Coll. Antropol. **36** (2012) 2: 441–445
Original scientific paper

Macular Thickness and Volume Parameters Measured Using Optical Coherence Tomography (OCT) for Evaluation of Glaucoma Patients

Freja Barišić, Ana Jurin Sičaja, Maja Malenica Ravlić, Katia Novak-Lauš, Renata Iveković and Zdravko Mandić

University of Zagreb, »Sestre milosrdnice« University Hospital Center, Department of Ophthalmology, Zagreb, Croatia

A B S T R A C T

The aim of this study was to evaluate macular thickness parameters in glaucoma patients and to compare them to normal subjects using Optical Coherence Tomography (OCT). This prospective, observational study included 20 primary open angle glaucoma patients (POAG) and 20 healthy subjects in control group. Exclusion criteria were diabetes and other macular pathology, like age-related macular degeneration, macular oedema, central serous retinopathy and high myopia >4.00 dsph. OCT imaging of peripapillar retina and macular area were performed using Cirrus HD OCT. In these two groups of patients we analyzed changes of macular thickness parameters (central subfield thickness, macular volume, and average macular thickness). The group of glaucoma patients had decreased values of the two macular thickness parameters: macular volume and average macular thickness, compared to control group. There was no difference in central macular thickness, presumably because of the absence of the ganglion cells in this layer. Macular imaging can be a useful additional method to determine glaucoma status and has a potential for tracking glaucoma progression.

Key words: *macular thickness, glaucoma, optical coherence tomography*

Introduction

Glaucoma is a multifactorial optic nerve neuropathy characterized by a loss of retinal ganglion cells with result in visual function impairment. It is diagnosed clinically by observing optic disc changes and by measurement of visual function with perimetry. Although perimetry and optic nerve cupping are subjective examinations and can be variously interpreted, they have the advantage of providing a topographical spatial representation of the visual loss, which can be compared to characteristic patterns of glaucomatous loss[1].

In addition to these diagnostic procedures, clinicians nowadays also use images from optical coherence tomography (OCT). OCT has been shown to be a useful tool for diagnosing and evaluating glaucoma, based on measurement of optic nerve and peripapillary retina as well as macular thickness parameters[2,3].

The macula contains over 50% of all retinal ganglion cells (RGCs) and is an ideal area for early detection of cell loss and changes over time because of high cell density. In the macular area ganglion cells are arranged in 4–6 layers making up 30% to 35% of retinal macular thickness, so that the loss of macular ganglion cells results in significant retinal or retinal nerve fibre layer (RNFL) thinning. Several studies indicated that in glaucomatous eyes decreases in macular thickness and volume are due to loss of RGCs and that this findings correlate with RNFL thickness and visual field defects[2,4–8]. Recent studies imply that thinning of RNFL is related to thinning of macular ganglion cell complex (GCC), which is defined as three innermost retinal layers: 1) RNFL (made of ganglion cell axons), 2) ganglion cell layer (GCL) made of ganglion cell bodies and 3) the inner plexiform layer (IPL) made out of ganglion cell dendrites. All three layers of ganglion cells complex are significantly thinner in glaucoma patients, reflecting the proportion of dead ganglion cells[8], although Tan et al. found that residual glial tissue maintains 50% thickness even when nearly all ganglion cells were lost[9].

Received for publication February 5, 2012

At the time of this writing, only with the RTVue Fourier domain (fd) OCT system (Optovue, Inc., Fremont CA) and upgraded version of Cirrus HD OCT was possible to measure the thickness of the two layers damaged by glaucoma, RNFL, which contains the axons of the RGCs, and the RGC plus IPL, which contains the RGC bodies as well as the connections of the cells of the inner nuclear layer to RGCs[10]. We have measured central subfield thickness, macular volume and average macular thickness with standard Cirrus HD OCT to evaluate the macular thickness in glaucomatous and normal eyes and to evaluate correlation of macular volume with the glaucoma status.

Materials and Methods

Our study included 40 eyes: 20 with glaucoma and 20 healthy subjects examined between January 2011 and July 2011 at the University of Zagreb, »Sestre milosrdnice« University Hospital Center, Department of Ophthalmology, Zagreb, Croatia. Informed consent was obtained from each participant before enrolment. Glaucoma participants (11 male and 9 female, mean age of 69.5 y±3.4) included patients with primary open-angle glaucoma (POAG). Twenty healthy participants (10 male and 10 female, with a mean age of 60.5 y±6.6) were also included in the study.

All glaucoma patients had undergone a complete ophthalmologic examination. This consisted of the following: medical history (including ocular and family histories), best corrected visual acuity (BCVA), slit lamp examination, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, gonioscopy, dilated fundus biomicroscopy using 78-diopter lens, and Octopus dG2 visual field testing. Each patient had a diagnosis of POAG, based on glaucomatous damage to the optic disc (optic nerve head cupping) and abnormal visual field with controlled IOP values (≤21 mmHg) on topical monotherapy or combined two hypotensive medications. All eyes with glaucoma had associated visual field loss (mean defect of 3.0–15.0 dB) in at least 2 consecutive examinations tested by the Octopus 900 visual field analyser. Exclusion criteria included diabetic retinopathy, macular degeneration, macular oedema, epiretinal membrane, retinal detachment, cataract, high myopia (greater than –4.00 dsph or 2.00 dcyl), presence of nonglaucomatous optic nerve diseases and previous ocular surgery or trauma. We have also excluded all patients with secondary glaucoma, chronic angle closure glaucoma and POAG treated surgically or by laser treatment, as well as the patients with BCVA ≤0.5 according to Snellen.

The control group included subjects with no history of glaucoma or retinal pathology, IOP<21 mm Hg, normal optic nerve head appearance, and normal visual field testing results (mean defect –2.0 – +2.0 dB). Normal eyes served as the control group.

All patients were scanned with Cirrus HD OCT, according to the manufacturer instructions, including imaging of peripapillary retina and macular area. We analysed changes of macular thickness parameters: central subfield thickness, macular volume and average macular thickness together with peripapillary retinal nerve fibre layer measurements. The borderline of RNFL values in control group was set at 80 μm according to Cirrus HD-OCT RNFL normative database[11]. In addition, we have divided glaucoma group of patients in two categories setting arbitrarily border of RNFL thickness at 53 μm, to be able to better distinguish the correlation between the RNFL thickness and macular volume parameters.

Statistical analysis was made using Mann Whitney´s test. A p value of 0.05 or less was considered to be statistically significant.

The study protocol adheres to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the »Sestre milosrdnice« University Hospital Center, Department of Ophthalmology, Zagreb, Croatia.

Results

We have investigated 40 eyes, 20 glaucoma patients and 20 normal subjects. Values of peripapillary RNFL and macular thickness parameters were compared in two examined groups (Table 1 and Table 2).

We observed significant changes in macular thickness parameters (macular volume and average macular thickness) in glaucomatous patients group, ($p<0.001$), while there were no changes in central macular thickness values. Normal eyes had significantly greater macular volume than subjects with advanced glaucoma ($p<0.001$). In this group we found 6 patients with RNFL less than 80 μm (range 74–78 μm) (Table 2). The X±SD macular volume for glaucomatous eyes was 9.0±0.7 and for normal eyes was 9.9±0.4 (Table 3).

We have divided glaucoma patients in two groups – those with retinal thickness <53μm and those ≥53μm. Table 4 gives values of peripapillary RNFL and macular thickness parameters in these two groups.

Discussion

Structural changes in glaucoma are manifested by thinning of RNFL, that may be used as an early marker to identify risk of progression of visual field defect, although histopathological studies imply that up to 40% of axonal loss could be lost before visual field defects are detected[12–14].

The studies have shown correlation between macular parameters and glaucoma status[2,4–8,15]. Zeimer et al. first observed a relationship between macular thickness and glaucomatous damage, based on prior animal studies in which primate models of glaucoma demonstrated a significant loss of RGCs in the perifoveal region[4,16]. To confirm Zeimer's hypothesis Lederer et al. evaluated macular volume in normal, glaucoma suspect, and glaucomatous subjects using a time domain optical coherence tomography (TD-OCT)[15]. Their results demonstrated a sig-

TABLE 1
PERIPAPILLARY RNFL AND MACULAR THICKNESS PARAMETERS IN GLAUCOMA PATIENTS

Glaucoma patients			
Peripapillar RNFL μm	CMT μm	V mm³	AMT μm
79	263	10.1	279
48	264	9.2	257
58	211	7.8	216
60	270	9.2	256
53	290	9.2	255
40	276	9.5	263
52	247	8.1	224
71	285	9.5	265
70	254	9.9	274
58	234	8.3	230
66	233	9.7	267
68	266	9.6	276
52	264	9.2	255
79	265	10.0	280
50	248	8.8	245
46	251	7.8	216
60	263	9.0	249
70	280	9.3	259
35	266	8.6	238
50	259	8.1	225

RNFL – retinal nerve fibre layer, CMT – central macular thickness, V – macular volume, AMT – average macular thickness; values ≤53 μm are marked in bold.

TABLE 2
PERIPAPILLARY RNFL AND MACULAR THICKNESS PARAMETERS IN CONTROL GROUP

Control group			
Peripapillar RNFL μm	CMT μm	V mm³	AMT μm
90	269	10.0	294
93	268	10.4	289
80	273	9.4	260
74	242	9.5	262
78	289	9.4	260
80	278	9.4	261
82	256	9.9	280
83	249	9.9	279
77	257	9.9	273
75	249	9.3	258
99	303	9.5	263
97	295	9.6	267
86	265	10.4	289
77	258	9.9	275
78	256	10.1	280
86	243	9.9	274
95	267	10.1	281
89	234	9.9	276
92	287	10.7	305
85	267	10.1	280

RNFL – retinal nerve fibre layer, CMT – central macular thickness, V – macular volume, AMT – average macular thickness; RNFL values<80 μm are marked in bold.

nificant correlation between macular volume and glaucoma status with decreased macular volume in patients with more advanced disease as well as significant difference of macular volume between normal and glaucomatous eyes.

OCT tomograms present volumetric analysis of macular thickness and some studies indicated that they may be useful method of documenting and monitoring patients with early and advanced glaucoma[6]. To test this, we investigated 20 glaucoma patients and 20 controls using Cirrus HD OCT. In these two groups of examinees we analyzed changes of macular thickness parameters (central subfield thickness, macular volume, and average macular thickness).

Our results show a significant correlation between macular volume, average macular thickness and advan-

TABLE 3
PERIPAPILLARY RNFL VALUES AND MACULAR THICKNESS PARAMETERS IN GLAUCOMA PATIENTS AND IN CONTROLS

	Glaucoma patients		Controls		U	p
	$\overline{X}$	SD	$\overline{X}$	SD		
RNFL μm	60.9	±15.2	84.8	±7.6	38	<0.001
CMT μm	259.5	±18.7	265.3	±18.4	170	0.429
Vmm³	9.0	±0.7	9.9	±0.4	63	<0.001
AMT μm	251.4	±20.5	275.3	±12.8	64.5	<0.001

RNFL – retinal nerve fibre layer, CMT – central macular thickness, V – macular volume, AMT – average macular thickness, $\overline{X}$ – mean, SD – standard deviation, Mann Whitney's U-test, p – p value

TABLE 4
PERIPAPILLARY RNFL AND MACULAR THICKNESS PARAMETERS IN GLAUCOMA PATIENTS

	RNFL<53 μm		RNFL >53 μm		U	p
	$\overline{X}$	SD	$\overline{X}$	SD		
V mm³	8.7	±0.6	9.3	±0.7	22.5	0.038
AMT μm	241.0	±17.0	259.1	±20.5	21.5	0.031

RNFL – retinal nerve fibre layer, CMT – central macular thickness, V – macular volume, AMT – average macular thickness, $\overline{X}$ – mean, SD – standard deviation, Mann Whitney´s U-test, p – p value

ced glaucoma status, with decreased values in patients with more advanced disease. Central macular thickness values did not change with the progression of glaucoma disease, presumably reflecting the absence of the ganglion cells in this layer.

Our study confirms that macular volume can be useful indicator for evaluating glaucoma status and glaucoma progression. Patients with RNFL <53 μm had thinner macular volume and average macular thickness compared to patients with RNFL ≥53.

It is of interest to notice that 6 patients in the normal group had RNFL less than 80 μm with no clinical or perimetric signs of the disease. These patients subsequently underwent a complete ophthalmologic examination and we excluded preperimetric glaucoma or optic neuropathy due to other causes. The follow up of these patients will continue in order to detect eventual appearance of preperimetric glaucoma or other nonglaucomatous optic neuropathy allowing timely treatment if indicated[17]. The limitations of our study are small sample size and elderly age of examinees that could correlate with macular pathology which is sometimes difficult to exclude entirely by clinical examination. Additionally, OCT imaging of the optic nerve, peripapillary RNFL, macular volume and macular thickness may be limited by signal quality and image artefact[18,19].

Several studies compared diagnostic ability of RNFL thickness using Time Domain and Spectral Domain OCT. SD-OCT presented higher diagnostic ability for preperimetric glaucoma[20–22]. Schuman showed that SD-OCT had better reproducibility in both peripapillary RNFL and macular scan thickness measurements over the TD--OCT, primarily for sectoral measurements which is important in earlier stage of glaucoma[23]. Studies using RTVue Fourier domain (fd) OCT system that has the ability to measure GCC have observed that thickness of this complex correlates best with the progression of glaucoma and visual field changes[24–27]. Tan et al. also pointed out that the outer retina which takes up to 65–70% of total retinal thickness is not much affected by glaucoma, and that isolated GCC measurement from the outer retina enhances our ability to discriminate between healthy and glaucomatous eyes.

According to Tan et al., although GCC and average RNFL parameters perform similarly in terms of glaucoma diagnosis, the GCC is more reproducible and therefore may be better for accurate tracking of glaucomatous progression. In their study, combining GCC parameters with standard RNFL parameters significantly increased the detection rate of both preperimetric and perimetric glaucoma. They found that GCC information added to RNFL thickness data increased the sensitivity of detection from 78% to 87% in the perimetric glaucoma group and from 45% to 56% in the group of pre-perimetric respondents [9]. The best GCC diagnostic parameters were focal volume and global loss of volume, both of which measure deviations from the normal pattern of GCC thickness.

Authors Moreno et al. also suggested that the GCC scan is showing a similar or even a slightly better ability to discriminate between healthy and early glaucomatous eyes compared to the peripapillary RNFL scan. Therefore, the authors conclude that the GCC macular scan is a useful tool for identification of early structural damage in patients with glaucoma[28].

Although we were not able to perform GCC measurement, we have clearly shown the correlation between RNFL thickness, macular volume parameters and glaucoma progression, confirming that measurement of any of these parameters is useful in follow up of glaucoma patients, regardless of the available equipment.

Further development of the Cirrus 6.0 software with the possibility of analysis of the complex ganglion cell-inner plexiform layer (GCIPL) will become available in future[29].

Ahmad et al. further suggested that newer OCT software algorithms will combine RNFL, optic nerve head, and GCC parameters to further increase diagnostic OCT spectrum as well as to provide faster, easier and more accurate monitoring of disease progression[30].

In conclusion, our study shows that macular volume can be a valuable indicator of glaucoma status, starting from early stages. For the measurement of this useful, objective and quantitative parameter for evaluating glaucoma disease progression we have different available technologies that are continuously improving. Further follow up of progression of changes in RNFL and macular thickness in asymptomatic patients is needed to establish their diagnostic and prognostic significance.

REFERENCES

1. DING Y, ZEIMER R, KNEZEVICH F, MARKS C, VITALE S, QUIGLEY H, FRIEDMAN DS, CONGDON N, JAMPEL H, Invest Ophthalmol Vis Sci, 44 (2003). — 2. GUEDES V, SCHUMAN JS, HERTZMARK E, WOLLSTEIN G, CORRENTI A, MANCINI R, LEDERER D, VOSKANIAN S, VELAZQUEZ L, PAKTER HM, PEDUT-KLOIZMAN T, FUJIMOTO JG, MATTOX C, Ophthalmology 110 (2003) 177. — 3. LEUNG CK, CHAN WM, YUNG WH, NG AC, WOO J, TSANG MK, TSE RK, Ophthalmology, 112 (2005) 391. DOI: 10.1016/j.ophtha.2004.10.020. — 4. ZEIMER R, ASRANI S, ZOU S, QUIGLEY H, JAMPEL H, Ophthalmology, 105 (1998) 224. DOI: 10.1016/S0161-6420(98)92743-9. — 5. GREENFIELD DS, BAGGA H, KNIGHTON RW, Arch Ophthalmol, 121 (2003) 41. — 6. GIOVANNINI A, AMATO G, MARIOTTI C, Acta Ophthalmologica Scandinavica, 236 (2002) 34. DOI: 10.1034/j.1600-0420.80.s236.44.x. — 7. WOLLSTEIN G, SCHUMAN JS, PRICE LL, AYDIN A, BEATON SA, STARK PC, FUJIMOTO JG, ISHIKAWA H, Am J Ophthalmol, 138 (2004) 218. DOI: 10.1016/j.ajo.2004.03.019. — 8. RAO HL, ZANGWILL LM, WEINREB RN, SAMPLE PA, ALENCAR LM, MEDEIROS FA, Ophthalmology, 117 (2010) 1692. DOI: 10.1016/j.ophtha.2010.01.031. — 9. TAN O, CHOPRA V, LU AT, SCHUMAN JS, ISHIKAWA H, WOLLSTEIN G, VARMA R, HUANG D, Ophthalmology, 116 (2009) 2305. DOI: 10.1016/j.ophtha.2009.05.025. — 10. HOOD DC, RAZA AS, Biomed Opt Express, 2 (2011) 1097. DOI: 10.1364/BOE.2.001097. — 11. Cirrus HD-OCT: How to read the Cirrus reports, accessed 26.05.2012. Available from: URL: http://www.meditec.zeiss.com/88256DE3007B916B/0/CB067066270D5460C125

7577003BBFC7/$file/5_en_cirrus-hd-oct_read-cirrus-reports.pdf. — 12. HARWERTH RS, CARTER-DAWSON L, SMITH EL 3RD, BARNES G, HOLT WF, CRAWFORD ML, Invest Ophthalmol Vis Sci, 45 (2004) 3152. DOI:10.1167/iovs.04-0227. — 13. BAGGA H, FEUER WJ, GREENFIELD DS, Arch Ophthalmol, 124 (2006) 169. DOI: 10.1001/archopht.124.2.169. — 14. CVENKEL B, KONTESTABILE AS, Graefes Arch Clin Exp Ophthalmol, 249 (2011) 575. DOI: 10.1007/s00417-010-1538-z. — 15. LEDERER DE, SCHUMAN JS, HERTZMARK E, HELTZER J, VELAZQUES LJ, FUJIMOTO JG, MATTOX C, Am J Ophthalmol, 135 (2003) 838. DOI: 10.1016/S0002-9394(02)02277-8. — 16. DESATNIK H, QUIGLEY HA, GLOVINSKY Y, J Glaucoma, 5 (1996) 46. — 17. GREENFIELD DS Point--Counterpoint: Do we need to diagnosis and treat pre-perimetric glaucoma? Yes. In: AMERICAN ACADEMY OF OPHTHALMOLOGY (Eds) Glaucoma 2010 Current concepts and future horizons (AAO, Chicago, 2010). — 18. MWANZA JC, BHORADE AM, SEKHON N, MCSOLEY JJ, YOO SH, FEUER WJ, BUDENZ DL J, Glaucoma, 20 (2011) 37. DOI: 10.1097/IJG.0b013e3181ccb93b. — 19. HAN IC, JAFFE GJ, Ophthalmology, 117 (2010) 1177. DOI: 10.1016/j.ophtha.2009.10.029. — 20. SAVINI G, CARBONELLI M, BARBONI P, Curr Opin Ophthalmol, 22 (2011) 115. DOI: 10.1097/ICU.0b013e3283437222. — 21. MORENO-MONTAÑÉS J, OLMO N, ALVAREZ A, GARCÍA N, ZARRANZ-VENTURA J, Invest Ophthalmol Vis Sci, 51 (2010) 335. DOI: 10.1167/iovs.08-2988. — 22. MORI S, HANGAI M, SAKAMOTO A, YOSHIMURA N, J Glaucoma, 19 (2010) 528. DOI: 10.1097/IJG.0b013e3181ca7acf. — 23. SCHUMAN JS, Trans Am Ophthalmol Soc, 106 (2008) 426. — 24.KIM NR, LEE ES, SEONG GJ, KIM JH, AN HG, KIM CY, Invest Ophthalmol Vis Sci, 51 (2010) 4646. DOI: 10.1167/iovs.09-5053. — 25. TAKAGI ST, KITA Y, TAKEYAMA A, TOMITA G, J Ophthalmol (2011). DOI: 10.1155/2011/914250. — 26. SCHULZE A, LAMPARTER J, PFEIFFER N, BERISHA F, SCHMIDTMANN I, HOFFMANN EM, Graefes Arch Clin Exp Ophthalmol, 249 (2011) 1039. DOI: 10.1007/s00417-010-1585-5. — 27. NA JH, KOOK MS, LEE Y, YU SJ, CHOI J, Graefes Arch Clin Exp Ophthalmol, (2012). DOI: 10.1007/s00417-011-1864-9. — 28. MORENO PA, KONNO B, LIMA VC, CASTRO DP, CASTRO LC, LEITE MT, PACHECO MA, LEE JM, PRATA TS, Can J Ophthalmol, 46 (2011) 543. — 29. MWANZA JC, OAKLEY JD, BUDENZ DL, CHANG RT, KNIGHT OJ, FEUER WJ, Invest Ophthalmol Vis Sci, 52 (2011) 8323. DOI: 10.1167/iovs.11-7962. — 30. AREF AA, BUDENZ DL, Ophthalmic Surg Lasers Imaging, 41 (2010) S15. DOI: 10.3928/15428877--20101031-01.

F. Barišić

University of Zagreb, »Sestre milosrdnice« University Hospital Center, Department of Ophthalmology, Vinogradska 29, 10 000 Zagreb, Croatia
e-mail: frejabarisic@yahoo.com

MJERENJE DEBLJINE I VOLUMENA MAKULARNOG PODRUČJA OPTIČKOM KOHERENTNOM TOMOGRAFIJOM U SVRHU PRAĆENJA PROGRESIJE GLAUKOMSKE BOLESTI

S A Ž E T A K

Cilj ovog ispitivanja bio je utvrditi debljinu makule kod bolesnika s glaukomom te je usporediti s kontrolnom skupinom zdravih osoba koristeći Optičku Koherentnu Tomografiju (OCT). Ova prospektivna, opservacijska studija uključuje 20 bolesnika s glaukomom otvorenog kuta i kontrolnu skupinu koju čini 20 osoba bez glaukoma. U ispitivanje nismo uključili bolesnike koji su imali dijabetičku i druge makulopatije, senilnu makularnu degeneraciju, makularni edem, centralnu seroznu retinopatiju i miopiju >4,00 dsph. Makularno područje i peripapilarna debljina živčanih niti snimljeni su Cirrusovim HD OCT-om. U ove dvije skupine ispitanika analizirali smo promjene u debljini makule (centralnu debljinu, makularni volumen i prosječnu debljinu makule). Pokazalo se da grupa bolesnika s glaukomom ima smanjenu vrijednost makularnih parametara u usporedbi sa kontrolnom skupinom, dok nije bilo razlike u debljini centralnog dijela makule. Studija pokazuje da analiza debljine makularnog područja može biti korisna dodatna metoda za određivanje statusa i praćenja progresije glaukomske bolesti.