Is there a correlation between structural alterations and retinal sensitivity in morphological patterns of diabetic macular edema?

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Spectral domain optical coherence tomography (SDOCT) enables enhanced visualization of retinal layers and delineation of structural alterations in diabetic macular edema (DME). Microperimetry (MP) is a new technique that allows fundus-related testing of local retinal sensitivity. Combination of these two techniques would enable a structure-function correlation with insights into pathomechanism of vision loss in DME. To correlate retinal structural derangement with retinal sensitivity alterations in cases with diabetic macular edema, using SDOCT and MP. Prospective study of 34 eyes of 30 patients with DME. All patients underwent comprehensive ophthalmic examination, fluorescein angiography, microperimetry and SDOCT. Four distinct morphological patterns of DME were identified-diffuse retinal thickening (DRT), cystoid macular edema (CME), schitic retinal thickening (SRT) and neourosensory detachment (NSD) of fovea. Some retinal loci presented with a mixture of above patterns There was significant difference in retinal thickness between groups (P<0.001). Focal retinal sensitivity measurement revealed relatively preserved retinal sensitivity in areas with DRT (13.8 dB), moderately reduced sensitivity (7.9 dB) in areas with CME, and gross retinal sensitivity loss in areas with SRT (1.2 dB) and NSD (4.7 dB) (P<0.001). Analysis of regional scotoma depth demonstrated similar pattern. Retinal sensitivity showed better correlation to OCT pattern (r=-0.68, P<0.001) than retinal thickness (r=-0.44, P<0.001). Structure-function correlation allows better understanding of the pathophysiology of visual loss in different morphological types of DME. Classification of macular edema into these categories has implications on the prognosis and predictive value of treatment.

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Diabetic macular edema (DME) is the leading cause of visual impairment among diabetics. Optical coherence tomography (OCT) imaging allows objective, reproducible, quantitative evaluation of DME. Modest correlation has been established between retinal thickness measured by the OCT and visual acuity.[1] There have been attempts at differentiating morphological patterns of DME on OCT.[2,3] Spectral domain OCT (SDOCT) permits detailed assessment of the anatomical derangement in DME, enabling a better understanding of the functional consequences. Retinal sensitivity measured by fundus-related microperimetry has demonstrated reduced retinal sensitivity in eyes with DME.[4]

Retinal sensitivity mapping provides a functional plot of the retina, while OCT imaging produces an anatomical plot. Combining information from both modalities can elucidate structure-function relationship in DME and be of predictive and prognostic value. Recent studies found significant correlation between retinal sensitivity and normalized macular thickness as measured by OCT.[5] However, differences in functional deficit between morphological variants of DME have not been explored hitherto.

This study was aimed at imaging morphological patterns in DME with SDOCT, and correlating these OCT patterns with retinal sensitivity measured by microperimetry.

Materials and Methods

Institutional review board exemption was obtained for the project. Thirty-four eyes of 30 patients with treatment naïve DME of less than 6-months duration were included in this prospective study from February 2008 to May 2008. Subjects were well-controlled (HbA_1C <8%) type 2 diabetics without renal dysfunction. Eight patients had systemic hypertension controlled with medication. Mean age of the patients was 48.7 years (±8.3 yrs) and males predominated (19 males, 11 females). Patients underwent complete ophthalmic clinical evaluation. Only eyes with clear media were included in this study. Patients with ischemic maculopathy were excluded by fundus fluorescein angiography. SDOCT imaging was performed with the Copernicus system (Optopol, Poland). Six millimeter line scans (asterix pattern-15 lines, 3183 A-scans/line, time-1.9 sec) were acquired. A blinded operator subsequently performed microperimetry using the MP1 instrument (Nidek, Japan). Macular 20° white-on-white perimetry with Goldmann III stimulus, 4-2-1 threshold strategy and 1° cross-fixation target was employed. Larger (3°-12°) fixation target was employed in patients with lower visual acuity. Point retinal sensitivity-fundus image overlays were obtained. These were analyzed with OCT images. The point retinal thickness measurement and type of anatomical derangement at retinal loci tested with microperimetry were noted. Anatomical derangement at a particular retinal locus was classified into one of four categories. Diffuse retinal thickening (DRT) was characterized by generalized decrease in reflectivity with uniform thickening of the inner retinal layers but without macroscopic optical empty spaces (Fig. 1, Locus A). Points with cystoid macular edema (CME) demonstrated macroscopic cystic spaces

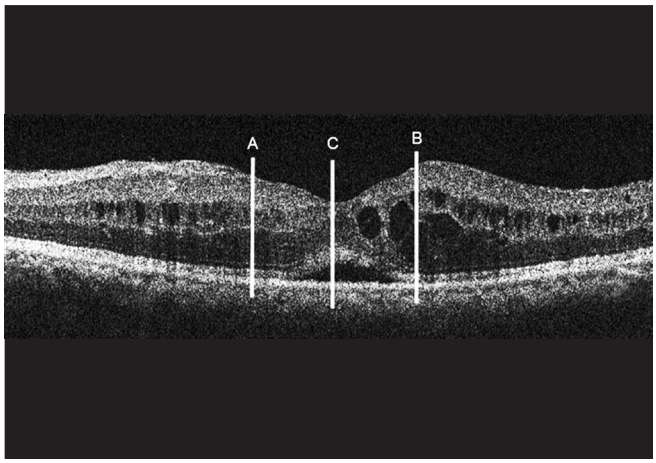

Figure 1: Type of anatomical derangement at individual retinal loci. At locus A, diffuse retinal thickening (DRT) is seen. Locus B demonstrates macroscopic well-defined cystic spaces or cystoid macular edema (CME). The fovea (Locus C) demonstrates neurosensory detachment (NSD)

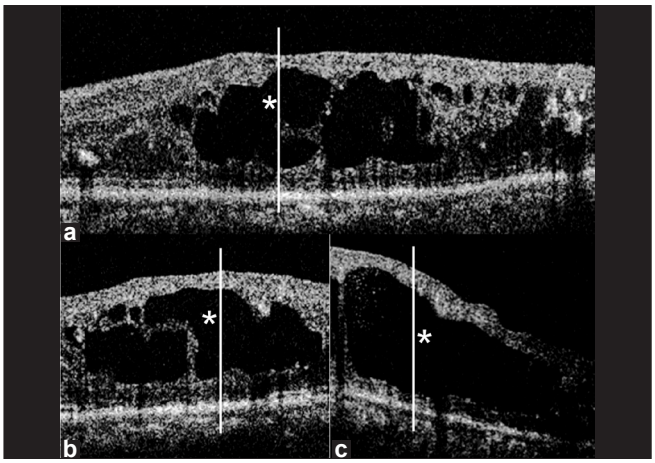

Figure 2: (a-c) Schitic retinal thickening in DME. Large cysts with breakdown of bridging tissue septae (asterix) between inner and outer retina at loci tested with microperimetry (vertical lines)

within the retina with intervening septae (Fig. 1, Locus B). Neurosensory detachment (NSD) was defined as presence of detachment of the neurosensory retina from the retinal pigment epithelium (Fig. 1, Locus C). Schitic retinal thickening (SRT) was said to exist when large coalescing cysts more than 400 μm in horizontal diameter were observed [Fig. 2 a-c]. This type of macular edema demonstrated evidence of tissue loss and broken bridging septae between inner and outer retinal layers. Some loci presented a mixture of above patterns. When the above types coexisted, the predominant derangement was taken into account. Fundus overlay images from MP1 and color-reconstructed image on SDOCT enabled precise correspondence between loci tested on the two instruments. Of the points at which retinal sensitivity was tested, those over vessels, hard exudates, hemorrhages and other visible fundus abnormalities were excluded. Additionally, topographic thickness maps were compared to microperimetry scotoma maps. Statistical analysis was performed using SPSS ver12.0 statistical package.

Results

The four defined morphological patterns of DME were analyzed for retinal thickness and sensitivity. The mean retinal thickness and retinal sensitivity of the groups is depicted in Table 1. There was significant difference in retinal thickness between groups (P<0.001). Focal retinal sensitivity measurements revealed relatively preserved retinal sensitivity in areas with DRT, moderately reduced sensitivity in areas with CME, and gross retinal sensitivity loss in areas with SRT and NSD (P<0.001). Analysis of regional scotoma demonstrated similar pattern, with dense scotomata in areas of SRT. Retinal sensitivity showed better correlation to the OCT pattern of DME (r=-0.68, P<0.001) than retinal thickness (r=-0.44, P<0.001).

Discussion

Previous studies have classified DME subtypes on the basis of OCT imaging into DRT, CME, serous retinal detachment, posterior hyaloid traction (PHT) without tractional retinal detachment (TRD) and PHT with TRD. This is primarily an anatomical classification, with overlap of visual function status between classes. Additionally, certain subtypes in this classification are based on the pathomechanism of macular edema, rather than the anatomical or functional consequence of the same. Our study divided DME into four classes based on anatomical derangement and demonstrated that these classes have distinct functional deficit. Such stratification of DME synthesizes information on structural and functional deficit.

An inverse correlation seen in the study between retinal thickness and retinal sensitivity could represent progressive loss of function with increasing tissue expansion. The most common morphological manifestations of DME were DRT and CME. DRT could represent an early stage of DME with extracellular fluid accumulation and tissue expansion causing mild functional (sensitivity) loss seen in the study. As the fluid load increases, microscopic fluid pockets could coalesce to form macroscopic cysts with associated damage to cells and interneural connections in the retina. This damage could account for the additional deterioration in retinal sensitivity observed in CME. Progressive fluid accumulation and tissue damage expands intraretinal cysts in the plexiform layers. Breakdown of intervening septae causes cysts to coalesce into large fluid spaces seen sometimes in DME. The breakdown of tissue connections between inner and outer retina at such loci would be expected to cause significant impairment of the predominantly vertical (outer to inner) transmission in the retina and consequent functional loss. Such precipitous loss in retinal sensitivity was indeed noted in our study in areas with large cysts and evidence of broken bridging septae. The retinal sensitivity in these loci was significantly worse than seen in loci with CME with similar point retinal thickness, indicating a more severe derangement. The distinct attributes of anatomical damage, evidenced on SDOCT as broken septae, and severe functional loss documented on microperimetry as dense scotomata, led us to segregate this type of edema from CME into a new class. We have labeled this derangement as SRT. SRT could thus represent the extreme end of the logical continuum of DME, starting from DRT.

We postulate that as DRT passes into CME and subsequently SRT, initially horizontal transmission and later vertical transmission within the retina is compromised. This results in

Table 1: Mean retinal thickness and retinal sensitivity of morphological subgroups

Morphological group	Number of points tested	Mean Retinal Thickness (μ) ± SD	Mean Retinal Sensitivity (dB)
DRT	168	328.2 ± 84.9	13.8
CME	140	480.8 ± 93.4	7.9
SRT	39	521.6 ± 104.7	1.2
NSD	48	410.8 ± 136.2	4.7

loss of sensitivity, greatest in SRT, which exhibits significant disconnection between the inner and outer retina.

Classification of DME based on anatomical and functional features allows us to prognosticate better. We observed a trend towards better outcomes with DRT. Patients with SRT fared considerably worse. These results await confirmation from a larger study with longer follow-up.

Conclusions

Correlation of retinal structural alteration with retinal sensitivity loss allows better understanding of the pathophysiology of visual loss in different morphological types of DME. Classification of macular edema into these categories could have implications on the prognosis and predictive value for treatment.

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