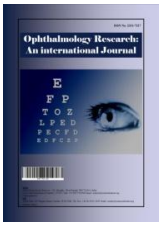

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Comparison of Structural Defects between Optic Disc and Ganglion Cell Complex in Patients with Glaucoma

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: To evaluate the agreement of glaucomatous structural defects of the ganglion cell complex (GCC) detected with the spectral domain optical coherence tomography (sdOCT) with the optic nerve head alterations detected with the Heidelberg retina tomography (HRT), of glaucoma patients with ocular hypertension or open angle glaucoma.
Material and Methods: Ninety patients eyes with structural glaucomatous defects were enrolled. All of them underwent imaging examination of GCC with sdOCT and the optic disk with HRT. The Cohen's kappa coefficient of agreement was used.
Results: The agreement between the optic disc and GCC using the parameters of the programs analysis of the HRT, the moorfields regression analysis (MRA) and glaucoma probability score (GPS) was not significant. Instead between MRA and GPS a good agreement was calculated. Significant agreements were found between MRA and GPS on one hand and GCC on the other, considering location and length of the glaucomatous damage, while non significant agreements

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were found between GPS and GCC for the location and the length of the glaucomatous structural defect.
Conclusions: There is no significance (Please explain further if you are referring to significance in terms of the difference, similarity or agreement) between HRT and sdOCT for the detection of the glaucomatous damage between the optic nerve head and the ganglion cell complex. Instead MRA and GCC detect comparable areas and lengths of the glaucomatous damage. On the other hand GPS records larger deficits relative to MRA and has not a significant agreement with the study of GCC.

Keywords: Complex; ganglion cell; glaucoma probability score; HRT; moorfields regression analysis; OCT.

1. INTRODUCTION

Glaucoma is a progressive optic neuropathy, characterized by an abnormal intraocular pressure (IOP) that exceeds nerve tissue resistance, with structural glaucomatous type damage of the nerve tissue, and finally optic neuropathy. There is permanent functional defects on the achromatic perimetry, when almost 40% of the nerve retinal tissue has already gone in apoptosis cellular death [1,2].

Early diagnosis of glaucoma is challenging and important because of the silent clinical progression, the irreversible nature of the glaucomatous damage and its impact on patients' life. Glaucoma is a chronic disease that leads to irreversible optic nerve damage and to permanent loss of vision [3]. It is mainly asymptomatic until its advanced stages when accumulative perimetric defects, narrow the visual fields of the patient [4]. The quality of life related to vision is affected at the early stages of glaucoma, whereas the socio-economic effects are also important [5].

The identification of glaucoma suspect is based on the presence of risk factors, such as an increased IOP, a positive family history for glaucoma, a thin central corneal thickness (CCT), the clinical appearance of the optic nerve head and others, but also on the structural and perimetrical defects, detected with several imaging methods [6].

The Optical Coherence Tomography (OCT) and the confocal scanning laser microscopy, with the Heidelberg Retina Tomography (HRT), are widely used in the clinical practice to detect the glaucomatous damage. Their prognostic value have already been studied. HRT studies the optic nerve head and calculates several quantitative and qualitative indices, whereas OCT focuses on the quantitative and qualitative analysis of the retinal nerve fiber layer (RNFL) and the optic disk [7].

The advance of OCT technology from time domain to spectral domain imaging with fourier analysis, enable the selective study of the innermost retinal layers known as ganglion cell complex (GCC), that includes ganglion cell body, dendrites and axons of the same cells. Early structural glaucomatous damage is thought to be focused on these retinal layers [8]. The clinical prognostic value and the diagnostic accuracy of GCC study for glaucoma have already been assessed with spectral domain OCT (sdOCT), and comparing GCC indices with RNFL and optic disk measurements [9]. The glaucomatous GCC damages have not yet been studied with the HRT quantitative and qualitative evaluation of the optic nerve head.

The main purpose of the present study is to assess the clinical agreement between GCC glaucomatous structural defects detected with sdOCT and the optic nerve head glaucomatous alterations detected with the HRT, in patients with ocular hypertension or open angle glaucoma.

2. MATERIALS AND METHODS

The present study was carried out by the glaucoma department of the University of Athens. It was designed according to the declaration of Helsinki and was approved by the ethical and deontological committee of the hospital. Informed consent was obtained from all participants of the study. All were examined, following a precise protocol including the record of the personal, familial and ophthalmic history, the clinical evaluation of the best corrected visual acuity (BCVA), the IOP measurement, the CCT measurement and the

imaging of the optic nerve head with HRT and the GCC with OCT.

The first one hundred patients that visited the department examined and met the inclusion criteria were chosen for the purpose of the study. Finally ninety patients' eyes were enrolled. Inclusion criteria were BCVA of or better on Snellen chart test with spherical refractive error from -6.00 D to + 3.00 D, ocular hypertension or open angle glaucoma with the presence of glaucomatous type structural defects on HRT or/and GCC examination with sdOCT and uncomplicated cataract surgery. Exclusion criteria were ocular comorbidities such as diseases of the cornea, anterior chamber, lens, vitreous cavity, and retina that may reduce visual acuity and history of intraocular surgery. (Please reframe/fragment the above sentence to: The clinician decided on the follow up time and treatment, based on his experience, the risk factors of each patient, the clinical examination and the imaging of the glaucomatous damage).

The best corrected visual acuity was determined from Snellen chart testing on the decimal form. Slit lamp examination was performed to evaluate the anterior and posterior chambers. Fundus examination was performed with a (+ 78) D lens after dilation of the pupil with 1% tropicamide and 2.5% phenylephrine drops. Intraocular pressure was determined with a Goldman applanation tonometer. Central corneal thickness was measured with an ophthalmic ultrasonography system (Ocuscan RxP, Alcon Alcon Laboratories Inc, USA, city, state). Heidelberg Retina Tomography III (Heidelberg Engineering GmbH, Heidelberg, Germany) was used to assess C/D and the other qualitative and quantitative indices of the nerve head. Both the programs analysis Glaucoma Probability Score (GPS) και Moorfields Regression Analysis (MRA) were used. The ivue - sdOCT (Optovue Corporation, Fremont, CA) was used to assess the ganglion cell complex and their indices.

The results of MRA and GPS of the optic nerve programs and GCC measurements were examined by the same clinician for the detection of the structural damage presence or absence on the HRT and sdOCT as well as the correspondence regarding the area and the length of the damage. The decision for the anatomical correspondence was based on the optic nerve fiber distribution and the way they converge towards the optic head, respecting the middle line.

2.1 Statistical Analysis

Data were analyzed using statistical software (SPSS for Windows 14.00, SPSS Inc., Chicago, IL). The Kolmogorov–Smirnov test was used to control the normality of the distribution. All the descriptive parameters were noted in the form of mean and standard deviation (SD) if the data were parametric or in the form of median with interquartile range if the data were nonparametric. The Cohen's kappa coefficient of agreement was used for the assessment of the results. Statistical significance was defined by $P \leq .05$.

3. RESULTS

One hundred patients (43 men and fifty seven women) were examined based on the study protocol. From the two hundred patients' eyes, 110 were excluded for not meeting the inclusion criteria and ninety eyes (40 rights and fifty lefts) were finally enrolled. Demographic data and clinical characteristics of the patients are presented in Table 1. The median age of the patients was 66 year, IOP was 18 mmHg, CCT was thin (518 μm) and the cup to disc ratio (C/D) was (Sixty patients' eyes were not on any treatment and thirty were under topical treatment, using at least one medication. Considering optic disk measurements with HRT and the MRA program, the patients of the study had median C/D (interquartile range 0,23 - 0,47), with median linear C/D 0.61ranged from 0,48 to 0,69, median rim 1,22 mm^2 (1,02 – 1,64), median mean cup depth 0,24 mm (0,17 – 0,32) and median mean RNFL thickness 0,21 mm. Table 2 presents the MRA – HRT indices of the optic nerve head.

Table 3 presents the indices of the optic disk of the GPS program analysis of the HRT. The mean glaucoma probability was 0,57 ± 0,33. GCC thickness measurements and the relative indices of the patients are presented in Table 4. The mean focal volume loss index (FLV) was 3,556 ± 3,69 and the global volume loss index (GLV) was 10,82 ± 10,17.

Table 5 presents the Cohen's kappa coefficients of agreement relative to the presence or not of the glaucomatous damage between HRT and GCC. There was no significant agreement between the HRT for the optic disk and GCC of sdOCT for both the analysis programs of the

Table 1. Descriptive data and clinical characteristics of the patients

Patients	43/57
Sex (male/female) (N=100)	
Eyes (Right / Left) (N=90)	40/50
Age (years)	66 (61-71)
BCVA	9.38 ± 1.1
IOP (mmHg)	18 (15 – 21)
treatment	0 (0 – 1)
no medication / under medication	60 / 30
CCT (μm)	518 (509 – 533)
C/D	0.38 (0.24 – 0.47)

BCVA = Best Corrected Visual Acuity, IOP = Intraocular pressure, CCT = Central Corneal Thickness, C/D = Cup to Disk ratio

Table 2. Moorfields regression analysis indices

Disk area (mm^2)	2,12 ± 0.46
Cup area (mm^2)	0.74 (0.51 – 1.001)
Rim area (mm^2)	1.22 (1.02 – 1.64)
Cup Volume (mm^3)	0.18 ± 0,13
Rim Volume (mm^3)	0.29 (0.2 – 0.41)
Cup/Disc Area Ratio	0.37 (0.23 – 0.47)
Linear Cup/Disk Ratio	0.61 (0.48 – 0.69)
Mean Cup Depth (mm)	0.24 (0.17 – 0.32)
Maximum Cup Depth (mm)	0.57 (0.42 – 0.75)
Cup Shape Measure	-0.14 (-0.2 – -0.08)
Height Variation Contour (mm)	0.94 ± 3.65
Mean RNFL Thickness (mm)	0.21 (0.11 – 0.25)
RNFL Cross Sectional Area (mm^2)	1.02 (0.58 – 1.24)

Table 3. Glaucoma probability score indices

Glaucoma probability	0.57 ± 0.33
Rim steepness	-0.26 (-0.61 - -0.14)
Cup Size (mm^2)	0.43 (0.25 - 0.56)
Cup depth (mm)	0.56 (0.41 – 0.76)
horizontal RNFL curvature	-0.04 (-0.1 - 0.00)
vertical RNFL curvature	-0.12 (-0.16 - -0.08)

Table 4. Ganglion cell complex indices

Total GCC Average Thickness (μm)	86.2 ± 12.28
Superior GCC Average Thickness (μm)	86.64 ± 11.56
Inferior GCC Average Thickness (μm)	85.89 ± 13.98
Intra Eye difference (S-I)	0 (-5 – 5)
FLV (%)	3.556 ± 3.69
GLV (%)	10.82 ± 10.17

S-I = Superior Area – Inferior Area, FLV = Focal loss volume, GLV = global loss volume

HRT, MRA and GPS (P = 0.205 and P = 0,624). However, between MRA and GPS a significant agreement was calculated (κ = 0.477, P= 0.0001).

A significant but moderate agreement was found between MRA and GCC (κ = 0,296 and P = 0.004), considering the location of the damage when both the examinations detected the glaucomatous defect, while a non significant agreement was found between GPS and GCC (P = 0,602). A significant and strong agreement (κ = 613, P = 0,0001) was calculated between MRA and GPS (Table 6).

A significant and strong agreement was calculated (κ = 0,442, P = 0.0001) between both MRA and GPS of HRT and GCC of sdOCT, considering the length of the glaucomatous damage when both the examinations detected the glaucomatous defect. Instead the agreements between GPS and MRA and GPS and GCC were not significant (P = 0.068 and P =0.256 respectively) (Table 7).

4. DISCUSSION

The thickness of ganglion cell complex is significantly thin in patients with pre-perimetric glaucoma. The advances in technology of OCT imaging offers the ability of a high diagnostic accuracy and repetitivity for GCC examination in different stages of the glaucomatous optic neuropathy [10,11]. Specificity of GCC examination is very high (91%) and the volume indices, calculated by ganglion cell complex analysis program, are useful in distinguishing glaucoma from healthy eyes. Arintawati and others have calculated the odds ratio (OR) of GCC volume indices and found that GLV is more precise for early (OR= 1,22) and pre-perimetric glaucoma (OR= 1,74), whereas the FLV indicator was more significant (OR = 2,32) in advanced glaucoma defects [12]. In the present study no agreement was recorded between the optic disc and GCC defects. GCC examination by itself does not offer a high prognostic accuracy for the detection of the glaucomatous defect for the group of pre-perimetric and glaucomatous patients of the study. These findings concern both optic nerve analysis programs of HRT, MRA and GPS.

GCC analysis has a significant correlation with RNFL study in both glaucoma patients and healthy individuals and probably has a higher diagnostic ability than RNFL, to detect the early glaucomatous damage [13]. Instead The correlations of GCC indices with the optic disk parameters are not equally strong (r>0,2), especially for GLV and FLV [14]. In patients with primary open angle glaucoma and glaucoma suspects patients the progression of the GCC damage follows the perimetric defects (P = 0.007) and presents a strong correlation (r > 0.60) with the visual fields indices [15,16]. A finding of this study is a non significant agreement, between HRT and sdOCT for the detection of the glaucomatous damage that is in accordance with the low correlation described between GCC defects and optic disc indices.

Table 5. Cohen's kappa coefficient of agreement between MRA, GPS and GCC

	MRA HRT	GPS HRT	GCC OCT
MRA HRT(P)	-	0.477(0.0001)	-0.133(0.205)
GPS HRT(P)	0.477(0.0001)	-	0.048(0.624)
GCC OCT(P)	-0.133(0.205)	0.048(0.624)	-

MRA = moorfields regression analysis, GPS = Glaucoma probability score, GCC = Ganglion Complex Cells, Probability (P) <0,05%

Table 6. Cohen's kappa coefficient of agreement for the location of the glaucomatous defect between MRA, GPS and GCC

	MRA HRT	GPS HRT	GCC OCT
MRA HRT	-	0.613(0.0001)	0,296(0.004)
GPS HRT	0.613(0.0001)	-	0.054(0.602)
GCC OCT	0.296(0.004)	0.054(0.602)	-

MRA = moorfields regression analysis, GPS = Glaucoma probability score, GCC = Ganglion Complex Cells, Probability (P) <0,05%

Table 7. Cohen's kappa coefficient of agreement for the length of the glaucomatous damage between MRA, GPS and GCC

	MRA HRT	GPS HRT	GCC OCT
MRA HRT	-	-0.167(0.068)	0.442(0.0001)
GPS HRT	-0.167(0.068)	-	-0.163(0.256)
GCC OCT	0.442(0.0001)	-0.163(0.256)	-

MRA = moorfields regression analysis, GPS = Glaucoma probability score, GCC = Ganglion Complex Cells, Probability (P) <0,05%

Confocal scanning laser microscopy (HRT) has a specificity of 95,8% and offers optic disk measurements of high accuracy. HRT indices, either independent in combination with the clinical findings and the risk factors present a high correlation with the glaucomatous damage progression [17] and can predict the risk of glaucoma [18]. HRT and especially the MRA analysis program can predict perimetrical defects [19]. HRT sensitivity is 84,3% [20] and the respective sensitivities of the programs MRA and GPS are 77,1% and 71,4% [21]. In the present study a significant agreement has also been calculated for the concordance regarding the location and the length of the damage between HRT and sdOCT that detect structural defects.

The sensitivities of GCC volume indices have been calculated and are 82,6% for the GLV and 81,5% for the FLV [22]. In contrast with these different sensitivities between HRT and GCC indices, the present study revealed a significant agreement regarding the location but especially the length of the damage, between GCC and MRA. Instead there was no agreement between GPS and GCC.

The agreement between MRA and GPS was significantly strong (κ = 0,613, P< 0,0001) for the location of the glaucomatous damage but no agreement was found for the length of the defect between the two analysis program of HRT with the GPS program to present a higher extension of the damage.

Limitation of the present study is the absence of a group of healthy patients that does not permit the sensitivity and specificity of the examinations. Also the present study does not calculate the correlations of the indices of HRT and GCC analysis programs. This can be the purpose of future studies to assess the appropriate indices for the detection and the follow up of the glaucomatous damage.

5. CONCLUSIONS

There is no significance (Please explain further if you are referring to the significance in terms of the difference, similarity or agreement) between HRT and sdOCT for the detection of the glaucomatous damage between the optic nerve head and the ganglion cell complex. Instead MRA and GCC detect comparable areas and lengths of the glaucomatous damage and they represent the indices that better follow the nerve damage area. On the other hand GPS records larger deficits relative to MRA and has no significant agreement with the study of GCC.

CONSENT

Informed written consent was obtained from all participants of the study.

ETHICAL APPROVAL

Ethical declaration of Helsinki was obtained and was approved by the ethical and deontological committee of the hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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