Diabetic Macular Edema: Correlation between Microperimetry and Optical Coherence Tomography Findings

Stela Vujosevic,[1] *Edoardo Midena,*[1,2] *Elisabetta Pilotto,*[2] *Pietro P. Radin,*[2] *Laura Chiesa,*[2] *and Fabiano Cavarzeran*[2]

Purpose. To compare the changes in macular sensitivity (microperimetry) and macular thickness with different degrees of diabetic macular edema.

Methods. Sixty-one eyes of 32 consecutive diabetic patients were included in this cross-sectional study. All included eyes underwent functional and morphologic examination of the macular area. Best corrected visual acuity (ETDRS charts), macular sensitivity, and macular thickness were quantified. Lesion-related macular sensitivity and retinal fixation were investigated with an advanced, automatic microperimeter. Optical coherence tomography (OCT) was used to quantify macular thickness.

Results. The 61 included eyes were graded, by two retinal specialists, for diabetic macular edema as follows: 16 were graded as no macular edema (NE), 30 as non–clinically significant macular edema (NCSME), and 15 as clinically significant macular edema (CSME). Macular thickness significantly increased from the NE to the CSME group ($P < 0.0001$), whereas macular sensitivity significantly decreased from the NE to the CSME group ($P < 0.0021$). A significant correlation coefficient was noted between retinal sensitivity and normalized macular thickness ($r = -0.37$, $P < 0.0001$). Linear regression analysis showed a decrease of 0.83 dB ($P < 0.0001$) for every 10% of deviation of retinal thickness from normal values. Visual acuity and central macular sensitivity correlated significantly in the NCSME group ($r = -0.6$, $P = 0.0008$), but not in the NE ($r = -0.144$, $P = 0.6$) or in the CSME ($r = -0.46$, $P = 0.11$) groups.

Conclusions. Macular edema may be better documented by adding macular sensitivity mapping by microperimetry to macular thickness measurement by OCT and visual acuity determination because macular sensitivity seems to be a relevant explanatory variable of visual function, independent of macular thickness data. Moreover, microperimetry may be of value in predicting the outcome of diabetic macular edema, because it incorporates a functional measure that may supplement the predictive value of OCT and visual acuity. (*Invest Ophthalmol Vis Sci.* 2006;47:3044–3051) DOI:10.1167/iovs.05-1141

From the [1]Fondazione G. B. Bietti per l'Oftalmologia, IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico), Roma, Italy; and the [2]Department of Ophthalmology, University of Padua, Padua, Italy.

Submitted for publication August 26, 2005; revised January 7, 2006; accepted May 1, 2006.

Disclosure: **S. Vujosevic**, None; **E. Midena**, None; **E. Pilotto**, None; **P.P. Radin**, None; **L. Chiesa**, None; **F. Cavarzeran**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Stela Vujosevic, Department of Ophthalmology, University of Padova, Via Giustiniani 2, 35128 Padova, Italy; stelavu@hotmail.com.

Diabetic maculopathy is the leading cause of visual impairment in the working-age population in developed countries and thus is one of the major ocular health problems worldwide.[1–3] Visual acuity assessment is currently used to determine the functional damage caused by edema, although it may not completely describe the functional condition of the patient. With the introduction of fundus-related perimetry, better known as microperimetry, we are able to determine macular sensitivity and to correlate it with a precise location of edema. Therefore, microperimetry is useful in determining the site of relative and absolute (dense) scotomas and also fixation characteristics. These parameters have been useful in quantifying and predict the functional impact of macular edema or other macular disorders.[4–11]

In this study, we quantified macular sensitivity and the fixation pattern in diabetic macular edema, by using a new automatic technique of microperimetry, and correlated it with macular thickness determined by optical coherence tomography (OCT).

Methods

We examined 64 eyes of 32 consecutive diabetic patients. All patients included in this cross-sectional study were recruited from the Diabetic Retinopathy Clinic at the Department of Ophthalmology, University of Padua. The exclusion criteria included previous macular laser photocoagulation treatment and significant media opacities that precluded fundus examination.

After a detailed explanation of the purpose of the study, a written consent form was completed by all patients. They then underwent a complete ophthalmic examination, including refraction and best corrected visual acuity determination, anterior segment examination, indirect ophthalmoscopy, 90-D lens biomicroscopy, fundus photography, OCT, and microperimetry.

Best corrected distance visual acuity in each eye was measured at 4 m with standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocols with a modified ETDRS distance chart transilluminated with a chart illuminator (Precision Vision, Bloomington, IL).[12] A different chart was used for each patient's right and left eyes and for refraction determination. If the patient was unable to read at least 20 letters at 4 m, visual acuity was measured at 1 m, adding a +0.75-sphere correction. If the patient was unable to read the largest letters at a distance of 1 m, a semiquantitative estimate of the visual acuity—counting fingers (CF), hand movements (HM), light perception (LP), or no LP—was obtained. Visual acuity was scored as the total number of letters read correctly and converted to the logarithm of the minimum angle of resolution (logMAR).

Stereo Fundus Photography

After adequate dilation, color stereoscopic fundus photographs were taken in all patients by a certified photographer using a 30° fundus camera (TRC 50IA; Topcon, Tokyo, Japan) and slide transparency film (Kodachrome; Eastman Kodak, Rochester, NY). The images were obtained according to the standard ETDRS seven stereoscopic fields protocol.[13] All color slides were mounted in transparent slide holders

in stereo pairs. Two retinal specialists independently graded each pair of slides that corresponded to ETDRS field 2, by using a Donaldson stereoscopic viewer. Retinal thickening was assessed in the same way as in the ETDRS protocol: Clinically significant macular edema (CSME) was assigned in cases of the presence of retinal thickening or hard exudates associated with adjacent retinal thickening within 500 μm of the center of the foveal avascular zone or the presence of an area or areas of retinal thickening of at least 1 disc diameter within 1 disc diameter from the center of the macula.[14] Retinal thickening observed in field 2 that did not meet these criteria on biomicroscopic examination was classified as non–clinically significant macular edema (NCSME), and the absence of any retinal thickening was classified as no edema (NE).

OCT Examination

OCT scanning was then performed (Stratus OCT scanner with version 3.0(0052) software; Carl Zeiss Meditec GmbH, Oberkochen, Germany). OCT is a high-resolution technique that permits cross-sectional visualization of the retinal structure with 10 μm of longitudinal resolution from the time delay of reflected light using low-coherence interferometry, as described previously in detail.[15–17]

The scanning protocol used for this study was the Fast Macular Thickness program, which creates a retinal map algorithm consisting of six radiating cross-sectional scans, each of 6-mm length that produces a circular plot in which the fovea is a central circular zone of 1.00-mm diameter. Superior, nasal, inferior, and temporal parafoveal zones represent annular bands in these respective sectors. There are another two concentric zones, the first having a diameter of 3 mm and the second one of 6 mm. The nine OCT zones have been called ETDRS-type regions because of their similarity to zones of analysis of photographs by ETDRS graders.[18,19] Macular thickness is converted to a false color value, with brighter colors indicating areas of increased retinal thickness. Retinal thickness data were averaged by computer in all nine sectors. For the purpose of this study, all measurements were performed automatically by the computer.

Microperimetry

Microperimetry was performed on all subjects with a recently introduced automatic fundus-related perimeter (MP1 Microperimeter; Nidek Technologies, Padova, Italy), which has been described elsewhere.[11] The fundus is imaged in real time on a video monitor with an infrared fundus camera (1392 × 1038-pixel resolution; 45° field of view). The fixation target and stimuli are projected onto the retina by a liquid crystal color monitor completely controlled by dedicated software. The operator views the retinal image on a monitor, with the stimulus as part of the image. Background illumination is set at 4 apostilbs (1.27 cd/m^2; 1 asb = 0.31831 cd/m^2; stimulus intensity may be varied on 1 (0.1 log) step scale from 0 to 20 dB, where 0 dB represents the brightest luminance of 400 asb (127 cd/m^2). Stimulus size may be varied by the examiner: from a Goldmann I to V standard size. The fixation target, set at 100 asb, may be varied in size and shape according to the patient's visual acuity and/or macular scotoma. The location and stability of fixation were classified and evaluated separately according to the previous classification made by Fujii et al.[20] Location was classified as predominantly central, poor central, and predominantly eccentric fixation. Fixation stability was classified as stable, relatively unstable, and unstable.

For the purpose of this study, the following parameters were used: a fixation target consisting of a red ring, 1° in diameter; a white, monochromatic background at 4 asb; stimulus size Goldman III, with 200 ms projection time; a customized radial grid of 45 stimuli covering central 12° (centered onto the fovea), 1° apart (inner stimuli) and 2° apart (outer stimuli; Fig. 1).

A 4-2-1 double-staircase strategy was used. The starting stimulus light attenuation was set at 10 dB. The stimulus was projected exactly onto the predefined retinal position by means of an automatic eye-tracker that compensates for eye movements. This allows a correct matching between the expected stimulus position onto the retina and the actual projection position. Light stimuli were randomly presented during the examination, as in standard static perimetry. Results are reported in decibels. A false-positive test stimulus was projected every 60 seconds onto the optic nerve head area to check for a false-positive answer. To allow for better clinical correlation between microperimetric data and retinal details, functional results were displayed on a color digital retinograph, acquired by a charge-coupled device color camera (1392 × 1038 pixels, xenon flash). Pretest training was performed in each subject and a 5-minute visual adaptation was allowed before the test began. All subjects underwent microperimetry with dilated pupils.

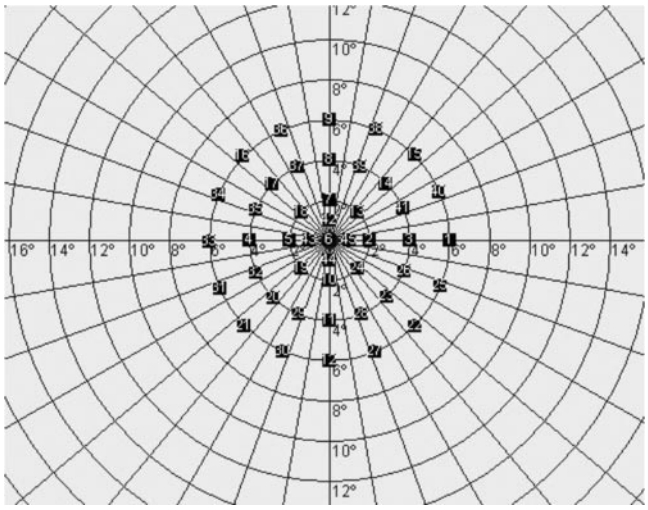

Figure 1. A microperimetric radial grid pattern used for diabetic patients covering central 12° of the macula, with starting attenuation of 10 dB and 45 stimuli.

This study was conducted in accordance with the tenets of the Declaration of Helsinki and with the approval of our institutional ethics committee.

To correlate retinal thickness data accurately with retinal sensitivity data, we compared the more central OCT fields 1 to 5 (ETDRS-type), and we excluded OCT fields 6 to 9, as the MP1 grid covered only a limited area of these latter fields.

Statistical Analysis

All data were analyzed with ANOVA test for repeated-measures analysis of variance. A complete two-factor model was considered with severity of maculopathy and ETDRS field as main factors and severity of maculopathy by ETDRS field as an interaction term. In cases of significant differences among various groups, the Tukey post-hoc comparison was performed. The Spearman coefficient was used in the analysis of correlation among different parameters.

Correlation between retinal thickness and retinal sensitivity was performed combining the measures from all fields in all patients, and the Spearman correlation coefficient was computed. For this analysis, the measures of retinal thickness were normalized and described as the percentage difference from the normal data, as reported by Chan and Duker,[21] where the normative central field thickness was 212 ± 20 μm.

Linear regression analysis was also performed, with retinal sensitivity as the dependent variable and normalized thickness as the explanatory variable. We assumed that data were significant if $P < 0.05$. Statistical software (SAS, Cary, NC) was used for all analyses.

Results

Of 32 examined patients, 11 had type 1 and 21 type 2 diabetes; 21 were men and 11 were women. Mean age was 56.1 ± 12.5

TABLE 1. Patients' Data

						Right Eye		Left Eye	
ID	**Gender**	**Age**	**Type**	**Duration**	**Eye**	**Edema**	**VA**	**Edema**	**VA**
1	F	69	1	30	R	NE	0 (20/20)		
2	M	58	1	23	R, L	NCSME	−0,3 (20/10)	NCSME	0,1 (20/26)
3	M	57	2	10	R, L	CSME	0,6 (20/80)	CSME	0,2 (20/32)
4	F	50	1	15	R, L	NCSME	−0,1 (20/16)	NCSME	−0,2 (20/13)
5	M	60	2	5	R, L	CSME	0 (20/20)	CSME	0 (20/20)
6	M	61	2	1	R, L	NE	−0,2 (20/13)	NE	−0,2 (20/13)
7	F	68	2	8	R, L	NCSME	0 (20/20)	NCSME	0,1 (20/26)
8	M	50	2	3	R, L	NCSME	−0,2 (20/13)	NCSME	−0,2 (20/13)
9	M	53	2	4	R, L	NCSME	−0,1 (20/16)	NCSME	−0,1 (20/16)
10	M	57	2	12	R, L	NCSME	1,6 (20/800)	NCSME	1,5 (20/640)
11	M	70	2	15	R, L	CSME	1,2 (20/320)	CSME	0,4 (20/50)
12	F	59	1	15	R, L	NCSME	0,1 (20/26)	CSME	0,5 (20/68)
13	F	54	2	1	R, L	NE	−0,2 (20/13)	NCSME	0 (20/20)
14	M	51	2	10	R, L	CSME	−0,3 (20/10)	NCSME	−0,3 (20/10)
15	M	65	1	20	R, L	CSME	0,4 (20/50)	CSME	−0,1 (20/16)
16	M	66	2	7	R, L	CSME	0,5 (20/68)	NCSME	0,1 (20/26)
17	F	38	1	23	R, L	NCSME	0,1 (20/26)	NE	0 (20/20)
18	F	50	2	4	R	CSME	0,4 (20/50)		
19	F	80	2	13	R, L	NE	0,4 (20/50)	NE	0,1 (20/26)
20	M	55	2	13	R, L	NCSME	0,1 (20/26)	NE	−0,3 (20/10)
21	M	49	1	27	L			NE	0 (20/20)
22	F	52	2	12	R, L	NCSME	0 (20/20)	NE	0 (20/20)
23	M	72	2	25	R, L	NE	0 (20/20)	NCSME	0 (20/20)
24	M	26	–	–	R, L	NCSME	−0,1 (20/16)	NCSME	0 (20/20)
25	M	44	1	10	R, L	CSME	0,4 (20/50)	NCSME	0,3 (20/40)
26	F	61	2	12	R, L	CSME	0,6 (20/80)	CSME	0,1 (20/26)
27	M	49	2	10	R, L	NCSME	0,3 (20/40)	NCSME	−0,1 (20/16)
28	M	77	2	15	R, L	NCSME	1,1 (20/250)	NCSME	0,5 (20/68)
29	M	–	–	–	R, L	NE	−0,3 (20/10)	NCSME	−0,3 (20/10)
30	M	26	1	14	R, L	NCSME	−0,2 (20/13)	NCSME	−0,2 (20/13)
31	F	59	2	3	R, L	NE	0 (20/20)	NE	0 (20/20)
32	M	57	1	30	R, L	NE	−0,2 (20/13)	NE	−0,2 (20/13)

years. Sixty-one eyes were eligible for the study. Three were excluded because of previous macular laser photocoagulation. There was no statistically significant difference in age, type, and duration of diabetes among the three different groups. Of 61 eligible eyes, 16 were graded as NE, 30 as NCSME, and 15 as CSME by two independent, masked retinal specialists (Table 1).

On OCT examination, mean retinal thickness in the central field (field 1) was 217 ± 27.1 μm in the NE group, 246.9 ± 34.8 in the NCSME group and 390.4 ± 93.8 μm in the CSME group ($P < 0.0001$).

Mean OCT five-field retinal thickness was not significantly different between the NE and NCSME groups. The difference was statistically significant between the NE and NCSME groups and the CSME group ($P < 0.05$). Mean retinal thickness was significantly different among the five fields of three groups, (ANOVA, $P < 0.0001$). Therefore, it may be more useful to use the term retinal thickness profile (all five OCT fields) rather than just retinal thickness. The retinal thickness profile varied significantly ($P = 0.005$) in the CSME group compared with the NCSME and the NE group; the latter ones were quite similar (both as values and profile; Fig. 2).

Mean macular sensitivities determined with the MP1 in the OCT corresponding central field, were: 11.9 ± 3.4 dB in the NE group, 9.6 ± 4.4 dB in the NCSME group, and 4.7 ± 3.5 dB in the CSME group ($P < 0.0001$). (Sensitivity raw data are reported in Table 2.) The average duration of the patient's MP1 examination was 9.2 ± 2.5 minutes.

There was no statistically significant difference in mean macular sensitivity (full macular grid) between the NE and NCSME groups. The difference was significant between the NE and NCSME groups and the CSME group ($P < 0.05$). Mean macular sensitivity was significantly different among the different fields of the three groups ($P < 0.0001$). Once again, we suggest the term sensitivity profile rather than sensitivity: The NE and the NCSME groups were similar, whereas the CSME group had a different and lower sensitivity profile (Fig. 3).

There was no statistically significant correlation between mean retinal thickness and mean retinal sensitivity in the NE ($r = 0.12$, $P = 0.30$) and the NCSME ($r = 0.02$, $P = 0.84$) groups. The correlation was significant in the CSME group ($r = -0.48$, $P < 0.0001$; Fig. 4).

Mean visual acuity was significantly different among the three groups: the NE group had −0.07 ± 0.18 logMAR; the NCSME, 0.12 ± 0.48 logMAR; and the CSME, 0.33 ± 0.36 logMAR ($P = 0.0252$).

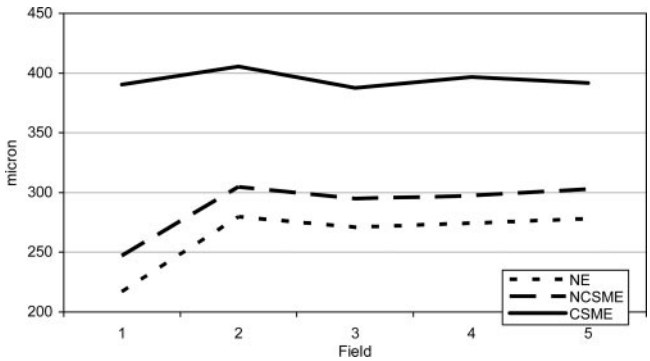

FIGURE 2. Macular thickness by field of assessment (1, central; 2, superior; 3, temporal; 4, inferior; 5, nasal) and severity of maculopathy.

TABLE 2. Classification of Macular Edema and Macular Sensitivity in the Five Examined OCT Fields

ID	Eye	Edema Degree	Mean Sensitivity (dB)				
			1	2	3	4	5
1	R	NE	7.6	8.0	9.6	10.8	6.4
2	L	NCSME	10.0	14.8	10.8	15.3	15.3
2	R	NCSME	10.4	15.3	14.5	15.8	12.3
3	L	CSME	0.4	6.4	3.4	1.1	4.3
3	R	CSME	1.0	3.9	4.5	1.4	1.0
4	L	NCSME	13.4	15.0	16.3	16.7	14.8
4	R	NCSME	13.0	14.0	15.8	16.5	16.3
5	L	CSME	11.6	14.5	16.5	16.0	16.3
5	R	CSME	8.8	16.0	16.0	14.5	11.5
6	L	NE	11.2	13.0	11.8	15.0	12.0
6	R	NE	15.2	14.3	15.0	15.0	15.5
7	L	NCSME	11.4	13.4	14.3	13.6	14.1
7	R	NCSME	8.8	13.8	15.4	14.1	13.6
8	L	NCSME	9.8	13.5	11.5	10.3	12.3
8	R	NCSME	6.6	13.3	11.8	13.3	13.8
9	L	NCSME	11.2	14.3	15.5	15.5	14.8
9	R	NCSME	12.2	15.0	16.8	15.5	15.5
10	L	NCSME	0.2	1.5	4.0	3.1	1.5
10	R	NCSME	0.0	2.0	1.9	1.3	0.0
11	L	CSME	3.2	3.9	0.8	4.3	8.6
11	R	CSME	–	–	–	–	–
12	L	CSME	7.8	10.9	6.6	7.4	12.3
12	R	NCSME	8.4	11.3	14.1	13.9	13.5
13	L	NCSME	12.8	13.8	12.5	13.0	15.0
13	R	NE	9.0	11.3	14.5	9.5	9.0
14	L	NCSME	14.6	14.0	15.0	15.8	13.5
14	R	CSME	7.0	11.8	11.8	15.0	14.5
15	L	CSME	5.4	9.3	6.0	10.5	12.0
15	R	CSME	2.2	2.2	7.0	8.3	2.2
16	L	NCSME	10.4	14.0	14.5	13.5	14.8
16	R	CSME	3.5	9.5	12.8	11.5	14.5
17	L	NE	14.2	16.0	17.3	17.0	16.5
17	R	NCSME	10.0	14.3	12.8	13.0	16.3
18	R	CSME	–	–	–	–	–
19	L	NE	9.2	12.3	14.5	11.8	11.3
19	R	NE	7.0	10.8	13.0	11.8	12.5
20	L	NE	10.8	13.8	15.0	15.0	14.0
20	R	NCSME	11.4	11.0	11.8	12.3	14.0
21	L	NE	14.4	8.3	9.9	7.1	6.5
22	L	NE	11.8	11.5	11.5	9.8	11.3
22	R	NCSME	1.2	0.0	4.0	6.3	0.2
23	L	NCSME	10.2	13.8	14.5	13.0	13.3
23	R	NE	10.8	15.0	16.0	13.0	16.5
24	L	NCSME	15.2	16.5	17.8	15.5	17.1
24	R	NCSME	14.8	16.0	17.3	15.3	17.3
25	L	NCSME	2.2	0.8	3.3	4.6	1.8
25	R	CSME	0.2	0.3	1.6	1.8	2.5
26	L	CSME	6.6	9.8	9.3	7.7	10.5
26	R	CSME	3.6	5.3	6.5	5.4	4.3
27	L	NCSME	14.4	10.3	10.3	7.6	8.3
27	R	NCSME	7.8	8.1	11.1	12.1	9.3
28	L	NCSME	–	–	–	–	–
28	R	NCSME	4.0	9.5	7.6	7.3	11.3
29	L	NCSME	–	–	–	–	–
29	R	NE	–	–	–	–	–
30	L	NCSME	13.2	15.8	16.0	15.8	17.0
30	R	NCSME	12.2	15.5	15.8	17.0	16.8
31	L	NE	20.0	16.0	15.7	15.0	16.7
31	R	NE	15.0	15.7	15.7	17.0	17.3
32	L	NE	9.4	11.8	13.3	12.3	14.0
32	R	NE	12.4	14.5	14.8	15.0	13.5

Field of assessment: 1, central; 2, superior; 3, temporal; 4, inferior; 5, nasal field; blank field, data not available.

There was no statistically significant correlation between visual acuity and sensitivity in any OCT retinal field in the NE group ($r = -0.144$, $P = 0.6$, central field), whereas the correlation was significant in the NCSME group ($r = -0.6$, $P = 0.0008$, field 1). In this group, four of five fields had a statistically significant correlation, whereas the nasal (field 5) had borderline significance. In the CSME group, there was no statistically significant correlation in four of five fields.

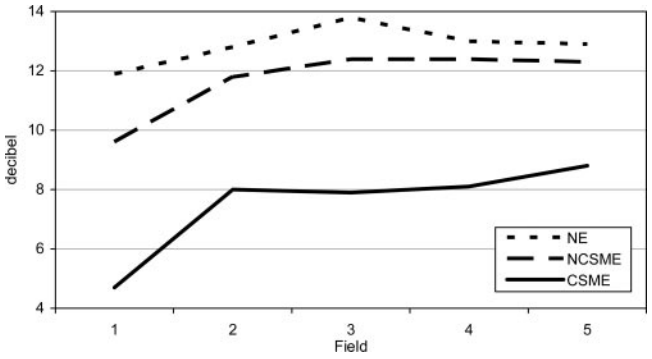

FIGURE 3. Macular sensitivity by field of assessment (see Fig. 2) and severity of maculopathy.

Correlation between visual acuity and retinal thickness in the first OCT field was not statistically significant in the NE group ($r = 0.21$, $P = 0.43$). Both the NCSME and the CSME groups showed a significant correlation between visual acuity and retinal thickness ($r = 0.43$, $P = 0.02$, $r = 0.63$, $P = 0.01$), respectively. All patients had stable and central fixation.

To overcome the possible bias existing between stereoscopic grading of macular edema and OCT thickness, we also analyzed the correlation between macular sensitivity and OCT normalized macular thicknesses, obtained on all fields in all patients and described as a percentage of deviation from the normal values. For normal average values of macular thickness, the data published by Chan and Duker[21] were used (Fig. 5).

There was a significant and fairly good correlation coefficient ($r = -0.37$, $P < 0.0001$) between macular sensitivity and normalized macular thickness. Linear regression analysis showed a significant inverse relationship between macular sensitivity and normalized macular thickness, with a decay of 0.83 dB ($P < 0.0001$) for every 10% of deviation of retinal thickness from normal values.

To evaluate the role of macular sensitivity and normalized macular thickness in explaining the visual outcome, a multiple regression model was used. Macular sensitivity data were statistically significant ($P < 0.0001$), whereas normalized thickness data were not ($P = 0.7260$).

DISCUSSION

Macular edema is the major cause of visual acuity impairment in diabetic patients, and laser photocoagulation has been effective in reducing severe vision loss caused by CSME.[19,22] Macular edema is currently diagnosed and investigated by fundus biomicroscopy, stereo fundus photography, and more recently by OCT. OCT has been claimed as a novel "standard " method for quantifying and monitoring macular edema, even diabetic macular edema.[23,24] Our OCT findings confirmed that retinal thickness progressively increases from the nonedema group toward the CSME group, as previously reported.[25,26] The functional impact of diabetic macular edema is currently quantified by visual acuity, even if this parameter represents just one (and not necessarily the most relevant) of the aspects of macular function.[27–29] Micoperimetry is able to quantify macular sensitivity (and fixation) in an exact, fundus-related fashion, thus adding detailed information about the degree and pattern of macular function alteration.[30] Microperimetry has been successfully used in the diagnosis and follow-up of different macular disorders, including age-related macular degeneration, myopic maculopathy, macular dystrophies, and diabetic macular edema.[4–8,11,30,31–33] Our microperimetry findings showed that macular sensitivity significantly decreases when diabetic macular edema develops and that macular sensitivity deteriorates in eyes at more severe stages of macular edema (Fig. 6).[5,30] We also observed a statistically significant correlation between retinal sensitivity and thickness, in the CSME group only. In the same group, retinal sensitivity decreased in the superior and temporal macular OCT fields (2 and 3) more than in the nasal one (field 5). Wolf et al.[34] emphasized that the temporal part of the macula is characterized by lower capillary density and thus is the first one to become ischemic. Remky et al.[35] demonstrated that the alteration of the perifoveal network are related to selective disturbances of visual function as measured by blue-on-yellow perimetry. Although we have not described the angiographic features of our subjects, all our patients with macular edema (NCSME and CSME groups) had macular leakage, but no signs of significant ischemic alterations. Thus, macular ischemia may not be the key factor explaining decreasing macular sensitivity in eyes affected by macular edema.

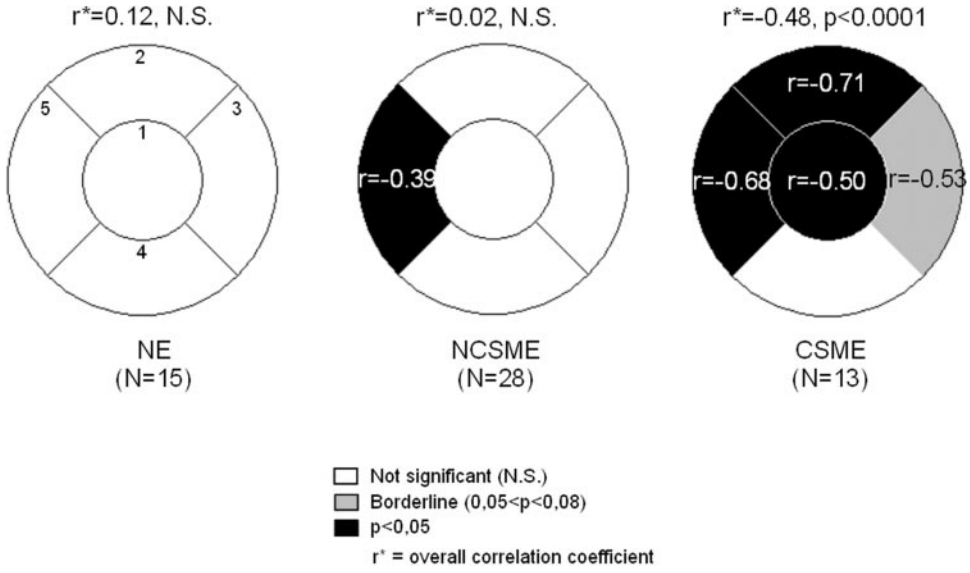

FIGURE 4. Spearman's correlation coefficient (r) between retinal thickness and sensitivity. Data for each field of assessment (a schematic drawing of the macular region corresponding to five OCT fields numbered for convenience only in the first chart: 1, central; 2, superior; 3, temporal; 4, inferior; 5, nasal field) and the overall correlation (r^*), regarding the three groups of macular edema severity are reported.

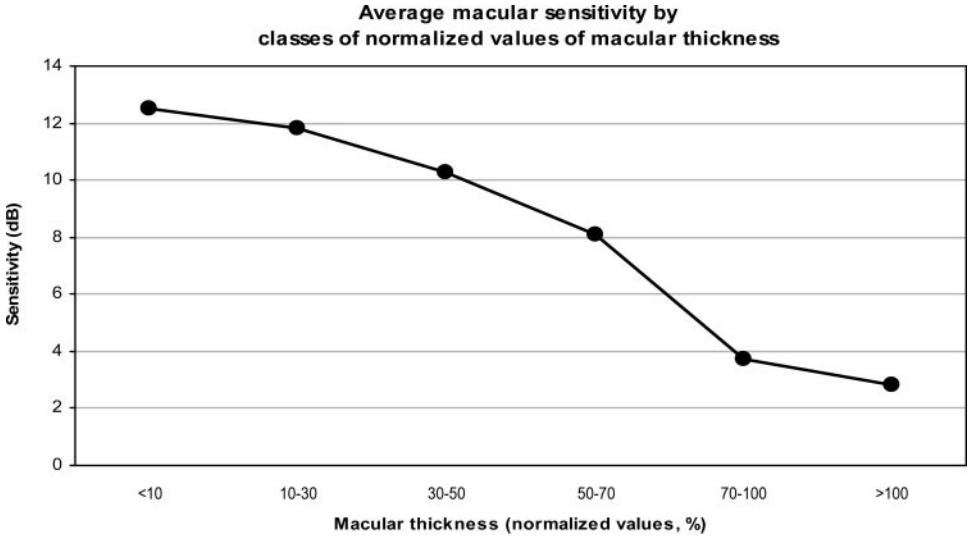

FIGURE 5. Correlation between macular sensitivity and normalized macular thicknesses in all five fields. The normalized thicknesses are described as a percentage of deviation from the normal average values for a given OCT field, published by Chan and Duker.[21]

To overcome any bias when describing correlation between macular thickness and sensitivity, we recalculated OCT data in all fields of all patients after normalizing OCT measurements, as suggested by Chan and Duker.[21] We found a significant inverse relationship between retinal sensitivity and normalized thicknesses, with a decay of 0.83 dB ($P < 0.0001$) for every 10% of deviation of retinal thickness from the normal measurements obtained with OCT. This means that normalized macular thick-

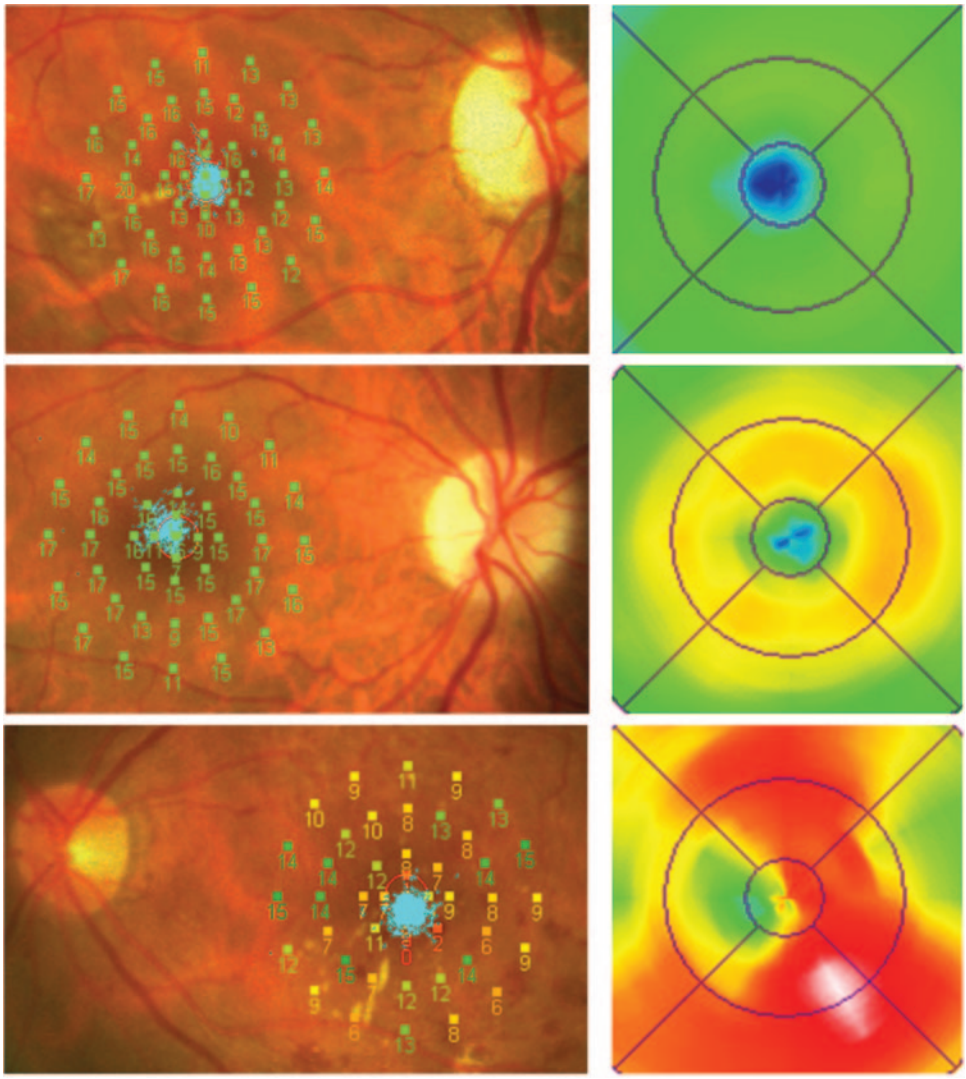

FIGURE 6. MP1 sensitivity and fixation stability maps and OCT five-field thickness maps. *Top*: a patient with NE. *Middle*: a patient with NCSME. *Bottom*: a patient with CSME.

ness agrees better with macular function than any absolute value.

Fixation was stable and central in almost all eyes, independent of edema classification. These data disagree with previous studies in which fixation stability was significantly decreased in diabetic patients compared with control subjects, particularly in eyes with CSME.[6,30] These results may be explained by the inclusion in the latter studies of eyes with long-standing foveal involvement by plaque exudates, which induce dense scotomas. Stability of fixation in eyes with diabetic macular edema (and no foveal plaque exudates) may be explained by the fact that diabetic retinopathy is not primarily a photoreceptor disease, but a vascular and neuronal disease.[36–38] Conversely, in other macular diseases such as age-related macular degeneration, Stargardt disease and others in which the photoreceptors layer is the first to be affected (as demonstrated by autofluorescence detection), fixation becomes unstable in the earlier stages of the disease.[39–41] In these conditions, the fixation pattern is often very unstable and eccentric, and visual outcome, especially the reading ability, is very poor.[11,42,43]

Visual acuity correlated significantly with retinal thickness of the central OCT field in both the NCSME and CSME groups. Because our clinical classification of diabetic macular edema was based on standard ETDRS stereoscopic grading, the NCSME group clinically showed no edema in the fovea.[13] Therefore foveal thickness should be normal or near normal, and visual acuity not significantly decreased by retinal edema in this group. But mean retinal thickness in the central field (field 1) of NCSME eyes was mildly increased (mean: 246.9 ± 34.8 μm) on OCT examination.[44] Therefore, OCT data seem to correlate better with visual acuity than the stereoscopic grading of diabetic macular edema.

The relationship among visual acuity, macular sensitivity, and macular thickness may be better understood when using OCT normalized data. Our data suggest that macular sensitivity is probably one of the best predictors of visual outcome in eyes with diabetic macular edema. A retinal sensitivity map gives more information about central macular function because it documents any individual area where function is altered. Moreover, a microperimetry map may be automatically performed over the same area during follow-up.[11,45] This allows monitoring central retinal function in detail, to document, for example, tiny scotomatous areas that may or may not affect visual acuity, but may be perceived by the patient as visual disturbances.

Over the past years we have been frequently struck by the apparent disparity between the appearance of macular edema and visual disturbances in patients with diabetic macular edema. Microperimetry findings point to the importance of factors not merely related to the thickness of the retina as prognosticators of macular function. Duration of edema and alterations of retinal neural elements may be among them. The parameter "duration, " which cannot be quantified in a cross-sectional study, may have a relevant impact on the survival and/or functional reserve of macular cells undergoing the mechanical and toxic stress induced by edema.[46] We need a long-term prospective study of diabetic eyes without edema at baseline to document the morphologic and functional natural history of diabetic macular edema. This study could also contribute indirectly to the clarification of why patients with similar edema characteristics and similar diabetic control have different prognoses after therapeutic intervention. The role of degeneration of neuronal retinal cells (particularly Müller, lateral interacting, and ganglion cells) in diabetic retinopathy has been recently re-emphasized.[36,47,48] The number of intact neural elements connecting the inner and outer retina layers in diabetic macular edema has been tentatively postulated as a predictive factor of visual function response to therapeutic intervention, better than central foveal thickness alone (Thomas RJ, et al. *IOVS* 2005:ARVO E-Abstract 388). The two reported parameters (edema duration and neural degeneration) are not necessarily independent, and their relationship needs more investigation. Duration of edema may be, in the future, one of the key factors explaining focal and diffuse retinal sensitivity damage, which is better documented with microperimetry rather than just observation of visual acuity.

In conclusion, retinal thickening due to diabetic macular edema can be adequately quantified using OCT, but microperimetry seems to offer a new insight in the analysis of the edematous macula, because it incorporates a functional measure that may potentially supplement the predictive value of OCT and visual acuity. Therefore, microperimetry may be of value in predicting the functional outcome of diabetic macular edema after interventions that seem equally effective in restoring normal foveal thickness. Prospective studies of larger samples are warranted to test the ability of microperimetry to make a point-by-point prediction of functional outcome after various forms of intervention.

References

1. Klein R, Moss SE, Klein BE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. XI. The incidence of macular edema. *Ophthalmology*. 1989;96:1501–1510.
2. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology*. 1998;105:1801–1815.
3. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21:1414–1431.
4. Mori F, Ishiko S, Kitaya N, et al. Scotoma and fixation patterns using scanning laser ophthalmoscope microperimetry in patients with macular dystrophy. *Am J Ophthalmol*. 2001;132:897–902.
5. Rohrschneider K, Bultmann S, Gluck R, et al. Scanning laser ophthalmoscope fundus perimetry before and after laser photocoagulation for clinically significant diabetic macular edema. *Am J Ophthalmol*. 2000;129:27–32.
6. Mori F, Ishiko S, Kitaya N, et al. Use of scanning laser ophthalmoscope microperimetry in clinically significant macular edema in type 2 diabetes mellitus. *Jpn J Ophthalmol*. 2002;46:650–655.
7. Rohrschneider K, Gluck R, Becker M, et al. Scanning laser fundus perimetry before laser photocoagulation of well defined choroidal neovascularisation. *Br J Ophthalmol*. 1997;81:568–573.
8. Sunness JS, Applegate CA, Haselwood D, et al. Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and Stargardt disease. *Ophthalmology*. 1996;103:1458–1466.
9. Sjaarda RN, Frank DA, Glaser BM, et al. Assessment of vision in idiopathic macular holes with macular microperimetry using the scanning laser ophthalmoscope. *Ophthalmology*. 1993;100:1513–1518.
10. Varano M, Scassa C, Capaldo N, et al. Development of macular pseudoholes: a 36-month period of follow-up. *Retina*. 2002;22:435–442.
11. Midena E, Radin PP, Pilotto E, et al. Fixation pattern and macular sensitivity in eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration: a microperimetry study. *Semin Ophthalmol*. 2004;19:55–61.
12. Ferris FL 3rd, Kassoff A, Bresnick GH, et al. New visual acuity charts for clinical research. *Am J Ophthalmol*. 1982;94:91–96.
13. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. 1991;98:786–806.
14. Early Treatment Diabetic Retinopathy Study Research Group. ETDRS report number 7: Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. *Ophthalmology*. 1991;98:741–756.

15. Hee MR, Puliafito CA, Wong C, et al. Quantitative assessment of macular edema with optical coherence tomography. *Arch Ophthalmol*. 1995;113:1019–1029.
16. Hee MR, Izatt JA, Swanson EA, et al. Optical coherence tomography of the human retina. *Arch Ophthalmol*. 1995;113:325–332.
17. Puliafito CA, Hee MR, Lin CP, et al. Imaging of macular diseases with optical coherence tomography. *Ophthalmology*. 1995;102:217–229.
18. Hee MR, Puliafito CA, Duker JS, et al. Topography of diabetic macular edema with optical coherence tomography. *Ophthalmology*. 1998;105:360–370.
19. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. *Ophthalmology.* 1978;85:82–106.
20. Fujii GY, De Juan E Jr, Sunness J, et al. Patient selection for macular translocation surgery using the scanning laser ophthalmoscope. *Ophthalmology*. 2002;109:1737–1744.
21. Chan A, Duker JS. A standardized method for reporting changes in macular thickening using optical coherence tomography. *Arch Ophthalmol*. 2005;123:939–943.
22. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology.* 1991;98:766–785.
23. Browning DJ, McOwen MD, Bowen RM Jr, et al. Comparison of the clinical diagnosis of diabetic macular edema with diagnosis by optical coherence tomography. *Ophthalmology*. 2004;111:712–715.
24. Strom C, Sander B, Larsen N, et al. Diabetic macular edema assessed with optical coherence tomography and stereo fundus photography. *Invest Ophthalmol Vis Sci*. 2002;43:241–245.
25. Tocino HS, Vidal AA, Maldonado MJ, et al. Retinal thickness study with optical coherence tomography in patients with diabetes. *Invest Ophthalmol Vis Sci*. 2002;43:1588–1594.
26. Yang CS, Cheng CY, Lee FL, et al. Quantitative assessment of retinal thickness in diabetic patients with and without clinically significant macular edema using optical coherence tomography. *Acta Ophthalmol Scand*. 2001;79:266–270.
27. Nussenblatt RB, Kaufman SC, Palestine AG, et al. Macular thickening and visual acuity: measurement in patients with cystoid macular edema. *Ophthalmology*. 1987;94:1134–1139.
28. Larsson J, Zhu M, Sutter F, et al. Relation between reduction of foveal thickness and visual acuity in diabetic macular edema treated with intravitreal triamcinolone. *Am J Ophthalmol*. 2005;139:802–806.
29. Campochiaro PA, C99-PKC412–003 Study Group. Reduction of diabetic macular edema by oral administration of the kinase inhibitor PKC412. *Invest Ophthalmol Vis Sci.* 2004;45:922–931.
30. Kube T, Schmidt S, Toonen F, et al. Fixation stability and macular light sensitivity in patients with diabetic maculopathy: a microperimetric study with a scanning laser ophthalmoscope. *Ophthalmologica*. 2005;219:16–20.
31. Loewenstein A, Sunness JS, Bressler NM, et al. Scanning laser ophthalmoscope fundus perimetry after surgery for choroidal neovascularization. *Am J Ophthalmol*. 1998;125:657–665.
32. Midena E. Psychophysical investigations in myopia. In: Midena E, ed. *Myopia and Related Diseases.* New York: Ophthalmic Communications Society; 2005;120–124.
33. Varano M, Parisi V, Tedeschi M, et al. Macular function after PDT in myopic maculopathy: psychophysical and electrophysiological evaluation. *Invest Ophthalmol Vis Sci*. 2005;46:1453–1462.
34. Wolf S, Arend O, Schulte K, et al. Quantification of retinal capillary density and flow velocity in patients with essential hypertension. *Hypertension*. 1994;23:464–467.
35. 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.
36. Lieth E, Gardner TW, Barber AJ, et al. Retinal neurodegeneration: early pathology in diabetes. *Clin Exp Ophthalmol*. 2000;28:3–8.
37. Barber AJ. A new view of diabetic retinopathy: a neurodegenerative disease of the eye. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27:283–290.
38. Martin PM, Roon P, Van Ells TK, et al. Death of retinal neurons in streptozotocin-induced diabetic mice. *Invest Ophthalmol Vis Sci*. 2004;45:3330–3336.
39. Einbock W, Moessner A, Schnurrbusch UE, et al. FAM Study Group. Changes in fundus autofluorescence in patients with age-related maculopathy: correlation to visual function: a prospective study. *Graefes Arch Clin Exp Ophthalmol*. 2005;243:300–305.
40. Bindewald A, Schmitz-Valckenberg S, Jorzik JJ, et al. Classification of abnormal fundus autofluorescence patterns in the junctional zone of geographic atrophy in patients with age related macular degeneration. *Br J Ophthalmol*. 2005;89:874–878.
41. Lois N, Halfyard AS, Bird AC, et al. Fundus autofluorescence in Stargardt macular dystrophy-fundus flavimaculatus. *Am J Ophthalmol*. 2004;138:55–63.
42. Fujii GY, De Juan E Jr, Humayun MS, et al. Characteristics of visual loss by scanning laser ophthalmoscope microperimetry in eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Am J Ophthalmol*. 2003;136:1067–1078.
43. Rohrschneider K, Gluck R, Blankenagel A, et al. Fixation behavior in Stargardt disease: fundus-controlled studies. *Ophthalmologe*. 1997;94:624–628.
44. Brown JC, Solomon SD, Bressler SB, et al. Detection of diabetic foveal edema: contact lens biomicroscopy compared with optical coherence tomography. *Arch Ophthalmol*. 2004;122:330–335.
45. Springer C, Bultmann S, Volcker HE, et al. Fundus perimetry with the Micro Perimeter 1 in normal individuals: comparison with conventional threshold perimetry. *Ophthalmology*. 2005;112:848–854.
46. Gardner TW, Antonetti DA, Barber AJ, et al. Diabetic retinopathy: more than meets the eye. *Surv Ophthalmol.* 2002;47(suppl 2):S253–S262.
47. Gerhardinger C, Costa MB, Coulombe MC, et al. Expression of acute-phase response proteins in retinal Müller cells in diabetes. *Invest Ophthalmol Vis Sci.* 2005;46:349–357.
48. Lecleire-Collet A, Tessier LH, Massin P, et al. Advanced glycation end products can induce glial reaction and neuronal degeneration in retinal explants. *Br J Ophthalmol*. 2005;89:1631–1633.