Original Research Article

Comparison of structural defects between optic disc and ganglion cell complex in patients with glaucoma

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 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 including both of the programs analysis of the HRT, the moorfields regression analysis (MRA) and glaucoma probability score (GPS) was not significant (P = 0.205 and P = 0,624). Instead between MRA and GPS a good agreement was calculated (κ = 0.477, P= 0.0001). Significant agreements were found between MRA and GPS and GCC considering location and length of the glaucomatous damage (κ = 0,296 and κ = 0,442 respectively), while non significant agreements were found between GPS and GCC (P = 0,602 and P =0.256 respectively) for the location and the length of the glaucomatous structural defect.

Conclusions: There is no significance 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.

Key words: OCT, HRT, Moorfields Regression Analysis, Ganglion Cell Complex, Glaucoma Probability Score

Introduction

Glaucoma is a progressive optic neuropathy, characterized by an abnormal intraocular pressure (IOP) that exceeds nerve tissue resistance, structural glaucomatous type damage of the nerve tissue and finally an optic neuropathy with the presence of functional permanent 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 suspect patients is challenging and important in the same time 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). Instead the quality of life related to vision is affected till the early stages of glaucoma, whereas the socioeconomical effects are also important (5).

The identification of glaucoma suspect patients 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 and their prognostic value have been already 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 nerve retinal fibber 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 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 (9). The clinical prognostic value and the diagnostic accuracy of GCC study for glaucoma have been already assessed with spectral domain OCT (sdOCT) and comparing GCC indices with RNFL and optic disk measurements (10). Instead 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 with the optic nerve head glaucomatous alterations detected with the HRT, in patients with ocular hypertension or open angle glaucoma.

Material and Methods

The present study was carried out by the glaucoma department of the University of Athens, was designed according to the declaration of Helsinki and was approved by the ethical and deontological committee of the hospital. Informed consent was obtained by all participants of the study. All of them were examined, following a precise protocol including the record of the personal, familiar 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 eyes of the patients were enrolled. Inclusion criteria were BCVA of 0,7 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. The clinician decided for the follow up time and the 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 fibber distribution and the way they converge towards the optic head, respecting the middle line.

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 $P \leq .05$.

Results

One hundred patients (43 men and fifty seven women) were examined based on the study protocol. From the two hundred 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 of age, IOP was 18 mmHg, CCT was thin (518μm) and the cup to disc ratio (C/D) was 0,38 (interquartile range 0,24 - 0,47). Sixty eyes did not use 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 0,37 (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 not a significant agreement between the HRT for the optic disk and GCC

of sdOCT for both the analysis programs of the HRT, MRA and GPS (P = 0.205 and P = 0,624). Instead between MRA and GPS a good 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).

Discussion

The thickness of ganglion cell complex is significantly thinnest in patients with preperimetric glaucoma. The advance of 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 (11,12). Specificity of GCC examination is very high (91%) and the volume indices, calculated by ganglion cell complex analysis program, are useful to distinguish 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 preperimetric glaucoma (OR= 1,74), whereas the FLV indicator was more significant (OR = 2,32) in advanced glaucoma defects (14). 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 preperimetric 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 (15). Instead the correlations of GCC indices with the optic disk parameters are not equally strong (r>0,2), especially for GLV and FLV (16). In patients with primary open angle glaucoma and glaucoma suspect 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 (17,18). 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.

Confocal scanning laser microscopy (HRT) has a specificity of 95,8% and offers optic disk measurements of high accuracy. HRT indices independent or combined with the clinical findings and the risk factors present a high correlation with the glaucomatous damage progression (19) and can predict the risk of glaucoma (20). HRT and especially the MRA analysis program can predict perimetrical defects (21). HRT sensitivity is 84,3% (22) and the respective sensitivities of the programs MRA and GPS are 77,1% and 71,4% (23). 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 (24). 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.

Conclusions

There is no significance 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 not a significant agreement with the study of GCC.

The conflict of interest

“The authors declare that there is no conflict of interest regarding the publication of this paper.”

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References

1. Khawaja AP, Viswanathan AC. Are we ready for genetic testing for primary open-angle glaucoma? Eye (Lond). 2018 Jan 30
2. Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. Am J Ophthalmol. 1989 May 15;107(5):453-64.
3. Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. Am J Ophthalmol. 2013 Oct;156(4):724-30
4. Fernandez Lopez E, Karaca EE, Ekici F, Waisbourd M, Spaeth GL. Symptoms reported by patients with varying stages of glaucoma: review of 401 cases. Can J Ophthalmol. 2014 Oct;49(5):420-5.
5. Maria Kazaki, Ilias Georgalas, Alexandros Damanakis, Georgios Labiris, Sergios Taliantzis, Chryssanthi Koutsandrea, Dimitris Papaconstantinou. Vision-Related Quality of Life in Ocular Hypertension Patients: Effects of Treatment. Open Journal of Ophthalmology, 2015, 5, 31-40
6. Blumberg D, Skaat A, Liebmann JM. Emerging risk factors for glaucoma onset and progression. Prog Brain Res. 2015;221:81-101
7. Choi YJ, Jeoung JW, Park KH, Kim DM. Clinical Use of an Optical Coherence Tomography Linear Discriminant Function for Differentiating Glaucoma From Normal Eyes. J Glaucoma. 2015 Jan 14.
8. Hoffmann EM, Miglior S, Zeyen T, Torri V, Rulli E, Aliyeva S, Floriani I, Cunha-Vaz J, Pfeiffer N. The Heidelberg retina tomograph ancillary study to the European glaucoma prevention study: study design and baseline factors. Acta Ophthalmol. 2013 Dec;91(8):e612-9.
9. Na JH, Lee K, Lee JR, Baek S, Yoo SJ, Kook MS. Detection of macular ganglion cell loss in preperimetric glaucoma patients with localized retinal nerve fibre defects by spectral-domain optical coherence tomography. Clin Exp Ophthalmol. 2013 Dec;41(9):870-80.
10. Le PV, Tan O, Chopra V, Francis BA, Ragab O, Varma R, Huang D. Regional correlation among ganglion cell complex, nerve fiber layer, and visual field loss in glaucoma. Invest Ophthalmol Vis Sci. 2013 Jun 21;54(6):4287-95.
11. Na JH, Lee K, Lee JR, Baek S, Yoo SJ, Kook MS. Detection of macular ganglion cell loss in preperimetric glaucoma patients with localized retinal nerve fibre defects by spectral-domain optical coherence tomography. Clin Experiment Ophthalmol. 2013 Dec;41(9):870-80.
12. Renard JP, Fénolland JR, El Chehab H, Francoz M, Marill AM, Messaoudi R, Delbarre M, Maréchal M, Michel S, Giraud JM. Analysis of macular ganglion cell complex (GCC) with spectral-domain optical coherence tomography (SD-OCT) in glaucoma. J Fr Ophtalmol. 2013 Apr;36(4):299-309.

13. Iverson SM, Feuer WJ, Shi W1, Greenfield DSFrequency of abnormal retinal nerve fibre layer and ganglion cell layer SDOCT scans in healthy eyes and glaucoma suspects in a prospective longitudinal study. Br J Ophthalmol. 2014 Jul;98(7):920-5.
14. Arintawati P, Sone T, Akita T, Tanaka J, Kiuchi Y. The applicability of ganglion cell complex parameters determined from SD-OCT images to detect glaucomatous eyes. J Glaucoma. 2013 Dec;22(9):713-8.
15. Moreno PA, Konno B, Lima VC, Castro DP, Castro LC, Leite MT, Pacheco MA, Lee JM, Prata TS. Spectral-domain optical coherence tomography for early glaucoma assessment: analysis of macular ganglion cell complex versus peripapillary retinal nerve fiber layer. Can J Ophthalmol. 2011 Dec;46(6):543-7.
16. Bresciani-Battilana E, Teixeira IC, Barbosa DT, Caixeta-Umbelino C, Paolera MD, Kasahara N. Correlation between the ganglion cell complex and structural measures of the optic disc and retinal nerve fiber layer in glaucoma. Int Ophthalmol. 2014 Sep 3.
17. Teixeira IC, Bresciani-Battilana E, Barbosa DT, Caixeta-Umbelino C, Paolera MD, Kasahara N. Correlation between the ganglion cell complex and functional measures in glaucoma patients and suspects. Int Ophthalmol. 2014 Nov 26.
18. Anraku A, Enomoto N, Takeyama A, Ito H, Tomita G. Baseline thickness of macular ganglion cell complex predicts progression of visual field loss. Graefes Arch Clin Exp Ophthalmol. 2014 Jan;252(1):109-15.
19. Miglior S, Zeyen T, Hoffmann EM, Torri V, Rulli E, Floriani I, Poli D, Aliyeva S, Cunha-Vaz J, Pfeiffer N. Predictive value of heidelberg retina tomograph parameters for the development of glaucoma in the European glaucoma prevention study. Am J Ophthalmol. 2015 Feb;159(2):265-76.e1.
20. Weinreb RN, Zangwill LM, Jain S, Becerra LM, Dirkes K, Piltz-Seymour JR, Cioffi GA, Trick GL, Coleman AL, Brandt JD, Liebmann JM, Gordon MO, Kass MA; OHTS CSLO Ancillary Study Group. Predicting the onset of glaucoma: the confocal scanning laser ophthalmoscopy ancillary study to theOcular Hypertension Treatment Study. Ophthalmology. 2010 Sep;117(9):1674-83.
21. Schrems-Hoesl LM, Schrems WA, Laemmer R, Horn FK, Juenemann AG, Kruse FE, Mardin CY. Confocal Laser Scanning Tomography to Predict Visual Field Conversion in Patients With Ocular Hypertension and Early Glaucoma. J Glaucoma. 2014 Oct 9.
22. Wollstein G, Garway-Heath DF, Fontana L, Hitchings RA. Identifying early glaucomatous changes. Comparison between expert clinical assessment of optic disc photographs and confocal scanning ophthalmoscopy. Ophthalmology. 2000 Dec;107(12):2272-7.
23. Harizman N, Zelefsky JR, Ilitchev E, Tello C, Ritch R, Liebmann JM. Detection of glaucoma using operator-dependent versus operator-independent classification in the Heidelberg retinal tomograph-III. Br J Ophthalmol. 2006 Nov;90(11):1390-2. Epub 2006 Jul 26.
24. Rao HL, Yadav RK, Addepalli UK, Begum VU, Senthil S, Choudhari NS, Garudadri CS.Comparing Spectral-Domain Optical Coherence

Tomography and Standard Automated Perimetry to Diagnose Glaucomatous Optic Neuropathy. J Glaucoma. 2014 Aug 20

Tables

Table 1. Descriptive data and clinical characteristics of the patients	
Patients Sex (male/female) (N=100)	43/57
Eyes (Right / Left) (N=90)	40/50
Age (years)	66 (61-71)
BCVA	9,38 ± 1,1
IOP (mmHg)	18 (15 – 21)
treatment no medication / under medication	0 (0 – 1) 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)

able 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)

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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	

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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%			

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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%

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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%			

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