Detection and Analysis of Hard Exudates by Polarization-Sensitive Optical Coherence Tomography in Patients With Diabetic Maculopathy

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METHODS. Twenty-two eyes of 16 patients with DME were imaged by using color fundus photography (CF) and PS-OCT. In PS-OCT, HEs were automatically detected by their distinct polarization-scrambling qualities. Color fundus images were manually graded for the presence of HEs by two masked graders and correlated with the corresponding PS-OCT HE maps: corresponding images were overlaid and an identical grid of 128 × 128 fields was used for correlation of detected HEs.

RESULTS. In all eyes, HEs were present owing to DME. Agreement of a pixel-to-pixel analysis of HEs in CF images was 0.72 (Cohen’s κ) between graders and 0.44 between graders and automated detection by PS-OCT. Mean ± SD detection of HEs was significantly higher in PS-OCT than in manual grading (1180.5 ± 1009.8 fields versus 828.8 ± 695.0 fields; P = 0.02). The higher detection rate of PS-OCT was confirmed by a linear regression analysis with a slope of β = 1.18 (r = 0.81).

CONCLUSIONS. PS-OCT enables not only two-dimensional imaging of the extent of HEs, as in CF, but also allows tissue-specific, three-dimensional imaging of HEs throughout retinal layers, based on their distinct polarization-scrambling characteristics. The higher detection rate in PS-OCT images indicates an increased sensitivity of PS-OCT imaging over conventional CF.

Keywords: hard exudates, diabetic retinopathy, polarization-sensitive OCT, diabetic maculopathy, color fundus photography

Diabetic retinopathy (DR) and diabetic macular edema (DME), common complications of diabetes mellitus, are among the leading causes of visual impairment in the Western world and will dramatically increase in other regions such as Asia and South America.1,2 The overall prevalence of DME in patients with diabetes is reported to be approximately 7% (6.8%–7.5%), with a five-fold increased risk for subjects with type 1 diabetes (duration > 20 years) compared to those with type 2 diabetes (duration < 10 years).3,4 The Wisconsin Epidemiologic Study of Diabetic Retinopathy has reported a 10-year incidence of DME of approximately 20% in individuals with type 1 diabetes and 14% to 25% in those with type 2 diabetes, and a 25-year incidence of 29% for DME and 17% for clinically significant DME in individuals with type 1 diabetes.5,6

Early detection of DR and DME is crucial for prevention of vision loss. Among other retinal changes, such as microaneurysms and intraretinal hemorrhages, hard exudates (HEs) are striking features of an impairment of the blood-retinal barrier, leading to retinal swelling and edema.7 Extravasation of lipids, proteinaceous material, and inflammatory cells lead to deposits primarily located in the outer plexiform and outer nuclear layer of the neural retina.8,9 Increasing numbers of HEs seem to be associated with an increased risk of visual loss.7 Furthermore, eyes with severe HEs also have an increased risk of developing subretinal fibrosis, an additional complication of macular edema.10

Retinal imaging is widely used by ophthalmologists and primary care physicians to screen for epidemic eye diseases such as DR and DME. Color fundus photography (CF) was previously the gold standard. Optical coherence tomography (OCT), however, has recently entered the field of retinal imaging in clinical daily routine. While CF provides a high sensitivity for a wide range of diabetic retinal changes two-dimensionally,11,12 OCT raster scanning offers important cross-sectional information about the retinal layers.13,14 Automatic detection of DR lesions, especially of HEs, is a difficult task in both CF and OCT imaging. Several attempts have been made to segment HEs in CF photographs with improving sensitivity and specificity.15-17 However, CF only provides two-dimensional information about the extent of HEs. Owing to their density and opacity, HEs are also distinguishable in OCT B-scans as hyperreflective lesions.9,18 OCT can additionally provide three-dimensional information about HE extent and distribution throughout the retinal layers. However, conventional spectral-domain (SD) OCT imaging and quantification of HEs are limited by the lack of automated segmentation.
algorithms: owing to the intensity-based image generation in SD-OCT, differentiation of HEs from other hyperreflective structures within the retinal layers remains unfeasible.

Polarization-sensitive OCT (PS-OCT) is a functional extension of OCT that enables high-resolution three-dimensional imaging of biological samples, based on their polarization properties, in addition to providing conventional OCT images based on the intensity of backscattered light.\textsuperscript{19,20} In PS-OCT, the sample is illuminated with one or more well-defined polarization states, and the OCT signal is detected in a polarization-sensitive fashion. By analyzing the detected polarization states, PS-OCT can distinguish tissues by the polarization of backscattered light and thus provides additional, tissue-specific contrast. In the human eye, PS-OCT can differentiate between birefringent (e.g., sclera, retinal nerve fiber layer [RNFL]), polarization-preserving (e.g., photoreceptor layer), and depolarizing tissues (e.g., retinal pigment epithelium [RPE]).\textsuperscript{21–29} A comprehensive review of PS-OCT and its application to ocular imaging can be found in a recent review.\textsuperscript{30} Hard exudates appear depolarizing in PS-OCT images in exudative diseases such as wet AMD, vein occlusion, and diabetic retinopathy with DME. This characteristic can be used for specific segmentation of HEs.

In this article, we systematically analyzed this phenomenon and compared this new imaging modality to the existing gold standard, namely color fundus photography. The aim of the study was to assess the capability of PS-OCT to selectively image HEs on a proof-of-principle basis and to compare the results with the current gold standard.

METHODS

Patients and Inclusion

In this prospective, cross-sectional, observational study, patients with DME secondary to DR were enrolled at the Department of Ophthalmology, Medical University of Vienna, Austria. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee. All participants signed an informed consent form after a detailed explanation of the study design, associated investigations for scientific purposes, and adjuvant imaging procedures.

Inclusion criteria for the study were DR due to type 2 diabetes mellitus, with presence of HEs in the macula and perimacular regions. Patients with media opacities (cornea, lens, vitreous) or macular alterations due to other diseases were excluded from the study.

Image Assessment

Standardized examination procedures were performed according to a study protocol: During a same-day examination, patients underwent a complete evaluation, including standardized corrected Early Treatment Diabetic Retinopathy Study Research Group (ETDRS) visual acuity testing, slit-lamp examination, fundoscopy, \(30^\circ\) and \(50^\circ\) macular CF (FF450 Fundus Camera; Carl Zeiss Meditec, Inc., Dublin, CA), SD OCT (Spectralis HRA+OCT; Heidelberg Engineering, Inc., Heidelberg, Germany) and PS-OCT imaging.

PS-OCT was conducted by using a prototype developed at the Center for Medical Physics and Biomedical Engineering, Medical University Vienna, Austria. A detailed description of the instrument can be found elsewhere.\textsuperscript{31} In brief, the system was based on SD PS-OCT\textsuperscript{21} and used a detection unit with two identical spectrometer units. The system operated at a center wavelength of 839 nm and provided an axial resolution of <5 \(\mu\)m in tissue. The imaging speed was 20,000 A-scans per second. PS-OCT data sets of \(512 \times 128\) A-scans were acquired in 3.3 seconds and covered an area of 6.2 mm (\(x\)-axis) \(\times\) 6.7 mm (\(y\)-axis) on the fundus.

Degree of polarization uniformity (DOPU) images were computed to assess depolarization information.\textsuperscript{32} DOPU is related to the degree of polarization (DOP) known from classical polarization optics, which, however, cannot be directly measured by a coherent imaging technique such as OCT. DOPU was calculated from the Stokes vectors, which are derived from the raw PS-OCT data and indicate the polarization states corresponding to the image pixels. However, unlike DOP calculations, for DOPU calculation the Stokes vector elements are averaged in a sliding evaluation window in order to provide a measure for the local variance of polarization states.\textsuperscript{32} The value of DOPU ranges from close to 1 for uniform polarization (as in most retinal layers such as, for instance, the polarization-preserving photoreceptors) to lower values in depolarizing structures (such as the RPE or hard exudates). To segment depolarizing image features, DOPU images were binarized with respect to a user-defined threshold (e.g., DOPU\textsubscript{thresh} = 0.8). All depolarizing pixels had values of DOPU < DOPU\textsubscript{thresh}. The locations of such depolarizing pixels could then be overlapped on intensity images (Figs. 1B, 1C, 1D, 1G).

In retinal PS-OCT images of DME patients, both HEs and the RPE appeared depolarizing. To segment solely the HEs, we developed a dedicated software tool (Hard Exudate Analysis Software Tool, HEAST), which first segmented both RPE and HEs, and subsequently isolated a band-shaped retinal portion including HEs. The basic concept of the segmentation algorithm relied on the ideas for segmentation of drusen and geographic atrophy described by Baumann et al.\textsuperscript{31} The internal limiting membrane (ILM) was segmented from the gradient in the intensity image. Depolarizing structures (i.e., RPE and HEs) were segmented by thresholding DOPU images (red structures in Fig. 1D, en face map in Fig. 1E). As described by Baumann et al.\textsuperscript{31} a smooth function was automatically adapted posteriorly to the RPE by using Savitzky-Golay filtering, approximating the position of Bruch’s membrane (BM). The posterior border of the HE segmentation band (light grey in Fig. 1F) was then defined by advancing the BM segmentation line a certain number of pixels anteriorly from the BM in order to exclude the RPE band, inner/outer segments of photoreceptors, and external limiting membrane. For each data set, this value was set to 60 pixels by default but could be adjusted manually if segmentation errors occurred. Analogously, the anterior border of the HE segmentation band was defined by the ILM segmentation line. Finally, the depolarizing pixels within the segmentation band, which were attributed to the HEs, were summed for each A-scan in order to generate en face HE thickness maps that could be compared to fundus photographs (Fig. 1H).

Image Analysis

To correlate the extent of HEs in both CF and polarization-sensitive HE maps, overlays of the two imaging types were generated. Corresponding images were imported into Adobe Photoshop (CS6 version 13.0; Adobe Systems, Inc., San Jose, CA). Using retinal vessels as landmarks, the dimensions of the CF images were adjusted to the size and orientation of the respective en face images of the PS-OCT and cropped for further use (Figs. 2A–2E). Two experienced and certified graders (JL, BG) from the Vienna Reading Center manually graded the cropped CF images independently and in a masked fashion. Areas of HEs (as described by the ETDRS\textsuperscript{31}: small white or yellowish-white deposits with sharp margins, often slightly waxy or glistening appearance) in the CF image were marked and exported as black-and-white (b/w) images.
For statistical analysis, image data were translated into data sheets: Using the free ImageJ plugin “Patch Detector Plus” (available in the public domain at http://microscopy.uni-graz.at/index.php?item=new1), a grid containing $128 \times 128$ fields was generated, based on the PS-OCT’s resolution of $512 \times 128$ pixels, and marked areas in all graded b/w exports and corresponding polarization-sensitive HE maps were automatically assessed. This alignment allowed for a detailed comparative analysis of HEs in CF and depolarizing spots in PS-OCT maps in 16,384 fields of each data set.

**Figure 1.** Segmentation of hard exudates by PS-OCT. (A) Color fundus photography of a DME patient with HEs. The dotted box indicates the location of the PS-OCT cube. (B) Fundus projection image generated from the PS-OCT data set. The yellow line indicates the location of the B-scan images on the right. (C) Intensity B-scan image. (D) Overlay of depolarizing pixels (DOPU $< 0.8$, red) on the intensity image. (E) En face image showing the summation of all depolarizing (red) pixels in every A-scan. The summed pixels include both the RPE and HEs. (F) Depolarizing pixels (red) within the HE segmentation band (light grey). (G) Segmented HEs (red) overlaid on intensity image. (H) HE thickness map generated by summing pixels within the HE segmentation band.

**Figure 2.** Superposition of CF and PS-OCT images. (A) Color fundus photograph of a left eye. The yellow box indicates the area scanned by PS-OCT. (B) Using retinal vessels as landmarks, the PS-OCT raster scan is superposed on the CF image. (C) The corresponding CF area is then cropped and exported for manual and automated assessment of HEs. (D) Overlay of the manual grading (in black, by grader 1). (E) Overlay of the automated assessment by PS-OCT (false color thickness map).
Statistical Analysis

Statistical analysis was performed with SPSS (SPSS for Windows, version 21; SPSS, Inc., Chicago, IL). For pairwise, interrater agreement, Cohen’s $\kappa$ was calculated for results of grader 1 and 2 (both in CF), grader 1 (in CF) and the PS-OCT, and grader 2 (in CF) and the PS-OCT. Bland-Altman plots were generated for each pair. For all calculations, a maximum $P$ value of 0.05 was considered as the level of significance.

RESULTS

Twenty-two eyes of 16 patients were analyzed in this study. Mean age ± SD was 61 ± 7.4 years, and 44% of patients were female. All eyes showed clinically detectable HEs due to DR at the posterior pole.

From all 22 eyes 360,448 individual grid fields were assessed by each grader (grader 1, grader 2, PS-OCT), resulting in a total of 1,081,344 analyzed grid fields. For manual assessment of CF images, grader 1 (JL) graded a mean ± SD of 836.6 ± 700.3 fields per eye as “HE detected,” while grader 2 (BG) graded 820.9 ± 711.1 fields. For automated detection of depolarizing signals in PS-OCT, 1309.0 ± 1240.5 fields per eye were graded as “HE detected.” Means did not differ between grader 1 and grader 2 ($P = 0.77$) but did differ between PS-OCT and the graders (both $P = 0.02$). Correlation between PS-OCT detection and the mean of graders was good, with a regression line slope of $\beta = 1.24$ and a Pearson’s $r = 0.70$ ($P < 0.001$) (Figs. 3A, 3B). Interrater reliability for the manual grading of HEs in the CF images of grader 1 and 2 was $\kappa = 0.72$. Agreement of results of the aligned PS-OCT images with the individual graders was $\kappa = 0.44$ for grader 1 and $\kappa = 0.43$ for grader 2. For agreement matrix, see the Table.

In the combined analysis of PS-OCT B-scans and aligned CF, depolarizing formations were mainly found in the outer nuclear layer (ONL) and outer plexiform layer (OPL) but also in the inner nuclear layer (INL) and inner plexiform layer as seen in PS-OCT (Figs. 1D, 1G, 4C, 5C). On PS-OCT, individual, small depolarizing foci (≤ 15 pixels in diameter) were distributed throughout all retinal layers (Fig. 5C), while larger formations accumulated at the border of the INL and OPL (Figs. 1D, 1G, 4C, 5C). All depolarizing foci and formations showed a shadowing phenomenon in the projection of the scanning beam, which is known to be typical for HEs in conventional SD-OCT imaging. In contrast, such small depolarizing foci could not be identified in the corresponding CF (Fig. 5A).

Artifacts could be identified in 4 of 22 PS-OCT data sets (four lowest data points in Fig. 3B), resulting from depolarizing formations in the RNFL caused by retinal vessels (data sets No.1, No.3, and No.19), hemorrhage (data set No.17), cotton-wool spots (data set No.1; Fig. 4), as well as errors of the RPE segmentation algorithm (data set No.19; Figs. 6A, 6B). To
compare uncorrected and corrected PS-OCT performance, artifacts were manually corrected in the corresponding B-scans and re-entered into the analysis (Figs. 6C, 6D).

Mean ± SD fields per eye graded as ’’HE detected’’ changed from 1309.0 ± 1240.5 (uncorrected) to 1180.5 ± 1009.8 (corrected; \( P = 0.1 \)) and still differed significantly from the results of both graders (both \( P < 0.02 \)). Agreement of the corrected results with the graders did not change significantly, with \( \kappa = 0.45 \) for grader 1 and \( \kappa = 0.44 \) for grader 2. However, Pearson’s correlation coefficient for linear regression improved to \( r = 0.81 \) (slope \( \beta = 1.18 \); Figs. 3C, 3D).

**DISCUSSION**

The aim of this study was to evaluate the feasibility of a new imaging modality for HE assessment, based on their intrinsic polarization properties in PS-OCT imaging in patients with diabetic maculopathy. Images obtained by using PS-OCT were systematically compared to CF, the existing gold standard for imaging HEs. Thickness maps of intraretinal depolarizing structures of the posterior pole were generated by using three-dimensional PS-OCT data sets and correlated with corresponding CF. Results of statistical image analysis showed a marked correlation between HEs in CF and intraretinal depolarizing structures. The findings suggest that these depolarizing structures represent HEs, and that PS-OCT may provide a novel method for assessing and quantifying HEs.

Automated assessment and segmentation of HEs is a difficult task in both CF and OCT. Automated HE detection in CF is aggravated by uneven illumination, changing contrast, and color variation of the retinal images. Several attempts have been made to segment HEs from the retinal background, based on grey level thresholding, homogeneity of HE illumination, and edge detection, or mixture models and clustering algorithms. Since these techniques are based on fundus photography assessment, quantifying the extent of HEs is limited to two-dimensional information. However, as known from histology and SD OCT, HEs are found throughout multiple retinal layers and tend to cluster and overlay each other. Recent studies have presented detailed analyses of the presence and

<table>
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<th>Rater</th>
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<th>BG</th>
<th>PS-OCT</th>
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<td></td>
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<tr>
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<td>4,978</td>
<td>18,405</td>
</tr>
<tr>
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<td>337,410</td>
<td>342,043</td>
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<tr>
<td>Total</td>
<td>18,060</td>
<td>342,388</td>
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Rating of grader 1 (JL) and grader 2 (BG) was performed manually from color fundus photography. In PS-OCT imaging, HEs were detected automatically from their depolarizing properties.

\* Cohen’s \( \kappa \).

**TABLE. Agreement Matrix for the Detection of HEs by the Three Different Raters in the Graded Fields**

**FIGURE 4.** Artifacts in PS-OCT segmentation. (A) Magnification of the graded area within a color fundus photograph. The arrow indicates a cotton-wool spot. (B) Overlay of the color fundus photograph and the HE thickness map generated by PS-OCT. Note how the vessels (arrowheads) and the cotton-wool spot (arrow) cause segmentation artifacts. The green lines in (B) indicate the location of the corresponding PS-OCT B-scans. (C) Depolarizing structures are segmented in red. Note the segmentation artifact at the location of the vessel (arrowhead) and the cotton-wool spot (arrow). Small arrows in (C) indicate nondepolarizing hyperreflective lesions.
distribution of HEs, based on high-resolution SD-OCT imaging. Bolz et al.\(^9\) first described HEs secondary to DME as hyperreflective lesions in SD-OCT mainly located at the border of the ONL and OPL. Additionally, clinically invisible precursors of HEs, microfoci, were detected in all retinal layers before condensing to larger, clinically visible aggregates over the course of time. Other studies have correlated the presence of such microfoci with decreased visual acuity\(^{36}\) or manually quantified and described the presence and course of HEs and precursors following treatments of DME.\(^{37,38}\) All of these studies underline the importance of OCT imaging of HEs and precursors for determining the extent of lipid extravasation resulting from blood–retina barrier breakdown. Further, the need for software-based demarcations and calculations is emphasized by these authors owing to the difficulties and limitations of the currently required manual grading.\(^{38}\)

The findings of our study suggest that PS-OCT overcomes the limitations of two-dimensional CF and intensity-based SD-OCT imaging for assessment of HEs. Based on their intrinsic property to change the state of polarized light, HEs could be automatically detected and segmented. By raster scanning the macular region of interest, thickness maps of HEs were generated from 128 individual B-scans. Good agreement with clinical findings of HEs (in this study represented by CF) was achieved with the new method.

The remaining discrepancies between the results obtained by CF and PS-OCT can be attributed to the following reasons: First, accuracy and precision of OCT imaging in general requires clear optical media, as well as sufficient compliance of the patient, to avoid imaging artifacts due to poor image quality or eye motion. This also affects PS-OCT. In this study, images of insufficient quality were eliminated by defining media opacities as exclusion criteria, and scans with evident motion artifacts were repeated until acceptable quality was achieved. Nonetheless, superimposing CF and PS-OCT images often did not reach perfect accuracy of retinal landmarks (e.g., vessels). This is likely caused by residual motion artifacts and can lead to a loss of exact matching between the compared imaging modalities. Such a slight mismatch has a large influence on the pixel-to-pixel correlation of small features such as tiny HEs.

**Figure 5.** Depolarizing signal of precursors of HEs. (A) Color fundus photograph of an eye with severe DR and clusters of HEs spread out over the posterior pole. (B) Overlay of the magnified color fundus photograph and the HE thickness map generated by PS-OCT. Note the numerous small depolarizing particles in the HE map (blue dots). (C) PS-OCT B-scans corresponding to the green lines in (A) and (B). The corresponding arrows (big versus small) point out examples of clinically invisible HE precursors (A) that are detected by PS-OCT (blue dots in [B], red dots in [C]). Small arrows in (C) indicate nondepolarizing hyperreflective lesions.

**Figure 6.** Correction of artifacts in PS-OCT segmentation. (A) Overlay of a color fundus photograph and the HE thickness map generated by PS-OCT before manual correction. Note how the vessels (arrowheads) and regions of RPE atrophy (dashed rectangle) cause segmentation artifacts. (B) PS-OCT B-scan corresponding to green line in (A): depolarizing structures are segmented in red. Note the segmentation artifacts at the location of the vessel (arrowhead) and the RPE atrophy (dashed rectangles). (C) PS-OCT B-scan after manual correction of segmentation artifacts (arrowhead, dashed rectangle). Corrected B-scans are then used to generate corrected HE thickness maps (D).
but should not influence the total count of HEs within the images, which is the relevant diagnostic quantity. Nevertheless, further improvement of PS-OCT image acquisition speed, as well as using a retinal tracker, could likely overcome this limitation in future generations of PS-OCT instruments.

Furthermore, errors in the segmentation algorithm may be caused by lesions such as cotton-wool spots, profound RPE atrophy, or blood vessels. In our cohort, four data sets contained noticeable segmentation artifacts. After manual correction of these data sets, linear correlation between the two modalities improved. However, neither means of detected fields nor interrater agreement of pixelwise HE detection differed significantly from the uncorrected data. This indicates a rather negligible effect of segmentation errors on the overall performance of HE detection in PS-OCT imaging.

Another explanation for some of the observed discrepancies might be found in a detailed breakdown of individual PS-OCT B-scans: In an analysis of all acquired B-scans, we found that HEs showed depolarizing properties, as did the previously described clinically invisible precursors of HEs. However, the depolarization behavior of these precursors (defined as small hyperreflective lesions in SD-OCT) was heterogeneous. While some hyperreflective lesions showed depolarizing signals, others did not. This was observed to be independent of size, degree of reflectivity in the intensity image, and location within the retinal layers (Figs. 1D, 1G, 4C, 5C). There are two possible explanations: First, the size of these precursors might be too small to provide a sufficient number of independent data points within the DOPU evaluation window to be picked up by the algorithm, which measures the variance of polarization states among neighboring image pixels. Second, different types of hyperreflective microfoci might exist: Using immunohistology, Cusick et al. have found and imaged not only a dense concentration of apolipoprotein B deposits surrounding retinal vessels (as in hyperreflective lesions), but also cellular components such as foam cells and leukocytes. Further studies will be required to describe and categorize these hyperreflective microfoci in more detail.

Since PS-OCT detects at least part of these precursors, it would be expected to have an increased sensitivity for HE detection, as compared to CF imaging. This was in accordance with the significantly higher rates of detected HE-containing fields in PS-OCT in 77.3% of cases as compared to the individual graders as well as the means of the graders (P = 0.02) (Table; Figs. 3, 5). Therefore, the total sensitivity of PS-OCT to detect any HE is indeed higher than that of CF.

Another advantage of PS-OCT for HE assessment is the three-dimensional component of the detection. Hard exudates were automatically segmented throughout all retinal layers. Therefore, their distribution within individual retinal layers as well as their volume can be obtained, quantities that are inaccessible to CF imaging. This might add valuable information to the understanding of DME and its underlying pathomechanisms.

Given the prototype state of our PS-OCT instrument, the preliminary segmentation algorithms, and the limited study population, our data provide satisfactory accuracy to prove the presented principle. Our results strongly suggest that the presented pattern of depolarizing structures in the retina represent HEs. Further studies are underway to assess the reliability and reproducibility of volumetric assessment of HEs by PS-OCT in order to provide a new tool in the analysis of DME and treatment responses.

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References
Hard Exudate Detection by PS-OCT in Diabetic Maculopathy


APPENDIX

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