Photoreceptor Function in Eyes with Macular Edema

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**Purpose.** The irreversible loss of visual acuity in macular edema is usually attributed to permanent loss of photoreceptor cells, although there is hardly any information on changes in photoreceptor function in macular edema. The purpose of this study was to assess photoreceptor function in various stages of macular edema and to relate the findings to visual acuity and angiographic changes.

**Methods.** Directional sensitivity (optical Stiles–Crawford effect) and visual pigment density of foveal cones was measured with a custom-built scanning laser ophthalmoscope (SLO) in 19 eyes of 19 patients. Twelve eyes exhibited macular edema: five of inflammatory origin, and seven of diabetic origin. Seven eyes with an intraocular inflammatory disease without clinical or angiographic evidence of edema were also included (four of which had previous macular edema and one of which had shown development of macular edema at the 1-year follow-up). Results of SLO measurements were related to findings using fluorescein angiography and Snellen visual acuity, both assessed at the time of SLO measurement and 6 months thereafter.

**Results.** Eyes with macular edema exhibited diminished directional sensitivity of photoreceptor cells in the fovea compared with eyes without ($P = 0.02$). Visual pigment density of eyes with macular edema was decreased and associated with both initial and follow-up visual function and with the angiographic macular edema grade at follow-up. Abnormal directional sensitivity and pigment density were already present in eyes with slight edematous changes and normal visual acuity.

**Conclusions.** Eyes with inflammatory or diabetic macular edema showed decreased directional sensitivity and visual pigment density in the macular area. These findings may support a role for SLO measurements in detecting retinal damage due to macular edema. (*Invest Ophthalmol Vis Sci.* 2000;41:4048–4053)

Macular edema consists of an accumulation of fluid in the outer plexiform and inner nuclear layers of the retina, causing retinal thickening. It complicates the course of many ocular diseases and is usually considered a nonspecific sign of these disorders. In patients with uveitis or diabetes mellitus, macular edema is reported to represent a major cause of visual loss. Diffuse macular edema, occasionally with cystoid changes resulting in a characteristic petaloid pattern, can be diagnosed by ophthalmoscopy or fluorescein angiography. In the early stages, visual function usually fluctuates and may recover after treatment.

The normal photopic visual system is sensitive to changes in the angle of incidence of light stimulating the photoreceptors. A light ray entering the eye parallel to the long axis of a photoreceptor is visually more efficient than a bundle entering the photoreceptor obliquely. This directional sensitivity of the eye is called the Stiles–Crawford effect (SCE) and is due principally to the directional properties of an individual photoreceptor, enhanced by the photoreceptor’s tapered inner segment. The function of photoreceptor cells and their alignment in eyes with macular edema are not well known. In the living eye, photoreceptor alignment and function can be inferred from measurements of the SCE with the scanning laser ophthalmoscope (SLO). The purpose of our study was to investigate photoreceptor function and alignment in eyes with macular edema and to evaluate whether SLO measurement might be a useful method to monitor residual retinal damage due to macular edema.

**Methods**
We examined 19 eyes of 19 patients with a mean age of 42.3 ± 11.1 (SD) years (range, 26–65 years). The male-to-female ratio was 10:9. Included were 12 eyes with inflammatory ($n = 5$) or diabetic ($n = 7$) macular edema, and 7 eyes with uveitis without edema. The latter category of eyes with subnormal visual acuity without evidence of edema on ophthalmoscopy or angiography consisted of four eyes with a history of macular edema, one eye in which macular edema developed approximately 1 year after SLO measurement, and two eyes without macular edema in the past or after a follow-up of 2 and 3 years. Patients with substantial media opacities were excluded. Corrected visual acuity was measured with the Snellen letter projector on the day of SLO measurement and 6 months thereafter. Diagnosis of macular edema was based on both clinical and angiographic criteria. A recent (less than 6 months
previously) fluorescein angiography was available for 17 patients. In two patients without edema in recent ophthalmoscopy (and no need for angiography), an angiogram was available from approximately 2 years before SLO measurement. Six months after SLO measurement, a follow-up fluorescein angiogram was made in all but three patients. Macular edema as shown on late-phase angiogram (approximately 10 minutes after injection of the dye), was graded by two masked observers: grade 0 when no edema was found (n = 7), grade 1 when less than 25% of the macular area was affected by edema (n = 4), grade 2 when the affected area was between 25% and 66% (2/3, n = 7), and grade 3 when more than 66% of the macular area was affected (n = 1). In case of discrepancy of grading, the two observers discussed the angiograms until they agreed on a final angiogram grade. Mean duration of macular edema was 3.3 years ± 3.1 months (SD), ranging from 7 months to 9 years.

Measurements were performed with a custom-built SLO (the apparatus and clinical use have been described earlier).7,8 Normal values for photoreceptor directionality and density were obtained by measuring 25 healthy volunteers (average age, 30 ± 11.3 years), 19 of whom were available for cross-section analysis. One or two drops of tropicamide (0.5%) were instilled into the eye to induce mydriasis. Accurate positioning and steady fixation of the eye were ensured by two forehead rests and a bite board with a dental compound. Subjects were asked to look at a fixation cross. Refraction was corrected if necessary. The SLO images covered a retinal area of 23° × 18° with the fovea as center. Directionality and visual pigment density of photoreceptor cells in the central 2° × 2° area were determined, because the optical density in this area is almost entirely due to photopigments of cones that primarily determine central visual acuity.9 The maximum reflectance was determined by finding the position at which the reflectance of the parafoveal cones was at its maximum.

As mentioned before, the optical SCE is due to the directionality of the photoreceptor cells. By the joint movement of entrance and exit beam across the pupil plane in healthy eyes, a change in reflectance was recorded, and a gaussian-like reflectance function with a peak close to the middle of the pupil plane was obtained.10 The peakedness of the curve, and thus the directional sensitivity, was defined as ρ. We used the parameter ρ as an indicator of directional sensitivity for a group of photoreceptors. The average value for directional sensitivity (ρ) of a normal subject was 0.24 ± 0.13 (2 SD). The SCE was recorded by finding the pupil position resulting in maximum parafoveal reflection, followed by acquiring a series of images (approximately every 0.25 mm) from the nasal to the temporal pupil edge.

For measurement of visual pigment density, the eye was adapted to a strong light that bleached away more than 95% of the visual pigments. Next, dark adaptation was performed during which visual pigments fully regenerated. For imaging and 2 minutes of bleaching at 514 nm (5.9 log troland [td]) was used. Dark adaptation was performed for 8 minutes (2.2 log td). A retinal aperture of 0.45° was used. The density of the visual pigments is estimated by taking the logarithm of the ratio of light reflection between the light-adapted and dark-adapted fundus.7 The implicit assumption was that the difference in the two images is caused by the appearance of visual pigment. The average value of a normal subject’s pigment density was 0.37 ± 0.11 (2 SD).

Strong reflections—for instance, from sources anterior to the photoreceptors—may lead to high levels of stray light. We determined these levels (average 32 ± 10 arbitrary units [AU]; normal range, 12-52 AU) by fitting a model of Gorrand and Delori10 through the data points, and we also calculated the reflectance centrally in the fovea.10-12 Cross-section images through the fovea (a line profile of the reflectance along a

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DM, diabetes mellitus.
* Not yet available for follow-up.
FIGURE 1. SCE in (A) an eye without macular edema (Table 1; subject 4) and (B) an eye with macular edema (Table 1; subject 15). Solid line represents model fit. Negative pupil position represents the nasal half of the horizontal meridian.
horizontal line through the fovea) were obtained in all patients with macular edema and in 19 normal eyes.

The study conformed with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participating patients, and the study protocol was approved by the Committee for Scientific Research in Humans of our hospital. Statistical analysis included Student’s $t$-test, $\chi^2$ test, Fisher’s exact test, correlation coefficients, and linear regression analysis. $P \leq 0.05$ was considered statistically significant.

**RESULTS**

An overview of the patients’ clinical data is given in Table 1. Visual acuity of eyes with macular edema was lower than that in eyes without edema ($0.6 \pm 0.27$ and $1.0 \pm 0.20$, respectively; $P = 0.03$). Initial visual acuity was correlated with the grade of macular edema ($r = 0.72, P = 0.008$). The grade of macular edema was correlated with the duration of the edema ($r = 0.62, P = 0.005$).

Eyes with macular edema exhibited a flattening of the normal Stiles–Crawford curve, resulting in a diminished directional sensitivity (mean $r = 0.08 \pm 0.05$, in eyes without macular edema: $r = 0.16 \pm 0.09$; $P = 0.02$). An example of data resulting in a normal $r$ is presented in Figure 1A; an example with an abnormal $r$ is given in Figure 1B. The higher the angiographic grade, the higher the percentage of eyes with an abnormal $r$ (eyes without macular edema: $29\%$ [2/7]; grades 1, 2, and 3: $50\%$ [2/4], $86\%$ [6/7], and $100\%$ [1/1], respectively), although this trend did not reach significance ($P = 0.3$). Initial visual acuity was related to $r$ ($r = 0.56, P = 0.01$), the duration of edema and the age of patients were not significantly related to $r$ ($P = 0.2$ and $P = 0.6$, respectively).

Five of the 11 eyes with a visual acuity exceeding 0.8 exhibited diminished $r$ (Fig. 2). All five eyes had manifest macular edema or a history of edema. Two of the seven eyes without macular edema had diminished $r$: One eye showed development of macular edema at 1-year follow-up, and the other had a history of macular edema. In three of five eyes with a history of macular edema but without recent clinical or angiographic edematous changes, $r$ was normal.

All eyes with manifest macular edema or a history of macular edema exhibited diminished visual pigment density (mean visual pigment density: $0.13 \pm 0.06$). The values of visual pigment density were associated with visual acuity ($r = -0.62, P = 0.005$). Visual pigment density was also related to edema grade on follow-up fluorescein angiogram ($P = 0.05$) and follow-up visual acuity ($P = 0.05$).

Two eyes exhibited normal $r$ and normal visual pigment density: they were the only eyes without a history of macular edema in which macular edema did not develop during follow-up.

SLO images always exhibit a central area of low reflection (Fig. 3). Reflection in the center of the fovea was significantly...
lower in eyes with macular edema (0.63%) compared with normal eyes (1.0%, \( P = 0.002 \)). When cross-section SLO images were compared, this area of low reflection appeared larger in eyes with macular edema compared with normal eyes (Fig. 3). The mean cross-sections are given in Figure 4, which illustrates the decrease of the reflectance of parafoveal cones in eyes with macular edema.

Stray light levels did not significantly differ between eyes with and without macular edema (mean value: 54.3 ± 21.9 AU, and 48.8 ± 18.0 AU, respectively, \( P = 0.6 \)). Although the mean stray light level was slightly increased in eyes with macular edema, the percentage of patients with an abnormal stray light level was similar for eyes with and without macular edema (57% and 67%, respectively; \( P = 0.5 \)).

DISCUSSION

In this study, we describe decreased optical SCE, visual pigment density, and reflection in eyes with diabetic or inflammatory macular edema, indicating a dysfunction of foveal photoreceptor cells. Our study confirms the findings in a case report that described an abnormal psychophysical SCE in two eyes with diabetic macular edema and a study that documented abnormalities in foveal cone electroretinographic responses in patients with nonproliferative diabetic retinopathy—particularly in eyes with macular edema.\(^{15,14}\) The correlation of the alignment of the photoreceptors and the measured optical density was described earlier by van Bockland.\(^{15}\)

In our series, macular edema was associated with a diminished directional sensitivity and visual pigment density of photoreceptor cells in the fovea. Five eyes with subnormal visual acuity exhibited a diminished directional sensitivity. Explanations for the reduced directional sensitivity of the foveal photoreceptor cells in eyes with macular edema involve changes in the alignment of cones, changes in the structure of individual cones, and/or loss of photoreceptor cells. In the early stages of macular edema, the mildly reduced visual acuity and still-reversible edema suggest disorientation rather than the structural change of photoreceptor cells, although the reduced visual pigment density in eyes with resolved edema suggests that some irreversible, but subclinical, damage has already occurred. We assume that despite their disorientation, the photoreceptors continue to absorb light and generate nerve signals, sometimes leading to almost normal visual acuity. In three eyes with a history of macular edema, \( p \) was (or returned to) normal, which suggests that photoreceptor cells remained unaffected or that reorientation of photoreceptor cells after retinal disease occurred.\(^{16}\)

Within the fovea, there is fine tuning between optical quality and potential resolution of the cone mosaic.\(^{17}\) The directionality of the cones depends on their shape. Foveal cones are more elongated, more rod-like, whereas parafoveal cones have the appearance commonly ascribed to cones.\(^{18}\) Parafoveal cones were demonstrated to have a more pronounced directional sensitivity than central foveal cones, resulting in a slightly higher parafoveal reflectance (see Fig. 4).\(^{18}\) Electron microscopic findings of an enucleated eye with an-
photoreceptor function. A reduction of visual pigment density may be caused by (a combination of) several factors including (1) a change in photoreceptor orientation (failure to capture light efficiently results in a reduction in effective optical density), (2) a reduced number of photoreceptor cells, (3) a decrease in length of the photoreceptor outer segment, (4) a metabolic change in phototopic regeneration kinetics, or (5) high levels of stray light.\textsuperscript{11,14,20,21} In our study, not all eyes with macular edema exhibited diminished directional sensitivity, but all eyes with manifest macular edema or a history of macular edema exhibited diminished visual pigment density. This indicates that abnormal photoreceptor orientation was not the only factor responsible for the outcome of decreased visual pigment density. A consistent finding in enucleated eyes with macular edema was a decrease in the number of photoreceptor cells.\textsuperscript{5} This suggests that a loss of photoreceptor cells may also contribute to the decrease of visual pigment density levels. To our knowledge no study has described a decrease in length of the photoreceptor outer segment or a metabolic change in phototopic regeneration kinetics due to macular edema. Stray light levels of eyes with macular edema were only slightly (not significantly) increased, and it is therefore unlikely that stray light played a major role in the loss of visual pigment density. The finding that visual pigment density was (or remained) abnormal even after (angiographic and clinical) resolution of macular edema suggests that SLO measurements are a more sensitive method than fluorescein angiography for diagnosing retinal damage due to macular edema. Nevertheless, SLO measurements require clear media and a wide pupil. These measurements are therefore sometimes impossible to perform in eyes with intraocular inflammatory disease. Today, it is not possible to perform these measurements with commercially available SLOs, because the optics and, more important, the signal amplification are unsuitable. However, future apparatus may be better equipped to perform these measurements.

In conclusion, we found decreased directional sensitivity, visual pigment density, and reflection in the macular area of eyes with macular edema. Furthermore, the association of these findings with visual acuity, angiographic edema grade, and relation to future angiographic changes suggests the possibility of detecting retinal damage due to macular edema, before loss of central vision has occurred. Periodically recording data from SLO measurements in high-risk patients, specifically in eyes with as yet uncompromised visual acuity, may be useful.

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References