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Original Article

Structure-Function correlation using optical coherence tomography in normal subjects, preperimetric and manifest primary open-angle glaucoma.

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Abstract

Background

Primary open-angle glaucoma is a chronic optic neuropathy. Diagnosis and monitoring require several functional and structural investigations. Structure-function correlation is a capital step of the management.
The aim of this study was to assess the correlation between tomographic and functional parameters in normal, preperimetric and manifest glaucoma cases.

Methods

This retrospective analytical study included 275 eyes (152 cases). Participants were divided into 3 groups: 33 normal subjects, 32 patients with preperimetric glaucoma and 87 patients with manifest glaucoma. All subjects underwent a complete ophthalmologic examination, a visual field and spectral-domain optical coherence tomography (SD-OCT).

Results

Correlation between functional and tomographic parameters was non-significant in the group of normal or preperimetric glaucoma subjects. Regarding manifest glaucoma group, mean deviation (MD) was significantly correlated with all tomographic parameters ($p<0.001$). The loss variance (LV) was significantly correlated with tomographic assessment of Retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC). The regression studies of (MD - RNFL /GCC) and (LV - GCC) had significant results with nonlinear models ($p <0.001$). Linear and polynomial models were used to correlate LV and average RNFL ($p=0,275$).

Conclusions

No structure-function correlation was observed at the preperimetric stage. However, MD correlated with tomographic parameters more than LV in manifest glaucoma group. Curvilinear function might be the appropriate model for the structure-function relationship assessment.

Key words

Primary open-angle glaucoma; Retinal ganglion cells; Retinal nerve fiber; Optical coherence tomography; Correlation.

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Introduction

Glaucomatous neuropathy is characterized by progressive loss of retinal ganglion cells (RGC) and optic nerve fibers. Visual field defects are caused by anatomical alteration. Dysfunctions are progressive and non-reversible in late stages.

Optical coherence tomography (OCT) has revolutionized the ophthalmological practice as one of the most accurate imaging techniques [1,2]. However, correlating functional organs with morphological OCT data may be of more significant clinical interest in glaucoma patients.

Patients and Methods

This 2 years study included 275 eyes of 152.

Participants were divided into 3 groups: 66 eyes from 33 normal subjects, 51 eyes of 32 preperimetric glaucoma patients, and 158 eyes of 87 manifest primary open-angle glaucoma (POAG) patients.

•Normal subjects were randomly selected from a cohort of non-glaucomatous individuals who met the inclusion criteria: Age> 40 years old, intraocular pressure <21 mmHg, normal papillae, normal visual field (VF) and normal OCT examination.

•Inclusion criteria for manifest glaucoma group were: Open iridocorneal angle (ICA), glaucomatous changes of optic disc, RNFL and GCC defect on SD-OCT, consistent glaucomatous pattern on VF examinations.

•For preperimetric glaucoma group, the criteria were: age> 40 years old, glaucomatous structural findings as stated above in criteria for manifest glaucoma group, and normal VF results.

Exclusion criteria were as follows: history of eye surgery (except uncomplicated phacoemulsification cataract surgery), presence of ophthalmological or other pathologies responsible for impaired vision or VF, narrow ICA and all other forms of secondary open-angle glaucoma (such as post-traumatic or post-uveitis).

Standard VF testing was performed using automated standard white-on-white perimetry (Octopus 101 Haag-Streit USA, Inc; normal test strategy, program 24-2). The test was considered reliable when fixation losses were less than 20% and false positive or false negative errors were less than 15%. Each VF defect was confirmed in at least two VF tests.

The mean value of VF sensitivity was calculated by a software and presented as mean deviation (MD) and Loss variance (LV); all studied parameters were expressed in decibels (dB).

Optic nerve head parameters, GCC and RNFL thicknesses were measured by SD-OCT RTVue-100 (Optovue, Inc., Fremont, CA, USA). RNFL thickness was determined by ONH mode, in which data along a 3.45-mm diameter circle around the optic disc was recalculated with a map created from en-face imaging that used 6 circular and 12 linear data inputs.

Average, superior, and inferior RNFL thicknesses were calculated. In addition, the SD-OCT RTVue 100 provide a sectoral analysis of the RNFL according to the following sectors: Superior temporal quadrant: (90 ° -180 °) RNFL st, inferior temporal quadrant: (180° -270 °) RNFL it, inferior nasal quadrant:
(270 ° -360 °) RNFL in, superior nasal quadrant: (360 -90 °) RNFL sn.

The GCC scan was centered 1-mm temporal to the fovea and covered a square grid (7 × 7 mm) on the central macula. GCC thickness was measured from the internal limiting membrane to the outer inner plexiform layer boundary, and average, superior, and inferior GCC thicknesses were calculated.

Two pattern-based diagnostic parameters were also obtained. Focal loss volume (FLV) was computed as the integral of deviation in areas of significant focal GCC loss divided by the map area.

Global loss volume (GLV) was computed as the sum of negative fractional deviation in the entire area. Only OCT results with a signal strength index "SSI"> 50 were retained. All statistical analyses were performed with IBM® SPSS® Statistics 23.0 software and Excel Microsoft Office 2016. Distribution's normality for numerical data were tested by the Kolmogorov-Smirnov test. Age-adjusted ANOVA test was adopted for the comparison between groups, and the Tukey-Kramer honest significant difference (HSD) post hoc test was used in order to adjust for multiple comparisons between groups

Correlations between quantitative variables were studied by Pearson correlation coefficient (r). Analysis of the relationship between structural (RNFL, GCC) and functional (MD, LV) parameters was performed with linear and nonlinear regression models (second and third-degree polynomial regression), in order to better understand the trend and evolutionary profile of the disease. The regression models were evaluated with Akaike Information Criterion (AIC); the model with the weakest Akaike information criterion is the most suitable, adjusted R2 and extra-sum-of square F test. The F test was used to check whether the alternative nonlinear model matched the presented data better than the linear model.

Results

The mean age in normal subjects group was statistically lower than manifest glaucoma and preperimetric glaucoma group ($P < 0.001$). (Table 1). Statistically significant differences were found between the three groups for the analysis of Average C/D area ratio, Average RNFL and Average GCC.

Table 1 : Age distribution, tomographic and perimetric parameters in different groups

	Normal subjects	Preperimetric glaucoma	manifest glaucoma	P
Age	49.24 +/- 14.58	53.3+/-9.4	62.15+/-14.12	**<0.001***
Average C/D area ratio	0.33+/-0.13	0.48+/-0.15	0.52 +/-0.2	**<0.001***
Average RNFL	102.26+/-8.3	94.84+/-7.9	84.03 +/- 16.2	**<0.001***
Average GCC	101.48+/-9.93	94.21+/-14.4	86.13 +/- 15.52	**<0.001***
MD (M±SD)	-0,43 +/- 0,5	-0,66 +/- 0,7	8,85 +/-6,69	A 0,094 **B <0,01***
LV (M±SD)	1,77 +/- 0,88	2,61 +/- 1,53	20,16 +/ 17,51	A 0,523 **B <0,01***

A: Comparison between normal subjects versus preperimetric glaucoma, B: Comparison between (normal subject/ preperimetric glaucoma) versus manifest glaucoma. MD, mean deviation; LV, loss variance; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex

No significant difference was found between normal subjects and preperimetric glaucoma group. However, the comparison between normal subjects and preperimetric glaucoma groups on one hand and manifest glaucoma group on the other hand, showed a significant difference ($p < 0.01$) for studied perimetric parameters (MD, LV).

Correlation of MD with tomographic parameters revealed that; in normal subjects and preperimetric glaucoma groups, no statistically significant correlation was found between tomographic parameters and MD. In manifest glaucoma group, MD was significantly correlated with most tomographic parameters.

Best correlations for MD were noted with the analysis of RNFL and GCC (highly significant <0.001).

In normal subjects and preperimetric glaucoma groups, LV did not show a significant correlation with most of tomographic parameters. However, in manifest glaucoma group, LV was significantly correlated with most of parameters. Best correlations for LV were noted with the analysis of GCC (highly significant <0.001) (table2,3).

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Table 2: Correlation OCT parameters /MD.

	Normal	Preperimetric glaucoma	Manifest glaucoma
Cup/Disc Area Ratio	r=0.75 p=0.548	r=0.036 p=0.8	r=0.52 p<0.001
VCDR	r=0.41 p=0.74	r=0.007 p=0.96	r=0.46 p<0.001
HCDR	r=0.077 p=0.54	r=-0.17 p=0.23	r=0.2 p=0.015
Rim Area	r=0.006 p=0.96	r=-0.052 p=0.71	r=-0.17 p=0.035
Disc Area	r=0.91 p=0.468	r=0.07 p=0.63	r=0.11 p=0.153
Cup Volume	r=-0.18 p=0.884	r=0.18 p=0.21	r=0.38 p<0.001
Average RNFL	r=0.188 p=0.131	r=-0.136 p=0.34	r=-0.47 p<0.001
Superior hemisphere RNFL	r=0.2 p=0.107	r=-0.16 p=0.26	r=-0.43 p<0.001
Inferior hemisphere RNFL	r=0.15 p=0.23	r=-0.09 p=0.53	r=-0.48 p<0.001
Superior temporal RNFL	r=0.2 p=0.1	r=-0.136 p=0.34	r=-0.34 p<0.001
Inferior temporal RNFL	r=0.1 p=0.43	r=-0.14 p=0.3	r=-0.32 p<0.001
Superior nasal RNFL	r=0.15 p=0.21	r=-0.18 p=0.2	r=-0.44 p<0.001
Inferior nasal RNFL	r=0.12 p=0.33	r=0.123 p=0.4	r=-0.51 p<0.001
Average GCC	r<0.001 p=0.99	r=0.095 p=0.51	r=-0.42 p<0.001
Superior hemisphere GCC	r=0.08 p=0.5	r=0.084 p=0.56	r=-0.4 p<0.001
Inferior hemisphere GCC	r=-0.1 p=0.44	r=0.095 p=0.51	r=-0.42 p<0.001
FLV %	r=-0.06 p=0.6	r=-0.08 p=0.54	r=0.5 p<0.001
GLV %	r=-0.07 p=0.57	r=-0.07 p=0.62	r=0.51 p<0.001

Table 3: Correlation OCT parameters/ LV.

	Normal subjects	Preperimetric glaucoma	Manifest glaucoma
Cup/Disc Area Ratio	r=0.18 p=0.14	**r=-0.27 p=0.05**	**r=0.3 p<0.001**
VCDR	r=0.14 p=0.24	r=-0.18 p=0.2	**r=0.27 p=0.001**
HCDR	r=0.23 p=0.06	r=-0.17 p=0.22	r=-0.85 p=0.3
Rim Area	r=-0.18 p=0.14	r=0.006 p=0.96	r=-0.03 p=0.7
Disc Area	r=-0.009 p=0.94	**r=-0.32 p=0.02**	r=-0.08 p=0.27
Cup Volume	r=0.05 p=0.686	r=-0.25 p=0.07	r=0.09 p=0.24
Average RNFL	r=-0.07 p=0.542	r=0.174 p=0.22	**r=-0.25 p=0.001**
Superior hemisphere RNFL	r=-0.05 p=0.67	r=0.08 p=0.54	**r=-0.22 p=0.005**
Inferior hemisphere RNFL	r=-0.06 p=0.61	r=0.22 p=0.12	**r=-0.26 p=0.001**
Superior temporal RNFL	r=-0.07 p=0.55	r=0.11 p=0.43	**r=-0.16 p=0.04**
Inferior temporal RNFL	r=0.09 p=0.44	**r=0.33 p=0.017**	r=-0.13 p=0.11
Superior nasal RNFL	r=-0.02 p=0.88	r=0.078 p=0.58	**r=-0.24 p=0.003**
Inferior nasal RNFL	r=-0.16 p=0.19	r=0.013 p=0.93	**r=-0.26 p=0.001**
Average GCC	r=0.12 p=0.33	r=-0.05 p=0.74	**r=-0.3 p<0.001**
Superior hemisphere GCC	r=0.06 p=0.64	r=-0.03 p=0.81	**r=-0.27 p<0.001**
Inferior hemisphere GCC	r=-0.15 p=0.21	r=-0.61 p=0.67	**r=-0.31 p<0.001**
FLV %	**r=-0.25 p=0.04**	r=-0.063 p=0.66	**r=0.28 p<0.001**
GLV %	**r=-0.31 p=0.01**	r=-0.07 p=0.61	**r=0.33 p<0.001**

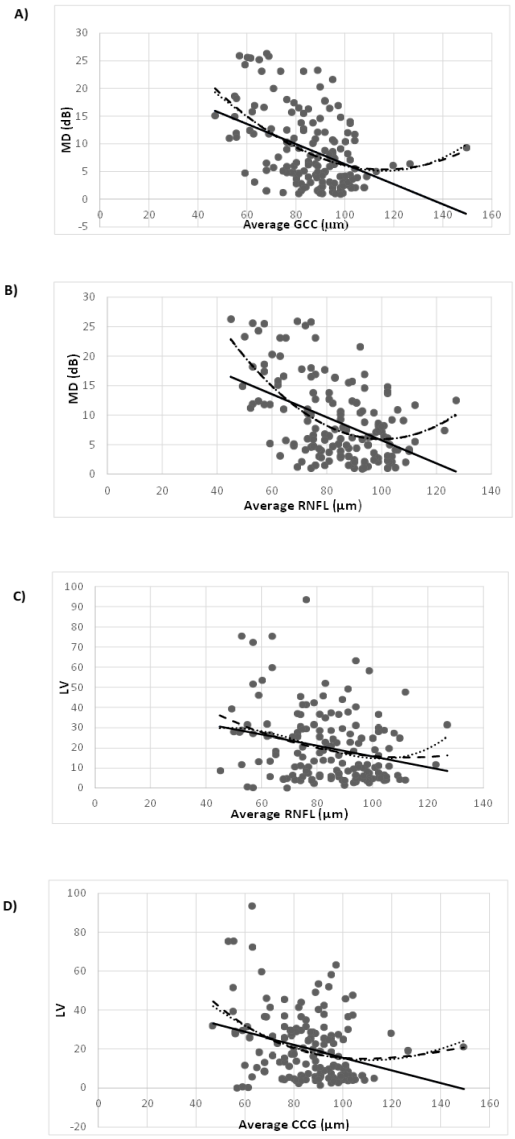
MD, mean deviation; HCDR, horizontal cup-to-disc ratio; VCDR, vertical cup-to-disc ratio; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; FLV, Focal loss volume; GLV, Global loss volume.

The relationships between visual field and SD-OCT parameters were evaluated by regression analysis. (Figures)

The relation between MD (dB) and average RNFL / GCC was better explained with a second-order polynomial model (R2 = 0.289, AIC = 550.06 and p <0.001 for average RNFL) and (R2 = 0.203, AIC = 567.95 and p <0.001 for average GCC).

Regression study between LV and RNFL did not show a statically significant difference between linear and non-linear model.

The regression between LV and average GCC was also better expressed by a second-order polynomial model (R2 = 0.1, AIC = 891 and p= 0.034) (Table 4).



(A) Mean Deviation (MD) versus average ganglion cell complex (GCC), linear and nonlinear regression (second-order and third-order polynomial).
(B) Mean Deviation (MD) versus average retinal nerve fiber layer (RNFL), linear and nonlinear regression (second-order and third-order polynomial).
(C) Loss variance (LV) versus average retinal nerve fiber layer (RNFL), linear and nonlinear regression (second-order and third-order polynomial).
(D) Loss variance (LV) versus average ganglion cell complex (GCC), linear and nonlinear regression (second-order and third-order polynomial)

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Table 4: Prediction of MD and LV from OCT parameters(regression analysis).

	Linear		Second-Order Polynomial				Third-Order Polynomial			
	R^2	AIC	R^2	AIC	F	P*	R^2	AIC	F	P†
MD -RNFL	0,219	563,77	0,289	550,06	16,21	<0,001	0,284	552,05	8,05	<0,001
MD - GCC	0,176	838,86	0,203	567,95	716,92	<0,001	0,2	569,85	356,43	<0,001
LV - RNFL	0,056	897,38	0,058	898,17	1,2	0,275	0,058	899,06	1,143	0,321
LV -GCC	0,084	833,7	0,1	891,13	4,54	0,034	0,094	892,96	2,34	0,1

P*; comparison of linear and second-order polynomial model, P†; comparison of linear and third-order polynomial model, RNFL, retinal nerve fiber layer; GCC, ganglion cell complex, AIC; Akaike Information Criterion, R2 ; regression coefficient, F; extra-sum-of square F test.

Discussion

No correlation between Mean Deviation (MD) and tomographic parameters in normal and preperimetric glaucoma groups could be found due to the normal visual field [2]. Analysis of glaucomatous eyes from eye bank showed that at least 25 to 35% loss of retinal ganglion cells (RGC) is required to detect the first functional alterations in visual field. In early stages, the neuronal loss is undetectable in automated perimetry [3].

In manifest glaucoma group, MD was significantly correlated with all parameters exploring RNFL, GCC and most of the Optic nerve head(ONH) parameters. Similar results have been reported in the literature [4,5]. However, objective correlation might be still questionable due to the heterogeneity of the published series and the difficulty of randomized trial establishment [6].

Regarding loss of variance, no significant correlations were found in normal subjects and preperimetric glaucoma groups. However, for manifest glaucoma group, the correlation was significant between LV and most tomographic parameters assessing RNFL and GCC. Best correlations were noted with parameters analyzing GCC. In the literature as in our work, correlations of structural parameters were more significant with MD than LV which represent more the variance of the local default [7-9]. LV index would be considerable in case of inhomogeneous localized deficit of retinal sensitivity. The correlation of LV with the ONH parameters was absent in manifest glaucoma group, except; Cup/Disc area ratio and Cup/Disc V ratio. This could be explained by the fact that, the overall severity of the disease in manifest glaucoma group was moderate with an average MD = 8,85 +/- 6,69. In fact, at early and moderate stage, neuronal loss particularly affects the upper and lower part of the optic disc responsible for the vertical elongation of the optic cup.

The study of linear and nonlinear regression models was mandatory to assess structure-function relationship. Regression functions would then be useful in order to understand the trend of disease progression and to select an appropriate monitoring strategy [10].

The structure-function relationship was better explained with nonlinear models (second and third-order model) evaluating MD (dB) with RNFL and GCC. However, linear models describe more the relationship between LV and average RNFL. The regression between LV and average GCC, was better explained by second-order polynomial model, but the difference was non-significant compared to linear model ($p = 0.034$). Similar results were seen in other studies adopting similar statistical methodology [11].

Logarithmic scale could minimize changes in retinal sensitivity at large dB values and optimize it at low dB values. Simple linear model could be an alternative of the curvilinear model to describe the relationship between perimetric and tomographic parameters in some glaucoma cases. However, it may transform MD into a non-logarithmic function and generate a biased curvilinear aspect for the scales expressed in decibel [12].

In the literature, curvilinear regression models, evaluating the relationship between RNFL and VF sensitivity, were the most effective. Likewise, the second and third order regression models correlating GCC and VF sensitivity, showed a stronger structure-function correlation compared to the first order regression models. The curvilinear regression models suggest that structural functional changes are not simultaneous in cases of Glaucoma. Non-axonal components thickness of RNFL increase with age and disease progression. Glial cells activation allows glial remodeling of the retinal nerve fiber layer during the response to neuronal injury. This gliosis may be hiding the decrease in RNFL and GCC thickness [13].

The functional impotence may be delayed in some advanced structural alterations. That would explain the concept of 'functional reserve' and the difficulties of the assessment in some cases. for curvilinear model, the correlation between VF sensitivity (on a logarithmic scale) and structural parameters (on a linear scale) seems to be more effective for early stage functional impairment.

Monitoring the glaucomatous neuropathy progression consists first in detecting the evolution of the retinal nerve fiber layer damages, then that of the macular ganglion cell complex. In order to assess damage progression to the targeted structures, the analysis should always be integrated with the measurement of the functional impairment [14].

Some type of regression curve minimizes visual field changes in early-stage glaucoma and maximizes them in severely affected glaucoma. It is recommended to rely more on structural investigations such as OCT for the monitoring of preperimetric and early glaucoma cases. Functional tests such as conventional static perimetry are more effective in the follow-up of advanced stage glaucoma.

Conclusions

Glaucoma is one of the leading causes of blindness worldwide and Optical Coherence Tomography (OCT) is the cornerstone imaging technique for its detection. Early detection of structural alterations and the prediction of related visual impairment was the challenging part of most of the published analytic studies.

Conflit of interest: None

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