RETINAL FIXATION IMPAIRMENT IN DIABETIC MACULAR EDEMA

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Purpose: To evaluate the characteristics of retinal fixation in patients with diabetic macular edema using microperimetry.

Methods: One hundred seventy nine eyes (98 patients) with untreated diabetic macular edema underwent best corrected visual acuity determination (Early Treatment Diabetic Retinopathy Study charts), digital color stereoscopic fundus photos, fluorescein angiography and Optical Coherence Tomography assessment of macula. Fixation and retinal thresholds were determined with an automatic microperimeter.

Results: Best corrected visual acuity (approximate Snellen equivalent) was: 20/25 or better in 90 (52%) eyes, 20/50 to 20/32 in 39 (22.5%) eyes, 20/200 to 20/62.5 in 35 (20.2%) eyes and inferior to 20/200 in 9 (5.2%) eyes. Fixation was central in 128(71.51%), poor central in 26(14.53%) and predominantly eccentric in 25(13.97%) eyes; stable in 133(74.3%), relatively unstable in 42(23.46%) and unstable in 4(2.23%) eyes. Both fixation location and stability were not significantly influenced by edema characteristics (diffuse, focal, cystoid, spongelike, with or without subfoveal neuroretinal detachment), ($P > 0.05$), whereas they were significantly influenced by the presence of subfoveal hard exudates, ($P = 0.004$ and $P = 0.0046$, respectively). Site and stability of fixation were significantly associated, ($P < 0.0001$). Retinal pseudofovea would have been covered by laser photocoagulation in 24(47%) eyes with poorly central and predominantly eccentric fixation and in 29(63%) eyes with relatively unstable and unstable fixation.

Conclusion: Microperimetry shows that fixation location and stability in patients with diabetic macular edema are independent of edema characteristics, except when subfoveal hard exudates are present. Location of pseudofovea may influence treatment strategy.

RETINA 28:1443–1450, 2008

Diabetic macular edema (DME) is the major cause of visual impairment in adult population.[1–3] Visual acuity is used as the gold standard for visual function evaluation in diabetic patients.[4–6] But visual acuity reflects just one of the characteristics of visual function, that frequently does not correlate with the patients' perception of disability.[7,8] Moreover, a recent multicentric, randomized study from Diabetic Retinopathy Clinical Research Network found modest correlation between visual acuity and retinal thickness measured with optical coherence tomography (OCT), and even modest correlation of changes in retinal thickening and visual acuity after focal laser treatment in patients with DME.[9] A better correlation between retinal thickness and visual function in DME may be achieved by means of retinal threshold quantification and fixation patterns determination.[10–15]

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Presentations partially presented at the Euretina Meeting, Monte Carlo, May 2007.

There is no conflict relationship and no conflict of interest.

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In the past, macular threshold was determined by means of Scanning Laser Ophthalmoscope fundus perimeter (SLO 101, Rodenstock Instruments, Germany). This technique does not allow a complete automatic evaluation especially during follow-up examination.[10–12] Microperimeter MP1 (Nidek Gamagori, Japan) is a fundus perimeter, which allows for a completely automatic determination of retinal sensitivity and fixation, that exactly correlates to fundus characteristics.[13–18] In a previous study an inverse relationship between normalized retinal thickness determined with OCT and retinal sensitivity determined with MP1 in patients with DME was found.[13,19]

Although different studies agree that macular sensitivity deteriorates in patients with DME, data about fixation characteristics are quite contrasting.[10–15] Knowledge of fixation characteristics, stability and location, may be important for understanding patient's quality of vision and perhaps planning laser treatment.[10,20,21]

In this study, we analyzed fixation pattern (stability and location) in a cohort of patients with untreated diabetic macular edema and correlated it to different characteristics of DME to determine the cause of fixation impairment in diabetic patients, and the use of this information in planning treatment strategies.

Materials and Methods

Study Population

In this prospective, clinic-based study we examined 179 eyes of 98 consecutive diabetic patients who presented diabetes-related macular edema and who accepted to participate in the study. All patients were recruited from Diabetic Retinopathy Clinics from 2005 to 2007. The exclusion criteria were: 1) any type of previous macular treatment (macular laser photocoagulation, vitrectomy, intraviteral steroids and/or antiangiogenic drugs); 2) ischemic maculopathy; 3) tractional maculopathy; and 4) significant media opacities that precluded fundus examination or imaging.

A written consent form was obtained from all patients as well as the approval from our institutional ethics committees. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

All patients underwent a complete ophthalmologic examination with refraction, best corrected visual acuity determination (BCVA), slit-lamp anterior segment evaluation, and 90-D lens fundus examination, as well as macular stereoscopic fundus photography, fluorescein angiography (FA), OCT and microperimetry.

Study Procedures

Best corrected distance visual acuity (BCVA) for each eye was measured by a certified tester using standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocol at 4 m distance with a modified ETDRS distance chart transilluminated with a chart illuminator (Precision Vision).[22] Visual acuity was scored as the total number of letters read correctly and expressed as Snellen equivalent.

Stereo Fundus Photography and Fluorescein Angiography. Color stereoscopic fundus photographs and FA of ETDRS field 2 were taken in all patients after an adequate dilatation by a certified photographer using the same TOPCON TRC 50IA 35 degree fundus camera (Topcon, Tokyo, Japan), and saved in JPEG format.[23] Two retinal specialists independently graded each pair of images on a 17-inch monitor dedicated for diabetic retinopathy screening. In case of disagreement, the final adjudication was given by the clinical head of the study (E.M.). Retinal thickening was assessed in the same way as in the ETDRS protocol: clinically significant macular edema (CSME) was assigned in case of presence of retinal thickening or hard exudates associated with adjacent retinal thickening within 500 μm of the center of the foveal avascular zone or a presence of an area or areas of retinal thickening of at least 1 disk diameter within 1 disk diameter from the center of the macula.[24] Retinal thickenings observed in field 2 that on biomicroscopic examination did not meet these criteria were classified as nonclinically significant macular edema (NCSME). The presence and site of hard exudates (subfoveal, juxtafoveal) were evaluated separately on color photos and FA images.

FA images were graded for capillary loss, presence and extent of fluorescein leakage (focal and diffuse), and cystoid abnormalities. Diffuse edema was assigned if leakage extended more than 2 disk diameters and was ill-defined.[25]

Optical Coherence Tomography. OCT scanning was performed on the Stratus OCT TM scanner (Zeiss Humphrey Instruments, Germany) with the 3.0 (0.052) version software. The scanning protocol used for this study was "fast macular thickness" program that creates a retinal map algorithm consisting in six radiating cross-sectional scans, each one of 6 mm length that produce a circular plot in which the foveal zone is the central circular zone of 1.00 mm in diameter. For the purpose of this study mean foveal thickness was used as the OCT measurement of foveal thickness. Each single linear scan was independently evaluated by two retinal specialists for vitreo-retinal relationship and for intraretinal structure. In case of

increased foveal thickening, DME was classified as: spongelike thickening, cystoid thickening and subfoveal serous neuroretinal detachment according to Otani et al.[26]

Microperimetry was performed on all subjects using a new automatic microperimeter: the MP1 Microperimeter (Nidek Gamagori, Japan). This instrument has been previously described in detail.[16] For the purpose of this study, the following parameters were used: a fixation target consisting of red ring, 1° in diameter; white, monochromatic background at 4 asb, stimulus size Goldman III, with 200 milliseconds projection time; customized radial grid of 45 stimuli covering central 12° (centered onto the fovea), 1° apart (inner stimuli) and 2° apart (outer stimuli). The starting stimulus light attenuation was set at 10 dB. A 4-2-1 double staircase strategy was used with an automatic eye tracker that compensates for eye movements.[16,17] To allow for better clinical correlation between microperimetric data and retinal details, functional results are always displayed onto a color digital retinography, acquired by the charge-coupled device color camera of MP1. Fixation patterns were analyzed based on data obtained during the sensitivity testing.

Pretest training was performed and 5 minutes visual adaptation was allowed before starting the test. All subjects underwent microperimetry with dilated pupils.

Fixation Classification

Location and stability of fixation were classified and evaluated separately according to the classification proposed by Fujii et al[27] as: predominantly central fixation when more than 50% of the preferred fixation points were located within a 2°-circle area centered in the fovea; poor central fixation when less than 50% but more than 25% of the preferred fixation points (PFP) were located within the 2°-circle; predominantly eccentric fixation when less than 25% of PFP were located within the 2°-circle; stable fixation if more than 75% of the fixation points were located within a predetermined circle area of 2°, regardless the position of the foveal center; relatively unstable fixation if less than 75% of the fixation points were located within a 2°-circle, but more than 75% of the fixation points were located within a 4°-circle; and unstable fixation if less than 75% were located within a 4°-circle.

Main Outcome Measures

To better correlate fixation patterns with different characteristics of DME, stereo-color photos, FA and OCT classifications were used.[23–26]

Initially, fixation patterns were correlated to the presence and type of edema determined on stereoscopic color images as NCSME and CSME, and then based on the type and the extent of FA leakage as focal or diffuse edema.

Fixation was then analyzed in regard to different OCT patterns of CSME as spongelike and cystoid, and subfoveal serous neuroretinal detachment. The presence and site of hard exudates, and its influence on fixation were evaluated on color photos and FA images.

Fixation characteristics were evaluated versus the area of laser treatment, according to the modified ETDRS macular laser photocoagulation protocol.[4]

Table 1. Clinical Characteristics of the Study Eyes

Patient Features	98 Patients
Age (yrs), mean ± SD	58.4 ± 11.2
No. women (%)	39 (39.8%)
Diabetes type, n (%)*	
Type 1	21 (21.2%)
Type 2	77 (78.8%)
Duration of diabetes (yrs), mean ± SD	16.5 ± 11.2
HbA_{1c} %, mean ± SD	7.4 ± 1.7
Eye characteristics	179 eyes
Visual acuity (approximate Snellen equivalent from letter score), n (%)†	
20/25 or better	90 (52.0%)
20/50–20/32	39 (22.5%)
20/200–20/62.5	35 (20.2%)
Worse than 20/200	9 (5.2%)
OCT mean foveal thickness (mm), mean ± SD	
NCSME (n = 32)	179.1 ± 28.4
CSME (n = 147)	317.6 ± 149.1
Cystoid CSME (n = 71)‡	408.6 ± 164.3
Sponge-like CSME (n = 76)‡	231.3 ± 50.2
Hard exudates, n (%)	
No exudates	68 (38.0%)
Juxtafoveal exudates	64 (35.7%)
Subfoveal exudates	47 (26.3%)
Subfoveal neuroretinal detachement, n (%)	
Yes	32 (17.9%)
No	147 (82.1%)
Mean macular sensitivity (dB), mean ± SD	
2 central degrees	
NCSME (n = 32)	15.1 ± 3.4
CSME (n = 147)	9.1 ± 5.6
4 central degrees	
NCSME (n = 32)	15.9 ± 3.3
CSME (n = 147)	10.2 ± 5.6

HbA_{1c} = glycosylated hemoglobin; NCSME = not clinically significant macular edema; CSME = clinically significant macular edema; SD = standard deviation.

*Type of diabetes was defined as insulin dependency before 30 yrs.

†Missing data for 6 eyes.

‡Student's t-test, $P < 0.0001$.

Table 2. Site and Stability of Fixation in NCME and CSME with Different OCT Patterns, n (%)

		CSME			
		Pattern†‡		Subfoveal Neuroretinal Detachment§¶	
Fixation Characteristics	NCSME* (N = 32)	Cystoid (N = 71)	Sponge-like (N = 76)	Yes (N = 31)	No (N = 116)
Site of fixation					
Central	29 (90.6%)	42 (59.2%)	57 (75.0%)	21 (67.8%)	78 (67.2%)
Poor central	2 (6.3%)	15 (21.1%)	9 (11.8%)	5 (16.1%)	19 (16.4%)
Eccentric	1 (3.1%)	14 (19.7%)	10 (13.2%)	5 (16.1%)	19 (16.4%)
Stability of fixation					
Stable	27 (84.4%)	47 (66.2%)	59 (77.6%)	19 (61.3%)	87 (75.0%)
Relatively unstable	5 (15.6%)	21 (29.6%)	16 (21.1%)	11 (35.5%)	26 (22.4%)
Unstable	0 (0.0%)	3 (4.2%)	1 (1.3%)	1 (3.2%)	3 (2.6%)

NCSME = not clinically significant macular edema; CSME = clinically significant macular edema.
*All eyes had sponge-like pattern of edema.
†Association with site of fixation: Fisher's exact test, P = 0.129, N.S.
‡Association with stability of fixation: Fisher's exact test, P = 0.260, N.S.
§Association with site of fixation: Fisher's exact test, P = 1.000, N.S.
¶Association with stability of fixation: Fisher's exact test, P = 0.216, N.S.

Statistical Methods

Group characteristics were summarized according to the usual methods of descriptive statistics. Associations between the site and stability of fixation and type of edema (NCSME and CSME) as well as topographical classification (focal and diffuse) were tested by means of Fisher's Exact Test applied to contingency tables.[28] Association between OCT patterns of DME such as: cystoid, spongelike and neuroretinal detachment and presence and site of hard exudates were tested by means of Fisher's Exact test. Mean values of foveal thickness in different OCT patterns of edema were compared by means of t-Student's test. Association between visual acuity and fixation's characteristics (site and stability) was tested by means of Fisher's Exact test. Mean values of foveal thickness among site and stability of fixation were compared by means of 2-way analysis of variance model. Relationship between site and stability of fixation and possible laser treatment was tested by means of Fisher's Exact test.

In all statistical analyses, $P < 0.05$ was considered statistically significant. All analyses were performed by SAS 9.1.3 statistical package on personal computer.[29]

Results

Of 98 examined patients, 59 were males and 39 females. Mean age was 58.4 ± 11.2 years. Eighty one patients had two study eyes and 17 patients had one study eye for a total of 179 eyes. All patients were white-European. Twenty one patients had Type 1 diabetes and 77 Type 2 diabetes with mean duration of 17 ± 11 years. Mean HbA1C was 7.4% ± 1.7%. Of 179 examined eyes, 32 were graded as NCSME and 147 as CSME. Location of fixation was: central in 128

Table 3. Site and Stability of Fixation by Site of Hard Exudates, n (%)

	Hard Exudates		
Fixation Characteristics	Subfoveal (N = 47)	Juxtafoveal (N = 64)	No Exudates (N = 68)
Site of fixation*			
Central	24 (51.1%)	49 (76.6%)	55 (80.9%)
Poor central	10 (21.3%)	7 (10.9%)	9 (13.2%)
Eccentric	13 (27.7%)	8 (12.5%)	4 (5.9%)
Stability of fixation†			
Stable	27 (57.5%)	52 (81%)	54 (79.4%)
Relatively unstable	16 (34.0%)	12 (19%)	14 (20.6%)
Unstable	4 (8.5%)	0 (0%)	0 (0.0%)

*Fisher's exact test, P = 0.004.
†Fisher's exact test, P = 0.005.

Table 4. Mean Foveal Thickness by Site and Stability of Fixation With and Without Subfoveal Hard Exudates

	Subfoveal Hard Exudates*		No or Iuxtafoveal Hard Exudates†	
	N	Mean (SD)	N	Mean (SD)
Site of fixation				
Central	24	305.5 (132.6)	104	261.5 (119.3)
Poor central	10	308.2 (100.1)	14	365.3 (181.3)
Eccentric	13	328.8 (149.4)	12	409.3 (256.0)
Stability of fixation				
Stable	27	296.3 (120.6)	105	262.2 (119.8)
Relatively unstable	16	301.6 (122.4)	25	387.8 (217.5)
Unstable	4	465.5 (143.7)	0	

*2-way ANOVA: Site factor P = 0.7864; Stability factor P = 0.1938.
†2-way ANOVA: Site factor P = 0.0041; Stability factor P = 0.0015.

(71.5%) eyes, poor central in 26 (14.5%) and predominantly eccentric in 25 (14%) eyes. Stability of fixation was: stable in 133 (74.3%) eyes, relatively unstable in 42 (23.5%) and unstable in 4 (2.2%) eyes.

NCSME Eyes. Seventeen (53.1%) eyes had focal DME and 15 (46.9%) eyes diffuse DME based on FA. On OCT all eyes had spongelike pattern. Fixation was central in 29 (91%) eyes and stable in 27 (84%) eyes.

CSME Eyes. Thirty-four (23.1%) had focal DME and 113 (76.9%) diffuse DME based on FA. OCT patterns were: cystoid pattern in 71 (48.3%) eyes and spongelike pattern in 76 (51.7%) eyes. Subfoveal neuroretinal detachment was present in 32 (17.9%) eyes. Mean central foveal thickness was 231.3 ± 50.2 μ in eyes with spongelike pattern, and 408.6 ± 164.3 μ in eyes with cystoid pattern, ($P < 0.0001$). Major clinical characteristics of the study eyes are reported in Table 1.

In CSME eyes, there was no significant difference between OCT pattern of edema and both location and stability of fixation, (Fisher's Exact test: P = 0.129, and P = 0.26, respectively). (Table 2.) There was no significant difference between location and stability of fixation and the presence/absence of subfoveal serous neuroretinal detachment, (Fisher's Exact test: P = 1.00 and P = 0.216, respectively) (Table 2.)

When subfoveal hard exudates were present fixation moved significantly to an eccentric site in 13 (28%) eyes and became unstable in 4(9%) eyes, when compared with both juxtafoveal exudates or no exudates, (Fisher's Exact test: P = 0.004 and P = 0.005, respectively) (Table 3).

In eyes without subfoveal hard exudates, increased retinal thickness was found when eccentric and relatively unstable fixation were present, (P = 0.0041 and P = 0.0015, respectively), whereas in eyes with subfoveal hard exudates retinal thickness was not significantly different among different fixation patterns (P = 0.79 and P = 0.19, respectively). (Table 4) There was significant association between site and stability of fixation and visual acuity ($P < 0.0001$, respectively) (Table 5.) Figure 1 shows the relation between site and stability of fixation.

When fixation is central and stable planned laser treatment (according to the ETDRS protocol) never

Table 5. Site and Stability of Fixation by Visual Acuity, n (%)

	Visual Acuity			
Fixation Characteristics	<20/200 (N = 9)	20/200–20/62.5 (N = 35)	20/50–20/32 (N = 39)	20/25 or better (N = 90)
Site of fixation*				
Central	2 (22.2%)	18 (51.4%)	26 (66.7%)	78 (86.7%)
Poor central	3 (33.3%)	8 (22.9%)	8 (20.5%)	7 (7.8%)
Eccentric	4 (44.4%)	9 (25.7%)	5 (12.8%)	5 (5.6%)
Stability of fixation†				
Stable	2 (22.2%)	19 (54.3%)	27 (69.2%)	80 (88.9%)
Relatively unstable	7 (77.8%)	13 (37.1%)	12 (30.8%)	9 (10.0%)
Unstable	0 (0.0%)	3 (8.6%)	0 (0.0%)	1 (1.1%)

*Fisher's exact test, $P < 0.0001$.
†Fisher's exact test, $P < 0.0001$.

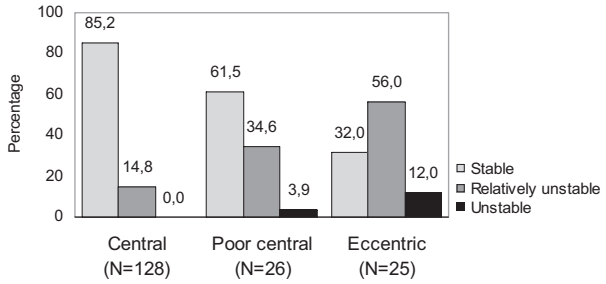

Fig. 1. Graph showing the relationship between 2 different fixation characteristics: site and stability expressed as percentage of 179 eyes.

impacts on fixation points. When fixation is neither central nor stable, retinal pseudofovea would be covered by laser in 24 (47%) eyes with poorly central and predominantly eccentric fixation and in 29 (63%) eyes with relatively unstable and unstable fixation.

Discussion

Microperimetry has been recently used for several macular disorders to exactly and directly correlate fundus details with retinal function.[13–18,30,31] In DME, correlation between retinal sensitivity determined with microperimetry and visual acuity in patients with CSME varies in different studies,[10,13,14] whereas, reduced retinal sensitivity is related to increasing retinal thickness.[12–14]

Microperimetry seems to represent a better functional testing than BCVA for quantifying visual function in diabetic patients, because it incorporates a functional measure that may potentially supplement the predictive value of OCT and visual acuity.[13,14]

Besides retinal sensitivity, microperimetry allows to quantify retinal fixation characteristics. Fixation characteristics (location and stability) are relevant parameters for the quality of vision, especially reading ability. Reading ability better correlates with subjective quality of vision rather than distant visual acuity.[10] In this study we evaluated fixation patterns obtained during microperimetry examination in a large cohort of patients with DME. Our data show that fixation patterns are not significantly influenced by either topographical extension of edema (focal or diffuse), or by the OCT classification of edema. We did not find significant difference between the presence of intraretinal cysts and fixation pattern. Kube et al. found decreased fixation stability in patients with DME using SLO-microperimetry.[12] Unfortunately, this technique is limited by the manual control of fixation versus stimulus presentation. Carpineto et al found that all eyes with eccentric or unstable fixation had cystoid DME.[15] Our data show that among eyes with eccentric fixation 58.3% (14 eyes) had cystoid pattern, whereas among eyes with unstable fixation cystoid pattern was found in 75% (3 eyes). We can speculate that the difference between our data and Carpineto et al data might be due to different duration of DME.[15] Duration of diabetic macular edema, which cannot be exactly quantified in a cross sectional study, might have a relevant impact on the survival and/or functional reserve of macular cells undergoing mechanical and toxic stress induced by edema. Only a prospective study of diabetic eyes without edema at baseline will be able to document the morphologic and functional natural history of diabetic macular edema.

We found a significant association between site and stability of fixation and visual acuity. Almost 80% of the eyes with BCVA $<$20/200 had poor central/eccentric and relatively unstable fixation, whereas approximately 90% of the eyes with BCVA $\geq$20/25 had central or stable fixation.

Moreover, our data document that fixation pattern is not significantly influenced by the presence of subfoveal serous neuroretinal detachment, showing a different fixation behavior compared with age related macular degeneration.[16] Significant fixation changes were found when subfoveal hard exudates were present, despite DME characteristics. Previous studies have shown that hard exudates may be associated with both photoreceptor and neuronal degeneration in the outer plexiform layer.[20,21,32] Foveal hard exudates may be early associated with dense scotoma and retinal fixation deterioration.[20,21,32] In these cases, knowledge of fixation location and stability is fundamental to avoid laser treatment complications due to the treatment of newly developed fixation area.

According to our data, in patients with DME without subfoveal hard exudates fixation is well preserved. This behavior differs from other macular disorders, such as age related macular degeneration, macular dystrophies etc., where fixation deteriorates at early stages.[16,33] It seems that in patients with DME, photoreceptor damage occurs as a late phenomenon, and probably is not related to intraretinal cysts formation. In diabetic retinopathy, retinal neurodegeneration may precede photoreceptor loss, as previously reported.[34]

Therefore, reduction of macular sensitivity may be observed before fixation impairment has occurred. From our data, a direct and simple relation between retinal cysts and fixation characteristics is at least questionable. The clinical impact of fixation data are, therefore, mainly limited to eyes with foveal hard exudates.

Currently, modified ETDRS photocoagulation is the standard in the treatment of DME with or without

hard exudates. According to our data, modified ETDRS grid may impair the new area of fixation (pseudofovea) which develops in these eyes. Therefore, we suggest that reducing foveal exudation with alternative therapies (such as intravitreal drugs) may be followed by return of central fixation, and then laser treatment could be safely applied, avoiding the anatomic and functional destruction of retinal pseudofovea. This hypothesis will be confirmed (or not) by the prospective analysis of this cohort.

Key words: diabetic macular edema, fluorescein angiography, microperimetry, OCT, retinal fixation.

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