

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 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 including both of the using the parameters 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 ($\kappa = 0.477$, $P = 0.0001$). Significant agreements were found between MRA and GPS on one hand and GCC on the other, considering location and length of the glaucomatous damage ($\kappa = 0.296$ and $\kappa = 0.442$ 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. (Please use acceptable decimal notation. Use "dot and not comma" for p values and other statistical data. Also P should always be italicized and capitalized. Zero "0" should not be placed in front of the decimal in P value. Refer to guidelines for reporting P values on the authors guidelines at <http://www.sciencedomain.org/journal/23/authors-instruction>)

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.

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

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46 Introduction (Citations should preferably be in brackets [] instead of
47 parenthesis (). Please refer to guidelines on citations on the authors
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49 Glaucoma is a progressive optic neuropathy, characterized by an abnormal
50 intraocular pressure (IOP) that exceeds nerve tissue resistance, with
51 structural glaucomatous type damage of the nerve tissue, and finally an optic
52 neuropathy. with the presence of functional There is permanent functional
53 defects on the achromatic perimetry, when almost 40% of the nerve retinal
54 tissue has already gone in apoptosis cellular death (1,2) [1, 2].

55 Early diagnosis of glaucoma suspect patients is challenging and important in
56 the same time because of the silent clinical progression, the irreversible
57 nature of the glaucomatous damage and its impact on patients' life. Glaucoma
58 is a chronic disease that leads to irreversible optic nerve damage and to
59 permanent loss of vision (3) [3]. It is mainly asymptomatic until its advanced
60 stages when accumulative perimetric defects, narrow the visual fields of the
61 patient (4). Instead the The quality of life related to vision is affected till at the
62 early stages of glaucoma, whereas the socioeconomical socio-economic
63 effects are also important (5).

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

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

76 The advance of OCT technology from time domain to spectral domain
77 imaging with fourier analysis, enable the selective study of the innermost

78 retinal layers known as ganglion cell complex (GCC), that includes ganglion
79 cell body, dendrites and axons of the same cells. Early structural
80 glaucomatous damage is thought to be focused on these retinal layers (9).
81 The clinical prognostic value and the diagnostic accuracy of GCC study for
82 glaucoma have been already been assessed with spectral domain OCT
83 (sdOCT), and comparing GCC indices with RNFL and optic disk
84 measurements (10). Instead The glaucomatous GCC damages have not yet
85 been studied with the HRT quantitative and qualitative evaluation of the optic
86 nerve head.

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

91 Material and Methods

92 The present study was carried out by the glaucoma department of the
93 University of Athens, was designed according to the declaration of Helsinki
94 and was approved by the ethical and deontological committee of the hospital.
95 (Please reframe/fragment the above sentence to: The present study was
96 carried out by the glaucoma department of the University of Athens. It was
97 designed according to the declaration of Helsinki and was approved by the
98 ethical and deontological committee of the hospital.) Informed consent was
99 obtained by from all participants of the study. All of them were examined,
100 following a precise protocol including the record of the personal, familiar
101 familiar and ophthalmic history, the clinical evaluation of the best corrected
102 visual acuity (BCVA), the IOP measurement, the CCT measurement and the
103 imaging of the optic nerve head with HRT and the GCC with OCT.

104 The first one hundred patients that visited the department examined and met
105 the inclusion criteria were chosen for the purpose of the study. Finally ninety
106 eyes of the patients patients' eyes were enrolled. Inclusion criteria were BCVA
107 of 0,7 or better on Snellen chart test with spherical refractive error from -6.00
108 D to + 3.00 D, ocular hypertension or open angle glaucoma with the presence
109 of glaucomatous type structural defects on HRT or/and GCC examination with
110 sdOCT and uncomplicated cataract surgery. Exclusion criteria were ocular
111 comorbidities such as diseases of the cornea, anterior chamber, lens, vitreous
112 cavity, and retina that may reduce visual acuity and history of intraocular
113 surgery. The clinician decided for the follow up time and the treatment based
114 on his experience, the risk factors of each patient, the clinical examination and
115 the imaging of the glaucomatous damage. (Please reframe/fragment the
116 above sentence to: The clinician decided on the follow up time and treatment,

117 based on his experience, the risk factors of each patient, the clinical
118 examination and the imaging of the glaucomatous damage.)

119

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

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

141 Statistical analysis

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

149 Results

150 (Please use acceptable decimal notation. Eg use “dot and not comma”
151 for p values and other statistical data. Also “P” should always be
152 italicized and capitalized. Zero “0” should not be placed in front of the
153 decimal in P value. Consider the decimal places. Refer to guidelines for

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157 One hundred patients (43 men and fifty seven women) were examined based
158 on the study protocol. From the two hundred patients' eyes, 110 were
159 excluded for not meeting the inclusion criteria and ninety eyes (40 rights and
160 fifty lefts) were finally enrolled. Demographic data and clinical characteristics
161 of the patients are presented in table 1. The median age of the patients was
162 66 year of age, IOP was 18 mmHg, CCT was thin (518 μ m) and the cup to
163 disc ratio (C/D) was 0,38 (interquartile range 0,24 - 0,47). Sixty patients' eyes
164 did not use were not on any treatment and thirty were under topical treatment,
165 using at least one medication. Considering optic disk measurements with HRT
166 and the MRA program, the patients of the study had median C/D 0,37
167 (interquartile range 0,23 - 0,47), with median linear C/D 0.61 ranged from 0,48
168 to 0,69, median rim 1,22 mm² (1,02 – 1,64), median mean cup depth 0,24 mm
169 (0,17 – 0,32) and median mean RNFL thickness 0,21 mm. Table 2 presents
170 the MRA – HRT indices of the optic nerve head.

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

176 Table 5 presents the Cohen's kappa coefficients of agreement relative to the
177 presence or not of the glaucomatous damage between HRT and GCC. There
178 was not a There was no significant agreement between the HRT for the optic
179 disk and GCC of sdOCT for both the analysis programs of the HRT, MRA and
180 GPS (P = 0.205 and P = 0,624). Instead However, between MRA and GPS a
181 good significant agreement was calculated (κ = 0.477, P= 0.0001).

182 A significant but moderate agreement was found between MRA and GCC (κ =
183 0,296 and P = 0.004), considering the location of the damage when both the
184 examinations detected the glaucomatous defect, while a non significant
185 agreement was found between GPS and GCC (P = 0,602). A significant and
186 strong agreement (κ = 0,613, P = 0,0001) was calculated between MRA and
187 GPS (table 6).

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

194

195 Discussion

196 The thickness of ganglion cell complex is significantly **thinnest thin** in patients
197 with preperimetric glaucoma. **The advance of** **The advances in** technology of
198 OCT imaging offers the ability of a high diagnostic accuracy and repetitivity for
199 GCC examination in different stages of the glaucomatous optic neuropathy
200 (11,12). Specificity of GCC examination is very high (91%) and the volume
201 indices, calculated by ganglion cell complex analysis program, are useful **to**
202 **distinguish in distinguishing** glaucoma from healthy eyes. Arintawati and
203 others have calculated the odds ratio (OR) of GCC volume indices and found
204 that GLV is more precise for early (OR= **1,22**) and preperimetric glaucoma
205 (OR= **1,74**), whereas the FLV indicator was more significant (OR = **2,32**) in
206 advanced glaucoma defects (14). In the present study no agreement was
207 recorded between the optic disc and GCC defects. GCC examination by itself
208 does not offer a high prognostic accuracy for the detection of the
209 glaucomatous defect for the group of preperimetric and glaucomatous
210 patients of the study. These findings concern both optic nerve analysis
211 programs of HRT, MRA and GPS.

212 GCC analysis has a significant correlation with RNFL study in both glaucoma
213 patients and healthy individuals and probably has a higher diagnostic ability
214 than RNFL, to detect the early glaucomatous damage (15). **Instead** **The**
215 correlations of GCC indices with the optic disk parameters are not equally
216 strong ($r > 0,2$), especially for GLV and FLV (16). In patients with primary open
217 angle glaucoma and glaucoma suspects **patients** the progression of the GCC
218 damage follows the perimetric defects ($P = 0.007$) and presents a strong
219 correlation ($r > 0.60$) with the visual fields indices (17,18). A finding of this
220 study is a non significant agreement, between HRT and sdOCT for the
221 detection of the glaucomatous damage that is in accordance with the low
222 correlation described between GCC defects and optic disc indices.

223 Confocal scanning laser microscopy (HRT) has a specificity of 95,8% and
224 offers optic disk measurements of high accuracy. HRT indices, **either**
225 independent **or combined in combination with** the clinical findings and the risk
226 factors present a high correlation with the glaucomatous damage progression
227 (19) and can predict the risk of glaucoma (20). HRT and especially the MRA
228 analysis program can predict perimetrical defects (21). HRT sensitivity is
229 84,3% (22) and the respective sensitivities of the programs MRA and GPS are
230 77,1% and 71,4% (23). In the present study a significant agreement has also
231 been calculated for the concordance regarding the location and the length of
232 the damage between HRT and sdOCT that detect structural defects.

233 The sensitivities of GCC volume indices have been calculated and are 82,6%
234 for the GLV and 81,5% for the FLV (24). In contrast with these different

235 sensitivities between HRT and GCC indices, the present study revealed a
236 significant agreement regarding the location but especially the length of the
237 damage, between GCC and MRA. Instead there was no agreement between
238 GPS and GCC.

239 The agreement between MRA and GPS was significantly strong ($\kappa = 0,613$,
240 $P < 0,0001$) for the location of the glaucomatous damage but no agreement
241 was found for the length of the defect between the two analysis program of
242 HRT with the GPS program to present a higher extension of the damage.

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

249

250 Conclusions

251 There is no significance (Please explain further if you are referring to the
252 significance in terms of the difference, similarity or agreement) between HRT
253 and sdOCT for the detection of the glaucomatous damage between the optic
254 nerve head and the ganglion cell complex. Instead MRA and GCC detect
255 comparable areas and lengths of the glaucomatous damage and they
256 represent the indices that better follow the nerve damage area. On the other
257 hand GPS records larger deficits relative to MRA and has not a no significant
258 agreement with the study of GCC.

259

260 The conflict of interest

261 "The authors declare that there is no conflict of interest regarding the
262 publication of this paper."

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264 There is no financial support

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267 References

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- 363

364 **Please kindly move the Tables and place them inside the text under the**
365 **Results, preferably after/below the explanations of the result.**

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367 **(Please use acceptable decimal notation, use "dot and not comma" for *p***
368 **values and other statistical data. Also *P* should always be italicized and**

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374 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	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	

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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)

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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)

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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 ± 1,56
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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382

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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	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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