speed at which the patient could read of all the lines that were successfully read.

The critical print size was the MNREAD phrase with the smallest font that the patient could read at the maximum reading speed. The font size was converted to a corresponding Snellen VA line that is automatically computed on the MNREAD reading cards. The critical print size served as a surrogate for the minimum size of the letters that the patient can read at the maximum reading speed, thereby indicating the ease with which subjects can read.

FDP

Participants performed FDP with the 24-2 protocol using the Matrix perimeter (Carl Zeiss Meditec, Dublin, CA, USA). The reliability criteria used were <33% fixation errors, <33% false positive errors, and <33% false negative errors. The FDP 24-2 strategy was performed on the Humphrey Matrix 715 Visual Field Analyzer® (Zeiss, Oberkochen, Germany). The stimulus was 0.25 cycles per degree monochrome sinusoidal grating of vertical grey stripes that was phase reversed at 18 Hz (Leeprechanon et al. 2007; Joltikov et al. 2017). The minimum contrast threshold of the 5° diameter stimulus was measured at each of 55 test locations (Joltikov et al. 2017). The testing time was approximately 5 min per eye. Subjects wore their own distance prescription glasses if needed. Foveal sensitivity, mean deviation (MD), and pattern standard deviation (SD) were recorded. Foveal sensitivity represents the minimum intensity of the stimulus at the fovea required for a patient response. Pattern SD measures localized deficits by factoring out generalized reductions in sensitivity.

Fundus photographs

A 200-degree colour photograph centred on the macula was taken of each study eye using a non-simultaneous stereoscopic, on-axis, non-steered, 200° ultrawide field imaging on the Optos camera (Optos®, Dunfermline, UK).

Statistical analysis

Descriptive statistics were used to summarize patient demographics, clinical measures of the study eye, tests of macular function and MNREAD testing performance, for the PRP study subjects and controls. Differences between PRP study subjects and controls were tested with two-sample *t*-tests and Wilcoxon tests for continuous measures, and with chi-square and Fisher's exact tests for categorical measures. Within the PRP study group, scatterplots and Pearson's correlations (*r*) were used to assess the association between performance on MNREAD testing with other visual function parameters. All measures of VA were converted to LogMAR (Holladay 1997) for analysis. p-values were adjusted for multiple comparisons with the Holm method. Associations were considered statistically significant when p-value <0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Thirty study patients who had PRP to treat their PDR and 15 age-matched, healthy controls were enrolled in this study. Table 1 compares the demographics of the PRP and control subjects. Panretinal photocoagulation (PRP) patients and controls were age-matched (mean ± SD; 58.6 ± 13.4 and 59.8 ± 17.8 years, respectively; p = 0.79) and had a similar gender distribution (both 60% male, p = 1.00). Groups were similar with respect to intraocular pressure (PRP group: 15.7 ± 2.8 mmHg; control group: 15.0 ± 3.7 mmHg; p = 0.46). The PRP-treated group had higher haemoglobin A_{1C} (7.4% ± 1.2 versus 5.5% ± 0.3, respectively) and a worse VA (0.17 ± 0.19 LogMAR units versus 0.08 ± 0.10 LogMAR units, respectively, as measured by Snellen). The PRP-treated group had an average diabetes duration of 36.3 years (SD = 12.6) and their PRP was an average of 13.3 years prior to testing (SD = 8.6), consistent with their inactive retinopathy.

MNREAD

Panretinal photocoagulation (PRP)-treated subjects had worse performance on the MNREAD test than controls for two of the three MNREAD testing measures (Table 2). The PRP group had significantly worse MNREAD acuity (p < 0.0001), corresponding to a Snellen acuity of 20/32 versus 20/20 for controls. There was also an increase in the critical print size for PRP-treated subjects compared to controls (p = 0.01), corresponding to a Snellen letter size of 20/200 for PRP subjects and 20/100 for controls. Although on average PRP-treated subjects exhibited reduced reading speed relative to controls, the difference was not statistically significant (157.1 ± 30.0 versus 170.9 ± 18.1

Table 1. Descriptive statistics summarizing the differences between the PRP and control subject samples.

	PRP group (*n* = 30) # (%)	Control group (*n* = 15) # (%)	p-value*
Male	18 (60)	9 (60)	1.0
Female	12 (40)	6 (40)	
	Mean (SD)	Mean (SD)	
Age (years; SD)	58.6 (13.4)	59.8 (17.8)	0.80
Duration diabetes mellitus (years)	36.3 (12.6)	NA	NA
Years Since PRP	13.3 (8.6)	NA	NA
Haemoglobin A_{1C} (%)	7.4 (1.2)	5.5 (0.3)	0.0001
LogMAR Snellen visual acuity	0.17 (0.19)	−0.08 (0.10)	0.0001
IOP (mm Hg)	15.7 (2.8)	15.0 (3.7)	0.46

ETDRS = Early Treatment Diabetic Retinopathy Study, IOP = intraocular pressure, PRP = panretinal photocoagulation, SD = standard deviation.
* Two-sample *t*-test for age, IOP, LogMAR visual acuity; two-sample Wilcoxon test for haemoglobin A1C; chi-square test for gender.

Table 2. Comparison of performance on the MNREAD testing and FDP between PRP-treated and control subjects.

	PRP group (n = 30) Mean (SD)	Control group (n = 15) Mean (SD)	p-value*
logMAR reading acuity	0.23 (0.27)	−0.05 (0.05)	0.0001
Maximum reading speed (characters/second)	157.1 (30.0)	170.9 (18.1)	0.062
LogMAR critical print size	0.98 (0.26)	0.75 (0.32)	0.013
FDP foveal sensitivity (decibels)	22.1 (7.4)	30.0 (5.1)	0.0002
FDP 24-2MD (decibels)	−8.20 (5.76)	1.09 (2.52)	0.0001

FDP = frequency doubing perimetry, MD = mean deviation, PRP = panretinal photocoagulation, SD = standard deviation.
* Two-sample t-test for maximum read speed and LogMAR critical print size; two-sample Wilcoxon test for LogMAR reading acuity. Two-sample Wilcoxon test for FDP foveal sensitivity and FDP MD.

characters/second, respectively, p = 0.06). Collectively, these results reveal significant impairment of reading ability in the PRP-treated individuals.

FDP

Table 2 also contains central visual field testing results on the FDP in PRP and control groups. Panretinal photocoagulation (PRP)-treated subjects showed reduced foveal threshold (22.1 ± 7.4 dB versus 30.0 ± 5.1 dB; p < 0.0001), and reduced MD on the FDP 24-2 (−8.20 ± 5.76 dB versus 1.09 ± 2.52 dB; p < 0.0001).

Correlations between MNREAD and other functional parameters

Table 3 and Fig. 1 summarize the association between performance on MNREAD testing and other central visual function tests in PRP-treated subjects. The logMAR reading acuity was significantly correlated with performance on central vision tests. Specifically, a strong positive correlation was noted with logMAR Snellen VA (r = 0.58, p = 0.0007), and strong negative correlations were noted with FDP foveal threshold (r = −0.63, p = 0.0002). The maximum reading speed correlated positively with the performance on FDP foveal threshold (r = 0.57, p = 0.0011), and FDP 24-2 MD (r = 0.51, p = 0.0036). The Snellen VA did not correlate with either the FDP foveal threshold or FDP MD. The critical print size correlated only with Snellen logMAR VA (r = 0.47, p = 0.0085), but this finding was not significant after adjustment for multiple comparisons (adjusted p = 0.093).

Discussion

Our study shows for the first time that PRP-treated patients have reduced reading performance on the MNREAD compared to controls. Although these deficits are expected due to a slightly worse VA in the PRP-treated group, the MNREAD test provides more information on central visual function than standard Snellen VA. First, the MNREAD assesses performance on a task that many patients with macular diseases, such as age-related macular degeneration, have difficulty with and believe is important for their QOL (Patel et al. 2011). The reading speed and critical print size yield more information about how easy or difficult subjects find reading. There were many examples of patients who read on the same acuity line but had very different reading speeds and critical print sizes (Fig. 2), suggesting that they have different levels of difficulty with reading. Furthermore, the deficits on MNREAD testing were associated with multiple deficits in central visual functioning, including VA, FDP MD, and FDP foveal threshold. The Snellen VA, however, did not have significant correlations with FDP sensitivities, suggesting that the MNREAD provides more information about global macular functioning. We advise clinicians to counsel patients undergoing PRP that they may experience difficulties with reading over time.

Notable strengths of this study are that we were able to detect significant reading deficits in PRP-treated subjects as compared to controls, and show that this test provides more information about visual functioning than standard Snellen VA alone. Weaknesses of this study include the small number of subjects, which may explain why maximum reading speed was not significantly reduced. Also, we did not have

Table 3. Correlation between performance on MNREAD and other visual function parameters, within PDR subjects treated with PRP (n = 30).

	LogMAR Snellen VA	FDP foveal threshold (dB)	FDP 24-2 MD (dB)
LogMAR MNREAD acuity	**0.58 (p = 0.0007) (adj p = 0.0098)**	**−0.63 (p = 0.0002) (adj p = 0.003)**	−0.43 (p = 0.0166) (adj p = 0.1149)
MNREAD maximum reading speed (characters/second)	−0.35 (p = 0.0595) (adj p = 0.4165)	**0.57 (p = 0.0011) (adj p = 0.0143)**	**0.51 (p = 0.0036) (adj p = 0.0432)**
LogMAR MNREAD critical print size	0.47 (p = 0.0085) (adj p = 0.0935)	−0.02 (p = 0.9283) (adj p = 1.0000)	0.09 (p = 0.6505) (adj p = 1.0000)

The correlation coefficient is listed with the p-value in parentheses. p-values adjusted for multiple comparisons by the Holm method are also provided. Statistically significant associations are highlighted in bold.
FDP = frequency doubling perimetry, MD = mean deviation, MNREAD, Minnesota Reading Test, PDR = proliferative diabetic retinopathy, PRP = panretinal photocoagulation, VA = visual acuity.

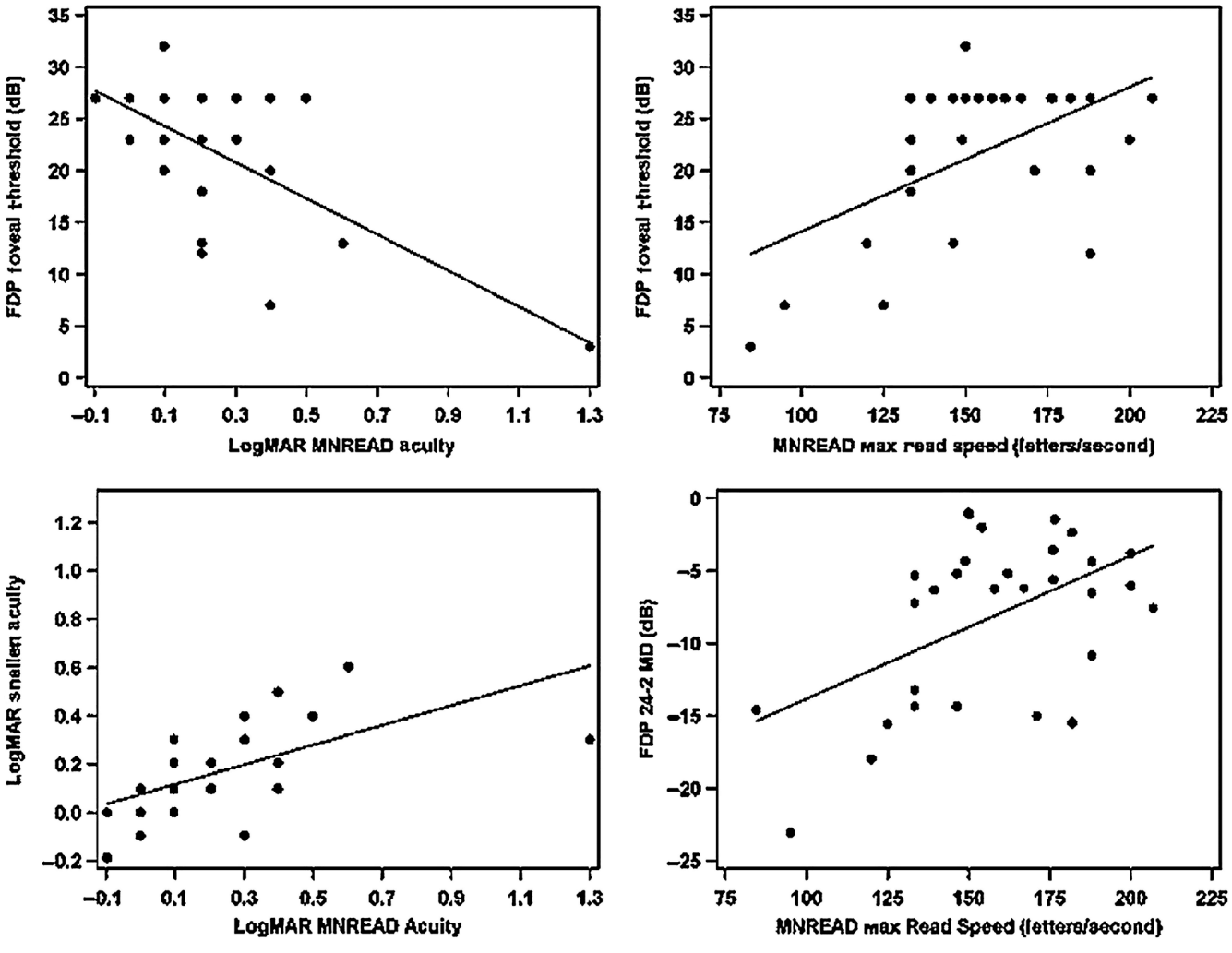

Fig. 1. Scatterplots displaying the relationship between performance on the Minnesota reading test and tests of central visual function, within proliferative diabetic retinopathy subjects treated with panretinal photocoagulation (n = 30).

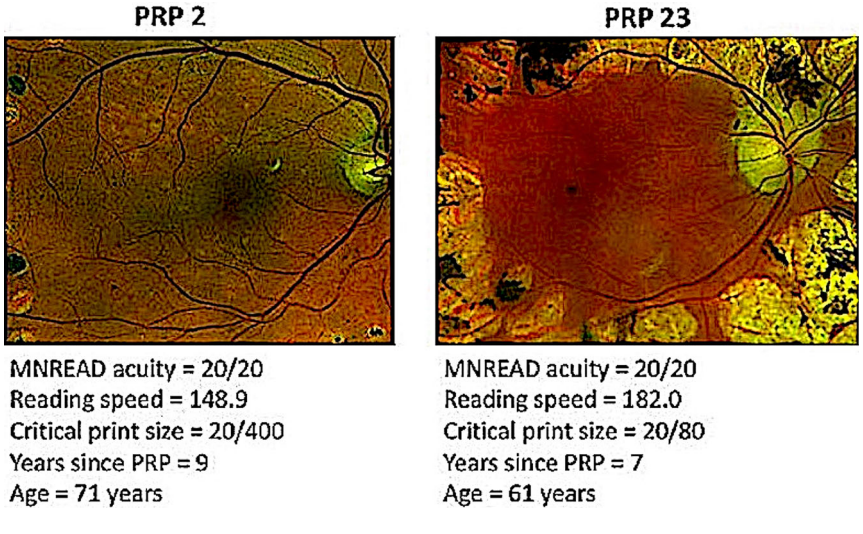

Fig. 2. Two panretinal photocoagulation (PRP) patients with the same Minnesota reading acuity and similar appearance of the macula on fundus photo. However, PRP treated subject 2 has a significantly reduced reading speed and increased critical print size as compared to PRP treated subject 23, suggesting that PRP subject 2 has much more difficulty with reading.

patients with PDR but no panretinal photocoagulation as a control to compare the effects of PRP alone. However, all of the PRP patients had quiescent retinopathy, so this is unlikely to have had an effect on the results of our study. Another limitation was the heterogeneity in both the length of time that patients had diabetes, and the number of years after they had PRP. We did not find any significant associations between any MNREAD parameters and either age or duration of diabetes. However, the number of years since PRP was negatively correlated with the maximum reading speed (r = −0.605, p = 0.002) but not with logMAR MNREAD acuity.

Clinical trials for diabetic retinopathy (Cai & Bressler 2017) and retinal dystrophies (Neto et al. 2017; Schatz et al. 2017) employ endpoints for

central vision function aimed at preserving and/or improving Snellen VA, but patients may have multiple visual function deficits that are missed when Snellen VA is used alone. Therefore, in developing future clinical trials to improve or restore central visual function for those with PDR treated by PRP, more comprehensive measures to quantify improvement and vision-related QOL are needed. Reading tests like the MNREAD may provide another endpoint for measuring visual function in therapeutic trials. Furthermore, reading tests may easily be integrated into clinical practice as an objective measure of central visual function.

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Correspondence:
Amro Omari
Kellogg Eye Center
1000 Wall Street, Ann Arbor
Michigan 48150
USA
Tel: +1 248-909-9230
Fax: +1 734-615-2734
Email: aaomari@med.umich.edu

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