

Correlation Between Retinal Nerve Fiber Layer, Optic Nerve Head and Macular Parameters and Structure Function Relationship in Glaucoma

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ABSTRACT

Purpose: To evaluate correlation between visual field indices and spectral domain optical coherence tomography (SD-OCT) parameters and correlation among SD-OCT parameters to have a better understanding of role of SD-OCT parameters in clinical practice.

Materials and Methods: This is a retrospective controlled clinical study. Three hundred forty-three eyes (91 healthy, 80 ocular hypertension, 97 preperimetric glaucoma and 75 early glaucoma eyes) were analyzed. Retinal nerve fiber layer (RNFL), macular, optic nerve head (ONH) parameters were measured with SD-OCT. Correlation between visual field indices and SD-OCT parameters and correlation among SD-OCT parameters were calculated.

Results: Average RNFL showed the best correlation with both mean deviation (MD) ($r = 0.624$) and pattern standard deviation (PSD) ($r = 0.614$). Other RNFL parameters, ganglion cell complex (GCC) parameters and total retina (TR) parameters showed moderate correlation whereas outer retina (OR) and ONH parameters showed poor correlation with MD. Correlation between RNFL and GCC parameters was strong. Correlation between RNFL and TR parameters was moderate. Poor correlation were found between OR parameters and both RNFL and GCC parameters. Moderate correlation was found between average RNFL and both rim area and rim volume. Other correlations with ONH parameters were poor.

Conclusion: Good structure function relationship is present between visual field indices and SD-OCT parameters like RNFL and GCC parameters. These parameters reflect the severity of glaucoma and can be used for glaucoma monitoring. TR and some ONH parameters like rim area and volume can give supplementary information to use in clinical practice.

Key Words: Ganglion cell complex, Optic nerve head; retinal nerve fiber layer, Spectral domain optical coherence tomography, Structure function relationship.

INTRODUCTION

Glaucoma is one of the worldwide leading cause of irreversible vision loss, in which progressive damage to the optic nerve leads to loss of ganglion cells and their axons.^{1,2} Early diagnosis and regulation of the treatment is very important to prevent disease progression. Visual field test is gold standard for diagnosis of glaucoma however there are many studies showing good diagnostic ability of spectral-domain optical coherence tomography (SD-OCT) parameters especially in preperimetric glaucoma.³⁻¹⁴ Diagnosis of glaucoma at preperimetric stage is more important since structural loss of ganglion cells generally precedes functional visual field defects.^{15,16}

Monitoring the progression of the optic nerve damage is of

paramount importance in the management of glaucoma. A thorough examination is done generally including intraocular pressure measurement, biomicroscopic examination of the optic disc, visual field test and SD-OCT in each visit. Severity of glaucoma is determined by the level of visual field loss.^{17,18} Visual field deterioration is a strong indicator of disease progression. Thus detecting the structure function relationship by correlating visual field test indices and SD-OCT parameters can show the significance of SD-OCT parameters for monitorization of disease progression.

Diagnostic ability of SD-OCT parameters in glaucoma has been researched in several studies.³⁻¹⁴ Besides retinal nerve fiber layer (RNFL) parameters, macular parameters

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Received: 01.11.2019

Accepted: 09.04.2020

Glo-Kat 2020; 15: 181-188

DOI: 10.37844/glauc.cat.2020.15.32

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have come forward for their use in glaucoma diagnosis.⁴⁻¹⁴ Glaucomatous damage most likely affects macular region since the retinal ganglion cells are densely packed in macular area.¹⁹ Optic nerve head (ONH) parameters are quantitative measures of optic disc's morphological features. The degree of correlation of these parameters with each other specifically with clinically widely used RNFL, is important in glaucoma diagnosis and optic neuropathy progression monitorization.

There are studies reporting relationship between visual field indices and SD-OCT parameters and also relationship among SD-OCT parameters.^{3-5,20-30} In this study correlation between visual field indices and SD-OCT parameters and correlation among SD-OCT parameters are investigated to have a better understanding of role of SD-OCT parameters in clinical practice.

MATERIALS AND METHODS

Study population

This is a retrospective controlled clinical study. Two hundred and fifty two eyes of 132 patients were included in this study. From those 252 eyes; 80 eyes were followed with ocular hypertension (OHT) diagnosis, 97 eyes were followed with preperimetric glaucoma (PPG) diagnosis and 75 eyes were followed with early glaucoma (EG) diagnosis. The patients were chosen from those who were followed by one particular glaucoma specialist at least for 2 years and whose diagnosis remained unchanged in this period. For healthy group, 91 eyes of 46 healthy subjects were selected randomly from hospital staff and their family members. Informed consent was obtained from all subjects. This study adhered to the tenets of the Declaration of Helsinki and the research protocol was approved from local ethic committee.

All study subjects underwent full ophthalmic examination including measurement of best corrected visual acuity (BCVA) and intraocular pressure (IOP) using Goldmann applanation tonometry, gonioscopy, dilated fundus examination with 90 D lens, ultrasound pachymetry, visual field examination with the Humphrey Field Analyzer (HFA) (Carl Zeiss Meditec, Jena, Germany) Swedish Interactive Threshold Algorithm (SITA) 24-2 test and measurement of RNFL, macular and ONH parameters with SD-OCT (RTVue-100; Optovue, Fremont, CA, USA).

Inclusion criteria include having BCVA of at least 20/40, spherical refraction $< \pm 6.0$ D, cylinder correction < 3.0 D, open angle with gonioscopy, at least two reliable HFA test results with a fixation loss of $< 20\%$, false-negative error of $< 15\%$ and false-positive error of $< 15\%$. Exclusion criteria were having coexisting retinal disease, non-glaucomatous

optic disc neuropathy, uveitis and other diseases that result in visual field defects.

Healthy eyes were defined as those who had no history of intraocular surgery, IOP < 21 mmHg, normal optic disc appearance and normal visual field test with mean deviation (MD) > -2 dB. OHT eyes were defined as those who had IOP of > 21 mmHg, normal optic disc appearance and normal visual field test with MD > -2 dB. PPG eyes were defined as those who had glaucomatous optic disc changes (focal/diffuse neuroretinal rim loss, notching, nerve fiber layer defects) during follow-up and normal visual field test with MD > -2 dB. EG eyes were defined as those who had glaucomatous optic disc changes (focal/diffuse neuroretinal rim loss, notching, nerve fiber layer defects) during follow-up and visual field defects typical for glaucoma (paracentral/arcuate scotomas, nasal step, hemifield defect or generalized depression) with MD > -6 dB.

Optical Coherence Tomography

OCT measurements were done using RTVue-100 (software version 6.1.0.4; Optovue Inc., Fremont, CA, USA). ONH and ganglion cell complex (GCC) protocols were used. Images with a signal strength index greater than or equal to 50 were included.

The ONH protocol was used for RNFL and ONH measurements. A polar RNFL thickness map is created from which RNFL thickness is measured, with the help of a circle 3.45 mm in diameter centered on the optic disc. Parameters including overall average, superior hemisphere and inferior hemisphere are calculated. In the measurement of ONH parameters 12 radial scans that are 3.4 mm in length and 13 concentric ring scans that are ranging from 1.3 to 4.9 mm in diameter are all centered on the optic disc. The optic disc margins are delineated automatically by joining the retina pigment epithelium (RPE) tips. The optic cup is also automatically defined by intersecting the nerve head inner boundary and a parallel line that is 150 μ m above the joining line of the RPE tips. Parameters including disc area, rim area, rim volume, vertical cup-to-disc (C/D) ratio, horizontal C/D ratio, cup area, cup volume and C/D area ratio are calculated.

The GCC protocol was used for macular measurements. GCC protocol scans a 7-mm square region with 15 vertical lines at 0.55-mm intervals and one horizontal line. A 6-mm diameter circle inside the scanned region is centered 1 mm temporal to the fovea. Total retinal measurement is composed of two layers: GCC and outer retinal layers. GCC layer is composed of ganglion cell layer, nerve fiber layer and inner plexiform layer. GCC layer parameters

including overall average thickness, superior thickness, inferior thickness, global loss volume (GLV) and focal loss volume (FLV) are calculated. GLV shows the average GCC loss over the entire GCC map and FLV shows local GCC loss using a pattern deviation map to correct for overall absolute changes. Total retinal and outer retinal parameters including overall average thickness, superior thickness and inferior thickness are also provided.

Statistical Analyses

All statistical analyses were done with NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software. Normality of distribution of numerical data was detected by Shapiro-Wilk test. Comparison of normally distributed data was done by linear mixed model and non-normally distributed data was done by generalized linear mixed model. Correlations between variables were evaluated by Pearson's correlation coefficients. $P < 0.05$ was taken as statistically significant.

RESULTS

Subject characteristics are shown in Table 1. The ages of the subjects were significantly different in all comparisons except for the comparison between OHT patients and PPG patients. MD and PSD values were significantly lower in EG patients than all other study groups.

Comparison of the SD-OCT parameters among the study groups are shown in Table 2. Besides from a few exceptions all parameters decreased from healthy subjects to EG patients. FLV, GLV, cup area, cup volume, horizontal and vertical C/D ratio values increased from healthy subjects to EG patients. All comparisons were statistically significant among the study groups except for comparisons between healthy subjects and OHT patients and comparisons involving OR parameters and disc area. Also comparisons of PPG patients with OHT and EG patients for the ONH parameters were not statistically significant.

All correlations between MD and SD-OCT parameters

achieved statistical significance except for disc area (Table 3). Average RNFL showed the best correlation with MD among other SD-OCT parameters ($r = 0.624$). Other RNFL parameters, GCC parameters and TR parameters showed moderate correlation whereas OR and ONH parameters showed poor correlation with MD (Table 3).

All correlations between PSD and SD-OCT parameters achieved statistical significance except for disc area (Table 4). Average RNFL showed the best correlation with PSD among other SD-OCT parameters ($r = -0.614$). Other RNFL parameters and GCC parameters showed moderate correlation whereas TR, OR and ONH parameters showed poor correlation with MD (Table 4).

Correlation between RNFL and GCC parameters was strong except for FLV, which was moderately correlated with average RNFL. Correlation between RNFL and TR parameters was moderate. Poor correlation was found between OR parameters and both RNFL and GCC parameters. Correlation between GCC and TR parameters was strong except for FLV, which was moderately correlated with average TR (Table 5).

Correlation between ONH parameters and average RNFL was shown in Table 6. Disc area has showed no correlation with average RNFL. Moderate correlation was found between average RNFL and both rim area and rim volume. Other correlations were poor. Correlation between ONH parameters and average GCC was shown in Table 7. Disc area has showed no correlation with average GCC. All of other correlations were poor.

DISCUSSION

Several instruments were used in the clinical practice for glaucoma diagnosis and optic nerve damage monitorization for the management of glaucoma. During monitorization visual field tests can be insufficient to detect mild signs of disease progression and other tests such as SD-OCT may be needed to verify the progression. Therefore relationship between visual field indices and SD-OCT parameters and

Table 1. Demographics and clinical characteristics of the study participants.

	Healthy	OHT	PPG	EG						
	91 eyes	80 eyes	97 eyes	75 eyes	P ^{1 vs 2}	P ^{1 vs 3}	P ^{1 vs 4}	P ^{2 vs 3}	P ^{2 vs 4}	P ^{3 vs 4}
Age (years)	34.2±10.1	51.8±8.1	52.1±10.1	56.4±9.2	<0.001	<0.001	<0.001	0.999	<0.001	<0.001
Male/Female	33/58	32/48	38/59	32/43	0.452*	0.594*	0.212*	0.849*	0.605*	0.442*
MD (dB)	-0.92±0.85	-1.11±0.81	-1.26±0.78	-3.88±1.27	0.999	0.025	<0.001	0.630	<0.001	<0.001
PSD (dB)	1.52±0.33	1.63±0.46	1.80±0.42	3.65±1.36	0.999	0.054	<0.001	0.751	<0.001	<0.001

Data are expressed as means±SDs, OHT; ocular hypertension; PPG, preperimetric glaucoma; EG, early glaucoma; MD, median deviation; PSD, pattern standard deviation; P: Linear Mixed Model; *: Pearson's chi square test

Table 2. Comparison of the SD-OCT parameters among the study groups.

	Healthy	OHT	PPG	EG						
	91 eyes	80 eyes	97 eyes	75 eyes	P ^{1 vs 2}	P ^{1 vs 3}	P ^{1 vs 4}	P ^{2 vs 3}	P ^{2 vs 4}	P ^{3 vs 4}
RNFL parameters										
Average	112.5±8.3	111.2±6.3	102.7±5.8	91.74±6.5	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
Superior	114.31±11.10	112.36±7.02	102.29±6.73	90.79±9.08	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
Inferior	111.31±8.77	112.10±7.84	102.63±7.80	91.03±9.40	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
GCC parameters										
Average	101.5±6.2	100.1±4.3	99.3±5.6	86.5±4.9	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
Superior	100.8±6.3	99.7±5.1	92.6±6.3	85.3±6.8	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
Inferior	100.0±5.3	100.8±5.0	93.8±5.6	87.1±8.1	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
FLV	0.3±0.3	0.4±0.2	0.7±0.9	2.2±2.3	0.999	0.363	<0.001	0.733	<0.001	<0.001
GLV	2.1±2.0	1.9±1.4	5.2±4.2	10.6±5.5	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
TR parameters										
Average	273.5±11.1	269.8±9.2	262.74±12.4	252.9±14.2	0.188	<0.001	<0.001	0.004	<0.001	<0.001
Superior	276.2±13.1	270.3±10.3	264.45±12.6	253.23±13.5	0.237	<0.001	<0.001	0.001	<0.001	<0.001
Inferior	271.3±11.7	267.2±9.7	261.33±11.8	251.94±12.1	0.253	<0.001	<0.001	0.045	<0.001	<0.001
OR parameters										
Average	172.0±8.0	169.7±8.2	163.44±9.1	166.4±9.0	0.068	0.003	0.002	0.999	0.999	0.999
Superior	175.4±7.7	170.6±8.1	171.85±9.2	167.93±9.2	0.067	0.004	<0.001	0.999	0.752	0.999
Inferior	171.3±8.1	166.4±7.9	167.53±8.9	164.84±8.7	0.072	0.003	0.005	0.999	0.999	0.999
ONH parameters										
Disc area	2.33±0.46	2.12±0.23	2.31±0.43	2.13±0.13	0.999	0.999	0.999	0.999	0.999	0.999
Cup area	0.56±0.32	0.78±0.38	0.99±0.44	1.03±0.48	0.082	<0.001	<0.001	0.213	<0.001	0.009
Rim area	1.64±0.48	1.39±0.35	1.25±0.37	1.13±0.33	0.004	<0.001	<0.001	0.478	<0.001	0.012
Rim volume	0.23±0.13	0.15±0.06	0.12±0.08	0.10±0.03	<0.001	<0.001	<0.001	0.083	<0.001	0.319
Cup volume	0.12±0.13	0.21±0.18	0.31±0.25	0.29±0.22	0.087	<0.001	<0.001	0.782	0.075	0.999
Horizontal C/D	0.52±0.21	0.65±0.15	0.71±0.18	0.73±0.16	0.012	<0.001	<0.001	0.819	0.008	0.107
Vertical C/D	0.45±0.19	0.56±0.12	0.63±0.16	0.68±0.14	0.009	<0.001	<0.001	0.167	<0.001	0.012

Data are expressed as means±SDs; SD-OCT, spectral domain optic coherence tomography; OHT, ocular hypertension; PPG, preperimetric glaucoma; EG, early glaucoma; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; FLV, focal loss volume; GLV, global loss volume; TR parameters, macular total retinal parameters; OR parameters, macular outer retinal parameters; ONH, optic nerve head; C/D ratio, cup-to-disc ratio; P: Linear Mixed Model

relationship among SD-OCT parameters must be defined well.

OHT, PPG and EG patients and healthy subjects were included in this study to observe the change in SD-OCT parameters in different patient groups. SD-OCT parameters showed increasing/decreasing pattern depending upon the parameter from healthy subjects to EG patients. Comparison of OHT patients with healthy subjects was not statistically significant.⁶ Comparison of PPG patients with EG patients and PPG patients with OHT patients for the ONH parameters was not statistically significant unlike RNFL, GCC and TR parameters. All OR parameters were affected less as shown in a study before.²⁹

In this study average RNFL showed strong correlation with MD ($r=0.624$). Kita et al. found strong relationship between MD and temporal RNFL ($r = 0.643$).²² Many other studies showed moderate correlation between MD and RNFL parameters.^{4,5,21,23-25} This findings suggest that RNFL parameters especially average RNFL as shown in our study, can reflect the severity of visual field defects hence severity of glaucoma and can be useful for monitoring glaucoma.

GCC parameters showed moderate correlation with MD. Other studies also found moderate relationship between MD and GCC parameters.^{5,21-24} Among GCC parameters GLV showed the best correlation with MD. Teixeira et al.²⁰ also found a strong relationship between MD and GLV. In

Table 3. Correlation between MD and SD-OCT parameters in all study groups.

	MD	
	r	p
RNFL parameters		
Average	0.624	<0.001
Superior	0.591	<0.001
Inferior	0.561	<0.001
GCC parameters		
Average	0.474	<0.001
Superior	0.453	<0.001
Inferior	0.461	<0.001
FLV	-0.418	<0.001
GLV	-0.486	<0.001
TR parameters		
Average	0.419	<0.001
Superior	0.415	<0.001
Inferior	0.413	<0.001
OR parameters		
Average	0.223	<0.001
Superior	0.229	<0.001
Inferior	0.211	<0.001
ONH parameters		
Disc area	0.078	0.161
Cup area	-0.217	<0.001
Rim area	0.303	<0.001
Rim volume	0.280	<0.001
Cup volume	-0.125	0.024
Horizontal C/D	-0.219	<0.001
Vertical C/D	-0.291	<0.001

MD; mean deviation; SD-OCT, spectral domain optic coherence tomography; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; FLV, focal loss volume; GLV, global loss volume; TR parameters, macular total retinal parameters; OR parameters, macular outer retinal parameters; ONH, optic nerve head; C/D ratio, cup-to-disc ratio; r: Pearson's correlation coefficient

some studies correlation between RNFL parameters and MD and correlation between GCC parameters and MD were comparable.^{5,23,24} Yamada et al.⁵ showed moderate correlation between MD and average TR. Also in our study TR parameters showed moderate correlation with MD. OR and ONH parameters showed poor relationship with MD indicating poor correlation with glaucoma severity.

Average RNFL showed strong correlation with PSD ($r=-0.614$). Some studies also showed moderate-strong relationship between PSD and average RNFL.^{21,24,25} GCC parameters showed moderate-strong relationship with PSD

Table 4. Correlation between PSD and SD-OCT parameters in all study groups.

	PSD	
	r	p
RNFL parameters		
Average	-0.614	<0.001
Superior	-0.593	<0.001
Inferior	-0.520	<0.001
GCC parameters		
Average	-0.492	<0.001
Superior	-0.464	<0.001
Inferior	-0.483	<0.001
FLV	0.404	<0.001
GLV	0.497	<0.001
TR parameters		
Average	-0.396	<0.001
Superior	-0.388	<0.001
Inferior	-0.390	<0.001
OR parameters		
Average	-0.183	0.001
Superior	-0.192	0.001
Inferior	-0.171	0.002
ONH parameters		
Disc area	-0.077	0.164
Cup area	0.215	<0.001
Rim area	-0.297	<0.001
Rim volume	-0.290	<0.001
Cup volume	0.131	0.018
Horizontal C/D	0.210	<0.001
Vertical C/D	0.306	<0.001

PSD; pattern standart deviation; SD-OCT, spectral domain optic coherence tomography; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; FLV, focal loss volume; GLV, global loss volume; TR parameters, macular total retinal parameters; OR parameters, macular outer retinal parameters; ONH, optic nerve head; C/D ratio, cup-to-disc ratio; r: Pearson's correlation coefficient

likewise.^{20,21,24} Overall RNFL and GCC parameters come forward for monitoring glaucoma since we found both parameters had moderate-strong relationship with both MD and PSD. TR, OR and ONH parameters showed poor relationship with PSD.

Strong correlation was found between RNFL and GCC parameters. Other studies also showed strong correlation between those parameters.^{22,24,27,28} GCC parameters can be contributory to RNFL parameters in case of glaucoma monitoring. There was moderate correlation between

Table 5. Correlation among SD-OCT parameters in all study groups.

	Average GCC	
	r	p
Average RNFL and average GCC	0.749	<0.001
Superior RNFL and superior GCC	0.709	<0.001
Inferior RNFL and inferior GCC	0.700	<0.001
Average RNFL and FLV	-0.447	<0.001
Average RNFL and GLV	-0.708	<0.001
Average RNFL and average TR	0.565	<0.001
Superior RNFL and superior TR	0.537	<0.001
Inferior RNFL and inferior TR	0.535	<0.001
Average RNFL and average OR	0.217	<0.001
Superior RNFL and superior OR	0.202	<0.001
Inferior RNFL and inferior OR	0.197	<0.001
Average GCC and average TR	0.811	<0.001
Superior GCC and superior TR	0.812	<0.001
Inferior GCC and inferior TR	0.810	<0.001
FLV and average TR	-0.423	<0.001
GLV and average TR	-0.740	<0.001
Average GCC and average OR	0.381	<0.001
Superior GCC and superior OR	0.373	<0.001
Inferior GCC and inferior OR	0.356	<0.001
FLV and average OR	-0.175	0.001
GLV and average OR	-0.343	<0.001

SD-OCT, spectral domain optic coherence tomography; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; FLV, focal loss volume; GLV, global loss volume; TR, total retina; OR, outer retina; r: Pearson's correlation coefficient

Table 6. Correlation between average RNFL and ONH parameters in all study groups.

	Average RNFL	
	r	P
ONH parameters		
Disc area	0.132	0.017
Cup area	-0.269	<0.001
Rim area	0.418	<0.001
Rim volume	0.417	<0.001
Cup volume	-0.161	0.003
Horizontal C/D	-0.257	<0.001
Vertical C/D	-0.361	<0.001

RNFL, retinal nerve fiber layer; ONH, optic nerve head; C/D ratio, cup-to-disc ratio; r: Pearson's correlation coefficient

Table 7. Correlation between average GCC and ONH parameters in all study groups.

	Average GCC	
	r	p
ONH parameters		
Disc area	0.048	0.383
Cup area	-0.251	<0.001
Rim area	0.310	<0.001
Rim volume	0.353	<0.001
Cup volume	-0.144	0.009
Horizontal C/D	-0.226	<0.001
Vertical C/D	-0.319	<0.001

GCC, ganglion cell complex; ONH, optic nerve head; C/D ratio, cup-to-disc ratio; r: Pearson's correlation coefficient

RNFL and TR parameters. GCC parameters showed a stronger relationship with TR parameters owing to the fact that GCC measurements are proportional to the TR measurements. OR parameters showed poor correlation both with RNFL and GCC parameters. This finding confirms other studies suggesting that OR parameters are affected less by the glaucoma.^{29,31}

Sung et al.³ conducted a study evaluating correlations between average RNFL and ONH parameters and reported strong correlation only between average RNFL and rim area ($r=0.663$). In our study moderate correlation was found between average RNFL and rim area ($r=0.418$) and also rim volume ($r=0.417$). Rim area and volume measurements are an expression of nerve fiber quantity at the optic disc hence good correlation with average RNFL is to be expected.

Correlation between average GCC and ONH parameters was poor. Rim volume showed the best correlation with average GCC among other ONH parameters ($r=0.353$). Bresciani-Battilana et al.²⁷ reported that rim area showed the best correlation with average GCC among other ONH parameters ($r=0.583$). Rim area and volume showing the best correlations with both average RNFL and GCC among other ONH parameters, can be useful at glaucoma monitoring.

In conclusion a good structure function relationship is present between visual field indices and SD-OCT parameters like RNFL and GCC parameters. These parameters reflect the severity of glaucoma and can be used for glaucoma monitoring. TR and some ONH parameters like rim area and volume can give supplementary information to use in clinical practice.

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