Structure-Function Correlation of Juxtapapillary Choroidal Thickness With Visual Field Analysis of Patients Suspected With Glaucoma

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ABSTRACT

Purpose: To conduct an evaluation of juxtapapillary choroidal thickness of patients suspected with glaucoma obtained through spectral domain optical coherence tomography (SD-OCT) and correlate it with perimetry results.

Methods Design: Cross-sectional **Study Population:** 175 eyes diagnosed as "glaucoma suspect" had standard automated perimetry (SAP) to document the presence of functional glaucomatous damage using optimal near-point correction using the Humphrey Visual Field Analyzer II, 30-2 or 24-2 SITA-standard program. SD-OCT imaging of the retinal nerve fiber layer (RNFL) was also done to look for structural glaucomatous damage and in using enhanced depth imaging of the optic nerve and the Cirrus caliper tool, choroidal thickness was measured at five predetermined points temporal and nasal from the optic nerve. The population was classified into two groups: Group 1 are those with structural or functional glaucomatous damage (n=68) and Group 2 were those without (n=107).

Results: One-Way Multivariate Analysis of Covariance was used in comparing the mean temporal and nasal choroidal thickness scores of the two groups. There are no statistical differences in terms of the mean temporal choroidal thickness (p=0.856) and mean nasal choroidal thickness (p=0.734) between patients with and without glaucomatous damage. The mean temporal and nasal choroidal thickness scores of the two groups at different juxtapapillary locations: 0 µm, 250 µm, 500 µm, 750 µm and 1000 µm away from the disc were also not statistically different.

Conclusion: Results show that from this present cohort of glaucoma suspect patients, juxtapapillary choroidal thickness is not correlated with structural and functional glaucomatous damage.

Keywords: juxtapapillary choroidal thickness, glaucoma suspect, standard automated perimetry, spectral domain optical coherence tomography, enhanced depth imaging, retinal nerve fiber layer

INTRODUCTION

Glaucomatous optic neuropathy is described as death of retinal ganglion cells and glial cells that will eventually develop distinctive patterns of visual dysfunction measured by perimetry.

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The diagnosis of a "glaucoma suspect" is made when patients have at least one clinical feature of the disease, including an elevated intraocular pressure (IOP), a suspicious optic nerve appearance, commonly referred to as "cupping," a repeatable visual field abnormality consistent with optic nerve damage, or a strong family history of glaucomatous disease.[1]

The pathogenesis of glaucoma is not fully understood. Multiple factors have been identified with elevated IOP as one of the primary risk factors. However, there are patients who have IOP within the normal range and still develop glaucoma and also patients who have IOP above normal and do not develop the disease.

Disturbance in vascular autoregulation is also a pathogenic factor. Studies have identified reduced ocular perfusion as a risk factor for glaucoma prevalence, incidence and progression.[2] While the branches of the central retinal artery supply the surface retinal nerve fiber layer, the primary blood supply of the prelaminar and laminar portion of the optic nerve is principally derived from the choroid. This led to the hypothesis that disturbance in the choroidal blood flow could contribute to glaucomatous optic neuropathy.

Evidence shows mixed results regarding the relationship of choroidal thickness and glaucoma. Sigler hypothesized that chronic IOP elevation may lead to distention and thinning of the peripapillary choroid.[3] Sullivan-Mee postulated that the region of the choroid that should be under investigation is the one that provides blood supply to the optic nerve, the region directly adjacent to it, hence focusing on juxtapapillary choroidal thickness.[2]

Spectral Domain Optical Coherence Tomography (SD-OCT) allows for non-invasive in vivo evaluation of intraocular anatomy at the micrometer level with high reliability and reproducibility. The aim of this study is to use SD-OCT with enhanced depth imaging (EDI) to measure juxtapapillary choroidal thickness and correlate it with visual field results of glaucoma suspect patients.

SUBJECTS AND METHODS

Study Design and Setting

This investigation is a cross-sectional study.

Study Population

Criteria for eligibility were: age ≥18 years; refractive error ≤5 diopters as it is established that choroidal thickness is smaller in highly myopic eyes [4]; no media opacities, no history of corneal or glaucoma surgery; no previous diagnosis of glaucoma; and no visual field loss due to non-glaucomatous pathology (including retinal, optic nerve or visual pathway disorders). Subjects with uncomplicated cataract surgery at least three months prior to SD-OCT choroidal imaging were eligible.

Methodology

One-way multivariate analysis of covariance (MANCOVA) was used in comparing the mean temporal and nasal choroidal thickness scores of the two groups. MANCOVA was utilized for two reasons: (1) the study has multiple dependent or outcome variables and (2) certain covariates (continuous-level confounders) were identified and can be statistically controlled. Multivariate analysis was used in order to compare the two dependent variables simultaneously instead of conducting two independent t-tests.

Data collection was done in 6 months' time. A total of 175 eyes of glaucoma suspect patients from the outpatient department as well as from the private clinics of different ophthalmologists of the same institution had standard automated perimetry (SAP) with optimal near-point correction using the Humphrey Visual Field Analyzer II, 30-2 or 24-2 SITA-standard program at 31.5 apostilbs, Stimulus III (Carl Zeiss Meditec, Inc., Dublin, CA). Visual fields were required to meet the following reliability criteria: false positives and false negatives <33%; fixation losses <20%. Functional glaucomatous damage is established if the patient has an abnormal glaucoma hemifield test with three or more non-edge points in the pattern deviation plot with a p-value of <5% or 1 point with a p-value of <1% with associated visual field patterns characteristic of death of retinal nerve fiber related defects: altitudinal, arcuate, partial arcuate, nasal step and temporal wedge.[5] The visual fields were assessed as normal even if there are non-specific visual field defects if their mean deviation (MD) and pattern standard deviation (PSD) values were within 95% of the confidence interval and if their glaucoma hemifield test falls "within normal limits".

SD-OCT imaging (Cirrus HD-OCT, Carl Zeiss Meditec, Inc., Dublin, CA) of the RNFL was done and in using EDI of the optic nerve, choroidal thickness was measured. To be included in the analysis, signal strength of the image has to be 5 or more. The patient is said to have structural damage if the RNFL thickness falls on the 1st to 5th percentile on the temporal–superior–nasal–inferior–temporal (TSNIT) graph and if there is blunting of its double hump appearance.

Measurement of juxtapapillary choroidal thickness using EDI

The HD 5 line raster scan was centered at the optic disc. The line bisecting the disc was selected. A single observer obtained the juxtapapillary choroidal thickness. It was measured using the Cirrus device caliper tool from the posterior edge of the retinal pigment epithelium to the choroid-sclera junction [6] in 5 points 250 um apart, nasally and temporally away from the disc (Figure 1).

The population was classified into two groups: those with structural or functional glaucomatous damage (Group 1) and those without (Group 2).

RESULTS

To compare choroidal thickness in glaucoma suspects, patients with structural or functional glaucomatous damage (n=68) were assigned to the first group, and those without damage (n=107) to the second group. The sample size of 175 eyes achieved a power of 0.9999 or 99.99% with an effect size of 0.1759 (Chart 2).

The demographic profile of the participants according to their group assignment is summarized in Table 1. The mean age of those with glaucomatous damage was 54.22 (16.46) while that without glaucomatous damage was 45.50 (16.21). Comparing these two revealed a p-value of 0.0007 denoting that the age of these two groups were statistically different. That is, glaucoma suspect patients deemed to have glaucomatous damage was statistically older than those without glaucomatous damage. In terms of sex, it can be seen that the sex distribution among patients with glaucomatous damage was equal (50%) while those without glaucomatous damage were mostly female. Comparative analysis using chi-square revealed a p-value of 0.763 denoting that the proportion of males and females between the two was not statistically different.

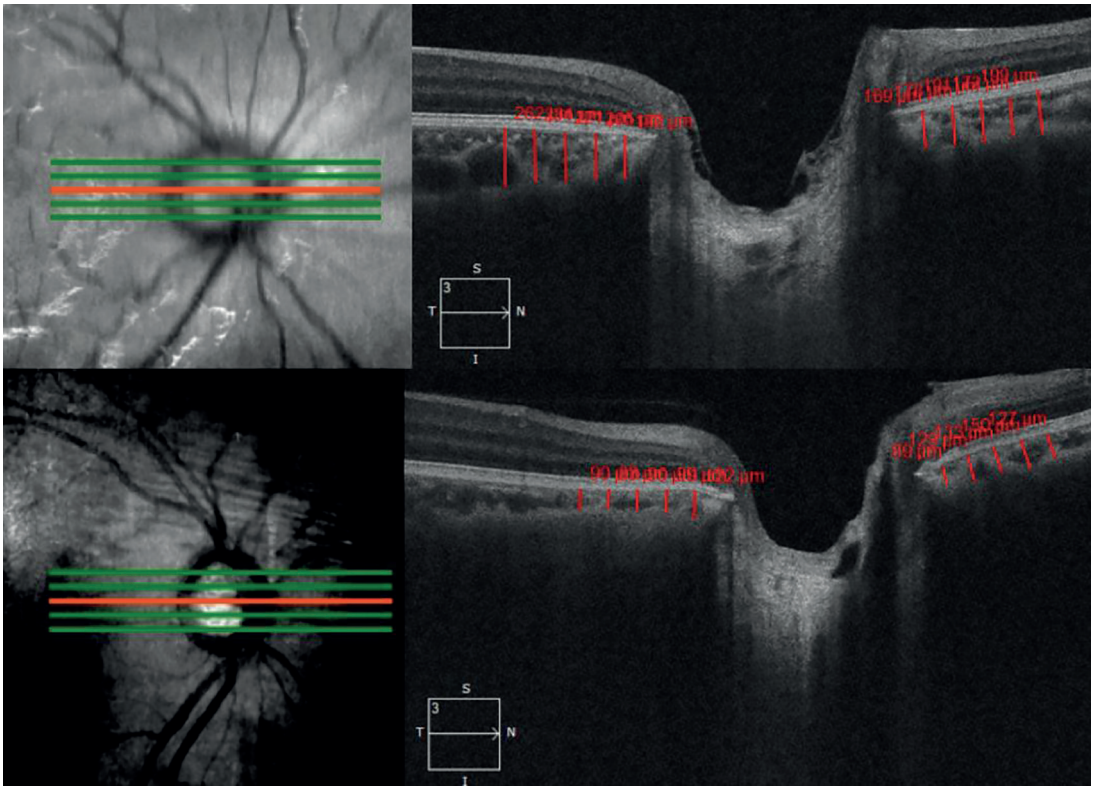

Figure 1. Illustrative scans of the right eye from a 22-year old (above) with a mean choroidal thickness of 175 μm and a 58-year old (below) with a mean choroidal thickness of 104 μm.

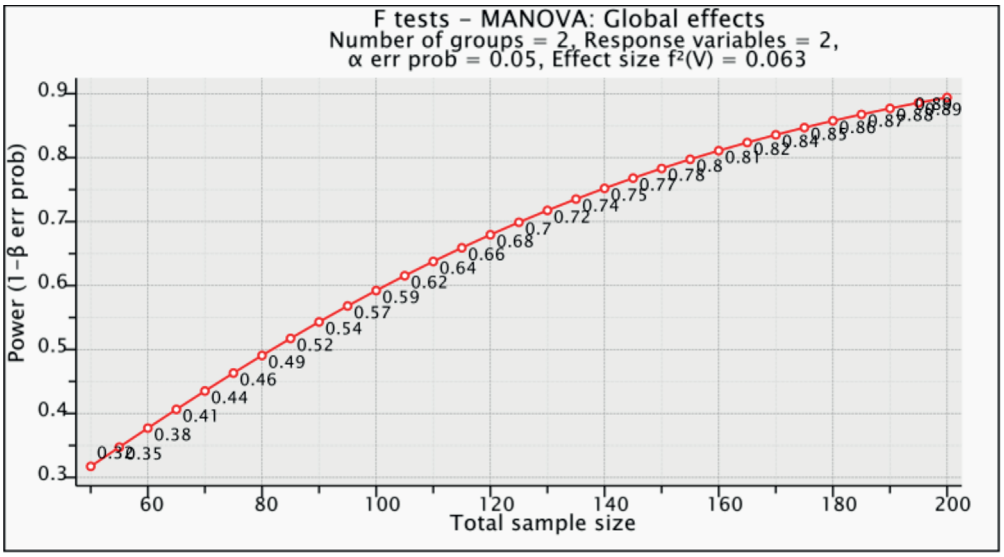

Chart 1. Sample size determination of patients suspected with glaucoma

F tests - MANOVA: Global effects			
Options:	Pillai V, O'Brien-Shieh Algorithm		
Analysis:	A priori: Compute required sample size		
Input:	Effect size $f^2(V)$	=	0.063
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	Number of groups	=	2
	Response variables	=	2
Output:	Noncentrality parameter λ	=	9.8280000
	Critical F	=	3.0551618
	Numerator df	=	2.0000000
	Denominator df	=	153
	Total sample size	=	156
	Actual power	=	0.8000917
	Pillai V	=	0.0592662
Non-Response:	Non-Response Rate	=	0.10
	No. of Non-Responders	=	18
	Non-response-inflated sample size	=	174

Table 2 shows the comparison of the mean temporal and mean nasal choroidal thickness scores between respondents with and without glaucomatous damage. After removing the confounding effects of covariates, specifically age, the adjusted mean temporal choroidal thickness in the glaucomatous damage group was 180.69 ± 6.46 while those without glaucomatous damage had adjusted mean temporal score of 182.21 ± 5.11. The mean nasal choroidal thickness in the glaucomatous damage group was 194.12 ± 6.20 while those without glaucomatous damage had adjusted mean nasal score of 191.39 ± 4.90. It can be seen that the computed p-value for mean temporal and mean nasal choroi-

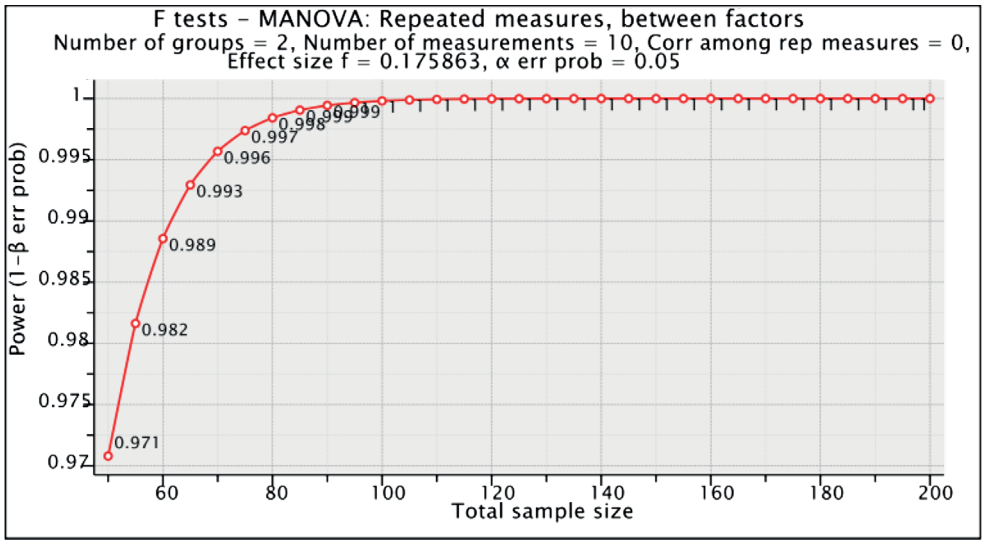

Chart 2. Sample size & power determination of patients suspected with glaucoma: Post-Hoc Power Analysis

F tests - MANOVA: Repeated measures, between factors			
Options:	Pillai V, O'Brien-Shieh Algorithm		
Analysis:	Post hoc: Compute achieved power		
Input:	Effect size f	=	0.1758631
	α err prob	=	0.05
	Total sample size	=	175
	Number of groups	=	2
	Number of measurements	=	10
	Corr among rep measures	=	0
Output:	Noncentrality parameter λ	=	54.1237024
	Critical F	=	3.8957733
	Numerator df	=	1.0000000
	Denominator df	=	173
	Power (1-β err prob)	=	1.0000000
	Pillai V	=	0.2362204

dal thicknesses were 0.856 and 0.734, respectively. Since the computed p-values were less than the alpha of 0.05, we can conclude that the comparison of mean temporal and mean nasal thickness scores were not statistically significant.

Table 3 shows the comparison of the temporal and nasal choroidal thickness scores (from 0 μm to 1,000 μm) between respondents with and without glaucomatous damage. On a multivariate level, the comparison using MANCOVA was not statistically significant (p=0.8892) even after controlling for the confounding effects of sex. Ideally, we no longer explore the univariate (per variable) comparison. However, for presentation purposes, the comparisons of 10 dependent variables are provided. All comparisons at different juxtapapillary locations were not statistically different.

DISCUSSION

The management of patients suspected with glaucoma can be difficult. On one hand, early treatment

Table 1. Demographic profile of respondents with and without glaucomatous damage (N = 175)

Characteristic	With Glaucomatous Damage (n=68)	Without Glaucomatous Damage (n=107)	p-value (Two-tailed)
Age (Mean ± SD)	54.22 ± 16.46	45.50 ± 16.21	0.0007
Sex (f, %)			0.763
Female	34 (50.00%)	51 (47.66%)	
Male	34 (50.00%)	56 (52.35%)	
Perimetric Glaucoma Damage (f, %)			0.0001
Yes	49 (72.06%)	0 (0.00%)	
No	19 (27.94%)	100 (100.00%)	
Cup Disc Ratio (Mean ± SD)	0.69 ± 0.08	0.64 ± 0.07	0.0001
Perimetric Defect (MD)	–5.08 ± 3.91	–3.52 ± 1.37	0.0002
RNFL Damage (f, %)			0.0001
Yes	48 (72.23%)	0 (0.00%)	
No	18 (27.27%)	103 (100.00%)	

**Significant* at 0.05
†Significant at 0.01
Glaucomatous damage is defined as having *functional damage* evident in the perimetry with an abnormal glaucoma hemifield test with 3 or more non-edge points in the pattern deviation plot with a p-value of <5% or 1 point with a p-value of <1% with visual field patterns such as altitudinal, arcuate, partial arcuate, nasal step and temporal wedge or *structural damage* if the RNFL thickness falls on the 1st to 5th percentile on the TSNIT graph and if there is blunting of its double hump appearance.

Table 2. Multivariate analysis of covariance for mean temporal and nasal choroidal thickness between patients with and without glaucomatous damage after controlling covariates (N = 175)

Dependent Variables	With Glaucomatous Damage (n=68)		Without Glaucomatous Damage (n=107)		F-value	p-value
	Unadjusted Mean ± SD	Adjusted Mean[a] ± SE	Unadjusted Mean ± SD	Adjusted Mean[a] ± SE		
Mean Temporal Choroidal Thickness	177.73 ± 60.94	180.69 ± 6.46	184.10 ± 49.32	182.21 ± 5.11	0.03	0.856
Mean Nasal Choroidal Thickness	190.29 ± 54.06	194.12 ± 6.20	193.82 ± 49.89	191.39 ± 4.90	0.12	0.734

Pillai Trace = 0.003, *F* = 0.24, *p*=0.7862
[a] Means were adjusted for age and sex
SE = Standard Error; SD = Standard Deviation
*Significant at ≤0.05 level
†Significant at ≤0.01 level

can be done to prevent irreversible glaucomatous optic neuropathy. On the other hand, if the patient does not have the disease, he may be started on unnecessary costly treatments and burdened with side effects. The most established risk calculator is based on data from the Ocular Hypertension Treatment Study and European Glaucoma Prevention Study.[7] Factors evaluated include: IOP, age, central corneal thickness, vertical cup-disc ratio and standard deviation pattern of the visual field. Still with all these factors, the accuracy of predicting the development of definitive glaucomatous damage in a suspect was only fair with the area under the receiver-operating curve of 0.68.[8] This is the reason why there is a need to identify other contributing factors.

Choroidal thickness was considered to be associated with glaucomatous optic neuropathy since its arbitraries supply a majority of the optic nerve. Studies using fluorescein angiography showed reduced retinal blood flow and choroidal perfusion defects.[9] Others used post-mortem histopathologic specimens which showed eyes with advanced glaucomatous damage after long-standing primary open-angle glaucoma exhibited several changes including decreased density of capillaries of the choriocapillaris and decreased density of large choroidal vessels.[10]

Table 3. Multivariate analysis of covariance for mean temporal and mean nasal choroidal thickness at 0 µm, 250 µm, 500 µm, 750 µm and 1,000 µm between patients with and without glaucomatous damage after controlling covariates (N = 175)

Dependent Variables	With Glaucomatous Damage (n=68)		Without Glaucomatous Damage (n=107)		F-value	p-value
	Unadjusted Mean ± SD	Adjusted Mean[a] ± SE	Unadjusted Mean ± SD	Adjusted Mean[a] ± SE		
Mean Temporal Choroidal Thickness 0 µm	169.04 ± 54.22	169.26 ± 5.82	171.73 ± 44.42	171.59 ± 4.64	0.10	0.754
Mean Temporal Choroidal Thickness 250 µm	173.22 ± 61.17	173.61 ± 6.39	178.91 ± 49.58	178.66 ± 5.10	0.38	0.538
Mean Temporal Choroidal Thickness 500 µm	178.65 ± 66.93	179.07 ± 6.87	182.97 ± 52.27	182.70 ± 5.48	0.17	0.680
Mean Temporal Choroidal Thickness 750 µm	182.97 ± 71.48	183.43 ± 7.68	190.28 ± 60.90	189.99 ± 6.12	0.45	0.506
Mean Temporal Choroidal Thickness 1,000 µm	184.78 ± 71.50	185.16 ± 8.05	196.59 ± 64.98	196.34 ± 6.42	1.18	0.279
Mean Nasal Choroidal Thickness 0 µm	172.25 ± 45.79	172.49 ± 5.49	179.30 ± 45.97	179.15 ± 4.37	0.90	0.344
Mean Nasal Choroidal Thickness 250 µm	186.75 ± 51.70	186.90 ± 5.82	191.61 ± 45.71	191.51 ± 4.64	0.38	0.536
Mean Nasal Choroidal Thickness 500 µm	195.11 ± 60.57	195.35 ± 7.08	197.67 ± 57.67	197.53 ± 5.65	0.06	0.810
Mean Nasal Choroidal Thickness 750 µm	199.04 ± 64.83	199.24 ± 7.40	200.16 ± 58.89	200.03 ± 5.90	0.01	0.933
Mean Nasal Choroidal Thickness 1,000 µm	198.31 ± 65.68	198.57 ± 7.44	200.36 ± 59.28	200.19 ± 5.93	0.03	0.865

Pillai Trace = 0.03, $F = 0.50$, p=0.8892
[a] Means were adjusted for sex
SE = Standard Error; SD = Standard Deviation
*Significant at ≤0.05 level
†Significant at ≤0.01 level

OCT is a fast-evolving technology that allows non-invasive analysis of the posterior pole in vivo, thereby aiding in the prompt evaluation and management of ocular disease. Its advantage lies in its ability of segmentation, which is notably important in the diagnosis and management of glaucoma.[11] Its algorithms allow measurement of segments such as the retinal nerve fiber layer and the ability to compare it to previous examinations.

A number of studies utilized SD-OCT to correlate choroidal thickness and glaucoma showing mixed results. Lee found juxtapapillary choroidal thickness in the inferotemporal and superotemporal sectors of eyes with normal tension glaucoma significantly thinner than that of the healthy population.[12] Lee found a significant juxtapapillary choroidal thinning in the inferotemporal region of patients with primary open angle glaucoma compared with healthy subjects.[13] Sacconi measured sub-foveal choroidal thickness and found that patients with advanced primary open angle glaucoma have thinner measurements than control.[14] Roberts concluded that patients with sclerotic optic disc damage defined as having shallow cupping with peripapillary atrophy have 25-30% thinner peripapillary choroid than that of those with focal and diffuse damage and healthy controls.[15] However, Erlich compared peripapillary choroidal thickness of eyes with primary open angle glaucoma to glaucoma suspect eyes and concluded that the primary open angle glaucoma group did not demonstrate a reduced choroidal thickness.[16] In our analysis, nasal and temporal juxtapapillary choroidal thicknesses were not significantly different between glaucoma suspect patients with evident structural or functional glaucomatous damage and those without. Our analysis revealed patients with glaucomatous damage to be statistically older (54.22 ± 16.46) and have a higher mean cup-disc ratio (0.69 ± 0.08) than those without glaucomatous damage. This finding that glaucoma is related to age is consistent with most literature.[12-15] The morphologic changes of the optic nerve head should

be monitored because this could lead to functional vision loss.[17]

Swept source optical coherence tomography (SS-OCT) has an advantage over SD-OCT as it has software that automatically detects and measures the choroid. Akil used deep range imaging (DRI), a feature of SS-OCT, which automatically segments and measures the choroid to evaluate glaucomatous, pre-perimetric and non-glaucomatous eyes and found a significant correlation of RNFL thickness and peripapillary choroidal thickness in 1, 2, 5 and 6 clock hours of glaucomatous eyes.[18]

A limitation of this method of measurement is that it can be prone to variation as the choroid-sclera junction was manually set by the investigator. There is no fully automated software commercially available to measure this in SD-OCT unlike in SS-OCT.[19] A validation study on the measurement of choroidal thickness in SD-OCT is needed. Another limitation of the study is that only the nasal and temporal peripapillary choroid was measured. The researchers suggest developing a way to measure the superior and inferior peripapillary choroid, locations which are associated with glaucomatous RNFL loss.

Due to the cross-sectional study design, it was unlikely to reveal the impact of glaucomatous progression or conversion and its relation with choroidal thickness. Longitudinal studies are suggested for this purpose.

OCT angiography is an emerging modality to consider. It characterizes vascular information at various user-defined retinal layers as a vessel density map and quantitatively as vessel density.[20] The investigators suggest making use of this in evaluating the microvasculature of the optic nerve.

CONCLUSION

Glaucoma is a multi-faceted disease. Results show that from this present cohort of glaucoma suspect patients, juxtapapillary choroidal thickness is not correlated with structural and functional glaucomatous damage.

Conflict of Interest

The researchers are not supported financially or any means by any organizations for the completion of the study. The researchers claim no conflicts of interest.

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