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Volumetric Measurement of Optic Nerve Head Drusen Using Swept Source Optical Coherence Tomography

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Keywords

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Introduction

Optic nerve head drusen (ONHD) are accumulations of hyaline material in the optic nerve which may become calcified.¹⁻² On clinical exam, they can appear as yellowish-white protuberances of the optic nerve head and can be associated with vision loss. In clinical studies, they have been reported to occur in 3.4 to 4.9 people per 1,000 individuals, but in autopsy examinations, an incidence as high as 20 per 1,000 individuals has been reported.³ Though many patients may be asymptomatic, the presence and growth of drusen have been associated with vascular abnormalities that include choroidal neovascularization and irregular branching of the retinal blood vessels.⁴ These vascular pathologies may in turn cause visual field defects due to ischemic optic neuropathy, central retinal vein occlusion, arterial occlusions, or retinal hemorrhages.^{3,5}

New technologies are needed to better diagnose and image drusen, especially in patients with concomitant glaucoma,⁶⁻⁸ because treatment dilemmas occur when it is unclear if worsening vision is due to glaucoma progression or enlarging drusen. These dilemmas occur because both ONHD and glaucoma may independently cause visual field defects and retinal nerve fiber layer (RNFL) thinning. In addition to funduscopy, ONHD have traditionally been imaged with ultrasonography, autofluorescence, computerized tomographic scanning, and

optical coherence tomography (OCT). However, none of these commercially available methods allow for quantification of the size and volume of drusen. Classically, ultrasound is considered the most sensitive means of diagnosis, but the low resolution of ultrasound biomicroscopy (30 microns at 50 MHz ultrasonic frequency)⁹ is insufficient to evaluate drusen structure and progression. Commercially available spectral-domain optical coherence tomography (SD-OCT) instruments have been used to qualitatively describe the appearance of drusen¹⁰⁻¹² and to distinguish ONHD from papilledema,^{6-8, 13-15} but they are limited to measurements of RNFL thinning and ganglion cell layer thinning, neither of which is specific to ONHD.^{16,17} Enhanced depth imaging (EDI) OCT and swept source (SS) OCT have also enabled qualitative descriptions of ONHD.¹⁸⁻²⁰ Although EDI-OCT, like SS-OCT, may allow for better visualization of deep ocular structures compared to SD-OCT, EDI-OCT, and SD-OCT in general, exhibits worse signal roll-off and reduced signal uniformity than SS-OCT.²¹ SS-OCT provides both high penetration of tissue and high axial uniformity of images, at the expense of slightly reduced image contrast. To our knowledge, the only study which has attempted to quantify the size, shape, and location of ONHD used an experimental SD-OCT instrument.²² Therefore, this study sought to determine if SS-OCT volume scans could be used to measure ONHD size, shape, and location.

Another secondary objective of this study was to correlate SS-OCT ONHD volume measurements with a traditional functional test, the Humphrey visual field exam. Although drusen are considered innocuous growths,²³ several reports have documented cases of severe vision loss.^{24 - 26} Since the mechanism of ONHD vision loss is poorly understood, it would help to understand what correlation, if any, exists between drusen volume and visual field loss. The ability to quantify drusen shape, volume, and location may also enable other studies on how ONHD cause optic nerve head damage, peripapillary RNFL thinning, and visual field loss.

Materials and Methods

Patients with optic nerve head drusen were recruited at Massachusetts Eye and Ear (MEE) between April and November 2015. The study was approved by the institutional review board of the same institution. Research was conducted in accordance with the tenets of the declaration of Helsinki and the regulations of the Health Insurance Portability and Accountability Act. All participants in the study underwent a comprehensive ocular examination by a glaucoma specialist (T.C.C.) that included a comprehensive history, visual acuity testing, refraction, Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, dilated ophthalmoscopy, ultrasound pachymetry, stereophotography (Visucam Pro NM; Carl Zeiss Inc), and visual field testing (Swedish Interactive Threshold Algorithm 24-2 test of the Humphrey visual field analyzer 750i; Carl Zeiss Meditec, Inc).

SD-OCT volume scans over the optic nerve were acquired using the Spectralis OCT device (Heidelberg Engineering, Heidelberg, Germany). The protocol consisted of 193 B-scans with three averages at each position. Enhanced Depth Imaging (EDI) mode was not used.

SS-OCT scans centered on the optic nerve head were then acquired with the Atlantis DRI OCT system (Topcon Medical Systems, Tokyo, Japan). This instrument uses light from a

swept frequency laser with a center wavelength of 1050 nm. This longer wavelength light penetrates greater depths of tissue than the 840 to 870 nm source commonly used in SD-OCT instruments because the longer wavelength light experiences reduced scattering. The swept source device has a scan rate of 100,000 A-scans per second. The volumetric protocol consisted of 64 images with 4 averages at each position over a region approximately 6 mm × 6 mm. Circumpapillary retinal nerve fiber layer thickness measurements were also made with the SS-OCT instrument.

The drusen were manually segmented by three trained graders using custom-built software written in C++. The software used the open source libraries Open Computer Vision library (OpenCV version 2.4.3, Willow Garage, Menlo Park, CA) and the Visualization Toolkit (VTK 6.3.0, Kitware, Clifton Park, NY). The QT application development framework (Qt 5.5.1, The QT Company, Oslo, Norway) was used to construct the graphical user interface. Each of the eight eyes was segmented twice by the three graders to assess measurement reproducibility. In the B-scan images, the borders of the drusen were delineated with a mouse. Multiple drusen within a B-scan could be demarcated and measured. After the drusen were identified, their volume in each frame was calculated using the following scaling factors: $x \text{ pixel} = 11.7 \text{ microns}$, $y \text{ pixel (spacing between scans)} = 93.75 \text{ microns}$, $z \text{ pixel} = 2.6 \text{ microns}$. Three-dimensional reconstructions of the drusen and the retinal surface were created to visualize the drusen orientation relative to the retinal surface.

Figure 1 illustrates this study's image acquisition and processing procedures. SS-OCT images [Figure 1(a)] were manually segmented [Figure 1(b)] with a mouse using the software. The segmented regions in each frame were measured by the program [Figure 1(c)] to calculate the drusen volume. The 64 B-scans of the volumetric dataset were combined to create an en face image of the retina [Figure 1(d)]. This allowed the relative position of each B-scan to be determined.

Results

Four patients with a mean age of 62.3 years (range: 52.5 – 71.8 years) were included in this study. Table 1 summarizes their demographic and clinical characteristics. Two subjects were female, and all were of white ethnicity.

All patients presented with bilateral drusen, and both eyes were analyzed. The visual field mean deviations were between -23.98 dB and -2.51 dB (Table 1). None of the patients had glaucoma, but one patient had ocular hypertension and another had been diagnosed with non-arteritic ischemic optic neuropathy (NAION) seventeen years prior. The patient with NAION was a 71.8 year old woman with hypertension, but no history of diabetes mellitus or anemia.

In all patients, the drusen appeared as hypo-reflective (signal-poor) regions with hyper-reflective borders and occasional hyper-reflective foci internally (Figure 2). In all cases, the drusen also distorted the normal cupping of the optic nerve head, such that the central optic nerve extended above the retinal surface. Drusen were noted to extend both above and below the level of Bruch's membrane opening.

In Figure 2, disc photographs, visual fields, three-dimensional views of the nerve head drusen and SS-OCT scans were juxtaposed in order to identify common clinical features. The disc photos in 2(a, b, d, e) displayed the most prominent lumpy-bumpy appearance from protrusion of large drusen close to the retinal surface. The inferior visual field was more severely damaged in 2(a, d, e, g, h), and the superior visual field was more extensively damaged in 2(b, c, f). Severe visual field damage, particularly in the inferior hemifield, was visible in 2(g, h), which represent the two eyes of a patient with a history of bilateral NAION, even though the drusen volumes were small.

The measured volume of ONHD averaged 0.56 mm^3 (range: $0.24 - 1.05 \text{ mm}^3$). Linear regression analysis showed that there was a good correlation between VF mean deviation and drusen volume [Figure 3(a)]. This analysis also suggested that if the total drusen volume were below approximately 0.2 mm^3 , the visual field would be normal. For each increase of one cubic millimeter in drusen volume, visual field mean deviation decreased by approximately 20 decibels. In Figure 3(b), the variation of global retinal nerve fiber layer thickness (SS-OCT measurements) with drusen volume was analyzed. As drusen volume increased, global retinal nerve fiber layer thickness decreased at a rate of 38 microns per cubic millimeter of drusen. The reproducibility of drusen measurements was analyzed using a Bland-Altman plot [Figure 3(c)], and the mean intra-test variability (coefficient of variation) was 5.4%. The mean inter-test variability was calculated by dividing the standard deviation of the three grader measurements by their mean value. The inter-test variability was 10.8%.

Spectralis SD-OCT images were also acquired. The posterior drusen borders could not be clearly seen in any patient, so the drusen volumes could not be determined using the SD-OCT volume scans. Comparison between the Spectralis infrared photo and the en face SS-OCT image revealed agreement of the retinal blood vessels.

Discussion

To the best of our knowledge, this is the first study to measure optic nerve head drusen volume from SS-OCT volume scans. SS-OCT enabled calculation of ONHD volume for all eyes. In contrast, with SD-OCT (non-EDI mode), no patient had full visualization of anterior and posterior drusen borders; therefore, ONHD volume could not be determined from SD-OCT volume scans for any eyes. In six eyes (Table 1, patients 1-3,), larger drusen were associated with greater visual field loss (Figure 3(a), $R = 0.92$). In a subject with a diagnosis of non-arteritic ischemic optic neuropathy (NAION) seventeen years prior to this study (Table 1, patient 4), large mean deviation values were measured in eyes with small drusen volumes; these points were treated as outliers (Figure 3(a)). In patient 4, the small drusen size did not correlate well with the large degree of visual field loss, because the history of bilateral NAION was felt to cause much of the vision loss. Although increasing visual field defects were well explained by increasing drusen volume in the other six eyes, the slope of this line (20 dB/mm^3) was smaller than that measured in the work of Yi et al (28.4 dB/mm^3). This may be explained by noting that the patients analyzed by Yi et al had glaucoma concomitant with the nerve head drusen, which may have increased the mean deviation. None of the patients in this study had concomitant glaucoma, but one patient had ocular

hypertension. A potential limitation of the linear regression analysis in this work was that two eyes from each patient were used. The mean deviation in each eye and the drusen volumes in each eye were not fully independent parameters, and correlations may have confounded the relationship between drusen volume and mean deviation. A larger study, involving one eye from each patient, may be necessary to better elucidate the effect of drusen size on functional vision loss, as different drusen locations may have different effects on visual field testing. For example, when ONHD originate in the nasal portion of the nerve, resulting visual field defects may be harder to detect since the temporal field is poorly sampled in automated perimetry. Therefore, significant temporal visual field damage may occur despite a relatively small change in visual field mean deviation.

Several mechanisms may explain drusen-related visual field loss. Drusen may compress the optic nerve and inhibit axonal transport.^{1,27} These abnormalities may progressively damage axons in the optic nerve¹⁷ or the prelaminar tissue or cause ischemia in the optic nerve head.²⁸⁻³⁰ Vision loss with ONHD can also be caused by ischemic events, such as NAION.³ While Patient 4's systemic hypertension may have precipitated the distant history of bilateral NAION,³⁰ the ischemic event could also have been triggered by the ONHD, which are known to be associated with anomalous vasculature. ONHD has been associated with vascular anomalies such as abnormal branching of retinal vessels, a higher incidence of cilioretinal arteries, and retino-choroidal collaterals. These anomalies may contribute to serious complications such as anterior ischemic optic neuropathy, central retinal vein or artery occlusions, subretinal neovascularization, and retinal hemorrhage.²³ NAION typically produces altitudinal visual field defects. However, the field damage in this patient did not respect the horizontal meridian [Figure 2(g, h)], possibly indicating drusen-related visual field damage super-imposed on a classic NAION presentation or simply an atypical presentation of NAION.

In patients 1 – 3 (Table 1), visual field damage from ONHD followed no clear patterns except that larger drusen were associated with more extensive field loss. Patient 1 [Figure 2 (a, b)] exhibited a variety of patterns: inferior arcuate, superior depression, superior nasal step with superior paracentral loss, and temporal depression. Patient 2 [Figure 2(d)] and patient 3 [Figure 2(e)] exhibited nasal defects that did not respect the horizontal midline. Patients 2 [Figure 2(c)] and patient 3 [Figure 2(f)] also showed diffuse visual field loss in the fellow eyes.

Mechanical damage from compression and disruption of axonal transport have been proposed as causes of the drusen-related loss of nerve fibers.^{23,31} Figure 3(b) shows that larger drusen volume is correlated with thinner retinal nerve fiber layer thickness values. However, at zero drusen volume, the simple linear model extrapolates to an RNFL thickness of 80 microns, below the normal mean of $97.3 \pm 9.6 \mu\text{m}$.³² This suggests that a linear model derived from this small case series may be too simplified. Anteriorly positioned drusen have been associated with high incidence of visual defects (71 – 87%).^{23,33,34} Roh et al created a four-step grading scale based on the size of visible drusen and correlated time-domain OCT RNFL thickness with drusen size.³⁵ The RNFL thickness in the inferior and superior quadrants was significantly thinner for drusen patients in the highest three grades than for normal controls. These results are qualitatively similar to ours, although the agreement

between time domain OCT and SS-OCT has not been established and the relation of the subjective scale to the true drusen volume is unclear. In contrast, Katz analyzed 58 eyes of 41 subjects with deeply buried drusen and found no differences in the RNFL thickness between the drusen group and normal controls.³⁶ Deeply buried drusen might cause less compressive nerve injury than superficially situated drusen, so drusen position as well as size may determine the extent of neuronal damage. The drusen of patients in this study were close to the retinal surface and could be detected from photographic examination (Figure 2). Gili et al found significant RNFL thinning in all quadrants except the temporal quadrant in patients with superficial drusen, but no significant thinning in patients with deeply buried drusen.¹⁷ Drusen are normally considered harmless, but these studies and ours suggest that when drusen are more superficially positioned, they may threaten vision. The damage they cause can confuse evaluation of glaucoma, and thus monitoring of both drusen size and position may be important. Volumetric measurements of optic nerve head drusen with SS-OCT may lead to new insights into retrograde nerve damage: drusen are “stones” in the nerve head that offer a model of compressive nerve injury.

Previous studies have focused on the qualitative features of drusen imaged with OCT. In Figure 2, drusen appeared as signal-poor regions with hyper-reflective foci and borders. The lobes of the drusen were revealed by the bright borders, and the hyper-reflective foci were most likely calcified hyaline material. Sato et al employed SS-OCT and EDI-OCT to examine 26 eyes of 15 patients.¹⁸ They described ONHD in these images as hypo-reflective tumefactions within the nerve that often contained hyper-reflective foci. The findings of this study were consistent with theirs. Sato et al also observed improved visibility of the posterior borders of the drusen with SS-OCT and EDI-OCT technologies relative to SD-OCT, but did not attempt volumetric measurement. Merchant et al reported better drusen visibility with EDI-OCT compared to standard SD-OCT.¹⁹ Detection of drusen in their study was enhanced relative to ultrasound, but drusen quantification was not performed. Silverman et al proposed measurement of drusen volume with SS-OCT but did not attempt it.²⁰ The only previous report of drusen quantification in OCT was performed by Yi et al in a study which used an experimental SD-OCT device.²²

Optic nerve head drusen may be diagnosed in many ways, and each method has its strengths and limitations for detecting progression over time. Prior to OCT, long-term follow-up was usually necessary to confirm the presence of drusen after initial observation of disc elevation. As drusen calcify over time and become more anteriorly situated, they may be detected by computed tomography, photography, ultrasound, and autofluorescence. Miller³⁷ and Spencer et al³⁸ used computed tomography to confirm growth of ONHD in patients who presented with disc elevation 1 to 16 years before. Computed tomography creates scans that are 1 - 2 mm thick and can potentially miss small drusen.³⁹ Hoover et al detected calcifications in ophthalmoscopic examination of three of ten patients with unexplained pseudopapilledema after monitoring the cohort for an average of 10.3 years.⁴⁰ The progression of drusen in four Finnish subjects over 1 to 6 years was documented in stereophotographs by Mustonen et al.⁴¹ Merchant et al reported improved diagnostic sensitivity of EDI-OCT relative to non-EDI OCT and ultrasound B-scan imaging.¹⁹ One study has suggested that the performance of SS-OCT is similar to EDI-OCT.¹⁸ The current study suggests that SS-OCT with volumetric analysis may permit earlier detection of deeply

buried drusen than SD-OCT and may be more effective in monitoring of their growth and calcification than other prior imaging technologies.

Non-EDI SD-OCT images were acquired as part of this study, but the posterior borders of the drusen could not consistently be distinguished by the graders in any patient (Figure 1). Therefore, calculation of drusen volume was not performed with the SD-OCT volume data. Other groups employing commercial SD-OCT instruments to study drusen also observed poor visibility of the posterior drusen border.^{7,10,11,12,13,18-20}

The small sample size of this study is a potential limitation. Optic nerve head drusen may have a different appearance in each patient, and SS-OCT may not be universally helpful in analyzing them. Figures 2 and 3 both illustrate the inherent variability of 3D drusen measurements using SS-OCT technology. The complete structure of ONHD can be difficult to discern, and this results in a coefficient of variation of 5.4% for intra-test variability despite time-intensive manual segmentation of ONHD borders. Manual delineation of ONHD borders remains challenging, because ONHD borders may appear both hyper-reflective and hypo-reflective in SS-OCT images. It is this variable appearance which hinders the development of reliable fully-automated analytical tools, so a partly manual approach might still be the best option when volumetric measurements are desired. Another limitation of the development of better software tools for quantitative evaluation of ONHD is the relative rarity of ONHD. For example, although our study hypothesized that drusen below about 0.2 mm³ may represent a critical threshold, below which visual field defects are not typically seen (Figure 3a), only a larger future study of perhaps routine SS-OCT scanning would uncover large enough numbers of asymptomatic ONHD cases to further test this hypothesis. The current study did not have any patients with ONHD but with normal visual fields. Another possible future study would be a longitudinal ONHD study to see if increase in ONHD size causes visual field progression. EDI-OCT has been reported to have similar performance to SS-OCT in imaging drusen,¹⁸⁻²⁰ so a future study which directly compares these technologies may be needed. However, despite the small sample size, this study did demonstrate the improved ability of SS-OCT over a commercially available SD-OCT to quantify drusen.

In conclusion, new 3D software has been developed to quantify optic nerve head drusen, and 3D images can be generated that depict drusen shape and location relative to the retinal surface. This 3D software can easily be extrapolated to other pathologies seen in SS-OCT images. SS-OCT visualization of the posterior drusen borders was enhanced compared to a commercially available SD-OCT machine. While optic nerve head drusen smaller than approximately 0.2 mm³ may produce no visual field defects, larger drusen may cause vision loss.

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Figure 1.

1(a): A swept source optical coherence tomography (SS-OCT) B-scan through the optic nerve head of the right eye of a 71.8 year old Caucasian female subject. The device is the Topcon DRI 1 (Topcon Medical Systems, Tokyo, Japan). 1(b): Manual segmentation (yellow border) of the drusen in 1(a). 1(c): Computer processing of the segmentation in 1(b). The identified drusen border (solid blue line) is filled in with a transparent blue-green color. 1(d): An en face reconstruction of the fundus from a volumetric dataset comprised of 64 SS-OCT B-scans. 1(e): An infrared reflectance photo (left) and spectral domain optical coherence tomography (SD-OCT) B-scan (right) through the optic nerve head of the right eye of the same subject in 1(a). The device is a Heidelberg Spectralis SD-OCT instrument (Heidelberg Engineering, Heidelberg, Germany).

Figure 2.

Data from the eyes of four patients. The image shows fundus photography (column 1), Humphrey visual field 24-2 testing (column 2), swept source optical coherence tomography reconstruction of optic nerve head drusen and the retinal surface (column 3) and swept source optical coherence tomography B-scans (column 4). Rows (a) and (b) show data from the right and left eyes of a 67 year old male subject and (c) and (d) from a 53 year old male subject. Rows (e) and (f) show data from the right and left eyes of a 58 year old female

subject and (g) and (h) from a 72 year old female subject. Color encodes the vertical position of the ONHD: yellow is high, green is low. (ONHD = optic nerve head drusen)

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Peripapillary retinal nerve fiber layer thickness versus optic nerve head volume

Figure 3.

(a) Correlation between optic nerve head drusen (ONHD) volume (mm^3) and the absolute value of the mean deviation (decibels) from Humphrey visual field testing. (b) Correlation between ONHD volume and global retinal nerve fiber layer thickness (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). (NAION = non-arteritic ischemic optic neuropathy) (c) A Bland-Altman diagram analyzing the reproducibility of ONHD volume measurements using swept source optical coherence tomography scans.

Table 1

The clinical characteristics of four optic nerve head drusen (ONHD) patients imaged with swept source optical coherence tomography. The ONHD volumes are the mean of measurements.

Patient	Sex/Age (years)	Eye	BVCA	Visual Field MD (dB)	Visual Field PSD (dB)	ONHD Volume (mm ³)	Global Retinal Nerve Fiber Layer Thickness (μm)	Concomitant Ocular Conditions
1	M/67.3	OD	20/20	-13.25	9.85	1.05	47	none
		OS	20/20	-11.75	6.79	0.76	43	
2	M/52.5	OD	20/20	-1.85	2.73	0.52	65	OHTN
		OS	20/20	-8.65	8.02	0.76	45	
3	F/57.5	OD	20/25	-5.65	5.23	0.58	57	none
		OS	20/20	-2.51	2.04	0.34	69	
4	F/71.8	OD	20/50	-17.86	9.8	0.24	34	NAION
		OS	20/40	-23.98	10.92	0.26	31	

BVCA - best corrected visual acuity, MD - mean deviation, PSD - pattern standard deviation, ONHD - optic nerve head drusen, M - male, F - female, OHTN - ocular hypertension, dB - decibels, NAION - non-arteritic ischemic optic neuropathy