Measurement of the Optic Disc Vertical Tilt Angle With Spectral-Domain Optical Coherence Tomography and Influencing Factors

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• PURPOSE: To report a novel method for measuring the vertical tilt angle of the optic nerve (ON) head and to investigate the associated factors.
• DESIGN: Cross-sectional diagnostic study.
• METHODS: One hundred and twelve normal, glaucomatous, and glaucoma suspect eyes (99 patients) were enrolled in this study. Subjects underwent a full eye examination, biometry, and spectral-domain optical coherence tomography (SDOCT). The vertical tilt angle was measured on high-resolution cross-sectional SDOCT images passing through the ON head and foveal centers using the inner edges of the Bruch membrane opening as the reference plane. The correlation between the vertical tilt angle with the ovality index and the potential associated factors was estimated with univariate and multivariate linear regression analyses.
• RESULTS: The median (interquartile range, [IQR]) axial length and visual field mean deviation were 24.5 (23.8-25.3) mm and −0.9 (−2.76 to 0.26) dB. The median (IQR) tilt angle was 3.5 (1.2-11.2) degrees. There was a moderate correlation between the ovality index and tilt angle (Spearman $\rho = 0.351$; $P < .001$). In univariate analyses, axial length, spherical equivalent, and mean deviation were correlated with the tilt angle ($P = .002$, $P = .011$, and $P = .013$, respectively). Axial length, mean deviation, and their interaction showed a statistically significant correlation with the tilt angle in multivariate analyses ($P = .044$ for axial length, $P = .039$ for mean deviation, and $P = .028$ for their interaction).
• CONCLUSIONS: We describe a new method for measuring the ON head vertical tilt angle with high-resolution SDOCT imaging. The ovality index demonstrated only a moderate correlation with the tilt angle measurements and hence is not a good proxy measure for the vertical ON head tilt angle. Axial length and visual field mean deviation are the main factors associated with the ON head vertical tilt angle. The underlying basis for the relationship of vertical tilt angle and glaucoma severity should be further explored. (Am J Ophthalmol 2013;156:737–744. © 2013 by Elsevier Inc. All rights reserved.)

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EVALUATION OF THE OPTIC NERVE (ON) HEAD IS AN essential part of a thorough eye examination. The optic nerve usually follows a slightly oblique course (tilt around the vertical axis) when leaving the eye, and in some eyes—particularly myopic eyes—the vertical tilt of the ON head is significant and can be appreciated ophthalmoscopically. In cases where there is significant vertical tilt, the ON head is seen as vertically oval because of the oblique angle of observation. Although ON head tilt has been described as a congenital anomaly of the optic nerve, there is recent evidence that it may also be acquired secondary to expansion of the posterior sclera in myopic eyes[1,2] and is commonly associated with significant temporal peripapillary atrophy.[3]

The presence and the degree of the ON head vertical tilt has been traditionally estimated based on subjective clinical evaluation of the optic disc in many published studies.[4–6] Simple objective methods for measuring the ON head vertical tilt angle have been developed according to optic disc shape and include ovality and tilt indices.[7] We herein report a new method for quantitative measurement of the ON head vertical tilt angle with spectral-domain optical coherence tomography (SDOCT). We also explored factors associated with vertical ON head tilt angle in a series of normal eyes, glaucoma suspects, and eyes with glaucoma.

METHODS

• STUDY SUBJECTS: The study subjects of this cross-seectional study were prospectively enrolled from a larger study (UCLA OCT Imaging Study). This study was approved by the Institutional Review Board at University of California Los Angeles (UCLA) and was carried out in accordance with the Declaration of Helsinki. Patients with a definite or suspected diagnosis of primary open-angle glaucoma (POAG) were prospectively identified

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and invited to be enrolled in the study if they met the following criteria: age ≥30 years, open angles, visual acuity ≥20/80, visual field mean deviation ≥−15 dB, refractive error ≤8.0 diopters (D), and astigmatism ≤3 D. Eyes with evidence of retinal or neurologic diseases or prior glaucoma surgery were excluded. A group of normal subjects recruited through advertising throughout UCLA or spouses of patients visiting the glaucoma clinic at the Jules Stein Eye Institute were also enrolled. The normal subjects were required to have no history of significant eye disease and a normal eye examination, including normal visual acuity (20/25 or better) and normal optic nerve head and visual fields.

• **EYE EXAMINATIONS:** All subjects underwent a comprehensive eye examination on the day of the imaging, which included the following: visual acuity, automated refraction, intraocular pressure (IOP) measurement, gonioscopy, slit-lamp examination, dilated fundus examination, and achromatic (standard achromatic perimetry, SAP) or short-wavelength automated perimetry (SWAP) fields. The axial length and keratometry were measured with the IOLMaster (Carl Zeiss Meditec, Dublin, California, USA). Central corneal thickness measurements were abstracted from patient charts, if available, or measured with a DGH 55 Pachmate (DGH Technology, Inc, Exton, Pennsylvania, USA). Optic disc photographs were reviewed by 2 experienced clinicians (K.N.M. and J.A.G.) and classified as glaucomatous, indeterminate, or normal. Evidence of glaucoma was based on the appearance of the neuroretinal rim, cup-to-disc asymmetry, retinal nerve fiber layer loss, and presence of disc hemorrhage, if any, but no formal criteria were used by the reviewers. In case of disagreement on classification of individual disc photographs, the final decision was adjudicated by a third reviewer (J.C.).

• **VISUAL FIELD ASSESSMENT:** The Swedish Interactive Thresholding Algorithm (SITA) standard testing strategy was used for both SAP and SWAP tests. Reliable visual fields were defined as those with a fixation loss or false-negative rate ≤33% and false-positive rate ≤20%. The visual fields were reviewed to exclude lid or lens artifacts. An abnormal SAP or SWAP visual field was defined as presence of a Glaucoma Hemifield Test (GHT) outside normal limits and presence of ≥4 abnormal test locations on the pattern deviation plot with $p < 5\%$, both confirmed at least once. These criteria have been shown to be highly specific and sensitive to early glaucomatous visual field loss.[8] Perimetric glaucoma was defined as evidence of reproducible visual field loss on SAP or SWAP regardless of IOP or disc appearance. Eyes with evidence of glaucomatous optic neuropathy based on review of stereoscopic disc photographs with normal or borderline SAP or SWAP visual fields (ie, visual fields that did not meet the criteria mentioned above for abnormality) were considered to be glaucoma suspects.

• **IMAGING AND IMAGE PROCESSING PROCEDURES:** The following imaging procedures were performed after dilation:

- Stereoscopic disc photographs: 35-mm ON head slides were scanned to high-resolution (2400 dpi) digital images with a Nikon slide scanner (Nikon LS-50 ED; Nikon Inc, Shinjuku, Tokyo, Japan).
- The HD 5-line raster imaging mode of the Cirrus HD-OCT (Carl Zeiss Meditec, Inc) was used to obtain a high-resolution cross-sectional image of the retina along a 9-mm line passing through the central part of the disc and the fovea. The line extended from the nasal side of the disc to well beyond the fovea. The single-line mode of the HD 5-line raster scan performs 4096 consecutive axial scans along the same predetermined line and the measurements are repeated 4 times and averaged to provide the final image.

Two experienced ophthalmic photographers with extensive experience in imaging with SDOCT performed all the imaging. If the OCT image quality was poor, as judged by the photographer performing the examination, imaging was repeated to obtain a better-quality scan. Inclusion criteria for OCT images were: (1) good linear raster OCT quality (signal strength >6); (2) good-quality en face OCT images so that adequate image registration could be done; (3) no retinal or optic nerve pathology or anomaly (other than possible vertical disc tilt); and (4) no motion artifacts on en face or linear raster OCT image. All the images were reviewed afterwards by one of the investigators (H.H.) and images with a signal strength of <6, obvious artifacts, or significant retinal pathology were excluded.

• **TILT INDEX AND TILT ANGLE MEASUREMENTS:** The digitized disc photographs were exported to Microsoft Office PowerPoint software (Microsoft Corporation, Redmond, Washington, USA) and an ellipse of best fit was defined for each disc while viewing the stereoscopic photographs. The vertical and horizontal diameters of the fitted ellipse were recorded in pixels. The "*ovality index*" was calculated by dividing the vertical disc diameter (ie, the disc diameter within 20 degrees of the vertical midline) by the horizontal disc diameter.[7]

The tilt angle was measured using cross-sectional HD 5-line raster image of Cirrus OCT as described here:

1) Color fundus photographs were manually registered to en face SDOCT images with Adobe Illustrator CS4 software (Adobe Systems Incorporated, San Jose, California, USA). Transparency of the color fundus photographs was set to 50% to allow visualization of the underlying en face image. Retinal vessels were used as guidelines to make a precise overlay image.
2) The corresponding cross-sectional linear SDOCT scan was then aligned under the overlay image with the blue-green scan line on the en face image (green line

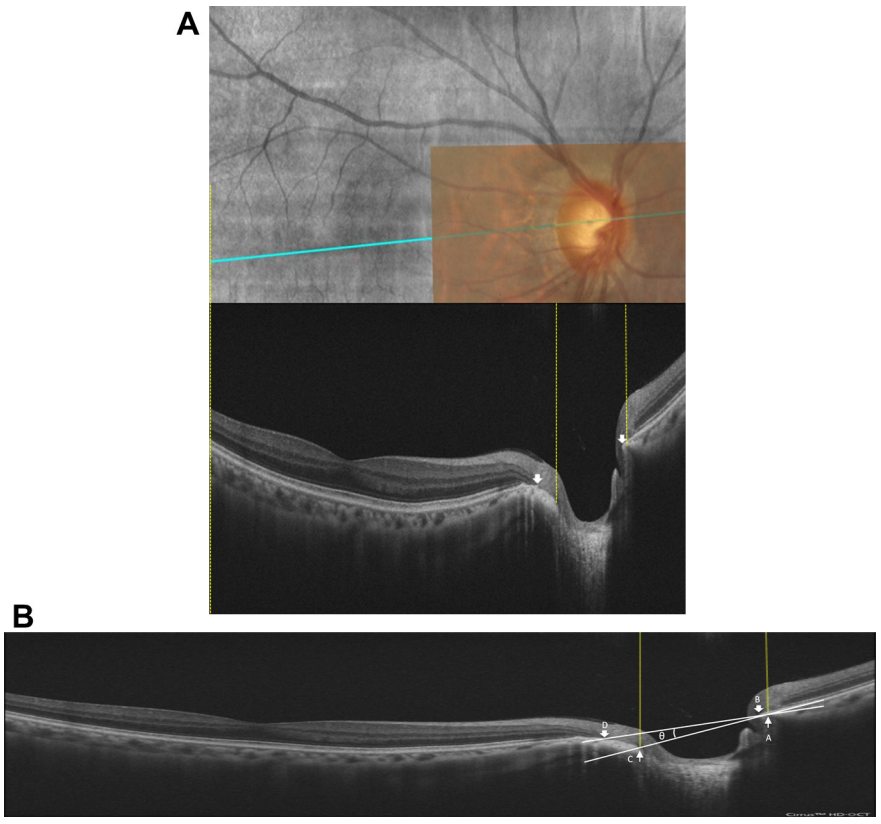

FIGURE 1. Methods used to estimate the vertical optic nerve head tilt angle with spectral-domain optical coherence tomography (SDOCT). (A) The triple overlay image used for marking the landmarks on the linear SDOCT scan consisted of a color fundus photograph, the en face SDOCT image, and the corresponding cross-sectional linear SDOCT image. By aligning the 3 images, we were able to mark the main landmarks on the linear SDOCT images. The yellow lines mark the clinical boundary of the disc and were continued downward to locate the respective points on the SDOCT image. The arrows show the inner edges of the Bruch membrane on each side of the optic nerve head. (B) The line BD, connecting the inner edges of the Bruch membrane on each side of the optic nerve head, was defined as the *reference plane*. The line AC connecting the 2 points marking the clinical disc margin on the SDOCT image (points A and C) was considered as the *optic nerve head plane*. The vertical tilt angle was defined as the angle between the reference and the optic nerve head planes (θ).

on Figure 1A). In this triple overlay image corresponding points on the color fundus photograph or en face OCT image are aligned with those on the linear scan.

3) The triple registered image was then exported to PowerPoint and while viewing stereo fundus photographs, the locations where the scan line crossed the temporal and nasal disc borders were identified and vertical lines were dropped down to determine the anatomic location corresponding to the temporal and nasal clinical disc borders on the cross-sectional linear SDOCT scan (Figure 1A and B).
4) The HD5 images were imported into ImageJ software (version 1.43u, National Institutes of Health, Bethesda, Maryland, USA; http//rsb.info.nih.gov//ij) and rescaled.
5) A line (line BD) connecting the inner tips of the Bruch membrane on each side of the ON head on the cross-sectional SDOCT image (points B and D, Figure 1B) was drawn and set as the *reference plane*.
6) A line (line AC) connecting the 2 points marking the clinical disc margin along the SDOCT scan was considered the *ON head plane* (Figure 1B). The disc border points (points A and C in Figure 1B) were where the yellow lines intersect the inner surface of the disc (Figure 1B).
7) The vertical tilt angle (angle θ) was defined as the angle between the reference plane (line BD) and ON head plane (line AC). Angle measurements were performed with the "angle tool" in the ImageJ software. Based on our method, a positive tilt angle represents vertical tilt as it is understood clinically, that is, the temporal edge of the disc is located more posterior than the nasal edge.

• **STATISTICAL ANALYSES:** The distribution of continuous parameters was verified with normal quartile plots and the Wilk-Shapiro test. Correlations between tilt angle and

potential associated factors such as age, ovality index, axial length, mean deviation (MD), spherical equivalent, and IOP were explored using bivariate scatterplots and univariate analyses. Multivariate linear regression analyses were performed to determine factors affecting the tilt angle in the study sample, taking into account the correlation of the 2 eyes from patients who had both eyes included. Statistical analyses were performed with Stata software (version 11.2, Stata Corp, College Station, Texas, USA). *P* values less than .05 were considered to be statistically significant.

RESULTS

ONE HUNDRED AND TWELVE EYES (FROM 99 PATIENTS) WERE included in this study. Table 1 shows the demographic and baseline characteristics of the enrolled patients. There were 39 normal eyes, 40 glaucoma suspects, and 33 glaucoma eyes. The median (interquartile range [IQR]) axial length and spherical equivalent were 24.5 (23.8-25.3) mm and −0.25 (−2.35 to +0.50) D, respectively.

Figure 2A through C demonstrates the distribution of the axial length, the vertical ON head tilt angle, and the ovality index, respectively, in the study sample. Both the vertical tilt angle and the ovality index showed a skewed distribution to the right, that is, a disproportionately higher prevalence of a higher ovality index or vertical tilt angle. The median (IQR) tilt angle was 3.5 (1.2-11.2) degrees. Figure 3 shows that the ovality index only partially predicted the vertical ON head tilt angle ($r = 0.484$, $P < .001$). Figure 4 demonstrates the correlation of the axial length with the tilt angle ($r = 0.399$, $P < .001$). Visual field severity based on MD had a negative correlation with the tilt angle ($r = -0.356$, $P < .001$; Figure 5).

Table 2 describes the results of the univariate analyses for factors potentially affecting the tilt angle. In univariate analyses, the axial length ($P = .002$), the spherical equivalent ($P = .011$), and the visual field MD ($P = .013$) had a statistically significant association with the vertical ON head tilt angle. The axial length, the MD, and their interaction showed statistically significant correlations with the vertical tilt angle in multivariate analyses (Table 3 and Figure 6).

TABLE 1. Demographic and Baseline Characteristics of the Study Sample of 112 Eyes From 99 Control Subjects and Patients With Suspected or Definite Glaucoma Enrolled to Measure the Optic Nerve Head Vertical Tilt Angle

Variables	
Number of eyes (patients)	112 (99)
Laterality (right/left)	92/20
Age (mean ± SD, y)	64.2 ± 9.3
Sex (female/male)	65/34
Ethnicity	
White, n (%)	69 (69.7%)
Asian	13 (13.1%)
African American	9 (9.1%)
Hispanic	6 (6.1%)
Other	2 (2.0%)
Diagnosis (eyes), n (%)	
Normal	39 (34.8%)
Glaucoma suspect	40 (35.7%)
Glaucoma	33 (29.5%)
Phakic/pseudophakic (eyes)	89/23
Visual acuity (median and IQR, logMAR)	0.10 (0-0.10)
Spherical equivalent (median and IQR, diopters)	−0.25 (−2.4 to +0.5)
Axial length (median and IQR, mm)	24.5 (23.8-25.3)
Central corneal thickness, (mean ± SD, μm)	557 ± 41
Keratometry reading (median and IQR, diopters)	43.5 (42.5-45.0)
Mean deviation (median and IQR, dB)	−0.9 (−2.76 to 0.26)
Pattern standard deviation (median and IQR, dB)	2.0 (1.6-3.1)
Intraocular pressure on the examination day (mean ± SD, mm Hg)	14.2 ± 3.3
Tilt angle (median and IQR, degrees)	3.5 (1.2-11.2)

IQR = interquartile range; LogMAR = logarithm of minimal angle of resolution.

DISCUSSION

WE DESCRIBED A NEW METHOD FOR MEASURING THE ON head vertical tilt angle with high-definition linear SDOCT images. This is a task that was virtually impossible before the advent of the current generation of SDOCTs. Our findings indicate that surrogate measures such as the ovality index are not good proxies for the assessment of the degree of optic nerve head vertical tilt. We also explored factors associated with the ON head vertical tilt angle and found that longer axial length and worse glaucoma severity, as determined by the visual field MD, and their interaction were the main statistical predictors for a larger ON head vertical tilt.

The magnitude of the ON head vertical tilt has long been determined through subjective estimation. In many prior studies, presence or absence of a tilted disc was adjudicated by experienced clinicians. This is probably why no consensus on the definition of a "tilted" ON head has been reached.[3] It is possible that the entity named "tilted disc" represents various morphologies of the disc that have all been lumped together. Since actual measurement of the ON head vertical tilt has not been possible to date, surrogate measures such as optic disc ovality, torsion, or tilt indices have been used.[9]

With the current generation of SDOCT, high-resolution images can be acquired that demonstrate, in vivo, anatomic structures both within and surrounding the optic nerve

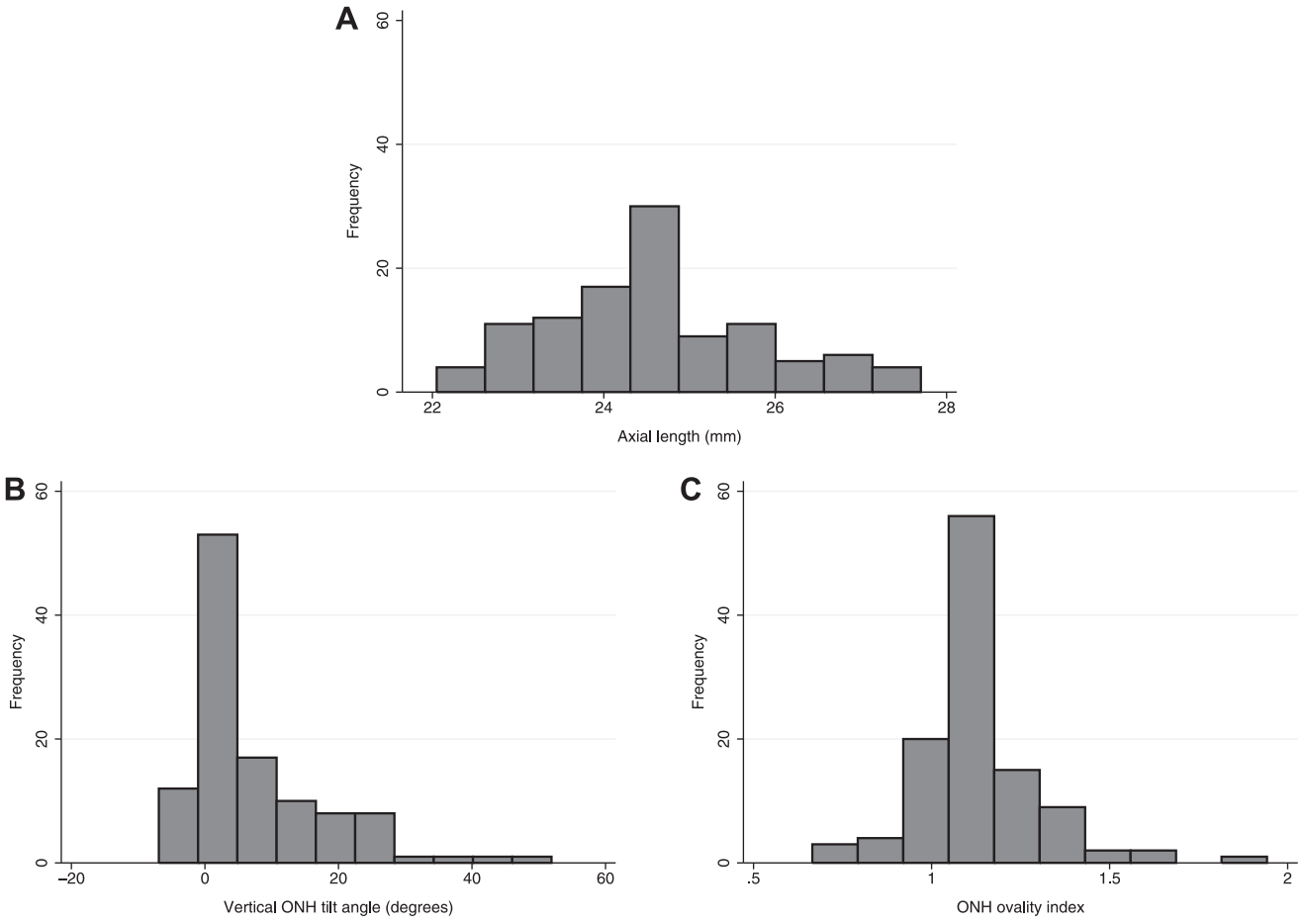

FIGURE 2. Frequency distribution of the axial length (A), the optic nerve head vertical tilt angle (B), and the optic nerve head ovality index (C) in the study sample, which consisted of 112 eyes from 99 control subjects and patients with suspected or definite glaucoma enrolled to measure the vertical optic nerve head tilt angle.

head, such as the inner edge of the Bruch membrane, lamina cribrosa, choroid, and various retinal layers. With high-resolution cross-sectional images of the optic nerve, we were able to measure the ON head vertical tilt angle by defining a reference plane based on the inner borders of the Bruch membrane to compensate for potential image tilt. Our study sample was biased towards eyes with longer axial length and higher myopia, as reflected by the skewed appearance of the axial length histogram (to the right) in Figure 2A. This was actually an advantage for the goals of this study, since it provided a wide spectrum of ON head vertical tilt angles for statistical analyses. Measurement of the vertical tilt angle has been recently reported with images obtained using the Cirrus SDOCT (200 × 200 Optic Disc Cube).[10] However, the authors did not address the major issue of image tilt that could adversely affect such measurements. Thus, we believe our method provides a superior approach by using a fairly stable reference plane for such measurements (ie, edges of the Bruch membrane).

An interesting finding was that the ovality index only moderately correlated with the tilt angle. This highlights the poor accuracy of surrogate measures for the tilt angle and emphasizes the need for an accurate and standard method for measuring the vertical ON head tilt angle. The ovality index is influenced not only by the amount of postnatal expansion of the posterior sclera[2] but also by the original shape of the neural canal opening. Similar to our findings, Kim and associates[2] found that the relationship between the increasing tilt angle and myopia was not as strong as expected. We speculate that other factors, such as scleral rigidity and the region of sclera undergoing expansion (ie, temporal to the ON head vs temporal and nasal to the ON head), among others, are likely at work.

Univariate regression analyses indicated that longer axial length, more myopic spherical equivalent, and worse visual field MD were associated with a larger vertical ON head tilt angle. Multivariate analyses suggested that the axial length and visual field MD and their interaction remained statistically significant predictors of the ON head vertical tilt angle in this group of patients. The association of higher myopia and tilted disc is well established in the literature.[4–6,11] As noted above, an increase in the

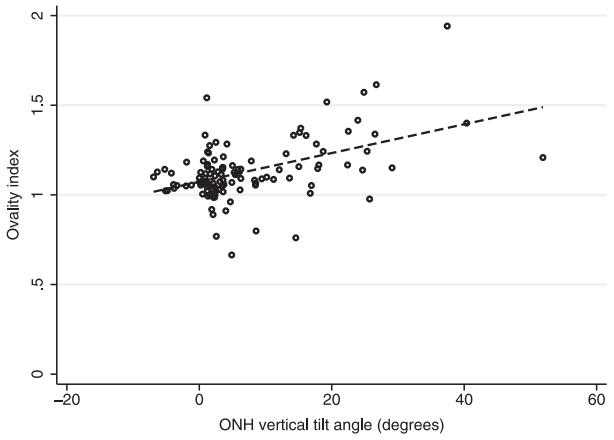

FIGURE 3. Scatterplot showing the correlation between the optic nerve head ovality index and the optic nerve head vertical tilt angle ($r = 0.484$, $P < .001$) in the study sample, which consisted of 112 eyes from 99 control subjects and patients with suspected or definite glaucoma.

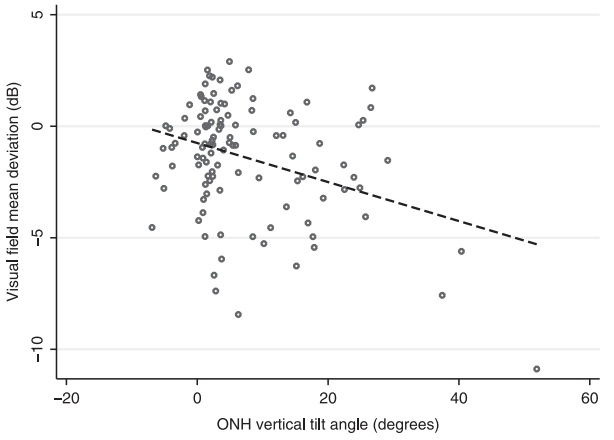

FIGURE 5. Scatterplot showing the correlation between visual field loss as indicated by mean deviation and the optic nerve head vertical tilt angle ($r = -0.356$, $P < .001$) in the study sample, which consisted of 112 eyes from 99 control subjects and patients with suspected or definite glaucoma.

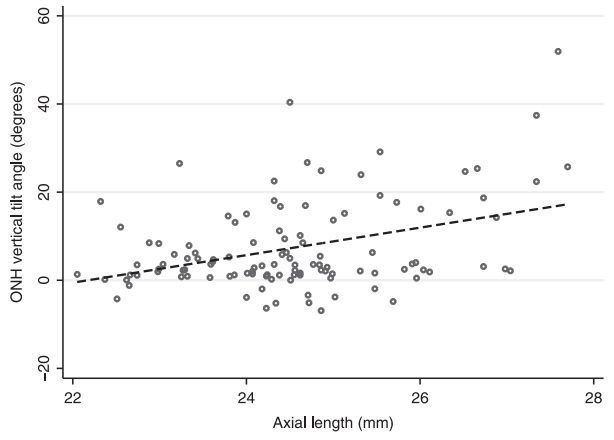

FIGURE 4. Scatterplot demonstrating the correlation between the axial length (mm) and the vertical optic nerve head tilt angle ($r = 0.399$, $P < .001$) in the study sample, which consisted of 112 eyes from 99 control subjects and patients with suspected or definite glaucoma enrolled to measure the vertical optic nerve head tilt angle.

TABLE 2. Association of Potential Clinical and Biometric Parameters With the Vertical Optic Nerve Head Tilt Angle Based on Univariate Analyses in 112 Eyes From 99 Control Subjects and Patients With Suspected or Definite Glaucoma Enrolled to Measure the Optic Nerve Head Vertical Tilt Angle

Variables	Coefficients (95% CI)	*P* Value
Age (per y)	0.10 (−0.21-0.42)	.514
Sex (reference: male)	−4.10 (−9.51-1.31)	.135
Axial length (per mm)	3.28 (1.27-5.29)	.002
Spherical equivalent (per diopter)	−1.20 (−2.12 to −0.27)	.011
Lens status (reference: phakic)	5.09 (−1.92-12.10)	.153
Central corneal thickness (per μm)	0.024 (−0.03-0.07)	.346
Intraocular pressure (per mm Hg)	0.23 (−0.36-0.81)	.443
Keratometry reading (per diopter)	−0.55 (−1.87-0.77)	.403
Mean deviation (per dB)	−1.42 (−2.53 to −0.31)	.013

CI = confidence interval.

vertical ON head tilt angle can occur postnatally.[2] The lack of an association between spherical equivalent and vertical ON head tilt angle on multivariate analyses can be explained by the high correlation between the axial length and refractive error ($r = -0.59$ for the entire group and $r = -0.73$ for phakic eyes) and inclusion of pseudophakic eyes in our study. Alternatively, one could argue that the axial length represents a better measure of eye size and its enlargement than the spherical equivalent, especially in eyes with truly axial myopia where a vertical ON head tilt is expected to occur more frequently. A closer look at Figure 4 shows that not all longer eyes have a vertical tilt significantly different from average eyes—that is, there is significant variability in the vertical ON head tilt angle even in very long eyes. We hypothesize that this is a consequence of regional distribution of posterior scleral expansion. Eyes in which most of the expansion occurs temporal to the ON head would have increased vertical ON head tilting, whereas eyes in which the expansion is fairly symmetrical around the ON head would have less or no significant vertical tilting of the optic disc. We should point out that, in this study, our main goal was to measure

TABLE 3. Results of Multivariate Analyses to Identify Factors Associated With the Optic Nerve Head Vertical Tilt Angle in 112 Eyes From 99 Control Subjects and Patients With Suspected or Definite Glaucoma

Variables	Coefficient (95% CI)	*P* Value
Axial length (per mm)	1.54 (0.04-3.04)	.044
Mean deviation (per dB)	14.71 (0.77-28.66)	.039
Interaction of axial length and mean deviation	−0.63 to (−1.19 to −0.070)	.028

CI = confidence interval.

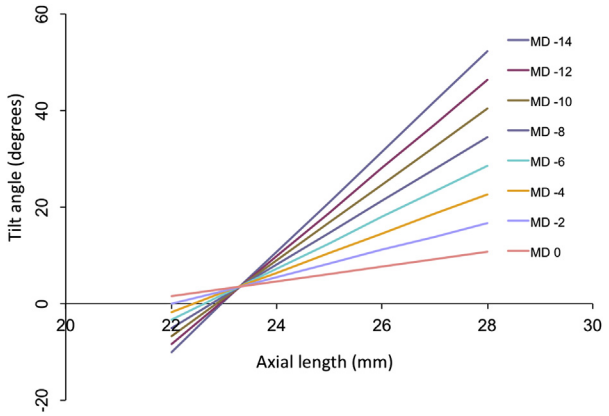

FIGURE 6. The relationship of the axial length and the optic nerve head vertical tilt angle as a function of glaucoma severity, as indicated by the visual field mean deviation. The study sample consisted of 112 eyes from 99 control subjects and patients with suspected or definite glaucoma.

the *vertical* tilt of the ON head commonly associated with progressive myopia. The findings do not necessarily apply to eyes with torted small discs known to frequently harbor inferonasal colobomas. In fact, the latter is a rare occurrence (0.4%-3.5%) in the general population,[3] although such estimates are not exact because of the lumping of various ON head anomalies into the same category. To our knowledge, our study is also the first to explore the association of axial length with vertical ON head tilt angle. Most prior studies used refractive error for exploring the relationship of tilted discs and myopia. We believe the current study is a first step to define the various ON head morphologies that have been collectively called tilted discs.

There is recent evidence suggesting that highly myopic eyes tend to demonstrate evidence of ganglion cell loss in the temporal area (papillomacular bundle) more frequently than nonmyopic eyes,[12] and it is plausible that vertical tilting of the ON head could potentially lead to various pathophysiological abnormalities such as stretching of the temporal axons, loss of structural support near the neural canal, or altered vascular supply in the vulnerable region of the ON head. The fact that a worse MD was associated with a larger vertical tilt angle in our study is of potential interest and is worth further exploration in future studies. Since our study sample included patients from a tertiary referral center, there might be an element of selection bias. Tilted disc is a common finding in patients with high myopia,[13] who are also prone to glaucoma.[14–16]

Although including normal eyes and eyes with various degrees of glaucomatous damage was an advantage, one could argue that a reference plane based on the Bruch membrane is not necessarily stable in glaucoma eyes, since the Bruch membrane surrounding the neural canal opening may slowly bend backwards in such eyes.[17] Despite this shortcoming, the Bruch membrane is probably the most stable structure among the tissues forming the neural canal opening. Also, in cases with sudden backward or forward bowing of the tip of the Bruch membrane, the innermost flat part of the Bruch membrane was used to define the reference plane to keep measurements consistent among eyes. Given the great variability in the vertical tilt angle as related to the axial length, it can be predicted that other unknown factors influence it. Such mechanical or physiological factors need to be better explored.

In summary, we reported a new method for objective measurement of the ON head vertical tilt angle based on high-resolution SDOCT imaging of the peripapillary tissue using the inner edge of the Bruch membrane as the reference plane. We found that the ovality index correlated only moderately with such measurements. The factors statistically associated with the ON head vertical tilt angle were axial length and glaucoma severity, as indicated by visual field mean deviation. Further studies are warranted to confirm our findings and to investigate this apparent relationship with glaucoma.

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Biosketch

Dr Hamid Hosseini received his medical degree from Tehran University of Medical Sciences, Tehran, Iran and completed his Ophthalmology residency and Vitreoretinal surgery fellowship at Shiraz University of Medical Sciences, Shiraz, Iran. He completed an international glaucoma fellowship at the UCLA's Jules Stein Eye Institute in 2011, and is currently an International Vitreoretinal surgery fellow at the Jules Stein Eye Institute. His main research interest is the role of imaging in glaucoma and retinal disorders.