# The Role of Optical Coherence Tomography in the Diagnosis of Early Age-related Maculopathy

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## Abstract

There has been increasing interest in improving imaging technologies to identify and grade early age-related maculopathy (ARM). Recently, advances in optical coherence tomography (OCT) has allowed a virtual biopsy of the retina and identification of different types of drusen in relation to early ARM. Several investigators have improved our understanding of both the qualitative and quantitative analyses of drusen, the clinical hallmark of ARM. The purpose of this article is to critically review the current literature in OCT in the evaluation of early ARM. Although seemingly useful and ideal, the current analysis of the retina using OCT is highly complex and lacking. It is currently too premature to use OCT as a grading tool for early ARM. However, the authors are hopeful that the rapid progress in this field will enable the use of an OCT-defined outcome measure in early ARM clinical trials in the foreseeable future.

## Keywords

Optical coherence tomography, Bruch's membrane, retinal pigment epithelium, drusen, age-related macular degeneration

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Age-related maculopathy (ARM) is characterised by drusen and/or retinal pigment epithelial changes. The more advanced form termed as age-related macular degeneration (AMD) may be either the atrophic (dry) form or the exudative (wet) form of AMD. The latter causes 70 % of blindness amongst AMD patients, whilst the rest are contributed by the atrophic AMD.[1–3]

Currently, the gold standard imaging modality for AMD, fluorescein angiography (FFA), is most reliable in the diagnosis of choroidal neovascularisation (CNV). Indocyanine green angiography (ICG), which uses the scanning laser ophthalmoscope (SLO) technology is often used to enable differentiation of polypoidal choroidal vasculopathy and chorioretinal anastomosis.[4–6] However, these tools are of limited use in early ARM. In fact, all classifications of severity of early ARM are based on colour photographs of the macula.[7–10]

## Technology of Optical Coherence Tomography and Age-related Macular Degeneration

Currently, although optical coherence tomography (OCT) remains an adjunct to FFA as a diagnostic tool in advanced disease, it is the most sensitive monitoring tool for treatment response and disease reactivation in wet AMD.[11–14] As the technology of OCT is advancing, this tool is gaining popularity amongst clinicians and vision scientists in the diagnosis and grading of early ARM.[15–17] However, being a relatively new technology with limited histopathological references, there have been contradicting views on the correlation of OCT characteristics with the anatomy of the retina. The numerous features described currently remains as inferences to the histopathology of disease states.[18–20] Our review article aims to critically analyse the currently known and novel OCT features and the associated postulations in the diagnosis and prognosis of early ARM.

The advent of OCT has provided useful information of the anatomical microstructure of the retina using the anteroposterior scans.[7] As an imaging modality itself, OCT has progressed tremendously, from the conventional time domain OCT (TD-OCT) to the modern day spectral domain OCT (SD-OCT) with a much higher resolution and better clarity from reduced noise levels and added advantage of faster image acquisition (see *Table 1*). Newer technologies such as 3D compilation or mapping, patient eye motion tracking, as well as retinal pigment epithelium (RPE) segmentation have increased the resolution of the images. Moreover, OCT is now an integral part of multimodal imaging.[13,21–24]

## Spectral Domain Optical Coherence Tomography

The development of SD-OCT is based on the Fourier transform mathematical equation.[25] Based on this method, the moving mirror in the path of the reference beam was deemed redundant. In SD-OCT, the interference signal is based on the optical wavelength and measured from the simultaneous echoes of light from the various layers of the retina. The interference between the two beams (sample and reference) would then be acquired and analysed simultaneously by a spectrometer.

This advancement of SD-OCT results in faster image acquisition speeds, allowing larger number of axial and hence B-scans to be obtained in a

**Table 1: Differences Between Different Devices of Optical Coherence Tomography**

| OCT | TD-OCT (Stratus) | SD-OCT (Optovue) | SD-OCT (Topcon 3D OCT 1000) | SD-OCT (Cirrus HD-OCT) | SD-OCT (spectralis) | SD-OCT (OTI) Spectral OCT/SLO) |
|---|---|---|---|---|---|---|
| Light source | SLD | SLD | SLD | SLD | SLD | SLD |
| Axial resolution | 10 um | 5 um | 5 um | 5 um | 7 um | 5–6 um |
| Transverse resolution | 20 um | 10–20 um | 10–20 um | 10–20 um | 10–20 um | 15 um |
| Acquisition speed (A-scans/sec) | 400 | 26,000 | 20,000 | 27,000 | 40,000 | 27,000 |
| Special features | | | | Software for automated segmentation of RPE-ILM; polarisation | ART, TruTrack; autofluorescence; angiography combination | Coronal scan; microperimetry; point–point pixilated correspondence |

*ART = automatic real time; HD-OCT = high-definition optical coherence tomography; OCT = optical coherence tomography; OTI = Ophthalmic Technologies Inc; RPE ILM = retinal pigment epithelium internal limiting membrane; SD-OCT = spectral domain optical coherence tomography; SLD = superluminescent diode; SLO = scanning laser ophthalmoscope; TD-OCT = time domain optical coherence tomography.*

shorter timeframe with reduction of patient motion artifacts as reduction or signal-to-noise ratio as well as high speed 3D reconstruction.[25–28] These characteristics of SD-OCT technology are particularly advantageous in the understanding of features of early ARM. The higher resolution SD-OCT image quality allows better discrimination between retina layers and abnormal structural abnormalities, such as drusen from the normal RPE. With SD-OCT, the following intraretinal layers can be defined:

- first hyper reflective layer – nerve fibre layer;
- low backscattering intraretinal layers – ganglion cell layer, inner nuclear layer, outer nuclear layer;
- less reflective layers such as the inner plexiform layer and the outer plexiform layer; and
- the thin hyper reflective layer which corresponds to the external limiting membrane.

The SD-OCT also enables differentiation of the inner segment and outer segment (IS/OS) interface of the photoreceptors from the RPE.[18,29,30] Reduced motion artifacts reduce the retinal – RPE junction distortion and hence, reduce errors with regard to a mistaken artifact for a lesion.[26] Reduced signal-to-noise ratio allows enhanced visualisation of the retina microstructure, allowing better definition of new features as well as more precise quantitative measurements of fluids for treatment monitoring purposes.[23] Using SD-OCT, Jiao et al. has created a summed voxel projection (SVP) which utilises the summation of the pixilated axial image to create a 2D image that is analogous to a fundus image. This allows simultaneous correlation between OCT and fundus images.[31]

## Optical Coherence Tomography in Qualitative Analyses of Age-related Macular Degeneration

Drusen are the hallmark of early ARM. Drusen are yellow lipid deposits and different subtypes are located in different layers of the RPE-Bruch's membrane interface resulting in decreased nutrition supply to the underlying neurosensory retina layer.[1,2,32,33] Stratification of severity of ARM is widely dependent on colour fundus photographs (CFP) for obvious drusen and pigmentary changes, with poor intergrader agreement. The advancement of OCT has fine-tuned the visualisation of the anatomical structures and changes of the posterior pole. Novel features have been described by several authors, resulting in new insights to the pathogenesis and possibly prognosis of the disease.[7–10]

Although the identification of drusen is relatively easy with other imaging modalities, clinicians are able to address several issues and qualify drusen on OCT in an unprecedented way. On OCT, soft drusen are recognised as an elevation of the RPE with a moderately reflective drusen cavity. There is minimal posterior shadowing associated with it. SD-OCT also demonstrates better visibility of reticular drusen, as a thickened band and undulations of the RPE with no altered outer nuclear layer. Khanifar et al. has evaluated and found 17 different types of drusen based on the shape, size, heterogenousity as well as internal reflectivity.[34] Also, in another study evaluating drusen area mapping on SD-OCT as well as CFP, Toth et al. found good correlation in drusen detection between SD-OCT and CFP. However, they also observed that SD-OCT had a better trend towards larger drusen identification, whilst smaller drusen were better seen on CFP.[35]

In addition to identification of drusen subtypes, several authors have used SD-OCT to define drusen material and hence predict prognosis. For instance, reticular drusen, which was first described in 1991,[36] was found by several authors to have a prevalence as high as 24 % amongst advanced AMD.[37–39] However, it has not been well adopted by the major grading centres such as Wisconsin Age-related Maculopathy Grading System and the associated epidemiological studies such as Age-Related Eye Disease Study (AREDS), Beaver Dam Eye Study, Blue Mountains Eye study. The International classification was used in the Rotterdam Eye Study. The former has considered reticular drusen as a form of soft drusen whilst the latter has no formal definition or inclusion of reticular drusen.[40–46]

Zweifel has also used SD-OCT to demonstrate that the location of reticular drusen is above the RPE and had different material compared with soft drusen (*Figure 1*).[37,47] Hence, there is no doubt about increasing consensus that SD-OCT will surpass CFP as the gold standard for better analysis of drusen ultrastructure and detection. As drusen progress in size, the surrounding RPE band, IS/OS interface, external limiting membrane as well as outer nuclear layer has been noted to be thinned (*Figure 2*). Johnson et al. has demonstrated both structural and functional photoreceptor changes over drusen in post-mortem eyes including change in photoreceptor cell density, gene expression and synapses over drusen.[48,49] Shuman et al. studied the neurosensory retina abnormalities in sites relative to drusen in early AMD and found a decreased thickening of photoreceptor layer (PRL) over drusen, suggesting a focal degenerative process with postulated eventual progress to visual loss, even in early stage AMD.[50] Other qualitative changes noted in relation to drusen on OCT include the absence of photoreceptor outer segment, disruption of the photoreceptor IS/OS junction and hyper-reflective foci adjacent and over drusen.[50,51]

Another risk factor of AMD includes the focal retina hyperpigmentation (*Figure 3*). Duker et al. has demonstrated foci of hyperpigmentation on SD-OCT in relation to CFP and postulated this to be an area of intraretinal RPE migration.[15] This indicates that SD-OCT may be a superior modality to demonstrate early indications of pigment clumps prior to visualisation on CFP. The ancillary study of AREDS 2 is currently studying this association.

Therefore, OCT gives us better insight into the early pathogenesis as well as an indicator of potential complications.

## Optical Coherence Tomography in Quantifying Age-related Macular Degeneration

Since Gass described the disappearance of drusen with laser photocoagulation in 1971,[52] large-scaled clinical trials such as the Choroidal Neovascularisation Prevention Trial (CNVPT) and the Complications of Age-related macular degeneration Prevention Trial (CAPT) as well as numerous smaller sized studies have been conducted with the aims to halt progression of AMD with the use of laser.[53–56] Drusen measurement in terms of numerical count on CFP or slit lamp biomicropscopy are often used as an important endpoint.[53–56] With further advancements to the latest SD-OCT (see *Table 1*), several authors have continued the pursuit of drusen quantification, now in terms of even more specific drusen area and volume.

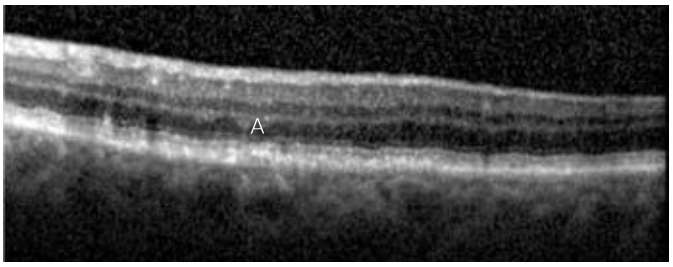
As mentioned, although the current gold standard, CFP has poor reliability for the identification and count of drusen. In his study, Schlanitz et al. has demonstrated that different types of SD-OCT machines were able to reliably identify higher drusen count compared with CFP.[13]

Several investigators have created algorithms for quantification techniques. However, the question arises with these methodologies, which, in common, uses RPE as the baseline for drusen segmentation. The idea of determining drusen geometric dimensions using the difference between RPE segmentation and a presumably normal RPE interpolation to generate measurements of RPE deformation from SD-OCT was developed not long after the technology was implemented in clinical work. Much of the work currently focuses on producing a robust and reproducible algorithm in developing fully automated software. There are several scientific as well as clinical issues that have yet to be addressed using the current methodologies.

Firstly, only 3D OCT-1000 and Cirrus HD-OCT (Carl Zeiss, Meditec Inc.) have incorporated automated RPE segmentation. However, as shown by Schlanitz et al. in a recent study, there is a high proportion of undetected small drusen and a moderate rate of error of height-to-diameter ratio of druse which indicates that the current automated algorithm of RPE segmentation is unable to account for steep deviations at the RPE contour level.[8] This is especially crucial if we base the underlying theory of a requirement of an 'ideal' RPE line which should follow the Bruch's membrane curvature closely. This error would be exaggerated in advanced disease of AMD (neovascularisation) or reticular drusen where the ideal RPE line is either disrupted or too steep. Hence, the current intensity-based RPE delineation automated technique may result in underdiagnosis of drusen. If the simple basis of the quantity of drusen is undermined, less could be expected of the area as well as its volume.

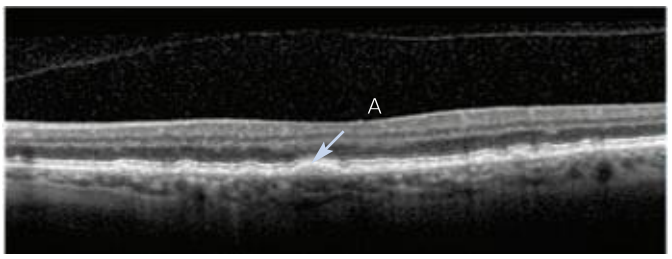
Secondly, as per *Table 1*, Yi et al. and Greogri et al. have used similar theories of determining drusen volume from difference of 'idea',

**Figure 1: Reticular Drusen**



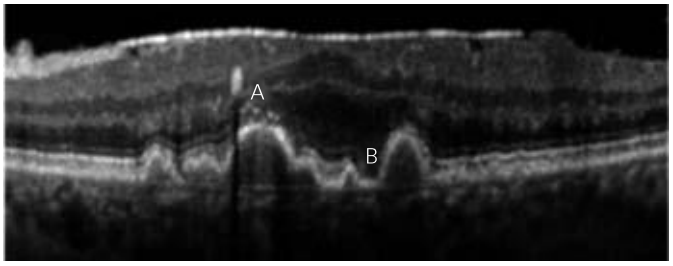

*A: Saw toothed shape indulations of RPE, reticular drusen.*

**Figure 2: Thinning of Photoreceptor Layer Above Drusen**




*A: Arrow pointing to thinning of photoreceptor layer above individual druse.*

**Figure 3: Pigmentation Migration on Optical Coherence Tomography**




*A: Pigment migration; B: soft druse.*

'interpolated' RPE baselines and deformation of RPE.[14,83] However, both of these techniques were only able to derive drusen volume from RPE elevations of 8.0 um as well as 19.5 um from their pixilated images, respectively. With the current knowledge, soft, large drusen (>125 um) were considered significant risk factors and with both Gregori and Yi's methodology, we would have to concur it is an excellent tool in identification of numerous drusen that is in keeping with the AREDS grading on CFP. So, the question arises as to why another tool is required when it is only as or less sensitive than CFP. We believe that the high resolution SD-OCT will provide further information on the sub-micro ultrastructure of the druse that is previously unknown or not easily identifiable with CFP. Also, as mentioned earlier, we now know that the soft confluent drusen is not the sole risk factor to progression of AMD. Numerous hard, small drusen, reticular drusen, which are visible on SD-OCT should be accounted for in the new technology for a better understanding as well as grading of the disease.[38,39] SD-OCT would be a good tool to visualise reticular drusen, and if possible, quantify them, especially since CFP was shown by Sarks et al. to be inadequate to qualify its evolution.[57]

Thirdly, from a clinicopathological standpoint, drusen are defined as focal deposits of extracellular material between the basal lamina RPE layer and the inner collagenous layer of the Bruch's membrane.[58] Segmentation of the outer retina even in high resolution OCT is

**Table 2: Studies Evaluating Drusen Segmentation on Optical Coherence Tomography**

| Study | Method | Number of Eyes | OCT Type | Outcome Measured | Results | Intergrader Reliability |
|---|---|---|---|---|---|---|
| 1. Toth et al.[35] | Areas of drusen on CFP and SD-OCT were mapped out and compared. Manual and automated segmentation (DOCTRAP) | 12 | SD-OCT (Bioptigen Inc.) | | Agreement between CFP and SD-OCT (82 ± 9 %). SD-OCT does not detect smaller drusen as well. Correlation between drusen volume and AREDS predeterrmined area and grading | NA |
| 2. Freeman et al.[9] | Manual segmentation, image J extrapolation of images. Drusen volume compared with AREDS grading and predetermined CFP area. Automated segmentation of posterior RPE. Using a second order polynomial to determine original RPE position (baseline). Difference between identified post-RPE border and calculated baseline equals geometric dimension of drusen. Only elevations >8 um chosen. | 36 | SD-OCT (spectralis, Heidelberg) | Drusen area and volume | A suggested new algorithm for drusen volume with RPE segmentation | Intra-observer: 98.1 % and 97.1 %, no interobserver |
| 3. Yi et al.[10] | Automated segmentation of RPE and RPE floor, virtual RPE free of deformations. Only elevations >19.5 um chosen. | 3 | Experimental SD-OCT using both TI: Sapphire laser and SLD | Drusen area and volume and proportion | The algorithm created drusen maps that permitted both qualitative and quantitative assessment of drusen area and volume that are highly reproducible | NA |
| 4. Gregori et al.[83] | Automated segmentation of RPE and druse evaluated according to its height and diameter post-automated segmentation and compared across three SD-OCT machines | 103 | SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditec Inc.) | Drusen area and volume | Automated segmentation of RPE by Cirrus made significantly fewer errors in drusen detection | Intra-class correlation coefficient >0.99 |
| 5. Schlanitz et al.[10] | | 12 | SDOCT (Cirrus, Carl Zeiss Meditec Inc; 3D OCT-1000, Topcon;HRA spectralis, Heidelberg) | Drusen count and size | | NA |

*AREDS = Age-Related Eye Disease Study; CFP = colour fundus photographs; DOCTRAP = Duke Optical Coherence Tomography Retinal Analysis Program; HD-OCT = high-definition optical coherence tomography; HRA = Heidelberg retina angiograph; OCT = optical coherence tomography; RPE = retinal pigment epithelium; SD-OCT = spectral domain optical coherence tomography; SLD = superluminescent diode; TI = titanium.*

incomplete. Normal Bruch's membrane measures 3–7 um and with the current resolution of OCT, it is impossible to define the structures of the outer retina. So it is often included within the highly reflective band representing the RPE. The RPE layer is composed of two distinct hyper reflective bands separated by a hypo-reflective region. Current hypothesis has the outer hyper-reflective band corresponding to RPE cells but the inner band remains undefined. Some studies have suggested that the band is the Verhoeff's membrane, constituting of tight junctions of RPE cells, whilst, other hypothesis corresponds the band to the basal infoldings and apical processes that encloses the photoreceptor outer segments.[59] Hence, with less than intricate segmentation algorithms, the drusen measurements of smaller drusen will not be accurate.

Fourthly, the current drusen volume mapping techniques does not account for possibilities of other materials elevating the RPE layer such as vitelliform material or heterogenous pigment epithelial detachments (PED). This technique will have a potential problem arising from confluency of large druse progressing into PED or missed occult CNV.

Fifthly, Bruch's membrane thickening was shown to be related to ageing and furthermore in ARM.[60-62] Hence, would increase in drusen be an accurate measure of progression of AMD? The Waterman five-year epidemiological study has shown that drusen does disappear even with progression of the disease.[62] Also, as mentioned, numerous prior drusen laser trials have shown a decrease in drusen as an outcome, however, this has no subsequent effect on slowing the rate of progression of AMD. The question therefore arises whether it is drusen that current ophthalmology research on non-exudative AMD should focus on, or if there is another structure which commands greater accuracy as an outcome measure of SD-OCT.

Lastly, the five studies which has been conducted were considered 'robust' in intragrading. However, no intergrader reliability has been tabulated. Given the difficult identification of various types of drusen

on SD-OCT, it would have been prudent to establish an intergrader reliability on the various techniques used before automation. The basis of qualifying the identification of druse, with results of the all previous studies done, is far from adequate.

## Challenges with Optical Coherence Tomography

The state of the art technology of OCT has advanced very rapidly over the last two decades. In the authors' article, they have reviewed the numerous new features and postulations garnered alongside OCT evolutions. However, several features such as segmentation of the retina into its 10 layers remains incomplete. Also, because the current technology has a 7–10 µm axial resolution, several important structures as the Bruch's membrane is far below the visible range of current SD-OCT. On the other end, the ultra-high resolution OCT with axial resolution of 3 µm compromises on the acquisition speed and hence loses the TruTrack™ facilities of spectralis on SD-OCT as well as the image quality.[63]

Future directions of OCT continue to focus on the current issues such as better axial resolution, transverse resolution, which is currently limited by ocular aberrations and image acquisition time, which determines transverse pixels acquired on OCT and the transformation into a 3D image. A particular focus to consider could be the ability to better visualise choroid thickness in early AMD as recent investigators have proven a correlation between the two.[64] Other areas that need to be improved include sensitivity of image detection and decreased noise level of image acquired, availability of functional enhancement of OCT (such as Doppler studies of blood flow) and birefringence or retinal activity in response to flash. The ideal OCT system would hence enable visualisation of tissue morphology at a cellular basis without the need of an optical biopsy, whilst providing the same essential information on metabolical, physiological as well as structural function of retina tissue. Examples of these include adaptive optics, ultra-high resolution OCT (UHR-OCT) and functional OCT. Adaptive optics work by correcting ocular optical aberrations in order to improve transverse resolution with the use of deformable mirrors. It works as an adjunct to other imaging modalities such as OCT to improve its function.[65,66] Combination of adaptive optics (AO) and UHR-OCT has allowed visualisation down to the cone mosaic with an axial and transverse resolution of 3 um.[7,66] The use of AO-UHR-OCT is thus far the only combination imaging modality that has such a refined cellular resolution.[67–74] Current axial resolution of OCT is limited by its bandwidth. UHR utilises femtosecond lasers as the light source and provides images with axial resolution of 3 um.[63] This facilitates segmentation of the 10 retina layers and provides cellular visualisation of individual cells in diseased states. However, these systems are slower than conventional TD-OCT with acquisition speed of 150–250 axial scans per second. The integration of OCT with several imaging modalities such as angiography and OCT (Spectralis) and microperimetry and coronal scan OCT (Ophthalmic Technologies Inc., [OTI] Canada) allows a more refined functional and structural diagnosis with more precise follow-ups of complications. Leitgeb and Makita et al. have demonstrated the use of Doppler OCT to the measure rate of retina blood flow,[75,76] whilst Yazandanfar et al. and Cense and associates have demonstrated the combination of OCT with tissue oxygenation on spectroscopy and intraretinal biological responses by bifringence.[77,78] Although seemingly ideal, these novel modalities are currently far too complex and expensive for a commercial and widespread clinical utilisation. Perhaps a recent development of swept source OCT (SS-OCT) which utilises a longer wavelength of 1,060 nm could result in deeper enhancement of retina to choroidal tissues, yielding further important information regarding pathogenesis as well as providing a clinical evaluation on the various stages of this disease. However, to note, high speed SS-OCT, despite its depth of image acquisition, would have low sensitivity as a major trade-off to the commercially available spectralis OCT.[79–82]

## Conclusion

In conclusion, OCT is arguably the most essential tool in the management of AMD today. We have witnessed unprecedented advancement of technology in the last 20 years with OCT which has allowed us to have better understanding of both the physiological as well as structural function of the eye without the need of invasive procedures. In this review article, we have analysed the various features and uses of the OCT in ARM and the currently unresolved technical difficulties with regards to this technology. ■


1. Zarbin MA, Current concepts in the pathogenesis of age-related macular degeneration, *Arch Ophthalmol,* 2004;122(4):598–614.
2. Spaide RF, Curcio CA, Zweifel SA, Drusen, an old but new frontier, *Retina*, 2010;30(8):1163–5.
3. Ying GS, Maguire MG, Alexander J, Description of the Age-Related Eye Disease Study 9-step severity scale applied to participants in the Complications of Age-related Macular Degeneration Prevention Trial, *Arch Ophthalmol,* 2009;127(9):1147–51.
4. Yannuzzi LA, Slakter JS, Sorenson JA, et al., Digital indocyanine green videoangiography and choroidal neovascularization, *Retina*, 2012;32(Suppl. 1):191.
5. Hyvärinen L, Flower RW, Indocyanine green fluorescence angiography, *Acta Ophthalmol (Copenh)*, 1980;58(4):528–38.
6. Hayashi K, de Laey JJ, Indocyanine green angiography of choroidal neovascular membranes, *Ophthalmologica*, 1985;190(1):30–9.
7. Huang D, Swanson EA, Lin CP, et al., Optical coherence tomography, *Science*, 1991;254(5035):1178–81.
8. Schlanitz FG, Ahlers C, Sacu S, et al., Performance of drusen detection by spectral-domain optical coherence tomography, *Invest Ophthalmol Vis Sci,* 2010;51(12):6715–21.
9. Freeman SR, Kozak I, Cheng L, et al., Optical coherence tomography-raster scanning and manual segmentation in determining drusen volume in age-related macular degeneration, *Retina*, 2010;30(3):431–5.
10. Yi K, Mujat M, Park BH, et al., Spectral domain optical coherence tomography for quantitative evaluation of drusen and associated structural changes in non-neovascular age-related macular degeneration, *Br J Ophthalmol,* 2009;93(2):176–81.
11. Coscas G, Coscas F, Zourdani A, Soubrane G, [Optical coherence tomography and ARMD], *J Fr Ophtalmol,* 2004;27(9 Pt 2):3S7–30.
12. Querques G, Forte R, Berboucha E, et al., Spectral-Domain versus Time Domain Optical Coherence Tomography before and after Ranibizumab for Age-Related Macular Degeneration, *Ophthalmic Res,* 2011;46(3):152–9.
13. Gabriel C, Saul A, Société française d'ophtalmologie, et al., Optical coherence tomography in age-related macular degeneration : OCT in AMD : annual report of the French Ophthalmic Society, Berlin, Heidelberg, Germany: Springer, 2009;2:15–34.
14. Malamos P, Sacu S, Georgopoulos M, et al., Correlation of high-definition optical coherence tomography and fluorescein angiography imaging in neovascular macular degeneration, *Invest Ophthalmol Vis Sci,* 2009;50(10):4926–33.
15. Ho J, Witkin AJ, Liu J, et al., Documentation of Intraretinal Retinal Pigment Epithelium Migration via High-Speed Ultrahigh-Resolution Optical Coherence Tomography, *Ophthalmology*, 2011;118(4):687–93.
16. Framme C, Wolf S, Wolf-Schnurrbusch U, Small dense particles in the retina observable by spectral-domain optical coherence tomography in age-related macular degeneration, *Invest Ophthalmol Vis Sci,* 2010;51(11):5965–9.
17. Zweifel SA, Engelbert M, Laud K, et al., Outer retinal tubulation: a novel optical coherence tomography finding, *Arch Ophthalmol,* 2009;127(12):1596–602.
18. 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(2):298–308.
19. Toth CA, Narayan DG, Boppart SA, et al., A comparison of retinal morphology viewed by optical coherence tomography and by light microscopy, *Arch Ophthalmol,* 1997;115(11):1425–8.
20. Fukuchi T, Takahashi K, Uyama M, Matsumura M, Comparative study of experimental choroidal neovascularization by optical coherence tomography and histopathology, *Jpn J Ophthalmol,* 2001;45(3):252–8.
21. Alam S, Zawadzki RJ, Choi S, et al., Clinical application of rapid serial fourier-domain optical coherence tomography for macular imaging, *Ophthalmology*, 2006;113(8):1425–31.
22. Menke MN, Sato E, Van De Velde FJ, Feke GT, Combined use of SLO microperimetry and OCT for retinal functional and structural testing, *Graefes Arch Clin Exp Ophthalmol,* 2006;244(5):634–8.
23. de Boer JF, Cense B, Park BH, et al., Improved signal-to-noise ratio in spectral-domain compared with time-domain optical coherence tomography, *Opt Lett,* 2003;28(21):2067–9.
24. Andrea Giani MC, Staurenghi G, Spectral-Domain OCT. In: Coscas G, OCT in AMD: Annual Report of the French Ophtalmic Societies, Berlin, Heidelberg, Germany: Springer, 2009;38–48.
25. Toth CA, Farsiu S, Khanifar A, Chong G, Applications of Spectral-Domain OCT in AMD. In: Coscas G (ed), *Optical Coherence Tomography in Age-Related Macular Degeneration,* 2009;15–34.
26. 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(11):2054.e1–14.
27. 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(12):1715–20.
28. Costa RA, Skaf M, Melo LA Jr, et al., Retinal assessment using optical coherence tomography, *Prog Retin Eye Res,* 2006;25(3):325–53.

29. Leitgeb R, Hitzenberger C, Fercher A, Performance of Fourier domain vs. time domain optical coherence tomography, *Opt Express,* 2003;11(8):889–94.
30. Choma M, Sarunic M, Yang C, Izatt J, Sensitivity advantage of swept-source and fourier-domain optical coherence tomography, *Opt Express,* 2003;11(18):2183–9.
31. Jiao S, Knighton R, Huang X, et al., Simultaneous acquisition of sectional and fundus ophthalmic images with spectral-domain optical coherence tomography, *Opt Express,* 2005;13(2):444–52.
32. Booij JC, Baas DC, Beisekeeva J, et al., The dynamic nature of Bruch's membrane, *Prog Retin Eye Res,* 2010;29(1):1–18.
33. Starita C, Hussain AA, Pagliarini S, Marshall J, Hydrodynamics of ageing Bruch's membrane: implications for macular disease, *Exp Eye Res,* 1996;62(5):565–72.
34. Khanifar AA, Koreishi AF, Izatt JA, Toth CA, Drusen ultrastructure imaging with spectral domain optical coherence tomography in age-related macular degeneration, *Ophthalmology*, 2008;115(11):1883–90.
35. Jain N, Farsiu S, Khanifar AA, et al., Quantitative comparison of drusen segmented on SD-OCT versus drusen delineated on color fundus photographs, *Invest Ophthalmol Vis Sci,* 2010;51(10):4875–83.
36. Mimoun G, Soubrane G, Coscas G, [Macular drusen], *Journal francais d'ophtalmologie,* 1990;13:511–30.
37. Zweifel SA, Imamura Y, Spaide TC, et al., Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration, *Ophthalmology*, 2010;117(9):1775–81.
38. Cohen SY, Dubois L, Tadayoni R, et al., Prevalence of reticular pseudodrusen in age-related macular degeneration with newly diagnosed choroidal neovascularisation, *Br J Ophthalmol,* 2007;91(3):354–9.
39. Klein R, Meuer SM, Knudtson MD, et al., The Epidemiology of Retinal Reticular Drusen, *American Journal of Ophthalmology,* 2008;145:317–26.
40. Wang JJ, Rochtchina E, Lee AJ, et al., Ten-year incidence and progression of age-related maculopathy: the blue Mountains Eye Study, *Ophthalmology*, 2007;114(1):92–8.
41. Klein R, Klein BE, Tomany SC, et al., Ten-year incidence and progression of age-related maculopathy: The Beaver Dam eye study, *Ophthalmology*, 2002;109(10):1767–79.
42. Klein R, Davis MD, Magli YL, et al., The Wisconsin age-related maculopathy grading system, *Ophthalmology*, 1991;98(7):1128–34.
43. Bird AC, Bressler NM, Bressler SB, et al., An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group, *Surv Ophthalmol,* 1995;39(5):367–74.
44. 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(5):668–81.
45. Ferris FL, Davis MD, Clemons TE, et al., A simplified severity scale for age-related macular degeneration: AREDS Report No. 18, *Arch Ophthalmol,* 2005;123(11):1570–4.
46. van Leeuwen R, Klaver CC, Vingerling JR, et al., The risk and natural course of age-related maculopathy: follow-up at 6 1/2 years in the Rotterdam study, *Arch Ophthalmol*. 2003;121(4):519–26.
47. Zweifel SA, Spaide RF, Curcio CA, et al., Reticular pseudodrusen are subretinal drusenoid deposits, *Ophthalmology*, 2010;117(2):303–12.e1.
48. Johnson PT, Lewis GP, Talaga KC, et al., Drusen-associated degeneration in the retina, *Invest Ophthalmol Vis Sci,* 2003;44(10):4481–8.
49. Johnson PT, Brown MN, Pulliam BC, et al., Synaptic pathology, altered gene expression, and degeneration in photoreceptors impacted by drusen, *Invest Ophthalmol Vis Sci,* 2005;46(12):4788–95.
50. Schuman SG, Koreishi AF, Farsiu S, et al., Photoreceptor layer thinning over drusen in eyes with age-related macular degeneration imaged in vivo with spectral-domain optical coherence tomography, *Ophthalmology*, 2009;116(3):488–96.e2.
51. Coscas G, Coscas F, Vismara S, et al., Clinical features and natural history of AMD. In: Coscas G, Coscas F, Vismara S, et al., *Optical coherence tomography in age-related macular degeneration,* Heidelberg, Germany: Springer, 2009;171–274.
52. Gass JD, Photocoagulation of macular lesions, *Trans Am Acad Ophthalmol Otolaryngol,* 1971;75:580–608.
53. Laser treatment in eyes with large drusen. Short-term effects seen in a pilot randomized clinical trial. Choroidal Neovascularization Prevention Trial Research Group, *Ophthalmology*, 1998;105(1):11–23.
54. Choroidal Neovascularization Prevention Trial Research Group, Laser treatment in fellow eyes with large drusen: updated findings from a pilot randomized clinical trial, *Ophthalmology*, 2003;110(5):971–8.
55. Complications of Age-Related Macular Degeneration Prevention Trial Research Group, Laser treatment in patients with bilateral large drusen: the complications of age-related macular degeneration prevention trial, *Ophthalmology*. 2006;113(11):1974–86.
56. Frennesson IC, Nilsson SE, Effects of argon (green) laser treatment of soft drusen in early age-related maculopathy: a 6 month prospective study, *Br J Ophthalmol,* 1995;79(10):905–9.
57. Sarks J, Arnold J, Ho IV, et al., Evolution of reticular pseudodrusen, *Br J Ophthalmol,* 2011;95(7):979–85.
58. Abdelsalam A, Del Priore L, Zarbin MA, Drusen in age-related macular degeneration: pathogenesis, natural course, and laser photocoagulation-induced regression, *Surv Ophthalmol,* 1999;44(1):1–29.
59. Alam S, Zaw adzki RJ, Choi S, et al., Clinical applications of rapid serial fourier-domain optical coherence tomography for macular imaging, *Ophthalmology*, 2006;113:1425–31.
60. Okubo A, Rosa RH Jr, Bunce CV, et al., The relationships of age changes in retinal pigment epithelium and Bruch's membrane, *Invest Ophthalmol Vis Sci,* 1999;40(2):443–9.
61. Guymer R, Luthert P, Bird A, Changes in Bruch's membrane and related structures with age, *Prog Retin Eye Res,* 1999;18(1):59–90.
62. Bressler NM, Munoz B, Maguire MG, et al., Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities. Waterman study, *Arch Ophthalmol,* 1995;113(3):301–8.
63. 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(2):191–7.
64. Querques G, Querques L, Forte R, et al., Choroidal changes associated with reticular pseudodrusen, *Invest Ophthalmol Vis Sci,* 2012;53(3):1258–63.
65. Miller DT, Kocaoglu OP, Wang Q, Lee S, Adaptive optics and the eye (super resolution OCT), *Eye (Lond)*, 2011;25(3):321–30.
66. Liang J, Williams DR, Miller DT, Supernormal vision and high-resolution retinal imaging through adaptive optics, *J Opt Soc Am A Opt Image Sci Vis,* 1997;14(11):2884–92.
67. Dreher AW, Bille JF, Weinreb RN, Active optical depth resolution improvement of the laser tomographic scanner, *Appl Opt,* 1989;28(4):804–8.
68. Roorda A, Romero-Borja F, Donnelly III W, et al., Adaptive optics scanning laser ophthalmoscopy, *Opt Express,* 2002;10:405–12.
69. Hermann B, Fernández EJ, Unterhuber A, et al., Adaptive-optics ultrahigh-resolution optical coherence tomography, *Opt Lett,* 2004;29(18):2142–4.
70. Merino D, Dainty C, Bradu A, Podoleanu AG, Adaptive optics enhanced simultaneous en-face optical coherence tomography and scanning laser ophthalmoscopy, *Opt Express,* 2006;14(8):3345–53.
71. Pircher M, Zawadzki RJ, Evans JW, et al., Simultaneous imaging of human cone mosaic with adaptive optics enhanced scanning laser ophthalmoscopy and high-speed transversal scanning optical coherence tomography, *Opt Lett,* 2008;33(1):22–4.
72. Zhang Y, Rha J, Jonnal R, Miller D, Adaptive optics parallel spectral domain optical coherence tomography for imaging the living retina, *Opt Express,* 2005;13(12):4792–811.
73. Zhang Y, Cense B, Rha J, et al., High-speed volumetric imaging of cone photoreceptors with adaptive optics spectral-domain optical coherence tomography, *Opt Express,* 2006;14(10):4380–94.
74. Bigelow CE, Iftimia NV, Ferguson RD, et al., Compact multimodal adaptive-optics spectral-domain optical coherence tomography instrument for retinal imaging, *J Opt Soc Am A Opt Image Sci Vis,* 2007;24(5):1327–36.
75. Leitgeb R, Drexler W, Unterhuber A, et al., Ultrahigh resolution Fourier domain optical coherence tomography, *Opt Express,* 2004;12(10):2156–65.
76. Makita S, Hong Y, Yamanari M, et al., Optical coherence angiography, *Opt Express,* 2006;14(17):7821–40.
77. Yazdanfar S, Rollins AM, Izatt JA, In vivo imaging of human retinal flow dynamics by color Doppler optical coherence tomography, *Arch Ophthalmol,* 2003;121(2):235–9.
78. Cense B, Chen TC, Nassif N, et al., Ultra-high speed and ultra-high resolution spectral-domain optical coherence tomography and optical Doppler tomography in ophthalmology, *Bull Soc Belge Ophtalmol,* 2006;(302):123–32.
79. Hirata M, Tsujikawa A, Matsumoto A, et al., Macular choroidal thickness and volume in normal subjects measured by swept-source optical coherence tomography, *Invest Ophthalmol Vis Sci,* 2011;52(8):4971–8.
80. Potsaid B, Baumann B, Huang D, et al., Ultrahigh speed 1050nm swept source/Fourier domain OCT retinal and anterior segment imaging at 100,000 to 400,000 axial scans per second, *Opt Express,* 2010;18(19):20029–48.
81. Unterhuber A, Povazay B, Hermann B, et al., In vivo retinal optical coherence tomography at 1040 nm - enhanced penetration into the choroid, *Opt Express*, 2005;13(9):3252–8.
82. Yasuno Y, Hong Y, Makita S, et al., In vivo high-contrast imaging of deep posterior eye by 1-microm swept source optical coherence tomography and scattering optical coherence angiography, *Opt Express,* 2007;15(10):6121–39.
83. Gregori G, Wang F, Rosenfeld PJ, et al., Spectral domain optical coherence tomography imaging of drusen in nonexudative age-related macular degeneration, *Ophthalmology*, 2011;118(7):1373–9.