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Suitability and Repeatability of a Photostress Recovery Test Device, the Macular Degeneration Detector (MDD-2), for Diabetes and Diabetic Retinopathy Assessment.

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SUITABILITY AND REPEATABILITY OF A PHOTOSTRESS RECOVERY TEST DEVICE, THE MACULAR DEGENERATION DETECTOR (MDD-2), FOR DIABETES AND DIABETIC RETINOPATHY ASSESSMENT

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Background: Diabetic retinopathy can result in impaired photostress recovery time despite normal visual acuity and fundoscopic appearance. The Macular Degeneration Detector (MDD-2) is a novel flash photostress recovery time device. In this study, we examine the repeatability of the MDD-2 in normal and diabetic subjects.

Methods: One hundred and ninety one (90 women, 101 men) subjects were recruited and divided into 1 of the 3 study groups (normal controls, n = 40; diabetes no retinopathy, n = 98; nonproliferative diabetic retinopathy, n = 53). Photostress recovery time was measured three times in the study eye using the MDD-2, each measurement separated by a 5-minute interval.

Results: Repeated measures analysis of variance revealed no statistically significant learning or fatigue effects on intrameasurement repeatability for any group. Photostress recovery time measures were broadly similar and typically not statistically significantly different between study groups. The coefficient of repeatability reached clinically acceptable levels once the initial photostress recovery time measure, which demonstrated increased variability and latency compared with all subsequent measures, was excluded.

Conclusion: The MDD-2 seems to provide repeatable photostress recovery time measurements among naive diabetic subjects. The device does not, however, seem capable of differentiating normal and nonproliferative diabetic eyes, and would not be suitable for inclusion in diabetic retinopathy screening protocol.

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The global population is aging and life expectancy is increasing. Current lifestyle habits are leading to an epidemic in obesity and cardiovascular disease, including diabetes.[1–5] Even in developing countries, where diabetic retinopathy (DR) has not been a historically significant cause of blindness, the demographic change and westernization of dietary and lifestyle habits are creating an emerging disease profile that includes diabetes and DR.[6–8]

The development of ocular complications in diabetes is related to disease control and longevity. After 20 years, more than 75% of patients will have some form of DR.[9] It has been suggested, however, that visual loss associated with the development of DR could be reduced for the majority of patients with proper and vigilant monitoring of diabetic eyes, and prompt treatment initiation where required.[10] Earlier detection and more effective management can delay disease progression, prevent debilitating sight loss, and thereby reduce future dependency on health care services. This is particularly important in light of the likely increase in visual impairment and blindness set to accompany increasing diabetes prevalence,[11] and

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the substantial personal and societal (including economic) costs associated with such avoidable visual impairment.[12] The possibilities for retarding disease progression including recent advances in pharmacologic management of diabetic maculopathy, best applied at the earliest stages of the development of abnormal pathology, further increase the priority that should be afforded to effective disease monitoring.[13–15]

Diabetic maculopathy is the most common cause of visual loss in diabetic patients. Visual acuity represents the most widely used test of visual, and in particular macular, function. Visual acuity alone, however, is an inadequate biomarker of visual function in macular disease, and can be relatively insensitive to the impact of functional deterioration in the early stages of diabetic macular disease.[16,17] Alternative tests of visual function have, however, proved capable of isolating macular functional loss in cases where visual acuity remains normal, including contrast sensitivity,[17–20] color vision,[21,22] and chromatic sensitivity.[23,24] In particular, photostress recovery has also been shown to be adversely affected by diabetic macular disease.[25–27]

Photostress recovery time (PSRT) describes the time required to regain normal visual function following exposure to intense light that bleaches the visual pigments and saturates the response of the macular photoreceptors, and thereby effects a transient loss of vision.[28] Normal recovery is dependent on the underlying retinal photoreceptor and pigment epithelium function.[29] The Macular Degeneration Detector (MDD-2) is a novel flash photostress recovery device. This device has previously been shown to be capable of detecting functional vision loss in age-related macular degeneration and diabetic maculopathy.[25] It has also been shown to provide reproducible measurements in a young healthy population.[30] No previous study, however, has explored the learning effect and repeatability of test measures among a diabetic population without maculopathy. In this study, we examine the repeatability of the MDD-2 in such a population in comparison to an age-matched normal population, as a means to determine 1) whether the device can provide clinically acceptable repeat test measures, and 2) whether diabetes, or nonproliferative DR in the absence of maculopathy, has an effect on PSRT compared with normal controls (NCs).

Materials and Methods

One hundred and ninety one subjects (90 women, 101 men) participated in this study which received local Research Ethics committee approval. Informed consent was obtained from each volunteer, and the experimental procedures adhered to the tenets of the Declaration of Helsinki.

Diabetic subjects were recruited from eligible retinal clinic attendees at the Mater Misericordiae hospital, Dublin, Ireland. Normal (nondiabetic) subjects were recruited at the National Optometry Centre at Dublin Institute of Technology, Dublin, Ireland. Subjects were assigned, on the basis of their diabetic and ocular health status, to 1 of the 3 study groups: diabetes no retinopathy, n = 98 (48 women, 50 men); nonProliferative DR, n = 53 (20 women, 33 men); NC, n = 40 (22 women; 18 men). The following diabetes relevant information was recorded for each diabetic participant: diabetes duration (years), diabetes type, diabetes medication, and retinopathy grade (graded according to modified two-field Early Treatment Diabetic Retinopathy Study protocol; grade range, R0 M0–R2 M0).[31]

Generic inclusion criteria were as follows: subjects were to be over 18 years of age, and have LogMAR visual acuity better than 0.2 (6/9) in the study eye; and subjects were required to be able to identify the baseline numeric stimulus presented by the device without their refractive correction. For normal subjects, exclusion criteria included any sign of retinal or ocular abnormality and the presence of Type 1 or Type 2 diabetes. Subjects with diabetes were excluded if they exhibited signs of ocular comorbidity (e.g., age-related macular degeneration, glaucoma, cataract), had previously undergone any form of treatment for DR or diabetic maculopathy, or if they exhibited any signs of proliferative retinopathy or maculopathy.

A computer generated LogMAR test chart (Thomson 2000 Pro; Thomson Software Solutions, Hatfield, United Kingdom) was used to determine LogMAR acuity. Iris color was recorded using an iris color classification scheme, with iris color matched to standard color photographs and classified into one of the five color categories (gray, blue, green, light brown, brown) as described by Seddon et al.[32] Slit-lamp indirect ophthalmoscopy and retinal photography (Zeiss Visucam Pro NM [Carl Zeiss Meditec, Germany], 45° field, 1 disk and 1 macula centered photograph) was conducted for all subjects.

Photostress recovery time was measured using the MDD-2 Macular Degeneration Detection device (Icandy Digital, LLC, FL). The MDD-2 is a relatively simple device, comprising a spectrally broadband xenon flash light source (with good short-term [$\sim$1%] and long-term [$\sim$3%] output stability), a UV and IR filter, and focusing (+8 diopters) lens. The test involves accurate identification (postflash photostress) of a large (0.41 radian/23.49° angular subtense) randomly generated number between 0 and 9. The target is viewed through a 12-mm central aperture in the

flash tube. The 200-μsecond duration flash is generated by a xenon flash source, mounted inside the flash tube within the subject's field of view, extending across an angular subtense of 38° of visual angle.

All subjects recruited into the study were naive to the MDD-2 test. The nature of the test and stimuli were described in detail to each subject, and the subject was requested to confirm their understanding of the task. The flash tube was positioned against the test eye, and the subject was required to correctly identify a baseline, prephotostress, numeric stimulus without their refractive correction. Subjects were instructed to fixate centrally at the position of the prebleach stimulus, and to avoid blinking at the onset of the photostress flash. When ready to commence the test proper, the subject pressed a button on the device that initiated three concurrent processes: the arc flash photostress, the photostress recovery timer, and a new random number, which was displayed continuously until a recognition response was given. The subject was required to verbally identify the new number, and simultaneously, to press the same button on the device to cease the test at the instant when vision recovered sufficiently to allow number recognition.

The study eye was selected as the eye with better visual acuity, or in cases of equal acuity, the right eye was selected as standard. The PSRT measurement was conducted in the study eye, and repeated on two further occasions, each separated by a 5-minute interval, providing a set of 3 PSRT measures (PSRT 1, PSRT 2, and PSRT 3). Incorrect identification of the test stimulus, at baseline, resulted in exclusion from the study. A single incorrect response during the test phase was permitted (result discarded and test repeated after a 5-minute interval), but a second incorrect response resulted in exclusion from the study. Where both eyes met the study inclusion criteria, PSRT measures were also recorded for the fellow eye to facilitate intereye comparison.

AQ : 2 The statistical software package SPSS (version 20; SPSS, Inc, Chicago, IL) was used for analysis. One-way analysis of variance was used to test for differences in study parameters between the groups. Repeated measures analysis of variance was used to test for learning or fatigue effects that might confound analysis of repeat measures in the study eye. Paired samples *t*-tests were used to test for PSRT differences between eyes. Pearson correlation coefficients were calculated to investigate the relationship between sequential measurements, and between eyes. Bland–Altman analysis and plots, and the limits of agreement, were used to quantify the agreement between repeat measures of PSRT.[33] Intrameasurement repeatability is expressed as a coefficient of repeatability, which was calculated as the standard deviation of the mean difference between measurements, and multiplied by 1.96. A 5% significance level was used throughout the analysis.

Results

All participants successfully identified the baseline pretest stimulus and advanced to the test phase of the investigation. Demographic and health status information, stratified according to study group, is presented in Table 1. T1

Intergroup Analysis

The mean (±standard deviation) visual acuity of each study group was: diabetes no retinopathy = logMAR −0.04 (±0.10); DR = logMAR −0.06 (±0.12); NC = logMAR −0.06 (±0.10). One-way analysis of variance revealed no statistically significant differences in sex ($P = 0.23$), iris color ($P = 0.34$), or visual acuity ($P = 0.70$) between the 3 study groups. Statistically significant differences were observed between groups, however, for age ($P < 0.01$) and diabetes duration ($P < 0.01$).

Mean (±standard deviation) PSRT for each of the 3 measurements in the study eye is presented in Table 2, T2 and demonstrates a trend toward improved PSRT with each sequential measurement in the study eye, with the most substantial improvement in PSRT immediately after the baseline test, between PSRT 1 and 2.

A statistically significant difference between groups was observed for PSRT 2 ($P = 0.01$), but not for PSRT 1 ($P = 0.13$) or PSRT 3 ($P = 0.09$) measures. Posthoc analysis (Scheffe test) isolated the variance in the PSRT 2 measure to the nonproliferative DR group, whose PSRT times were statistically significantly shorter than those of the NC ($P = 0.01$) and diabetes no retinopathy ($P = 0.04$) groups. No other pairwise differences were observed.

Intragroup Analysis

Repeated measures analysis of variance, using a general linear model approach with age, sex, and iris color as covariates, demonstrated no significant differences between repeat PSRT measures for all subjects combined and for individual study groups (Combined: $P = 0.86$; NC: $P = 0.51$; diabetes no retinopathy: $P = 0.74$; DR: $P = 0.20$—Greenhouse–Geisser correction for sphericity violation applied to all), which suggests the absence of a significant learning or fatigue effect, despite the gradual shortening of successive PSRT measures for each study group.

AQ : 9 Table 1. Demographic, Anthropometric and Health Status Information of Study Participants

Characteristic	NC (N = 40)	Diabetes No Retinopathy (N = 98)	Diabetes Nonproliferative Retinopathy (N = 53)	Statistical Significance (ANOVA), *P*
Sex (%)				
Male	45	51	62	0.23
Female	55	49	38	
Age (Mean ± SD, years)	56 ± 10	56 ± 16	49 ± 10	<0.01
Iris Color (%)				
Blue	43	56	53	0.34
Brown	15	16	19	
Hazel	25	14	11	
Green	17	14	19	
Diabetes Type (%)				
Type 1	0	DM = 20	55	<0.01
Type 2	0	DM = 80	45	
Diabetes Medication (%)				
Insulin	0	20	47	<0.01
Oral HypoG	0	64	40	
Combined	0	11	13	
None	100	5	0	
Diabetes Duration (Mean ± SD, years)	0	7.48 ± 6.62	15.63 ± 9.56	<0.01
Visual Acuity	–0.06 ± 0.10	–0.04 ± 0.10	–0.06 ± 0.12	0.70

ANOVA, analysis of variance; Oral HypoG, oral hypoglycemics; SD, standard deviation.

AQ : 3 Pearson's correlation revealed a moderate-to-strong and statistically significant relationship between the 3 PSRT measures in the study eye, for all subjects combined (r = 0.44–0.70, $P < 0.01$ for all; Figure 1) and for grouped comparisons (r = 0.39–0.71, $P = 0.01$–0.04). Paired samples *t*-tests revealed no PSRT differences between the study and fellow eye for any subgroup ($P > 0.05$ for all).

Bland–Altman analysis and plots were used to assess the agreement between successive PSRT measures in the study eye. The difference in mean recovery time between PSRT 2 and 3 in the study eye for all subjects (0.34 seconds), and limits of agreement are presented in Figure 2. The coefficient of repeatability for all subjects was 4.01 seconds, and for 59% of the subjects, the difference in recovery time between PSRT 2 and PSRT 3 was ≤1 second (≤2 seconds for 80% of the subjects), indicating good within-eye repeatability. The difference in mean recovery time and coefficient of repeatability, calculated for individual study groups, closely aligns to the overall figures (mean differences range, 0.2–0.6 seconds; coefficient of repeatability range, 3.92–4.12 seconds). When comparing PSRT 1 with PSRT 3, the mean difference between recovery time measures is significantly larger (range, 2.4–3.4 seconds across study groups) and the coefficient of repeatability is significantly poorer for the overall group at 6.29 seconds, and across individual study groups. In addition, differences between recorded recovery times were ≤1 second for only 38% of the subjects, indicating poorer repeatability when using the initial PSRT 1 as the baseline value.

Relationship Between Photostress Recovery Time and Other Variables

Independent samples *t*-tests revealed no significant effect of gender ($P = 0.26$–0.96 across study groups), iris color ($P = 0.06$–0.98 across study groups), or diabetes type ($P = 0.05$–0.36 across study groups) on any

Table 2. Mean PSRT For the First (PSRT 1), Second (PSRT 2), and Third (PSRT 3) Measurements in the Study Eye Across Study Groups

	NCs Mean ± SD (s)	Diabetes No Retinopathy Mean ± SD (s)	Diabetes Nonproliferative Retinopathy Mean ± SD (s)	Statistical Significance (ANOVA) *P*
PSRT 1	9.94 ± 3.56	8.98 ± 3.52	8.33 ± 3.27	0.13
PSRT 2	7.63 ± 2.85	7.16 ± 2.84	6.04 ± 1.44	0.01
PSRT 3	7.03 ± 2.41	6.77 ± 2.91	5.90 ± 2.36	0.09

ANOVA, analysis of variance; s, seconds; SD, standard deviation.

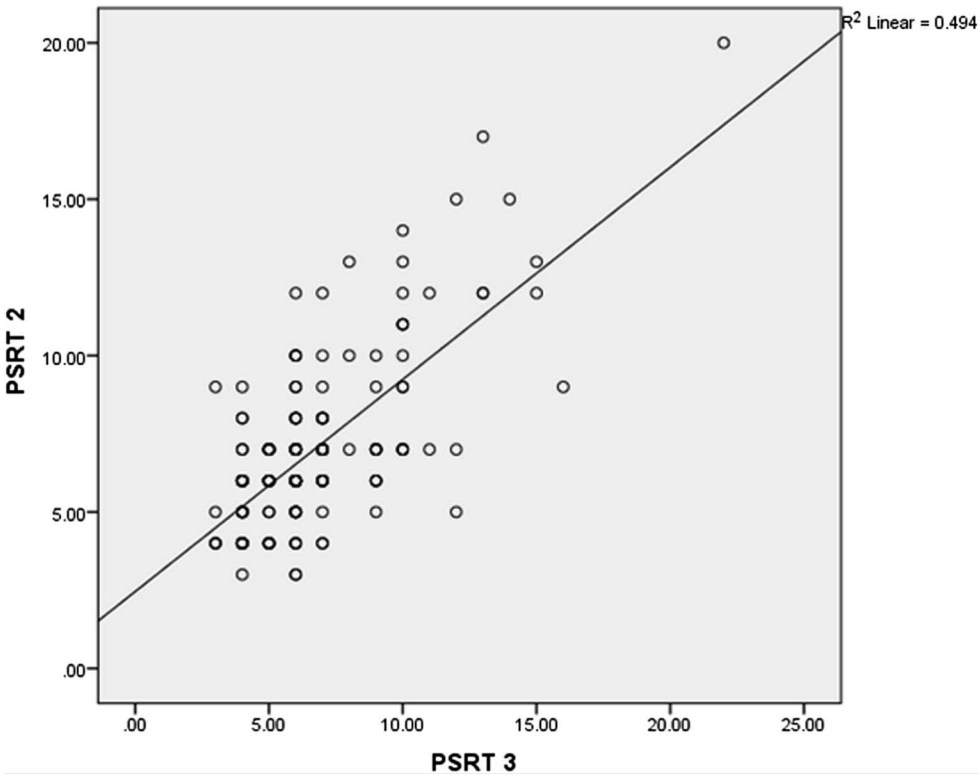

Fig. 1. Scatterplot demonstrating a strong and statistically significant correlation between PSRT 2 and PSRT 3 measures for all subjects.

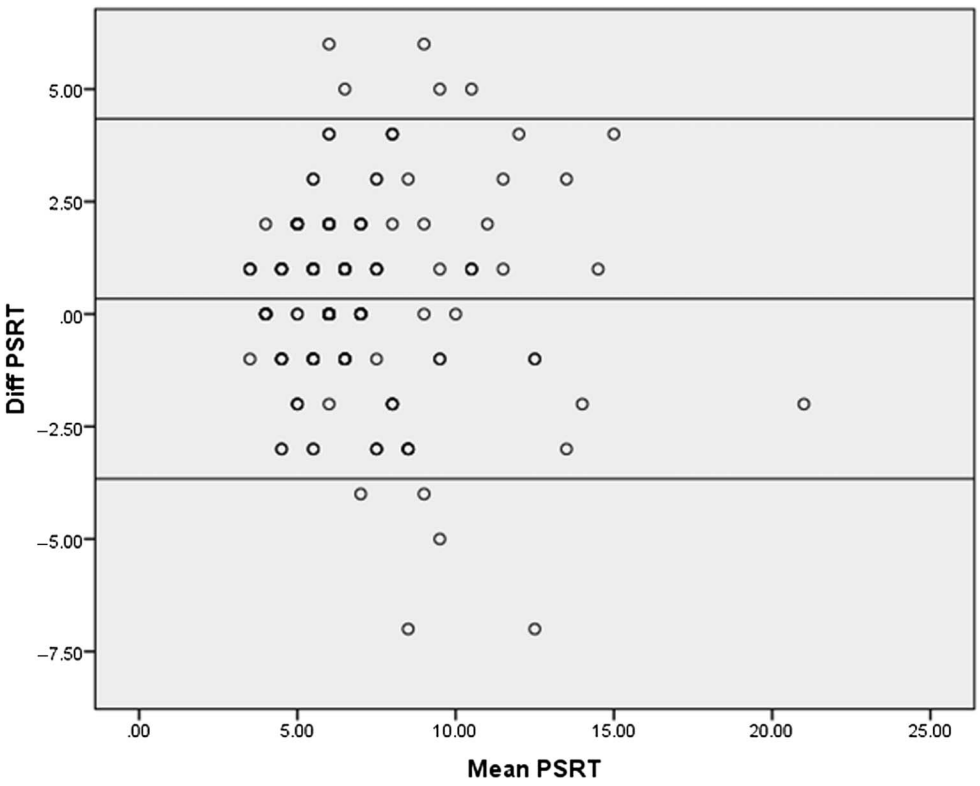

Fig. 2. Bland–Altman plot showing mean difference and 95% limits of agreement (0.34 ± 4.01 seconds) for repeat measurements in the study eye (PSRT 2 and PSRT 3) for the overall subject group.

of the 3 PSRT measures. Pearson's correlation, controlling for age and diabetes duration, revealed no significant relationship between PSRT and visual acuity overall (r = –0.05, $P = 0.54$) and across study groups (r = –0.03–0.09, $P = 0.41$–0.90). A statistically significant relationship was found, however, between PSRT and age overall, Figure 3 (r = 0.15–0.25, $P = 0.001$–0.04), and for the NC subgroup for all 3 PSRT measures (r = 0.37–0.45, $P = 0.003$–0.04). For diabetes subgroups, however, the relationship with age was not statistically significant ($P > 0.05$), other than for PSRT 1 measure in the DR subgroup (r = 0.34, $P = 0.02$).

F3

Discussion

Photostress recovery devices including the Scotometer,[34] the Brightness Acuity Test,[35] and the Eger Macular Stressometer,[36] have been developed for the assessment of ocular health but none have translated into routine clinical practice. More traditional devices including the ophthalmoscope and automated perimeter have also been adapted to provide PSRT measures,[37,38] but as of yet no device or technique has provided a universally acceptable and repeatable PSRT test that is capable of detecting disease presence or monitoring progression.

It has previously been shown that PSRT is adversely affected by conditions affecting the macula, including central serous retinopathy,[39] age-related macular degeneration,[25] and diabetic maculopathy.[25–27] Disruption of the retinal pigment epithelium–retina relationship, because of serous retinal detachment or macular edema for example, has been shown to be an important factor in the prolongation of PSRT in such macular disease.[40] Importantly, PSRT deficits have been observed in asymptomatic subjects where visual acuity is relatively preserved, indicating that a suitably designed test might provide an effective indicator of early disease or disease progression.[41]

This study is the first to explore the effect of diabetes including nonproliferative DR, on PSRT in comparison to NCs, and to evaluate the repeatability of PSRT measures among naive subjects with and without nonproliferative DR. The trend toward shorter PSRT measures on repeat testing is in general agreement with previous observations among younger participants, although the trends were not statistically significant in this study.[30] Similar trends have been observed for other devices, such as the Eger Macular Stressometer, which was shown to provide repeatable results and a subtle shortening of PSRT on repeat testing.[36] The general recommendation, however, that a single practice measure is sufficient to overcome any possible learning effect, and thereby facilitates a valid

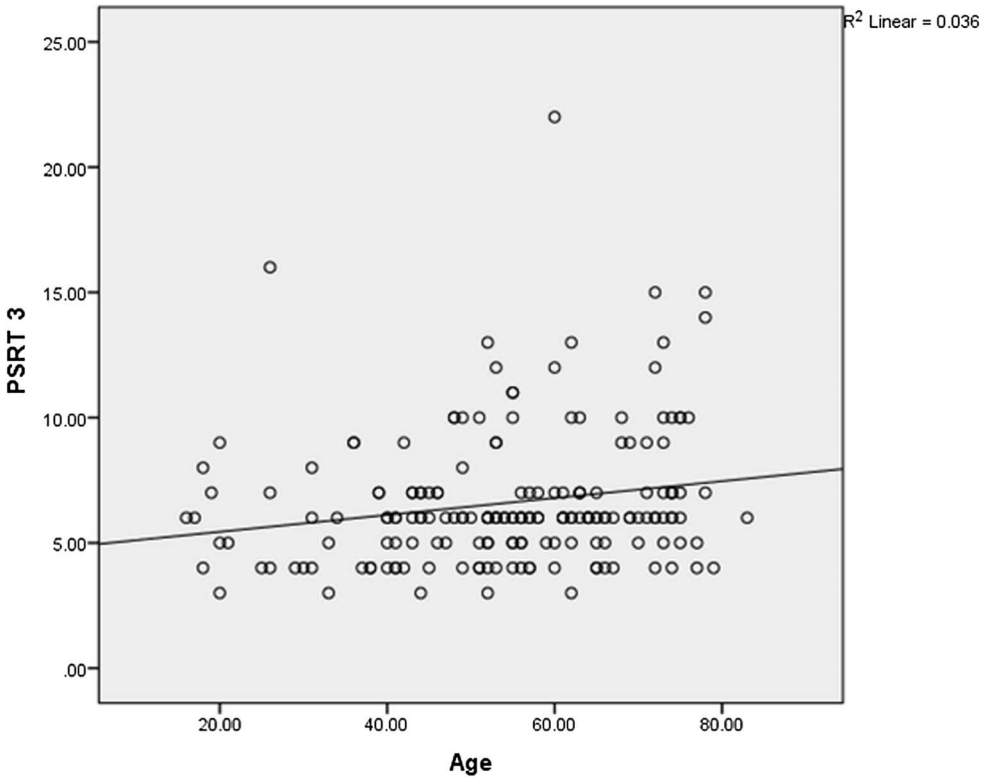

Fig. 3. Scatterplot demonstrating the relationship between age and PSRT 3 for the overall subject group.

baseline PSRT measure would seem applicable across both younger and older populations with and without nonproliferative DR.

It is interesting to note the shorter PSRT measures obtained in both diabetic subgroups, in particular the DR group, when compared with NCs for all three PSRT measures in the study eye. These differences were largely nonsignificant from a statistical perspective, and certainly insignificant from a clinical perspective. The observed differences most likely reflect the age differences observed between the study groups, given that the DR group was statistically younger than the other two groups, and that the NC subgroup exhibited a positive and significant association between PSRT and age. The age differences observed in the NC subgroup, and for the overall study sample, are in general agreement with previous observations on the relationship between PSRT measures and age.[34,41,42] In addition, the mean PSRT of the NC group observed herein (7.03 ± 2.41 seconds for PSRT 3) is longer than that previously observed in a younger (mean age, 35 years) normal cohort using the same device (5.11 ± 1.51 seconds for PSRT 3).[30] In the absence of any age-defined normative values for the device, such age dependency is of clinical relevance and suggests that eye health practitioners should interpret individual PSRT measures with caution, except where evidence exists of intereye asymmetry or elongation of PSRT over time on repeated measures. Of note, PSRT was also measured in the fellow eye in this study where eligible and no intereye differences were observed for any PSRT measure, which could prove diagnostic for unilateral disease.

These findings suggest that neither the diabetes condition itself nor the presence of nonproliferative DR as a consequence has an adverse effect on PSRT as measured using this flash recovery device. The device would not, therefore, seem capable of detecting the presence of diabetes or nonproliferative DR, or distinguishing such eyes as distinct from those of normal persons without diabetes. These findings are somewhat in agreement with previous observations of the impact of early DR on macular recovery dynamics made using alternate methods. The recovery times among subjects with background DR were comparable with those observed among NCs using a macular photostress test,[43] whereas the Eger Macular Stressometer proved similarly incapable of detecting functional losses associated with DR and other ocular diseases.[36] Macular recovery measured using nyctometry has, however, been shown to be impaired in early DR.[26,27]

The presence of diabetic maculopathy, however, has previously been shown to elongate PSRT measures and also to cause a prolongation of PSRT on 5-minute repeat testing. Among subjects with diabetic macular edema, PSRT measures using the same MDD-2 device averaged in excess of 20 seconds, more than 3 times the average measures obtained here, for diabetic subjects without maculopathy.[25] These allied findings suggest that the flash recovery device is sensitive to macular changes, and furthermore, that photostress losses in patients with diabetes are particular to the development of diabetic maculopathy, the most common cause of visual impairment. This is an important finding given that the instrument design is not intuitively suited to the isolation of macular function and recovery dynamics (the flash area [38°] and stimulus size [23°] extend significantly beyond the central macular area).

The findings of this study suggest that the MDD-2 may not be sensitive to diabetes, although the device provides repeatable PSRT measures among normal and diabetic subjects, with or without nonproliferative DR. As such, the value of the device would seem limited to the transition to more advanced diabetic or other forms of maculopathy, and therefore it is not of tremendous value as a DR screening tool. Further research is required to determine whether the device is a useful tool for longitudinal assessment of macular function in diabetes and other ocular diseases that present a risk to macular integrity, and whether it is useful as an outcome measure in evaluating therapeutic interventions.

Key words: photostress recovery, diabetic retinopathy, maculopathy, repeatability, MDD-2.

References

1. Resnikoff S, Pascolini D, Ety'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004; 82:844–851.
2. Aiello LM, Cavallerano JD, Aiello LP, et al. Diabetic Retinopathy. Retina Vitreous Macula. 1999;2:316–344. AQ : 4
3. World Health Organization. Prevention of Blindness From Diabetes Mellitus. Report of a WHO Consultation in Geneva, Switzerland, 9–11 November 2005. Geneva, Switzerland: World Health Organization; 2006. AQ : 5
4. Bhavsar AR, Emerson GG, Emerson MV, et al. Epidemiology of Diabetic Retinopathy. New York, NY: Springer; 2010.
5. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. JAMA 2010;304: 649–656.
6. Williams R, Airey M, Baxter H, et al. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. Eye (Lond) 2004;18:963–983.
7. Gupta R, Kumar P. Global diabetes landscape-type 2 diabetes mellitus in South Asia: epidemiology, risk factors, and control. Insulin 2008;3:78–94.
8. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes, estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053.

9. Barcelo A, Aedo C, Rajpathak S, et al. The cost of diabetes in Latin America and the Caribbean. Bull World Health Organ 2003;81:19–27.
10. Tapp RJ, Shaw JE, Harper CA, et al. The prevalence of and factors associated with diabetic retinopathy in the Australian population. Diabetes Care 2003;26:1731–1737.
11. Kelliher C, Kenny D, O'Brien C. Trends in blind registration in the adult population of the Republic of Ireland 1996-2003. Br J Ophthalmol 2006;90:367–371.
12. Frick KD, Foster A. The magnitude and cost of global blindness: an increasing problem that can be alleviated. Am J Ophthalmol 2003;135:471–476.
13. O'Malley PG. Comparative effectiveness of anti-growth factor therapies for diabetic macular edema: summary of primary findings and conclusions. Arch Intern Med 2012;172:1014–1015.
14. Arevalo JF, Garcia-Amaris RA. Intravitreal bevacizumab for diabetic retinopathy. Curr Diabetes Rev 2009;5:39–46.
15. Rodriguez-Fontal M, Alfaro V, Kerrison JB, Jablon EP. Ranibizumab for diabetic retinopathy. Curr Diabetes Rev 2009;5: 47–51.
16. Feigl B, Greaves A, Brown B. Functional outcomes after multiple treatments with ranibizumab in neovascular age-related macular degeneration beyond visual acuity. Clin Ophthalmol 2007;1:167–175.
17. Regan D, Neima D. Low-contrast letter charts in early diabetic retinopathy, ocular hypertension, glaucoma, and Parkinson's disease. Br J Ophthalmol 1984;68:885–889.
18. Sokol S, Moskowitz A, Skarf B, et al. Contrast sensitivity in diabetics with and without background retinopathy. Arch Ophthalmol 1985;103:51–54.
19. Harris A, Arend O, Danis RP, et al. Hyperoxia improves contrast sensitivity in early diabetic retinopathy. Br J Ophthalmol 1996;80:209–213.
20. Arend O, Remky A, Evans DW, et al. Contrast sensitivity loss is coupled with capillary drop out in diabetic patients with unaffected visual acuity. Invest Ophthalmol Vis Sci 1997;38: 1819–1824.
21. Green FD, Ghafour IM, Allan D, et al. Colour vision of diabetics. Br J Ophthalmol 1985;69:533–536.
22. Bresnick GH, Condit R, Palta M. Association of hue discrimination loss and diabetic retinopathy. Arch Ophthalmol 1985; 103:1317–1324.
23. Remky A, Arend O, Hendricks S. Short-wavelength automated perimetry and capillary density in early diabetic maculopathy. Invest Ophthalmol Vis Sci 2000;41:274–281.
24. O'Neill-Biba M, Sivaprasad S, Rodriguez-Carmona M, et al. Loss of chromatic sensitivity in AMD and diabetes: a comparative study. Ophthalmic Physiol Opt 2010;30:705–716.
25. Newsome DA, Negreiro M. Reproducible measurement of macular light flash recovery time using a novel device can indicate the presence and worsening of macular disease. Curr Eye Res 2009;34:162–170.
26. Frost-Larsen K, Larsen HW. Macular recovery time recorded by nyctometry—a screening method for selection of patients who are at risk of developing proliferative diabetic retinopathy. Arch Ophthalmol 1985;63:39–47. AQ : 6
27. Midena E, Segato C, Giuliano M, et al. Macular recovery function (nyctometry) in diabetics with and without retinopathy. Br J Ophthalmol 1990;74:106–108.
28. Lacey JA, Jacobs RJ. The macular photostress test. Aus J Optom 1983;66:147–150.
29. Glaser JS, Savino PJ, Sumers KD, et al. The photostress recovery test in the clinical assessment of visual function. Am J Ophthalmol 1977;83:255–260.
30. Loughman J, Hewitt C, Judge C, et al. Clinical applicability of the macular degeneration detection device (MDD-2); a novel photostress recovery measurement device. Clin Exp Optom 2013;96:272–277.
31. Stellingwerf C, Hardus PL, Hooymans JM. Assessing diabetic retinopathy using two-field digital photography and the influence of jpeg-compression. Doc Ophthalmol 2004;108:203–209.
32. Seddon JM, Sahagian C, Glynn R, et al. Evaluation of an iris color classification system. Invest Ophthalmol Vis Sci 1990; 31:1592–1598.
33. Bland J, Altman D. Measuring agreement in method comparison studies. Stat Methods Med Res 1989;8:135–160. AQ : 7
34. Henkind P, Siegel IM. The scotometer: a device for measuring macular recovery time. Am J Ophthalmol 1967;64:314–315.
35. Nousiainen I, Kalviainen R, Mantyjarvi M. Contrast and glare sensitivity in epilepsy patients treated with vigabatrin or carbamazepine monotherapy compared with healthy volunteers. Br J Ophthalmol 2000;84:622–625.
36. Wolffsohn J, Anderson SJ, Mitchell J, et al. Effect of age-related macular degeneration on the Eger macular stressometer photostress recovery time. Br J Ophthalmol 2006;90:432–434.
37. Margrain TH, Thomson D. Sources of variability in the clinical photostress test. Ophthalmic Physiol Opt 2002;22:61–67.
38. Dhalla MS, Fantin A. Macular photostress testing: sensitivity and recovery with an automated perimeter. Retina 2005;25: 189–192.
39. Horiguchi M, Ito Y, Miyake Y. Extrafoveal photostress recovery test in glaucoma and idiopathic central serous chorioretinopathy. Br J Ophthalmol 1998;82:1007–1012. AQ : 8
40. Krastel H, Alexandridis E. Recovery from macular photostress and slow retinal potentials in cured retinal detachment. Ophthalmologica 1980;181:47–52.
41. Newsome DA. A randomized, prospective, placebo-controlled clinical trial of novel zinc-monocysteine compound in age-related macular degeneration. Curr Eye Res 2008;33:591–598.
42. Lovasik J. An electrophysiological investigation of the macular photostress test. Invest Ophthalmol Vis Sci 1983;24:437–441.
43. Wu G, Weiter JJ, Santos S, et al. The macular photostress test in diabetic retinopathy and age-related macular degeneration. Arch Ophthalmol 1990;108:1556–1558.