Correlation between retinal sensitivity and cystoid space characteristics in diabetic macular edema

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Purpose: To evaluate the correlation between retinal sensitivity and cystoid space characteristics in eyes with diabetic macular edema (DME). **Materials and Methods:** Prospective cross-sectional study of 22 subjects with DME (32 treatment-naïve eyes). All study subjects underwent complete ophthalmic examination, including slit-lamp biomicroscopy and dilated fundus examination. All subjects underwent spectral domain optical coherence tomography (SD-OCT) and microperimetry (MP). Intraretinal cystoid space (ICS) volume was generated after manual delineation of cystoid space boundaries using the three-dimensional-OCT software. Various SD-OCT parameters, including retinal thickness, retinal volume, cystoid space volume, cystoid space intensity, and outer retinal structure integrity, were correlated with MP parameters and best-corrected visual acuity (BCVA). **Results:** Subject's mean age was 57 ± 9 years. The mean logarithm of minimum angle of resolution BCVA was 0.4 ± 0.2. The intraclass correlation coefficient for inter- and intra-grader assessment of cystoid space volume by manual delineation was 0.99 and 0.99, respectively. Mean total ICS volume was 0.4 ± 0.4 mm^3 and for the foveal center, subfield was 0.1 ± 0.1 mm^3. Mean retinal sensitivity was 12.89 ± 10 dB; however, foveal retinal sensitivity was 12.3 ± 11.1 dB. We found no significant correlation between BCVA and total cystoid space volume (r = 0.33, P = 0.06). Correlation between total retinal sensitivity and total ICS was negative and nonsignificant (r = −0.17, P = 0.36). Correlation between foveal retinal sensitivity and foveal cystoid space intensity was moderate and marginally significant (r = −0.43, P = 0.05). **Conclusion:** Total cystoid space volume was not significantly correlated with BCVA or total retinal sensitivity in subjects with DME. Foveal cystoid space optical intensity was negatively correlated with foveal retinal sensitivity. These findings suggest further investigation of cystoid space characteristics in the setting of DME may be of value.

Key words: Cystoid space analysis, diabetic maculae edema, optical coherence tomography, retinal imaging

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Diabetic macular edema (DME) is the commonest cause of visual acuity loss in diabetes.[1] It may affect central vision from the early stages of retinopathy, and its role in the course of vision loss in diabetic patients and its occurrence in the evolution of the retinopathy are being increasingly recognized.

Visual acuity measurement alone, however, does not completely quantify the functional deficit experienced by patients with DME. Retinal sensitivity assessment has been shown to correlate better with the extent of retinal edema and may be a useful parameter in predicting outcomes following therapy for DME.[2,3] Similarly, various anatomic parameters on optical coherence tomography (OCT) including outer retinal structure integrity, patterns of edema, the extent of cystoid spaces, hyperreflective foci, and microaneurysms have also been reported to have predictive value for visual acuity in these eyes.[4,5] In DME, accumulation of extracellular fluid and expansion of tissue causing sensitivity (functional) loss. Progression breakdown of intervening septae causing cysts to coalesce, predominant connections between inner and outer retina are expected to cause significant impairment and consequently functional loss. Chronicity of cysts characterized by retinal degeneration and atrophy can cause a profound disruption of the retinal architecture is resistant to therapy holding a poor visual prognosis.[6] With the advantage of OCT an optical signal acquisition principle to capture reflected signal from retinal optical scattering media, we can estimate the optical properties (optical intensity) of the cystoid spaces.[7,8] The relationship between these morphologic characteristics of edema (in particular, the cystoid space characteristics) and retinal sensitivity, however, has not been explored.

In this study, we correlate various spectral-domain (SD) OCT parameters including cystoid space volume, cystoid space intensity, and outer retinal structure integrity with retinal sensitivity and visual acuity in treatment naïve eyes with DME.

Materials and Methods

Thirty-two eyes of 22 subjects with cystoid macular edema secondary to diabetic retinopathy were enrolled in this

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prospective cross-sectional study. All subjects were recruited between August 2013 and March 2014. The study protocol was approved by the Institutional Review Board of the L V Prasad Eye Institute, and the study was conducted in accordance with the tenets set forth in the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Inclusion criteria included treatment-naïve eyes with cystoid macular edema due only to diabetic retinopathy, age above 40 years, ocular media sufficiently clear to permit high-quality imaging, best-corrected visual acuity (BCVA) of 20/200 or better, and refractive error less than three-dimensional (3D) spherical equivalent (with less than two-dimensional of cylinder). Exclusion criteria included the presence of neurosensory detachment on SD-OCT, edema secondary to disease other than diabetes, significant media opacity, poor signal strength (<7) of OCT scans, unreliable microperimetry (MP), history of other retinal disease, history of retinal treatment including macular laser photocoagulation or intravitreal injections, macular scarring/fibrosis, subfoveal exudates, and subjects with macular ischemia in fundus fluorescein angiography.

All subjects underwent comprehensive ophthalmic examination including best-refracted visual acuity, tonometry, slit-lamp biomicroscopy, and indirect ophthalmoscopy. Subjects with significant media opacity such as cataracts were excluded from the study. Diabetic retinopathy severity was graded using indirect ophthalmoscopy examination, and proliferative diabetic retinopathy (PDR) was confirmed using fluorescence angiography as per physician discretion.

Spectral domain optical coherence tomography

SD-OCT scans were performed in all eyes using the Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Dublin, CA, USA) through a dilated pupil while the operator monitored the reconstructed video image of the central retina. The acquisition protocol was a 512 × 128 macular cube within a 6 mm^2 × 6 mm^2 centered on the fovea. Raw OCT data (Digital Imaging and Communications in Medicine format) were exported from the Cirrus® OCT and imported into previously described[9,10] and validated SD-OCT-reading center grading software known as 3D OCTOR (created by Doheny Image Reading Center software engineers, Los Angeles, CA, USA).

Microperimetry

MP (MAIA, CenterVue, Padova, Italy) was performed in all study subjects under mydriatic (minimum pupil diameter 2.5 mm), mesopic conditions without dark adaptation. After successful completion of the training protocol, the optic disk was marked for tracking purposes, and the automated sensitivity testing was performed. The testing protocol consisted of 37 points within a 10° area of the macula centered on the fovea. The eye-tracking system of the device was enabled during testing.

We used a stimulus size equivalent to a Goldmann III test spot (Φ =26 arc/min) and a 4–2 double staircase strategy. The fixation target for all the subjects was a 1° single cross. Stimuli were projected with a presentation time of 200 ms against a white background with an illumination of 1.27 cd/m^2.

Fixation stability

Fixation stability was measured by calculating the percentage of fixation points (%) located within a distance of 1° and 2°, respectively (P1 and P2). Fixation was classified as "stable" if more than 75% of the fixation points were located within P1; "relatively unstable" if < 75% of the fixation points were located within P1, but more than 75% of the fixation points were located within P2; and "unstable" if <75% were located within P2. During the MP testing procedure, the instrument randomly projected stimuli on the optic disc (blind spot) to measure the false positive rate for the test. Based on false positives during the test, the instrument calculated a reliability index. A reliability index of >50% was considered reliable.

Macular integrity index

Macular integrity index is a numerical value (not in dB), which provides the likelihood that a subject's sensitivity results are normal (0–40), borderline/"suspect" (40–60), or abnormal (60–100), compared to age-adjusted normative data.

Computer-assisted grading software

The 3D OCTOR software has been described and validated in previous reports.[9-11] Volumes (cubic millimeters) of structures of interest were obtained by multiplying the average thickness measurements by the sampled area. Cystoid space intensity was calculated by averaging the intensity of all pixels within the space.[7] Our intra- and inter-grader reproducibility for measurement of layer thicknesses and cystoid spaces have been previously reported.[12]

Grading protocol

Intraretinal cystoid space (ICS) boundaries were drawn [Fig. 1] in OCT B-scans for each study subject. Output parameters for the various spaces, including the entire neurosensory retina and the ICS volume and cystoid space optical intensity, were calculated by 3D OCTOR. The intensity of all bright pixels was averaged to generate a mean intensity of cystoid spaces for each eye.[7] Similarly, the brightness of all pixels in foveal center subfield (FCS) was used to generate foveal center cystoid space intensity. The unit of intensity measurements is log units. In accordance with previous studies, very small candidate cystoid spaces (<5 × 5 pixels),[9,12] which are not easily drawn or reliably recognized, were not included. The integrity/continuity of the outer retinal bands, the external limiting membrane (ELM) and inner segment-outer

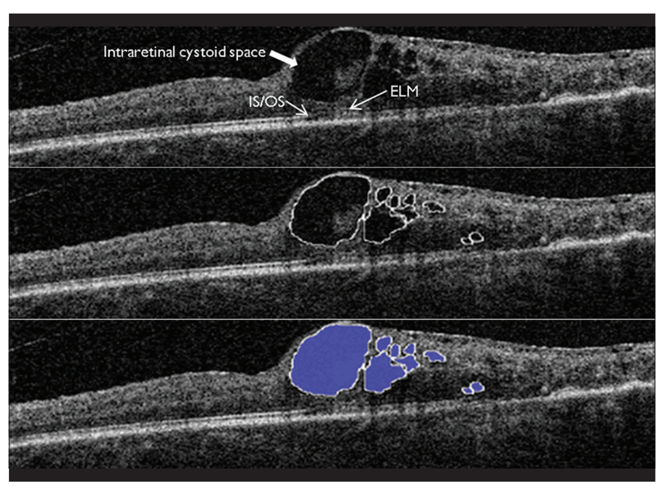

Figure 1: Spectral domain optical coherence tomography B-scan (top) demonstrating intraretinal cystoid spaces. The clinically relevant boundaries (middle) were graded by the masked graders using three-dimensional OCTOR software. Color shaded areas: Demonstration of (bottom) graded intraretinal cystoid space

segment junction (ellipsoid zone), was assessed subjectively in all OCT B-scans passing through the foveal center. Any discontinuity of the retinal layer was considered disrupted. Integrity was graded in five categories: Normal, continuous band throughout the foveal center in all scans; mild, band disruption in 0–20% of scans; moderate, band disruption in 21–50% of scans; severe, band disruption in >50% of scans; and absent, complete loss of the band.

Statistical analysis

Mean and standard deviation for each study eye were computed for retinal thickness, cystoid space volume, and cystoid space intensity within the total scanned area and in the FCS. MP parameters, including mean retinal sensitivity, foveal sensitivity, macular integrity, and fixation characteristics, were collected. Snellen BCVA was converted to logarithm of minimum angle of resolution (LogMAR) notation to facilitate statistical analysis.

The Kolmogorov–Smirnov test was used to determine whether the collected data followed a normal distribution. Bivariate correlations were performed using Pearson correlation to test the correlations between the variables. The reproducibility of ICS volume measurements was assessed by two masked graders in 12 randomly selected eyes. Intraclass correlation coefficients (ICCs) were computed to assess intra-and intergrader reproducibility.

A Type I error of 5% was considered statistically significant. All analysis was performed by SPSS ver. 18.0 (Statistical Package for Social Sciences, Chicago, Illinois, USA).

Results

Thirty-two eyes of 22 subjects with DME were included in this study. The population included 18 (82%) men and 4 (18%) women. The average age was 57 ± 9 years (range 40–72). The mean duration of diabetes was 10.8 ± 6.6 years (range: 3–25). Of the 32 eyes enrolled in the study, 34% eyes had moderate non-PDR (NPDR), 44% eyes had severe NPDR, and 22% eyes had PDR.

Clinical parameters

The mean LogMAR BCVA was 0.4 (Snellen equivalent ~ 20/50). The mean retinal sensitivity was 12.89 dB. The mean macular integrity on MP was 91.4. The retinal volume and cystoid space volume in the total scanned area was 11.24 mm^3 and 0.4 mm^3. Total cystoid space intensity (log units) was 0.1931. A summary of the demographic and clinical parameters is shown in Table 1.

Fixation assessment [Table 1] revealed stable fixation in 11 eyes (34.4%), relatively unstable fixation in 12 eyes (37.5%) and unstable fixation in 9 eyes (28.1%). There was no significant difference in BCVA (P = 0.24) and mean retinal sensitivity (P = 0.65) between fixation stability groups.

Foveal center subfield retinal layer integrity

The ELM was severely disrupted in 4 (12.5%) and absent in 3 (9.4%) of the 32 eyes. Ellipsoid zone integrity was severely disrupted in 6 eyes (18.7%) and absent in 5 (15.6%) [Table 2]. LogMAR visual acuity was significantly (P = 0.03) worse in subjects with complete loss of ELM (0.66 ± 0.29) than in those with normal appearing ELM (0.26 ± 0.21); however, there was no difference in retinal sensitivity between these subgroups [Table 3].

Correlations

Correlations were calculated between visual acuity, SD-OCT parameters, and MP parameters using bivariate parametric Pearson correlations.

Overall correlation

We found no significant correlation between BCVA and total cystoid space volume (r = 0.33, P = 0.06), [Fig. 2]. A negative trend was observed between total retinal sensitivity and total cystoid space volume (r = −0.17, P = 0.36), but the correlation

Table 1: Demographic and clinical data of the study population

Variable (n=32 eyes)	Mean±SD	Range
Age (years)	57±8.9	40-70
Duration of diabetes (years)	10.8±6.6	3-25
LogMAR visual acuity	4±2	0-1
Refractive error (D)*	0.1±2.1	−3.50-3
SD-OCT parameters		
Total scan area		
Retinal thickness (microns)	327.48±54.78	14-1441.4
Retinal volume (mm^3)	11.24±2.78	0.24-14.36
Retinal intensity (log units)	0.2851±0.0235	0.2388-0.3423
Cystoid space volume (mm^3)	0.4±0.4	0.0-2.2
Cystoid space intensity (log units)	0.1931±0.0104	0.1644-0.2107
Foveal center subfield		
Retinal thickness (microns)	396.16±127.56	90-667.9
Retinal volume (mm^3)	0.31±0.10	0.07-0.52
Retinal intensity (log units)	0.2486±0.0309	0.1915-0.3342
Cystoid space volume (mm^3)	0.1±0.1	0.0-0.2
Cystoid space intensity (log units)	0.2062±0.0907	0.1401-0.6800
MP parameters		
Mean retinal sensitivity (dB)	12.89±10.00	0-31.6
Foveal center retinal sensitivity (dB)	12.3±11.10	0-34
Fixation characteristics		
Within 1° (%)	53.46±30.01	4-99
Within 2° (%)	76.87±25.94	18-100

*Refractive errors were converted into spherical equivalent. SD: Standard deviation, SD-OCT: Spectral domain-optical coherence tomography, LogMAR: Logarithm of the minimum angle of resolution, MP: Microperimetry

Table 2: Frequency distribution of retinal layer integrity in foveal center subfield

Category	Layer integrity	
	ELM n (%)	IS/OS n (%)
Normal	5 (15.6)	4 (12.5)
Mild disrupted	10 (31.25)	7 (21.88)
Moderate disrupted	10 (31.25)	10 (31.25)
Severely disrupted	4 (12.25)	6 (18.75)
Absent	3 (9.38)	5 (15.63)

ELM: External limiting membrane, IS/OS: Inner and outer segments junction of photoreceptors

Table 3: Logarithm of the minimum angle of resolution visual acuity and mean retinal sensitivity differences among retinal layer integrity groups

Retinal layer integrity	Mean±SD (range)					*P*
	Normal	Mild disrupted	Moderate disrupted	Severe disrupted	Absent	
External limiting membrane						
n (eyes)	5	10	10	4	3	
LogMAR VA	0.26±0.21 (0-0.50)	0.36±0.18 (0.10-0.70)	0.42±0.18 (0.20-0.70)	0.20±0.14 (0.20-0.30)	0.67±0.29 (0.50-1.00)	0.03
Mean retinal sensitivity (dB)	11.32±10.62 (0-21.6)	16.19±10.94 (0-30.40)	12.39±10.9 (0-31.60)	14.7±3.32 (10.40-17.90)	3.80±6.58 (0-11.40)	0.45
Inner/outer segments of photoreceptors layer						
n (eyes)	4	7	10	6	5	
LogMAR VA	0.33±0.17 (0.1-0.50)	0.31±0.18 (0-0.50)	0.36±0.16 (0.20-0.70)	0.33±0.24 (0-0.70)	0.56±0.33 (0.10-1.00)	0.33
Mean retinal sensitivity (dB)	14.15±9.84 (0-21.6)	16.96±10.53 (0-30.40)	13.25±11.83 (0-31.60)	13.07±7.17 (0-19.60)	5.28±7.34 (0-15)	0.41

SD: Standard deviation, LogMAR VA: Logarithm of the minimum angle of resolution visual acuity

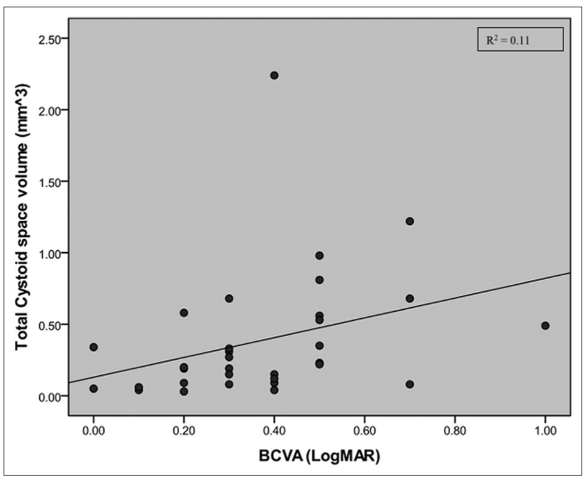

Figure 2: Scatter diagram showing best-corrected visual acuity and total cystoid space volume in study subjects

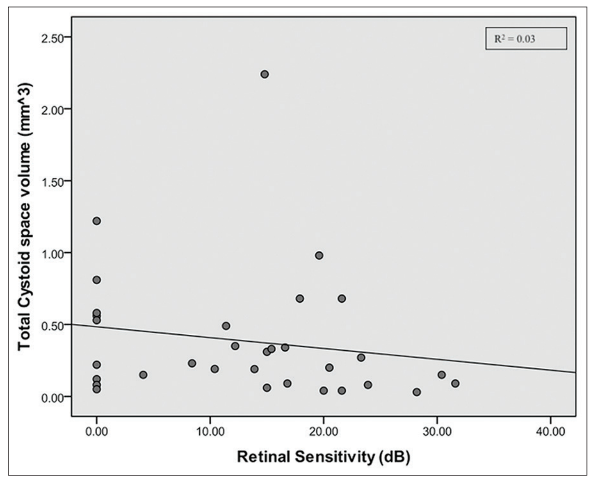

Figure 3: Scatter diagram showing retinal sensitivity and total cystoid space volume in study subjects

was not statistically significant [Fig. 3]. There was no significant correlation between BCVA and total retinal sensitivity (r = −0.23, P = 0.20). Total cystoid space intensity was poorly correlated with both BCVA (r = 0.27, P = 0.14) and total retinal sensitivity (r = −0.22, P = 0.22) [Table 4].

Foveal central subfield correlations

No significant correlation was found between BCVA and FCS volume (r = 0.13, P = 0.51), [Fig. 4]. Similarly, no significant correlation was found between foveal sensitivity and FCS volume (r = −0.19, P = 0.42), [Fig. 5]. Total cystoid space intensity was poorly correlated with both BCVA (r = 0.09, P = 0.42) and total retinal sensitivity (r = −0.43, P = 0.05) [Table 5].

Reproducibility

Intra-grader reproducibility

The mean cystoid space volumes for the first and second gradings were 0.22 ± 0.15 mm^3 and 0.22 ± 0.15 mm^3, respectively, with a mean absolute difference of 0.001 ± 0.01. The ICC was 0.99 (95% confidence interval [CI]: 0.997–1.00) [Fig. 6].

Inter-grader reproducibility

The mean cystoid space volumes computed by grader 1 and grader 2 were 0.22 ± 0.15 and 0.20 ± 0.13, respectively, with a mean absolute difference of 0.05 ± 0.03. The ICC was 0.97 (95% CI: 0.88–0.99) Fig. 6.

Discussion

We found no significant correlation found between total retinal sensitivity and total cystoid space volume. Moreover, no significant correlation was found between foveal retinal sensitivity and foveal cystoid space volume.

Retinal sensitivity is an important predictive parameter in subjects with diabetic retinopathy and DME.[3,13-15] Previously, Reznicek *et al.*[16] showed a significant correlation between retinal sensitivity and outer nuclear layer cyst size. In this study, we measured cystoid space volume in the total scanned area and the foveal central subfield; but these measurements were not significantly correlated with retinal sensitivity. Total retinal sensitivity is an average threshold of all 37 stimuli projected in the central 10° area. Thus, some of these threshold responses would likely originate from relatively normal appearing retina without significant morphological changes from DME. However, there are other potential explanations for the lack of correlation between ICS volume, retinal sensitivity, and BCVA. First, accumulation of fluid in cystoid spaces in the inner retina early in the course of DME may not impair retinal function if the neuronal components of the retina are otherwise intact.[3] Second, quantification of the outer retinal layers alone may provide better correlation.[3] When the severity of disruption of the outer retinal layers was assessed, 84% of the eyes tested were found to have some level of ELM disruption, and 88% had ellipsoid zone junction disruption. A reduction in retinal sensitivity and BCVA in subjects with severely damaged or absent outer retinal layers was observed, similar to the findings reported by Yohannan *et al*.[3] Third, although distance BCVA and total retinal sensitivity were not correlated with cystoid space volume in this study, other parameters of visual function not included in this study, such as contrast sensitivity and reading speed, may show better correlations.

Cystoid space intensity (or reflectivity) is an indicator of the brightness of the reflected light from the cystoid spaces and may provide additional information regarding the effects of retinal disease, which is not conveyed by layer thickness alone.[17] SDOCT allows direct visualization of retinal morphology and architecture. It is an optical signal acquisition and processing method that captures the reflected signal from the retinal optical scattering media (i.e., the retinal tissue), and thus can be used for the quantitative analysis of the tissue optical properties. Because of the interferometric technique, the SD-OCT image is essentially the intensity profiles of the reflected light of retinal layers.[11] The various layers of the retina may exhibit different optical properties affected differentially by various diseases. Quantification of the optical properties of these layers may facilitate the understanding of retinal disease. The importance of tissue intensity has been reported in neovascular age-related macular degeneration[18] but has not been well studied in diabetic retinopathy and DME. In this study, the mean intensity of cystoid spaces in the foveal central subfield area showed a negative correlation with foveal retinal sensitivity. It has been suggested that cystoid space optical intensity may be a useful indicator of disease chronicity.[19] With increasing chronicity of the disease, it is possible that thin cellular bridges (not clearly apparent on the OCT) that traverse the cystoid spaces may disappear and that their disappearance may be associated with a decrease in the overall optical reflectivity, as well a reduction in intensity. If these results are confirmed in larger, prospective, longitudinal

Table 4: Correlation analysis (Pearson) between functional parameters best-corrected visual acuity, microperimetry and spectral domain optical coherence tomography parameters in total scan area

Variable	BCVA		MP retinal sensitivity	
	r	*P*	*r*	*P*
Retinal thickness	−0.04	0.83	−0.19	0.33
Retinal volume	−0.15	0.44	0.14	0.48
Retinal intensity	0.29	0.13	−0.17	0.38
Cystoid space volume	0.33	0.06	−0.17	0.36
Cystoid space intensity	0.27	0.14	−0.22	0.22
Macular integrity index	0.003	0.99	−0.53	0.002

BCVA: Best-corrected visual acuity, MP: Microperimetry

Table 5: Correlation analysis (Pearson) between functional parameters best-corrected visual acuity, microperimetry and spectral domain optical coherence tomography parameters in foveal center subfield

Variable	BCVA		MP retinal sensitivity	
	r	*P*	*r*	*P*
Retinal thickness	0.15	0.44	−0.29	0.2
Retinal volume	0.15	0.45	−0.3	0.19
Retinal intensity	−0.04	0.85	0.16	0.48
Cystoid space volume	0.13	0.51	−0.19	0.42
Cystoid space intensity	0.09	0.64	−0.43	0.05

BCVA: Best-corrected visual acuity, MP: Microperimetry

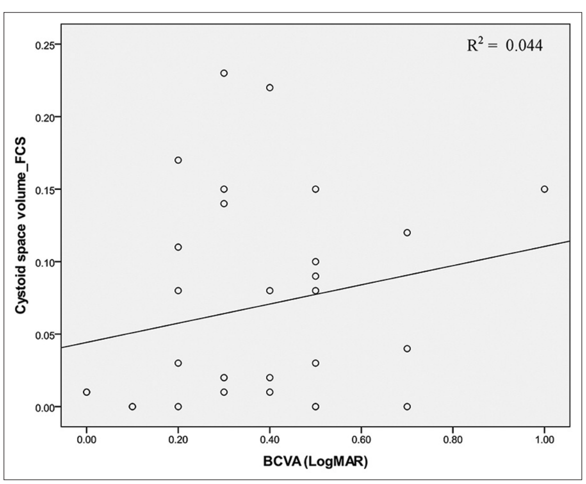

Figure 4: Scatter diagram showing best-corrected visual acuity and foveal cystoid space volume in study subjects

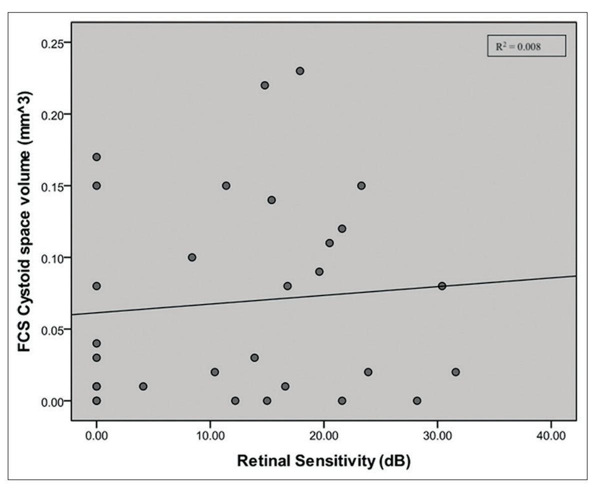

Figure 5: Scatter diagram showing retinal sensitivity and foveal central subfield cystoid space volume in study subjects

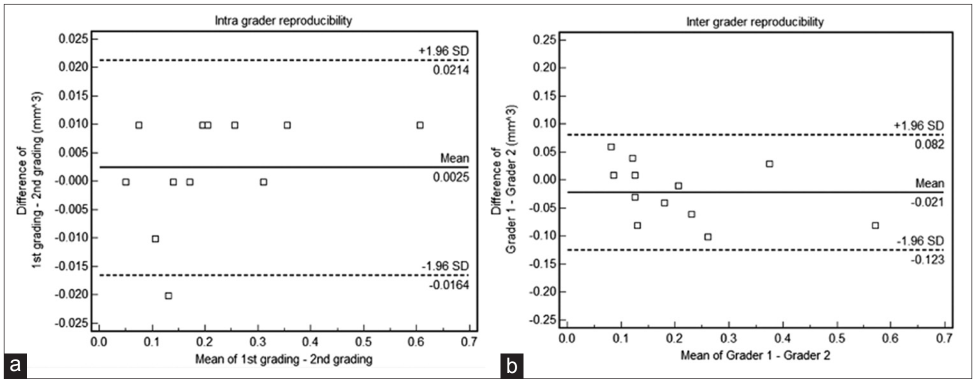

Figure 6: Bland–Altman plots demonstrating intra- (a) and inter-grader (b) reproducibility of intraretinal cystoid space demarcation in the total scan area. Dashed lines: 95% limits of agreement

studies, cystoid space intensity could provide an additional anatomic parameter for monitoring disease progression and evaluating treatment response.

In this study, 34% of subjects showed stable fixation and 66% showed unstable fixation. Fixation stability can be affected by diabetic retinopathy or DME. Subjects with unstable fixation showed reduced BCVA and retinal sensitivity when compared to stable fixation, but the difference was not significant.[13,20]

To our knowledge, this is the first study to quantitatively evaluate both cystoid space volume and sensitivity in the setting of DME and to evaluate the relationship of these parameters with visual function. However, our study has important limitations when assessing our findings. First, the sample size of the cohort was limited; but it should be noted that manual segmentation of all cystoid spaces in every B-scan of a dense OCT volume scan is a laborious task. Second, as our study was cross-sectional in nature, we could not assess variability in cystoid space volume and the effect of such longitudinal variations on visual function.

In summary, ICS volume was not significantly correlated with either BCVA or total retinal sensitivity in this cohort. Interestingly, however, foveal central subfield cystoid space optical intensity was negatively correlated with foveal retinal sensitivity.

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Conflicts of interest

There are no conflicts of interest.

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