Sensitivity of Ganglion Cell Complex Thicknessversus Retinal Nerve Fiber Layer Thickness in Diagnosis of Primary Open-Angle Glaucoma

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Received: 31-8-2024, Accepted: 11-9-2024, Published online:16-12-2024

EJO(MOC) 2024;4(4):237-246.

Short title: Sensitivity of Ganglion Cell Complex versus RNFL inDiagnosis of POAG.

Abstract

Purpose: The current study aims to evaluate and assess the utility of OCT in the diagnosis of primary open angle glaucoma (OAG) by measuring the thickness of the retinal nerve fibre layer (RNFL) and the macular ganglion cell complex (GCC).

Patients and methods: 132 patients' 220 eyes were included for the study, and patients were split into 2 groups: Group 1 comprised 120 eyes from 82 individuals over forty years old with a primary OAG diagnosis. Group 2 comprised 50 control participants and 100 normal eyes. Additional classifications for glaucomatous eyes were: Moderate glaucoma (47 eyes) and mild, (63 eyes) glaucoma (47 eyes) and ten eyes with severe glaucoma. The RNFL parameters (average total thickness, superior average thickness, and total average thickness, superior average thickness, and inferior average thickness) as well as the ganglion cell complex (GCC) characteristics were assessed using 3D-OCT 2000 (Topcon) OCT.

Result: Regarding RNFL thickness, cup-to-disc ratio, and intraocular pressure (IOP), GCC thickness, and best corrected visual acuity (BCVA), there was a positive statistically significant connection of high likelihood ($P<0.001$).

Conclusion: Imaging of the GCC has a good diagnostic capacity to RNFL, When it comes to early diagnosis and discrimination between glaucoma patients and healthy individuals,

Keywords: Ganglion cell, Glaucoma, Optical coherence tomography, Retinal nerve fiber.

INTRODUCTION:

The most common cause of permanent blindness is glaucoma, a multifactorial progressive neurological illness. According to current estimates, there will be 111.8 million glaucoma sufferers globally by 2040, up from 76.5 million in 2020[1].

The main pathologic change in glaucoma is the loss of retinal ganglion cells (RGCs), which causes atrophy of all related inner retinal layers: the retinal nerve fibre layer (RNFL), which houses the GCs' axons, the ganglion cell layer (GCL), which houses the GCs' body, and the inner plexiform layer (IPL), which houses the GCs' dendrites[2].

While measuring RNFL thickness has shown promise in the diagnosis of glaucoma, measuring RGC (the layer that precedes RNFL loss) aids in the early detection of the condition[3].

It is easy to distinguish glaucomatous individuals from normal people if there is a visual field impairment. When vision field is normal, the difficulty lies in telling a glaucoma suspect from normal[4].

A cutting-edge medical diagnostic imaging technique called optical coherence tomography (OCT) allows micron resolution tomographic or cross-sectional imaging regarding biological tissues[5]. OCT is particularly well-suited for ophthalmology diagnostic applications because to its optical access to the anterior and posterior eye[6].

Spectral domain-optical coherence tomography (SD-OCT) technology has made macular imaging a worthy tool for glaucoma monitoring and diagnosis[7]. Compared to traditional RNFL thickness assessment, the ganglion cell analysis (GCA) achieved by the Cirrus HD-OCT system (Topcon) segments

and evaluates the thickness of the GCL and IPL, boosting diagnostic accuracy[8].

PATIENTS AND METHODS

An observational non-randomized case-control study conducted. We gathered patients with regulated POAG from the Mansoura Ophthalmic Centre outpatient clinic.

There were two groups of patients:

120 eyes from 82 individuals older than 40 years with primary OAG were included in Group 1.

Group 2 comprised 100 normal eyes of 50 control participants.

Depending on the severity of the condition, glaucoma-affected eyes were further divided into:

Early-stage mild glaucoma: 63 eyes.

47 eyes have moderate glaucoma.

Ten eyes with severe glaucoma.

Ethics and Consent:

Before beginning the present investigation on November 10, 2022, the Mansoura University Faculty of Medicine's IRB was consulted (code number MS.22.09.2136). Each participant signed a written informed consent form before to beginning the study. During the study, the 1964 Helsinki Declaration, all subsequent changes, and comparable ethical guidelines were adhered to.

Inclusion criteria

Normal eyes have normal optic nerve head appearance based on clinical stereoscopic examination, normal visual field, and an intraocular pressure (IOP) of 21 mmHg or less measured by Goldmann applanation tonometry. They also have no history or indication of ocular disease, surgery, laser treatment, or family history of glaucoma.

The following requirements must be met by a person diagnosed with primary open-angle glaucoma: they must be older than 40, have best corrected visual acuity greater than 6/60, have an open anterior chamber angle on gonioscopy, exhibit glaucomatous changes on the Humphrey 24-2 visual field test, and show signs of glaucomatous damage to the optic nerve head. Finally, their refractive error must be less than 3.0 diopters astigmatism and less than 2.0 diopter anisometropia (such as neuroretinal rim thinning).

The patients were classified as exhibiting one of three types of glaucoma: moderate glaucoma (MD<-12dB, less than 50% of points were depressed <5% and less than 20 points were depressed <1% on a pattern deviation plot), late glaucoma (MD<-12dB, less than 25% of points are depressed <5% and less than 10 points are depressed <1% on a pattern deviation plot), or early glaucoma (all points in the central 5 degree >15dB). At least one point in the centre 5 degree can have a sensitivity of 0dB in severe glaucoma (MD>-12dB), when more than 50% of points are depressed <5% or more than 20 points were depressed <1% on a pattern deviation plot, there can be no points in the centre 5 degree with a sensitivity of 0dB, and only one hemifield can have a point with a sensitivity of <15dB within 5 degree of fixation. and points inside the central 5 degree with sensitivity <15dB in both hemifields).

Exclusion criteria:

Cases where there was any media opacity that interferes with good quality, such as cataracts, angle closure glaucoma, coexisting secondary glaucoma and retinal diseases (like diabetic retinopathy), history of intraocular diseases, previous intraocular surgery, other conditions impacting the visual field, or the use of drugs known to impair sensitivity to the visual field.

Tests:

A comprehensive ocular assessment was performed on all patients, which included obtaining their medical histories, measuring their slit-lamp biomicroscopy, a stereoscopic fundus examination with a 90.0 D lens optic disc, and their best-corrected visual acuity (IOP) using Goldmann applanation tonometry. Imaging using OCT: An optical coherence tomography examination was conducted utilising the Topcon 3D OCT-1000 mark II (Topcon, Tokyo, Japan).

Statistical analysis:

Version 10.0 of SPSS for Windows (SPSS Inc., Chicago, Illinois, USA) was adopted to analyse data. For every variable that was measured, descriptive statistics were calculated.

RESULT:

Our Study included 220 eyes of 132 persons

1. Control group (normal eyes): included 100 eyes of 50 subjects.
2. Patient group (glaucomatous eyes). included 120 eyes of 82 patients.

Presentation of the study results will include the following

items:

1)Disease severity:

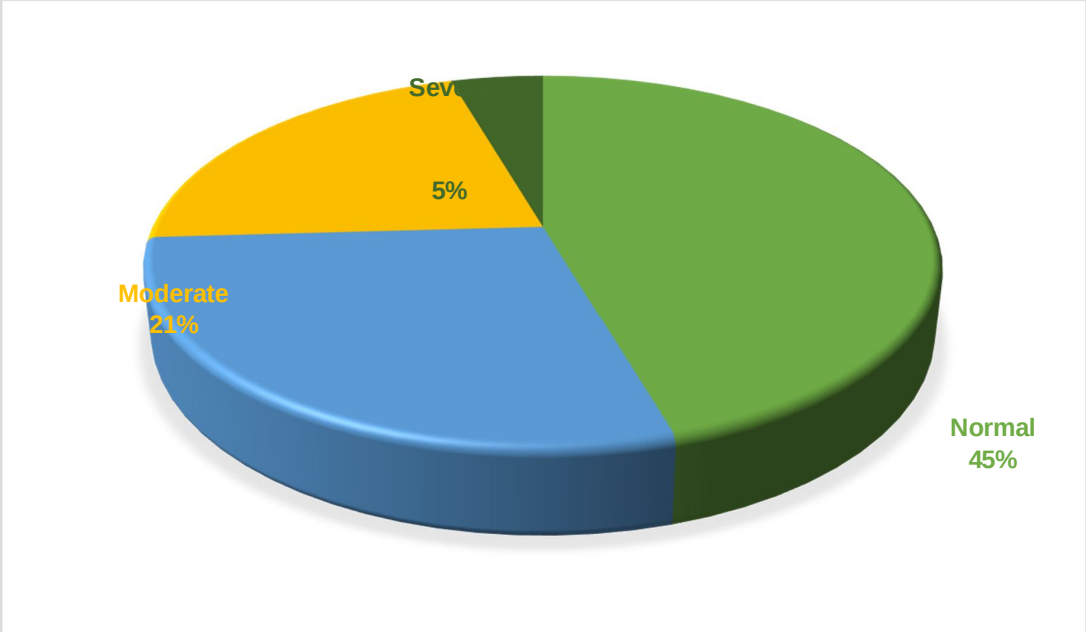

Fig. (1): Pie chart for stages distribution

As shown in **Fig (1)** Glaucomatous eyes classified into:

Mild(early) glaucoma: 63 eyes.

Moderate glaucoma: 47 eyes.

Severe glaucoma: 10 eyes.

2) Sex:

The percentages of the normal and glaucoma groups according to sex did not differ significantly.

3)Age:

Participants in normal group aged from 41 to 69 years, mean age was (55.1 ± 7.2 years). Table 1 demonstrates mean age of the glaucoma group (56.9 ± 6.9 years), with a range of 41 to 75 years. There was no discernible age difference between the glaucoma and normal groups.

Table (1): Age of the studied groups.

Age (years)	Normal	Glaucomatous	Test	P-Value
Mean ± SD	55.1 ± 6.9	56.9 ± 6.9	T =1.8	0.072
Median	55.2	58.0		
Range	(41- 69)	(41 - 75)		

4) Best Corrected visual acuity (BCVA):

Table (2) indicates that between the groups with normal and glaucoma grades, there was a statistically significant difference in the BCVA.

Table (2): Comparison between normal and glaucoma grades group according to BCV

Groups BCVA (logmar)	**norma l**	**Glaucoma**	**Test**	**P-Value**	**Early**	**moderate**	**severe**	**FTest**	**P-Value**
Means±SD	0.9 ±0.1	0.5 ± 0.2	U=11.2	> 0.001	0.6±0.2	0.5 ± 0.2	0.3±0.1	129.5	<0.01
Median	1.0	0.5			0.7	0.5	0.2		
Range	0.7-1	0-1			0.2-1	0.2-0.7	0-0.5		

5)Intra ocular pressure

Table (3) demonstrates that the IOP with chance varied statistically significantly ($p < 0.001$) amongst the four groups.

Normal group had mean IOP of 11.87 ± 1.1 ranging from 11 to 15 mmHg.

Early glaucoma group had a mean IOP of 15. 8 ± 2.6 ranging from 12 -22 mmHg.

Moderate glaucoma group had mean IOP of 15.7 ± 2.4 ranging from 12 -26 mmHg.

Severe glaucoma group had mean IOP of 21.6 ± 3.6 ranging from 17-26 mmHg.

Table (3): Comparison between the four groups according to IOP.

IOP	Normal	Early	Moderate	Severe	F-test	P-value
Means±SD	11.87 ± 1.1	15.8 ± 2.6	15.7 ± 2.4	21.6 ± 3.6	85.0	< 0.001
Median	12	15	15	24		
Range	11 - 15	12- 22	12 - 26	17 - 26		

6)Cup-to-disc ratio:

The present study showed that the

normal group had an average cup-to- disc (C/D) area ratio 0.14 ± 0.1, ranging from 0.2 - 0.5.

In **early glaucoma group,** average C/D ratio was 0.4 ± 0.1ranging from 0.2-0.9.

In **moderate glaucoma group,** average C/D ratio was 0.5 ± 0.2 ranging from 0.1-1.

In **sever glaucoma group**, the average C/D ratio was 0.7 ± 0.3 ranging from 0.1-1.

Table (4) displays statistically significant ($P<0.001$) difference in the C/D ratio between the phases and groups.

Table (4): Comparison among the four groups according to C/D ratio.

C/D ratio	Normal	Early	Moderate	Severe	F test	P-Value
Means±SD	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.2	0.7 ± 0.3	21.4	<0.001
Median	0.4	0.4	0.5	0.9		
Range	0.2- 0.5	0.2- 0.9	0.1- 1	0.1- 1		

Optical coherence tomography findings:

1) Retinal nerve fiber layer (RNFL) thickness of studied groups

Table (5) demonstrates statistically significant difference about mean (superior, inferior, and total) RNFL thickness between patients with normal and glaucoma grades, with a P-value of less than 0.001.

Between individuals with early and intermediate glaucoma, no statistically significant difference (P-value: 0.928 for superior RNFL, 0.675 for inferior RNFL, and 0.087 for total RNFL).

The normal group's RNFL thickness ranged from 34 to 49 µm, with an average of 41.0 ± 3.2 µ. With a range of 32 to 46 µm, the superior average thickness was 38.6 ± 3.1 µm. With a range of 33 to 48 µm, the inferior average thickness was 41.6 ± 3.3 µm. The RNFL thickness of the early glaucoma group ranged from 32 to 48 µm, with an average thickness of 38.8 ± 3.4 µm. With a range of 30 to 43 µm, the superior average thickness was 36.5 ± 3.1 µm. The thickness ranged from 33 to 48 µm, with an inferior average of 39.3 ±3.9 µm.

Table (5): Comparison between glaucoma grades and normal group regarding RNFL thickness

	Superior RNFL	Inferior RNFL	Total RNFL
Normal group **Means+-SD Range**	38.6±3.1 (32-46)	41.6± 3.3 (33-48)	41.0±3.2 (34-49)
Early glaucoma **Means+-SD Range**	36.5±3.1 (30-43)	39.3± 3.9 (33-48)	41.0±3.2 (32-48)
Moderate glaucoma **Means+-SD Range**	35.9±3.6 (30-44)	38.4±3.8 (29-43)	37.2 (29-44)
Severe glaucoma **Means+-SD Range**	25.6±5 (17-32)	25.9±3.9 (17-30)	24.8±3.5 (17-30)
P-value	<0.001	<0.001	<0.001
Normal vs. Early	<0.001	<0.001	<0.001
Normal vs. Moderate	<0.001	<0.001	<0.001
Normal vs.Severe	<0.001	<0.001	<0.001
Early vs. Moderate	0.928	0.675	0.087
Early vs.Severe	<0.001	<0.001	<0.001
Moderate vs.Severe	<0.001	<0.001	<0.001

Ganglion cell complex (GCC) thickness of the studied groups:

According to **table (6),** the current study demonstrated a statistically significant difference in GCC thickness between patients with normal and glaucoma grades, with respect to mean thickness (superior, inferior, and total), with a P-value of less than 0.001.

The GCC thickness of the normal group ranged from 95 to 121 µm, with an average of 107.5 ± 4.8 µm. The GCC had a superior average thickness of 106.3 ±5.1 µm, with a range of 92 to 121 µm. With a range of 99 to 121 µm, the inferior average thickness was 108.1 ± 5.3 µm.The GCC thickness of the early glaucoma group ranged from 82 to 115 µm, with an average of 98.8 ± 5.6 µm. The GCC had a superior average thickness of 99.1 ± 5.7 µm, with a range of 81 to 115 µm. **Table (6)** shows inferior average thickness ranged from 69 to 116 µm, with an average thickness of 98.6±6.5µm.

Table (6): Testing the GCC thickness in normal and in different stages of glaucoma.

	Superior GCC	Inferior GCC	Total GCC
Normal group	106.3±5.1	108.1±5.3	107.5±4.8
Means+-SD Range	(92-121)	(99-121)	(95-121)
Earlyglaucoma	99.1±5.7	98.6±6.5	98.8±5.6
Means+-SD Range	(81-115)	(69-116)	(82-115)
Moderate glaucoma	93±8.1	93.6±8.1	93.6± 7
Means+-SD Range	(72-117)	(69-116)	(74-115)
Severe glaucoma	79.4±5.3	78.4±6.4	79.8±4.8
Means+-SD Range	(68-85)	(68-85)	(71-88)
P-value	<0.001	<0.001	<0.001
Normal vs.Early	<0.001	<0.001	<0.001
Normal vs. Moderate	<0.001	<0.001	<0.001
Normal vs.Severe	<0.001	<0.001	<0.001
Early vs. Moderate	<0.001	<0.001	<0.001
Early vs. Severe	<0.001	<0.001	<0.001
Moderate vs. Severe	<0.001	<0.001	<0.001

RNFL and GCC thickness's capacity to distinguish between normal and early glaucoma using the area under the ROC curve:

With 90.0% GCC sensitivity appearing larger than RNFL, the average GCC thickness (AUC, 0.894) in early glaucoma appeared having a higher diagnostic value than average RNFL thickness (AUC, 0.668). **Table (7)** displays the cutoff values for average RNFL and average GCC, which were 38.5-103.5 and ($P < 0.001$), respectively.

Table (7): OCT parameters taking into account as diagnostic tests using the ROC curve's area under the curve.

Variables	Area	Cut off point	Sensitivity	Specificity	P-value	95%CI
BCVA	0.889	0.85	92.1%	72.0%	<0.001	0.836-0.942
CD Ratio	0.558	0.45	34.9%	86.0%	0.209	0.462-0.655
IOP	0.926	13.2	84.1%	90.0%	<0.001	0.888-0.964
Superior RNFL	0.678	38.5	77.8%	49.0%	<0.001	0.593_0.762
Inferior RNFL	0.675	38.5	44.4%	87.0%	<0.001	0.588_0.763
Total RNFL	0.668	38.5	49.2%	80.0%	<0.001	0.582_0.754
Superior GCC	0.841	101.5	60.3%	92.0%	<0.001	0.777_0.904
Inferior GCC	0.891	103.5	90.5%	75.0%	<0.001	0.838_0.944
Total GCC	0.894	103.5	90.5%	79.0%	<0.001	0.84_0.948

DISCUSSION

Patients with glaucoma suffer permanent harm to their eyes' functional and structural architecture. Forty percent of the nerve tissues are already destroyed by the time it is detected. Visual field is gold standard for POAG diagnosis as of right now[9]. OCT a more recent diagnostic technique that shows the condition of the retina's many layers. Using an objective and numerical method, OCT determines thickness of the retinal nerve fibre layer (RNFL) by determining the echo time delay caused by light scattered

back from various retinal layers[10]. This tool is quick, requires less time, and is gentle on patients[11]. Cirrus SD-OCT has demonstrated the ability to assess peripapillary RNFL thickness in healthy eyes with consistent reproducibility, little measurement variance, as demonstrated by Hong S. et al[12].

Because glaucoma is caused by RGC death, macular thickness can be used as a helpful glaucoma discriminator because of the concentration of RGCs at the macula. Given that 50% of RGCs in the retina are found in macula, assessing macular GCL seems to be a useful method for determining GC death even if the GCC and RNFL are evaluated at separate places in the retina. Axons of GCs converge on the optic disc prior to exiting the eye make up the RNFL measured around the disc[13].

Therefore, the current study aimed to examine, using optical coherence tomography (OCT), sensitivity of retinal nerve fibres, ganglion cell complex between glaucomatous patients in different grades.

This case-control observational study held in Mansoura University ophthalmic center on a sample size of 220 eyes underwent O.C.T macula. Eyes were divided into 2 groups; glaucoma group which include (120 eyes) and control group of normal subjects (100 eyes).

Regarding the demographic information, highly statistically significant variances were in terms of BCVA, IOP, and cup-to-disc (C/D) ratio, but no statistically significant differences in terms of age or sex. Soliman et al.[14] found no statistically significant differences with regard to gender, but they opposed the current study regarding age and BCVA and statistically significant differences with regard to IOP and cup-to-disc ratio. These findings are consistent with our own findings. Furthermore, a different study by Chan et al.[15] also noted a notable decline in visual acuity in glaucoma patients.

Takagi et al.[16] observed that the thickness of the macular GCC in the normal hemifield of glaucomatous eyes was much lower than in normal eyes, which is consistent with the findings of the current investigation. However, there was no discernible difference in the overall thickness of the macular area between the eyes of the glaucomatous and normal individuals.

Furthermore, Takagi et al.[17] reported a strong correlation between the overall deviation in visual field parameters of the corresponding area and thicknesses of macular GCC and RNFL in normal hemisphere of glaucomatous eyes.

The current result is in line with a study by Cennamo et al.[18], which showed that GCC characteristics are superior than RNFL as a modality for early glaucoma detection. There are two possible explanations for this finding: First, as cell body loss may be seen prior to axonal loss, GCC is a direct sign of RGC integrity. Secondly, macular GCC characteristics were demonstrated to be an early predictor in comparison to RNFL ones. Second, because this method uses a 7mm x 7mm grid centred on the central macula for the macular GCC scan, it makes it easy to detect early glaucomatous damage that starts in the paracentral region (10°–20°). Kim and associates[19].

According to a research by Sevim et al.[20], fourier domain OCT (FD-OCT) measurements of GCC and RNFL thickness shown a high degree of diagnostic ability in glaucoma detection.

According to Moreno et al.'s research[21], macular GC-IPL parameters have a higher and better capacity than pRNFL and ONH parameters to distinguish between normal eyes and eyes with early glaucoma.

While SD-OCT's diagnostic accuracy in advanced glaucoma is fair, it falls short of clinical criteria in early glaucoma, according to Michelessi et al.[22]. According to this study, the GCC thickness measures were more accurate in detecting early glaucoma than the RNFL thickness values. These were consistent with Naghizadeh and colleagues[23].

According to a research by Schulze et al.[24], FD-OCT (RTVue-100) imaging of the GCC may distinguish between glaucoma patients and healthy individuals with a diagnostic capacity comparable to RNFL and OHN measures. Regarding ONH, RNFL, and GCC parameters, there were no differences between participants who were normal and those who had OHT.

The current investigation differs slightly from that of Oddone et al.[25], which found RNFL parameters are still more accurate than macular measures in the diagnosis of

manifest glaucoma.

The results of this study contradict those of Mwanza et al.[26], Akman[27], and others, who claimed that the inferior quadrant of RNFL is thought to be the best RNFL measure for differentiating between those with glaucoma and those without it. Lisboa et al.[28], as well as Bussel et al.[29], highlighted superiority of RNFL over GCC measures in identifying onset of glaucoma and tracking its course.

Sung et al.[30] discovered, in contrast to these findings, average RNFL superior than average GCC in diagnosing glaucoma.

According to a research by Bambo et al.[31] both RNFL thickness and macular GCC thickness showed a comparable diagnostic significance as a marker for all stages of glaucoma. In high myopia instances, the diagnostic capacity of glaucoma using macular GCC thickness was comparable to peri-papillary RNFL (ppRNFL) Kim et al.[32].

CONCLUSION

Since glaucoma is primary cause of permanent blindness, it is critical in diagnosing the condition early and start treatment as soon as possible to prevent or delay the progression of visual loss. Measurements of the RNFL and GCC with SD-OCT may offer crucial knowledge for the early diagnosis and evaluation of glaucoma. In glaucomatous individuals, a significant positive association between thickness of GCC and RNFL. GCC imaging is very diagnostically capable of helping RNFL distinguish between individuals with glaucoma and healthy individuals early on.

ACKNOWLEDGEMENT: None

Data Availability: The authors declare that all data supporting the findings of this study are available within the article and its supplementary information file.

Competing interests: The authors declare no competing interests.

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Ethics declarations: All procedures performed in the study followed the 1964 Helsinki declaration and its later amendments, University Ethics Committee approved the project.

Conflict of interest

All authors have no conflicts of interest that are directly relevant to the content of this review.

Funding: No sources of funding were used to conduct this review.

Reviewer disclosures: No relevant financial or other relationships to disclose.

Declaration of interest: No financial affiliations or financial involvement with any organization or entity with a financial competing with the subject matter or materials discussed in the review.

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