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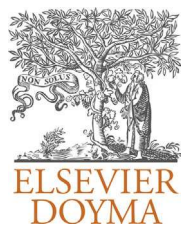13 PUBLICATIONS   39 CITATIONS

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ORIGINAL ARTICLE

Retinal nerve fiber layer thickness in glaucomatous Nepalese eyes and its relation with visual field sensitivity

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Abstract
Background: To evaluate peripapillary retinal nerve fiber layer (RNFL) thickness in glaucomatous Nepalese eyes using spectral domain optical coherence tomography (SD-OCT) and study its relationship with visual field sensitivity.
Methods: A total of 120 eyes comprising primary open angle glaucoma (POAG), glaucoma suspects (GS), normal tension glaucoma (NTG) and healthy subjects ($n = 30$ cases in each group) underwent a complete ophthalmic examination, including optic nerve head (ONH) evaluation and standard automated perimetry (SAP). RNFL thickness measurements around the optic disk were taken with circular spectral domain optical coherence tomography (SD-OCT) scans. Analysis of variance (ANOVA) was used for comparison of RNFL parameters among various study groups. The relationship of RNFL parameters with visual field (VF) global indices was evaluated with regression analysis.
Results: The mean pRNFL thickness was significantly less in the POAG ($64.30 \pm 14.45 \,\mu$m, $p < 0.01$), NTG ($85.43 \pm 9.79 \,\mu$m, $p < 0.001$) and GS ($102.0 \pm 9.37 \,\mu$m, $p < 0.001$) groups than in the healthy group ($109.8 \pm 8.32 \,\mu$m). The RNFL was significantly thinner across all quadrants in all study group pairs ($p < 0.05$) except for normal vs. GS (only superior and inferior quadrant, significant). Linear regression plots with RNFL thickness as a predictor of MD and LV demonstrated a strong and statistically significant degree of determination in the POAG group ($R^2 = 0.203$ and 0.175, $p = 0.013$ and 0.021).

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Conclusion: The RNFL thickness measurements with SD-OCT are lower in glaucomatous eyes as compared to age-matched GS and normal eyes in the Nepalese population. A high resolution SD-OCT could aid significantly in the early diagnosis of glaucoma in Nepal.

Grosor de las capas de fibras nerviosas retinianas en pacientes nepalís con glaucoma, y su relación con la sensibilidad del campo visual

Resumen
Antecedentes: Evaluar el grosor de la capa peripapilar de fibras del nervio óptico retiniano (RNFL) en ojos de pacientes con glaucoma de Nepal, utilizando la tomografía de coherencia óptica de dominio espectral (TCO-DE), y estudiar su relación con la sensibilidad del campo visual.
Métodos: Se sometió a un examen oftalmológico completo a un total de 120 ojos que incluían: glaucoma de ángulo abierto (POAG), sospecha de glaucoma (GS), glaucoma de tensión normal (NTG) y sujetos sanos (n = 30 casos en cada grupo), incluyendo evaluación de la cabeza del nervio óptico (ONH) y perimetría automatizada estándar (SAP). Se realizaron las mediciones del grosor de RNFL alrededor del disco óptico mediante tomografía de coherencia óptica de dominio espectral circular (TCO-DE). Se utilizó el análisis de varianza (ANOVA) para comparar los parámetros de RNFL entre los diversos grupos de estudio. Se evaluó la relación de los parámetros de RNFL con los índices globales del campo visual (CV), mediante un análisis de regresión.
Resultados: El grosor medio de pRNFL fue considerablemente menor en el grupo de POAG (64,30 ± 14,45 μm, p < 0,01), NTG (85,43 ± 9,79 μm, p < 0,001) y GS (102,0 ± 9,37 μm, p < 0,001), que en el grupo sano (109,8 ± 8,32 μm). El RNFL fue significativamente menor en todos los cuadrantes de todos los pares de grupos de estudio (p < 0,05) excepto para el grupo normal frente al GS (únicamente fueron significativos los cuadrantes superior e inferior). Las gráficas de regresión lineal, utilizando RNFL como factor predictivo de MD y LV demostraron un grado sólido y estadísticamente significativo de determinación en el grupo de POAG (R2 = 0,203 y 0,175, p = 0,013 y 0,021).
Conclusión: Los valores del grosor de RNFL medidos mediante TCO-DE son inferiores en ojos con glaucoma, en comparación a ojos con GS de sujetos con rangos de edades equivalentes así como a los ojos normales en la población nepalí. Una TCO-DE de alta resolución podría ayudar considerablemente al diagnóstico precoz del glaucoma en Nepal.

Glaucoma is characterized by slow progressive degeneration of retinal ganglion cells (RGCs) and their axons, resulting in a distinct appearance of the optic disk and a concomitant pattern of visual loss.[1] Glaucomatous disease is usually diagnosed and managed with measurements of structural and functional alterations associated with losses of RGCs and their axons.[2] According to the World Health Organization (WHO), glaucoma is the leading cause of blindness in the world, second only to cataracts, and is considered the principal cause of irreversible blindness worldwide.[3] A recent report estimated that there are 60.5 million people worldwide with glaucoma which will increase to 80 million by 2020,[4] and glaucoma is responsible for 8% of all causes of global blindness.[5] Glaucoma is also a major cause of blindness in Nepal. According to National Blindness Survey, it is the fourth major cause of bilateral blindness with a prevalence of 3.2% among various causes.[6] Recent glaucoma surveys done in different ethnic groups in Nepal revealed the prevalence of glaucoma ranging from 1.38% to 12.4%.[7,8]

Furthermore, a study reported that the knowledge of glaucoma is very low in a hospital presenting population in Eastern Nepal.[9]

Standard Automated Perimetry (SAP) has remained the gold standard in glaucoma diagnosis and management, and without it, modern glaucoma management is not possible.[10] However, the last decade has seen the emergence of a variety of new technologies for the objective, non-invasive, measurement of structural changes secondary to RGC damage. Newer versions of OCT that incorporate spectral domain (SD) technology provide higher scan resolution and higher speed than conventional time domain (TD) OCT.[11,12] The Spectralis HRA + OCT (Heidelberg Engineering) is the combination of a confocal scanning laser ophthalmoscopy (CSLO) and a SD-OCT that enables the operator to capture a wide variety of retinal images with high resolution and superior quality.

RNFL loss precedes measurable ONH and VF damage and is observed in 60% of eyes approximately six years

before any detectable VF defects in glaucoma.[13] Intuitively, it seems necessary for losses in visual function to be preceded by structural changes. However, some studies show that functional losses can be detected prior to structural changes. For example, the OHTS study showed that 41.7% of patients with ocular hypertension reached the visual end-point before reaching the structural end-point.[14] While structural changes are likely occurring, they may not be detectable by the currently available technology. Another explanation could be that the cells become dysfunctional, but retain their structural integrity for a period of time. Furthermore, there are differences in OAG prevalence in Nepal compared to that in other parts of the world.[30–34] The lower overall prevalence of OAG (1.24%) reported in Bhaktapur Glaucoma Study compared to Beaver Damn Eye Study (BDES) (2.07%) and Los Angeles Latino Eye Study (LALES) (4.65%) might be due to the fact that the BGS did not quantify in great detail the structural and functional relations. For these reasons, our goal was to carefully categorize the structure and function of eyes with glaucoma in Nepalese patients. To the best of our knowledge, there have been no reports regarding the nerve fiber layer thickness measurements in glaucomatous Nepalese eye using OCT.

Material and methods

Study population

This was an analytical, cross-sectional, hospital-based study that included a total of 120 participants. Thirty age-matched participants were included in each of the four groups: glaucoma suspects, healthy subjects, normal tension glaucoma and primary open angle glaucoma. Participants were recruited from Outpatient department (healthy controls) and Glaucoma clinic (glaucoma patients) of the B.P. Koirala Lions Center for Ophthalmic Studies (BPKLCOS), Institute of Medicine, Tribhuvan University Teaching Hospital. The research adhered to the tenets of the Declaration of Helsinki for research involving human subjects. The study protocol was approved by the Institutional Review Board of Institute of Medicine, and informed consent was obtained from all the participants of the study.

The participants included in the POAG group had a glaucomatous appearance of optic disk on binocular indirect ophthalmoscopy; glaucomatous VF defects on SAP confirmed on two consecutive VF tests and had a history of elevated IOP. Similarly, patients with NTG had a glaucomatous appearance of optic disk on binocular indirect ophthalmoscopy, glaucomatous VF defects on SAP confirmed on two consecutive VF tests and no history of elevated IOP. Glaucoma suspects had glaucomatous appearance of optic disk on clinical examination (suspects based on increased cupping), corrected IOP greater than 21 mmHg (ocular hypertensives) or glaucoma family history but no associated VF defect on SAP. Healthy eyes had normal optic nerve head appearance, IOP of 21 mmHg or less, no history of ocular hypertension and normal visual field result with SAP with no history of ocular diseases and no experience of intraocular or laser surgery other than uncomplicated cataract surgery.

Procedures

Complete ophthalmic examination was performed for enrollment into the study including refraction, anterior segment evaluation by slit lamp biomicroscopy, fundus evaluation after full dilatation using 90D lens (Volk) and 20D lens, intraocular pressure measurement with Goldmann applanation tonometry, ultrasonic pachymetry (Axis II PR, Quantel Medical) and SAP (Octopus 301 Haag-Streit, Interzeag International-AG, Schlieren, Switzerland). Indirect gonioscopic examination with Goldmann one mirror gonio-lens was also performed in all cases.

Inclusion criteria: We included all patients who fulfilled the following criteria: age older than 35 years; patients diagnosed as glaucoma suspects (GS), normal tension glaucoma (NTG) and primary open angle glaucoma (POAG); open angles; good-quality scans obtained in peripapillary RNFL thickness evaluation by OCT defined as a signal-to-noise ratio of >35; reliable SAP performed at ±1 month from OCT imaging; and refractive error within a ±5 spherical diopter range, with less than ±3 cylinder diopters. One eye was randomly selected for inclusion in the study when both eyes were eligible.

Exclusion criteria: Criteria for exclusion of a patient from the study were best corrected visual acuity on the Snellen chart worse than 20/60, any ocular conditions including corneal and vitro-retinal diseases which could interfere with obtaining reliable visual fields (VFs) or good quality retina scans, or significant parapapillary atrophy that caused blind spot enlargement on the visual field tests, interfered with VF readings, or causing false nerve fiber layer thickness data by OCT evaluation. Patients who could not undergo complete reliable VF test with three attempts and those with any other ophthalmic or neurologic conditions that could result in SAP defects were excluded as well.

Standard automated perimetry

SAP was performed with Normal strategy on OCTOPUS 301 (Haag-Streit, Interzeag International-AG, Schlieren, Switzerland) after dark adapting the participant for 3–5 min prior to the test. A reliable VF test was defined as one with less than 33% fixation loss and less than 20% positive and negative catch trials. Glaucomatous VF defect was defined as MD > +2.0 dB or LV > 6.0 dB^2 (equivalent to being triggered at the 5% level on the Humphrey Field Analyzer)[15] or both in at least two reliable examinations, and the global indices obtained in the second examination were included in the study to minimize the impact of learning, particularly in the group with healthy eyes who were naive to visual field testing. SAP was performed by the same operator in all cases. For comparison, Octopus global indices MD and LV were used.

Spectral domain optical coherence tomography

All patients were scanned using the commercially available SD-OCT Spectralis HRA + OCT (Heidelberg Engineering). This instrument uses a wavelength of 820 nm in the near infrared spectrum in the SLO mode. The light source of the SD-OCT is a super luminescent diode with a wavelength of 870 nm. Infrared images and OCT scans (40,000 A-Scans/s) of the dual

Table 1 Descriptive characteristics of the study population in different study groups.

	GS ($n = 30$)	NTG ($n = 30$)	POAG ($n = 30$)	Normal ($n = 30$)	P
Age (yrs)	47.13 ± 11.10	50.97 ± 10.03	52.00 ± 9.58	47.00 ± 8.16	0.10[a]
Sex (M/F)	1:1	0.67:1	0.88:1	0.88:1	0.89[b]
BCVA (logMAR)	0.05 ± 0.10	0.05 ± 0.10	0.09 ± 0.12	0.07 ± 0.10	0.40[a]
Refractive error (D)	-0.92 ± 0.99	0.16 ± 0.73	0.33 ± 0.56	0.26 ± 0.53	0.07[a]
MD (dB)	-0.04 ± 0.95	3.10 ± 0.87	5.88 ± 4.07	0.38 ± 0.82	<0.001[c]
LV (dB)	3.24 ± 1.59	8.49 ± 3.59	23.4 ± 16.2	2.68 ± 0.90	<0.001[c]

GS, glaucoma suspects; NTG, normal tension glaucoma; POAG, primary open angle glaucoma; BCVA, best corrected visual acuity; MD, mean deviation; LV, loss variance.
[a] One-way ANOVA.
[b] Chi-square test.
[c] One way ANOVA using Games-Howell adjustment for pairwise comparisons.

laser scanning systems are acquired simultaneously. Sixteen consecutive circular B-scans (3.4-mm diameter, 768 A-scans) centered at the optic disk were automatically averaged to reduce speckle noise. An online tracking system compensated for eye movements. The Spectralis software version 3.2.1 allows separate measurements of the total retinal thickness and the RNFL thickness. The RNFL borders were clearly identified and marked automatically by the segmentation software. The retinal vessels within the RNFL were considered to be part of the RNFL. To show the distribution of RNFL thickness around the optic disk, thickness data of the circular scans were averaged for 4 sectors (45-degree each) and the superior and inferior segments each were further grouped into 2 sectors (22.5-degree each) as supero-temporal, supero-nasal, infero-temporal and infero-nasal. A single user performed at least two retinal scans in all the cases, and the scans with the best image quality were considered. All the sectoral RNFL thickness measurements along with average RNFL thickness measurements were included in the study.

Statistical methods

All the variables studied followed a normal distribution as verified by the Wilk–Shapiro test. To compare quantitative variables among the different groups, ANOVA was used with Games-Howell (for unequal variances) and Tukey Honestly Significant Difference (for equal variances) corrections. The relationship between RNFL thickness and visual field (VF) global indices, expressed as mean deviation (MD) and loss variance (LV), was evaluated with regression analysis and Pearson's correlation coefficients. Statistical analyses were performed with SPSS 19.0 (SPSS Inc., Chicago, IL) and the level of significance was $\alpha = 0.05$ in all statistical tests.

Results

A total of 120 eyes comprising 30 normal, 30 eyes with glaucoma suspect, 30 eyes with NTG and 30 eyes with POAG were included in the study (Table 1).

There was no statistically significant differences in age [$F(3, 116) = 2.097$, $p = .104$]; gender [$\chi^2 (120) = 0.638$, $p = .888$]; BCVA [$F(3, 116) = 0.999$, $p = .396$] and refractive error [$F(3, 116) = 0.754$, $p = .068$] between the study groups.

Similarly, the visual field indices, MD and LV, were significantly higher in glaucomatous groups than that in normal [$F(3, 116) = 40.160$, $p < 001$] and GS [$F(3, 116) = 55.105$, $p < 0.001$], respectively. Post hoc adjustments for multiple comparisons using Games-Howell adjustment revealed a statistically significant difference in MD between all within group comparisons except for GS and normal ($p = .348$ for MD; $p = .348$ for LV).

RNFL thickness

The mean (95% CI) RNFL thickness decreased significantly from normal, 109.8 μm (106.7–112.9 μm), to GS, 102.0 μm (98.57–105.6 μm), NTG, 85.43 μm (81.78–89.09 μm), and POAG, 64.30 μm (58.90–69.70 μm) [$F(3, 116) = 105.5$, $p < 0.001$] (Fig. 1). A characteristic double hump pattern peaking at superior and inferior quadrants was revealed on analyzing average RNFL thickness in different study groups separately. There was marked depression of the double hump pattern in POAG and NTG groups compared with GS and normal groups (Fig. 2).

RNFL thicknesses in various quadrants were analyzed to assess the quadrants in which the diagnostic study groups
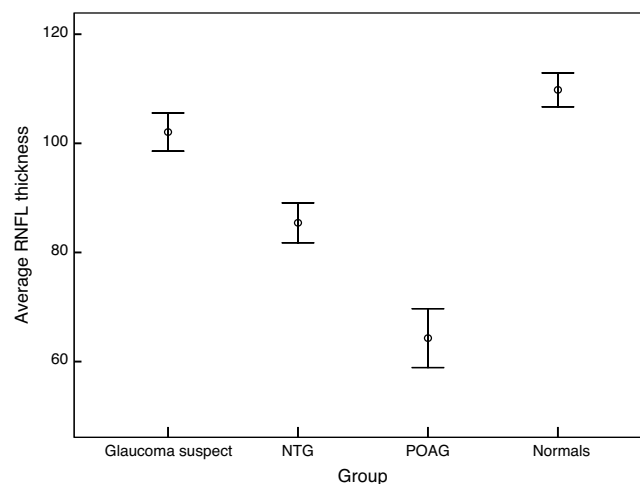

Figure 1 Average retinal nerve fiber layer thickness (micrometers) for 4 study groups. Error bars represent 95% confidence intervals.
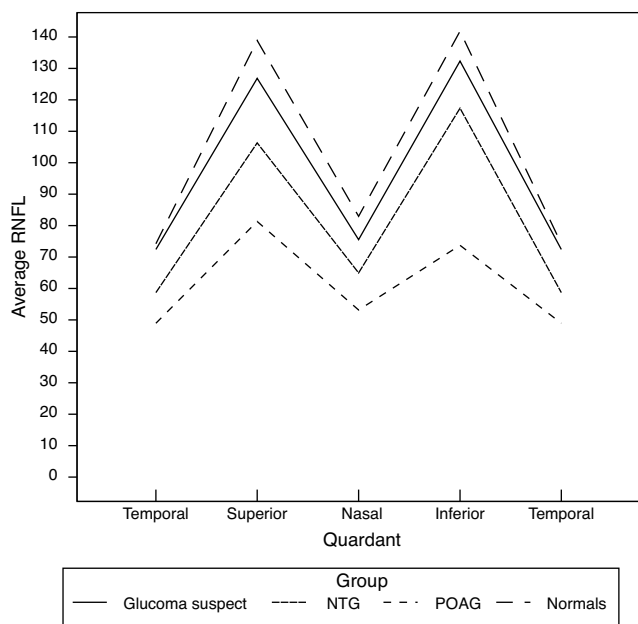
Figure 2 Retinal nerve fiber layer thickness (micrometers) in each quadrant for 4 study groups. Temporal quadrant = 316–45° (on unit circle measurement), superior quadrant = 46–135° measurement, nasal quadrant = 136–225° measurement, and inferior quadrant = 226–315° measurement.

differed significantly. Table 2 shows the summary of mean (95% CI) RNFL thickness in superior, nasal, inferior and temporal quadrants in normal, GS, NTG and POAG. Post hoc tests using Tukey HSD and Games-Howell adjustments revealed significant differences in quadratic RNFL thickness across all comparison groups except for normal vs. GS in which nasal and temporal RNFL thickness did not differ significantly ($p > 0.05$) (Table 3).

There was no statistically significant correlation between average RNFL and visual field indices, MD and LV in normal, GS and NTG groups. However, the correlations between average RNFL and MD/LV were significant ($p < 0.05$) in the POAG group, with the correlation coefficients being −0.450 and −0.418, respectively (Table 4).

The relationship between average RNFL thickness as a predictor of VF parameter (MD) within groups were further characterized by regression analyses using linear models, the latter giving the best curve fit in the POAG group for average RNFL thickness, with higher coefficients of determination (R^2). Scatterplots with regression curves of average RNFL thickness and MD for various groups are shown in Fig. 3.

Discussion

Glaucomatous damage is usually quantified by the observation of structural changes in RNFL and ONH and visual field sensitivity tests. In Nepal, SAP has been the mainstay of evaluation of glaucomtous damage in the absence of newer imaging modalities including optical coherence tomography. An understanding of the differences in RNFL thicknesses in various sub-groups of glaucomatous Nepalese populations and the structure-function relationship in glaucoma is of great significance in proper diagnosis as well as accurate monitoring of glaucomatous damage progression in this part of the world. The BGS has reported the prevalence of OAG to be 1.24%.[31] There are differences in OAG prevalence in Nepal compared to that in other parts of the world.[30,32–34] The overall prevalence of OAG was 2.07% in BDES and 4.65% in LALES, considerably higher than that reported by BGS. The BGS also showed lower prevalence of OAG in middle aged people (40–49 yrs), but the prevalence of OAG in older people (50 yrs and above) was higher compared to that of BDES and LALES. This suggests something unique about the pattern of glaucoma in Nepalese eyes. This might also be due to

Table 2 Average and quadratic RNFL thickness in different study groups.

Quadrant	GS ($n = 30$)	NTG ($n = 30$)	POAG ($n = 30$)	Normal ($n = 30$)
Superior	126.9 (121.8–132.0)	106.3 (101.0–111.7)	81.33 (73.02–89.65)	139.0 (133.0–144.8)
Nasal	75.53 (69.92–81.15)	64.97 (59.16–70.78)	53.17 (46.48–59.85)	82.97 (78.97–86.96)
Inferior	132.3 (127.3–137.4)	117.3 (111.0–123.7)	73.73 (64.42–83.05)	141.9 (137.5–146.2)
Temporal	72.43 (68.45–76.42)	58.67 (55.47–61.86)	48.93 (45.48–52.39)	74.23 (70.44–78.02)
Average	102.0 (98.57–105.6)	85.43 (81.78–89.09)	64.30 (58.90–69.70)	109.8 (106.7–112.9)

Values are expressed in micrometers as mean (95%CI of mean).
GS, glaucoma suspect; NTG, normal tension glaucoma; POAG, primary open angle glaucoma; RNFL, retinal nerve fiber layer.

Table 3 Comparison of mean RNFL thickness for all quadrants between various study groups.

RNFL thickness	P^1 Normal-GS	P^2 Normal-POAG	P^3 Normal-NTG	P^4 GS-POAG	P^5 GS-NTG	P^6 POAG-NTG
Average[a]	<.01	<.001	<.001	<.001	<.001	<.001
Superior[a]	<.05	<.001	<.001	<.001	<.001	<.001
Nasal[b]	.227	<.001	<.001	<.001	<.05	<.05
Inferior[a]	<.05	<.001	<.001	<.001	<.01	<.001
Temporal[b]	.889	<.001	<.001	<.001	<.001	<.01

[a] One way ANOVA using Games-Howell adjustment for pairwise comparisons (equal variances not assumed).
[b] One way ANOVA using Tukey HSD adjustment for pairwise comparisons (equal variances assumed).

Table 4 Correlation of average RNFL thickness with VF indices, MD and LV.

	MD				LV			
	Normal (n = 30)	GS (n = 30)	NTG (n = 30)	POAG (n = 30)	Normal (n = 30)	GS (n = 30)	NTG (n = 30)	POAG (n = 30)
Avg. RNFL	0.191	0.146	0.130	−0.450[a]	−0.223	0.136	0.159	−0.418[a]

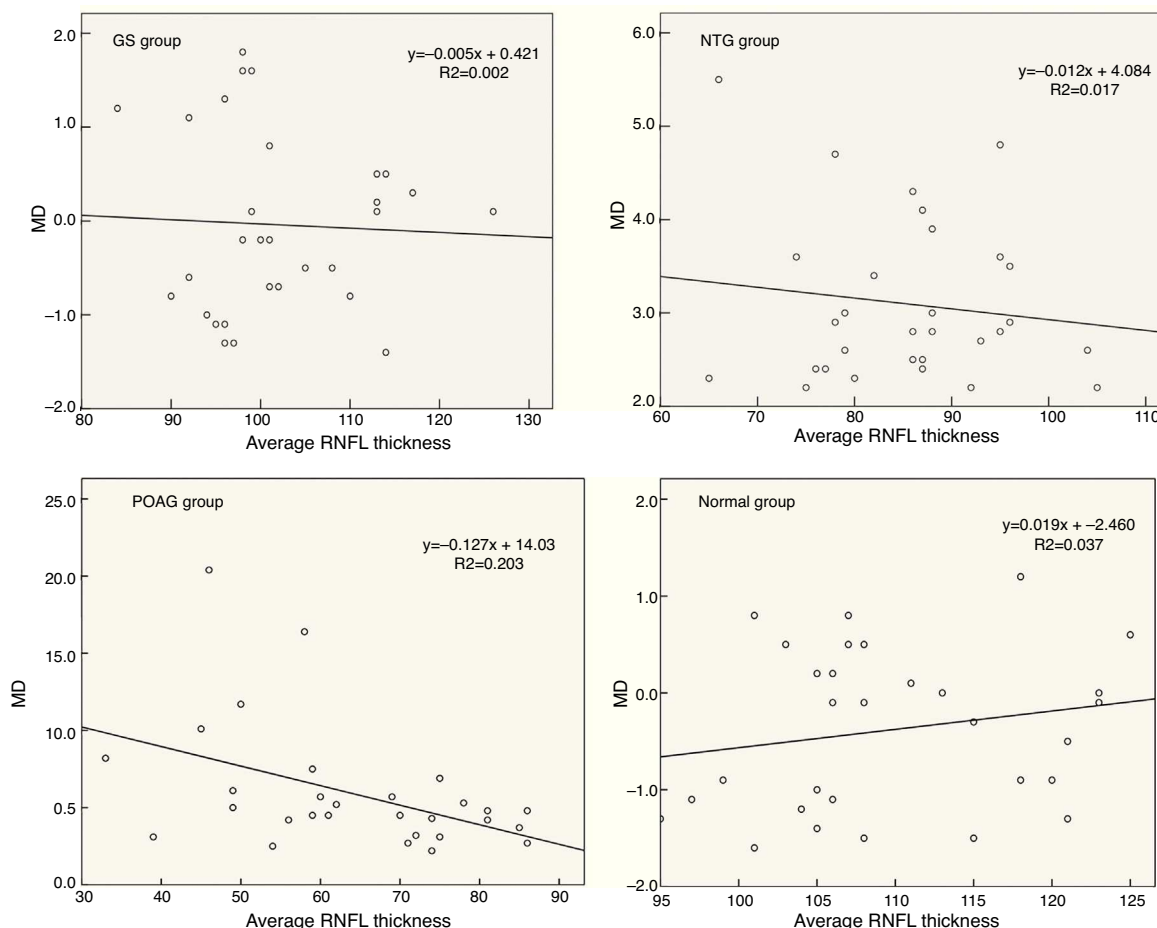[a] Correlation is significant at $p < 05$.

Figure 3 Scatterplots of average RNFL thickness vs. MD in GS, NTG, POAG and normal. Average RNFL thickness expressed in micrometers, MD in decibels. POAG indicates primary open angle glaucoma; GS, glaucoma suspects; NTG, normal tension glaucoma; MD, mean deviation; RNFL, retinal nerve fiber layer thickness.

the fact that the BGS did not quantify in great detail the strucure and function which might have accounted for the lower overall prevalence of OAG. Because of these differences in prevalences, we sought to carefully characterize the structure and function of eyes with glaucoma in Nepal. To the best of our knowledge, this is the first study conducted to analyze the RNFL thickness in glaucomatous Nepalese eyes using a third generation optical coherence tomography.

The differences in RNFL thickness in glaucomatous and normal eyes are well documented.[16–20] In our study, the mean RNFL thickness was $109.8 \pm 8.32\,\mu m$ in normal eyes, $102.0 \pm 9.37\,\mu m$ in GS, $85.43 \pm 9.79\,\mu m$ in eyes with NTG and $64.30 \pm 14.45\,\mu m$ in eyes with POAG. It is not surprising that

we found significant thinning of RNFL in glaucomatous eyes compared with GS and normal eyes. The arching temporal fibers form the arcuate nerve fiber bundles enter the optic nerve head at the superior and inferior poles, whereas the papillomacular fibers from the central retina and the fibers from the nasal retina course directly from their cell bodies to the disk.[21] Damage to the inferior and superior poles of the nerve results in the loss of the arcuate nerve fiber bundles.

Our results are consistent with Hoh et al.[22] who reported significantly thinner mean RNFL measured with OCT in glaucomatous eyes $(56.9 \pm 21.5\,\mu m)$ compared with ocular hypertensive $(83.70 \pm 16.57\,\mu m)$ and normal

($90.86 \pm 14.17\,\mu m$) eyes, and concluded that although RNFL thickness tended to be greater in normal than in ocular hypertensive eyes, this difference was not statistically significant. Bowd et al.[17] in their study concluded that the mean (95% CI) RNFL thickness was significantly lower in glaucomatous eyes, $44.4\,\mu m$ (36.4–$52.6\,\mu m$), than in OHT eyes, $72.8\,\mu m$ (66.4–$78.1\,\mu m$), and was significantly lower in OHT eyes than in normal eyes, $85.8\,\mu m$ (80.2–$91.7\,\mu m$). In a study from India,[13] mean RNFL thickness was reported as $52.95 \pm 31.10\,\mu m$ in glaucomatous eyes, $82.87 \pm 17.21\,\mu m$ in the ocular hypertensives and $94.26 \pm 12.36\,\mu m$ in the normal eyes. The results of such investigations showing significant differences in RNFL between GS and normal eyes are less established. Our result suggests than thinner RNFL may be characteristic of glaucoma suspect eyes as well. The higher RNFL thickness measurements in all the study groups in our study may be due to the higher axial resolution provided by the Spectralis SD-OCT as compared to Stratus OCT used in the above studies, as RNFL thickness is measured as the difference in pixels between the anterior and posterior edges of RNFL. Furthermore, RNFL thickness difference in our population compared to that in the Western population may have racial causes or is a physical phenomenon. Darker choroid in this part of the world may alter B-scan thickness in comparison to lighter choroid due to altered reflectance of laser light.

There was also progressive thinning of RNFL thickness in all retinal quadrants from normal eyes to GS, NTG and POAG. All the quadrants differed significantly between the study groups; however, only the superior and inferior RNFL were thinned significantly between normal and GS eyes. It may be due to the fact that the superior and inferior poles of the ONH are most vulnerable to glaucomatous damage. It has been postulated that these areas may be watershed areas at the junction of the vascular supply from adjacent ciliary vessels. Ultrastructural examination of the lamina cribrosa shows that the pores in the superotemporal and inferotemporal areas are larger. These larger pores may make these regions more vulnerable to compression.[23]

The RNFL thickness distribution in normal eyes was such that the inferior quadrant was the thickest followed by superior, nasal and temporal quadrants. This follows the convention that is often referred to as ISNT rule in glaucoma.[24] Analysis of RNFL thickness in the glaucomatous, GS and normal eyes revealed a characteristic double hump pattern with RNFL peaks in the superior and inferior quadrants and troughs in the nasal and temporal quadrants in all groups, although this pattern was quite depressed in glaucomatous eyes, further emphasizing the greater reduction in superior and inferior thickness with more progression of glaucomatous damage.

Guedes et al.[25] reported that the mean RNFL was the only parameter in which a statistically significant difference was observed between the normal and GS groups. We observed a statistically significant decrease in superior and inferior RNFL thickness as well as average RNFL thickness between all the study groups. The fact that the nasal and temporal RNFL thickness did not differ significantly between GS and normal further emphasizes the need for the evaluation of vertical neuroretinal rim (NRR) thickening for early detection of glaucoma. The average RNFL thickness, being the best parameter for glaucoma discrimination, signifies considerable loss in NRR that takes place very early in the disease.

It is possible that the thinner RNFL in GS is an early form of glaucoma threat which precedes detectable optic nerve or visual field defects. Other researchers have implicated RNFL thinning as a risk factor in future glaucomatous VF loss. Quigley et al.[26] showed pre-existing RNFL defects in 57% of GS eyes that converted from normal to defective visual fields. Pre-existing RNFL defects were also present in 35% of nonconverted eyes. Moreover, the risk of conversion of defective visual fields in GS eyes increased with the increase in RNFL damage.[27] Another possibility is that the RNFL in GS may be initially thin in the inferior quadrant, making these eyes particularly susceptive to the effects of increased IOP. Several studies have failed to find a significant difference in RNFL thickness between glaucoma suspects and normal.[28,29] It is possible that these normal results are related to the sensitivity of the measuring instruments, sample size, or difference in study population.

We also compared the VF global indices among various groups using multiple comparisons after performing analysis of variance. There was statistically significant difference between VF global indices, MD and LV for all the study group pairs except for normal vs. GS in which the global indices did not differ significantly. Furthermore, the correlation between average RNFL thickness and visual field indices, MD and LV was significant only for the POAG group, whereas the correlations were weak for GS and NTG groups. Since average RNFL was statistically significant in differentiating these two groups from normal, we can conclude that average RNFL measured with high resolution imaging modality such as OCT can be a useful investigative tool in picking up glaucoma early in accordance with the fact that RNFL loss precedes measurable optic nerve head and visual field damage.[13]

We further characterized the relation between RNFL thickness and VF parameters within groups by regression analyses using linear models, the latter giving the best fit in the POAG group, with higher coefficient of determination. This might be due to the overlap of RNFL thickness and VF distribution in normal and early glaucoma. It may emphasize that the average RNFL thickness can be established as a predictor of VF defect in POAG in which a significant loss of RNFL thickness occurs in comparison to GS and NTG.

In summary, a high-resolution SD-OCT revealed statistically significant quantitative differences in RNFL thickness in glaucomatous eyes as compared to that in age-matched GS and normal eyes in the Nepalese population. OCT could aid significantly in early diagnosis of glaucoma and monitoring of its progression in Nepal. Furthermore, this demands longitudinal studies aimed at determining whether these differences in RNFL thickness result in an increased likelihood of conversion from normal to glaucomatous VF defects.

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet*. 2004;363:1711–1720.
2. Wheat JL, Rangaswamy NV, Harwerth RS. Correlating RNFL thickness by OCT with perimetric sensitivity in glaucoma patients. *J Glaucoma*. 2012;21:95–101.
3. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Org*. 2004;82:844–851.
4. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262–267.
5. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *Br J Ophthalmol*. 2012;96:614–618. Epub 03.12.11.
6. Brilliant LB, Pokhrel RP, Grasset NC, et al. Epidemiology of blindness in Nepal. *Bull World Health Org*. 1985;63:375–386.
7. Shakya S, Dulal S, Maharjan I. Pseudoexfoliation syndrome in various ethnic population of Nepal. *NMCJ*. 2008;10:147–150.
8. Thapa SS, Paudyal I, Khanal S, et al. A population-based survey of the prevalence and types of glaucoma in Nepal: the Bhaktapur Glaucoma Study. *Ophthalmology*. 2012;119:759–764.
9. Gyawali R, Sarkar N. Glaucoma awareness in a hospital presenting population in Eastern Nepal. *J Glaucoma*. 2013.
10. Thomas R, George R. Interpreting automated perimetry. *Indian J Ophthalmol*. 2001;49:125–140.
11. Wojtkowski M, Bajraszewski T, Gorczynska I, et al. Ophthalmic imaging by spectral optical coherence tomography. *Am J Ophthalmol*. 2004;138:412–419.
12. Wojtkowski M, Srinivasan V, Fujimoto JG, et al. Three-dimensional retinal imaging with high-speed ultrahigh-resolution optical coherence tomography. *Ophthalmology*. 2005;112:1734–1746.
13. Subbiah S, Sankarnanarayanan S, Thomas PA, Jesudasam CAN. Comparative evaluation of glaucoma in ocular hypertensives, glaucomatous and normal eyes. *Indian J Ophthalmol*. 2007;55:283–287.
14. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertensive treatment study. *Arch Ophthalmol*. 2002;120:701–713.
15. Weijland A, Fankhauser F, Bebie H, Flammer J. *Automated perimetry*. Visual Field Digest USA: Haag-Streit Publ.; 2004.
16. Airaksinen PJ, Drance SM, Douglas GR, Mawson DK, Nieminen H. Diffuse and localized nerve fiber loss in glaucoma. *Am J Ophthalmol*. 1984;98:566–571.
17. Bowd C, Weinreb RN, Williams JM, Zangwill LM. The retinal nerve fiber layer thickness in ocular hypertensive, normal, and glaucomatous eyes with optical coherence tomography. *Arch Ophthalmol*. 2000;118:122.
18. Caprioli J, Miller JM. Measurement of relative nerve fiber layer surface height in glaucoma. *Ophthalmology*. 1989;96:633–639, discussion 9–41, Epub 01.05.89.
19. Quigley HA, Miller NR, George T. Clinical evaluation of nerve fiber layer atrophy as an indicator of glaucomatous optic nerve damage. *Arch Ophthalmol*. 1980;98:1564–1571. Epub 01.09.80.
20. Schuman JS, Hee MR, Arya AV, et al. Optical coherence tomography: a new tool for glaucoma diagnosis. *Curr Opin Ophthalmol*. 1995;6:89–95.
21. Minckler DS. The organization of nerve fiber bundles in the primate optic nerve head. *Arch Ophthalmol*. 1980;98:1630–1636.
22. Hoh ST, Greenfield DS, Mistlberger A, Liebmann JM, Ishikawa H, Ritch R. Optical coherence tomography and scanning laser polarimetry in normal, ocular hypertensive, and glaucomatous eyes. *Am J Ophthalmol*. 2000;129:129–135.
23. Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. *Arch Ophthalmol*. 1981;99:635–649.
24. Morgan JE, Bourtsoukli I, Rajkumar KN, et al. The accuracy of the inferior>superior>nasal>temporal neuroretinal rim area rule for diagnosing glaucomatous optic disc damage. *Ophthalmology*. 2012;119:723–730.
25. Guedes V, Schuman JS, Hertzmark E, et al. Optical coherence tomography measurement of macular and nerve fiber layer thickness in normal and glaucomatous human eyes. *Ophthalmology*. 2003;110:177–189. Epub 04.01.03.
26. Quigley HA, Katz J, Derick RJ, Gilbert D, Sommer A. An evaluation of optic disc and nerve fiber layer examinations in monitoring progression of early glaucoma damage. *Ophthalmology*. 1992;99:19–28. Epub 01.01.92.
27. Quigley HA, Enger C, Katz J, Sommer A, Scott R, Gilbert D. Risk factors for the development of glaucomatous visual field loss in ocular hypertension. *Arch Ophthalmol*. 1994;112:644–649.
28. Iester M, Broadway DC, Mikelberg FS, Drance SM. A comparison of healthy, ocular hypertensive, and glaucomatous optic disc topographic parameters. *J Glaucoma*. 1997;6:363–370.
29. Lachkar Y, Cohn H. Nerve fiber analysis and optic disc parameters with the glaucoma-scope. *Int Ophthalmol*. 1996;20(1–3):33–38. Epub 01.01.96.
30. Klein BE, Klein R, Sponsel WE, et al. Prevalence of glaucoma: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99:1499–1504.
31. Thapa SS, Paudyal I, Khanal S, et al. A population-based survey of the prevalence and types of glaucoma in Nepal: the Bhaktapur Glaucoma Study. *Ophthalmology*. 2012;119:759–764.
32. Varma R, Wang D, Wu C, et al. Four-year incidence of open-angle glaucoma and ocular hypertension: the Los Angeles Latino Eye Study. *Am J Ophthalmol*. 2012;154:315–325.
33. Coffey M, Reidy A, Wormald R, Xian WX, Wright L, Courtney P. Prevalence of glaucoma in the west of Ireland. *Br J Ophthalmol*. 1993;77:17–21.
34. Shiose Y, Kitazawa Y, Tsukahara S, et al. Epidemiology of glaucoma in Japan—a nationwide glaucoma survey. *Jpn J Ophthalmol*. 1991;35:133–155.