Communications between intraretinal and subretinal space on optical coherence tomography of neurosensory retinal detachment in diabetic macular edema

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Introduction

Diabetic macular edema (DME) is the leading cause of visual loss in diabetes. Neurosensory retinal detachment (NSD) is a known pattern of DME, apart from cystoid macular edema (CME) and diffuse retinal thickening. NSD under the fovea has been reported in 5-31% of the patients with DME. The proposed pathogenesis of DME is multifactorial. However, the pathogenesis of NSD in DME is not yet fully understood. Spectral domain optical coherence tomography (SD-OCT) has enabled detailed evaluation of the morphological features of NSD beneath edematous and cystic macula. Because the development of NSD in DME impairs vision severely, recent

Background: The pathogenesis of development and progression of neurosensory retinal detachment (NSD) in diabetic macular edema (DME) is not yet fully understood. The purpose of this study is to describe the spectral domain optical coherence tomography (SD-OCT) morphological characteristics of NSD associated with DME in the form of outer retinal communications and to assess the correlation between the size of communications and various factors.

Materials and Methods: This was an observational retrospective nonconsecutive case series in a tertiary care eye institute. We imaged NSD and outer retinal communications in 17 eyes of 16 patients having NSD associated with DME using SD-OCT. We measured manually the size of the outer openings of these communications and studied its correlation with various factors. Statistical analysis (correlation test) was performed using the Statistical Package for Social Sciences (SPSS) software (version 14.0). The main outcome measures were correlation of the size of communications with dimensions of NSD, presence of subretinal hyper-reflective dots, and best-corrected visual acuity (BCVA).

Results: The communications were seen as focal defects of the outer layers of elevated retina. With increasing size of communication, there was increase in height of NSD (r = 0.701, P = 0.002), horizontal diameter of NSD (r = 0.695, P = 0.002), and the number of hyper-reflective dots in the subretinal space (r = 0.729, P = 0.002). The minimum angle of resolution (logMAR) BCVA increased with the increasing size of communications (r = 0.827, P < 0.0001).

Conclusions: Outer retinal communications between intra and subretinal space were noted in eyes having NSD associated with DME. The size of communications correlated positively with the size of NSD and subretinal detachment space hyper-reflective dots, and inversely with BCVA.

Keywords: Diabetic macular edema, neurosensory detachment, outer retinal communications, spectral domain optical coherence tomography, subretinal detachment space hyper-reflective dots

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reports have focused upon the SD-OCT study of the morphologic changes associated with NSD.\textsuperscript{[17,18]} Recently, Ota et al.\textsuperscript{[17]} reported the presence of discontinuity at the outer border of the detached retina in eyes having NSD in DME. However, the significance of these discontinuities, in terms of their correlation with size of NSD and with visual acuity, remains unknown.

The purpose of this study is to report the presence of outer retinal communications, traversing between intraretinal fluid pockets and subretinal space in eyes having NSD in DME. We also assess the correlation of size of these communications with the size of NSD, with subretinal detachment space hyper-reflective echoes, and with visual acuity.

**Materials and Methods**

This was an observational retrospective case series, which included 17 eyes of 16 diabetic patients. Of all the cases of DME with NSD who visited our institute between January 2011 and June 2011, SD-OCT scans were reviewed. The eyes that were found to have outer retinal communications between intraretinal fluid pockets/ cysts and subretinal fluid on SD-OCT were included. Macular edema was diagnosed by stereoscopic biomicroscopy according to the criteria reported by the Early Treatment Diabetic Retinopathy Study (ETDRS).\textsuperscript{[19]} The exclusion criteria included <3 OCT scans, dense cataract or preretinal hemorrhages that did not allow OCT, advanced proliferative diabetic retinopathy, epiretinal membrane or vitreomacular traction, macular pucker, and eyes post vitrectomy.

All the research adhered to the tenets of the Declaration of Helsinki\textsuperscript{[20]} and was approved by the ethics committee. All patients underwent a comprehensive ophthalmologic examination, which included best-corrected visual acuity (BCVA) measurements, slit lamp biomicroscopy, intraocular pressure measurements using Goldmann applanation tonometry, dilated indirect ophthalmoscopy, SD-OCT with macular thickness measurement, and fluorescein angiography.

**SD-OCT**

A prototype SD-OCT system (Topcon 3D1000 and/or Cirrus HD-OCT Carl Zeiss Meditec) was used with an axial resolution of 6 μm and acquisition rate of approximately 18,000 scans per second. High-resolution images by using radial and three-dimensional (3D) scan protocols were obtained through a dilated pupil. High-intensity scans were used with maximum differentiation of inner and outer layers. The presumed fovea was defined as the central area in the absence of inner retinal layers, nerve fiber layer, ganglion cell layer, inner plexiform layer, and inner nuclear layer. NSD was defined as subfoveal fluid accumulation identified as a distinct outer border of the retina seen elevated above the outer border of the highly reflective band, regarded as the signal generated mainly by the retinal pigment epithelium (RPE), with or without overlying foveal thickening. Using the computer-based caliper measurement tool in the SD-OCT system, the height of the NSD was measured by measuring the distance between the elevated outer edge of the sensory retina and the inner edge of the RPE, at the point of maximum elevation, whether foveal or extrafoveal. The horizontal diameter of NSD was measured as the width of the subretinal space, limited at both sides by the junction of the elevated outer edge of sensory retina and the inner edge of the RPE. All the measurements were calculated in microns.

A single experienced optometrist examined all eyes using SD-OCT to investigate the retinal microstructures. Communication was identified as an open outer border of the cyst or of edematous retina, which communicated with the NSD. In all the included eyes, there were no intraretinal lipid exudates overlying the communications, so as to ensure that the hyporeflectivity associated with the shadowing from exudates was not mistaken as an outer retinal defect.

The scan with the largest diameter of communication was selected for measurements. To standardize the measurements, a uniform protocol of measurement was followed in all the eyes. Two perpendicular lines were drawn from the two edges of the communication to the RPE, and the distance between those two points on the RPE was measured with calipers. Regarding the communications opening obliquely on the slanting outer surface of the detached retina, we found that direct measurement of the distance between the edges of communication and indirect measurement on the RPE (as already described) did not show significant difference. Hence, for standardization of measurements, the same measurement protocol (indirect measurements on the RPE) was used for all the communications, including those opening obliquely on the slanting outer surface of the detached retina. The findings were confirmed independently by another retinal specialist.

For the analysis, the communications were divided into small (<190 μm), intermediate (191-225 μm), and large (>225 μm)-sized communications on the basis of measured size.

The presence of the hyper-reflective dots within the subretinal detachment space was graded as no dots, few dots, or many dots.\textsuperscript{[17]} BCVA was measured with a Snellen's chart and converted into a logarithm of the minimum angle of resolution (logMAR). The relationship was analyzed between size of communication on the one hand and NSD height, NSD horizontal diameter, and BCVA on the other.

**Statistical analysis**

Statistical analysis (correlation test) was performed using SPSS (Statistical Package for Social Sciences, version 14.0, Chicago, IL, USA). The results were expressed as mean + standard deviation (SD) if the variables were continuous and as percentage, if categorical. The data were summarized with descriptive statistics. Means were compared with independent samples’ t-test. Categorical data were analyzed with the Chi-square test. A P < 0.05 was considered significant.

**Results**

In the current study, we examined 17 eyes of 16 subjects having DME, including 13 males and 3 females. All patients had type 2
diabetes mellitus. The mean age was 55.5 ± 6.8 years (range: 44-69 years). The clinical characteristics of the 17 eyes are shown in Table 1. The eyes were numbered from 1 to 17 in the order of increasing size of communication. The right eye was affected in nine (52.9%) eyes and the left eye in eight (47.1%) eyes. The pattern of DME in the retina overlying the NSD was a combination of CME and diffuse thickening in 14 (82.4%) eyes, and CME alone (17.6%) in 3 eyes. Within the subretinal detachment space, no hyper-reflective dots were seen in seven eyes, a few dots were seen in five eyes, and many dots were seen in five eyes.

Figures 1-6 depict the SD-OCT images of all the 17 study eyes showing outer retinal communications between intraretinal fluid pockets and the subretinal space in the form of defects in the external limiting membrane (ELM) and the photoreceptor layer of the elevated retina. The communications are seen as discontinuity of the outer retina, with no overlying lipid exudates or no hyporeflectivity of the underlying RPE to exclude the effect of backshadowing. Figures 1 and 2 show the images of eyes 1-6 having small-sized communications. The associated NSDs are small, and the subretinal detachment space appears clear without any hyper-reflective dots. Only eye 3 has a few hyper-reflective dots in the subretinal detachment space. Figures 3 and 4 show the images of eyes 7-12 having intermediate-sized communications. The size of the associated NSDs is larger, and hyper-reflective dots are visible in the subretinal detachment space (eyes 8, 9, and 12 have a few dots, and eyes 10 and 11 have many dots). Figures 5 and 6 show the images of eyes 13-17 having large-sized communications between intraretinal fluid pockets and the subretinal space. The associated NSDs appear large, and a larger number of hyper-reflective dots is seen in the subretinal detachment space (eyes 13, 15, and 17 have many dots, and eyes 14 and 16 have a few dots).

We also assessed the correlation between the size of communication and height of NSD, horizontal diameter of NSD, presence of hyper-reflective dots within the subretinal detachment space, and BCVA in Table 2. As noted, the size of communication positively

### Table 1: Clinical characteristics of study eyes

<table>
<thead>
<tr>
<th>Age (years)/Gender</th>
<th>Duration of DM (years)</th>
<th>Size of communication (µm)</th>
<th>Height of NSD (µm)</th>
<th>Horizontal size of NSD (µm)</th>
<th>BCVA (logMAR)</th>
<th>Stage of DR</th>
<th>Type of DME</th>
<th>Dots*</th>
</tr>
</thead>
<tbody>
<tr>
<td>62/M</td>
<td>9</td>
<td>44</td>
<td>67</td>
<td>856</td>
<td>0.3</td>
<td>Severe NPDR</td>
<td>CME</td>
<td>No</td>
</tr>
<tr>
<td>48/M</td>
<td>1</td>
<td>72</td>
<td>119</td>
<td>1185</td>
<td>0.4</td>
<td>Mod NPDR</td>
<td>CME+diffuse</td>
<td>No</td>
</tr>
<tr>
<td>52/M</td>
<td>4</td>
<td>95</td>
<td>137</td>
<td>681</td>
<td>0.18</td>
<td>Mod NPDR</td>
<td>CME</td>
<td>Few</td>
</tr>
<tr>
<td>63/M</td>
<td>13</td>
<td>103</td>
<td>120</td>
<td>215</td>
<td>0.6</td>
<td>Mild NPDR</td>
<td>CME+diffuse</td>
<td>No</td>
</tr>
<tr>
<td>46/F</td>
<td>4</td>
<td>127</td>
<td>123</td>
<td>1286</td>
<td>0.6</td>
<td>Mild NPDR</td>
<td>CME</td>
<td>No</td>
</tr>
<tr>
<td>69/M</td>
<td>8</td>
<td>183</td>
<td>108</td>
<td>2070</td>
<td>0.78</td>
<td>Mod NPDR</td>
<td>CME+diffuse</td>
<td>No</td>
</tr>
<tr>
<td>49/M</td>
<td>1</td>
<td>191</td>
<td>175</td>
<td>1782</td>
<td>0.48</td>
<td>PDR</td>
<td>CME+diffuse</td>
<td>No</td>
</tr>
<tr>
<td>44/M</td>
<td>0.5</td>
<td>199</td>
<td>111</td>
<td>1287</td>
<td>0.3</td>
<td>PDR</td>
<td>CME+diffuse</td>
<td>Few</td>
</tr>
<tr>
<td>54/F</td>
<td>5</td>
<td>191</td>
<td>127</td>
<td>1229</td>
<td>0.3</td>
<td>Mild NPDR</td>
<td>CME+diffuse</td>
<td>Few</td>
</tr>
<tr>
<td>52/M</td>
<td>6</td>
<td>192</td>
<td>196</td>
<td>3432</td>
<td>0.6</td>
<td>PDR</td>
<td>CME+diffuse</td>
<td>Many</td>
</tr>
<tr>
<td>53/F</td>
<td>13</td>
<td>199</td>
<td>191</td>
<td>1630</td>
<td>1</td>
<td>PDR</td>
<td>CME+diffuse</td>
<td>Many</td>
</tr>
<tr>
<td>55/M</td>
<td>18</td>
<td>223</td>
<td>91</td>
<td>1205</td>
<td>0.18</td>
<td>Mod NPDR</td>
<td>CME+diffuse</td>
<td>Few</td>
</tr>
<tr>
<td>61/M</td>
<td>13</td>
<td>231</td>
<td>463</td>
<td>2961</td>
<td>1.3</td>
<td>Mod NPDR</td>
<td>CME+diffuse</td>
<td>Many</td>
</tr>
<tr>
<td>58/M</td>
<td>16</td>
<td>303</td>
<td>196</td>
<td>1686</td>
<td>0.48</td>
<td>Severe NPDR</td>
<td>CME+diffuse</td>
<td>Few</td>
</tr>
<tr>
<td>57/M</td>
<td>15</td>
<td>389</td>
<td>402</td>
<td>1822</td>
<td>1.5</td>
<td>Mod NPDR</td>
<td>CME+diffuse</td>
<td>Many</td>
</tr>
<tr>
<td>58/M</td>
<td>16</td>
<td>446</td>
<td>239</td>
<td>1995</td>
<td>0.48</td>
<td>Severe NPDR</td>
<td>CME+diffuse</td>
<td>Few</td>
</tr>
<tr>
<td>63/M</td>
<td>13</td>
<td>518</td>
<td>407</td>
<td>3775</td>
<td>1</td>
<td>Mod NPDR</td>
<td>CME+diffuse</td>
<td>Many</td>
</tr>
</tbody>
</table>

correlated with the height of NSD ($r = 0.701$, $P = 0.002$), with the horizontal diameter of NSD ($r = 0.695$, $P = 0.002$), with the number of hyper-reflective dots within the subretinal detachment space ($r = 0.729$, $P = 0.002$), and with logMAR BCVA ($r = 0.827$, $P < 0.0001$).

**Discussion**

The pathogenesis of DME includes intracellular and extracellular edema. Muller cells’ necrosis leads to cystoid
Continuous leakage of fluid into the subretinal space. The size of communication also correlated positively with the presence of subretinal hyper-reflective dots. Ota et al. reported the presence of more hyper-reflective dots in eyes with communications than in those without. Hyper-reflective dots represent hard exudates, which may flow into the subretinal space in a larger quantity if the size of the communication is larger. A few subretinal dots are precursors of subfoveal hard exudate clump, which is a poor prognostic factor; hence, the importance of prompt treatment in the presence of subfoveal hyper-reflective dots and ELM defects. We also found that eyes with larger communications had poorer visual acuities. The same may be explained by the presence of larger NSDs and more subretinal hyper-reflective dots in such eyes. Post-treatment BCVA has been noted to be poor in eyes with many hyper-reflective dots than that in those with few dots. However, BCVA depends on many other factors including chronicity of edema, macular ischemia/perfusion, and the health of RPE and photoreceptors, and studies with larger sample size are required to evaluate this association. Tsujikawa et al. reported the presence of outer retinal discontinuities in 9/91 eyes with NSD in branch retinal vein occlusion (BRVO). They observed that the presence of discontinuity did not necessarily lead to poor vision. However, they did not correlate BCVA with the size of discontinuities.

Though the exact significance of the detection of outer retinal communications is not known at present, it definitely helps to better understand the pathophysiology of NSD in DME. The correlation of the size of communications with the size of NSD is interesting and needs to be evaluated further. The limitations of the present study include small sample size and smaller subgroups—hence, the statistical values lack power or significance. Because of nonconsecutive selection of study eyes, the incidence of communications in eyes having NSD in DME cannot be predicted. Another limitation is the cross-sectional study design, which does not prove the speculation that the communications are responsible for fluid passage into the subretinal space. Furthermore, correlation of the fundus fluorescein angiography findings was not done with the presence of communications. Hence, the role of ischemia causing RPE damage could not be evaluated. However, the primary aim of study is to report the presence of communications and their correlation with dimensions of NSD and BCVA. Controlled prospective studies showing future course of these communications, and its influence on NSD, will be required with a larger sample size to validate our findings.

### References


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