Performance of Automated Drusen Detection by Polarization-Sensitive Optical Coherence Tomography

Ferdinand G. Schlanitz, Bernhard Baumann, Tobias Spalek, Christian Schütze, Christian Ahlers, Michael Pircher, Eric Götzinger, Christoph K. Hitzenberger, and Ursula Schmidt-Erfurth

Purpose. To estimate the potential of polarization-sensitive optical coherence tomography (PS-OCT) for quantitative assessment of drusen in patients with early age-related macular degeneration (AMD).

Methods. Fifteen eyes from 13 patients presenting drusen consistent with Age-Related Eye Disease Study classifications (grades 2 and 3) were examined ophthalmoscopically, followed by fundus photography, autofluorescence imaging, and three-dimensional scanning using a PS-OCT. For the automated evaluation of drusen location, area, and volume, a novel segmentation algorithm was developed based on the polarization scrambling characteristics of the retinal pigment epithelium (RPE) and applied to each complete data set. Subsequently, the drusen in each individual B-scan were identified by two independent expert graders. Concordance between manual and automated segmentation results was analyzed. Errors in the automated segmentation performance were classified as nonsignificant, moderate, or severe.

Results. In all, 2,355 individual drusen, with a mean of 157 drusen per eye, were analyzed. Of drusen seen in the individual B-scans, 91.4% were detected manually by both expert graders. The automated segmentation algorithm identified 96.5% of all drusen without significant error. The mean difference in manual and automated drusen area (mean, 4.65 mm²) was 0.150. The number of detected drusen was significantly higher with automated than that with manual segmentation. PS-OCT segmentation was generally superior to fundus photography (P < 0.001). Particularly in nondetected drusen, a large variability in drusen morphology was noted.

Conclusions. Automated drusen detection based on PS-OCT technology allows a fast and accurate determination of drusen location, number, and total area. (Invest Ophthalmol Vis Sci. 2011;51:4571–4579) DOI:10.1167/iovs.10-6846

Drusen constitute the first of clinical findings in the development of age-related macular degeneration (AMD), the leading cause of irreversible vision loss in the developed world.1,2 The lesions consist of small, focal subretinal deposits of extracellular debris between the basal lamina of the retinal pigment epithelium (RPE) and Bruch’s membrane (BM).3 Pathohistologic studies have partially unveiled the different stages of drusen development4–6 as well as the origin and composition of their contents.7,8 Although there is still no agreement about the exact mechanism of drusen formation, it is generally accepted that the RPE plays a pivotal role in this process.9 According to recent studies, an altered RPE layer, injured by various proposed mechanisms including gene mutations, light damage, and oxidative stress, provides a basis for immune-mediated and inflammatory events in the subretinal space, which lead to the deposition of drusen-associated constituents.10 As drusen become larger and more numerous, the overlying RPE cells degenerate, subsequently accompanied by a focal loss of photoreceptors.4,11,12 The progressive spread of degenerative events throughout the macula finally lead to a decline of central visual acuity, the main characteristic of advanced atrophic AMD. Alternatively, a focal disruption of the RPE–BM barrier toward the underlying choriocapillary layer, together with an angiogenic/inflammatory stimulus, may stimulate growth of a neovascular membrane in exudative AMD.13

Therefore, drusen have been identified as a major risk factor for the development of advanced AMD.14 The reported 5-year risk of developing choroidal neovascularization among patients with bilateral drusen ranges from 0.2% to 40%.15,16 The individual risk likely depends on various factors, including drusen parameters such as size, area, and volume,2 as well as on the drusen type.17 Clinically, drusen can be roughly differentiated into “hard” and “soft,” depending on the appearance of their distinct or indistinct margins.18 The presence of soft drusen > 65 μm establishes the diagnosis of age-related maculopathy (ARM), also called “early” AMD.20 The Age-Related Eye Disease Study (AREDS), a multicenter study of the natural history of AMD and cataracts,21 could identify drusen size and total area as important clinical risk factors for developing advanced AMD.22–24 However, the AREDS study found only moderate agreement between gradings of these parameters based exclusively on standard fundus photography.25 Furthermore, a grading system using overlaid grids and manual delineation of individual lesions is inapplicable in clinical practice. Other studies proposed an automated analysis of drusen on the base of digital fundus photography, but with unsatisfying outcomes due to the limitations of fundus photography such as nonuniform illumination, their dependence on clear optical media, and a limited contrast between yellowish lesions in an orange surrounding.26,27 Other imaging methods, such as scanning laser ophthalmoscopy (SLO)—indocyanine green dye angiography and fluorescein angiography, provide additional information about drusen morphology, but again with...
several limitations, especially regarding the definition of the drusen boundaries.\textsuperscript{28}

The introduction of spectral-domain optical coherence tomography (SD-OCT),\textsuperscript{29–31} a noninvasive imaging technique, might overcome such limitations in automated lesion detection. By depth-resolved measurement of backscattered light from the retina, SD-OCT is able to retrieve a three-dimensional (3D) data set with high resolution.\textsuperscript{32} Various studies have shown that SD-OCT is of great value for research as well as clinical practice in ophthalmology, especially for the evaluation of advanced forms of AMD such as exudative AMD.\textsuperscript{33–36}

Several attempts have been made to design segmentation algorithms based on SD-OCT data capable of delivering parameters useful for clinical practice in a fast and objective manner, such as the integrity and thickness of retinal layers.\textsuperscript{37–39} However, previous work of our group showed that the intensity-based segmentation algorithms often fail to depict especially discrete alterations of the retina and RPE, such as drusen, mostly due to only marginal dissimilarities in reflectivity and interpolation of the segmentation lines.\textsuperscript{40}

Polarization-sensitive SD-OCT (PS-SD-OCT)\textsuperscript{41} combines the advantage of SD-OCT imaging (i.e., high-resolution raster scanning) with a selective identification of the polarization state of backscattered light. Because the melanosomes of the RPE change the polarization state in a random fashion, PS-OCT is capable of precisely depicting its exact location and configuration.\textsuperscript{42–44} This selectivity can be used for a reliable automated segmentation of alterations at the retina–RPE boundary.\textsuperscript{45} Previous studies from our group have already highlighted the potential of PS-OCT to image the condition of the RPE in patients with AMD.\textsuperscript{46,47}

In this study, we evaluated the performance of a novel segmentation algorithm for automated in vivo detection of drusen by comparison with manual segmentation. The algorithm is based on the ability of PS-OCT to measure and image the depolarizing property of the RPE, the primary site of drusen development.

METHODS

Patients

Patients were selected in accordance with the standard AREDS classification to avoid the potential impact of pathologies other than focal drusen on the segmentation procedure. Only eyes with drusen of AREDS categories 2 and 3 were included in this study. Category 2 is defined by the presence of extensive small (<63 μm in diameter) or nonextensive intermediate drusen (between 63 and 125 μm) or pigment–epithelial abnormalities in at least one eye. Category 3 is in accordance with extensive intermediate or large (>125 μm) drusen and/or noncentral geographic atrophy (GA) in at least one eye\textsuperscript{21}. By addition, however, eyes with additional GA were excluded. Eyes were examined ophthalmoscopically by an experienced retinologist.

Patients presenting with opacity of the ocular media by cornea or lens or diseases that could potentially influence scan quality as well as eyes with macular edema were excluded. Additionally, patients with history of ocular trauma or surgery other than uncomplicated cataract surgery were not included.

Imaging Protocol

Patients meeting the protocol criteria were informed about the study aims and procedures. After informed consent was given, patients were included in the study and underwent a complete standardized ophthalmic examination according to a protocol that was approved by the ethics committee of the Medical University of Vienna. The study adhered to the Declaration of Helsinki. The best corrected visual acuity (BCVA) of the patient was obtained, the intraocular pressure was measured, and mydriatic eye drops were administered. At maximal mydriasis, a digital photograph at 30° of the fundus, including both the macula and the optic disc, was taken (FF 450plus Fundus Camera; Carl Zeiss Meditec, Inc., Dublin, CA). Furthermore, a near-infrared autofluorescence image (average of 15 frames) was obtained, using a confocal scanning laser ophthalmoscope (cSLO) at 787-nm wavelength mode and a filter with a cutoff at 800 nm (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). Afterward, all eyes were scanned with the PS-OCT using a 128 × 512 scan pattern covering an area of 20° × 20°.

PS-OCT Technology

The PS-OCT prototype used in this study is described in detail elsewhere.\textsuperscript{41,48} To summarize, the system is able to retrieve several parameters simultaneously: the intensity of the backscattered light (as in standard SD-OCT imaging), retardation (phase shift between two orthogonal linear polarization states caused by birefringence), fast axis orientation (birefringent axis orientation of the sample relative to the orientation of the instrument), and degree of polarization uniformity (DOPU).\textsuperscript{49} A superluminescent diode (Superlum Diodes, Moscow, Russia) centered at 859 nm with a full width at half-maximum bandwidth of 58 nm served as light source. The laser power incident on the cornea was well below the American National Standards Institute and International Electrotechnical Commission standards.\textsuperscript{49,50} SLO images and OCT B-scan images were recorded and displayed in real time to allow an optimized alignment of the eye under investigation. 3D data sets covering a scan field of 20° × 20° (approximately 6 × 6 mm\textsuperscript{2}) with an imaging depth of 3.5 mm in air were recorded at an operating speed of 20,000 A-scans/s. One of three sampling patterns (64 × 1024, 128 × 512, 256 × 256) could be selected. For this study, only data sets recorded with the 128 × 512 scan pattern (i.e., 128 B-scans consisting of 512 A-scans) were used. Scans that were assessed to be of unacceptable quality (e.g., motion artifacts) were repeated until satisfactory results were achieved.

Segmentation of Drusen

A special segmentation algorithm able to identify drusen on the base of the DOPU values was developed. Details of the algorithm and the reproducibility of the segmentation results were published recently.\textsuperscript{51}

Subsumed, the algorithm is based on the intrinsic tissue property of the RPE, which scrambles the polarization state of the backscattered light beam.\textsuperscript{43} This polarization scrambling or "depolarizing" can be described with the use of Stokes vector analysis of the backscattered light. By calculating the mean value of the Stokes vectors within a 20° (approximately 6 × 6 mm\textsuperscript{2}) area of interest, the DOPU was developed. Details of the algorithm and the fast axis orientation of the sample relative to the orientation of the instrument, and degree of polarization uniformity (DOPU).\textsuperscript{41,48} A superluminescent diode (Superlum Diodes, Moscow, Russia) centered at 859 nm with a full width at half-maximum bandwidth of 58 nm served as light source. The laser power incident on the cornea was well below the American National Standards Institute and International Electrotechnical Commission standards.\textsuperscript{49,50} SLO images and OCT B-scan images were recorded and displayed in real time to allow an optimized alignment of the eye under investigation. 3D data sets covering a scan field of 20° × 20° (approximately 6 × 6 mm\textsuperscript{2}) with an imaging depth of 3.5 mm in air were recorded at an operating speed of 20,000 A-scans/s. One of three sampling patterns (64 × 1024, 128 × 512, 256 × 256) could be selected. For this study, only data sets recorded with the 128 × 512 scan pattern (i.e., 128 B-scans consisting of 512 A-scans) were used. Scans that were assessed to be of unacceptable quality (e.g., motion artifacts) were repeated until satisfactory results were achieved.

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The segmentation algorithm for drusen detection uses the depolarizing layer extracted from the DOPU values for exact localization of the RPE. This idea is based on the fact that drusen cause a subtle focal bending of the RPE, often resembling pigment–epithelial detachment.\textsuperscript{52} The BM is detected by an algorithm that uses the segmented RPE as a “backbone.” The algorithm generates a function (resembled by a curved line) that is iteratively adapted so that it nestles to the lower side of the RPE relief (see Fig. 1B3, green line). A detailed description of the algorithm can be found in the study reported by Baumann et al.\textsuperscript{51}

By measuring the difference between the center of the segmented RPE and the segmented BM in each B-scan, the program is able to delineate the drusen (Fig. 1C). A former test on healthy drusen-free retinas of Caucasian adults indicated that differences between the BM and the center of the segmented RPE exceeding 8 pixels (approximately 25 μm) are considered as normal. By displaying these small differences white, the “raw” RPE-elevation map is transformed to a map where the drusen can be measured (Fig. 1D). Shadows in the B-scan image, mostly caused by blood vessels, lead

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to a complete absence of OCT signal (no calculation of DOPU is possible) and are displayed gray. They can easily be excluded for further calculation in the lower layers of drusen parameters. Out of a complete 3D data set, both the total drusen area and their volume are calculated automatically. The displayed drusen map also allows a manual counting of the drusen. Furthermore, not only is the thickness between the inner limiting membrane and the RPE measured and displayed, but also the thickness of the segmented RPE layer (Figs. 1E, 1F).

**Data Analysis and Statistical Methods**

To test the ability of the segmentation algorithm to detect drusen, we graded the errors of the automated segmentation lines using a standardized scheme. This scheme is similar to that we introduced in our previous work, with an exception regarding the moderate error, because the DOPU-based algorithm does not use interpolation. According to the histopathologic definition of drusen and other studies, which previously identified drusen in OCT images, each localized drusenoid pigment–epithelial detachment was called a druse. According to the generally accepted assumption of the anatomic structures seen in SD-OCT images, the line of strong continuous distal intensity signal was determined as the “actual” position of the RPE. Consequently, B-scans evaluated in this study were composed of the intensity image and the segmentation lines. Two experienced examiners identified each druse on every single B-scan by carefully delineating the actual contour of the RPE layer. The beginning, ending, and the maximum height (in pixels) of every druse were documented, as well as its identification by the automated segmentation line. Errors in the automated delineation were graded in their relation to the expert’s graded extension of the druse based on the intensity image using the standardized scheme described in Table 1 for all patients.

Errors of grade 1 were labeled as nonsignificant, grade 2 as moderate. According to the AREDS classification of drusen, which defines drusen of a diameter of 63–92 μm as small, we decided to label an error of grade 3 as moderate if the druse was classified as small and as severe only in drusen of 92–110 μm in diameter.

The segmentation algorithm additionally estimates a reference line for segmentation of the original RPE position, which ideally should follow the BM (Fig. 1B3, green line). Errors of this BM segmentation line were graded as significant if the discrepancy between the line and the expert-graded position of the BM was larger than the thickness of the RPE layer seen in the intensity image (~30 μm).

To test for correspondence of the manual grading of drusen as well as the error classification scheme, the delineation results and the concordant classification of each druse in five randomly chosen eyes were compared between the two graders.

Drusen that were delineated with significant error by automated segmentation were inspected additionally in the corresponding B-scans to evaluate possible sources for algorithm malfunction.

**FIGURE 1.** Measuring of drusen using PS-OCT. (A) The fundus of a 69-year-old female. The black window indicates the scanned area. (B) Each step toward segmentation: first, the polarization state of the backscattered light beam is measured and DOPU is calculated by the mean of the Stokes vectors within a rectangular window (B1). Using the information provided by the DOPU image, the RPE layer is segmented (B2, red line). Differences between the center of this layer and the segmented BM (red and green lines in B3) are displayed in a three-dimensional map (C). Neglecting differences <25 μm generates the drusen map (D). (E) The retinal thickness. (F) The thickness of the segmented depolarizing layer. All scales in μm.
TABLE 1. Error Classification of the Automatic Delineation Errors in Their Relation to the Drusen’s Actual Height and Actual Diameter, Identified by the Experienced Examiners

<table>
<thead>
<tr>
<th>Error Classifications</th>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsignificant</td>
<td>1</td>
<td>(</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>The difference between the delineated and the actual druse (in height and/or diameter) is between one third and two thirds in accordance with the druse’s actual values</td>
</tr>
<tr>
<td>Moderate if diameter of druse is &lt;63 μm</td>
<td>3</td>
<td>The difference between the delineated and the actual druse is greater than two thirds (in height and/or diameter) in accordance with the druse’s actual values</td>
</tr>
<tr>
<td>Severe if diameter of druse is &gt;63 μm</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Statistical analyses were carried out using a statistical summary approach for individual variables (PASW Statistics 18.0; SPSS Inc., Chicago, IL; and Matlab 7.1; The MathWorks Inc., Natick, MA). To test the correspondence of the manual detection and grading of drusen, each druse of single B-scans and its classification were compared between the two graders. Furthermore, the total drusen area was segmented by both graders and the difference of the results of both graders was compared with the mean total drusen area for each eye, similar to Bland–Altman plots.54

The manually outlined location and height of the identified drusen of each of the 15 eyes were allocated to a matrix. Using this matrix, a custom-made statistical analysis program (Matlab) displayed a drusen map for each eye connatural to a pseudo-SLO image using a height-correlated colormap. Using this map, the drusen were counted manually and compared with the amount of drusen seen in fundus photographs. Drusen in photographs were counted by enlarging the digital images on the monitor followed by a careful marking of each yellowish-white spot within the scanned area of the fundus, which was estimated using the pseudo-SLO image out of PS-OCT. After this, the drusen numbers out of manual OCT segmentation and fundus photography were compared for each eye using the paired two-sample \( t \)-test. The statistical analysis program (Matlab) also calculated the manually delineated total drusen area, which was compared with the automated results of the segmentation algorithm. Because the area of drusen can only vaguely be assessed by fundus photography, we decided not to compare it with the accurate results from OCT segmentation.

RESULTS

In all, 15 eyes of 13 consecutive patients were examined. Eight patients were female, and the mean age was 70 years (SD 7.3; range, 60–90 years). The mean BCVA was 0.99 (SD 0.17; range, 0.8–1.25). Two patients were pseudophakic. The mean number of drusen counted in the standard photography of the fundus was 157 (SD 116; range, 60–90 years). The mean BCVA was 0.99 (SD 0.17; range, 0.8–1.25). Two patients were pseudophakic. The mean number of drusen was compared with the automated results of the segmentation algorithm. Figure 2 shows a correlation of the results between manual and automated segmentation. The average total area of manual delineated drusen was five randomly chosen eyes, with a total number of 524 drusen; 91.4% of all drusen identified in the individual B-scans were detected by both graders. Drusen that were detected by only one grader had a mean diameter of 58.0 μm. The agreement of the error classification for each druse was 95.0%. The calculated total drusen area of the five eyes was in the range of 0.253–4.357 mm², with a mean area of 1.773 mm². The mean difference between the graders in relation to the mean area was 0.084.

For all 15 eyes, the automated segmentation algorithm based on the DOPU values detected 96.5% of all drusen identified in the single B-scans without significant error; 2.5% were classified as moderate and 1.0% as severe error. The median diameter of a druse detected with negligible error was 152.4 μm (Table 2).

BM segmentation demonstrated errors in 8.5% of all B-scans. The most frequent errors occurred at both lateral ends of the B-scan image (6.0% of all slices), followed by a higher, that is, too anterior (1.9%) or posterior (0.6%), delineation than the actual position of BM. An erroneous higher delineation occurred only in cases with soft confluent drusen with an overall diameter of >3.1 mm.

The total drusen area of all 15 eyes was calculated automatically by the segmentation algorithm. Figure 2 shows a correlation of the results between manual and automated segmentation. The average total area of manual delineated drusen was

TABLE 2. Descriptive Statistic Results of Error for the Automated Drusen Delineation

<table>
<thead>
<tr>
<th>Error Classification</th>
<th>Amount</th>
<th>Druse &lt; 63 μm</th>
<th>Druse &gt; 63 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Nonsignificant</td>
<td>7146</td>
<td>96.5</td>
<td>818</td>
</tr>
<tr>
<td>Moderate</td>
<td>185</td>
<td>2.5</td>
<td>91</td>
</tr>
<tr>
<td>Severe</td>
<td>77</td>
<td>1.0</td>
<td>0</td>
</tr>
</tbody>
</table>

\( n \), amount of drusen slices.

FIGURE 2. Scatterplot comparing the total drusen area calculated from automated (x-axis) and manual (y-axis) drusen segmentation. Scale is in mm².
4.782 mm² (SD 4.04; range, 0.322–13.978 mm²); the average area of automated segmentation was 4.517 mm² (SD 4.01; range, 0.297–13.516 mm²).

Counting the overall number of drusen on the maps generated by manual delineation resulted in a significantly ($P < 0.05$) larger number of drusen (mean 208.9, SD 109.7; range, 43–429) than that compared with the findings in the standard photography of the fundus (mean 157.1, SD 116.0; range, 7–399) (see Fig. 3).

Additionally, the number of drusen depicted by the automated segmentation results was significantly higher than that of both the fundus photographs and manual segmentation results (mean 489.5, SD 277.1; range, 107-1082) ($P < 0.001$) (also see Figs. 4A–C).

Drusen that were detected with significant error showed different morphologic features than those of regular drusen types (Figs. 4 and 5). Three groups of sources for algorithm failure could be identified (see Table 3): drusen that contain depolarizing material, drusen with discontinuous overlying RPE, and a combination of both.

The most frequently observed morphologic characteristic was a depolarizing content, ranging from single core-like structures to completely solid filled drusen (89.3% of all misdetected drusen slices; see Figs. 4D and 5C), followed by drusen with discontinuous overlying RPE (7.3%, Fig. 5B). A combination of both, which leads to significant segmentation errors, was rarely observed (3.4%, Fig. 4E).

Drusen with discontinuous overlying RPE, leading to severe segmentation errors, had a significantly larger mean diameter than that of both the other morphologic groups and drusen $> 63 \mu m$ segmented with moderate error ($P < 0.05$, one-way ANOVA).

**DISCUSSION**

In this study, we evaluated the performance of an automated drusen segmentation algorithm that is based on the depolarizing effect of the RPE imaged and analyzed with PS-OCT.

The results strongly corroborate the conceptual advantage of such an algorithm. In our previous work, in which...
we evaluated the performance of different segmentation algorithms for drusen detection in commercially available SD-OCT devices, we found an error rate of approximately 30% of nonsignificant errors within the best-performing SD-OCT device.40 Therefore, the additional information provided by PS-OCT seems to provide better performance. The drusen map generated by the algorithm was shown to be nearly congruent with the one originating from manual segmentation.

The outstanding performance of the automated segmentation algorithm is based on both the ability of PS-OCT to depict the RPE reliably and the current definition of drusen as localized pigment–epithelial detachments. However, in clinical practice, our definition of drusen as focal pigment–epithelial detachments cannot distinguish between retinal diseases with similar appearances, such as serous RPE detachments or detachments found in the boundaries of geographic atrophies. The BM segmentation, which serves as a basis for calculating definite drusen parameters such as size, volume, and total area, was found to fail occasionally, mostly at the lateral edges of the B-scan image. This type of error might be a consequence of low illumination of these locations. The second most frequent error type arose from an estimated delineation of BM anterior to its actual position. This type was exclusively observed in B-scans of large confluent, soft drusen. Nevertheless, by using the segmented RPE as a “backbone,” the BM-delineation algorithm should still be more robust than an algorithm based on intensity alone. One has to consider that the delicate BM can be observed only at locations of RPE detachment and in images of excellent scan quality. Ho et al.55 showed that with nonneovascular AMD, the percentage of RPE misidentification was 33% within the best-performing SD-OCT volume scan.

Examining the drusen in single OCT scans revealed various drusen characteristics with differing polarization scrambling properties. The majority of these did not have an effect on the segmentation results, such as small focal RPE interruptions, also called “skip lesions” (see Fig. 3A2, white arrows) or additional “foci” above drusen, indicating RPE alterations. Both characteristics have been observed in previous OCT studies.46,52

![FIGURE 5. Different drusen types that were segmented with moderate to severe error. (A) Fundus of a 57-year-old male. The black line in (A-1) indicates the position of the B-scans of PS-OCT (A-2) and SD-OCT (A-3) (here a dual-beam simultaneous 496 × 1024 B-scan; 80 frames averaged). The blue arrows point to a druse filled with depolarizing material, the yellow arrows to a lesion with complete absence of RPE (drusenoid structure). The white arrowheads indicate skip lesions. (A-4) shows the corresponding NIR-AF image. (B) Fundus of a 67-year-old female. The druse in the center of the fundus photography (B-1) demonstrates a discontinuous RPE in PS-OCT (B-2). (B-4) shows the corresponding drusen map, in which the druse is encased by grayish spots; (B-5) depicts the thickness map of depolarizing material; (B-6) shows the corresponding NIR-AF image. (C) Fundus of a 69-year-old female. The druse in the center is characterized by indistinct borders and shows an irregular distribution of depolarizing material. As a result, the druse is delineated somewhat irregularly, especially in the inferior right area (C-4). The corresponding thickness map of depolarizing material (C-5) and NIR-AF image (C-6) have a mottled appearance. The white arrow in (C-1) and (C-2) points to a drusenoid structure, which is obviously located above the RPE.

TABLE 3. Morphologic Characteristics of Drusen Detected with Moderate to Severe Error

<table>
<thead>
<tr>
<th>Drusen Diameter</th>
<th>Moderate Error</th>
<th>Severe Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drusen &lt; 63 μm</td>
<td>Drusen &gt; 63 μm</td>
<td></td>
</tr>
<tr>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Depolarizing content</td>
<td>86</td>
<td>94.4</td>
</tr>
<tr>
<td>Discontinuous RPE</td>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>Combination</td>
<td>1 + 2</td>
<td>1</td>
</tr>
</tbody>
</table>

∅, mean diameter in μm.
Performance of Drusen Segmentation by PS-OCT
4577

automated segmentation could be a consequence of the size of the rectangular evaluation window, which was used to calculate the mean of the Stokes vectors and finally the DOPU image. The bigger this size was chosen, the more robust the identification of the RPE, with a consequent risk of merging small RPE alterations. However, the results also showed that only 10% of all small drusen could not be detected. Another reason for algorithm failure could be the nature of small preclinical drusen. As described by Sarks et al., these drusen are filled with dense material and can reach clinical size (>30 μm).

In all, 171 (2.6%) of all intermediate to large drusen observed in single PS-OCT scans were detected with an error greater than one third of the actual drusen’s values or were not detected at all. In this study, we did not reassemble each of the drusen slices back to single whole drusen. Because intermediate to large drusen are met by several B-scans, the overall nondetection rate of drusen might be even less.

Basically, two morphologic characteristics of drusen delineated with moderate to severe error could be observed. The first type demonstrated inclusions of depolarizing material. These inclusions ranged from small, single core-like deposits at the center to a completely solid filled druse. According to recent studies, concerning the nature of depolarizing material seen in PS-OCT, two possible causes might be responsible for this feature: pigment (e.g., melanin), as described earlier, or mineralized components, as described in dental PS-OCT studies. Both materials could be identified as potential components of drusen. However, an exact identification must involve other imaging technologies and needs further investigations. The second type that could not be segmented with negligible error by the automated algorithm was characterized by an attenuated or even completely absent overlying RPE (see Figs. 4E and 5A, yellow arrows). In the case of a completely missing RPE, the term “druse” is not applicable because the definition criteria are no longer satisfied. However, as shown in Figure 5A (yellow arrows), such material deposit lesions can still resemble drusen in fundus images, for which reason we called it a “drusenoid structure.” Additionally, drusen with advanced disintegration of the RPE, leading to severe segmentation errors, were shown to be significantly larger in diameter. Several histologic studies described a progressive degeneration of the RPE overlying drusen, assuming that this event represents a key step in a process that finally leads to AMD. In this case, the additional information given by the thickness map of depolarizing material might be of interest. As the PS-OCT illustrates, the distribution of retinal pigment is similar to that of an autofluorescence image taken in the near-infrared mode (787-nm excitation wavelength). The near-infrared autofluorescence images mainly ocular melanin. Figures 5B-5 and 5B-6 show the similarities between both imaging methods. It is essential to understand whether such a druse type with missing RPE characteristics will collapse in the near future and trigger the beginning of geographic atrophy, as assumed, among others by Sarks et al.

Particularly in one patient, a special form of drusenoid structures undetectable by PS-OCT was abundantly present. These structures resemble drusen in fundus photography and SD-OCT images, but the PS-OCT clearly showed that the lesions are located above the RPE (see Fig. 5C-2, white arrow). A possible explanation for this phenomenon is based on reticular or “pseudo” drusen described by Arnold et al. Recently, the appearance of such subretinal drusenoid deposits was investigated in histologic as well as in SD-OCT imaging studies. Because such structures are not features of a classic druse, their nondetection by the automated algorithm is not referred to as error. However, because such lesions cannot be distinguished from “classic” drusen by fundus photography, this individual patient is responsible for the outlier in the comparison of the amount of drusen between the PS-OCT and standard fundus photography (Fig. 3, arrow). For all other patients, the number of drusen identified by manual segmentation from B-scans was significantly larger. This observation was also made in our previous work and is largely accounted for on the better differentiation between neighboring drusen and a more accurate detection of small drusen. In our study, approximately 30% of all detected drusen were considered as small. However, one has to be very careful to interpret this result in a histologic fashion. The agreement for manual detection showed that the smaller the druse, the more uncertainty remains about their actual lesion character. This fact and the only moderate resolution of the images may be considered as a current limitation for drusen detection by OCT. Furthermore, the automated segmentation algorithm depicted much more drusen than that compared with manual segmentation out of the same images. The majority of these “drusen” measured only one pixel (~11.7 μm) in diameter (also see Fig. 4B). We therefore suggest to introduce a lower size limit for drusen grading, depending on image resolution. Because small hard drusen are very common in the healthy population, they are not considered as a sign of ARM or AMD. Consequently, such a limit would not affect the clinical value of the automated segmentation algorithm.

Concluding, the additional information provided by PS-OCT proved to be of considerable importance for a realistic and reliable detection of drusen. The size and total area of drusen, two factors that have been shown to be relevant for the prognosis of advanced AMD in the AREDS study, can be measured accurately in a fast and objective manner. Drusen with quantitative or qualitative characteristics, which make them undetectable by PS-OCT, account for only 3.5% of all drusen seen in the single B-scans. It might be interesting to see whether this proportion is increased in eyes suffering from advanced forms of AMD. Therefore, further developments of segmentation algorithm are in progress. This will make the program even more robust and might finally provide a promising tool for research and clinical practice.

References

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