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THE LOSS OF INFRARED LIGHT SENSITIVITY OF PHOTORECEPTOR CELLS MEASURED WITH TWO-PHOTON EXCITATION AS AN INDICATOR OF DIABETIC RETINOPATHY

A Pilot Study

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Purpose: Human photoreceptors are sensitive to infrared light (IR). This sensitivity can be used as a novel indicator of retinal function. Diabetic retinopathy patients were assessed using in vivo two-photon excitation and compared their scotopic IR threshold with that of healthy patients.

Methods: Sixty-two participants, 28 healthy and 34 with diabetic retinopathy, underwent a comprehensive eye examination, where visual acuity and contrast sensitivity were assessed. Infrared thresholds were measured in the fovea and parafovea following 30-minute dark adaptation. A two-photon excitation device was used with integrated pulsed laser light (1,045 nm) for sensitivity testing and scanning laser ophthalmoscopy for fundus imaging.

Results: The mean Snellen visual acuity of diabetic patients (6/7.7) was worse than that of the healthy patients (6/5.5), which was significantly different ($P < 0.001$). Disease patients had decreased contrast sensitivity, especially at 6 and 18 cycles/degree. The mean retinal sensitivity to IR light in eyes with diabetic retinopathy (11.6 ± 2.0 dB) was significantly ($P < 0.001$) lower than that in normal eyes (15.5 ± 1.3 dB).

Conclusion: Compared with healthy control subjects, the IR light sensitivity of diabetic patients was significantly impaired. Two-photon measurements can be used in the assessment of retinal disease, but further studies are needed to validate IR light stimulation in various stages of diabetic retinopathy.

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The concept of infrared (IR) vision has been overlooked in clinical ophthalmic practice because it is generally held that IR light cannot produce visual sensations and so it is deemed not clinically relevant.

However, in 1947, Griffin et al¹ confirmed that the human eye, unaided, can indeed perceive IR radiation. Though, retinal sensitivity to IR light (1,050 nm) is about 13 orders of magnitude lower than the perception of green (505 nm) outside the fovea.¹ This perception was described as colorless for both foveal and parafoveal stimulation.¹ Although IR light cannot produce chromatic sensations in standard, single-photon vision, the

perception of color has been demonstrated to be triggered by two-photon excitation, a mechanism that has only recently been elucidated.^{2,3} The clinical application and its significance have yet to be determined.

Diabetic retinopathy is the leading cause of preventable vision loss in the working-age population worldwide.⁴ Recent predictions suggest that the diabetic population will increase from its present 463 million to 578 million by 2030 and 700 million by 2045.⁵ Consequently, the prevalence of uncorrected visual difficulties or blindness caused by diabetic retinopathy is set to increase if the trend is not averted.

Various imaging techniques, that is, optical coherence tomography (OCT), fluorescein angiography, and fundus photography, have been proposed to facilitate the diagnosis of retinal abnormality.⁶ However, those methods do not provide information about the functional implications of observed structural changes at the retina. Although visual acuity and contrast sensitivity tests are valid measures of foveal function, the paracentral areas of the retina are typically not tested using these metrics. Microperimetry has been introduced to address these limitations by providing simultaneous morphological and functional testing.^{7–11} So far, two methods have been used for the fundus observation: scanning laser ophthalmoscopy (SLO) and fundus photography.^{7–11} Visual function is measured by projecting a stimulus at precise retinal locations, enabling the correlation of retinal sensitivity maps and fundus images. Contemporary microperimetry offers polychromatic (white) and monochromatic procedures,^{7–11} but IR stimulation has never been used. Yet IR light has advantages over visible light, such as lower lenticular and macular pigment absorption,^{12,13}

better penetration through opacified ocular media,³ and a minimal impact on pupil size.¹⁴

In this clinical pilot study, we assessed retinal sensitivity to IR stimuli, perceived as green through the process of the two-photon absorption, in patients with diabetic retinopathy and compared the results with those of healthy control subjects. We also tested the feasibility of using IR light stimulation in the assessment of retinal abnormality.

Methods

This study was carried out at the Ophthalmology Department of the Heidelberg University Hospital and was approved by a local ethics committee. The tenets of the Declaration of Helsinki were followed. Written informed consent was obtained from each participant after a detailed explanation of the nature of the study.

Patient Selection

Diabetic retinopathy patients were recruited from the Outpatient Department of the Heidelberg University Eye Clinic.

The inclusion criteria were as follows:

1. Age \geq 18 years
2. A minimum logarithm of the minimum angle of resolution visual acuity of 0.40 (Snellen equivalent 6/15.1)
3. Documented diabetic retinopathy with no other concomitant eye disease
4. No history of ocular surgery except cataract extraction and intraocular lens implantation.

Patients with retinal abnormalities, such as central vein occlusion or macular ischemia, were excluded.

The control group comprised healthy participants with a logarithm of the minimum angle of resolution visual acuity of 0.1 (Snellen equivalent 6/7.6) or better. The criterion of spherical equivalent \pm 4.0 diopters (D) and low astigmatism ($<$ 1.50 D), dictated by a limited refractive-error correction of a study device, was applied in the selection for both groups. If a pseudophakic patient was recruited, measurements were taken at least three months after the surgery. In total, 62 participants (34 diabetic patients and 28 healthy controls) were enrolled in this study.

Clinical Assessment

Best-corrected visual acuity was measured with an Early Treatment Diabetic Retinopathy Study chart placed at 4 m. A CSV-1000E (VectorVision, Greenville, OH) contrast sensitivity test was performed at

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2.5 m and for four spatial frequencies (i.e., 3, 6, 12, and 18 cycles/degree). Contrast sensitivity was assessed under photopic conditions with a background luminance of 85 cd/m². Following visual quality testing, a mydriatic agent was instilled (tropicamide 5 mg/mL, Mydriaticum Stulln; Pharma Stulln GmbH, Stulln, Germany) to perform a comprehensive slit-lamp examination. In addition, OCT imaging (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was used with a 30° scan angle. Foveal thickness, defined as the distance between the internal limiting membrane and the outer surface of the retinal pigment epithelium, was obtained from OCT images.^{15,16} The position of the central subfield was carefully checked before taking a measured foveal thickness value.

One eye per subject was included in IR light two-photon stimulation and further statistical analysis. We selected the study eye as the better of the two eyes based solely on visual acuity. If both eyes had the same visual acuity, then we randomly chose the study eye. We classified diabetic retinopathy into three categories: no diabetic macular edema (no DME), nonclinically (NCSME) significant, or clinically significant (CSME) macular edema, based on the location of retinal thickening hard exudates and the presence of retinal thickening blot hemorrhages, a grading of diabetic retinopathy fully described by Fleming et al.¹⁷

Sensitivity of scotopic eye to IR light was assessed following 30-minute dark adaptation and under pupil dilation. The detailed description of the setup is presented in the **Supplemental Digital Content 1** (<http://links.lww.com/IAE/B347>). In brief, a patient was instructed to look at a red (630 nm) fixation point while IR stimuli (Goldmann-size II) were consecutively projected onto the retina. Standard 200-millisecond stimulus duration was used. For each visual stimulation, the patient manually increased the light power until the visibility threshold was reached (the method of adjustment).¹⁸ A customized grid was used to test sensitivity at the fovea, then 2° from the center in three quadrants (superior, inferior, and nasal), and finally 2°, 6°, and 8° from the center in the temporal quadrant. Thus, in total, seven retinal loci were assessed five times, resulting in 35 measurements per study eye. The patient's gaze was manually controlled by monitoring 1) eye movements using an infrared camera and 2) fundus image displacement through an integrated SLO module. If it was noticed that a patient had fixation problems or showed poor compliance, the test was aborted, and the results excluded from the analysis.

The stimulus was produced by a pulsed femtosecond laser (HighQ-2; Spectra-Physics, CA) with a wavelength of 1,045 nm and strictly followed ANSI Z136.1 laser safety standards. The permissible

exposure-limit calculations are given in **Supplemental Digital Content 2**, <http://links.lww.com/IAE/B348>. The IR light sensitivity was assessed on a decibel (D) scale from 0 to 26 dB, which corresponded to the maximum (400 μW) and minimum (1 μW) stimulus intensity, respectively.

Statistics

A Kolmogorov–Smirnov test was performed to check data conformity to the normal distribution. The visual outcomes of the two study groups were compared using the independent samples *t*-test and presented as the mean ± SD. If data were not normally distributed, then the Mann–Whitney *U* test was used, and the median (range) as a descriptive statistic. Differences in IR sensitivity between the seven retinal loci were assessed with one-way analysis of variance (ANOVA) and the Bonferroni method for a post hoc test. The statistical analysis was performed using MATLAB (Mathworks, Inc, Natick, MA).

Results

The mean age of the diabetic-retinopathy patients was 60.3 ± 11.8 years, and for the healthy group, it was 56.2 ± 15.7 years. This difference was not statistically significant (*t*-test, *P* = 0.29). Of the 34 diabetic patients, 10 had Type I diabetes; the remaining 24 had Type II diabetes with the average duration of diabetes mellitus being 18.6 ± 11.0 years. Clinically significant macular edema was noted in 27 eyes, seven were classified as no DME, and none had NCSME.

The median spherical equivalent in normal and pathologic eyes was 0 D (range, −4.4 D to 2.0 D) and −0.3 D (range, −3.8–0.6 D), respectively, and the difference was not statistically significant (Mann–Whitney *U* test, *P* = 0.95).

Best-corrected visual acuity was significantly compromised (*t*-test, *P* < 0.001) in the diabetic patients with the mean logarithm of the minimum angle of resolution value being 0.11 ± 0.16 (Snellen equivalent 6/7.7) compared with −0.04 ± 0.08 (Snellen equivalent 6/5.5) in the control subjects. Furthermore, the disease group demonstrated decreased contrast sensitivity, with the differences being significant at two spatial frequencies (Figure 1). The central subfield thickness differed significantly (*t*-test, *P* = 0.03) between the two populations, as in the healthy group, we found 277.1 ± 19.5 μm and 299.0 ± 50.0 μm in eyes with diabetic retinopathy.

The mean retinal sensitivity to IR light was 15.5 ± 1.3 dB in the control eyes, which was significantly

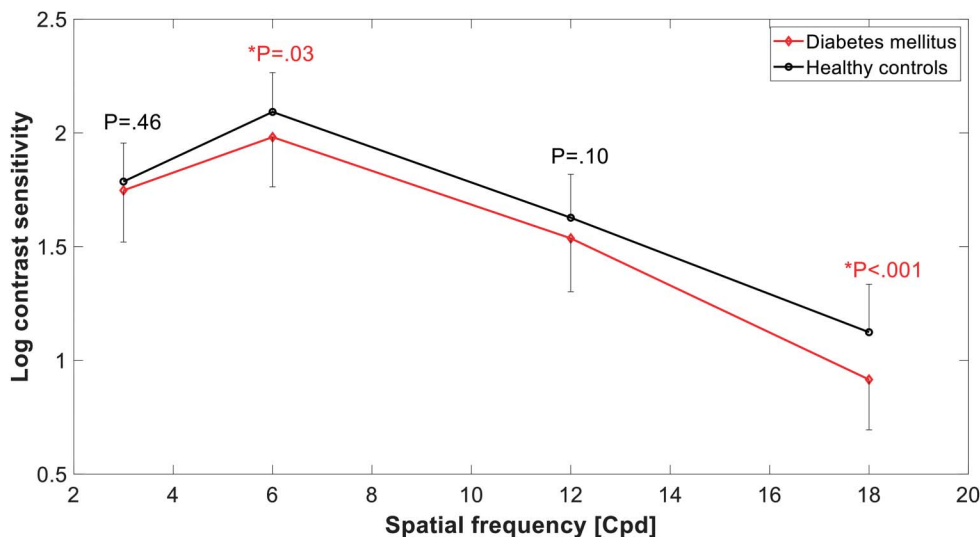


Fig. 1. Log contrast sensitivity of healthy and diabetic retinopathy patients measured at four spatial frequencies. *Statistically significant differences (*t*-test; $P < 0.05$); error bars = standard deviation.

higher (*t*-test, $P < 0.001$) than 11.6 ± 2.0 dB in the disease group.

Figure 2 shows the comparison of the IR threshold in the two groups and the retinal locations. In both groups, the ANOVA revealed that the retinal sensitivity significantly differs ($P < 0.001$) between the seven eccentricities. However, the post hoc test demonstrated that only the foveal sensitivity is significantly ($P < 0.001$) decreased from that measured at all but one paracentral stimulus position. The one exception was found in the diabetic group at 2° temporal, which did not differ significantly from the foveal sensitivity ($P = 0.08$), despite being lower by 1.6 dB (Figure 2B). The average sensitivity values as a function of age are presented in Figure 3. The diabetic populations per-

formed worse, on average, at all ages than the control group.

Discussion

The perception of color after exposure to pulsed IR light was first reported in 1976.¹⁹ Since then, the origin of this phenomenon has been the subject of many studies.^{2,3,20,21} Only recently, however, Palczewska et al² demonstrated that IR vision results from two-photon absorption by photoreceptor cells. They performed a series of experiments on mouse photoreceptors and their response to visible and IR light. Recorded transretinal electroretinograms confirmed the direct isomerization of the visual chromophore

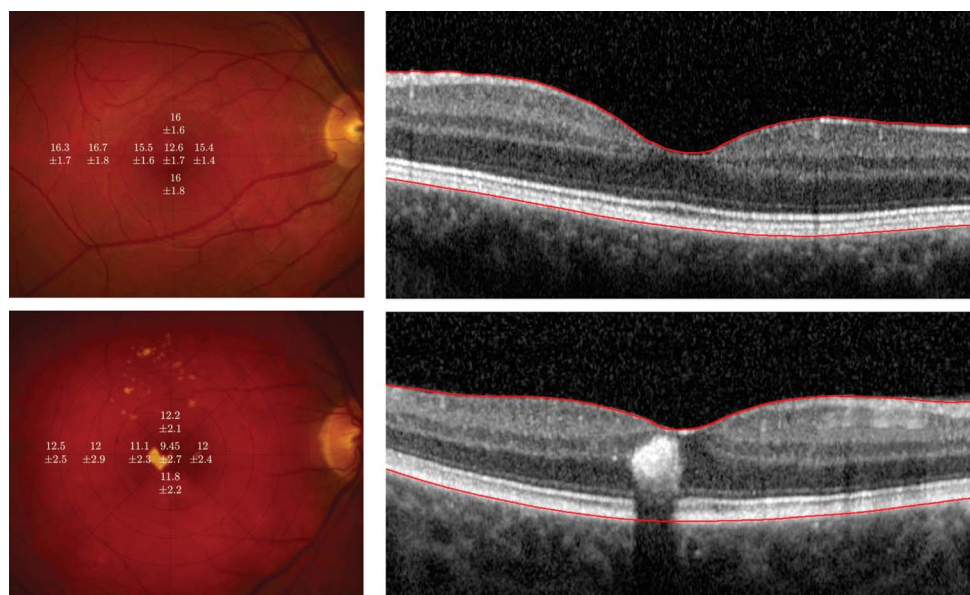


Fig. 2. Infrared light sensitivity maps of healthy (upper panels) and diabetic retinopathy (lower panels) overlaid on exemplary fundus images with respective OCT scans.

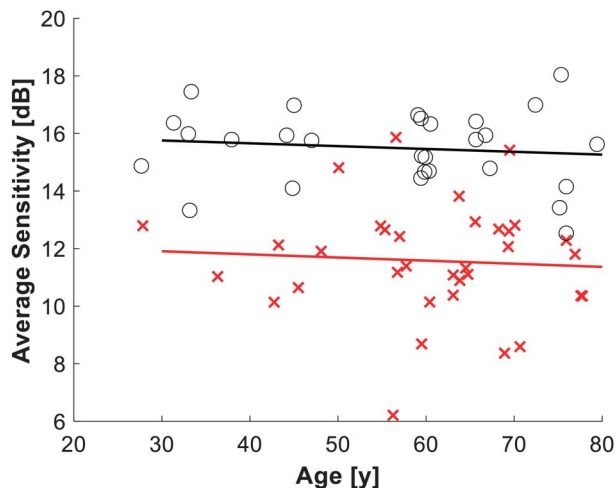


Fig. 3. Infrared light sensitivity as a function of age. The comparison between healthy (black circles) and diabetic retinopathy (red crosses) patients. The solid lines refer to a linear regression model.

by IR radiation, which, unlike standard one-photon perception, was governed by a nonlinear optical process.² In addition, Palczewska et al² studied IR vision in human subjects by means of a psychophysical test. That experiment involved matching the color of a pulsed laser beam (wavelength ranging from 950 nm to 1,200 nm) with one produced by a standard halogen lamp and a monochromator in the 400 to 700 nm range.² They confirmed that the eye perceives pulsed IR light with a color closely (but not exactly) corresponding to half of the wavelength used. The perception of a range of colors (from blue to red) suggested cone-mediated vision.

However, in that study, rod perception was also documented in a subject with autosomal recessive achromatopsia, who could see IR light, but in that case, it appeared colorless.² A later study confirmed that both photoreceptors are activated by IR light.³ Yet, rods proved more sensitive to IR light than cones, which is in agreement with the results of this study. Although the eye perceives the 1045-nm laser beam as green, its sensitivity to that region is decreased by 86 dB compared with 522.5 nm.³ Thus, one may conjecture that retinal abnormality might disturb IR vision earlier than it affects the parameters measured in visible light. The study by Palczewska et al showed that the IR threshold of dark adapted rods and cones differs only by a factor of 2.^{2,3} By contrast, the scotopic sensitivity of rods is about 100-fold higher than cones in 550-nm light.²² This broad dynamic range of retinal photoreceptors in the visible spectrum is difficult to replicate, which may be the cause of the “floor and ceiling” effects observed in clinical testing.¹¹ The use of IR instead of visible light may also yield higher repeatability of thresh-

old measurements, which stems from the nonlinearity of the two-photon absorption.^{2,3}

Artal et al²³ tried to show that visual acuity in IR is superior over visual acuity measured in visible light. But those efforts failed to provide the evidence of improved spatial resolution in healthy subjects, which may be the result of limiting neural factors that are independent of optical ones.^{23,24} One may wonder, however, whether such improvement could not be found in subjects with cataract. A recent study by Ruminski et al³ demonstrated that IR light is less affected by lenticular opacification than green light. Thus, the impact on the visibility threshold was noted to be smaller in measurements taken at 1,045 nm than 522.5 nm,³ which may be particularly important in monitoring retinal abnormality progression in cases with developing cataract. More study is needed to verify the benefits of IR light two-photon stimulation in cataractous eyes.

The functional effects of diabetic retinopathy have often been assessed using an MP1 (Nidek) microperimeter that operates in the visible range.^{7–11} In our study, IR light produced the stimulus, and this has to be borne in mind as we make a direct comparison with work that used visible-light microperimetry. Despite existing differences, both approaches proved sensitive to detect visual impairment in diabetic patients.

Vujosevic et al²⁵ recruited patients with diabetic retinopathy who were divided into three groups (no DME, NCSME, and CSME) depending on the severity of the disease. Interestingly, a difference of 2.3 dB, on average, between the no DME and NCSME groups did not reach a significance level.²⁵ But the reduction of visual function in their CSME population was indeed significant, which differed by 7.2 dB and 4.9 dB from the no DME and NCSME cases, respectively.²⁵ In the current study, the severity score of the population was more homogenous, with the majority (74%) having CSME, so the comparison between the groups was not feasible. We typically see at our clinic patients with advanced disease who are referred by their local ophthalmologists for treatment; thus, we find the overrepresentation of CSME cases. Despite the high severity score of the included patients, their visual acuity was better than that found in CSME eyes of the study by Vujosevic et al²⁵ (6/12.8 Snellen). The difference of two lines indicates that our patients preserved good visual function, but still, the IR sensitivity was significantly decreased.

Verma et al⁸ in another analysis of retinal function, assessed healthy subjects versus diabetes mellitus patients without diabetic retinopathy. They found a significant decrease in visual function in the latter group with the mean difference of (approximately)

2 dB measured in the central 20° area. Later, Nittala et al⁹ reported a reduction in the mean sensitivity in patients with subclinical diabetic retinopathy, but the mean difference was lower, approximately 0.5 dB. In cases with confirmed diabetic retinopathy, the impact on retinal sensitivity was found to be significant, which was 4 dB lower than that in the control subjects.⁹ A similar decline was found in our study. However, Nittala et al also included patients at the severe stage of the disease, who presented with a mean visual acuity of 6/10.7 to 6/10.9 Snellen.⁹ By contrast, we found 6/7.7 in our population, which is comparable to the level found in cases with moderate diabetic retinopathy reported by Nittala et al.⁹ However, we did not include diabetes patients who are free of retinopathy, and we aim to address this problem in a large-population study in collaboration with the Department of Medicine I and Clinical Chemistry of the University of Heidelberg.

Visual acuity and contrast sensitivity are common metrics of the functional quality of vision. As one might have expected, the presence of diabetic retinopathy in the study population resulted in significantly decreased visual acuity. Despite the 1.5-line difference, a visual acuity of 6/7.7 still appears to be relatively good, which may contrast with data presented in the literature,^{9,10,25} as discussed above. This could be explained by the inclusion criteria of a minimal visual acuity of 6/15.1 and the selection of a better eye, which were set to test the ability of two-photon stimulation in detecting less severe abnormality. Although overall contrast sensitivity was decreased in the diabetic group, only at two spatial frequencies, the difference was statistically significant. These results are in line with those reported by Safi et al,²⁶ who also found a significant contrast reduction only at 6 and 18 cycles/degree in diabetic patients. Verrotti et al²⁷ studied visual function in adolescent subjects with poorly controlled diabetes and compared against an age-matched normal population. In their group with diabetes and documented retinopathy, contrast discrimination was significantly impaired at 12 and 18 cycles/degree. However, after the improvement of metabolic control via intensive insulin therapy, contrast sensitivity significantly improved at all spatial frequencies.²⁷ But, the reversibility of contrast reduction was not achievable in patients with (pre)proliferative retinopathy, whose contrast reduction was significant at all frequencies.²⁷ This underlines the importance of early detection of diabetic retinopathy and its early treatment.

Retinal thickening observed in OCT images is often the indicator of diabetic macular edema. Indeed, in the current study, we found a significant increase in the central subfield thickness in patients with diabetic retinopathy compared with the healthy controls: corre-

sponding to the findings reported separately by Augustin et al and by Goebel et al.^{28,29} However, besides dissimilarity in the severity of macular edema between patients,²⁸ the absolute values also differ because of variability in employed OCT devices and anatomical landmarks used for measurements. Thus, we could only compare our results accurately with those from studies where the Spectralis instrument was used.

Edington et al¹⁰ reported 309.3 μm in patients with CSME, which was slightly higher (by 10 μm) than the level found in the current study. The foveal thickness of the healthy subjects also conforms to data from the literature. Menke et al¹⁵ and Grove et al¹⁶ measured thickness in the central subfield of healthy volunteers and found 286 μm and 270 μm , respectively, which, on average, is very close to 277 μm reported in this study. A comparable level was revealed in diabetic patients with minimal or no diabetic retinopathy,³⁰ which suggests that the foveal thickness alone might not be effective in the early detection of retinal abnormality.

In conclusion, to the best of our knowledge, this pilot study is the first clinical assessment of patients with retinal abnormality using two-photon excitation. We demonstrated that this novel method could be integrated into clinical practice. Also, IR threshold measurements provide a novel indicator of retinal function. The application of this (new) parameter showed that sensitivity of scotopic eyes in patients with diabetic retinopathy is significantly impaired compared with healthy subjects. Thus, IR light stimulation is a sensitive measure to detect diabetic retinopathy. It would be reasonable to expect that our technique can be successfully applied to detect and monitor the progression of other abnormalities, such as AMD, or glaucoma. Mutations in rhodopsin that affect folding cause autosomal dominant retinitis pigmentosa as a result of an accumulation of protein in the endoplasmic reticulum, which might also lead to early IR sensitivity reduction. This warrants further investigation.

Key words: two-photon excitation, infrared vision, diabetic retinopathy, visual function, diabetes, retinal sensitivity.

Acknowledgments

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