Characterization of Inner Retinal Spots With Inverted Reflectivity on En Face Optical Coherence Tomography in Diabetic Retinopathy

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PURPOSE. The purpose of this study was to characterize inner retinal spots with inverted reflectivity on en face images of swept-source optical coherence tomography (SS-OCT) in diabetic retinopathy (DR).

METHODS. We retrospectively reviewed seventy-five eyes of 75 patients with DR (15 eyes with individual grades of DR severity). We obtained three-dimensional images (6×6 mm) centered on the fovea, followed by the generation of en face images. We investigated the morphologic characteristics of spots with inverted reflectivity, which had lower reflectivity than the surrounding areas in the nerve fiber layer (NFL) and higher reflectivity in the ganglion cell layer (GCL).

RESULTS. Thirty-seven of 45 eyes (82.2%) with moderate nonproliferative diabetic retinopathy (NPDR) or more severe grades were accompanied with well-defined spots with inverted reflectivity, whereas 30 eyes with no apparent retinopathy or mild NPDR had no such lesions. These spots had various shapes in the NFL and GCL on en face OCT images; the mean area was 0.126±0.052mm² at the NFL level. In all 75 eyes, 153 of 184 spots (83.2%) were localized in the NFL and GCL, whereas 31 spots (16.8%) extended to retinal layers deeper than the GCL. One-hundred sixty-nine spots (91.8%) were not visible on color fundus photographs, and 15 spots (8.2%) were accompanied by whitish-yellow lesions in the corresponding areas. In 45 eyes for which fluorescein angiography images were obtained, mild hypofluorescence was seen in 156 spots (84.8%) and focal nonperfused areas in 17 spots (9.2%).

CONCLUSIONS. En face images of SS-OCT showed spots with inverted reflectivity in the NFL and GCL in DR.

Keywords: diabetic retinopathy, optical coherence tomography, reflectivity

Diabetic retinopathy (DR) often leads to severe visual impairment, worldwide, because of neovascular complications and diabetic macular edema (DME).1–5 Diabetes disrupts neurovascular units in the retina and leads to development of nonperfused areas and subsequent proliferation of fibrovascular tissues.4 Despite definite clinical findings on fluorescein angiography (FA) and optical coherence tomography (OCT) images, the pathophysiologic and histologic mechanisms should be elucidated in DR.

Four laminar plexuses in the retinal vasculature, which reside in the nerve fiber layer (NFL), ganglion cell layer (GCL), and the deep portions of the superficial nuclear layer (SINL) and those of the deep portions of the inner nuclear layer (DINL), respectively, perfuse and nourish neuroglial tissues in the inner retinal layers in healthy eyes.5,6 All capillary beds disappear in typical nonperfused areas, and concomitantly reduced metabolism or hypoxia leads to degenerative or atrophic processes in the inner retinal layers, or vice versa, before neurodegeneration by diabetes decreases the expression of angiogenic factors and subsequently leads to capillary loss.7–11 Cotton wool spots appear to be grayish-white lesions with fluffy margins and appear as focal nonperfused areas on FA images. Generally, microinfarctions or focal ischemia in the NFL is thought to disturb axoplasmic transport with concomitant deposition of axonal cargoes.12–14 Recent publications have reported that obstruction of the deep capillary layers including the SINL and DINL induces deep capillary ischemia and a concomitant increase in OCT reflectivity in the middle layers alone, referred to as paracentral acute middle maculopathy.15,16 Compared to these findings, the kinds of clinical findings that represent laminar ischemia in GCL remain unclear.

Advanced OCT technology facilitates an appreciation of the retinal parenchymal lesions in DR and objective evaluation of the edematous changes in DME.17,18 Neurodegenerative changes have been reported in DR and were confirmed by basic research.19,20 In vivo OCT imaging showed that the inner retinal thickness decreases in DR, although it remains ill defined whether the pathogenesis is mediated via diabetes-induced biochemical pathways or ischemic changes.21–25 Despite the feasibility of OCT, clinicians cannot discriminate the inner retinal thinning in DR from mild loss of the ganglion cell complex in glaucoma.24 In addition to morphologic findings, the changes in OCT reflectivity levels also represent the pathogenesis. For example, the reflectivity levels were
increased in the middle retinal layers in eyes with paracentral acute middle maculopathy, and DME eyes have cystoid spaces with the various reflectivity levels.\textsuperscript{15,16,25} However, OCT reflectivity of the diabetic lesions in the NFL and GCL remains ill-defined.

In the current study, we identified the three-dimensional (3D) characteristics of a novel OCT finding, that is, spots with inverted reflectivity in the NFL and GCL in eyes with moderate nonproliferative diabetic retinopathy (NPDR) and more severe disease grades.

**METHODS**

**Patients**

We retrospectively reviewed 75 eyes of 75 patients with diabetes for whom swept-source OCT (SS-OCT) images and color fundus photographs of sufficient quality were acquired. In eyes with moderate NPDR or more severe grades, FA and optical coherence tomography angiography (OCTA) images were also obtained. Exclusion criteria were the presence of any other chorioretinal disease, abnormalities in the vitreoretinal interface on SS-OCT images, optic nerve diseases including glaucoma and ischemic optic neuropathy, a history of treatment of DME, cataract surgery within 3 months, or any intraocular surgery other than cataract extraction. We also evaluated 30 unaffected fellow eyes of retinal vein occlusion patients which did not meet the exclusion criteria described above (mean age was 62.1 ± 12.4 years old) as nondiabetic control subjects. All research and measurements adhered to the tenets of the Declaration of Helsinki. The ethics committee of our institution approved the study protocol and all participants provided written informed consent.

**Swept-Source Optical Coherence Tomography**

After patients were given a comprehensive ophthalmic examination, we obtained retinal volumetric images in a 6 × 6-mm square centered on the fovea, using SS-OCT (DRI OCT-1; Topcon, Tokyo, Japan), followed by construction of 3D images. This OCT system operates at higher scan speed of 100,000 A-scans/second, using a light source with longer wavelength (central wavelength of 1050 nm). In addition, invisible scan lines and an eye-tracking system further improve the continuity between B-scan images and reduce lateral displacement in volumetric images. We first input the axial length quantified by partial coherence interferometry (IOLMaster; Carl Zeiss AG, Oberkochen, Germany) to correct the horizontal scan length and acquired 256 horizontal B-scans generated from 512 A-scans using the 3D scan mode.

Several publications have reported neurodegenerative changes in the NFL and GCL in DR, which prompted us to investigate the structural changes on en face images in these layers.\textsuperscript{19–23} The raw data of volumetric images were exported through the OCT Viewer (Topcon), followed by image processing using EnView software (Topcon). The moving average of individual B-scan images provided reduced speckle noises and improved the resolution of sectional images and the continuity between B-scan images. The NFL and GCL were flattened by the flattening function, using the NFL/GCL boundary as a reference surface, and subsequent seven pixels (18.2 μm) were averaged along the z-axis led to generation of the slab images at the levels of the NFL or GCL (4 pixels inner or outer than the NFL/GCL boundary). One pixel Gaussian blur was further applied using ImageJ software (National Institutes of Health, Bethesda, MD, USA) followed by further analyses of the lesions in these layers (Fig. 1).

To manually measure the size of spots with inverted reflectivity at the NFL level, we traced the boundary of the lesions using the freehand line selection function of the ImageJ software, followed by pixel quantification in the areas. Lesions were delineated in at least the NFL and GCL, and some lesions extended to the outer retinal layers. Lesion depth was determined on the B-scan images after application of the moving average function by using EnView software.

**Color Fundus Photography**

Color fundus photographs of 45° were centered on the fovea and obtained using a fundus camera (TRC-NW8F; Topcon). We evaluated the fundus findings corresponding to the spots with inverted reflectivity in the central 6 × 6-mm areas.

**Fluorescein Angiography**

We acquired 30° × 30° FA images centered on the fovea (1536 × 1536 pixels), using Heidelberg retinal angiography 2 unit (HRA2; Heidelberg Engineering, Heidelberg, Germany). We evaluated and categorized the perfusion status (i.e., typical nonperfused areas, perfused areas, and mild hypofluorescence). The well-demarcated areas with homogeneous and significant reduction of fluorescence levels were defined as typical nonperfused areas, after the exclusion of blocked fluorescence by retinal hemorrhages and hard exudates. We further defined focal and mild hypofluorescent areas with vague border as mild hypofluorescence in this study.

**Optical Coherence Tomographic Angiography**

Optical coherence tomographic angiography images centered on the fovea (3 × 3 mm) were obtained using spectral-domain (SD)-OCT (RTVue XR Avanti; Optovue, Inc.), which allowed us to evaluate the structural changes in capillaries in 4 capillary layers (i.e., NFL, GCL, SINL, and DINL).\textsuperscript{26–27} Thin slices (30-μm thickness) using inner border of the INL as a reference surface were constructed. We screened slab images from the vitreous cavity to the retinal pigment epithelium, comparing to the decorrelation signals around the lesions on the B-scan images. The first capillary layer was delineated in the NFL around the optic disc or vascular arcades. Capillary layers in the GCL, SINL, and DINL were in order depicted around the lesions. The status of the decorrelation signals was evaluated in these four layers. Capillary plexus in the NFL was not definite in the macula, which led us to assess three capillary layers (i.e., GCL, SINL, and DINL).

We further investigated en face 3D-OCT images in the NFL and GCL. We selected the inner plexiform layer (IPL/INL) boundary as a reference surface, and generated the slab images with 18-μm thickness using the manufacturer’s software. The position was shifted to the inner retinal layers along z-axis, and created the en face images in the NFL and GCL. We evaluated 10 μm inner and outer en face images than the NFL/GCL boundary which was manually determined on the B-scan images around the lesions.

**Statistical Analysis**

Two masked retinal specialists evaluated all qualitative and quantitative parameters in all modalities, followed by the decision of a third specialist if there was a disagreement. En face SS-OCT images in the NFL and GCL were objectively generated. Two masked specialists then assessed the characteristics of the spots with inverted reflectivity in the same datasets. Once the spots were determined on SS-OCT images, the corresponding lesions on fundus photography, FA, and...
OCTA were further evaluated. To assess the interevaluator agreements, we calculated the intraclass correlation coefficient (ICC). The results are expressed as the mean standard deviation for the parameters with normal distributions and equal variance or otherwise the median (interquartile range [IQR]). Significant differences in sampling distributions were determined using the Fisher exact test or chi-square test. Spearman rank correlation coefficients were used to determine statistical correlation of the number of the spots to age, hemoglobin A1c, or the logarithm of the minimum angle of resolution visual acuity (logMAR VA). Areas under the receiver operating characteristic (ROC) curve (AROC) were calculated to evaluate the DR-discriminating power of the total number of spots with inverted reflectivity. Briefly, we determined the sensitivity and specificity for moderate NPDR or more severe grades, severe NPDR, or more severe grades, or proliferative diabetic retinopathy (PDR) according to the number of the spots, and the ROC curve was generated. The AROC was calculated and presented as a mean value and 95% confidence interval (CI). A P value of < 0.05 was considered significant.

RESULTS

Three-Dimensional Characterization of Spots With Inverted OCT Reflectivity

We evaluated SS-OCT images in 75 eyes of 75 patients (mean 62.4 ± 14.3 years of age) in this study. Eyes with individual grades of DR severity ranging from no apparent retinopathy, to mild NPDR, moderate NPDR, severe NPDR, and PDR were selected randomly (n = 15 for each grade).

En face images at the levels of the NFL and the GCL delineated arcuate retinal nerve fibers and larger retinal vessels respectively but no other structural findings were seen in either layer in 30 nondiabetic control eyes (Figs. 1E, 1H). In contrast, we found a novel finding, inner retinal spots with
The quantified reflectivity levels along the smaller areas with higher reflectivity in the GCL (reduced reflectivity in the NFL (inverted OCT reflectivity in DR. En face images in the NFL (inverted reflectivity was 0.126 were not as distinct at the level of the GCL. The manual spots at the level of the NFL, whereas their boundaries outer nuclear layer; 9.8%, 3.3%, 2.2%, and 1.6%, respectively). The margins of the lesions were well defined by the lower inverted OCT reflectivity, delineated on en face OCT images. Margins of the lesions were well defined by the lower inverted OCT reflectivity, delineated on en face OCT images. Three-dimensional images of the inner retinal spots with inverted reflectivity, delineated on en face OCT images. Three-dimensional images of the inner retinal spots with inverted reflectivity, delineated on en face OCT images. Of all spots with inverted reflectivity delineated on en face OCT images, 169 spots (91.8%) did not have corresponding findings on the color fundus photographs (Fig. 4A, arrowheads). In contrast, 15 spots (8.2%) were accompanied by whitish-yellow spots with shapes similar but not identical to those on the en face SS-OCT images (Fig. 4A, arrows). Boundaries were indistinct and did not appear to be fluffy in contrast to typical cotton wool spots. Comparison with B-scan images showed a trend that 6 (40.0%) of the 15 spots with a corresponding finding on the color fundus images reached retinal layers deeper than the GCL, whereas only 25 of 169 lesions (14.8%) without any finding on the color fundus images extended into deeper layers (P = 0.023; Table).

We then investigated the association of these spots with FA in 45 eyes, for which both SS-OCT and FA images were obtained. A total of 156 spots (84.8%) were accompanied by mild hypofluorescence in the corresponding areas (Fig. 5B), and 17 spots (9.2%) with typical nonperfused areas (Fig. 5C). All spots in perfused areas or 140 of 156 spots (89.7%) with mild hypofluorescence were in the NFL and GCL alone, whereas 15 of 17 spots (88.2%) accompanied by focal nonperfused areas extended to retinal layers deeper than the GCL (P < 0.001) (Table).

Optical coherence tomographic angiography images were compared to SS-OCT images in 45 eyes with moderate NPDR or more severe grades (Fig. 5). Vascular plexus in the GCL was reduced or absent in 69 of 71 spots (97.2%) with inverted reflectivity in the central 3- × 3-mm areas (Figs. 5M–P), and capillaries in the NFL were also absent around the optic disc or vascular arcades (Figs. 5E–H). In contrast, capillaries in the SINV or DINL were delineated in the corresponding areas of 67 spots (94.4%). Four spots especially with focal nonperfused areas were noted to not have any capillary plexuses.

Relationship to Diabetic Retinopathy Severity Scale

Spots with inverted OCT reflectivity were quantified by two independent retinal specialists, with higher interevaluator agreements (ICC = 0.992; P < 0.001). Further investigation demonstrated that spots with inverted reflectivity were seen in eyes with moderate NPDR, severe NPDR, and PDR, 3 (IQR: 1–7), 5 (IQR: 2–9), and 5 (IQR: 2–11.75), respectively, compared to FA images in 45 eyes with moderate NPDR or more severe grades (Fig. 6). The AROC for moderate NPDR or more severe grades of the number of spots with inverted OCT reflectivity was 0.911 (95% CI: 0.842–0.980), suggesting the diagnostic significance of the severity of DR (Fig. 6B). The AROC for severe NPDR or more severe grades or PDR was not as significant (0.829 [95% CI: 0.730–0.927] or 0.735 [95% CI: 0.590–0.880], respectively) (Figs. 6C, 6D). We further investigated but did not find the association between the number of the spots with age (ρ = −0.089; P = 0.416), hemoglobin A1c (ρ = 0.042; P = 0.803), or logMAR VA (ρ = 0.226; P = 0.052).

Comparison of OCT Images With Color Photography and Fluorescein Angiography

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DISCUSSION

In this study, we have reported for the first time detecting spots with inverted OCT reflectivity in the NFL and GCL in DR and investigated the 3D morphologic characteristics of the spots and compared them to findings on fundus photographs and FA images. Most such spots were accompanied by mild hypofluorescence, suggesting a novel pathologic mechanism regarding disruption of the neurovascular units in diabetic retinas. Among many fundus findings, microaneurysms, intraretinal hemorrhages, and venous beading, intraretinal microvascular abnormalities are considered important predictors of development of PDR. En face images of SS-OCT also showed the diagnostic relevance of spots with inverted reflectivity, because they were seen in eyes with moderate NPDR and more severe grades alone, with higher sensitivity and specificity.

To the best of our knowledge, no previous publications have provided a reasonable interpretation of the kinds of histologic lesions corresponding to this novel OCT finding. Considering the morphologic and reflective characteristics of spots with inverted reflectivity, we propose a few possible cellular mechanisms (i.e., apoptotic or necrotic changes in ganglion cells or gliosis in the inner retinal layers). Several basic and clinical research reports have supported cellular damage in ganglion cells in DR. During the process of cell death, the reflective properties were modulated by changes in the organelles, which might be compatible with the reflectivity levels of the NFL and GCL seen in the current OCT findings. Another possibility is that spots with inverted reflectivity correspond to the gliotic mass after neurodegenerative changes in the ganglion cells, regardless of whether the glial cells are derived from astrocytes or Müller cells. Several...
Other studies have reported that in paracentral acute decorrelation signals in the superficial or deep layers in FA images are not necessarily identical to the absence of blocked fluorescence. It is well established that focal capillaries in the NFL and/or GCL suggest the possibility of plexuses in the NFL and/or GCL, although two spots with were accompanied by laminar nonperfusion in the capillary angiography found that most spots with inverted reflectivity either blocked fluorescence or nonperfusion in some but not mild hypofluorescence in corresponding areas, suggesting the superficial layers on OCTA images. Nonperfused areas on retinal vessels may correspond to the decorrelation signals in between capillaries on FA and OCTA images. Fluorescence in same spectra of pathologic changes. speculate that these individual lesions to some extent share the where both lesions showed laminar ischemia. We therefore hypothesized that spots with inverted OCT reflectivity was associated with a novel laminar ischemia in GCL and NFL. Chronic changes in neurovascular units promote neurodegeneration and vascular lesions in DR, although it is unclear whether the neuroglial component or vasculature is damaged primarily. The morphologic characteristics of spots with inverted reflectivity, such as the histologic size, various shapes, and well-defined borders, encouraged us to speculate that disrupted blood flow might induce neuroglial damage, because such spots were present between but not on larger vessels. However, we could not completely exclude the possibility that ganglion cell death may lead to loss of the vascular plexus in the GCL via reduced angiogenic factors from the neuroglial components, which may be compatible with the eleven spots with inverted reflectivity in the perfused areas. In addition, the 31 spots extending to layers deeper than the GCL also may support the precedent neurodegeneration. Because capillaries in the NFL, SINL, and DINL branch off from proximal larger vessels in the GCL, laminar ischemic changes, such as cotton wool spots or paracentral acute middle maculopathy, can emerge in individual retinal layers rather than in vertical columnar units in the neuroglial components.

Investigation of the relationship to ocular characteristics showed that spots with inverted OCT reflectivity were present only in eyes with moderate NPDR and more severe grades, whereas there were no associations with age or logMAR VA. Although the number of spots tended to increase with the severity of the DR, a longitudinal study should be undertaken to elucidate whether this OCT finding can predict progression to PDR, as shown by the 4-2-1 rule in fundus findings. In addition, intraretinal hemorrhages and cotton-wool spots develop in other retinal vascular diseases including hypertensive retinopathy, retinal vein occlusion, or interferon-associated retinopathy, although it remains to be determined whether spots with inverted reflectivity are specific to DR rather than other retinal vascular diseases.

We compared the SD-OCT images to the en face SS-OCT images and found that the reflectivity changes were similar in both instruments, although the boundary was frequently indistinct in the NFL on SD-OCT images. The different appearances might depend on the different methods of image acquisition including the wavelength of light source or different image processing procedures including registration, segmentation, and the reference surfaces for slab images. We might speculate that several technologies in SS-OCT might provide the better continuity between scanning lines in en face images and contribute to the clearer boundary of spots with inverted OCT reflectivity in this study.

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<th>Location of Spots With Inverted Reflectivity</th>
<th>NFL and GCL Alone</th>
<th>NFL to Deeper Layers Than GCL</th>
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<tr>
<td>Whitish-yellow spot</td>
<td>Present</td>
<td>9</td>
<td>6</td>
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<tr>
<td></td>
<td>Absent</td>
<td>144</td>
<td>25</td>
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<td>FA finding</td>
<td>Focal nonperfused area</td>
<td>2</td>
<td>15</td>
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<td></td>
<td>Mild hypofluorescence</td>
<td>140</td>
<td>16</td>
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<td></td>
<td>Perfused area</td>
<td>11</td>
<td>0</td>
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<0.001

FA, fluorescein angiography; GCL, ganglion cell layer; NFL, nerve fiber layer.

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<th>Table</th>
<th>Relationship Between Depth of Inner Retinal Spots Using Inverted OCT Reflectivity and Findings on Color Fundus Photography and Fluorescein Angiography in Diabetic Retinopathy</th>
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| Figure 4. Color fundus findings of inner retinal spots with inverted reflectivity in DR (A) Color fundus photographs show no definite findings (arrowheads) or whitish-yellow spots (arrows) in areas corresponding to the inner retinal spots delineated on en face images of the NFL (B) and the GCL (C). |
Figure 5. Fluorescein angiography findings of inner retinal spots with inverted reflectivity in DR. Perfused areas (A), mild hypofluorescence (B), and typical nonperfused areas (C) are seen in the areas corresponding to the inner retinal spots (arrowheads).

Figure 6. Relationship between the number of inner retinal spots with inverted OCT reflectivity with DR severity grades. (A) The number of spots in individual DR grades. The ROC curve for DR severity (moderate NPDR or more severe grades [B], severe NPDR or more severe grades [C], or PDR [D]) of the number of spots with inverted reflectivity.
In the current study, we identified the morphologic characteristics of a novel OCT finding, that is, spots with inverted OCT reflectivity in eyes with moderate NPDR and more severe grades, suggesting the diagnostic relevance and pathogenesis of the disruption of the neurovascular units.

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