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Clinicopathologic Correlation of Disc and Peripapillary Region Using SD-OCT

Eric J. Sigler^{*}, Kristy G. Mascarenhas^{*}, James C. Tsai^{*}, and Nils A. Loewen[†]

Division of Vitreoretinal Surgery, Charles Retina Institute, Memphis, Tennessee (EJS); Yale University School of Medicine, Department of Ophthalmology and Visual Science, New Haven, Connecticut (KGM, JCT); and Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (NAL)

Abstract

Purpose—To describe a technique for evaluating peripapillary and optic nerve head (ONH) anatomy using spectral domain optical coherence tomography (SD-OCT) raster scanning in humans and compare quantifiable parameters between diagnosis categories.

Methods—Ninety-five eyes of 51 consecutive patients were evaluated in this retrospective cross-sectional pilot study. Cirrus 5-line raster SD-OCTs with a resolution of 5 to 15 μm obtained through the ONH were included. A single observer manually measured neural canal opening (NCO), prelaminar canal depth (PLCD), peripapillary choroidal thickness (PPCT), and canal nerve fiber layer (CNFL) in normals, ocular hypertension, primary open-angle glaucoma (POAG), low-pressure glaucoma (LPG), secondary glaucoma, and early atrophic age-related macular degeneration. Clinical information, including central corneal thickness (CCT), was obtained via medical record review. Mean anatomical values within diagnosis categories were compared using one-way analysis of variance and multivariate analysis. Bivariate analysis was used to investigate relationships between continuous variables, and significant ($p < 0.05$) relationships were incorporated into the final statistical model.

Results—Horizontal NCO was significantly greater in eyes with LPG than that in normals ($p = 0.021$). The PPCT was thinner in age-related macular degeneration ($p = 0.001$) and glaucoma ($p = 0.004$) compared with that in controls (normals). Mean CNFL was thinner in POAG ($p < 0.001$) and LPG ($p = 0.053$) compared with that in normals. Vertical NCO was inversely correlated to CCT ($p = 0.013$). Multivariate analysis indicated a positive correlation between PLCD and PPCT ($p = 0.008$) and an inverse correlation between CNFL and PLCD ($p < 0.001$). Controlling for PPCT, PLCD and CCT were inversely correlated ($p < 0.001$).

Conclusions—The SD-OCT raster scanning may be used to quantify ONH anatomy in humans. The NCO differences between POAG and LPG may indicate a distinct structural vulnerability in LPG. In addition, CNFL, PPCT, and PLCD may be important parameters to consider in glaucoma. The PLCD correlates with PPCT and should be considered in new models of glaucoma pathogenesis.

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Nils A. Loewen, Eye and Ear Institute 203 Lothrop Street, Suite 819 Pittsburgh, PA 15213 loewenna@upmc.edu.

^{*}MD

[†]MD, PhD

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Keywords

Fourier domain OCT; spectral domain OCT; SD-OCT; low-pressure glaucoma; optic disc size; prelaminar canal depth; peripapillary choroidal thickness

The advent of spectral domain optical coherence tomography (SD-OCT) has brought about new insight into aspects of ocular anatomy that cannot be seen during slit lamp examination and provides a powerful tool for the evaluation of ocular disease. Optic nerve OCT has been previously described and is a validated method for evaluating the diagnosis and progression of glaucomatous optic neuropathy (GON).^{1–7} Current SD-OCTs use automated methods to determine the optic disc border, measure the peripapillary retinal nerve fiber layer (RNFL) thickness, and generate topographic graphs and maps to evaluate the optic nerve head (ONH).^{2,6,8,9} The SD-OCT allows for the fast, noninvasive, *in vivo* visualization of intraocular anatomy at the micrometer level.^{6–9} Although high-definition two-dimensional b-scan images of the optic nerve are feasible, these scans are not part of most clinical ONH protocols and are thus often overlooked or not performed in the evaluation of glaucoma.

Recent studies examined additional anatomical parameters^{10–12} that may be important in glaucoma risk, such as disc size,^{13–17} prelaminar tissue volume and distensibility,^{18–21} and peripapillary choroidal thickness.^{19,22–26} These variables have now been quantified in experimental monkey,^{18,19,27} rodent,²⁵ and porcine²⁸ models of glaucoma and highlight the importance of early changes in peripapillary structures²⁵ and the laminar insertion.²⁹ We hypothesized that (1) chronic intraocular pressure elevation, combined with specific ONH phenotypes, may lead to distention and thinning of the peripapillary choroid and disk border tissue, as evaluated by SD-OCT; and (2) ganglion cell axon layer may be quantified by the thickness of tissue central to the termination of Bruch membrane on SD-OCT and may correlate to the presence of glaucomatous optic neuropathy.

This descriptive pilot study set out to quantify several anatomical variables evident on SD-OCT raster scanning of the ONH to attempt to identify anatomical characteristics common in patients with GON. To our knowledge, this is the first morphology-based human SD-OCT raster scanning correlate to the above animal models. We compared anatomical variables including canal nerve fiber layer (CNFL), disc size (neural canal opening [NCO]), axial distance of disc border to lamina cribrosa (or prelaminar canal depth [PLCD]), and peripapillary choroidal thickness (PPCT) between eyes with disease and normals. We further emphasize the potential importance of manual, high-resolution, cross-sectional viewing of the ONH with SD-OCT as an adjunct to automated topography and in specific clinical situations.

METHODS

Patients

The study conformed to the tenets set forth in the Declaration of Helsinki and was approved by the Yale Human Investigations Committee. All patients were evaluated at the Yale Eye Center, Department of Ophthalmology and Visual Science, Yale University School of Medicine. Consecutive patients receiving OCT scans of the ONH were recruited for additional raster scanning during a 6-month institution-approved study period. A single operator performed all scans from November 2010 to April 2011. Power calculation for one-way analysis of variance (ANOVA) (five groups, $\alpha = 0.05$, $\beta = 2$) indicated a 90% chance of discovery of a 30- μm least significant difference between means for the anatomical variables considered, with a recruitment target of at least 42 samples. Cirrus SD-OCT (software version 5.1; Carl Zeiss Meditec, Dublin, Calif) high-definition 5-line raster gray

scale scans were performed both vertically and horizontally through the optic disc. This modality uses 4096 a-scans/b-scan (point-axial/brightness cross-sectional two-dimensional) and has an axial resolution of 15 μm and a transverse resolution of 5 μm .⁹ Raster scans 6 mm in length were manually aligned with the disc border and spaced 0.25 mm apart. Two 5-line raster scans were performed for each eye; one vertical at 90 degrees and one horizontal at 0 degrees. Fig. 1 shows an example of the scan protocol and b-scan image output. The data set therefore represented central, polar, and average values of ONH and peripapillary tissue thickness at 0 and 90 degrees. A single observer masked to diagnosis and patient initially identified and reviewed consecutive scans in the image database and excluded those with signal strengths less than 8/10. Additional inclusion criteria included the presence of a clearly defined posterior peripapillary choroidal border and a clearly defined anterior lamina cribrosa with a sharp linear transition in hyperreflectance at the anterior laminar surface. One hundred four scans met image protocol and signal strength requirements. Nine scans were excluded because of failure to meet additional clarity criteria. Ninety-five scans (91%) were included in the anatomical evaluation. All scans were assigned a computer-generated random number and were stripped of any additional information before viewing for measurement.

All anatomical variables were manually quantified in two dimensions by a single observer (author E.J.S.) using the Cirrus device caliper tool, and definitions are presented in Fig. 2. For disc size, NCO was defined as the distance between opposite borders of Bruch membrane termination, or the most proximal central extent of the anterior choroidal surface. The two most central raster measurements were used and averaged in both the horizontal meridian and vertical meridian for all polar variables.

For cup width, after the NCO was measured, the caliper line was retracted to the central border of the optic nerve fiber layer at the two most central rasters and averaged at each pole for both the vertical meridian and horizontal meridian. Thus, cup width was measured at the level of NCO. Vertical and horizontal cup-to-canal ratio (C/C) was then calculated separately by dividing cup width by NCO for both the vertical meridian and horizontal meridian. Cup depth was evaluated by extending three separate lines from the centralmost raster NCO line, both vertically and horizontally, to the anterior nerve fiber layer over the lamina cribrosa at the center of the NCO line and at 250 μm peripheral to this central point. This was performed horizontally and vertically (total, six data points) and averaged for the final overall cup depth measurement.

Optic nerve head thickness, or CNFL, was defined as the thickness of the ONH at the level of the NCO. This technique was used in an effort to ensure both a stable reproducible landmark with an anatomical basis and exclude any retinal tissue elements other than the ganglion cell layer at this location. After measurement of the NCO, the caliper line was retracted to the border of the nerve fiber layer at the level of the NCO measurement and the CNFL measurement obtained in the transverse plane as demonstrated. Because of the frequent presence of nasal quadrant vascular shadowing, we measured only the most peripheral extent of the nerve fiber layer up to but not including the vascular shadow in this location, as presented in Fig. 3. If the vascular shadow occurred at the canal border or immediately adjacent to the termination of Bruch membrane, CNFL measurement was only obtained if there was clearly bare nerve fiber layer present central to the vascular shadow and the central CNFL excluding the vascular shadow was used for the final measurement. Thus, there was an inherent underestimation of the nasal CNFL. We believe that this may approximate the minimum CNFL at this location (equivalent to subtracting all vascular shadowing, which represented all artifacts at this location, from the measurement). Vascular shadowing was a component of 17/95 nasal CNFL measurements and was absent from

measurements at all other poles. Finally, measurements from each pole were combined, and the overall average CNFL was calculated.

The PLCD was defined as the distance from the NCO border to the anterior lamina cribrosa surface. For the PLCD measurement, a line was drawn from the NCO border to the anterior laminar surface, and measurements from two separate rasters at each pole were obtained and averaged for the final measurement. Finally, each pole average was added, and the overall average PLCD was calculated.

Peripapillary choroidal thickness was measured from Bruch membrane to the anterior scleral surface. In contrast to an automated or disk-centric approach to this evaluation, an anatomical method was used to determine the location of the measurement relative to the disc (NCO) border. In both peripapillary OCT scans and postmortem histological sections, a peripapillary scleral flange can usually be seen adjacent to the ONH, extending from the neural canal border tissue to the base of the peripapillary choroid (Fig. 2). In this study, this occurred within 750 μm of the neural canal border in all identifiable scans. Choroidal thickness was measured perpendicular to Bruch membrane to the anterior scleral border at the base of this wedge for two separate rasters at each pole (Fig. 2). In 11 of 95 eyes, no distinct scleral flange was seen, and the choroid seemed flat adjacent to the neural canal. Therefore, the measurements were taken at 500 and 750 μm from the neural canal border and averaged. This was done at two separate rasters for each pole, values for each pole were combined, and the overall average PPCT was calculated. Subsequent to the anatomical quantification, a medical record review was performed and clinical variables including age, ethnicity, Goldmann intraocular pressure (IOP) applanation, diagnosis, central corneal thickness (CCT), Humphrey Visual Field (HVF) mean deviation, and spherical equivalent were recorded. Patients with decreased best-corrected visual acuity because of media opacity or retinal disease were excluded. Patients were assigned a diagnosis category and were divided into normal (no ocular disease), ocular hypertension (OHTN), low-pressure glaucoma (LPG), primary open-angle glaucoma (POAG), secondary glaucoma, and atrophic age-related macular degeneration (ARMD). To be classified as OHTN, IOP had to be above 21 mm Hg on two different visits and be free of GON by glaucoma specialist examination or SD-OCT rating as well as visual field defects. Low-pressure glaucoma signified pressures less than 21 mm Hg before treatment but progressive GON or GON matching a glaucomatous visual field defect, whereas POAG and secondary glaucoma patients had the same criteria but IOP had to be greater than or equal to 21 mm Hg. Patients were classified as having glaucomatous visual field damage if they had at two reliable standard automated perimetry examinations with either a pattern SD outside the 95% normal limits or a glaucoma hemifield test result outside the 99% normal limits. Only patients with drusen and without visually significant (best-corrected visual acuity 20/25 or better) retinal atrophy or choroidal neovascularization were included in the ARMD group, as established by a retina specialist.

Data Analysis

All data analysis was performed using JMP 9 (SAS, Cary, NC). Means $\pm$ SDs were compared between diagnosis categories for each anatomical variable. Means were compared using one-way ANOVA and verified using the Tukey-Kramer test. Pairwise differences in means were calculated via Student *t* test. Means were compared with those of controls (normals) using Dunnett method. Variables with a known impact on anatomical variables such as age and spherical equivalent were investigated using bivariate analysis for all anatomical variables. Any significant correlations identified were then controlled for in subsequent statistical evaluations. A linear multivariate model incorporating the bivariate interactions previously identified (PPCT weighted by age), including age, CCT, PPCT, HVF mean deviation, CNFL, vertical C/C, and PLCD, was then constructed to further investigate

significant variables. Pairwise correlations were generated with the restricted maximum likelihood method.

RESULTS

A total of 95 eyes were included in the following diagnosis groups: normal ($n = 32$), OHTN ($n = 13$), POAG ($n = 24$), LPG ($n = 7$), secondary glaucoma ($n = 11$), and ARMD ($n = 8$). The secondary glaucoma group consisted of exfoliation syndrome ($n = 5$), chronic angle closure glaucoma ($n = 3$), and uveitic glaucoma ($n = 3$). The overall mean age was 64 ± 21.2 years. Mean age for the subgroups were as follows: OHTN, 49 ± 13 years; normal, 50 ± 21 years; POAG, 79 ± 10 years; LPG, 77 ± 14 years; secondary glaucoma, 68 ± 10 years. The OHTN and normals were significantly younger than GON ($p < 0.015$ for all comparisons). Ethnic groups included were white ($n = 60$), African American ($n = 23$), Asian ($n = 2$), and Hispanic ($n = 10$). Eyes with OHTN were significantly more myopic than average, however, it should be noted that there were only two patients in the high myopia range, both in the normal group and between -6 and -8 diopter spherical equivalent.

There were no baseline differences in NCO between ethnic groups. Overall mean vertical NCO was $1565 \pm 172 \mu\text{m}$. Comparison of mean NCO by diagnosis category is presented in Fig. 4. Mean vertical NCO was not statistically different among groups from overall mean or from normals (mean, $1583 \mu\text{m}$; $p = 0.068$) using Dunnett method. Student t test did demonstrate a statistically larger vertical NCO among LPG eyes (mean, $1719 \mu\text{m}$) compared with OHTN (mean, $1509 \mu\text{m}$; $p = 0.011$) and compared with POAG eyes (mean, $1513 \mu\text{m}$; $p = 0.007$). Mean vertical NCO of LPG eyes was larger than normals and approached statistical significance by Student t test ($p = 0.061$). Overall mean horizontal NCO was $1523 \pm 155 \mu\text{m}$. Eyes with LPG had larger horizontal NCO (mean, $1696 \mu\text{m}$) compared with normals (mean, $1543 \mu\text{m}$; $p = 0.021$), OHTN (mean, $1494 \mu\text{m}$; $p = 0.007$), POAG (mean, 1440 ; $p < 0.001$), and ARMD (mean, $1521 \mu\text{m}$; $p = 0.034$) by pairwise comparisons using Student t test. Mean horizontal NCO for POAG eyes was less than for normals ($p = 0.015$) or secondary glaucoma (mean, $1570 \mu\text{m}$; $p = 0.024$). Mean CCT by diagnosis category was as follows: normal = $560 \pm 52 \mu\text{m}$; OHTN = $575 \pm 47 \mu\text{m}$; POAG = $535 \pm 43 \mu\text{m}$; LPG = $537 \pm 42 \mu\text{m}$; ARMD = $562 \pm 22 \mu\text{m}$. Vertical NCO was inversely correlated with CCT via first-order line fit in a bivariate model ($p = 0.013$) across all eyes. No significant correlation was found between horizontal NCO and CCT. Table 1 is a summary of mean PPCT by pole. There were no significant differences in PPCT among ethnic groups. Overall mean PPCT was $217 \pm 105 \mu\text{m}$. Dunnett method revealed statistically significantly thinner inferior PPCT compared with normals (mean, $281 \mu\text{m}$) for POAG (mean, $183 \mu\text{m}$; $p = 0.004$), secondary glaucoma (mean, $184 \mu\text{m}$; $p = 0.046$), and ARMD (mean, $123 \mu\text{m}$; $p = 0.001$). A thinner inferior PPCT was observed for LPG that approached statistical significance (mean, $169 \mu\text{m}$; $p = 0.056$). The pattern of thinner PPCT in patients with glaucoma and ARMD persisted throughout each quadrant and overall average PPCT. The most statistically significant values were observed for inferior PPCT.

There were no differences in CNFL between ethnic groups. Overall mean CNFL was $285 \pm 104 \mu\text{m}$. For inferior CNFL (mean, $300 \pm 121 \mu\text{m}$), a significantly thinner mean was observed for POAG (mean, $183 \mu\text{m}$; $p < 0.001$) and LPG (mean, $216 \mu\text{m}$; $p = 0.022$) compared with that in normals. Measurements at the inferior pole led to the greatest statistical differences between diagnosis categories. By Student t test, mean average CNFL was statistically thicker for normals than for POAG ($p < 0.001$) and LPG ($p = 0.011$). Table 2 is a summary of average CNFL by pole with significant differences in means by diagnosis. Table 3 is a summary of average PLCD by ONH quadrant.

There were no statistically significant differences in PLCD among diagnosis categories or between ethnic groups. Overall, mean average PLCD was $898 \pm 89 \mu\text{m}$. Mean average PLCD was shallowest for the ARMD group ($698 \pm 160 \mu\text{m}$) and was significantly more shallow than for the POAG group by Student *t* test ($p = 0.011$). A summary of PLCD by pole is shown in Fig. 8. Note, for diagnoses related to IOP-related pathology, PLCD was deepest for the superior pole. This is in contrast to those in normals and ARMD, in which the deepest pole was nasal. These differences did not reach statistical significance, however.

A multivariate model was constructed and included age, CCT, PPCT, HVF mean deviation, CNFL, vertical C/C, and PLCD. The PPCT was weighted by age within the model. Pairwise correlations were generated, and significant values are presented in Table 4. Mean deviation was negatively correlated with age and positively correlated with CNFL. The CNFL was negatively correlated with PLCD. The PLCD was positively correlated with vertical C/C ratio and with PPCT. We therefore constructed a bivariate model to further delineate the relationship between PLCD and PPCT. As a positive linear relationship was identified ($p = 0.008$), we then controlled for this variable and investigated the relationship between PLCD and CCT. This bivariate model demonstrated a highly significant linear inverse correlation between PLCD and CCT (PLCD, $2140 \mu\text{m} \cdot 2.1 \times (\text{CCT } \mu\text{m})$) ($p < 0.001$).

DISCUSSION

Standard SD-OCT is a useful method for investigating anatomical parameters of various ocular segments *in vivo* with high reliability and reproducibility.^{6–9} In this retrospective cross-sectional pilot study, we hypothesized that the ONH can be studied with high-resolution gray-scale imaging by quantification of various novel ONH parameters. Our findings suggest that this underused modality of SD-OCT allows discovery of details of the ONH and peripapillary tissue that are not usually considered with standard OCT protocols. The lamina cribrosa may be the primary location where axonal transport is impeded and cell injury occurs in glaucoma because of increased IOP.^{30,31} Although the degree of pressure reduction is well correlated to reduced visual field progression in POAG,^{32–34} this correlation is much less present in LPG.^{35,36} A recent study found a decreased lamina cribrosa thickness in LPG patients.^{11,12} We found a larger vertical and horizontal NCO in LPG than POAG that may indicate a specific anatomical vulnerability of LPG patients to IOP and IOP fluctuations. This finding is consistent with early descriptions of increased disc size in LPG.^{37–39}

Responses of prelaminar tissue to IOP changes have recently been examined in human subject and animal studies.^{18–21,25,27,29,40–45} By systematically measuring PLCD, we found a correlation of PLCD and PPCT in OHTN, normals, and GON. At the other end of the spectrum of ONH topography, this relationship may be reflected in the relatively shallow PLCD in ARMD in our study and, considering the relationship of PPCT to PLCD, is consistent with the recently described age-related choroidal atrophy.^{22,23} A recent study indicated that PLCD may be relatively resistant to acute IOP elevations in humans and that alterations occur primarily in prelaminar tissue depth (distance from retinal pigment epithelium termination to anterior prelaminar neural tissue; cup depth in the present study),²⁰ but that study lacked a control for the adjacent PPCT. In contrast, we found no differences in cup depth among glaucoma patients and normals. This is consistent with the finding in a histomorphometric analysis of monkey experimental glaucoma that early cupping consists predominantly of expansion of collagenous structures, and thickening, rather than thinning of prelaminar neural tissue,⁴¹ along with posterior displacement of the lamina cribrosa.^{27,29,41,42} By controlling for the relationship between PPCT and prelaminar depth, we found an inverse correlation between CCT and PLCD. Consistent with the description of an inverse correlation of CCT and disc size (area) by Pakravan et al.,¹⁶ we

saw a significant correlation of vertical, but not horizontal, disc diameter with CCT. We hypothesize that the glaucoma risk factor of a thin CCT^{46–48} may be related to increased IOP-related distention of prelaminar tissue rather than being primarily an underestimation of IOP,^{49,50} and that PPCT must be taken into consideration when evaluating PLCD or prelaminar tissue alterations. We postulate that a thin CCT in some patients may reflect a susceptible corneo-scleral phenotype that predisposes to prelaminar tissue distention, potentially disinsertion of the lamellar border tissue, and posterior stretching of CNFL (ganglion cell axons). This may underlie glaucoma pathogenesis.

Whereas current OCT RNFL measurements are a validated way of identifying glaucoma and progression,^{1–7,9} CNFL is an additional parameter that could be used when automated assessment yields indeterminate results or to evaluate prelaminar tissue in acute and subacute IOP elevation, similar to previous investigations.^{20,21,27,41,43,51} Our study supports the notion that one may quantify CNFL for areas of thinning at the level of the NCO. Mean deviation and age have both previously been demonstrated to correlate with ganglion cell axon structure and retinal nerve fiber layer thickness.^{7–9} Our findings were identical to these relationships when using CNFL as a measure of retinal nerve fiber layer axons. As axons are confined to a smaller circumferential space within the NCO compared with the peripapillary retina, measuring CNFL may lead to improved detection of glaucoma progression, especially in the temporal region, where pallor and tilt may lead to underestimation of true glaucomatous atrophy. We used a two-dimensional, morphology-based approach to ONH evaluation without a three-dimensional component. Current volumetric scans require increased acquisition times compared with 5-line raster scanning but have the advantage of computer averaging and progression analysis. Manual measurement and an observer-based morphologic analysis have the theoretical advantage of avoiding or identifying artifacts and incorporating specific anatomical details that are excluded from topographic analysis.

As seen in postmortem histologic correlations of a thin peripapillary choroid and decreased thickness of the choriocapillaris in glaucoma,^{52–54} our study indicates that a thin peripapillary choroid is associated with GON *in vivo* (Tables 1 and 4). Additional studies of the choroid in glaucoma have reported mixed results with either a thin,²² thick,^{55,56} or not significantly different²⁴ choroidal thickness in patients with glaucoma compared with normals and glaucoma suspects. Compared to these, we used a strict anatomical localization for PPCT measurement that accounted for disc size (NCO border) and manual quantification. It is possible that automated OCT measurements have a tendency to measure an oblique PPCT section and thus overestimate this parameter. The observation of a particularly thin peripapillary choroid among eyes with secondary glaucoma (Table 1) agrees with one previous histologic study of the peripapillary region in eyes with elevated IOP secondary to ciliary body melanoma.⁵³ Interestingly, ARMD patients had a particularly thin peripapillary choroid but no GON. It is possible that this is caused by a global choroidal atrophy that includes the macula, as opposed to a more focal peripapillary choroidal thinning in glaucoma.

As a retrospective cross-sectional analysis, this descriptive pilot study is limited by a small study population, small subgroups, and lack of age-matched controls. The data were obtained by manual measurements, which may initially make these parameters difficult to standardize between observers. In addition, patients with POAG, LPG, and OHT were recruited from glaucoma clinics at an academic medical center and may have more advanced disease than would be found in a wider population of glaucoma patients. The present study lacked the presence of a three-dimensional quantification parameter, which may be important in SD-OCT quantification of GON. Raster scanning also has several current limitations, such as lack of standardized proprietary interpretation algorithms, need for practitioner to make a morphologic interpretation, and quantification limited to cross-

sectional, two-dimensional locations that do not capture tissue thickness outside of raster locations. In addition, the scan pattern selected may be subject to artifact induced by patient movement, saccades, and media opacity. However, only signal strength of greater than 8/10 were included, and no saccade or movement artifact was evident in scans included.

Our data show that high-resolution increased depth assessment of the ONH with SD-OCT allows one to quantify parameters and correlate them to anatomical and clinical pathology in GON to potentially improve theories on glaucoma pathogenesis. We hypothesize that exposure of ganglion cell axons to an environment devoid of intervening compressible tissue elements (such as outer retinal layers or adjacent choroid) or the lengthening of such segments (increased PLCD or NCO) leads to increased susceptibility to IOP-related stress and cell death. This may occur at two locations: deep to the peripapillary RNFL where outer retina, retinal pigment epithelium, and choroid are absent because of an acquired or congenital etiology (e.g., peripapillary atrophy) and within the prelaminar ONH, adjacent to the prelaminar border tissue, which is captured in the length of CNFL throughout PLCD in the present study. Thus, ganglion cell axons exist with only vitreous and sclera adjacent to their boundaries at two potential locations, peripapillary atrophy or within the prelaminar canal. Theoretically, posterior displacement of the lamina cribrosa combined with thinning of peripapillary tissue would increase the length of this neural segment of the ONH without support structures. This could lead to mechanical stretching of axons, impedance to cellular transport and ischemia, and may explain how increased disc size, increased PLCD, and thin PPCT may be important in glaucoma pathogenesis.

The appearance of a thin elongated ONH region seems to be possible in human GON, similar to that seen in experimental glaucoma. We conclude that evaluation of the ONH using high-resolution SD-OCT raster scanning in humans can provide quantifiable parameters that correlate with known patterns of anatomical and clinical pathology in GON. Increased disc size (NCO) seems to be related to CCT and may be associated with LPG. The PLCD is related to PPCT and may have an inverse correlation with CCT. A thin PPCT seems to be associated with advanced age, ARMD, and glaucoma. The ability to quantify these papillary and peripapillary changes at high resolution may allow enhancement of current and future models of glaucoma pathogenesis. In particular, a physician-observer-based anatomical approach to the cross-sectional evaluation of the ONH with SD-OCT seems feasible and may enhance currently used clinical ONH examinations.

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FIGURE 1.

Cirrus SD-OCT ONH scan protocol and examples: (A) vertical 5-line raster centered on the ONH with a 6-mm raster length and a 0.25-mm raster spacing; (B) horizontal 5-line raster centered on ONH; (C) gray-scale B-scan image in a normal subject with no cross-sectional cup at the level of Bruch membrane; (D) cross-sectional cup of patient with ocular hypertension; (E) POAG with visual field defects and severe ONH tissue loss proximal to termination of Bruch membrane at the temporal border.

FIGURE 2.

OCT measurements (green caliper tracings) and definitions. (A) NCO: distance between opposite terminations of Bruch membrane or the most central extent of the anterior choroidal surface; (B) cup width: after NCO was determined, the line was retracted to the neural border to obtain this measurement; (C) cup depth: three parallel lines were extended from the NCO line at the center of the optic nerve and at 250 μm peripheral to the center; (D) PLCD: measured from NCO border to the anterior lamina cribrosa surface; (E) anatomical localization of the PPCT: in 84 of 95 eyes, a peripapillary choroidal wedge was seen adjacent to the scleral flange (asterisk), and PPCT was measured at the base of this triangle (within 750 μm of NCO border in all eyes) from the base of the retinal pigment epithelium to the anterior scleral surface (left); (F) CNFL: distance along NCO from border to most proximal extent of nerve fiber layer.

FIGURE 3.

Method for assessing CNFL in the presence of nasal vascular shadowing. (A) SD-OCT demonstrating CNFL (green caliper tracing) with adjacent vascular shadow (asterisks): the vascular shadow was not included in the final measurement; in this case, there is no clear neural tissue central to the vascular shadow; (B) SD-OCT demonstrating vascular shadowing beginning at the most peripheral border of NCO: there is clear neural tissue central to the vascular shadow, therefore, CNFL was measured central to the shadow; (C) A vascular shadow is present within the CNFL: with clear neural tissue on either side of the shadow, CNFL was measured both central and peripheral to the shadow and the values combined.

FIGURE 4.

Comparison of NCO among diagnosis categories. (A) One-way ANOVA for vertical NCO in micrometers for various diagnoses included ($p = 0.068$). OHTN, ocular hypertension; POAG, primary open-angle glaucoma; LPG, low-pressure glaucoma; nl, normal; ARMD, age-related macular degeneration; sec, secondary. Diamonds centered on mean, horizontal width proportional to sample size, vertical height spans 1 SD. (B) Analysis of variance for horizontal NCO depicted as for A. *Significantly ($p < 0.05$) different from OHTN and normals by Student t test pairwise comparison; †Significantly different from overall mean by one-way ANOVA ($p = 0.006$).

TABLE 1

Summary of average peripapillary choroidal thickness by optic nerve head quadrant in micrometers

Diagnosis	Inferior	Superior	Nasal	Temporal	Average
Normal	281	303	301	297	296
OHTN	231	290	310	281	284
POAG	183 *	249	246	237	229
LPG	169 *	195	216	219	200
ARM	123 *	149 *	186 *	163 *	156 *
Secondary glaucoma	184 *	217	179 *	166 *	193 *

* Statistically significantly ($p < 0.05$) different from normal controls by Dunnett method.

[†]OHTN, ocular hypertension; POAG, primary open-angle glaucoma; LPG, low-pressure glaucoma; ARM, atrophic age-related macular degeneration.

TABLE 2

Summary of average canal nerve fiber layer thickness by optic nerve head quadrant in micrometers

Diagnosis	Inferior	Superior	Nasal	Temporal	Average
Normal	363	308	335	326	326
OHTN [†]	382	383	354	360	360
POAG [†]	183 [*]	208 [*]	229 [*]	205 [*]	205 [*]
LPG [†]	216 [*]	176 [*]	311	214 [*]	214 [*]
ARMD [†]	380	400	396	348	372
Secondary glaucoma	267	253	271	241	259

* Statistically significantly different ($p < 0.5$) than normal controls by Dunnett method.

OHTN, ocular hypertension; POAG, primary open-angle glaucoma; LPG, low-pressure glaucoma; ARMD, atrophic age-related macular degeneration.

TABLE 3

Summary of average prelaminar canal depth by optic nerve head quadrant in micrometers

Diagnosis	Inferior	Superior	Nasal	Temporal	Average
Normal	910	965	978 *	820	917
OHTN	892	920 *	907	760	870
POAG	944	1032 *	929	874	953
LPG	821	914 *	831	848	854
ARMED	711	712	746 *†	623	698
Secondary glaucoma	928	1026 *	927	862	936

* Maximum value for diagnosis category.

† Significantly ($p = 0.011$) different from POAG by Student t test pairwise comparison.

OHTN, ocular hypertension; POAG, primary open-angle glaucoma; LPG, low-pressure glaucoma; ARMED, age-related macular degeneration.

TABLE 4Multivariate analysis of clinical and anatomical optic nerve variables^{*}

Variable	By variable	Correlation	p
Mean deviation	Age	−0.3066	0.007
C/C vertical	Age	0.2439	0.017
C/C vertical	Mean deviation	−0.4541	<0.001
C/C vertical	CCT	−0.2845	0.034
C/C vertical	PLCD	0.3585	0.001
PPCT [†]	PLCD	0.2719	0.008
CNFL	Mean deviation	0.6622	<0.001
CNFL	PLCD	−0.3966	<0.001
CNFL	PPCT [†]	0.2005	0.051

^{*} Significant ($p < 0.05$) pairwise correlations generated from multivariate analysis of seven variables (restricted maximum likelihood method).

[†] PPCT weighted by age within multivariate model.

C/C, cup/canal ratio; PPCT, average peripapillary choroidal thickness; CNFL, average canal nerve fiber layer; PLCD, prelaminar canal depth.