Visual Field and Optical Coherence Tomography Parameters With and Without Positive Family History of Glaucoma

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ABSTRACT

Background: To evaluate the Retinal Nerve Fiber Layer and Ganglion Cell Complex thickness using Spectral Domain Optical Coherence Tomography with and without positive family history of Primary Open Angle Glaucoma and its relation to visual field.

Methods: Total 120 eyes with each subjects with positive family history of Primary Open Angle Glaucoma (Group I, n=30) and healthy subjects without positive family history of Primary Open Angle Glaucoma (Group II, n=30) undergone complete ophthalmic evaluation with Retinal Nerve Fiber Layer, Ganglion Cell Complex and VF obtained from Spectral Domain Optical Coherence Tomography RTVue-100 and Humphrey visual field respectively .The measurements were analyzed and compared among two groups using independent-t test by using SPSS version 23.The relationship of Retinal Nerve Fiber Layer with visual field were evaluated with correlation analysis.

Results: The Intra Ocular Pressure and vertical Cup Disc Ratio were significantly higher in Group I with mean difference of 2.48±0.43 ($p<0.001$) and 0.18±0.23 ($p<0.001$) respectively. The average, superior, inferior, nasal, temporal RNFL and average Ganglion Cell Complex was significantly lower and thinner in Group I with mean difference of -8.53±2.30 µm ($p<0.001$), -7.35±3.34 µm ($p<0.001$), -8.52±3.58µm ($p<0.001$),-11.87±2.24µm ($p<0.001$), -5.31±1.95µm ($p<0.001$) and -8.05±1.52µm ($p<0.001$) respectively. Correlation plot with Retinal Nerve Fiber Layer thickness as predictor of Mean Deviation and Pattern Standard Deviation indicated statistically significant degree of determination in Group I ($r=0.455$ and $r=0.623$, $p<0.001$ and $p<0.001$).

Conclusions: The Optical Coherence Tomography and visual field Parameters are lower in group I and used as an early predictor, diagnosis, monitoring and management.

Keywords: Family history; first degree relatives; ganglion cell complex; primary open angle glaucoma; retinal nerve fiber layer.

INTRODUCTION

Glaucoma is a progressive neurodegeneration of retinal ganglion cells and RNFL damaging optic nerve head with VF loss.[1-5] Asia account for second highest and Nepal with third highest prevalence of glaucoma with 60% and 3.2% respectively.[6-8] Positive family history has been reported in 13 to 50 % affected by POAG with relative risk of 2.1.[9] Approximately there is 18-fold risk of developing glaucoma with prevalence 10.4% with positive family history compared to 0.7% in normal controls.[10,11] Positive family history has genetic link of myocilin accounting 2% to 4% of POAG cases.[12,13] OCT evaluation for RNFL and GCC is an important parameter to detect early 30-50% ganglion cell loss at inferotemporal region lead to superionasal VF changes, progression and early intervention.[14-18] Till this date there are no study related to comparison of VF and OCT parameters in subjects with a positive family history of glaucoma in Nepalese eye.

METHODS

This was an analytical, cross-sectional, prospective and hospital-based study included 120 eyes of 60 adults. Using independent t-test by using mean values and standard deviation in previously published research article published in International Journal of Open Access Ophthalmology, 2019 as a base line value using formula n = {[(Zα - (-Zβ) (s.d.)]/[X¤1 - X¤2]} ^2 where Zα for $p<0.05$ was 1.96, Zβ = beta<0.10 was 1.28 and finally

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the total sample size for the study was 30 in each group selected purposively in study participants of Himalaya Eye Hospital. Only one offspring with 1st degree relative of POAG patient was included in Group I for high reliability of data and minimize the confounding gene factor. Only one offspring without positive family history of POAG was included in Group II as the six month prior family history of ocular examination of parents taken from healthy subjects. Informed consent was obtained from all the study participants and was recruited from Outpatient Department and Glaucoma clinic (First degree relative of POAG patients).The research adhered to the tenets of the Declaration of Helsinki and the study protocol was approved by the Nepal Health Research council, Kathmandu, Nepal.

Complete ophthalmic examination was performed including refraction, slit lamp evaluation using 90D lens (Volk), Intraocular Pressure (IOP) measurement with Goldmann Applanation Tonometry (GAT), Central Corneal Thickness (CCT) with Ultrasonic Pachymetry (Nidek Co, Limited, Japan) Indirect gonioscopic examination with Goldmann one mirror gonio-lens in all participants.

Inclusion criteria: This study included all the participants with between 18-45 years and Best Corrected Visual Acuity (BCVA) 20/20; Group I: refractive error with Spherical Equivalent (SE) between -1.5 and +1.5D; Group II: IOP equal to or less than 21 mmHg, Normal optic disc appearance; Normal VF with the fixation losses < 20 %, the false-positive and false-negative rates <15%. *Exclusion criteria:* All participants not satisfying inclusion criteria, any systemic, neuro-ophthalmological disorders and ocular disease affecting VF disturbance and retinal scans.

Humphrey VF evaluation by Humphrey II Visual Field Analyzer (Carl Zeiss Humphrey Field Analyzer 745i) with 24-2 Swedish Interactive Threshold Algorithm (SITA) Fast strategy and full threshold test system was performed including MD and PSD for both groups with reviewing reliability indices.

All subjects underwent the Glaucoma Protocol of SD-OCT RTVue-100 (Optovue Inc. Fremont, Ca). All eyes were scanned three times by the same examiner. RNFL assessment was done at optic nerve head (ONH) scan mode which consists of 12 radial lines with 6 concentric rings centered on the optic disc and used to create a peripapillary RNFL map in radial line diameter of 3.40 mm. Average, superior, inferior, nasal and temporal RNFL thicknesses were calculated. The scan of the macular GCC covered a 6×6 mm area centred temporal to the fovea and average GCC thicknesses were obtained.

Normal distribution of variables was studied by Wilk Shapiro test. To compare quantitative variables among two groups, Independent t-test was used with Games-Howell (for unequal variances) and Tukey Honestly for Significant Difference (for equal variances) corrections. Relationship between RNFL thickness and VF global indices expressed as MD and PSD was evaluated using Pearson's correlation at a confidence level of 95% .Statistical analyses were performed with Statistical Package for the Social Sciences version 23.0 (SPSS Inc., Chicago, IL) and $p<0.05$ was considered statistically significant in all tests.

RESULTS

Complete ocular examination with investigative procedures was performed in 120 eyes of 60 participants; 30 from each group were included for the analysis. Mean age of group I was 29.20±9.45 and group II was 29.93±7.57 with age range 18-45 for both group. In group I 16 (53%) were male and 14 (47%) were female and in group II, 15 (50%) were male and 15 (50%) were female. About 90% participants were unaware regarding family history as risk factor of having POAG. Group I was found to be myopic by -0.087 ±0.33D ($p<0.001$). The mean IOP was 18.20±2.86 and15.71±1.77 in Group I and Group II respectively and relatively in higher side by (2.48±0.43 mmHg, $p<0.001$) in Group I with 4 subjects had IOP >21 mmHg. The mean vertical cup disc ratio (CDR) was higher by (0.18±0.23; $p<0.001$) indicating that there may be higher risk of axonal and RNFL loss in Group I with glaucomatous damage in near future. The number of cases with vertical CDR value more than 0.5 were 10 in Group I. Likewise the value of MD was higher sided by (-2.85±0.38dB; $p<0.001$) with MD more than -2.0 dB were 17 in group I .The PSD was higher by (1.73±0.31dB; $p<0.001$) and the value more than 2 dB were 17 in group I. Descriptive characteristics for both groups were presented on **(Table 1).** The mean RNFL thickness was consistently lower in group I which by (-8.53 ±2.30 µm; $p<0.001$) is presented on **(Table 2)** and **Figure1 .**The mean GCC was 91.37 ±10.89 µm (58 µm -99 µm) in Group I and 99.41 ±4.57 µm (91 µm -109 µm) in group II and was statistically significant -8.05 ±1.52 µm, $p<0.0001$ which was consistently lower in group I **(Table 3).** Correlation was used to assess relation between the RNFL thickness, MD and PSD which was found to be moderately positively correlated with Pearson correlation coefficient 0.455 and significance level 0.01(2-tailed) and moderately negatively correlated with Pearson correlation coefficient -0.623 with significance level 0.01(2-tailed)

(Table 4). RNFL thickness as a predictor of MD and PSD in Group I was characterized by simple linear regression giving the best curve fit with higher coefficients of determination (R^2). Scatter plot with regression curve of average RNFL thickness for MD and PSD in Group I is shown in **Figure 2.**

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

	Group I (n=30)	Group II (n=30)	Mean difference	p value (2-tailed)
Intra Ocular Pressure	18.20±2.86 (12-26)	15.71±1.77 (11-19)	2.48±0.43	<0.001
Central Corneal Thickness	555.47±41.11 (476-643)	548.35±18.76 (513- 602)	7.11±5.83	0.22
Vertical Cup Disc Ratio	0.51±1.65 (0.30-0.85)	0.33±0.73 (0.2-0.50)	0.18±0.23	<0.001
Spherical Equivalent	-0.09±0.26 (-1.00-0.00)	0.00-0.00 (0.00-0.00)	-0.087±0.33	0.01
Mean Deviation	-3.89±2.90 (-11.17-0.23)	-1.03±0.63 (-2.53-0.51)	-2.85±0.38	<0.001
Pattern Standard Deviation	3.17±2.43 (1.04-12.37)	1.43±0.29 (0.91-2.20)	1.73±0.31	<0.001

Mean difference using Independent t-Test, significance level p<0.05 and p<0.001 (2-tailed)
Values are expressed in micrometers as mean (95% CI of mean)

Table 2. Comparison of mean RNFL thickness in different study groups.

RNFL thickness	Group I (n=30)	Group II (n=30)	Mean difference	p value (2-tailed)
Average	98.57±16.70 (43-117)	107.10±6.36 (97-124)	-8.53±2.30	<0.001
Superior	127.60±23.07 (65-172)	134.95±11.86 (117-163)	-7.35±3.34	0.031
Inferior	126.25±25.73 (44-162)	134.76±11.86 (108-155)	-8.52±3.58	0.02
Nasal	70.63±14.72 (31-101)	82.50±9.17 (55-103)	-11.87±2.24	<0.001
Temporal	70.45±13.14 (25-91)	75.77±7.47 (64-95)	-5.31±1.95	0.007

Independent t-Test, significance level p<0.05 and p<0.001 (2-tailed)
Values are expressed in micrometers as mean (95% CI of mean)

Table 3. Comparison of average Ganglion Cell Complex in different study groups.

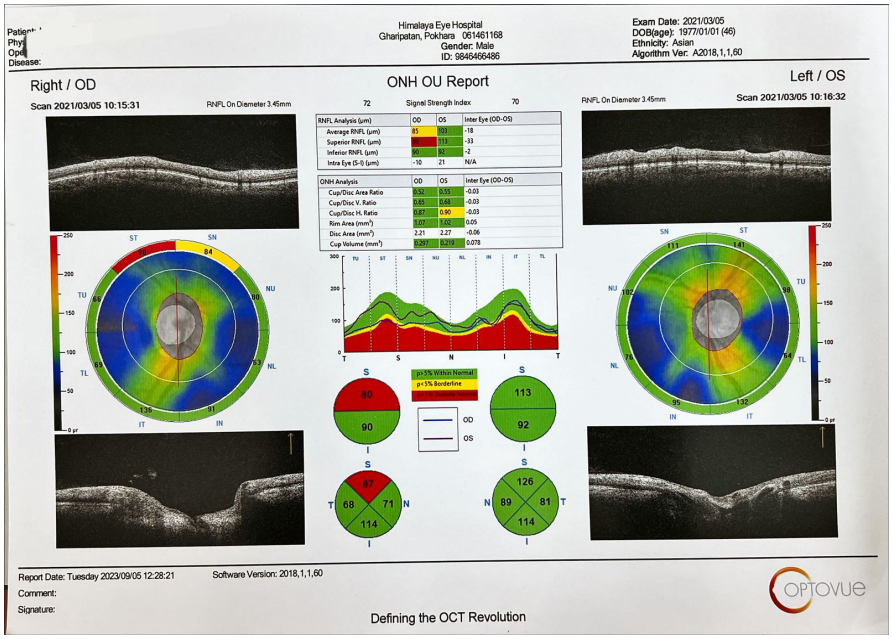
Ganglion Cell Complex thickness	Group I (n=30)	Group II (n=30)	Mean difference	p value (2-tailed)
Average	91.37±10.89 (58-99)	99.41±4.57 (91-109)	-8.05±1.52	<0.001

Independent t-Test, significance level p<0.05 and p<0.001 (2-tailed)
Values are expressed in micrometers as mean (95% CI of mean)

Table 4. Correlation between average RNFL thickness and Visual Field indices Group I.

Average Retinal Nerve Fiber Layer thickness		
		Pearson correlation
Mean Deviation	Coefficient	(r)
	0.455**	<0.001
Pattern Standard Deviation	-0.623**	<0.001

**Significant correlation defined as 0.01 levels (2-tailed)



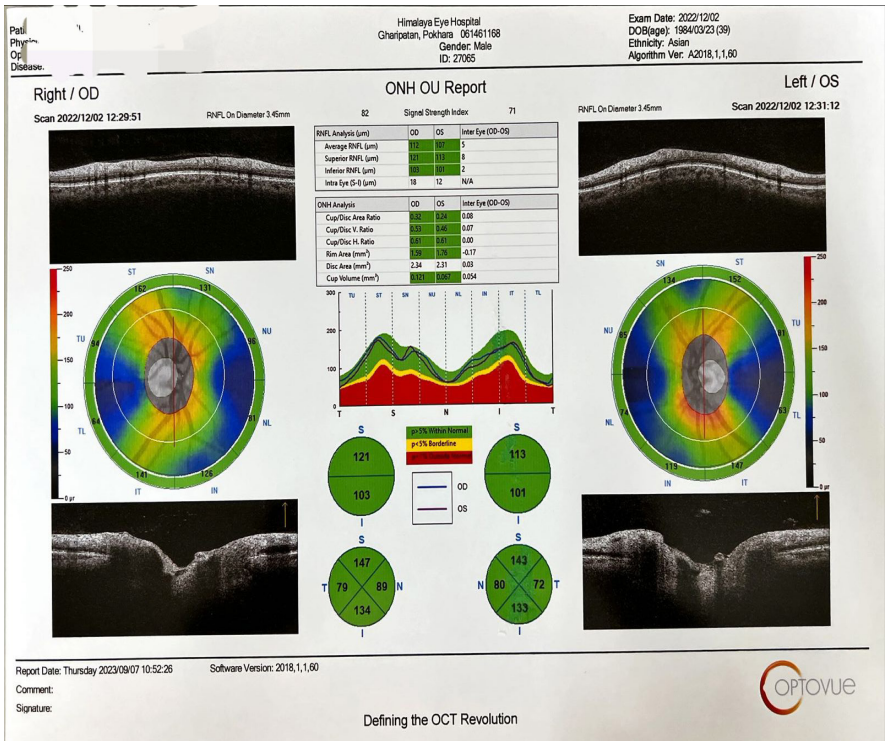
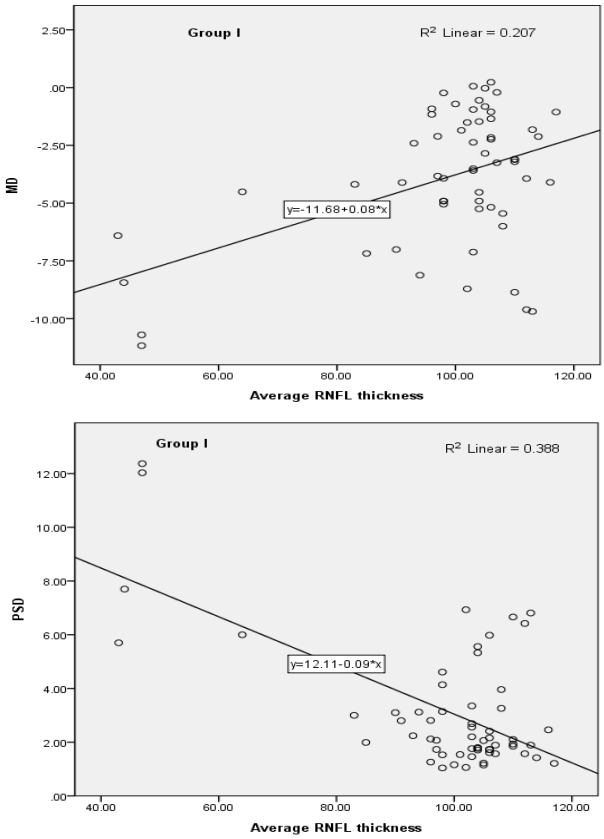


Figure 1. Retinal nerve fiber layer thickness in Group I and Group II



from Left to Right from Examiner point of view by SD-OCT RTVue-100; normally are colour coded green, borderline value are coded yellow and below normality value are coded by red.

Figure 2. Scatter plot showing the relationship between average Retinal Nerve Fiber Layer thickness and Mean Deviation in Group I, showing the decrease in RNFL thickness with increase in negative value of mean deviation.

DISCUSSION

Evaluation of RNFL, GCC and VF are the mainstay of glaucoma assessment in modern eye care practice. Five participants with diagnosed POAG had positive family history which suggest that positive family history has high risk of developing ocular hypertension into POAG .[9] This study has showed that higher proportion of male with positive family history are in higher risk which may be due to longer axial length and deeper anterior chamber depth (RR 1.28, 95% CI1.12 ~ 1.45, p < 0.01).[6] Subjects in Group I were found to be myopic and higher IOP which may be the risk factor of having POAG.[19] RNFL thickness was found similar and comparable to previous and found to be 109.8± 8.32 µm (106.7 to112.9 µm) in healthy Nepalese eyes with Caucasian eyes had smaller RNFL 100.1±11.6µm than that of Asian 105.8±9.2 (Thai population= 109.3 ±10.5µm, Taiwanese= 108.7±9.4µm, Chinese=111.5 ±4.12) .[20-22] RNFL thickness was significantly thinner in group I which may be due to the pores in the superotemporal and inferotemporal areas are larger with more vulnerable to compression and early VF changes.[1,20,23] The average GCC value for group II was found to be 99.41 ±4.57 µm and results was agreed previously and found to be 99.26±6.51 µm.[18,24] Group I have high change of axonal death with more than 5µm axonal loss specially on inferotemporal region that would eventually result in superionasal VF defect normally 7 month later after progressive axonal loss.[18] The mean deviation in group II was -1.03±0.63 dB and the similar results was published previously and found to be 1.21 ± 0.45 dB (−2.10-1.79).[1] Similarly the PSD in group II was 1.43±0.29 dB and these results was agreed in previous study and found to be 1.40 ±0.53dB.[25] Six visual field examinations should be performed in the first 2 years to rule out the presence of rapid progression (-2 dB/year or worse) and establishes a good set of baseline data.[26]

CONCLUSIONS

First degree relatives of POAG must have to do early glaucoma screening, monitoring and even medical treatment to slow down the progressive loss of GCC and RNFL thickness. Cohort studies are needed for any progressive RNFL thinning and significant VF changes. Additional randomized control trial should be needed to find out whether early antiglaucoma medication used as prophylaxis slow down the progressive deterioration.

ACKNOWLEDGEMENTS

I am thankful to all the subjects participated in this study as well as administrative, clinical staffs, faculties.

CONFLICT OF INTEREST

No

REFERENCES

1. Karti O, Yuksel B, Uzunel UD, Karahan E, Zengin MO, Kusbeci T. The assessment of optical coherence tomographic parameters in subjects with a positive family history of glaucoma. *Clin Exp Optom*. 2017;100(6):663-667. doi:10.1111/cxo.12523

2. Ocansey S, Abu EK, Owusu-Ansah A, Mensah S,

Oduro-Boateng J, Kojo RA, et al. Normative values of retinal nerve fibre layer thickness and optic nerve head parameters and their association with visual function in an African population. Journal of ophthalmology. 2020 Feb 11;2020. doi:10.1155/2020/7150673

3. Scuderi G, Fragiotta S, Scuderi L, Iodice CM, Perdicchi A. Ganglion cell complex analysis in glaucoma patients: What can it tell us? *Eye Brain*. 2020;12:33-44. doi:10.2147/EB.S226319

4. Geng W, Wang D, Han J. Trends in the Retinal Nerve Fiber Layer Thickness Changes with Different Degrees of Visual Field Defects. *J Ophthalmol*. 2020;2020. doi:10.1155/2020/4874876

5. Batool A, Azam S, Nehal I. To evaluate the retinal nerve fiber layer thickness in different types of glaucoma. Adv Ophthalmol Vis Syst. 2021;11(1):5-9. doi:10.15406/aovs.2021.11.00400

6. Zhang N, Wang J, Li Y, Jiang B. Prevalence of primary open angle glaucoma in the last 20 years: a meta-analysis and systematic review. *Sci Rep*. 2021;11(1):1-12. doi:10.1038/s41598-021-92971-w

7. Allison K, Patel D, Alabi O. Epidemiology of Glaucoma: The Past, Present, and Predictions for the Future. *Cureus*. 2020;12(11). doi:10.7759/cureus.11686

8. Brilliant LB, Pokhrel RP, Grasset NC, Lepkowski JM, Kolstad A, Hawks W, et al. Epidemiology of blindness in Nepal. Bulletin of the World Health Organization. 1985;63(2):375.[Article]

9. Ramadan SR, Aly MM, Ashry SH El. Macular Thickness Asymmetry Measurements in Relatives of Primary Open Angle Glaucoma Patients. 2019;76(July):4182-4188.[Article]

10. O'Brien JM, Salowe RJ, Fertig R, Salinas J, Pistilli M, Sankar PS, Miller-Ellis E, Lehman A, Murphy WHA, Homsher M, Gordon K, Ying GS. Family History in the Primary Open-Angle African American Glaucoma Genetics Study Cohort. Am J Ophthalmol. 2018 Aug;192:239-247. doi: 10.1016/j.ajo.2018.03.014. Epub 2018 Mar 17. PMID: 29555482; PMCID: PMC6064667.

11. McMonnies CW. Historial de glaucoma y factores de riesgo. *J Optom*. 2017;10(2):71-78. doi:10.1016/j.optom.2016.02.003

12. Kumar S, Malik MA, Kaur J, Sihota R. Genetic variants associated with primary open angle glaucoma in Indian population. *Genomics*. 2017;109(1):27-35. doi:10.1016/j.ygeno.2016.11.003

13. Zanon-Moreno V, Ortega-Azorin C, Asensio-Marquez EM, Garcia-Medina JJ, Pinazo-Duran MD, Coltell O, et al. A multi-locus genetic risk score for primary open-angle glaucoma (POAG) variants is associated with POAG risk in a Mediterranean population: inverse correlations with plasma vitamin c and e concentrations. International Journal of Molecular Sciences. 2017 Nov 1;18(11):2302. doi:10.3390/ijms18112302

14. Rolle T, Dallorto L, Briamonte C, Penna RR. Retinal nerve fibre layer and macular thickness analysis with Fourier domain optical coherence tomography in subjects with a positive family history for primary open angle glaucoma. *Br J Ophthalmol*. 2014;98(9):1240-1244. doi:10.1136/bjophthalmol-2013-304519

15. Oli A, Joshi D. Can ganglion cell complex assessment on cirrus HD OCT aid in detection of early glaucoma? *Saudi J Ophthalmol*. 2015;29(3):201-204. doi:10.1016/j.sjopt.2015.02.007

16. Sihota R, Sony P, Gupta V, Dada T, Singh R. Diagnostic capability of optical coherence tomography in evaluating the degree of glaucomatous retinal nerve fiber damage. *Investig Ophthalmol Vis Sci*. 2006;47(5):2006-2010. doi:10.1167/iovs.05-1102

17. Medeiros FA, Lisboa R, Weinreb RN, Liebmann JM, Girkin C, Zangwill LM. Retinal ganglion cell count estimates associated with early development of visual field defects in glaucoma. *Ophthalmology*. 2013;120(4):736-744. doi:10.1016/j.ophtha.2012.09.039

18. Lakkis G. The ganglion cell complex and glaucoma. *Pharma*. 2014;(March):28-32.

19. Tham YC, Aung T, Fan Q, Saw SM, Siantar RG, Wong TY, et al. Joint effects of intraocular pressure and myopia on risk of primary open-angle glaucoma: the singapore epidemiology of eye diseases study. Scientific reports. 2016 Jan 13;6(1):19320. doi:10.1038/srep19320

20. Khanal S, Thapa M, Racette L, Johnson R, Davey PG, Joshi MR, et al. Retinal nerve fiber layer thickness in glaucomatous Nepalese eyes and its relation with visual field sensitivity. Journal of Optometry. 2014 Oct 1;7(4):217-24.doi:10.1016/j.optom.2014.05.002

21. Malik A, Singh M, Arya SK, Sood S, Ichhpujani P. Retinal nerve fiber layer thickness in Indian eyes with optical coherence tomography. *Nepal J Ophthalmol*. 2012;4(1):59-63. doi:10.3126/nepjoph.v4i1.5852

22. Cubuk M, Sahinoglu-Keskek N, Keskek SO. Retinal nerve fber layer thickness in a healthy Turkish population measured by optical coherence tomography. *Ann Saudi Med*. 2016;36(6):409-413. doi:10.5144/0256-4947.2016.409

23. Godar ST, Kaini K. Study of Retinal Nerve Fiber Layer Thickness by Optical Coherence Tomography in Primary Open Angle Glaucoma, Glaucoma Suspect and Normal Nepalese Population. *Nepal Med Coll J*. 2020;22(3):135-140. doi:10.3126/nmcj.v22i3.32635

24. Holló G, Naghizadeh F, Vargha P. Accuracy of macular ganglion-cell complex thickness to total retina thickness ratio to detect glaucoma in white Europeans. *J Glaucoma*. 2014;23(8):e132-e137. doi:10.1097/IJG.0000000000000030

25. Miljkovic A, Babic N, Sofija D, Barisic S, Ljikar J, Jovanovic S. Peripapillary retinal nerve fibre thickness in patients with primary open-angle glaucoma. Published online 2019:1-19. doi:10.21203/rs.2.16429/v1

26. Chauhan BC, Garway-Heath DF, Goñi FJ, Rossetti L, Bengtsson B, Viswanathan AC, et al. Practical recommendations for measuring rates of visual field change in glaucoma. British Journal of Ophthalmology. 2008 Apr 1;92(4):569-73. doi:10.1136/bjo.2007.135012