Chapter 5

Evaluation of Retinal Nerve Fiber Layer and Inner Macular Layers in Primary Open-Angle Glaucoma with Spectral-Domain Optical Coherence Tomography

Bilyana Mihaylova and Galina Dimitrova

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79102

Abstract

The aim of our research is to assess and compare the peripapillary retinal nerve fiber layer (pRNFL) thickness diagnostic capability with those of three macular parameters—macular RNFL (mRNFL) thickness, GCL+ (ganglion cell layer with inner plexiform layer thickness), and GCL++ (mRNFL and GCL+) in primary open-angle glaucoma patients with spectral-domain optical coherence tomography (SD-OCT).

The 414 participants (483 eyes) aged 45–84 years in this prospective study were recruited from Eye Clinic at the University Hospital "Alexandrovska" (Sofia, Bulgaria). They were divided into 6 groups: controls, ocular hypertension, preperimetric glaucoma (PPG), and three groups of perimetric glaucoma stages—early, moderate, and advanced. OCT was performed using Topcon 3D OCT 2000 device, as eight parameters from two protocols (Circle and Glaucoma Analysis—Macula) were analyzed. The results showed that the RNFL highest diagnostic capability parameter is Total mRNFL (AUROC 0.879 in PPG and 0.929 in early glaucoma stage). The macular highest diagnostic accuracy parameter was found GCL++ without any significance from mRNFL diagnostic possibilities.

The results of current research showed that mRNFL possesses high diagnostic accuracy in comparison analysis with other pRNFL and macular OCT parameters in early glaucomatous changes. Macular RNFL and its highest diagnostic possibilities could be successfully used as an individual diagnostic parameter separated from the whole ganglion cell complex in the early glaucoma changes.

Keywords: primary open-angle glaucoma, retinal nerve fiber layer, inner macular layers, optical coherence tomography

1. Introduction

According to the American Academy of Ophthalmology the medical term glaucoma is used for a group of diseases that damage the optic nerve (ON) as distinctive type of optic neuropathy characterized by structural (cupping of optic nerve head—ONH, changes in connective tissue structural elements and number of the nerve fibers in ON) and functional changes (typical visual field defects). Increased intraocular pressure (IOP) is one of the most common risk factors associated with developing and progressing of the disease, but its presence or absence does not change the above-mentioned glaucoma definition [1].

Epidemiological studies found that the glaucoma at the end of twentieth century covered more than 60 million people around the world. Prognostic studies show an increasing trend of the number of affected patients, and in 2020 it is going to be approximately 80 million people, and in 2040 approximately 112 million [2–4]. Cataract and glaucoma are leading causes of blindness worldwide. Because of the reversibility of the vision after cataract extraction, the glaucoma remains the leading cause of irreversible blindness. The large number of glaucoma patients, irreversible vision loss and the impact on the life quality of the affected people are just part of the reasons for making glaucoma one of the diseases with big social influence.

Glaucoma is characterized by irreversible loss of ganglion cells, which axons form the ON. Ganglion cells are localized in three retinal layers—inner plexiform layer or IPL (their dendrites), ganglion cell layer or GCL (their bodies), and retinal nerve fiber layer or RNFL (their axons). Therefore exactly the above-mentioned layers are those, which glaucoma affects accompanying typical visual field defects [5]. Chronic and progressive loss of neuroretinal tissue is cardinal feature of glaucomatous optic neuropathy (GON) and criterion for diagnosis [6].

1.1. Anatomical aspects of the RNFL

All afferent pathways in the ON start from a layer of photoreceptors (cones and rods), which is located in the retina on area more than 1000 mm^2. In ONH all fibers are concentrated on surface with approximately 2–3 mm^2 area [7, 8]. From the body of each ganglion cell comes out a nerve fiber or axon, which moves toward the ONH. So that it can be called conglomerate consisted of all converging axons, which are as mentioned above part of the retina and form a layer—RNFL [9]. Nowhere else the ganglions' nerve fibers are not so much compact as they are in ONH, and this is what determines the importance of peripapillary RNFL thickness in diagnosis and follow up of patients with GON.

These are some characteristics of RNFL [9, 10]:

1. Papillomacular nerve fiber bundle—it starts from ganglion cells in the foveolar region. The nerve fibers from nasal foveolar area move straight toward the temporal border of ONH, and those from the temporal part make a slight arc around the nasal nerve fibers and then join to the straight bundle.
2. Superior and inferior retinal arcades—they are created by later formed nerve fibers and ganglion cells originating temporal to the fovea. They arc around the macula and papillomacular bundle to enter the ONH.

3. Temporal raphe or seam—it extends from the fovea to the temporal part of the retina and consists of very few axons, because by rule the nerve fibers from the upper half of the retina do not pass the horizontal meridian to the arcuate course of the nerve fibers from the lower part of the retina, and vice versa.
4. An extremely large collection of nerve fibers in the superior and inferior quadrant of the ONH—namely these two regions are set to be more vulnerable for glaucomatous damages.
5. Nasal nerve fibers—they move radially toward the ONH.
6. Exact location of the nerve fibers in the ONH according to their position in the fundus—the more peripheral retinal location the more central ONH localization.

Basic features, used to make an assessment of RNFL images [9]:

1. Striations of RNFL—normally RNFL can be seen as striated bright and dark lines in the areas of superior and inferior temporal blood vessels in healthy eyes. If atrophy is presented (<50 μm RNFL thickness) the striations of the background disappear and bright lines cannot be seen because of the RNFL loss [11] (see **Figure 1**).
2. Defects of the background brightness—they can be diffuse loss and localized defects (wedge-shaped and cleft-shaped). The width in the cleft-shaped defects is the same along the full length, however the width in wedge-shaped defects is different, peripherally they are wider and become narrower toward the ONH. This could be explained with convergent course of the nerve fibers. Diffuse defects have an impact over the complete RNFL thickness in the fundus and also their diagnosis is more difficult from localized defects.
3. Visualization of the blood vessels—normally RNFL covers retinal blood vessels. That's why small and medium-sized blood vessels have unclear contours and look misty. When RNFL atrophy appears, then blood vessels can be seen clearly because of the less covering from the nerve fiber layer.

All nerve fibers are arranged in a specific way in the ONH not only in each and every human being but also in each and every of the human eyes. Equal quantity nerve fibers may look in a different way in the borders of ONHs with dissimilar disc area, depth of the lamina cribrosa, and height of the scleral canal [12]. Equal functional capacitate could be presented by different looking structures and vice versa—equal looking structures could have different functional activity [13–15].

The RNFL thickness depends on: age, ethnicity, number and thickness of the nerve fibers, quantity of the glia, quantity of the blood vessels, disk area of the ONH, axial length of the eye (Ax). The thickness of the measured RNFL depends also on: the stage of peripapillary atrophy/conus myopicus, vitreoretinal tractions. The excavation (cupping) depends on: disc area, number and thickness of the nerve fibers, quantity of the glia [14]. Normally in the course of time the RNFL thickness decreases with age normally with 4000–5000 axons per year [16–19] and this is approximately 2.0 μm/decade or 0.2% per year at mean thickness 100 μm [20]. The ON consists of 700,000–1.4 million nerve fibers and the RNFL thickness in healthy people has a wide variety of a norm. The usage of absolute values restricts the process of distinguishing

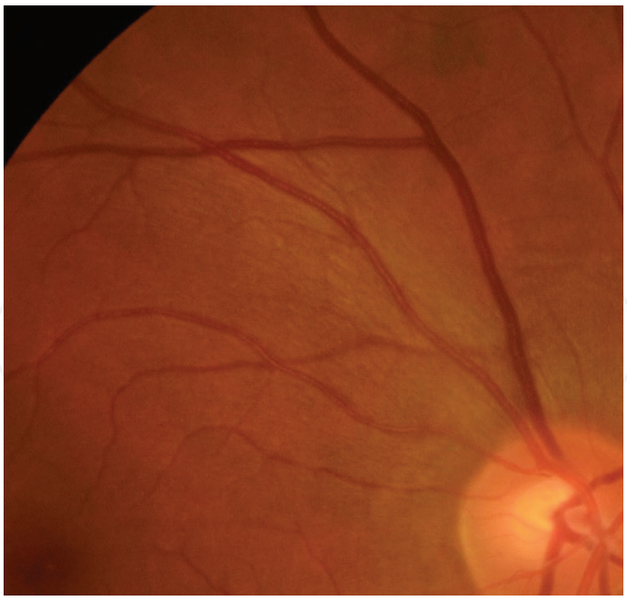

Figure 1. RNFL striations in superior temporal area of the fundus in healthy eye of 52 years old female.

healthy from glaucoma patients [20]. Therefore some authors talk about "modulation of RNFL thickness"—it shows the relative loss of nerve fibers as difference between the biggest and smallest measured value of RNFL thickness in a retinal region of interest [21].

1.2. RNFL and glaucoma

When assessing glaucomatous damages it is appropriate to measure the RNFL thickness, because thinning of this layer correlated directly with ganglion cells loss, which is the basic pathophysiological event [22]. Evaluation of the RNFL thickness is important for early glaucoma diagnosis before appearing of the clinical manifestations of the disease. It is proven that 40–50% of the nerve fibers are should be dropped out before developing of the visual field defects [23]. Clinical evaluation of the RNFL with red-free photography shows that thinning of the layer can be seen in 60% of the pictures 6 years before appearing of clinical manifestation of the defects in visual field [24]. These facts show that structural changes occur before the functional ones. Typical visual field defects in glaucoma are nasal step, arcuate scotoma, paracentral scotoma, generalized depression, and progressive worsening of the indices of the standard automated perimetry (SAP) [25].

Sometimes in glaucoma visual field defects can be seen without appearance of structural glaucomatous changes. It is possible also in equal RNFL loss to be obtained a different clinical finding according to initial RNFL thickness. This could be explained with the following: visual field defects appear after 40% loss of the nerve fibers. Each man is born with different quantity nerve fibers. If a person owns very thick for human population RNFL, the loss of 40% nerve fibers probably will not give any significant results in optical coherence tomography (OCT)—the line thickness will be in the middle of the green zone, the zone shows lack of disease. Then this individual is going to have functional defects with normal RNFL thickness. If another person is born with thin RNFL, the loss of 40% nerve

fibers will give significant results—OCT line thickness will be close to the yellow zone or in the zone. Then this individual is going to have functional defects with pathological thin RNFL [14, 15].

In the early glaucoma stage it is considered that the affected ganglion cells decrease their functional processes before they die and this leads to decreasing of the visual functions without an obvious structural changes. This is the reason why a patient has functional manifestations of glaucoma in combination with normal RNFL thickness [14].

The most distant nerve fibers from ONH originate exactly from these farthest parts of the ganglion cells in the retina and they are located deeply in the RNFL. They pass closely to the scleral edge and most peripherally in the ON [26]. These nerve fibers that originate from the closest to the ONH parts of the retina are located superficially in the RNFL and pass centrally in the ON. It is thought that the nerve fibers, which are located superficially in the RNFL, are more vulnerable in glaucoma, and their damage is associated with an enlargement of the blind spot.

It is also believed that chronically increased IOP leads to compression of the circulation of the Elschnig's border tissue and its atrophy. Then lamina cribrosa starts posteriorization. It is considered therefore that it is a reason for stretching and rupturing of the nerve fibers which are closest to the scleral edge. Only nerve fibers in prelaminar region can drop out consequently, because they are separated and not in bundles. The affecting of the nerve fibers is from peripheral to central region [26, 27]. Unordered affecting of the nerve fibers can be seen in acute angle closure glaucoma.

2. Retinal nerve fiber layer and inner macular layers evaluation in primary open-angle glaucoma with spectral-domain optical coherence tomography

2.1. Purpose

The aim of our research is to assess and compare the peripapillary RNFL (pRNFL) thickness diagnostic capability with those of three macular parameters—macular RNFL (mRNFL) thickness, GCL+ (ganglion cell layer with inner plexiform layer thickness), and GCL++ (mRNFL and GCL+) in primary open-angle glaucoma patients with spectral-domain OCT (SD-OCT).

2.2. Material and methods

2.2.1. Material

All participants (healthy volunteers and patients) included in current clinical study were examined in the university eye clinic of Alexandrovska Hospital, Sofia, Bulgaria for total period of time—a year and 3 months. This is a prospective observational study of 414 participants (483 eyes) aged 45–84 years (mean 66.7 ± 8.7), male—132, and female—282. All patients were distributed into six groups:

Ist group (**Controls**)—150 eyes, 150 healthy volunteers, mean age 63.0 ± 9.

IInd group (**Ocular hypertension** (OH))—50 eyes, 31 patients, mean age 60.1 ± 9.2.

IIIrd group (**Preperimetric glaucoma** (PPG))—62 eyes, 49 patients, mean age 66.3 ± 7.5.

IVth group (**Early perimetric POAG**)—96 eyes, 80 patients, mean age 69.7 ± 7.9.

Vth group (**Moderate perimetric POAG**)—40 eyes, 34 patients, mean age 70.4 ± 8.5.

VIth group (**Advanced perimetric POAG**)—85 eyes, 70 patients, mean age 69.5 ± 9.8.

The following inclusion and exclusion criteria were defined for the groups:

Inclusion criteria for the control group: healthy participants without congenital or acquired general or eye diseases exception of early age-related cataract; people without family history and other risk factors for glaucoma; best corrected visual acuity (BCVA) = 1.0; refraction error in ±4.00 dsph and ±1.00 dcyl; IOP under 21 mmHg measured with Goldmann tonometer according to central corneal thickness (CCT) values; open anterior chamber angle class III–IV Shaffer Angle Classification System; ocular fundus without glaucomatous damages—vital optic nerve head (ONH), ISNT rule in norm, C/D Ratio < 0.5 PD and interocular asymmetry in C/D Ratio ≤ 0.2 PD; normal SAP (Glaucoma Hemifield Test—within normal limits, $p > 0.05$ for MD and PSD indices).

Inclusion criteria for OH group: patients with OH and any other coexisting ocular and general pathology; BCVA = 1.0; refraction error in ±4.00 dsph and ±1.00 dcyl; permanent elevation of IOP more than 21 mmHg measured with Goldmann tonometer without treatment and corrected according to the CCT values and daytime pressure curves; open anterior chamber angle; lack of pathological changes in the fundus; normal SAP.

Inclusion criteria for Preperimetric glaucoma group: BCVA = 1.0; refraction error in already shown limits; permanent elevation of IOP more than 21 mmHg; open anterior chamber angle; fundus glaucomatous changes: interocular asymmetry in C/D Ratio ≥ 0.2 PD, vertical elongated excavation, thinning of optic disc rim, local thinning of neuroretinal rim, violated ISNT rule, defects in RNFL thickness (diffuse or local), normal SAP.

Inclusion criteria for perimetric glaucoma groups: BCVA = 1.0 for early stage glaucoma group and BCVA ≥ 0.2 for moderate and advanced stage of POAG; refraction error in already shown limits; permanent elevation of IOP more than 21 mmHg; open anterior chamber angle; fundus glaucomatous changes: interocular asymmetry in C/D Ratio ≥ 0.2 PD, vertical elongated excavation, thinning of optic disc rim, local thinning of neuroretinal rim, violated ISNT rule, defects in RNFL thickness (diffuse or local), ONH hemorrhages; typical for glaucoma visual field defects in SAP corresponding with changes in ONH; glaucoma perimetric stage was defined as changes in SAP based on Hodapp-Parrish-Anderson classification.

Exclusion criteria: best corrected visual acuity ≤ 0.2; age < 45 years and > 85 years; refraction error beyond already shown limits; normotensive glaucoma, angle closure glaucoma; macular pathology, diabetic retinopathy, nonglaucomatous opticopathy; previous eye surgery (exception cataract refractive surgery with intraocular lens implantation); coexisting neurological pathology which can influence on the visual field results.

http://dx.doi.org/10.5772/intechopen.79102

2.2.2. Methods

All patients underwent full ophthalmological examination including: a complete case history for eye and general diseases; family history; refraction and best corrected visual acuity; slit-lamp examination; indirect fundus biomicroscopy; contact ultrasound pachymetry (OcuScan RxP - Alcon, Forth Worth, Texas, USA); Goldmann tonometry; indirect gonioscopy (Goldmann three-mirror gonioprism/Shaffer classification, 1960); SAP - SITA Standard 24-2, HFA II (Carl Zeiss Meditec, Dublin, CA, USA) with near correction if necessary. Only reliable perimetry results with total error rate (loss of fixation and false-positive and false-negative results) lower than 25%. The stage of POAG changes was determined using Hodapp-Parrish-Anderson classification.

Optical coherence tomography: All patients underwent SD-OCT of both eyes with dilated pupils by one examiner using Topcon 3D OCT 2000 (FA plus) (Topcon Corporation, Japan), software version - 8.11.

The following programs were used:

- Circle program evaluated peripapillary RNFL thickness. From Circle protocol we analyzed the following parameters: (1) Total pRNFL—showed the average thickness in 360°; (2) Sup pRNFL—showed the thickness in the superior 90°; (3) Inf pRNFL—showed the thickness in the inferior 90°; (4) Nas pRNFL—showed the thickness in the nasal 90°; (5) Temp pRNFL—showed the thickness in the temporal 90° (see **Figure 2**, right).
- 3D Macula (V) program is used for the internal macular layers thickness evaluation in area of 7 mm^2. The following parameters were analyzed: (1) Sup mRNFL (Sup mRNFL)—mRNFL thickness in the upper half; (2) Inf mRNFL (Inf mRNFL)—in the lower half; (3) Total mRNFL (Total mRNFL)—in the whole macular area (see **Figure 2**, left).

Only OCT protocols with scan quality over 50%, no artifacts from eye or body movements, blinking, and lack of macular pathology (edema, drusen, holes) were included in the analysis.

Statistical methods: For statistically significant were considered the differences with P values <0.05. We used descriptive, dispersion and ROC-analysis to evaluate diagnostic accuracy, specificity, and sensitivity. A comparison was made between Ist group and IInd, Ist and IIIrd and so long. With comparison analysis we searched for statistical significant difference between some of the parameters' values in specificity and sensitivity.

2.3. Results

The descriptive statistics can be seen in **Table 1**, and mean values of the all RNFL parameters in **Table 2**. In **Table 3** can be seen the ROC analysis and the diagnostic capabilities of the eight OCT parameters in each group. The RNFL parameter with highest diagnostic potential in the groups—PPG (AUROC = 0.879), early (AUROC = 0.929), moderate (AUROC = 0.989) and advanced glaucoma (AUROC = 1.000) is Total mRNFL followed by Inf mRNFL and Inf pRNFL. The RNFL parameters with lowest diagnostic potential in all glaucoma stages are Nas pRNFL, Temp RNFL. A single RNFL parameter (Total mRNFL) was measured with

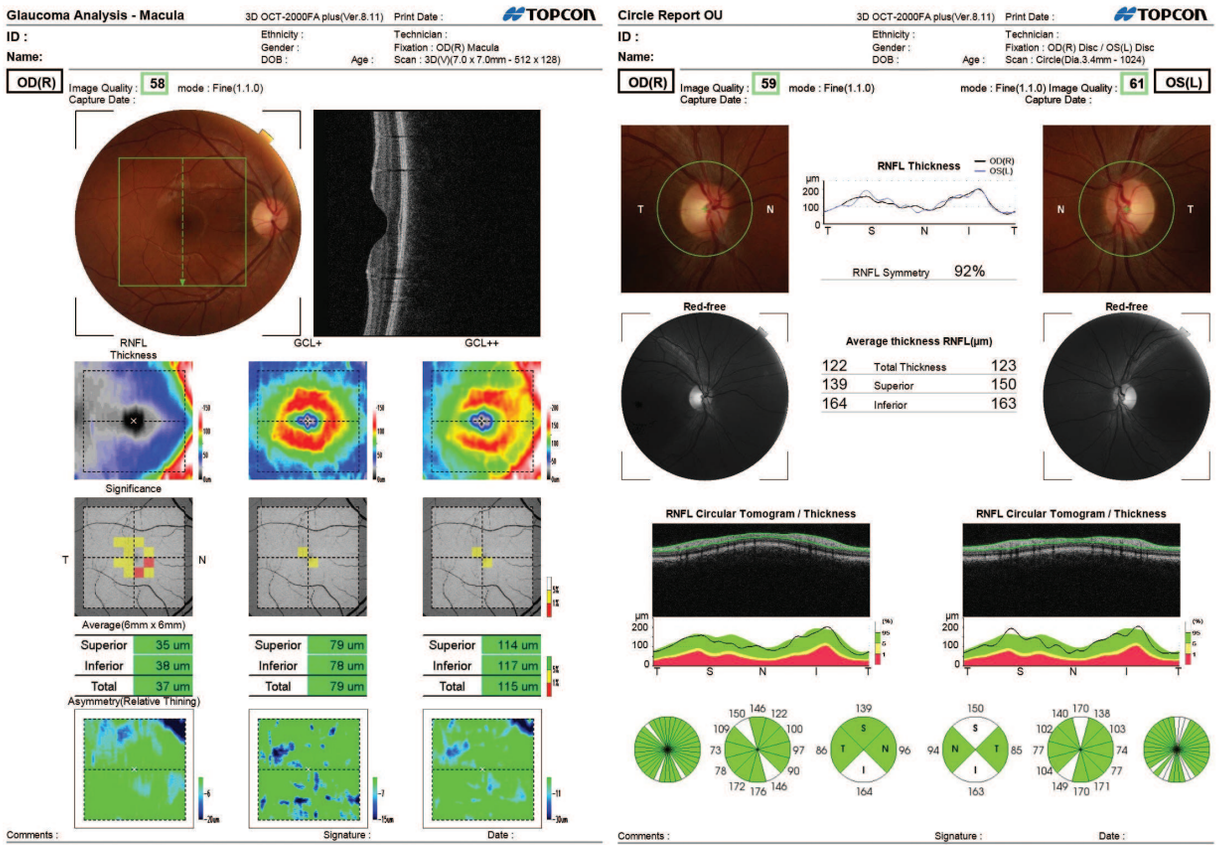

Figure 2. Glaucoma analysis—Macula protocol (left) and Circle protocol (right).

highest diagnostic accuracy for glaucoma in all of its stages - from PPG to advanced glaucoma. In the current investigation, it is shown for the first time the higher diagnostic ability of macular RNFL from those of peripapillary RNFL. In OH group, we found that Inf mRNFL has the highest diagnostic possibilities but without any clinical significance, because none of the RNFL parameters change significantly in patients with OH in comparison with control group.

AUROC values allowed us to create ROC curves in all groups as we included the five RNFL parameters with the best results (**Figures 3**–**6**).

After that we used comparison analysis to demonstrate if statistical significant difference exists between diagnostic possibilities of RNFL parameters in all groups. In **Table 4** can be seen only two significant differences in AUROC values between Sup mRNFL (0.907) and Total mRNFL, and between Total mRNFL (0.929) and Inf pRNFL (0.867). Although, we found the highest diagnostic potential in all glaucoma groups for Total mRNFL, our comparison analysis showed that these possibilities are not statistical significant with exception of the above-mentioned two examples. For instance, in the stage of PPG, we were not able to find any statistical significant differences between the best five diagnostic RNFL parameters (**Table 4**), so they have equal abilities to diagnose glaucoma patients in this particular stage. In the stage of early POAG, we found significant difference in diagnostic abilities between Inf pRNFL and Total mRNFL, so that it would be better if the clinician uses not the first five but the four best diagnostic parameters from **Table 3**.

http://dx.doi.org/10.5772/intechopen.79102

Group	Sex	Number	Age (years)			
			Mean	SD	Min	Max
Controls	Men—m	30	61.7	9.7	48.0	81.0
	Women—f	120	63.4	8.9	45.0	84.0
	All	150	63.0	9.0	45.0	84.0
OH	m	10	59.4	10.6	45.0	76.0
	f	21	60.4	8.6	45.0	72.0
	All	31	60.1	9.2	45.0	76.0
Preperimetric glaucoma	m	20	68.6	6.9	51.0	81.0
	f	29	64.7	7.6	45.0	74.0
	All	49	66.3	7.5	45.0	81.0
Early glaucoma	m	30	71.7	6.0	58.0	81.0
	f	50	68.5	8.7	45.0	82.0
	All	80	69.7	7.9	45.0	82.0
Moderate glaucoma	m	11	70.5	10.2	45.0	82.0
	f	23	70.4	7.9	57.0	81.0
	All	34	70.4	8.5	45.0	82.0
Advanced glaucoma	m	31	67.7	11.5	45.0	83.0
	f	39	70.7	8.2	45.0	84.0
	All	70	69.5	9.8	45.0	84.0

Table 1. Descriptive statistics.

We evaluated also sensitivity, specificity and cut-off values for the same RNFL parameters. In PPG group there are two parameters with highest and almost equal values of the sensitivity and specificity—Total mRNFL (sensitivity—0.83, specificity—0.77) and Inf mRNFL (sensitivity—0.82, specificity—0.79). These two parameters keep their high and close values of sensitivity also in the group of early perimetric glaucoma: Total mRNFL—0.93 и Inf mRNFL—0.90. The parameter with highest value of specificity in the same group is Total pRNFL—0.89, and after it are these parameters: Total mRNFL—0.81 and Inf mRNFL—0.79. In the PPG group with highest values is Total mRNFL (sensitivity—0.97 and specificity—0.95), and after it is Inf mRNFL (sensitivity—0.94 and specificity—0.85). It is observed very small differences in the values between investigated parameters, which decrease in advanced glaucoma group. With highest sensitivity (1.00) and specificity (1.00) in advanced glaucoma group is Total mRNFL, and after it is Inf pRNFL (1.00; 0.99) and Inf mRNFL (0.99, 0.99).

In **Table 5** can be seen the AUROC values of the macular parameters—Total mRNFL, Total GCL+ (ganglion cell layer/GCL + inner plexiform layer/IPL) and Total GCL++ (GCL + IPL + mRNFL) from protocol Glaucoma Analysis—Macula (see **Figure 3**, left). Lowest diagnostic

Parameter (μm)	Controls	OH	Preperimetric glaucoma	Early glaucoma	Moderate glaucoma	Advanced glaucoma
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
MD [dB]	−0.24 ± 1.30	−0.05 ± 1.15	−0.60 ± 1.13	−2.73 ± 1.85	−8.65 ± 1.77	−21.44 ± 5.81
PSD [dB]	1.72 ± 0.38	1.59 ± 0.32	1.82 ± 0.33	3.72 ± 1.73	7.84 ± 2.66	9.26 ± 3.15
Sup mRNFL	36.09 ± 4.30	36.46 ± 5.77	30.58 ± 3.75	28.90 ± 4.90	24.60 ± 6.85	16.78 ± 6.58
Inf mRNFL	39.22 ± 5.27	38.16 ± 4.69	31.34 ± 5.01	29.44 ± 5.81	25.05 ± 7.04	14.20 ± 6.33
Total mRNFL	37.67 ± 4.23	37.30 ± 4.67	31.05 ± 4.06	29.21 ± 4.37	25.00 ± 4.75	15.48 ± 5.58
Sup pRNFL	122.31 ± 12.09	128.70 ± 14.86	111.34 ± 17.17	101.47 ± 14.18	90.38 ± 20.29	77.47 ± 16.26
Inf pRNFL	136.86 ± 14.46	137.66 ± 14.65	115.74 ± 18.14	108.05 ± 22.62	90.53 ± 23.59	69.22 ± 15.03
Nas pRNFL	90.55 ± 14.73	92.24 ± 18.47	81.98 ± 19.99	82.23 ± 18.00	74.58 ± 19.36	66.99 ± 16.63
Temp pRNFL	81.62 ± 11.76	85.92 ± 16.12	74.26 ± 14.88	72.98 ± 15.62	69.28 ± 17.88	60.35 ± 15.76
Total pRNFL	107.84 ± 7.95	111.14 ± 10.25	95.92 ± 12.26	90.81 ± 12.48	81.15 ± 15.28	68.46 ± 12.32

Table 2. Mean values and standard deviation (SD) of RNFL in all groups.

Parameter	OH	Preperimetric glaucoma	Early glaucoma	Moderate glaucoma	Advanced glaucoma
	AUROC	AUROC	AUROC	AUROC	AUROC
Sup pRNFL	0.364	0.694	0.866	0.903	0.983
Inf pRNFL	0.472	0.820	0.867	0.957	0.999
Nas pRNFL	0.486	0.627	0.643	0.731	0.874
Temp pRNFL	0.428	0.678	0.687	0.719	0.893
Total pRNFL	0.412	0.791	0.900	0.947	0.993
Sup mRNFL	0.514	0.839	0.886	0.907	0.996
Inf mRNFL	**0.563**	0.864	0.907	0.951	0.997
Total mRNFL	0.535	**0.879**	**0.929**	**0.989**	**1.000**

Table 3. ROC-analysis.

accuracy for glaucoma in all investigated stages possesses the parameter—GCL+. The highest area under the curve has GCL++ (0.919, 0.932) in PPG group, Total mRNFL in the moderate glaucoma group (0.989), and the both parameters reach maximal possibilities for diagnosis in advanced glaucoma group (1.000). We also applied comparison analysis to find significance in diagnostic capabilities (AUROC values) between macular parameters. The results from this analysis could be seen in **Table 6**. Significance can be seen in the values between Total mRNFL and Total GCL+, and between Total GCL++ and Total GCL+. We did not find a difference between Total mRNFL and Total GCL++. This mean that the whole ganglion cell

http://dx.doi.org/10.5772/intechopen.79102

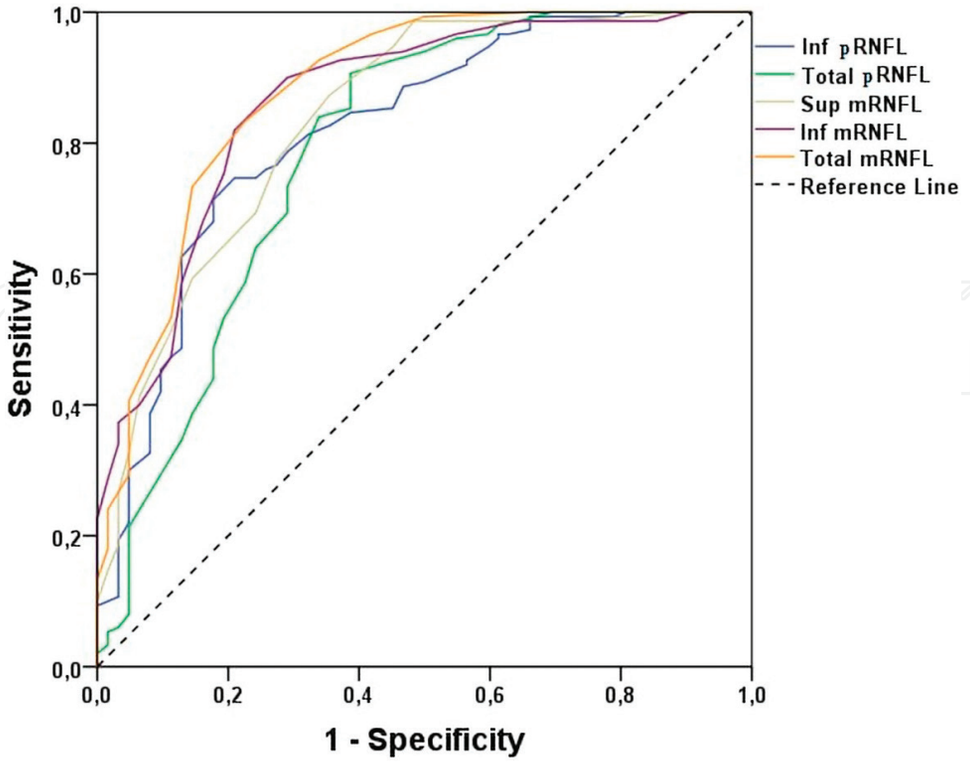

Figure 3. PPG.

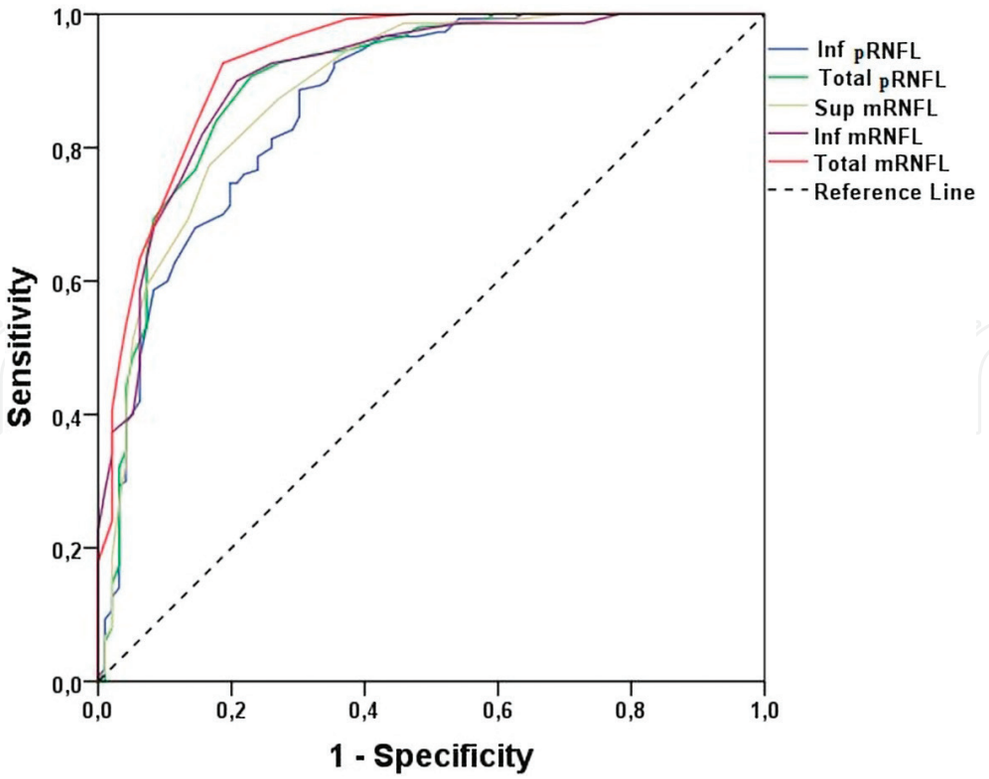

Figure 4. Early glaucoma.

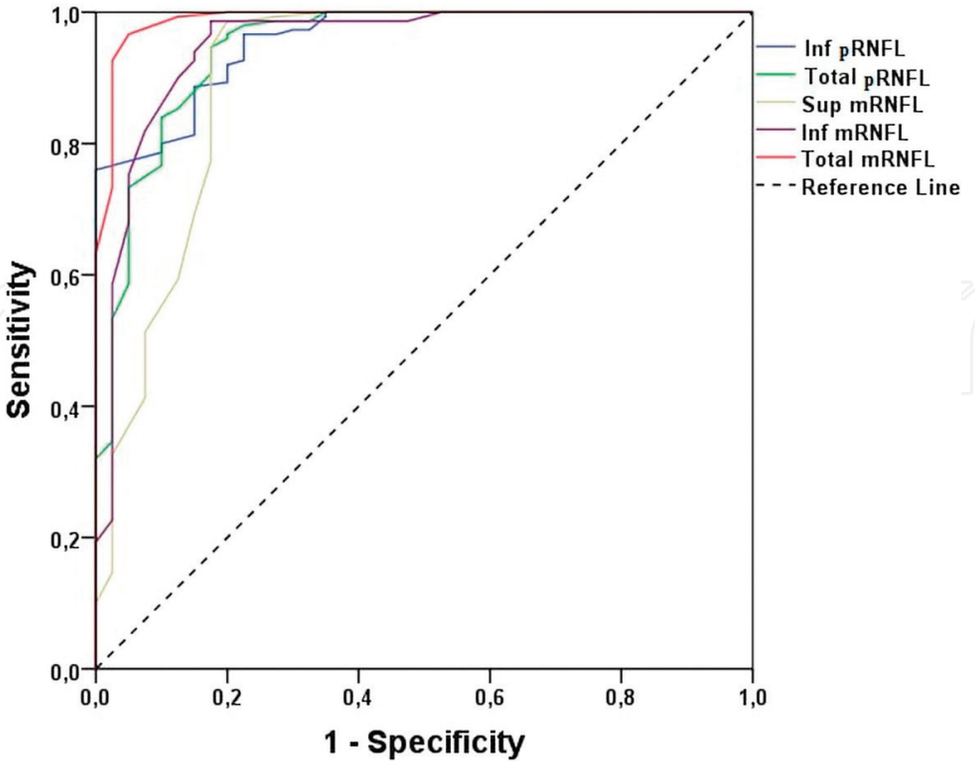

Figure 5. Moderate glaucoma.

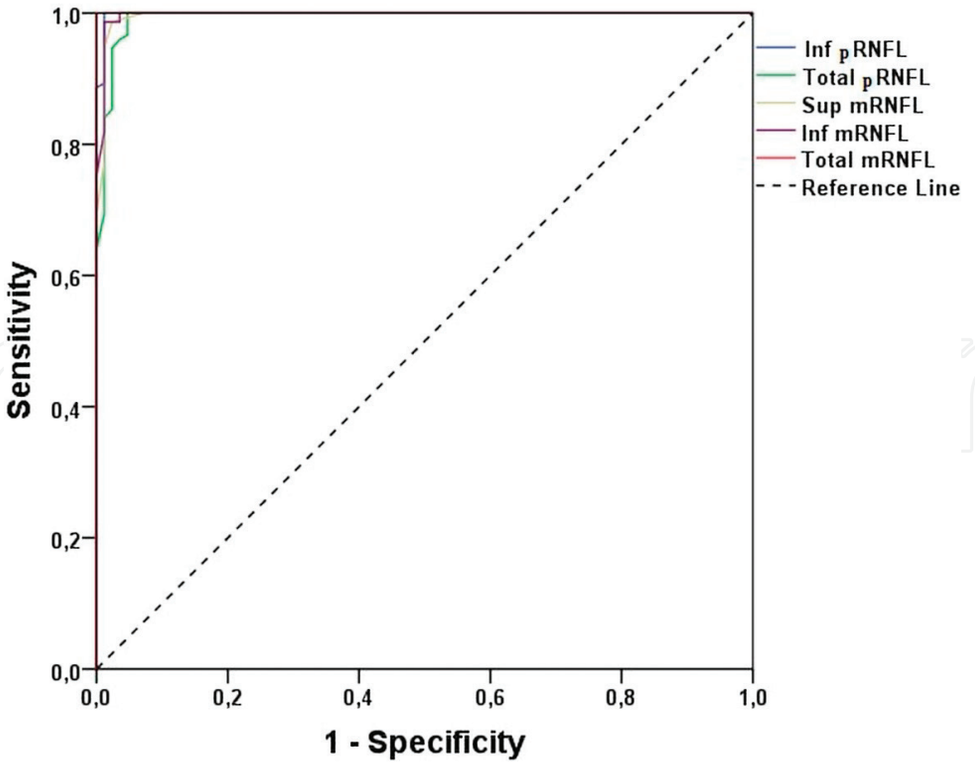

Figure 6. Advanced glaucoma.

AUROC comparisons		Controls vs.			
		PPG	Early glaucoma	Moderate glaucoma	Advanced glaucoma
		p	p	p	p
Sup mRNFL	Inf mRNFL	0.587	0.486	0.280	0.806
Sup mRNFL	Total mRNFL	0.339	0.136	**0.019**	0.238
Sup mRNFL	Inf pRNFL	0.680	0.571	0.178	0.469
Sup mRNFL	Total pRNFL	0.329	0.673	0.327	0.603
Inf mRNFL	Total mRNFL	0.702	0.410	0.115	0.275
Inf mRNFL	Inf pRNFL	0.315	0.204	0.832	0.601
Inf mRNFL	Total pRNFL	0.125	0.796	0.884	0.451
Total mRNFL	Inf pRNFL	0.172	**0.041**	0.050	0.339
Total mRNFL	Total pRNFL	0.062	0.296	0.068	0.132
Inf pRNFL	Total pRNFL	0.558	0.326	0.694	0.245

Table 4. Comparison analysis in AUROC values in all groups.

Parameter	Controls vs.			
	PPG	Early glaucoma	Moderate glaucoma	Advanced glaucoma
	AUROC	AUROC	AUROC	AUROC
Total mRNFL	0.879	0.929	0.989	1.000
Total GCL+	0.839	0.858	0.939	0.993
Total GCL++	0.919	0.932	0.987	1.000

Table 5. AUROC values of the GCL map parameters.

layer (consists of three sub-layers), which is presented by GCL++ parameter, has an equivalent diagnostic potential of those of Total mRNFL, which presents only one of the macular sub-layers (the most inner layer consists of the nerve fibers). The less accurate diagnostic potential from macular OCT parameters we found for GCL++. Therefore we exclude this parameter as an accurate in glaucoma diagnosis.

2.4. Discussion

In the current research we found that the Topcon OCT parameter—Total mRNFL has the highest diagnostic accuracy in the very early stage of glaucoma, in which only structural changes could be seen (PPG). It is important to know its diagnostic possibilities compared with those of other OCT parameters, because it allows the clinicians to precise the early diagnosis, appropriate treatment and the most important for the patients—prevention of the vision loss. The

AUROC comparisons		Controls vs.			
		PPG	Early glaucoma	Moderate glaucoma	Advanced glaucoma
		p	p	p	p
Total mRNFL	Total GCL+	0.336	**0.022**	**0.024**	**0.034**
Total mRNFL	Total GCL++	0.268	0.897	0.819	1.000
Total GCL+	Total GCL++	**0.036**	**0.018**	**0.028**	**0.034**

Table 6. Comparison analysis between macular parameters' AUROC values.

results showed that this parameter also has the highest diagnostic possibilities in all perimetric glaucoma stages. These conclusions we made only after comparative analysis in diagnostic accuracy between all OCT parameters (peripapillary and macular) had been applied.

There are not many researches, which investigate macular RNFL as a separate parameter not as a part of whole ganglion cell complex. Not enough data was collected about characteristics, correlations and diagnostic possibilities of mRNFL.

In 2005 for the first time was created software algorithm for automated segmentation of retinal layers in Stratus OCT (OCT III). It helped authors differentiate four macular layers—macular nerve fiber layer (mNFL); inner retinal complex (IRC) consisting of ganglion cells, inner plexiform layer and inner nuclear layer; outer plexiform layer (OPL); outer retinal complex (ORC), consisting of outer nuclear layer, inner and outer photoreceptor segments. When the authors investigated diagnostic accuracy they found the highest values in mNFL+IRC (0.97), and lowest in OPL (0.56). Diagnostic accuracy of OPL and ORC was significantly lower from mNFL, IRC, mNFL+IRC and circumpapillary nerve fiber layer (cpNFL) ($p \leq 0.01$). They found that AUROC values of IRC, mNFL+IRC and cpNFL were significantly higher from whole retinal thickness ($p \leq 0.049$). It was not found significant differences between parameters with best diagnostic possibilities—mNFL, IRC, mNFL+IRC and cpNFL ($p \geq 0.15$). The two parameters—ORC and OPL were found also to have almost permanent thickness in patients with glaucoma in comparison with healthy volunteers [28].

In the beginning of the era "OCT diagnostics in glaucoma" was found that the whole retinal thickness decreases. Later with the initiation of spectral domain OCT (SD-OCT) in the clinical practice inner macular layers (mRNFL, GCL, IPL) were called a complex (ganglion cell complex—GCC), which consists of the bodies, dendrites and axons of the ganglion cells [29]. A self-evident fact is that GCC has significantly higher possibilities for glaucoma diagnosis than the thickness of the whole retina.

Mwanza et al. investigated diagnostic accuracy of GCIPL (ganglion cell + inner plexiform layer), RNFL ONH parameters [30]. They found that GCIPL diagnostic possibilities are between 0.918 and 0.956, and there values are comparable with the best diagnostic parameters—RNFL (between 0.933 and 0.939) and ONH parameters (0.910 and 0.962) without statistically significant difference between them.

There are two conceptions of ganglion cell loss in glaucoma. In the first—the dendrites die before the bodies, and the most resistant part of the cell of glaucoma damage are their

http://dx.doi.org/10.5772/intechopen.79102

axons. Therefore, it is reasonable to investigate the thickness of GCL + IPL separately from mRNFL. On the other hand IPL consists of the dendrites not only the ganglion cells but also the bipolar cells, and it is believed as more correctly to measure the thickness of mRNFL+GCL together.

2.5. Conclusion

Peripapillary RNFL is a proved glaucoma diagnostic parameter and also ganglion cell complex. Predominantly of the glaucoma comparisons in diagnostic accuracy are between pRNFL and GCC in different OCT devices.

The current research investigate a new SD-OCT macular parameter—mRNFL and its diagnostic possibilities for different stages of POAG. It proves that mRNFL could be used in every day clinical practice of the ophthalmologist as independent parameter with very high diagnostic possibilities for early stages of glaucoma when only structural changes are visible.

Now we are working on creating of staging system based on Total mRNFL values (cut-off values) in each glaucoma group. It could give possibilities for the ophthalmologists to use the values of this parameter in everyday clinical practice to make diagnosis and follow-up of the glaucoma patients. This grading system will be the only of the OCT structural systems created up to date. Total mRNFL has the potential to be one of the best OCT diagnostic parameters and we as researchers must find how to use it in the diagnosis of very early glaucoma changes.

Acknowledgements

We would like to acknowledge with much appreciation the crucial role of: Assoc. Prof. Todor Kundurjiev, PhD (Medical University of Sofia, Bulgaria, Department of Social Medicine and Health Management) who made the whole statistical analysis for the current research.

Conflict interest

The authors declare that there is no conflict of interest.

Notes/Thanks/Other declarations

I would like to express my special appreciation and thanks to my teacher:

Associate Professor Galina G. Dimitrova, MD, PhD.

You have been a tremendous mentor for me. I would like to thank you for encouraging my work and for allowing me to grow as a research scientist. Your advice on both science and on my clinical practice has been invaluable. I appreciate this more than you know.

Author details

Bilyana Mihaylova* and Galina Dimitrova

*Address all correspondence to: b51@abv.bg

Department of Ophthalmology, Medical University of Sofia, University Hospital 'Alexandrovska', Sofia, Bulgaria

References

[1] American Academy of Ophthalmology. Base and Clinical Science Course, 2015/2016. Section 10 - Glaucoma. Chapter 1 - Introduction to Glaucoma: Terminology, Epidemiology, and Heredity. American Academy of Ophthalmology. p16

[2] Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. The British Journal of Ophthalmology. 2006;**90**:262-267

[3] Quigley HA, Sanchez RM, Dunkelberger GR, et al. Chronic glaucoma selectively damages large optic nerve fibers. Investigative Ophthalmology & Visual Science. 1987;**28**(6): 913-920

[4] Tham YC, Li X, Wong TY, Quigley HA, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. Ophthalmology. 2014;**121**(11):2081-2090

[5] Wollstein G, Beaton S, Paunescu A, et al. Optical coherence tomography in glaucoma. In: Schuman JS, Puliafito CA, Fujimoto JG, editors. Optical Coherence Tomography of Ocular Diseases. Thorofare, NJ: SLACK Inc.; 2004. pp. 483-610

[6] Medeiros FA, Zangwill LM, Bowd C, et al. Use of progressive glaucomatous optic disk change as the reference standard for evaluation of diagnostic tests in glaucoma. American Journal of Ophthalmology. 2005;**139**:1010-1018

[7] Jonas JB, Gusek GC, Naumann GOH. Optic disk, cup and neuroretinal rim size, configuration, and correlations in normal eyes. Investigative Ophthalmology & Visual Science. 1988;**29**:1151-1158

[8] Panda-Jonas S, Jonas JB, Jakobczyk M, et al. Retinal photoreceptor count, retinal surface area, and optic disc size in normal human eyes. Ophthalmology. 1994;**101**:519-523

[9] Tanev V, Tanev IV. Possibilities for retinal nerve fiber layer visualization. In: Glaucomas. 1st ed. Steno; 2006. pp. 99-112

[10] Hood DC, Raza AS, de Moraes CG, et al. Glaucomatous damage of the macula. Progress in Retinal and Eye Research. 2013;**32**:1-21

[11] Quigley HA. Quantitative studies of retinal nerve fiber layer loss in monkey and human glaucoma. Transactions of the American Ophthalmological Society. 1987;**84**:920-966

[12] Samsonova B, Pr G-I. Analysis of factors, influencing the RNFL thickness and the optic disc rim width (Part II). Bulgarian Forum Glaucoma. 2014;**4**(5):201-207

[13] Samsonova B, Pr G-I. Analysis of factors, influencing the RNFL thickness and the optic disc rim width (Part I). Bulgarian Forum Glaucoma. 2014;**4**(4):161-168

[14] Samsonova B. Curious discrepancies between functional and structural findings in patients with glaucoma and suspicious for glaucoma (Part 1). Bulgarian Forum Glaucoma. 2013;**3**(1):10-14

[15] Samsonova B. Curious discrepancies between functional and structural findings in patients with glaucoma and suspicious for glaucoma (Part 2). Bulgarian Forum Glaucoma. 2013;**3**(2):60-72

[16] Balazsi AG, Rootman J, Drance SM, et al. The effect of age on the nerve fiber population of the human optic nerve. American Journal of Ophthalmology. 1984;**97**:760-766

[17] Mikelberg FS, Drance SM, Schuler M, et al. The normal human optic nerve. Ophthalmology. 1989;**96**:1325-1328

[18] Jonas JB, Muller-Berg JA, Schlotzer-Schrehardt UM, et al. Histomorphometry of the human optic nerve. Investigative Ophthalmology & Visual Science. 1990;**31**:736-744

[19] Jonas JB, Schmidt AM, Muller-Berg JA, et al. Human optic nerve fibre count and optic disc size. Investigative Ophthalmology & Visual Science. 1992;**33**:2012-2018

[20] Budenz DL, Anderson DR, Varma R, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology. 2007;**114**:1046-1052

[21] Xu L, Chen PP, Chen YY, et al. Quantitative nerve fiber layer measurement using scanning laser polarimetry and modulation parameters in the detection of glaucoma. Journal of Glaucoma. 1998;**7**:270-277

[22] Blumenthal EZ, Weinreb RN. Assessment of the retinal nerve fiber layer in clinical trials of glaucoma neuroprotection. Survey of Ophthalmology. 2001;**45**(Suppl 3):S305-S312; S332-S334

[23] Wu H, De Boer J, Chen T. Diagnostic capability of spectral-domain optical coherence tomography for glaucoma. American Journal of Ophthalmology. 2012;**153**(5):815-826

[24] Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous filed loss. Archives of Ophthalmology. 1991;**109**(1):77-83

[25] Harwerth RS, Carter-Dawson L, Shen F, et al. Ganglion cell losses underlying visual field defects from experimental glaucoma. Investigative Ophthalmology & Visual Science. 1999;**40**:2242-2250

[26] Hasnain SS. The missing piece in glaucoma? Open Journal of Ophthalmology. 2016;**6**: 56-62

[27] Hasnain SS. Pathogenesis of orderly loss of nerve fibers in glaucoma. Optometry: Open Access. 2016;**1**(2):110. DOI: 10.4172/2476-2075.1000110

[28] Ishikawa H, Stein DM, Wollstein G, et al. Macular segmentation with optical coherence tomography. Investigative Ophthalmology & Visual Science. 2005;**46**(6):2012-2017

[29] Tan O, Li G, Lu A, Varma R, Huang D. Advanced imaging for glaucoma study group. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. Ophthalmology. 2008;**115**:949-956

[30] Mwanza JC, Durbin MK, Budenz DL, et al. Glaucoma diagnostic accuracy of ganglion cell–inner plexiform layer thickness: Comparison with nerve fiber layer and optic nerve head. Ophthalmology. 2012;**119**(6):1151-1158