ORIGINAL RESEARCH

DOI: 10.5336/worldclin.2015-48636

Comparison of Retinal Nerve Fiber Layer and Ganglion Cell Complex with Optical Coherence Tomography in Thyroid-Associated Orbitopathy

Burcu DİRİM,[a]
Selam Yekta ŞENDÜL,[a]
Pınar AKARSU,[a]
Zeynep ACAR,[a]
Mehmet DEMİR,[a]
Ali OLGUN,[a]
Semra TİRYAKİ,[a]
Erdem ERGEN,[a]
Dilek GÜVEN[a]

[a]Clinic of Ophthalmology
Şişli Hamidiye Etfal Training and Research Hospital, İstanbul

Received: 20.11.2015
Accepted: 19.12.2016

Correspondence:
Selam Yekta ŞENDÜL
Şişli Hamidiye Etfal Training and Research Hospital,
Clinic of Ophthalmology,
İstanbul, TURKEY
sysendul@hotmail.com

ABSTRACT Objective: To compare retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness in eyes with Thyroid associated orbitopathy (TAO), in eyes with ocular hypertension (OHT)+TAO and in a control group of healthy eyes. **Material and Methods:** In this retrospective and cross-sectional study, we compared 54 eyes of 54 patients diagnosed with TAO with 35 eyes of 35 healthy patients. Patients with TAO were divided into two subgroups according to their intraocular pressure (IOP) values. Patients with IOP levels ≤ 21 mmHg were classified as Group 1 (33 eyes of 33 patients) and patients with IOP levels > 21 mmHg were classified as Group 2 (21 eyes of 21 patients). **Results:** Among 54 eyes with TAO, there were no significant differences in RNFL and GCC patterns between Group 1, Group 2 and the control group (Group 3). The mean deviation and pattern standard deviation were not significantly different between the groups. The FD-OCT parameters showed a strong correlation with MD and PSD values. **Conclusion:** RNFL and GCC thickness values were evaluated with FD-OCT in eyes with TAO and OHT. Although there was no difference in the RNFL and GCC parameters between the patient and control groups, we think that RNFL and GCC thickness evaluation with eye-tracking OCT could represent on objective diagnostic technique for detecting optic neuropathy in TAO.

Key Words: Ocular hypertension; exophthalmos; glaucoma

World Clin J Med Sci 2017;1(1):20-5

Dysthyroid eye disease is the most common cause of proptosis in adults, which typically presents as Graves' disease at the third and fourth decade of life. Sight is threatened by corneal exposure due to incomplete eyelid closure over a proptotic globe, uncontrolled ocular hypertension or optic nerve compression. Prevalence of glaucoma is reported to be greater in patients with Graves' orbitopathy (GO) than the general population.[1]

Prevalence of OHT in patients with GO is estimated to be between 5 to 24%.[2-5] This can be due to the enlargement of the extraocular muscles, adipose and connective tissue volume.[6] In such cases, visual field examination often shows diffuse nonglaucomatous abnormalities because of conjunctival and corneal disorders.[6] Early detection is therefore essential for the institution of a pressure-reducing treatment in order to stop or delay progressive loss of visual function. In clinical practice, glaucoma diagnosis is performed using ophthalmoscopic examination of the optic nerve head and visual field testing with standard automatic perimetry.[7,8]

In recent years, OCT has been most widely used for early detection of structural damage. The FD-OCT RTVue-100 (Optovue Inc, Fremont, CA) provides comprehensive glaucoma evaluation by measuring RNFL thickness and ganglion cell complex thickness which is defined as a combination of nerve fiber, ganglion cell and inner plexiform layers.

In this study we aimed to evaluate the glaucoma discrimination ability of GCC and RNFL thickness measured by the FD-OCT RTVue-100 in eyes with TAO and compare the data with the control group. The study was conducted in accordance with the tenets of the Declaration of Helsinki by obtaining written consent from all patients, with the approval of the local ethical review board.

MATERIAL AND METHODS

All patients with TAO who were referred to the Ophthalmology Department of the Research and Education Hospital between March 2011 and September 2012 were enrolled in this cross-sectional study. A total of 54 eyes of 54 patients diagnosed with TAO were classified into 2 groups according to their IOP. The eyes in Group 1 had an IOP ≤21 mmHg and the eyes in Group 2 (TAO+OHT group) had an IOP > 21 mmHg. The mean followup time of patients with TAO was 23,51 ± 18,16 months in the Group 1 and 28,09 ± 18,93 months in the Group 2.

We considered 35 healthy patients (35 eyes) as the control group. Inclusion criteria in the control group were lack of any previous thyroid disease or orbitopathy, an IOP < 21 mm Hg and normal optic nerve heads based on biomicroscopic fundus evaluation.

All patients underwent complete ophthalmic examination, including slit-lamp biomicroscopy of anterior and posterior segment, gonioscopy, Goldmann applanation tonometry, ultrasound pachymetry, papiller and macular imaging using FD-OCT. The standard visual field indices (mean deviation [MD], pattern standard deviation [PSD]) were obtained from visual field (VF) examination using 30-2 standard automated perimetry (SAP) performed with a Humphrey Field Analyzer (HFA) (Carl Zeiss Meditec, Jena, Germany). Exclusion criteria for all groups were best corrected visual acuity < 20/40, spherical equivalent refractive error > +3.00 or <-6.00 diopters, diabetic retinopathy or other diseases that could cause VF loss or optic disc abnormalities and previous intraocular surgery.

The GCC and RNFL thickness values of the patients were measured by scanning with the RTVue-100 FD-OCT system (Optovue) in which glaucoma protocols include RNFL scan, optic nerve head scan, three dimensional disc scan and GCC scan.

TABLE 1: Characteristics of patients in the three groups: Group 1, normotansive thyroid associated orbitopathy group Group 2, hypertansive thyroid associated orbitopathy group Group 3, control group.

				Group I		Group II		Group III	p
Age		Mean±s.d.	44	46.4 ± 12.0	41	45.7±7.8	43	46.8±7.4	0.936[K]
		Med (Min-Max)		27-77		40-63		39-62	
Female		n (%)		26 (78.8%)		12 (57.1%)		26 (74.3%)	0.208[χ²]
Male		n (%)		7 (21.2%)		9 (42.9%)		9 (25.7%)	
Smoking	yes	n (%)		17 (51.5%)		12 (57.1%)		18 (51.4%)	0.902[χ²]
	no	n (%)		16 (48.5%)		9 (42.9%)		17 (48.6%)	
Hertel		Mean±s.d.	20	20.6±3.2	25	25.7±4.6			0.000[m]
		Med (Min-Max)		15.0-29.0		19.0-32.0			
TO		Mean±s.d.	17	16.6±2.9	26	25.6±2.1			0.000[m]
		Med (Min-Max)		10.0-21.0		22.0-29.0			

IOP, intraocular pressure; TAO: Thyroid associated orbitopathy.

[K]: Kruskal-wallis; [m]: Mann-whitney u test; [χ²]: Chi-square test.

TABLE 2: Mean RNFL and GCC values in the patient and control group.

			Group I		Group II		Group III	p
RNLF								
RNFL AVG	Mean±s.d	101	103.9±9.9	100	104.6±11.6	102	103.4±9.8	0.929[K]
	Med (Min-Max)		85.0-135.0		88.0-124.0		87.0-121.0	
RNFL SUP	Mean±s.d	103	104.2±10.4	99	103.7±16.6	104	103.7±12.1	0.972[K]
	Med (Min-Max)		89.0-133.0		77.0-125.0		81.0-125.0	
RNLF INF	Mean±s.d	103	103.6±11.8	100	104.4±9.5	104	103.2±9.2	0.957[K]
	Med (Min-Max)		74.0-137.0		94.0-123.0		85.0-123.0	
GCC								
Average	Mean±s.d	98	97.4±7.6	102	103.2±5.4	99	98.1±6.8	0.009[K]
	Med (Min-Max)		82.1-114.8		95.4-111.5		84.7-115.5	
Superior	Mean±s.d.	98	96.5±8.7	103	106.5±12.5	97	97.1±6.9	0.001[K]
	Med (Min-Max)		79.1±116.5		96.8-134.9		84.8-114.1	
Inferior	Mean±s.d.	98	98.4±7.0	99	98.0±12.9	100	99.2±7.3	0.856[K]
	Med (Min-Max)		85.9-113.1		71.9-114.5		82.9-116.9	

[K]: Kruskal-wallis.

* Difference with Group II p<0.05.

GCC: Ganglion cell complex; RNFL: Retinal nerve fiber layer; SUP: Superior; INF: Inferior.

For all parameters, the instrument–provided classification is indicated in a color-coded manner which reflects the probability that the parameter falls within or outside the normal range determined by the normative database. All comparisons were adjusted for known effects of age, optic disc size and ethnicity.

If the value falls within the normal range (5-95%), it is colored green in order to indicate the classification "Within Normal Limits". If the value falls below the normal range (1-5%), it is colored yellow in order to indicate the classification "Borderline". If the value falls outside the normal range (<1%), it is colored red in order to reflect the classification "Outside Normal Limits".

STATISTICAL ANALYSIS

In the descriptive statistics of the data; mean, standard variation, median, lowest, highest, frequency and ratio values were used. In the analysis of quantitative data, chi-square test was used. The distribution of the variables was measured by the Kolmogorov-Smirnov test. In the analysis of qualitative data, the Kruskal-Wallis test was used whereas the Mann-Whitney U test was used in the sub analyses. SPSS 22.0 program was utilized in the analyses.

RESULTS

The clinical characteristics of the 3 groups are shown in Table 1. The average, superior and inferior thickness values of RNFL and GCC in the evaluated groups are shown in Table 2. No significant differences were present among the groups in terms of age and visual acuity. In all cases, the iridocorneal angle was open on gonioscopy. No cases of optic nerve head atrophy were present.

In the control group, the mean visual acuity was 20/20, the mean IOP was 18±0.3 mmHg and the mean RNFL and GCC thickness values were 106±10.2 μm and 97.8±7.0 μm respectively.

We considered 54 eyes of 54 patients with TAO (16 males and 38 females). Among them, Group 1 included 33 eyes of 33 patients with normal IOP (≤0.21 mm Hg). Group 2 included 21 eyes of 21 patients with OHT (IOP> 21 mm Hg). The best corrected visual acuity was 20/20 in all groups. The mean IOP was 16.6±2.9 mmHg in Group 1 and 25.6±2.1 mmHg in Group 2 (Table 1). The mean

TABLE 3: Mean CCT, MD and PSD values of the groups.

			Group 1		Group 2		Group 3	p
CCT	Avg±s.d.	552	551.6±16.0	542	544.1±18.2	551	549.4±36.8	0.184
	Med (Min-Max)		510-580		508-578		453-648	
MD	Avg.±s.d.	-0.9	-0.9±1.1	-0.9	-1.1±1.4	1.3	-1.2±1.3	0.508
	Med (Min-Max)		-3.3-1.2		-4.3-0.7		-3.9-2.3	
PSD	Avg.±s.d.	1.9	1.9±0.7	1.7	2.0±0.9	1.7	1.7±0.5	0.187
	Med (Min-Max)		1.1-5.7		1.2-5.7		1.0-3.9	

CCT: Central corneal thickness; MD: Mean deviation; PSD: Pattern standard deviation; Avg.: Average.

RNFL thickness values were 103.9±9.9 μm in Group 1 and 104.6±11.6 μm in Group 2. Further, the mean GCC thickness values were 97.4±7.6 μm in Group 1 and 103.2±5.4 μm in Group 2 (Table 2). The mean central corneal thickness (CCT), MD, PSD values of patients are shown in Table 3.

No significant differences were observed between the patients in Group 1 and Group 2 in terms of age, gender or rate of smoking ($p>0.05$). The mean Hertel and TAO values in Group 1 were significantly lower than those in Group 2 ($p<0.05$) (Figure 1, Table 1). Also the average MD and PSD values did not differ between the groups and showed a strong correlation with the FD-OCT parameters ($p>0.05$). There were no significant differences in neither groups or the control group in terms of RNFL Avg, superiorand inferior values (Figure 2, Table 2) ($p>0.05$). In the group 2, the average and superior GCC values were higher than the group 1 and 3 ($p<0,05$) (Table 2). But average, superior and inferior GCC values did not differ between the group 1 and 3 ($p>0,05$) (Table 2).

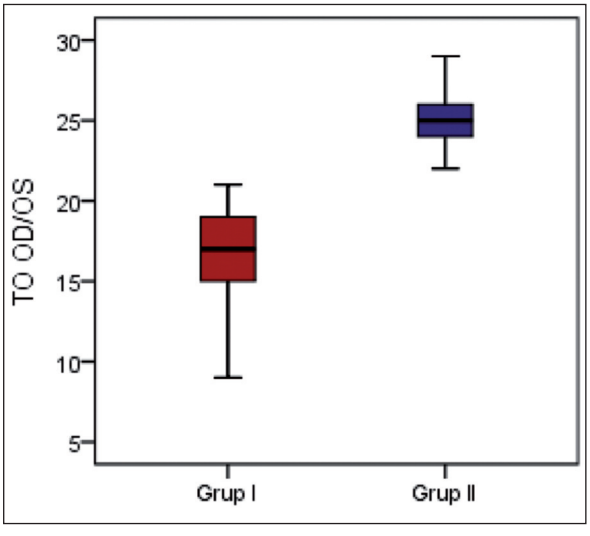

FIGURE 1: İOP comparison of Group 1 and Group 2.

DISCUSSION

This observational cross-sectional study reported the evaluation of RNFL and GCC thickness values in patients with TAO and in a control group. In this study, there was no significant difference between the patients with TAO (Group 1), patients with TAO and OHT (Group 2) and the control group (Group 3) in terms of RNFL values of superior and inferior quadrant and mean RNFL values. Further, the mean GCC values did not differ within the 3 groups.

Among all eyes with TAO and the control group, a high correlation was found between RNFL and GCC thickness values, and also these values were correlated with visual field (VF) defects.

Autopsy studies of glaucoma cases have shown that standard automated perimetry (SAP) does not detect VF defects until approximately 30-50% of the retinal ganglion cell axons have been lost.[9,10] Several authors affirm that in primary open angle glaucoma and in compressive optic neuropathy, VF defects are anticipated by a loss of RNFL and this loss can be detected with OCT with moderate sensitivity and high specificity.[10-12] Our data suggests that abnormal values of RNFL and GCC in TAO may indicate an optic neuropathy masquerading as conjunctival and corneal disorder-related nonspecific VF defects.

OCT has shown high sensitivity, specificity and reproducibility in assessing RNFL and GCC thickness and in detecting early damage in glaucoma and compressive optic neuropathy.[10-17] In the absence of glaucomatous VF defects, RNFL and GCC thinning in the eyes with TAO, OHT and normal optic discs could suggest the presence of an early optic neuropathy.

OHT in TAO was present in 9 eyes (12%) which may be due to primary glaucoma or increased secondary compressive intraocular pressure.[18-20] In compressive optic neuropathy, RNFL thinning is related to the site of compression.[17,21] Localized RNFL defects could be attributed to early glaucoma and may require an antiglaucomatous treatment.[22,23]

The purpose of this study is to detect the extent to which the RNFL and also GCC thickness values are affected in patients with TAO using the RTVue-100 FD-OCT system. To obtain better imaging quality for separating retinal layers, devices that have high resolution and provide improved signal quality are required. Leitgeb et al. reported the advantages of FD-OCT in terms of detailed imaging in their study comparing the new FD-OCT technique with time-domain OCT.[24]

Although decrease in macular thickness and asymmetric changes were observed in association with glaucomatous retinal ganglion cell loss in previous studies, there is limited information about the clinical value of GCC measurements in glaucoma disease.[25]

We aimed at quantitatively detecting the mean GCC and RNFL thickness values according to glaucoma suspicion in patients with TAO. In our study, we observed that GCC and RNFL values did not differ between the control and patient groups. This may be due to the fact that there was inadequate time for glaucomatous changes to occur in the patients with TAO.

A limitation of this study lies in the impossibility to exactly separate the glaucoma-associated RNFL thinning from thinning due to other forms of compressive optic neuropathy. Our results suggest a suspicious role of OCT in detecting early glaucoma in eyes with TAO+OHT. On the other hand, while VF results may contain changes unrelated to the optic nerve, RNFL and GCC imaging analysis seems advisable for detecting optic nerve pathologies in the evaluation of TAO.

In conclusion, RNFL and GCC thickness values were evaluated with FD-OCT in eyes with TAO and OHT. Although there was no difference in the RNFL and GCC parameters between the patients and control groups, we think that RNFL and GCC thickness evaluation with eye-tracking OCT could represent on objective diagnostic technique for detecting optic neuropathy in TAO.

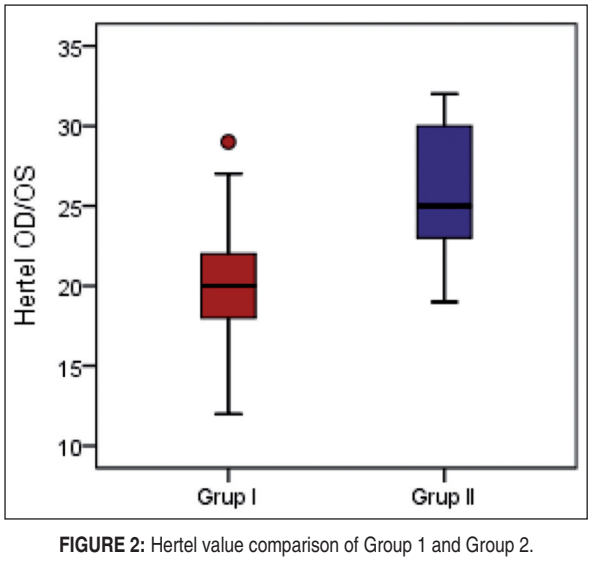

FIGURE 2: Hertel value comparison of Group 1 and Group 2.

Acknowledgments

Thanks are due to Ayse Unal Ersonmez and Barbara Reid for editing the paper in terms of English.

Ethics Committee

Sisli Hamidiye Etfal Training and Research Hospital Local Ethical Committee.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Burcu Dirim and Selam Yekta Şendül performed examination, and follow-up of the patients and contributed in drafting the manuscript; Burcu Dirim and Pınar Akarsu contributed in study design and drafting; Pınar Akarsu and Erdem Ergen col-

lected and examined retrospective patient files; Semra Tiryaki and Zeynep Acar contributed in study design and drafting; Ali Olgun and Mehmet Demir examined patient files and contributed in drafting the manuscript; Burcu Dirim and Selam Yekta Şendül performed statistical analysis; Erdem Ergen contributed in study design and obtaining the ethical committee approval; Mehmet Demir contributed in drafting and editing the manuscript; Dilek Güven carried out the study and performed final editing of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Ohtsuka K, Nakamura Y. Open-angle glaucoma associated with Grave's disease. Am J Ophthalmol 2000;129(5):613-7.
2. Cockerham KP, Pal C, Jani B, Wolter A, Kennerdell JS. The prevalence and implications of ocular hypertension and glaucoma in thyroid-associated orbitopathy. Ophthalmology 1997; 104(6):914-7.
3. Manor RS, Kurz O, Lewitus Z. Intraocular pressure in endocrinological patients with exophthalmos. Ophthalmologica 1974;168(4): 241-52.
4. Algvere P, Almqvist S, Backlund EO. Pterional orbital decompression in progressive ophthalmopathy of Graves' disease. I. Short-term effects. Acta Ophthalmol (Copenh) 1973;51(4): 461-74.
5. Haddad HM. Tonography and visual fields in endocrine exophthalmos. Report on 29 patients. Am J Ophthalmol 1967;64(1):63-7.
6. Ben Ayed H, Hamedani M, Bok C, Barraco P, Oubaaz A, Morax S. [Intraocular high pressure in thyroid-associated orbitopathy: physiopathological mechanisms, diagnosis, and management. Three case reports]. J Fr Ophtalmol 2002;25(1):15-22.
7. Deleón-Ortega JE, Arthur SN, McGwin G Jr, Xie A, Monheit BE, Girkin CA. Discrimination between glaucomatous and nonglaucomatous eyes using quantitative imaging devices and subjective optic nevre head assesment. Invest Ophthalmol Vis Sci 2006;47(8):3374-80.
8. Chen TC, Zeng A, Sun W, Mujat M, de Boer JF. Spectral domain optical coherence tomography and glaucoma. Int Ophthalmol Clin 2008;48(4):29-45.
9. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic optic neuropathy, papilledema, and toxic optic neuropathy. Arch Ophthalmol 1982;100(1):135-46.
10. Mikelberg FS, Yidegiligne HM, Shulzer M. Optic nerve axon count and axon diameter in patients with ocular hypertension and normal visual fields. Ophthalmology 1995;102(2):342-8.
11. Kanamori A, Nakamura M, Escano MF, Seya R, Maeda H, Negi A. Evaluation of the glaucomatous damage on retinal nerve fiber layer thickness measured by optical coherence tomography. Am J Ophthalmol 2003;135(4): 513-20.
12. Huang ML, Chen HY. Development and comparison of automated classifiers for glaucoma diagnosis using Stratus optical coherence tomography. Invest Ophthalmol Vis Sci 2005;46(11):4121-9.
13. Schuman JS, Pedut-Kloizman T, Hertzmark E, Hee MR, Wilkins JR, Coker JG, et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. Ophthalmology 1996;103(11): 1889-98.
14. Hoyt WF, Frisén L, Newman NM. Funduscopy of nerve fiber layer defects in glaucoma. Invest Ophthalmol 1973;12(11):814-29.
15. Soliman MA, Van Den Berg TJ, Ismaeil AA, De Jong LA, De Smet MD. Retinal nerve fiber layer analysis: relationship between optical coherence tomography and red-free photography. Am J Ophthalmol 2002;133(2):187-95.
16. Parikh RS, Parikh S, Sekhar GC, Kumar RS, Prabakaran S, Babu JG, et al. Diagnostic capability of optical coherence tomography (Stratus OCT 3) in early glaucoma. Ophthalmol 2007;114(12):2238-43.
17. Danesh-Meyer HV, Papchenko T, Savino PJ, Law A, Evans J, Gamble GD. In vivo retinal nerve fiber layer thickness measured by optical coherence tomography predicts visual recovery after surgery for parachiasmal tumors. Invest Ophthalmol Vis Sci 2008;49(5):1879-85.
18. Ben Ayed H, Hamedani M, Bok C, Barraco P, Qubaaz A, Morax S. [Intraocular high pressure in thyroid associated orbitopathy: physiopathological mechanisms, diagnosis, and management. Three case reports]. J Fr Ophthalmol 2002;25(1):15-22.
19. Shields MB. Intraocular pressure and tonometry. In: Allingham RR, ed. Text Book of Glaucoma. 4thed. Philadelphia: Williams & Wilkins; 1998. p.46-65.
20. McKeag D, Lane C, Lazarus JH, Baldeschi L, Boboridis K, Dickinson AJ, et al; European Group on Graves' Orbitopathy (EUGOGO). Clinical features of dysthyroid optic neuropathy: a European Group on Graves' Orbitopathy (EUGOGO) survey. Br J Ophthalmol 2007;91(4):455-8.
21. Danesh-Meyer HV, Carroll SC, Foroozan R, Savino PJ, Fan J, Jiang Y, et al. Relationship between retinal nerve fiber layer and visual field sensitivity as measured by optical coherence tomography in chiasmal compression. Invest Ophthalmol Vis Sci 2006;47(11):4827-35.
22. Quigley HA, Miller NR, George T. Clinical evaluation of nerve fiber layer atrophy as an indicator of glaucomatous optic nerve damage. Arch Ophthalmol 1980;98(9):1564-71.
23. Airaksinen PJ, Drance SM, Douglas GR, Mawson DK, Nieminen H. Diffuse and localized nerve fiber loss in glaucoma. Am J Ophthalmol 1984;98(5):566-71.
24. Leitgeb R, Hitzenberger CK, Fercher AF. Performance of fourier domain vs. time domain optical coherence tomography. Opt Express 2003;11(8):889-94.
25. Tan O, Li G, Lu AT, Varma R, Huang D. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. Ophthalmology 2008;115(6):949-56.