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The correlation between frequency doubling technology matrix mean deviation and peripapillary retinal nerve fiber thickness of newly diagnosed glaucoma patients

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Abstract
Objective: To evaluate the relationship between glaucomatous structural damage assessed by RTVue SD-OCT and functional loss as measured by Frequency Doubling Technology (FDT) perimetry.
Materials and methods: One hundred and forty eyes of 70 newly diagnosed glaucomatous patients irrespective of intraocular pressure level were recruited from a private Tertiary Eye hospital in Lagos Nigeria. All the eyes underwent testing with Avanti RTVue XR SD-OCT (Optovue Inc., Fremont CA USA) and Frequency Doubling Technology (FDT) 24-2 threshold (Humphrey Matrix 800, 2011 Carl Zeiss Meditec, Dublin, CA). The relationship between average peripapillary retinal nerve fiber layer (pRNFL) and mean deviation on the FDT Matrix perimetry was evaluated using Pearson's correlation coefficient regression analysis.
Results: A total of 30 males (42.86%) and 40 (57.14%) females with mean age of 56±14 years with a range of 33-77 years. There were 46 (65.71%) patients with Primary Open-Angle Glaucoma (POAG) and 24 (34.29%) with chronic Primary Angle Closure Glaucoma (PACG). The FDT mean deviation was -14.68±10.59 dB and -10.88 ±8.34 dB for the Right eye (RE) and Left eye (LE) respectively. The mean average pRNFL thickness was 82.26±18.56 and 91.37±15.32 for RE and LE respectively. The Mean deviation significantly correlated with the average peripapillary RNFL thickness (Pearson correlation coefficient, r= 0.88, r^2 = 0.77, p-value 0.001 for RE and r= 0.851, r^2= 0.72, p-value 0.001 for LE).
Conclusion: In this cohort of glaucoma patients, at least 70% of average peripapillary retinal nerve layer thinning measured with RTVue SD-OCT was associated with correspondent visual field loss in glaucoma.

Keywords: Correlation, mean deviation, peripapillary RNFL thickness

Introduction
Glaucoma has remained the commonest cause of irreversible blindness globally accounting for 8.4 million blind persons [1]. It has been projected that at the end of this year, almost 80 million persons will be affected and 111.8 million persons by 2040 [2]. Sub-Saharan African is said to have the highest burden of glaucoma [3]. The prevalence of Glaucoma is Nigeria is said to be 5.02% for persons 40 years above with 70% being the Primary Open-Angle variant [4]. Glaucoma is characterized by retinal ganglion cells (RGCs) apoptosis resulting in characteristic optic neuropathy. The diagnosis is made from the structural changes in the optic nerve head and visual field changes. The White-on-White Standard Automated Perimetry (SAP) is the gold standard for glaucoma diagnosis and monitoring of progression [5]. However, SAP only detects visual changes after substantive structural damage [6]. Quigley *et al*. [7] reported that about 20% to 40% of the RGCs could be destroyed by the time visual field (VF) defects are detected by SAP, suggesting that there is substantial structural damage in the pre-perimetric stage of glaucoma. Newer perimetric technologies such Frequency Doubling technology and Pulsar perimetry have been able to detect functional deficits in the early stages of the disease process [8, 9]. For example, Prokesch and Eter [10] reported a sensitivity of 62.5% with FDT compared with 40% with SAP in the diagnosis of early, although SAP has higher specificity.
The advent of optical coherence tomography (OCT) has revolutionized the evaluation of structural deficits in glaucoma and make early detection of the disease possible [11].

It is also veritable tool in the monitoring of the disease progression [11].

This study aims to evaluate the structure-function relationship between Retinal nerve fiber layer (RNFL) thickness measured by spectral Domain Optical Coherence Tomography (SD-OCT) and visual field mean deviation (MD) measured by Frequency Doubling Technology (FDT) Matrix in glaucomatous patients. To best of our knowledge, this is the first structure-function relationship study in glaucoma in Nigeria using the SD-OCT and FDT.

Patients and Methods

It was a hospital based prospective study correlating the mean deviation of the FDT perimetry and the average peripapillary RNFL of newly diagnosed glaucoma patients seen over a period of one year.

Seventy newly diagnosed Primary Open Angle Glaucoma (POAG) and chronic Primary Angle Closure Glaucoma patients regardless of the level of the intraocular pressure level seen at Eye Foundation Hospital, Ikeja Lagos, a referral private tertiary training Eye center; between February 2018 and February 2019 who met the inclusion criteria were recruited into the study. The Ethical committee of the institution granted approval for the study and the tenets of Helsinki Declaration involving the use of human subjects were adhered to. Informed written consent from the patients was obtained.

The patients had a minimum Snellen acuity of 6/24, a reproducible and reliable (fixation loss and false negative error <20% and false-positive error <15%) glaucomatous VF defect obtained using the Frequency Doubling Technology (FDT) 24-2 threshold protocol (Humphrey Matrix 800, 2011 Carl Zeiss Meditec, Dublin, CA). Glaucomatous visual field abnormality is as three or more adjacent points in an expected location of the central 24° field that have *P* less than 5% on the pattern deviation plot, one of which must have *P* less than 1% and Glaucoma Hemifield test outside normal limits. The Mean deviation was computed and used to classify the visual field loss into mild, moderate and severe according to the Hodapp, Parrish and Anderson classification. Open anterior chamber angle was defined as visualization of at trabecular meshwork in at least 3 quadrants while closed angle was defined as iridocorneal contact in at least 3 quadrants using the Shaffer's grading on indirect gonioscopy.

Patients with dense cataract that affected visual field and RNFL measurements, diabetic retinopathy and macular edema were excluded. The glaucomatous fundus changes included an enlarged vertical cup-to-disc ratio (>0.6), thinning of the rim width, and/or a RNFL defect.

Optical coherence tomographic examination was performed by an experienced examiner using Avanti RTVue XR SD-OCT (Optovue Inc., Fremont CA USA). RNFL measurements were recorded as an average over four quadrants, 12 clock hours and mean thickness of the total circumpapillary scan. Depending on the instrument's normative database, any RNFL measurements outside 95% normal limits that were confirmed on at least two of three repeat scans were highlighted as abnormal thinning in red or yellow according to the severity of thinning. The average peripapillary RNFL thickness for each eye was recorded and correlated with the mean deviation for each corresponding eye.

Statistical Analyses

All data were cross checked for accuracy entered in a proforma and were analyzed using commercially available statistical data management software- Statistical Package for Social Sciences (IBM-SPSS) version 25. Continuous variables were illustrated in the form of mean ±SD and categorical variables were shown in the form of frequency and percent. Comparison among continuous data was done using Anova, whereas categorical data were analyzed using χ^2-test. Pearson's correlation coefficient was used to investigate the relation between variables. *P* value less than 0.05 was considered statistically significant.

Results

There were 30 males (42.86%) and 40 females (57.14%). The mean age of the subjects was *56.23 ± 14.52 years* with range of 33-77 years. Majority of the subjects was in the 50-59 years age bracket (28%). Forty-six (65.71%) of the subjects had POAG while 24 (34.29%) had PACG. Majority of the subjects (88.57%) had formal education. Table 1.

Table 1: Socio-demographic and clinical Characteristics

Characteristics	Frequency (n=70)	Percentage (%)
Age		
30-39	12	17.14
40-49	8	11.43
50-59	20	28.57
60-69	14	20.00
70-79	16	22.86
Mean [Range]	56.23 ± 14.52 years [33-77]	
Sex		
Male	30	42.86
Female	40	57.14
Educational Status		
None	8	11.43
Secondary	14	20.00
Tertiary	48	68.57
Type of Glaucoma		
POAG	24	65.71
PACG	46	34.29

Mean Deviation and the average peripapillary Retinal Nerve Fiber Layer thickness

The mean value of the FDT matrix mean deviation indicated that most of the both eyes had moderate-to-severe glaucoma (Table 2). There was no statistical significant difference between the mean deviation of the eyes with POAG and PACG. Similarly, there was no statistical significant difference between the mean RNFL thickness in eyes with POAG and PACG. Table 3.

Results also showed that eyes with early disease had significantly higher average RNFL measurements when compared with eyes with moderate and severe disease except in the left eye where eyes with moderate glaucoma had slightly higher average RNFL measurement than those with mild glaucoma (Table 4).

Table 2: CVF Mean deviation and RNFL thickness

Characteristics	Mean ± SD (n=70)	Range (min – max)
Mean Deviation (dB)		
RE	-14.68 ±10.59	-31.37 to -1.37
LE	-10.88 ± 8.34	-25.43 to -1.64
Average p RNFL thickness(µm)		
RE	82.26 ± 18.56	55 – 109.37
LE	91.37 ± 15.32	60-118

Table 3: Association between types of glaucoma and mean deviation, and Average RNFL thickness

Characteristics	RE Mean ± SD	LE Mean ± SD
Mean Deviation (dB)		
POAG	-14.56 ± 9.76	-12.15 ± 9.72
PACG	-14.90 ± 12.24	-8.45 ± 3.84
t test (p-value)	0.13 (0.898)	1.79 (0.078)
Average pRNFL thickness(µm)		
POAG	79.52 ± 16.31	89.69 ± 17.69
PACG	87.49 ± 20.61	94.58 ± 8.66
t test (p-value)	1.77 (0.08)	1.27 (0.207)

Table 4: Association between severity of glaucoma and average pRNFL thickness

CVF Mean deviation	pRNFL RE	ANOVA (p-value)
Mean ± SD		
Mild	95.74±8.05	52.88 (0.001)*
Moderate	94.70±5.97	
Severe	66.89±5.97	
CVF Mean deviation	**pRNFL LE**	
Mild	101.93±8.42	109.69 (0.001)*
Moderate	102.86±86	
Severe	75.07±8.30	

* Statistically significant (p<0.05)

Correlation between average peripapillary RNFL thickness and FDT mean deviation

A statistically significantly strong linear correlation exists between structural damage and visual field loss measured by the Mean deviation from FDT Matrix perimeter. For as the average retinal nerve layer thickness is decreasing, mean deviation is decreasing: RE (r=0.88), LE (r=0.851); (*p=0.001)*. R-Square (r^2) is between 0.72-0.77, showing that between 72-78% of the structural damage values are correlating with the visual field loss as measured by the mean deviation (Table 4, Figures 1 and 2)

Table 4: Correlation between structural damage and visual field loss using OCT peripapillary nerve fiber thickness (in micrometer) and the mean deviation (MD) in decibel from central visual field.

OCT RNFL	CVF MD	
RE	**RE**	
	The Pearson correlation coefficient, r	0.88
	R-Square (r^2)	0.77
	p-value	*0.001**
	95% CI	-0.59 – (-0.45)
	LE	
LE	The Pearson correlation coefficient, r	0.851
	R-Square (r^2)	0.72
	p-value	*0.001**
	95% CI	-0.53 – (-0.39)

* Statistically significant (p<0.05)

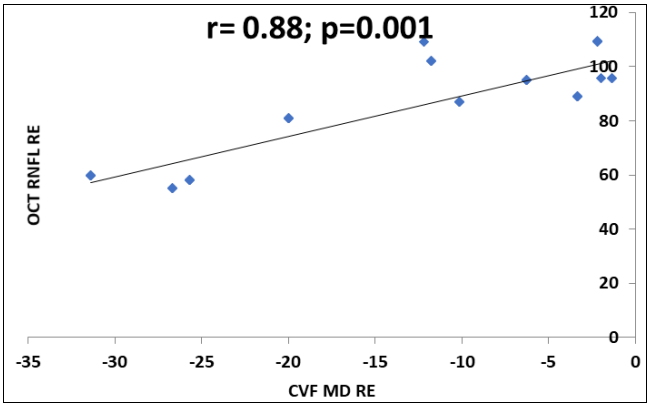

Fig 1: Correlation between OCT RNFL RE and CVF MD RE

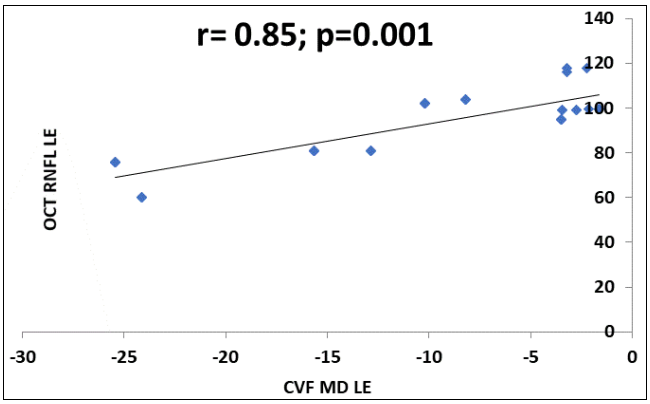

Fig 2: Correlation between OCT RNFL LE and CVF MD LE

Discussion

In this study, we considered newly diagnosed glaucoma patients with either primary open-angle glaucoma and chronic primary close-angle glaucoma which had not been done before. Retinal ganglion cells death is the common pathway for all glaucoma. We did not observe any statistical significant difference in the mean deviation and retinal nerve fiber layer thickness between the two types of glaucoma (Table 3). In this study, the mean FDT mean deviation of -14.68±10.59 decibel and -10.8±8.34 decibel (Tablet 2) for the right eye and left eye respectively indicated that most of the eyes of these cohort of patients had moderate-to-severe glaucoma. It has been observed that glaucoma patients in Nigeria like most developing countries present late when the disease process has gone far [12, 13]. In a clinic-based study by Olawoye[12] and colleague, 48.5% of 669 eyes of 336 glaucoma patients at presentation had mean deviation of > -12 dB. Similarly, Abdull *et al.* [13] found that in Northern Nigeria, over 70% of glaucoma patients presented with the advanced disease. So, it is important to increase the awareness and need for those above 40 years to go for comprehensive eye check.

The relationship between the structural and functional changes in glaucoma has been studied extensively. However, most of the studies correlated SAP and RNFL thickness and they found strong correlation between mean deviation and RNFL thickness [11, 14-15]. Few studies have studied correlation between mean deviation using FDT perimetry and spectral domain OCT. In our study, we found a correlation between the average peripapillary RNFL and mean deviation using Pearson's correlation coefficient, r to be 0.88 to 0.851 (p-value 0.001) for the right eye and left eye respectively. Our finding is quite higher than what was obtained in other studies. Hayashi *et al.* [16] reported a correlation using the same Pearson's correlation coefficient (r) of 0.384. They used FDT perimetry and RTVue SD-OCT. Also, Silva *et al.* [17] using FDT perimetry and RTVue SD-OCT, got r value of 0.41. The association between structural and functional measures have been found to increase with severity of the disease with RNFL thickness linearly related to SAP loss at advanced disease [18-19]. This observation was fully demonstrated in our study (Figures 1 and 2). As noted earlier, most of the subjects in our study have moderate-to-advanced disease compared with these other studies which had mild-to-moderate disease and this might explain why our figure was higher than those reported by these other studies.

In the same study, Silva and colleagues reported Pearson's coefficient of 0.32 when RNFL was compared with SAP. That finding is an indication that Frequency doubling technology (FDT) perimetry is more sensitive in detecting visual field changes compare with SAP. Even in glaucoma suspects and ocular hypertensives, FDT mean deviation has been found to be significantly correlated with RNFL thickness. So FDT perimetry and OCT are useful adjuncts in the early detection of glaucoma [20].

Conclusion

This cohort of newly diagnosed glaucoma patients presented with mostly moderate-to-advanced disease and at least 70% of average peripapillary retinal nerve layer thinning measured with RTVue SD-OCT was associated with correspondent visual field loss measured with FDT Matrix perimeter. Combining SD-OCT and FDT perimetry is useful in objectively quantifying the amount of glaucomatous damage.

Conflict of interest: Nil

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