A Systematic Correlation between Morphology and Functional Alterations in Diabetic Macular Edema

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PURPOSE. The aim of this study was to correlate different types of retinal morphologic alterations secondary to diabetic macular disease with their characteristic impact on retinal function.

METHODS. In the present cross-sectional study, 26 eyes of 26 diabetic patients with clinically significant macular edema were examined. All patients underwent complete standardized ophthalmologic examination, including SD-OCT and microperimetry. Microperimetric values were projected over the scanning laser ophthalmoscope image of the OCT device, allowing direct correlation of functional and morphologic parameters. Results over all 1066 individual areas were analyzed using a general linear model.

RESULTS. All the characteristic morphologic alterations demonstrated a significant effect on retinal function (P < 0.0002), except for outer nuclear layer (ONL) hyporeflectivity and small ONL cysts. Large ONL cysts (>220 µm) and serous retinal detachment had the greatest estimated negative effect on retinal sensitivity (−3.86 and −3.66 dB), followed by mediumsized ONL cysts, hard exudates associated with an extinction of the scan signal, and inner nuclear layer cysts.

CONCLUSIONS. In diabetic macular edema, serous retinal detachment and large ONL cysts are the two morphologic changes with the greatest negative impact on retinal function. (Invest Ophthalmol Vis Sci. 2010;51:6710–6714) DOI:10.1167/iovs.09-5064

Diabetic retinopathy is the leading cause of blindness in the working population in industrially developed countries.1,2 With the rising incidence of diabetes mellitus, this ocular disease will be an even greater worldwide health issue in the near future than it is already today.3

In everyday patient care, the widely used retinal function parameter is testing central visual acuity, though it is known that visual acuity alone does not entirely describe the visual performance of an individual patient. The recently introduced automated fundus tracking microperimeter (MP-1; Nidek Technologies Srl, Padova, Italy) allows quick patient- and examiner-friendly assessment of macular sensitivity. With its integrated infrared camera, the MP-1 microperimeter is able to track eye movements in the x- and y-axes with a 25/s frame rate, thus allowing presentation of the stimulus in a predefined position. The stimuli can be offered in different grid patterns and sensitivity levels. Furthermore, the system allows the projection of the sensitivity results on the color fundus image, achieving a spatial correlation of clinical and functional features. The MP-1 method, therefore, offers a realistic and precise mapping of central retinal function.4–7

Apart from visual function testing, imaging of morphologic changes secondary to diabetic maculopathy also improved throughout the past decade. Fourth-generation spectral domain–optical coherence tomography (SD-OCT) devices enable the morphologic evaluation of retinal structures in greatest detail (i.e., a 5-µm axial and 10-µm transversal resolution). The spectral domain technology allows not just improved resolution but a much faster scanning speed and the opportunity to map the entire 20° × 20° macular area in a raster pattern. The raster scan strategy is essential for providing comprehensive measurements from all locations of the macular region.

Since the Early Treatment Diabetic Retinopathy Study (ETDRS) defined diagnostic principles, stereoscopic color fundus photography, stereo microimetry, and fluorescein angiography (FA) have been the diagnostic tools to describe diabetic macular edema (DME).8 During the past decade, OCT developed rapidly, and, with its capability to assess retinal morphology quickly and in a noninvasive manner, it evolved to be an important imaging technique.9 Studies correlating FA findings with OCT values demonstrated a reliable correlation between FA and OCT features regarding cystic changes.10 As novel therapeutic modalities are being developed, there is an increasing need to gain a precise understanding of the specific pathophysiologic features in the diagnosis of DME. For the evaluation of therapeutic strategies, it is of key importance to identify those morphologic biomarkers that have the highest relevance for the visual performance of patients.

Hence, the aim of this study was to determine, in a prospective and standardized protocol, to what extent specific morphologic alterations in DME documented by SD-OCT demonstrate a direct correlation with macular function as assessed with fundus tracking microperimetry.

PATIENTS AND METHODS

The study was performed by the Department of Ophthalmology of the Medical University of Vienna. All research and measurements adhered to the tenets of the Declaration of Helsinki. The study was approved by the local ethics committee, and informed consent was obtained from all participants after a detailed discussion of the nature and possible consequences of the study procedures.

Twenty-six consecutive patients with clinically significant macular edema (CSME) caused by diabetes mellitus who did not undergo previous treatment were enrolled in this cross-sectional study. Inclusion criteria were clinically significant macular edema caused by diabetes mellitus, no previous treatment of the CSME of any kind, no ocular surgery in the past 3 months, and clarity of optical media to
enable detailed fundus imaging. After a complete ophthalmologic examination, including best-corrected visual acuity testing (using the ETDRS logarithmic charts from 2 m), slit lamp examination, funduscopy and stereo fundus photography, all patients underwent standardized microperimetry and SD-OCT in accordance with the study protocol.

Mapping of macular function was performed before fundus photography and fundus biomicroscopy using an MP-1 microperimeter. This instrument allows the examiner to conduct automated static perimetry. Furthermore, using a built-in infrared camera, the instrument tracks the patient’s eye movements and presents the stimulus exactly at the predefined retinal positions in a controlled setting.

For the present study, the settings used were a homogeneous monochromatic white background illumination of 4 apostilbs (1.27 cd/m²) and a 3° red cross as fixation target. The Goldmann III size stimulus was presented in random order with the standard 4-2-1 double staircase strategy. The stimulus intensity varied from 0 to 20 dB with 1-dB steps, and the starting intensity was 12 dB (0 dB refers to the strongest signal of 400 apostilbs (127 cd/m²). Room lighting was dimmed. The fellow eye was firmly patched. For testing, we used a grid pattern consisting of 41 stimuli (12° × 12°) (Fig. 1), which was automatically centered on the fixation point of the patient. Before testing, 5 minutes were allowed for dark adaptation, and a short training was performed by all patients to familiarize them with the examination. At the end of each examination, a color fundus photograph was taken with the built-in 45° xenon flash fundus camera of the MP-1. With two landmark points, the instrument creates an overlay image indicating the examination points on the color fundus image.

After MP testing a 512 × 128-pixel raster scan (128 horizontal scans with 512 pixel resolution) was performed with SD-OCT (Cirrus; Zeiss Meditec, Dublin, CA.). With special software (Research Browser 3.0; Zeiss Meditec), color fundus photography was imported, together with the overlaid microperimetric examination points into the OCT software. Using the software’s internal image algorithms, the imported image was aligned to substitute the OCT infrared fundus image. The precision of alignment was confirmed by checking five fundus landmark points on the SD-OCT scans (Fig. 2). To correct for possible registration errors, a ±1 scan deviation (46.9 µm) in the y-axis and ±50 µm in the x-axis was accepted. If one of the checkpoints was not within the accepted range on the fundus registration compared with the OCT image, further adjustments were made to correct the positioning. After a perfect alignment was achieved, each microperimetry examination point was identified on the OCT scans with the use of the x- and y-axis slides (Fig. 2). At each of the 1066 microperimetry examination locations, the following morphologic changes were evaluated on the OCT images by two readers masked for anonymity (GGD, MR) of the Vienna Reading Center: diffuse outer nuclear layer (ONL) swelling without cyst formation, ONL cysts, inner nuclear layer (INL) cysts, serous retinal detachment (SRD), and presence of hyperreflective hard exudates with extinction of the scan signal beneath. ONL cyst grading was further divided into three subgroups, depending on the largest diameter of the intraretinal cysts: small (<110 µm), medium (110 to <220 µm), and giant (>220 µm) cysts. In case of disagreement between the two readers, a consensus reading was performed.

Statistical analysis was performed using a commercial software package (SPSS Inc., version 16.0; SPSS, Chicago, IL). The correlation of OCT characteristics with retinal sensitivity was analyzed using a general linear regression model with fixed factors, covariates, and patient as random factors. To examine the correlation between retinal sensitivity and visual acuity or duration of disease, Pearson’s and Spearman’s correlations, respectively, were used.

**RESULTS**

The study population included 11 female and 15 male patients with type 2 diabetes mellitus (DM) and clinically significant macular edema. The mean age of patients was 60 years (range, 35–82 years), and their visual acuity ranged from 0.0 to 1.0 with a mean (± SD) of 0.35 ± 0.28 logMAR units. The patients reported a mean (± SD) duration of DM of 14.1 ± 11.33 years and a mean (± SD) HbA1c of 7.5 ± 1.7.

In microperimetry, the mean overall test duration was 14:50 minutes (SD, 5:40 minutes), and fixation stability (percentage of fixation falling within the central 2° and 4’) was 63.5% ± 26.5% and 88.2% ± 16.4% (mean ± SD, respectively). A marked reduction of retinal sensitivity in the macular area was observed in all patients. In 58%, the patient did not recognize one or more presented test marks at all, even at the highest intensity (absolute scotoma). The mean sensitivity in the entire macular region was 8.7 log units (SD, ±3.3 log units). Best-corrected visual acuity showed a strong correlation with retinal sensitivity (r = −0.7; P < 0.0001). Retinal sensitivity did not correlate significantly to the duration of diabetes mellitus or to the duration of subjective symptoms reported by the patient (r = −0.35, P = 0.21; r = −0.09 P = 0.68).

In SD-OCT, the main findings were diffuse thickening and hyporeflectivity of the ONL, cystic spaces in the ONL with thinning of the inner layers or cystic spaces within the INL, serous neuroretinal detachment of the macula and hard exudates seen as focal hyperreflective conglomerates at the border of the inner nuclear and outer plexiform layers associated with signal blockage in the outer nuclear and retinal pigment epi-

**FIGURE 2.** Identification of a fundus landmark point. (A) Fundus registration of the microperimeter imported in the OCT software. Horizontal turquoise line: scan line (scan 78). Vertical pink line: point 342 crosses the scan at the center of a hard exudate. (B) OCT scan 78. The vertical pink line crosses the scan exactly at a round hyperreflective area at the level of the ONL, representing the hard exudate seen on the fundus registration.
thelial layers. The mean central retinal thickness measured in the central 1-mm region was 459.6 ± 114.3 μm.

Figure 3 shows some examples of these pathologies with the corresponding retinal sensitivities. In Figures 3A and 3B, the measurement point of the MP-1 is at a location of giant ONL cysts and a small serous retinal detachment. The retinal function is reduced (3 dB). In Figures 3C and 3D, a giant ONL cyst is seen. It is noticeable that the patient has marked eccentric fixation. Retinal sensitivity at the ONL cyst is 0 dB. Figures 3E and 3F show a hard exudate (hyperreflective conglomerate at the apical side of the ONL with signal blocking beneath) that reduces retinal sensitivity to a 1-dB level. In Figures 3G and 3H, a serous retinal detachment is seen in the fovea that causes an absolute scotoma in microperimetric testing.

In the total 1066 individual test areas, a severely reduced sensitivity (sensitivity <8 dB) was seen in 376 (35.3%) test areas. Such a severe sensitivity reduction was seen in 23.9% of the ONL swelling, 41.3% of small, 56.7% of medium, and 79.5% of the giant ONL cyst cases. Serous retinal detachment, hard exudates, and INL cysts caused severe sensitivity reduction in 91.9%, 50.7%, and 53.9% of the graded cases, respectively.

All the examined OCT pathologies showed a significant correlation to retinal sensitivity, except for diffuse swelling of the ONL without cyst formation and the presence of ONL cysts smaller than 110 μm. However, the intensity of loss in retinal sensitivity correlated in a specific pattern with the underlying morphologic condition: giant (>220 μm) cysts in the ONL and serous neuroretinal detachment had the greatest impact on retinal function, followed by medium-sized ONL cysts, focal hyperreflectivity from hard exudates, and finally INL cysts (Table 1).

**DISCUSSION**

In the present study, we analyzed the correlation of retinal morphologic changes documented by OCT imaging associated with DME with retinal sensitivity assessed with microperimetry. Our results indicate that serous retinal detachment and large ONL cysts have the greatest negative impact on retinal function. Nevertheless, to a certain extent, most classic pathologic changes detected by OCT examination had a significant influence on retinal function.

Large ONL cysts and subretinal fluid accumulation appear relatively late during the course of DME. In both pathologic features, protein- and lipid-rich extracellular fluid accumulates and creates a major disorganization of the affected retinal structure. Smaller amounts of fluid accumulations, such as medium or small cysts or INL cyst, demonstrated a lesser, though statistically significant, effect on retinal function. Interestingly, the reported duration of symptom caused by these pathologies did not show a significant association with retinal sensitivity.

The correlation between larger ONL cysts or subretinal fluid with decreased retinal sensitivity is probably due to the fact that protein-rich subretinal fluid has an effect on both oxygenation and elimination of metabolites from the photoreceptor layer, thus decreasing retinal sensitivity. The presence of subretinal fluid was also found to be significantly correlated with best-corrected visual acuity during anti–VEGF therapy in exudative age-related macular degeneration, a completely different disease entity. In DME, subretinal fluid accumulation and large ONL cyst formation is assumed to be one of the latest steps in the development of diabetic macular disease because it marks the end point in retinal layer alteration secondary to intraretinal vascular leakage.

Neuroretinal detachment was first described by Otani et al., examining the morphologic changes in DME with conventional OCT. Ozdemir et al. reported serous macular detachment to be a much more common finding in DME than previously described and highlighted that, in contrast to OCT findings, FA did not identify any subretinal dye pooling in these patients. The same observation was published by Bolz et al., who identified a clear correlation of angiographic leakage patterns and the type of morphologic alteration in SD-OCT in general with the exception of subretinal fluid, which was detected by SD-OCT only and was missed by FA imaging. If the presence of subretinal exudate is of such high clinical relevance with respect to retinal function, FA is compromised as a diagnostic modality.

Other studies have also evaluated the correlation of OCT findings and retinal sensitivity. Okada et al. found significantly lower macular sensitivity values in DME and a tight correlation between macular sensitivity, visual acuity, and central retinal thickness in their retrospective study. Vujosevic et al. compared areas with no macular edema, nonclinically

**Figure 3.** Examples of OCT pathologies affecting retinal sensitivity. (A, B) Giant ONL cysts and a small serous retinal detachment. (C, D) Giant ONL cyst. (E, F) Hard exudate (hyperreflective conglomerate at the apical side of the outer nuclear layer with signal blocking beneath). (G, H) Serous retinal detachment.
significant macular edema, and clinically significant macular edema regarding retinal thickness in the central 5 ETDRS field with visual acuity and macular sensitivity. They found similar correlations not just in the central area but also in paracentral fields regarding retinal thickness and retinal sensitivity. However, one has to consider that in these two studies, conventional OCT 3 was used, providing only six radial scans, and that there was no opportunity to directly correlate functionality to morphology with respect to retinal topography. Our study combines raster scanning, resulting in complete morphologic mapping and similar functional mapping with a detailed point-to-point correlation of all macular central and paracentral locations.

In a recent work by Unoki et al., FA and macular sensitivity were compared in a topographic manner in patients with capillary nonperfusion caused by diabetic retinopathy. The authors found absolute scotomas to be located within areas of nonperfusion and noted that retinal sensitivity was already reduced in the transition zone of nonperfusion areas. Again, the investigators did not correlate retinal sensitivity with macular edema or specified types of morphologic alterations.

Limitations of the study were the relatively small number of patients. However, by analyzing a total of 41 examination points of the microperimetric testing grid in each eye, we graded 1066 separate retinal locations, providing the satisfactory reliability of statistical analysis. Another key feature of our study was the direct alignment of the fundus image to the scanning laser ophthalmoscope image of the OCT. Because this step was made with dedicated software developed by the OCT manufacturing company, the certified readers tested every alignment thoroughly before each grading, and a tolerance range was introduced eliminating the possibility of a major misalignment.

In this pilot study, evidence was provided for the first time that ONL cysts greater than 220 μm in diameter and serous neuroretinal detachment may be the two most important retinal function threatening pathologic changes in DME. The results may have major relevance regarding the therapeutic management of diabetic macular disease. Treatment of DME before the development of these morphologic changes may be beneficial for the patient regarding the maintenance of retinal function over a longer time. Future studies are necessary to determine whether resolution of ONL cysts or subretinal fluid with different treatment modalities is accompanied by a significant change in retinal function. If so, these specific biomarkers should be used to quantify therapeutic effects specifically and to replace less relevant values such as central retinal thickness, which was clearly found not to provide a correlation between anatomy and function. Nevertheless, there is a direct association between specific retinal morphologic alterations and retinal functionality as described in this study. Consequently, appropriate methods to identify these changes, such as raster scanning SD-OCT, will be of great diagnostic help in the future.

References


