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Original Article / *Özgün Araştırma*

Assessment of Macular Sensitivity and Fixation Stability by MP-1 Microperimetry in Diabetic Macular Edema

Diabetik Makula Ödeminde MP-1 Mikroperimetri ile Fiksasyon Stabilitesi ve Makuler Duyarlılığın Değerlendirilmesi

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Summary

Purpose: To evaluate macular light sensitivity and fixation stability in subjects with clinically significant macular edema (CSME) related to diabetes mellitus.

Material and Method: Thirty eyes of 22 patients with CSME, as defined by Early Treatment Diabetic Retinopathy Study, and 32 eyes of 32 healthy subjects were enrolled in this study. Microperimetry was performed with the Micro Perimeter MP-1 in both groups. The mean retinal sensitivities at central 4°, at central 12° and at central 20° were measured. The mean extent of preferred retinal locus (PRL), fixation stability and fixation location were calculated using fixation test in MP-1 microperimeter. Statistical analysis was performed using student t-test and chi-square test.

Results: The mean best-corrected visual acuity (BCVA) was significantly lower in the CSME group than the control group ($p<0.001$). The mean retinal sensitivities at central 4°, 12° and 20° areas were significantly lower in the CSME group compared to the control group ($p<0.001$, for each central degrees). In subjects with CSME, fixation stability was detected as stable in 8 (26.7%) eyes, relatively unstable in 21 (70%) eyes and unstable in 1 (3.3%) eye. Significant decrease was found in fixation stability and fixation location scores in eyes with CSME compared to control subjects ($p<0.001$). The difference of mean extent in PRL between the groups was statistically significant ($p<0.001$).

Discussion: The macular light sensitivity and fixation stability are affected in patients with CSME. MP-1 micropeimetry might be helpful to evaluate the extent of PRL and useful for evaluation of severity and progression of diabetic macular edema. *(Turk J Ophthalmol 2012; 42: 310-5)*

Key Words: Clinically significant macular edema, fixation stability, MP-1 microperimetry, preferred retinal locus

Özet

Amaç: Diabetes mellitusa bağlı klinik olarak anlamlı makula ödemi (KAMÖ) olgularında fiksasyon stabilitesi ve makula ışık duyarlılığını değerlendirmek.

Gereç ve Yöntem: Diabetik Retinopati Erken Tedavi Çalışması tanı kriterlerine göre klinik olarak anlamlı makula ödemli 22 olgunun 30 gözü ve sağlıklı 32 olgunun 32 gözü çalışmaya dahil edildi. Tüm olgulara Micro Perimeter MP-1 ile mikroperimetri uygulandı. Santral 4, 12 ve 20 derecelik alanlarda ortalama retinal duyarlılık ölçüldü. MP-1 mikroperimetrede fiksasyon testi kullanılarak tercih edilen retinal alan (TERA) genişliği, fiksasyon stabilitesi ve alanı hesaplandı. Student t testi ve ki kare testi kullanılarak istatistiksel analiz yapıldı.

Sonuçlar: KAMÖ grubunda ortalama en iyi düzeltilmiş görme keskinliği (EDGK) kontrol grubuna göre anlamlı olarak düşüktü ($p<0,001$). KAMÖ grubunda santral 4, 12 ve 20 derecelik alanlarda ortalama retinal duyarlılık kontrol grubuna göre anlamlı olarak daha düşüktü ($p<0,001$, her derece için). KAMÖ olgularında fiksasyon stabilitesi, 8 (%26,7) gözde stabil, 21 (%70) gözde rölatif stabil ve 1 (%3,3) gözde unstabil olarak saptandı. KAMÖ'li gözlerde kontrol grubuna gore fiksasyon stabilesi ve fiksasyon alan skorları anlamlı olarak düşük bulundu ($p<0,001$). Gruplar arasında TERA ortalama genişliği farkı istatistiksel olarak anlamlıydı ($p<0,001$).

Tartışma: KAMÖ'li hastalarda makula ışık duyarlılığı ve fiksasyon stabilitesi etkilenmektedir. MP-1 mikroperimetre TERA genişliğinin incelenmesinde yardımcı ve diabetik makula ödeminin düzeyi ve progresyonun değerlendirilmesinde kullanışlı olabilir.*(Turk J Ophthalmol 2012; 42: 310-5)*

Anahtar Kelimeler: Klinik anlamlı makula ödemi, fiksasyon stabilitesi, MP-1 mikroperimetre, tercih edilen retinal alan

Introduction

Diabetic maculopathy is a sight-threatening complication in diabetes mellitus, frequently leading to legal blindness.[1,2] Before central visual acuity is deteriorated, patients with macular edema may suffer from some disturbances of visual function such as metamorphopsia, blurring, relative scotoma, loss of fixation and decrease of contrast sensitivity, which are not assessed and quantified in routine examination.[3,4] Thus, evaluation of visual acuity alone may not represent the visual function and the

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severity of diabetic maculopathy sufficiently. However, the functional effect of diabetic macular edema is currently quantified by visual acuity which represents one of the aspects of macular function. Fixation characteristics are critical for reading and visual performances, and any variation of size, shape, and intensity of scotoma may affect visual function. Microperimetry allows to exactly quantify the location and stability of fixation, and retinal threshold in the macular area[5-10].

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[5-13]. Microperimetry, used for the examination of macular function, is able to quantify macular sensitivity and fixation adding detailed information about the degree and pattern of macular function alteration. Microperimetry has been shown to correspond with visual parameters and macular morphology[10,14-16].

Fundus-related microperimeter, MP-1 (Nidek Technologies, Padua, Italy), can be used to provide quantitative and reliable assessment of retinal sensitivity by tracking eye movements, while the patient is focused on a fixation target. This system uses a high-speed tracking software which monitors fundus movements to ensure that the anatomic landmarks revealed in fundus photographs are precisely aligned with the sensitivity maps generated by the perimeter. This instrument allows the overlaying of retinal sensitivities onto a real-colour fundus image to indicate the retinal areas where visual defects coincide with visible structural anomalies[13,17,18].

In this study, we evaluated macular light sensitivity and fixation characteristics by MP-1 microperimetry in patients with diabetic macular edema and compared it with age-matched healthy controls.

Material and Methods

Thirty eyes of 22 diabetic patients with clinically significant macular edema (CSME) as defined by Early Treatment Diabetic Retinopathy Study were included in this study.[19] The age of the patients ranged from 45 to 71 years (mean: 60.5±8.5 years). After medical and ocular history, all patients underwent a complete ophthalmic examination, including determination of best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, indirect ophthalmoscopy, and fundus fluorescein angiography (FFA). BCVA expressed as logMAR was obtained at a distance of 4 m. The macular edema was determined by stereoscopic fundus examination using the 90-diopter lens or the Goldmann three-mirror lens. For confirmation, a FFA was performed in all eyes. For patients with CSME, subjects with systemic disease except diabetes mellitus, previous intraocular surgery and inflammation, a history of ocular trauma and retinal diseases were excluded from the study. The control group consisted of 32 healthy volunteers aged between 48-70 years (mean: 58.0±6.3 years), without any ophthalmic or systemic disease that could affect visual or macular function. Microperimetric evaluation was done with MP-1 microperimetry in patients with CSME and control subjects. The study was conducted in accordance with the tenets of the Declaration of Helsinki Principle. Informed consent was obtained from all subjects.

Microperimetry was performed with the Micro Perimeter MP-1 (MP-1, Software 1.6.0, Nidek Technologies, Italy). The MP-1 provides a 45° nonmydriatic view of the fundus with automated correction for eye movements. A 4-2 staircase strategy with Goldmann III white stimulus was used, and a circular test grid with 76 stimulus locations covering an area of 20° was examined. The fixation target was 1° red cross. The contralateral eye was occluded during examination. The background luminance of the instrument is 1.27 cd/m^2, whereas the luminance of the highest stimulus intensity is 127cd/m^2. The stimuli attenuations range from 0 to 20 dB with Goldmann-type size. The stimuli were presented for 200 milliseconds. A 4-2 staircase strategy was then carried out, and the last seen threshold value was taken as the final threshold. The mean retinal sensitivities at 28 locations covering the central 4°, at 48 locations covering central 12°, and at 76 locations covering central 20° were determined. The mean retinal sensitivities were compared by calculating selected points in a polygon, which were averaged automatically by the MP-1 microperimetry software.

The recorded fixation points were classified into three categories for fixation stability analysis (stable, relatively unstable, and unstable). Fixation was regarded as 'stable' if more than 75% of the fixation points were inside the 2° diameter circle, as 'relatively unstable' if less than 75% were inside the 2° diameter circle but more than 75% inside the 4° diameter circle, and as 'unstable' if less than 75% of the fixation points were inside the 4° diameter circle. To assess fixation location, a standard, the standard 2° circle was placed by looking for the centre of the foveal avascular zone (FAZ). Fixation location was regarded as 'predominantly central' if more than 50% of fixation points were located inside the 2° circle foveal circle, as 'poor central' if 25% - 50% of fixation points inside the circle and as 'predominantly eccentric' if less than 25% of fixation points were inside the circle. Fixation characteristics were classified automatically by the MP-1 microperimetry software, after a landmark had been positioned in the centre of the FAZ.

The fundus movements were tracked during the patient gazed at the fixation target for the assessment of fixation. The horizontal and vertical shifts relative to a reference frame were calculated and a map of the patient's eye movements during the examination was drawn by autotracking system. The extent of preferred retinal locus (PRL) in the fixation test was shown as the

X- and Y-degree index. The mean extent of PRL was calculated from the doubling of the square root of the product of the X- and Y-degree indices. [6]

Data obtained from both groups showed normal distribution which was tested using the Kolmogoroff-Smirnov test. Results were expressed as mean ± standard deviation. Statistical analysis was performed using SPSS package program version 13.0. Mean values were compared using the student's t-test. Fixation stability and fixation localization values were analyzed with chi-square test between groups. For correlations, Pearson correlation analysis was used. A p-value of <0.05 was considered statistically significant.

Results

Mean duration of diabetes mellitus was 11.2±4.9 years in the CSME group. The mean BCVA was significantly lower in the CSME group compared to the control group (p<0.001). The BCVA and mean retinal sensitivities at central 4°, 12°, and 20° areas measured with the MP-1 are given in Table 1. Mean retinal sensitivities at central 4°, 12°, and 20° areas were also significantly lower in the CSME group compared to the control group (p<0.001, for each central degrees). Mean examination time in the CSME group was significantly higher than the control group (p<0.001). Mean defect was detected as -10.3±3.4 in the CSME group and as 0.84±0.8 in the control group (p<0.001).

Fixation stability was detected as stable in 8 (26.7%) eyes, relatively unstable in 21 (70%) eyes and unstable in 1 (3.3%) eye in the CSME group, whereas 32 (100%) eyes were stable in the control group (p<0.001). Both the percentage of fixation points within central 2° and the percentage of fixation points within central 4° were significantly lower in the CSME group compared to the control group (p<0.001). Fixation location was detected as predominantly central in 18 (60%) eyes, poor central in 11 (36.7%) eyes, predominantly eccentric in 1 (3.3%) eye in the CSME group, whereas 32 (100%) eyes were predominantly central in the control group (p<0.001). Percentage of fixation points within the central 2° in patients with predominantly central fixation in the CSME group was significantly lower than in patients with predominantly central in the control group (p<0.001) (Figure 1, 2).

The mean extent of PRL with MP-1 fixation test was 8.5±3.7 (ranged from 0.4° to 6.3°) in the CSME group and 4.5±2.3 (ranged from 0.5° to 3.3°) in the control group. The difference in mean extent of PRL between the groups was statistically significant (p<0.001) (Table 2).

The mean retinal sensitivity at central 4° correlated with BCVA (r=0.37, p=0.04), but no correlation with BCVA was found at central 12° (r=0.23, p=0.213) and at central 20° (r=0.21, p=0.248) in the CSME group. There was no correlation between fixation stability score and BCVA (r=-0.05, p=0.767) and between fixation location score and BCVA (r=0.07, p=0.696) in the CSME group. The mean extent was not significantly correlated with BCVA in the CSME group (r=0.14, p=0.462).

Table 1. Demographic data and mean retinal sensitivies measured with MP-1 microperimetry in patient and control groups. (mean±SD, range)

	CSME group (n=30)	Control group (n=32)	p value
Age, years	60.48±8.5	58±6.3	0.212
Sex (female/male)	16/14	16/16	0.993
Diabetes mellitus, years	11.2±4.9	None	
BCVA (logMAR)	0.5±0.21	0.09±0.02	0.001
Mean examination time	21.8±5.1	9.1±2.7	0.001
Mean retinal sensitivity (dB)			
Central 4°	7.1±4.0	18.9±0.9	0.001
Central 12°	8.1±3.7	19.1±0.6	0.001
Central 20°	8.2±3.7	18.7±0.9	0.001
Mean defect (dB)	-10.3±3.4	0.84±0.8	0.001

CSME: Clinically significant macular edema, BCVA: Best-corrected visual acuity

Table 2. Fixation characteristics classified automatically with MP-1 microperimetry in patient and control groups

	CSME group (n=30)	Control group (n=32)	p value
Fixation stability*			0.001
Stable	8 (26.7%)	32 (100%)	
Relatively unstable	21 (70%)	None	
Unstable	1 (3.3%)	None	
Percentage of fixation points within the central 2°	61.8±21	92.8±2.7	0.001
Percentage of fixation points within the central 4°	91.6±8.6	98.5±2.4	0.001
Fixation location*			0.001
Predominantly central	18 (60%)	32 (100%)	
Percentage of fixation points within the central 2°	72.2±15.2	93.6±7.4	0.001
Poor central	11 (36.7%)	None	
Percentage of fixation points within the central 2°	42.1±4.9	-	
Predominantly eccentric	1 (3.3%)	None	
Percentage of fixation points within the central 2°	24	-	
Mean extent of PRL	8.5±3.7	4.5±2.3	0.001

* Chi-square test, CSME: Clinically significant macular edema, PRL: Preferred retinal locus

Discussion

Diabetic macular edema is one of the main causes of visual acuity loss in patients with diabetes mellitus.[1-4] Assessment of visual acuity measurements gives limited information about the intensity and localization of the retinal damage in macular edema. Accurate testing of light sensitivity of macular area and determination of the location of fixation may play an important role providing further help in managing CSME patients. MP-1 microperimetry have a capability of accurate evaluation of retinal sensitivity and fixation stability in patients with macular diseases.[6,18,20] The characteristics of fixation are easily and exactly determined with microperimetry.

Mean light sensitivity has been known to be markedly decreased in diabetic macular edema.[6-9] In our study, consistent with previous studies, a significant decrease in mean light sensitivity was also found. Retinal sensitivity and stability of fixation in CSME were reported to be reduced compared with normal values.[5] Mean light sensitivity decreases progressively with the severity and duration of macular alteration. This decrease is mostly due to a localized loss of light sensitivity in areas with severe tissue alteration and to a lesser extent due to diffuse loss of light sensitivity.[9]

Fixation characteristic are critical for many visual tasks like reading. Variations of size, shape, and intensity of scotoma greatly influence visual performance. The MP-1 has the capacity to examine fixation upon the target independently of microperimetry. Evaluation of location and stability of fixation by MP-1 was previously reported in some macular diseases such as age-related macular degeneration and central serous retinopathy.[6,11] Previous studies have shown that fixation stability was significantly decreased in diabetic patients compared with control subjects, particularly in eyes with CSME.[7,9] Kube et al.[9] detected that fixation stability was significantly decreased in diabetic patients in comparison to control with scanning laser ophthalmoscopy (SLO). In contrast, Vujosevic et al.[21] reported that fixation was stable and central in patients with different degrees of diabetic macula edema. They detected a correlation between mean retinal thickness and mean retinal sensitivity without a correlation between visual acuity and retinal sensitivity in CSME patients. Chalam et al.[16] also reported, however, that the mean retinal sensitivity and fixation stability measured with Liquid Crystal Display (LCD) microperimeter was measured reliably in eyes with various macular pathologies and found to be correlated with visual acuity. In another study, fixation stability scores were correlated inversely with visual acuity but not with the loss in mean light sensitivity.[9] In our study, fixation stability was detected as relatively unstable or unstable in 22 (73%) eyes in the CSME group, whereas 32 (100%) eyes were stable in the control group.

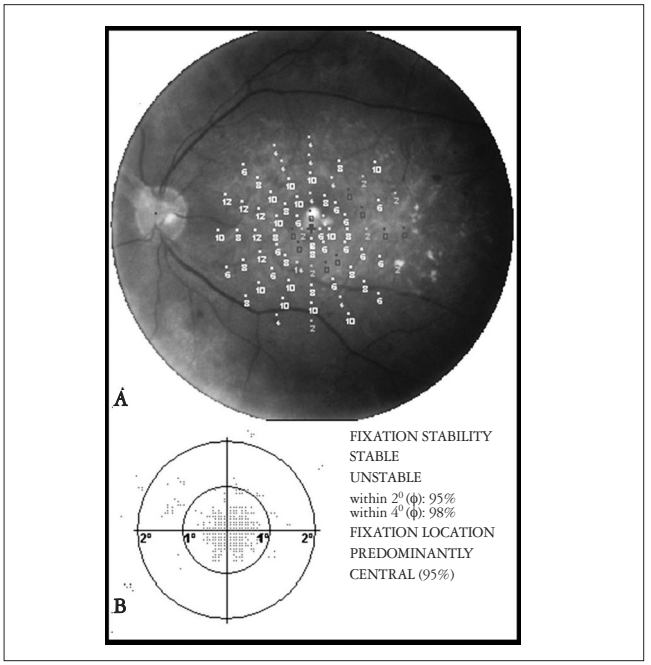

Figure 1. Fundus image and MP-1microperimetry data of a patient with diabetic macular edema. **A)** Macular sensitivity was examined by testing the mean decibels at 76 points of the central 20 degrees of the macula. Numeric values are shown: mean retinal sensitivity at the 76 locations covering central 20°. **B)** Fixation was regarded as "stable" and fixation location was regarded as "predominantly central"

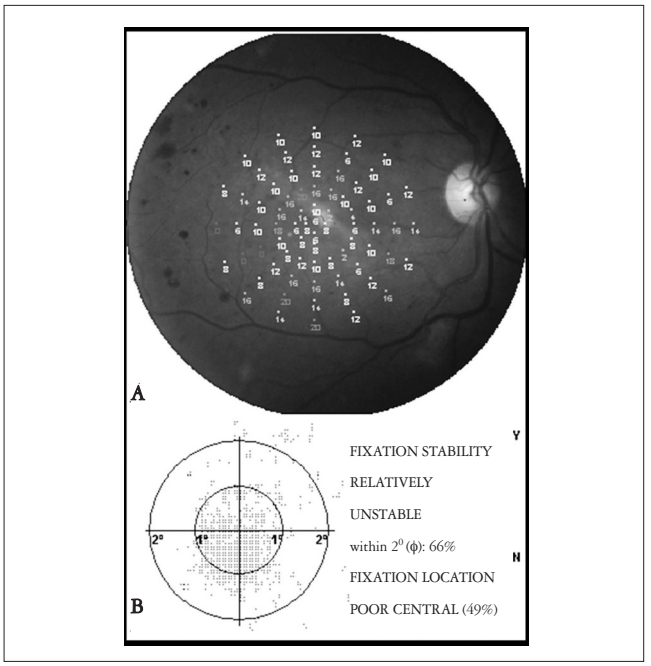

Figure 2. Fundus image and MP-1microperimetry data of a patient with diabetic macular edema. **A)** Macular sensitivity was examined by testing the mean decibels at 76 points of the central 20 degrees of the macula. Numeric values are shown: mean retinal sensitivity at the 76 locations covering central 20°. **B)** Fixation was regarded as "relatively unstable" and fixation location was regarded as "poor central"

The percentage of fixation points within the both central 2° and central 4° were significantly lower in the CSME group than the control group. However, we did not detect correlation between fixation stability score and BCVA in this study.

The central 1.2°-1.7° area of the fovea, area of central fixation, is named ''optimal locus''.[12,14-15] In subjects with diabetic macular edema, central fixation has been affected, therefore the area of preferred retinal locus can be developed. In our study, fixation location was detected as predominantly central in 60% of eyes, whereas it was poor central or predominantly eccentric in 40% of eyes in the CSME group. The percentage of fixation point within the central 2° in patients with predominantly central in the CSME group was significantly lower than in patients with predominantly central in the control group. However, we could not detect a correlation between fixation location score and BCVA in this study. We found that the mean extent of PRL increased approximately two fold in the CSME group compared to the control group. However, in this study, the mean extent was not significantly correlated with BCVA in the CSME group. Similarly, Sawa et al.[6] detected that the mean extent was not significantly correlated with BCVA.

Although microperimetry using the SLO allows measurement of limited focal retinal sensitivity and its effectiveness has been reported in the evaluation of focal retinal sensitivity in eyes with several macular diseases, it did not allow to perform fully automatic examination of the retinal points tested during baseline microperimetry. MP-1 microperimeter automatically compensates for eye movements during the examination via a software module that tracks the eye movements with respect to an initial frame.[13,18] MP-1 microperimetry map may be automatically performed over the same area during follow-up.[17] This may provide detailed monitoring of central retinal function to reveal very small scotomatous areas. These areas may not affect visual acuity, but may be perceived by the patient as visual disturbances.[20]

Morphological and functional analyses of diabetic macular edema by optic coherence tomography (OCT) and multifocal electroretinograms (mfERG) were performed to correlate retinal structural changes with retinal function.[22] Menke et al.[23] showed a highly significant correlation between scotoma size measured by SLO microperimetry and structural damage assessed with OCT. It has been shown that OCT-determined foveal thickness significantly correlated with the BCVA in eyes with diabetic macular edema.[20,24] The retinal sensitivity in the macular area measured by MP-1 is significantly correlated with the visual acuity and foveal thickness in diabetic macular edema.[8] Kube et al.[9] reported no correlation between visual acuity and mean light sensitivity in patients with diabetic maculopathy. They also reported that no correlation was found between visual acuity and foveal light sensitivity and foveal fixation, respectively. In our study, although, retinal thickness was not evaluated by OCT, a significant correlation between the BCVA and central 4 degree retinal sensitivity was determined. Carpineto et el.[25] showed that central 8° retinal sensitivity has a stronger correlation with visual acuity than central 2° retinal sensitivity in patients with macular edema. The differences in the characteristics of CSME (duration, retinal thickness, etc) may account for the disparity between these studies. We accept that retinal thickness analyses by OCT measurements would have been beneficial to evaluate the correlation between visual acuity and retinal sensitivity. One limitation of our study was the inability to use OCT.

In conclusion, mean light sensitivity was found to be decreased in patients with CSME. Fixation stability was significantly decreased and fixation location was changed in patients with CSME compared with control subjects. The MP-1 microperimeter may be useful for measuring PRL, fixation stability and assessment of macular light sensitivity. It might be helpful to evaluate the foveal function during the management of diabetic retinopathy accompanied by CSME.

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