Published in final edited form as:

Ophthalmology. 2008 November ; 115(11): 1883–1890. doi:10.1016/j.ophtha.2008.04.041.

Drusen Ultrastructure Imaging with Spectral Domain Optical Coherence Tomography in Age-related Macular Degeneration

Aziz A. Khanifar, MD¹, Anjum F. Koreishi, BSE¹, Joseph A. Izatt, PhD², and Cynthia A. Toth, MD^{1,2}

¹Duke University Medical Center, Department of Ophthalmology, Durham, North Carolina

²Duke University Pratt School of Engineering, Department of Biomedical Engineering, Durham, North Carolina

Abstract

Purpose—To categorize drusen ultrastructure in age-related macular degeneration (AMD) using spectral domain optical coherence tomography (SDOCT) and correlate the tomographic and photographic drusen appearances.

Design—Prospective case series.

Participants—Thirty-one eyes of 31 patients with non-neovascular AMD.

Methods—Subjects with drusen and a clinical diagnosis of AMD were enrolled in an SDOCT imaging study from August of 2005 to May of 2007. Foveal linear scans were acquired, and the image data were processed for analysis. Drusen were scored by 4 morphologic categories: shape, predominant internal reflectivity, homogeneity, and presence of overlying hyper-reflective foci. The prevalences of each morphologic pattern and combinations of morphologic patterns observed were calculated. The photographic appearance of each druse was compared with the tomographic classification. Interobserver and intraobserver agreement analysis was performed.

Main Outcome Measures—Prevalence of morphologic parameters using SDOCT.

Results—Twenty-one eyes of 21 patients had SDOCT B-scans of adequate quality for analysis. On the basis of the above morphologic categories, 17 different drusen patterns were found in 120 total drusen. The most common was convex, homogeneous, with medium internal reflectivity, and without overlying hyper-reflective foci, present in 17 of 21 eyes (81%). Of the 16 eyes (76%) with nonhomogeneous drusen, 5 had a distinct hyper-reflective core. Hyper-reflective foci overlying drusen were in 7 eyes (33%). Although half of the photographically soft-indistinct drusen were convex with medium internal reflectivity and homogeneous without overlying hyper-reflective foci, the other half had significant variability in their tomographic appearance. Both interobserver and intraobserver agreement in drusen grading were high. Readers agreed the most when grading drusen shape and reflectivity, whereas the least agreement was for drusen homogeneity.

Conclusions—Drusen ultrastructure can be imaged with SDOCT and characterized with a simple grading system. Photographic appearance may predict some but not all tomographic

© 2008 by the American Academy of Ophthalmology.

Correspondence: Cynthia A. Toth, MD, Duke University Eye Center, DUMC 3802, Durham, NC 27710. toth0004@mc.duke.edu.

Financial Disclosure(s):

Two optical coherence tomography machines were used in this study: one built in Dr Joseph Izatt's laboratory at Duke and one built by Bioptigen. Supported by iCo Therapeutics Inc (AAK); Bioptigen Inc (JAI); Genentech, Sirion Therapeutics, Bioptigen, Inc, Alcon Laboratories, Inc (CAT); National Institutes of Health R21 EY017393 (this project, JAI, CAT).

Duke University Medical Center requires authors to disclose all financial relationships, not just those specifically related to the content of the article.

appearances. Trained observers have a high level of agreement with this grading system. These in vivo morphologic characteristics imaged with SDOCT may be distinct subclasses of drusen types, may relate closely to ultrastructural drusen elements identified in cadaveric eyes, and may be useful imaging biomarkers for disease severity or risk of progression. This will require validation from further studies.

Drusen are a distinguishing feature of non-neovascular age-related macular degeneration (AMD). Attempts to determine their composition have been driven by the need to understand the pathogenesis of AMD and to identify prognostic factors of disease progression. Researchers have demonstrated unique substructural elements of drusen, some containing amyloid β ¹ or activated complement products,² in donor human eyes with AMD. In addition, cores of both glycoproteins and those associated with choroidal dendritic cells have been demonstrated.³ These findings have fueled speculation as to the role of inflammation, and more specifically, complement activation, in the initiating stages of AMD. Thus far, genetic linking of these histologic phenotypes in an attempt to stratify risk of disease progression has not been possible.

Currently, in vivo imaging of drusen has been limited to fundus photography, the gold standard of phenotyping for epidemiologic studies; and fluorescein angiography in selected cases.^{4,5} Optical coherence tomography (OCT) allows imaging of drusen and other areas of retinal pigment epithelium (RPE) elevation in cross-section.^{6–12} The more than 40-fold increase in imaging speed, and the increase in resolution, with spectral domain OCT (SDOCT), eliminates most of the movement artifact present in time-domain scanning and allows for greater scan density and greater area of scanning in living patients. In the time required to capture 6 time-domain low-resolution scans, more than 100 high-resolution SDOCT scans are acquired. Also, the summed-voxel-projection (SVP, a representative 2-dimensional en face image created by collapsing each B-scan along the anterior-posterior axis) of a 3-dimensional OCT stack may be used to orient the drusen seen tomographically with respect to retinal vasculature seen on color photographs. Consequently, with the increase in resolution and sampling of SDOCT, one can more accurately orient and image drusen and the ultrastructure within drusen in vivo in greater detail. Pieroni et al⁶ have suggested that there are 3 patterns of drusen in non-exudative AMD revealed by ultrahigh-resolution time-domain OCT. Given the variety of drusen phenotypes revealed by histologic analysis,^{1–3} there may be many more patterns of drusen revealed by SDOCT imaging. The purpose of this study was to categorize the various ultra-structural patterns of drusen, visible with high-resolution SDOCT imaging, using a simple grading system with basic morphologic characteristics. The results of this pilot study will be used in an upcoming large-scale 5-year study to correlate these tomographic features with severity of disease and risk of progression in AMD.

Materials and Methods

All subjects provided informed consent for SDOCT scanning of the posterior pole and investigator access to ophthalmic records. This study was approved by the institutional review board of the Duke University Medical Center. The enrollment period for this pilot study extended from August 9, 2005, to May 1, 2007. For inclusion in the study, subjects had a clinical diagnosis of non-neovascular AMD and a standard set of 10 or 12-mm scans with sufficient resolution of retinal layers for grading. Subjects with pathology other than drusen were excluded from the study.

One SDOCT system for this study is an investigational device developed in the laboratory of Dr Joseph A. Izatt, in the Duke University Department of Biomedical Engineering, and enhanced for macular imaging of AMD in collaboration with Dr Cynthia A. Toth, and the

other was developed by Bioptigen Inc (Research Triangle Park, NC). The light source for these systems is a super-luminescent diode developed by Superlum Diodes Ltd (Moscow, Russia) and is centered at a wavelength of 840 nm with a bandwidth of 49 nm. Whereas other high-resolution OCT devices may use a titanium-sapphire laser,⁶ a superluminescent diode is more cost-efficient.^{11,13} The power incident on a patient's eye is $500 \pm 50 \mu\text{W}$, below the American National Standards Institute extended exposure limit of $700 \mu\text{W}$ over 8 hours.¹⁴

In each study eye, a series of 15 horizontal SDOCT B-scans, with 1000 A-scans per B-scan, were captured through the fovea in approximately 0.75 second. Bioptigen SDOCT software (version 1.4; Bioptigen Inc) was used for SDOCT scanning and image acquisition. The lateral dimension of the scans was 12 or 10 mm. All scans were subsequently scaled for proper comparison.

The stacks of 15 horizontal SDOCT B-scans were imported to ImageJ (freeware Java version; National Institutes of Health; Bethesda, MD) for analysis. The B-scans were registered using the StackReg plug-in (Biomedical Imaging Group; Swiss Federal Institute of Technology, Lausanne, Switzerland) for ImageJ.¹⁵ Scans that either did not register or were not centered on the fovea were excluded, leaving 8 to 15 well-registered B-scans to be summed in ImageJ to reduce noise, creating a single registered and summed B-scan per study eye. As seen in Figure 1, 2 raw scans and the single registered, summed scan produced from the processed stack are compared. The processed scan from each eye was used for drusen characterization.

The image quality of the SDOCT scans were evaluated by 2 graders (CAT, AFK), and scans with poor resolution of retinal layers were excluded.

For all areas of RPE elevation in the final image, 4 morphologic parameters were analyzed, annotated, and scored by 1 grader (AAK) as follows:

1. Shape: Shape of the RPE elevation was characterized as
 - a. concave (pointed),
 - b. convex (dome-shaped), or
 - c. saw-toothed (small, jagged-elevations of RPE).
2. Reflectivity: The predominant internal reflectivity between the area of RPE elevation and the choroid was characterized as
 - a. low: isoreflective or hyporeflective relative to the photoreceptor layer,
 - b. medium: hyper-reflective relative to the photoreceptor layer and hyporeflective relative to the RPE, or
 - c. high: isoreflective or hyper-reflective relative to the RPE.
3. Homogeneity: The homogeneity of reflectivity between the area of RPE elevation and the choroid was characterized as
 - a. homogeneous (relatively uniform internal reflectivity),
 - b. nonhomogeneous with a central core (varying internal reflectivity with a distinct single focus of hyper-reflectivity), or
 - c. nonhomogeneous without a central core.

4. Foci of hyper-reflectivity: The presence or absence of hyper-reflective (high, as defined above) points within the neurosensory retina overlying areas of RPE elevation was noted.

Those areas of RPE elevation judged to be saw-toothed in shape were too small to allow grading of internal reflectivity or homogeneity by definition. The prevalence (number of eyes and number of drusen) of each basic morphologic pattern and the prevalence of each combination of morphologic patterns was calculated.

To compare the tomographic appearance of the drusen with the photographic appearance, SDOCT volume scans were performed. In each study eye, volume scans of a 10×10 -mm or 12×12 -mm square area of the retina centered on the fovea were also acquired. These consisted of 100 SDOCT B-scans acquired in approximately 5 seconds, with 1000 A-scans per B-scan, and with lateral dimensions of 10 or 12 mm, respectively. Each B-scan was acquired in the nasal to temporal direction, with the volume being acquired in an inferior to superior direction. The interval between B-scans throughout the volume scan was 100 or $120 \mu\text{m}$ for 10 or 12-mm scans, respectively. All scans were subsequently scaled for proper comparison.

The volume stacks were used to precisely denote the location of the linear foveal SDOCT scans on a fundus photograph. Each volume stack of 100 B-scans was imported into ImageJ and aligned using the StackReg plug-in for ImageJ. The SVP was used to orient the SDOCT B-scans with the color fundus photographs and consisted of 1000 lateral pixels by 100 vertical pixels, each having an intensity representative of a line of pixels along the anterior-posterior axis of the volume scan.¹⁶ For example, retinal vessels cause shadowing of the underlying retina on OCT, and this appears as a dark pixel on the SVP, denoting the site of the vessel. On the SVP, a horizontal line consisting of a single vertical pixel and the corresponding 1000 lateral pixels represents a linear B-scan.

By using the BiopTigen SDOCT capture software, the location of the linear B-scan used for analysis was found with the SVP. Thirteen SVPs with sufficient visualization of retinal vasculature were manually overlaid onto the respective fundus photograph in Photoshop (version 7.0, Adobe Systems, San Jose, CA) using the retinal vasculature as landmarks. The location of the linear B-scan was already denoted on the SVP and now was extrapolated to the fundus photograph. For 8 SVPs with insufficient visualization of retinal vessels for overlay, the location of the linear B-scan on the fundus photograph was approximated using nerve location or other surrounding landmarks such as vessels.

Photographic appearance of drusen along the site of the B-scan was graded by 1 author (AAK) as hard, soft distinct, soft indistinct, reticular, or calcified, according to the Age-Related Eye Disease Study System.⁵ The prevalence (number of eyes and number of drusen) of each photographic drusen type and the prevalence of each basic morphologic pattern for each photographic type was calculated.

To assess the agreement between observers, 2 certified OCT readers were trained by the authors to interpret the linear B-scans using the above drusen grading system. Agreement in this study was defined as concordance, which occurred when both readers recorded the same grade for the morphologic characteristic in question. Percentage agreement was computed as the number of concordant pairs divided by the total number of pairs times 100 and is reported in this study for each morphologic characteristic (shape, reflectivity, homogeneity, foci of hyper-reflectivity). Each observer graded the drusen of a single subject 3 times: 2 unprocessed (non-summed) linear scans and 1 processed (summed) scan. Each B-scan was unlabeled to prevent the observer from knowing the identification of the subject or whether the image was processed. Interobserver agreement was calculated for each non-summed

image and for the summed image. Intraobserver agreement was calculated for each observer in the following manner: (1) summed image versus non-summed image 1, (2) summed image versus non-summed image 2, and (3) non-summed image 1 versus non-summed image 2.

Results

SDOCT was performed on 31 eyes of 31 patients with a clinical diagnosis of non-neovascular AMD with drusen. Ten eyes did not have sufficient resolution of retinal layers for grading. Thus, 21 eyes underwent analysis. Patient ages ranged from 54 to 83 years with a median of 72 years. Nine patients were female.

Variable morphologic patterns of drusen could be observed within a single scan (Figure 1). The prevalence of each of the 4 basic morphologic categories is shown in Table 1. Convex-shaped drusen were seen in 20 eyes (95%) and 85 drusen (71%). Twenty eyes (95%) and 85 drusen (71%) had medium internal reflectivity. Seventeen eyes (81%) and 67 drusen (56%) had homogeneous internal reflectivity. Seven (33%) of the eyes had 13 drusen (11%) with overlying hyper-reflective foci.

By combining the 4 basic morphologic parameters above, 17 different tomographic appearances of drusen were observed. The prevalence of each combination of the 4 parameters is shown in Table 2, and an example of each drusen pattern combination is shown in Figure 2(A,H,K,M,Q) (Fig 2A–Q available at <http://aaojournal.org>). The most common drusen pattern was convex-shaped and homogeneous, with an internal reflectivity between that of the photoreceptor layer and the RPE without overlying foci of hyper-reflectivity (Figure 2H). This pattern was found in 56 drusen (47%) and 17 eyes (81%). None of the saw-toothed drusen had overlying hyper-reflective foci. All areas of RPE elevation were able to be characterized by our grading system.

In the assessment of the color photographic appearance of drusen (Table 3), the soft-indistinct type was by far the most common pattern: 102 of 120 drusen (85%) and 19 of 21 eyes (90%). Nine drusen (8%) were calcified; this type was observed in 5 eyes (24%). Less common were the soft-distinct, 4 drusen (3%) in 2 eyes (10%), and reticular types, 2 drusen (2%) in 2 eyes (10%). Three drusen (3%) in 3 eyes (14%) were seen on SDOCT scanning but could not be found on the color photograph (Figure 3).

Photographically characterized soft-indistinct drusen tended to be convex in shape, homogeneous, with medium internal reflectivity, and without overlying hyper-reflective foci (Figure 4). This pattern was seen in 51 (50%) of 102 soft-indistinct drusen; thus, half of the soft-indistinct drusen showed a range of different tomographic appearances other than this combination. Calcified drusen were usually convex-shaped, predominantly hyporeflective, nonhomogeneous with or without a core, and were more likely than soft-indistinct drusen to have overlying foci of hyper-reflectivity (Figure 5, druse number 5). The prevalence of each morphologic parameter for each photographic drusen type is detailed in Table 4.

Interobserver and intraobserver agreement in drusen grading is shown in Tables 5 and 6. In summary, the interobserver agreement was highest for reflectivity (range 89.6%–94.4%), followed by shape (range 90.4%–93.6%), presence of hyper-reflective foci (range 84.0%–88.8%), and homogeneity (range 77.6%–79.2%). Intraobserver agreement was similar among the 3 comparison groups: comparing the summed scans to the first non-summed scans, the summed scans to the second non-summed scans, and the non-summed scans to each other. Observer 2 had slightly higher intraobserver agreement than observer 1.

Discussion

Drusen ultrastructure can be imaged with SDOCT and reliably characterized by readers viewing unprocessed high-resolution scans. The high resolution and lack of motion artifact in SDOCT scans allow the assessment of multiple morphologic parameters and thus makes possible more precise characterization of drusen than previous imaging modalities. This grading system will be useful for longitudinal clinical trials to correlate these intradrusen characteristics with genotype, severity of disease, and risk of progression in AMD.

With this grading system, we were able to identify unique drusen tomographic findings and validate previous ones. Our observation that most of the drusen graded as calcified photographically were of low predominant internal reflectivity tomographically is consistent with clinicopathologic OCT studies that observed calcific sites in atherosclerosis¹⁷ and with clinical studies of calcific ocular lesions imaged with conventional OCT.¹⁸ As did Pieroni and colleagues,⁶ who used a time-domain system, we observed a “saw-toothed” pattern of RPE elevation in a majority of eyes (Figure 2Q). Likewise, we found that some drusen have hyper-reflective foci overlying them (Figures 2B, E, G, I, L, M, and P, available at <http://aaojournal.org>). It has been suggested that these hyper-reflective foci represent RPE cell migration,⁶ although in this study only 4 of 13 sites (31%) showed any hyperpigmentation on the color photograph. Histologic correlation would aid in sorting this out. In addition, the patterns of “RPE excrescences overlying moderately reflective material” (Figure 2C–E, H–M, available at <http://aaojournal.org>) and “disruptions of the RPE” (Figures 2A, E, F, available at <http://aaojournal.org>), reported by Pieroni et al,⁶ were clearly resolved with this imaging system. However, with the SDOCT system, we were able to specify the relative degree of internal reflectivity and assess homogeneity to add greater precision to drusen assessment. We elucidated several patterns of drusen characteristics that have not been described in earlier studies. For example, we found convex nonhomogeneous drusen that had predominantly low internal reflectivity (Figure 5B, druse number 5). Also, we were able to demonstrate convex-shaped drusen with predominantly high internal reflectivity, nonhomogeneous, and without overlying foci of hyper-reflectivity (Figure 2O, available at <http://aaojournal.org>). Finally, with high-resolution SDOCT imaging we were able to identify 5 eyes with drusen that had hyper-reflective “cores” within them (Figure 2B, G, K, and M [available at <http://aaojournal.org>]). This finding has not been reported with OCT drusen imaging and may relate to drusen structures associated with complement activity as seen in ex vivum studies.^{2,3} The non-core, nonhomogeneous reflectivity patterns within drusen may reflect distribution of other components such as amyloid β .¹ OCT imaging is based on narrow angle reflectance from tissue, and this modality has been used to differentiate fibrous, fibrocalcific, and lipid-rich sites within atherosclerotic plaques and to identify cellular processes and alignment in engineered tissue.^{17,19} Until we have clinicopathologic correlation of SDOCT imaged drusen, we will not know which specific components are responsible for these SDOCT image characteristics.

Although several drusen with a similar photographic appearance had a similar tomographic appearance (Figure 4), there was also great tomographic variability in many photographically similar drusen (Figures 1, 3, and 5). Although most of the soft indistinct drusen were convex with medium internal reflectivity, homogeneous, and without overlying foci when imaged with SDOCT, making these the most common photographic and tomographic drusen types seen in our study, it is important to remember that 50% of the soft-indistinct drusen have a different tomographic appearance. These sites of different tomographic appearance may be precursors of change; whether of drusen growth, clearing, choroidal neovascularization, or atrophy. Sites of unique drusen reflectivity may predict focal change at that locus, or the presence of these drusen may predict risk status for the eye

or the patient overall. These questions will be examined in the upcoming 5-year Age-related Eye Disease Study 2 Ancillary SDOCT Study.

There was considerable interobserver and intraobserver agreement for each of the morphologic parameters, ranging from agreement on drusen reflectivity and shape, which was generally more than 90%, to drusen homogeneity, which had the lowest (albeit still >75%) agreement. Overall, the level of interobserver agreement was high. When compared with other systems that graded drusen type in AMD using color photography, our results are favorable.^{4,5} In the Wisconsin age-related maculopathy grading system, interobserver agreement for drusen type was 70.6% and intraobserver agreement was 62.5%.⁴ The AREDS Research Group found the contemporaneous reproducibility of drusen type to be 77.5% (exact agreement) and the temporal reproducibility of drusen type to be 59.0% (exact agreement).⁵

We would have predicted better interobserver agreement in summed (processed) scans and less intraobserver agreement when comparing non-summed (unprocessed) to summed scans because of the decrease in noise (hyper-reflective “speckle”) in summed scans (Figure 1). This is important because acquiring multiple scans at 1 site to sum the data and remove speckle noise decreases the overall number of different retinal sites that can be sampled during the same time interval. However, the interobserver agreement appeared to be higher with the non-summed scans than the summed scan even for the overlying foci of hyper-reflectivity, a morphologic characteristic that potentially could be hidden in speckle noise. Although the reason for this outcome is unclear, the result is reassuring at least. The majority of commercial devices that currently perform spectral domain OCT do not implement techniques to reduce noise during volumetric scan acquisition. However, the clinical utility of this grading system will be maximized when acquiring volumetric scans of patients’ maculae (a possibility with SDOCT), not with single linear scans through the fovea (the *only* possibility with conventional time-domain OCT). Thus, our grading system should be reliable and reproducible in clinical practice regardless of the SDOCT device being used and regardless of whether post-acquisition noise-reducing image processing occurs.

One limitation of our study is small sample size. Although we successfully identified 17 different drusen types (using combinations of the 4 above parameters) in our 21 eyes and 120 total drusen, based on our grading methodology, a total of 38 different drusen patterns could mathematically exist (concave or convex [2] × degree of internal reflectivity [3] × homogeneity [3] × overlying hyper-reflective foci presence [2] + saw-toothed with overlying hyper-reflective foci [1] + saw-toothed without overlying hyper-reflective foci = 36 + 1 + 1 + 38). We have no reason to believe that there are in fact actually 38 different drusen patterns that exist, but there may be more than the 17 we found. This large number of theoretic possibilities suggests that searching for phenotypic and genotypic links will be difficult. However, we think that it is important to first describe all the possible tomographic patterns before grouping them into larger, more functional categories, if warranted.

The goals of this study were to categorize the various drusen substructures with SDOCT and to correlate these tomographic appearances with photographic appearance, the current gold standard. Future studies should aim to correlate these structures with function, disease status, and genotype. This would be aided not only by correlation with appearance on fluorescein angiography or autofluorescence but also by histologic analysis. These correlation studies are under way. In addition, this study did not address total drusen area or volume or drusen size, because this is the focus of a separate semiautomated computer segmentation algorithm study that is reported separately.²⁰ Future studies include refinement of computer algorithms to identify and characterize drusen with this grading system automatically in an effort to speed the process of drusen analysis, quantify these characteristics, and eliminate potential

observer disagreement by standardizing the morphologic parameters. These further enhancements in drusen analysis would be used for longitudinal studies that could potentially produce prohibitively large amounts of data for manual analysis.

Likely future advances in pharmacologic therapy for non-neovascular AMD and the need for improved phenotyping for genetic studies will demand a level of precision in both clinical trials and the clinical setting that is not possible with color photography alone. The existence of diverse tomographic patterns of drusen is consistent with the considerable histologic variability of drusen but may be problematic in future attempts to automate drusen recognition based on internal characteristics. These in vivo morphologic parameters may relate closely to substructural elements imaged with light and electron microscopy of cadaveric eyes. Our imaging findings may very well have pathologic implications. For example, the appearance of hyper-reflective foci over drusen may represent retinal pigment migration⁶ or liberation that may signal a progression of disease. Also, the cores of hyper-reflectivity may relate to the presence of known drusen substructures, such as the above-mentioned glycoprotein cores or processes of choroidal dendritic cells. They could also represent the degree of complement-related activity in patients' eyes or the beginning of a choroidal neovascular membrane and may potentially be an imaging biomarker for level of disease or risk of progression. The potential for tomographic diversity in drusen features even among similar-appearing, photographically soft-indistinct drusen, for example, cannot be overstated. The additional information regarding drusen structure revealed by SDOCT could provide an evolutionary step in our current paradigm of risk determination in AMD (Figure 2).

Acknowledgments

We thank Michelle McCall, Katrina Winter, and Neeru Sarin for insight and discussion on grading methodology. We thank Dr Sandra Stinnett for performing the extensive statistical analysis.

References

1. Anderson DH, Talaga KC, Rivest AJ, et al. Characterization of beta amyloid assemblies in drusen: the deposits associated with aging and age-related macular degeneration. *Exp Eye Res.* 2004; 78:243–56. [PubMed: 14729357]
2. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. *Am J Ophthalmol.* 2002; 134:411–31. [PubMed: 12208254]
3. Hageman GS, Luthert PJ, Victor Chong NH, et al. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Retin Eye Res.* 2001; 20:705–32. [PubMed: 11587915]
4. Klein R, Davis MD, Magli YL, et al. The Wisconsin Age-Related Maculopathy Grading System. *Ophthalmology.* 1991; 98:1128–34. [PubMed: 1843453]
5. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study report number 6. *Am J Ophthalmol.* 2001; 132:668– 81. [PubMed: 11704028]
6. Pieroni CG, Witkin AJ, Ko TH, et al. Ultrahigh resolution optical coherence tomography in non-exudative age related macular degeneration. *Br J Ophthalmol.* 2006; 90:191–7. [PubMed: 16424532]
7. Hee MR, Bauman CR, Puliafito CA, et al. Optical coherence tomography of age-related macular degeneration and choroidal neovascularization. *Ophthalmology.* 1996; 103:1260–70. [PubMed: 8764797]
8. Srinivasan VJ, Wojtkowski M, Witkin AJ, et al. High-definition and 3-dimensional imaging of macular pathologies with high-speed ultrahigh-resolution optical coherence tomography. *Ophthalmology.* 2006; 113:2054– 65. [PubMed: 17074565]

9. Wojtkowski M, Srinivasan V, Fujimoto JG, et al. Three-dimensional retinal imaging with high-speed ultrahigh-resolution optical coherence tomography. *Ophthalmology*. 2005; 112:1734–46. [PubMed: 16140383]
10. Puliafito CA, Hee MR, Lin CP, et al. Imaging of macular diseases with optical coherence tomography. *Ophthalmology*. 1995; 102:217–29. [PubMed: 7862410]
11. Drexler W, Sattmann H, Hermann B, et al. Enhanced visualization of macular pathology with the use of ultrahigh-resolution optical coherence tomography. *Arch Ophthalmol*. 2003; 121:695–706. [PubMed: 12742848]
12. Stopa M, Bower BA, Davies E, et al. Correlation of pathologic features in spectral domain optical coherence tomography with conventional retinal studies. *Retina*. 2008; 28:298–308. [PubMed: 18301035]
13. Chen TC, Cense B, Pierce MC, et al. Spectral domain optical coherence tomography: ultra-high speed, ultra-high resolution ophthalmic imaging. *Arch Ophthalmol*. 2005; 123:1715–20. [PubMed: 16344444]
14. American National Standard for the Safe Use of Lasers. ANSI Z136.1-2000. Orlando, FL: Laser Institute of America; 2000.
15. Thevenaz P, Ruttimann UE, Unser M. A pyramid approach to subpixel registration based on intensity. *IEEE Trans Image Process*. 1998; 7:27–41. [PubMed: 18267377]
16. Jiao S, Knighton R, Huang X, et al. Simultaneous acquisition of sectional and fundus ophthalmic images with spectral-domain optical coherence tomography. *Opt Express* [serial online]. 2005; 13:444–52. Available at: <http://www.opticsexpress.org/abstract.cfm?id=82381>.
17. Yabushita H, Bouma BE, Houser SL, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002; 106:1640–5. [PubMed: 12270856]
18. Shields CL, Benevides R, Materin MA, Shields JA. Optical coherence tomography of retinal astrocytic hamartoma in 15 cases. *Ophthalmology*. 2006; 113:1553–7. [PubMed: 16949441]
19. Yang Y, Dubois A, Qin XP, et al. Investigation of optical coherence tomography as an imaging modality in tissue engineering. *Phys Med Biol*. 2006; 51:1649–59. [PubMed: 16552095]
20. Farsiu, S.; Chiu, SJ.; Izatt, JA.; Toth, CA. Fast detection and segmentation of drusen in retinal optical coherence tomography images. Paper presented at: SPIE Photonics West; 2008; San Jose, California.

Figure 1.

Two unprocessed (non-summed) scans and a registered, summed scan produced from the processed stack are compared. (A, B) Two raw linear SDOCT B-scans before summing and registration. (C) A registered and summed linear SDOCT B-scan. Considerable variability in drusen morphology in a single linear scan is demonstrated. (D) Color fundus photograph corresponding to above SDOCT scans. Line shows location of SDOCT scans. Observed drusen are numbered.

Figure 2.

The 17 combined morphologic drusen patterns observed: **(A)** Pattern 1: concave, low reflectivity, nonhomogeneous without core, no overlying foci. **(B)** Pattern 2: concave, low reflectivity, nonhomogeneous with core, overlying foci. **(C)** Pattern 3: concave, medium reflectivity, homogeneous, no overlying foci. **(D)** Pattern 4 (marked with *): concave, medium reflectivity, nonhomogeneous without core, no overlying foci. **(E)** Pattern 5 (marked with *): concave, medium reflectivity, nonhomogeneous without core, overlying foci. **(F)** Pattern 6 (marked with *): concave, high reflectivity, homogeneous, no overlying foci. **(G)** Pattern 7: convex, low reflectivity, nonhomogeneous with core, overlying foci. **(H)** Pattern 8: convex, medium reflectivity, homogeneous, no overlying foci. **(I)** Pattern 9: convex, medium reflectivity, homogeneous, overlying foci. **(J)** Pattern 10: convex, medium reflectivity, nonhomogeneous without core, no overlying foci. **(K)** Pattern 11: convex, medium reflectivity, nonhomogeneous with core, no overlying foci. **(L)** Pattern 12: convex, medium reflectivity, nonhomogeneous without core, overlying foci. **(M)** Pattern 13: convex, medium reflectivity, nonhomogeneous with core, overlying foci. **(N)** Pattern 14 (marked with *): convex, high reflectivity, homogeneous, no overlying foci. **(O)** Pattern 15 (marked with *): convex, high reflectivity, nonhomogeneous without core, no overlying foci. **(P)**

Pattern 16 (marked with *): convex, high reflectivity, nonhomogeneous without core, overlying foci. (Q) Pattern 17: saw-tooth, no overlying foci.

\$watermark-text

\$watermark-text

\$watermark-text

Figure 3.

(A) Linear SDOCT scan to correlate soft-indistinct drusen with the tomographic appearance on SDOCT. Druse 4 has a spot of increased pigmentation that may be represented by the hyper-reflective foci seen in (B). Druse 5 from the SDOCT B-scan is not visualized on the color photograph. (B) Corresponding linear SDOCT B-scan. Although all the visualized drusen in the photograph are soft-indistinct, there is considerable variability in shape, predominant internal reflectivity, homogeneity, and the presence of hyper-reflective foci.

Figure 4.

(A) Linear scan through fovea superimposed on color photograph to correlate soft-indistinct drusen type with tomographic appearance. (B) Corresponding linear SDOCT B-scan.

Figure 5.
(A) Linear scan through fovea superimposed on color photograph to correlate a calcific druse (5) type with tomographic appearance. (B) Corresponding linear SDOCT B-scan.

Table 1

Summary of Drusen Patterns Seen, Organized by Basic Morphologic Parameters

	No. Drusen	% Drusen	No. Eyes	% Eyes
Shape				
Concave	15	13	9	43
Convex	85	71	20	95
Saw-toothed	20	17	13	62
Reflectivity				
Low (PRL)	5	4	4	19
Medium (between PRL and RPE)	85	71	20	95
High (RPE)	10	8	6	29
Homogeneity				
Homogeneous	67	56	17	81
Nonhomogeneous with core	6	5	5	24
Nonhomogeneous without core	27	23	11	52
Hyper-reflective Present	13	11	7	33
Foci over drusen				
Not present	107	89	21	100

PRL = photoreceptor layer; RPE = retinal pigment epithelium.

\$watermark-text

\$watermark-text

\$watermark-text

Table 2

Summary of Drusen Patterns, Based on Combinations of Morphologic Parameters

Drusen Pattern	Shape			Internal Reflectivity			Homogeneity			Foci over Drusen		Drusen		Eyes	
	Concave	Convex		Low	Medium	High	Homogeneous	Core	No Core	Present	Absent	#	%	#	%
1	x			x					x		x	3	3	2	10
2	x			x				x		x		1	1	1	5
3	x				x		x				x	4	3	4	19
4	x			x					x		x	3	3	2	10
5	x			x				x		x		2	2	2	10
6	x					x	x				x	2	2	2	10
7		x		x				x		x		1	1	1	5
8		x			x		x				x	56	47	17	81
9		x			x		x			x		3	3	2	10
10		x			x				x		x	11	9	6	29
11		x			x			x			x	1	1	1	5
12		x			x				x		x	2	2	2	10
13		x			x			x		x		3	3	2	10
14		x				x	x				x	2	2	2	10
15		x				x			x		x	5	4	2	10
16		x				x		x		x		1	1	1	5
17	Saw-toothed										x	20	17	13	62

Table 3

Prevalence of Photographic Drusen Types, in Percentage of Drusen and Percentage of Eyes

Drusen Type	Drusen		Eyes	
	No.	%	No.	%
Soft-indistinct	102	85	19	90
Soft-distinct	4	3	2	10
Hard	0	0	0	0
Reticular	2	2	2	10
Calcified	9	8	5	24
Unseen	3	3	3	14

Table 4

Prevalence of Tomographic Morphologic Parameters for Each Photographic Drusen Type

Drusen Type	Shape						Reflectivity						Homogeneity						Foci over Drusen														
	Concave			Convex			Saw-tooth			Low			Medium			High			Homo-geneous			Core			No Core			Present			Absent		
	#	%	#	#	%	#	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%			
Soft-indistinct	102	11	11	72	71	19	19	0	0	74	73	9	9	9	9	61	60	2	2	20	20	9	9	93	92								
Soft-distinct	4	0	0	4	100	0	0	0	0	4	100	0	0	0	0	2	50	0	0	2	50	0	0	4	100								
Hard	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0								
Reticular	2	0	0	2	100	0	0	0	0	2	100	0	0	0	0	2	100	0	0	0	0	0	0	2	100								
Calcified	9	4	44	5	56	0	0	5	56	3	33	1	11	11	0	0	4	44	5	56	3	33	6	67									
Unseen	3	0	0	2	67	1	33	0	0	2	67	0	0	0	0	2	67	0	0	0	0	0	0	3	100								

Table 5

Interobserver Agreement in Drusen Grading of Each Morphologic Parameter by Type of Scan

Scan	Morphologic Parameter			
	Shape	Reflectivity	Homogeneity	Foci
NS1	93.6	94.4	79.2	88.8
NS2	93.6	92.8	77.6	87.2
SUM	90.4	89.6	79.2	84.0

NS1 = non-summed image 1; NS2 = non-summed image 2; SUM = summed image.

Foci refers to the presence of hyper-reflective foci overlying drusen.

\$watermark-text

\$watermark-text

\$watermark-text

Table 6
Intraobserver Agreement in Drusen Grading of Each Morphologic Parameter Comparing Different Scan Types

Scan	Morphologic Parameter							
	Shape		Reflectivity		Homogeneity		Foci	
	Obs1	Obs2	Obs1	Obs2	Obs1	Obs2	Obs1	Obs2
SUM vs NS1	86.4	92.0	85.6	93.6	70.4	87.2	85.6	83.2
SUM vs NS2	92.8	92.8	89.6	92.0	84.0	89.6	94.4	81.6
NS1 vs NS2	86.4	91.2	84.8	92.8	74.4	86.4	86.4	82.4

NS1 = non-summed image 1; NS2 = non-summed image 2; SUM = summed image;
Obs1 = observer 1; Obs2 = observer 2.
Foci refers to the presence of hyper-reflective foci overlying drusen.