Evaluation of Correlations of Macular Choroidal Thickness and Central Macular Thickness with Ganglion Cell Complex Parameters in Exfoliation Patients

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ABSTRACT

Purpose: To evaluate the macular choroidal thickness (CT) and central macular thickness (CMT) in exfoliation syndrome (XFS), exfoliation glaucoma (XFG) and age-matched healthy subjects using spectral-domain optical coherence tomography (SD-OCT) and to investigate the correlations of CT and CMT with ganglion cell complex (GCC).

Materials and Methods: This study included patients diagnosed with XFS, XFG, and healthy volunteers. CMT was analyzed with standard OCT protocol while CT was analyzed with enhanced depth imaging (EDI) modality in all subjects.

Results: The study included; 41 eyes with XFS, 62 eyes with XFG and 30 eyes of healthy subjects. The mean CMT were; 253.3 ± 35.8 µm, 258.5 ± 43.4 µm and 255.1 ± 29.9 µm in the XFS, XFG and control group respectively (p=0.52). The mean CT in XFS group was significantly thinner than XFG and control (p<0.001). In XFS group, we detected weak positive correlations of average ganglion cell layer+inner plexiform layer (GCL+IPL) thickness and minimum GCL+IPL thickness with CT (R= +0.23, R=+0.21 respectively, p=0.15, p=0.19). In XFG patients, average GCL+IPL thickness and minimum GCL+ IPL thickness showed weak negative correlations with CMT (R= -0.22, R= -0.18 respectively, p=0.008, p=0.15), but there was no correlation between GCC parameters and CT measurements (R= -0.12, R= -0.09 respectively, p=0.32, p=0.52).

Conclusions: In XFS group, choroidal changes may be an early indicator for transformation of XFS to XFG. Relatively thicker choroid in XFG group may be related to the reversibility of this situation with treatment.

Keywords: Exfoliation syndrome, Exfoliation glaucoma, Choroidal thickness, Central macular thickness, Ganglion cell complex

INTRODUCTION

Exfoliation syndrome (XFS) and exfoliation glaucoma (XFG) are diseases of elderly, characterized by increased production and accumulation of the extracellular fibril material in various ocular tissues. In the electron microscope studies; exfoliation material has been shown to accumulate in posterior segment structures such as posterior ciliary artery, central retinal artery, and vortex venules.[1] Although exfoliation pathogenesis remains mostly unclear, Yaz et al.[2] showed that single nucleotide polymorphisms in the Lysyl oxidase-like 1 (LOXL1) gene which codes for a cross-linking matrix enzyme, may increase the susceptibility to exfoliation glaucoma.

In recent studies, with the widespread use of optical coherence tomography (OCT), these patients were visualized in-vivo and some studies reported that the choroidal thickness was found to be thinner in the XFS and XFG cases than in the normal population, suggesting exfoliation material to accumulate in the vascular wall, deteriorate choroidal nutrition and thus predisposing to development of glaucoma.[3,4] In 2016 Demircan et al.[5] prospectively reviewed 43 patients with XFG, 45 patients with XFS, and 48 controls and demonstrated that retinal nerve fiber layer (RNFL) thickness was thinner in XFG group compared to XFS and control.

The purpose of this study was to evaluate the central macular thickness, subfoveal choroidal thickness in XFS, XFG and age-matched healthy subjects using spectral-

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domain optical coherence tomography and to investigate the correlations of choroidal thickness (CT) and central macular thickness (CMT) with ganglion cell complex (GCC) parameters.

MATERIALS AND METHODS

This study included patients from the Glaucoma Service of the Department of Ophthalmology of the Medical School of Ankara University and healthy participants from the outpatient clinic for a routine visit. Clinically evident XFS was defined as (1) having exfoliation material deposits on the pupillary margin and/or the anterior lens capsule (2) intraocular pressure (IOP) of less than 21 mmHg (3) absence of glaucomatous optic disc appearance (4) normal visual field testing. Exfoliation glaucoma diagnosis was made with (1) exfoliation material presence on the pupillary margin and/or the anterior lens capsule (2) IOP of more than 21 mmHg (3) presence of glaucomatous optic disc changes (4) presence of glaucomatous field defects. Patients with retinal or macular disorders, those with marked cataracts and histories of ocular surgeries were excluded. Patients were also excluded if they had a history of any systemic disease that may interfere with the choroidal circulation, such as hypertension, diabetes or kidney failure. To minimize the effect of axial length on choroidal thickness, patients with a refractive error greater than -5.0 D and +3.0 D were excluded from the study.

Central macular thickness, RNFL, GCC, and CT measurements were made with OCT device (Carl Zeiss Meditec Inc., Dublin, California, V/8.0). Automated measurement of central macular thickness, global and four-quadrant average RNFL thickness data and ganglion cell complex analysis was provided by the built-in software. Choroidal thickness measurements were performed using enhanced depth imaging mode after pupil dilation. The choroid was measured from the outer border of the retinal pigment epithelium to the inner border of the sclera. These measurements were made at the fovea, 1500 µm nasal and 1500 µm temporal from the center of the fovea and average of these measurements is taken into consideration (Figure 1). CMT was analyzed (macular cube 512x128, a computer algorithm was used to select the inner and outer retinal borders, and the retinal thickness was computed automatically from these borders) by Cirrus OCT.

The clinical and OCT records were prospectively reviewed for patients' demographics, clinical diagnoses, and biomicroscopic examination findings. Intraocular pressure was measured with Goldmann applanation tonometer (Haag Streit International, OH, USA).

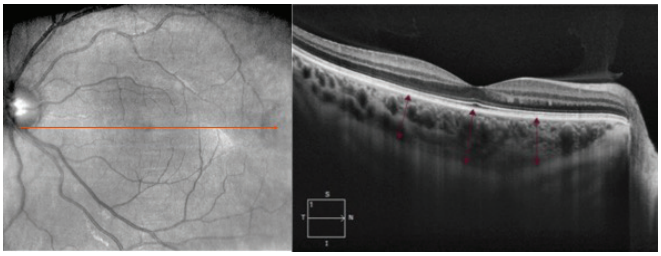

Figure 1. *Evaluation of correlations of macular choroidal thickness and central macular thickness with ganglion cell complex parameters in exfoliation patients. En face scan and corresponding optical coherence tomography image showing the choroidal thickness in an exfoliation glaucoma case. Lines indicate the choroidal thickness measurements at the fovea, 1500 µm temporal to the fovea, and 1500 µm nasal to the fovea.*

Visual field evaluation was carried out using the Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Inc, CA, USA). SITA Standard 24:2 algorithm was selected. Test reliability was assessed by the manufacturer's recommendations; a false positive value >15% or fixation losses >20% were classified as low reliability.

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ankara University Faculty University Institutional Review Board and Ethics Committee. Informed consent was obtained prior to each individual's participation in the study.

Statistical analysis was done using the Statistical Package for Social Science (SPSS) by IBM, version 20 (IBM Corp., Armonk, NY). Continuous variables were expressed as the mean ± standard deviation. Chi-Square test was used to analyze categorical values. The ANOVA test was used to investigate differences in continuous values between groups. When there was a significant difference, the Bonferroni test was used to explore comparisons between groups. Correlation was assessed by calculating the Pearson correlation coefficient between GCC parameters with CT and CMT. A 2-tailed "p" value of <0.05 was considered statistically significant in all analyses.

RESULTS

There were 41 eyes with XFS, 62 eyes with XFG and 30 eyes of healthy subjects in this series. The patient demographics and baseline characteristics of the participants are listed in Table 1. A comparison by diagnostic group (XFS vs. XFG vs. control) revealed no difference in sex, age, and IOP at date last seen. IOP at date first seen was higher in XFG (18.5 vs. 24.8 vs. 17.1, p=0.04). Regarding visual field,

Table 1: *Evaluation of correlations of macular choroidal thickness and central macular thickness with ganglion cell complex parameters in exfoliation patients. Clinical and demographic characteristics.*

	XFS	XFG	Control group	p-value
Age (years)	74.3 ± 10.1	71.3 ± 8.7	69.3 ± 8.4	0.23
Sex (f/m)	19 / 10	22 / 23	15 / 15	0.48
IOP at DFS	18.5 ± 4.1	24.8 ± 5.9	17.1 ± 3.1	**0.04**
IOP at DLS	17.1 ± 3.5	17.6 ± 2.5	16.8 ± 2.1	0.07

Abbreviations: **XFS:** exfoliation syndrome, **XFG:** exfoliation glaucoma, **IOP:** intraocular pressure, **DFS:** date first seen, **DLS:** date last seen **Bold** values indicate significant p-values.

XFG cases had worse mean deviation (MD) (-2.4 ± 4.8 vs. -5.45 ± 8.2, p=0.04) and similar pattern standard deviation (PSD) (3.5 ± 2.3 vs. 5.33 ± 8.7, p=0.27) compared to XFS.

The mean retinal nerve fiber layer thicknesses by diagnosis are listed in Table 2. A comparison by diagnostic group (XFS vs. XFG vs. control) revealed thinner average RNFL thickness (88.8 vs. 75.3 vs. 91.2, p<0.001), superior RNFL thickness (103.4 vs. 93.9 vs. 112.0, p=0.01), inferior RNFL thickness (116.5 vs. 89.4 vs. 114.6, p<0.001) and temporal RNFL thickness (73.5 vs. 57.2 vs. 66.0, p<0.001) in XFG group compared to XFS and control group. There was no difference in nasal RNFL thickness.

Ganglion cell complex and central macular thickness analysis is listed in Table 3. A comparison by diagnostic group (XFS vs. XFG vs. control) revealed thinner average ganglion cell layer+inner plexiform layer (GCL+IPL) thickness (70.7 vs. 70.0 vs. 76.4, p=0.89), minimum GCL+IPL thickness (60.7 vs. 58.3 vs. 61.7, p=0.82) in XFS and XFG group compared to control group. There was no difference in mean CMT measurements (253.3 vs. 258.5 vs. 255.1, p=0.52).

The mean CT values were; 321.5 ± 12.8 µm, 381.1 ± 11.7 µm and 417.7 ± 19.6 µm in the XFS, XFG and control group respectively. The mean CT in XFS group was significantly thinner than XFG and control (p<0.001, p<0.01 respectively). Although XFG patients had thinner choroid compared to control group, the difference was not

Table 2: *Evaluation of correlations of macular choroidal thickness and central macular thickness with ganglion cell complex parameters in exfoliation patients. Comparison of RNFL thicknesses.*

		XFS	XFG	Control group	p-value
RNFLT	Average	88.8 ± 14.0	75.3 ± 20.2	91.2 ± 10.5	**<0.001**
	Superior	103.4 ± 23.9	93.9 ± 26.9	112.0 ± 16.2	**0.01**
	Nasal	62.2 ± 15.1	64.8 ± 14.2	72.4 ± 13.0	0.05
	Inferior	116.5 ± 20.2	89.4 ± 37.5	114.6 ± 18.8	**<0.001**
	Temporal	73.5 ± 25.1	57.2 ± 16.4	66.0 ± 12.9	**<0.001**

Abbreviations: **XFS:** exfoliation syndrome, **XFG:** exfoliation glaucoma, **RNFLT:** retinal nerve fiber layer thickness
Bold values indicate significant p-values.

Table 3: *Evaluation of correlations of macular choroidal thickness and central macular thickness with ganglion cell complex parameters in exfoliation patients. Comparison of OCT findings by diagnostic groups.*

	XFS	XFG	Control group	p-value
Average GCL +IPL (µm)	70.7 ± 21.4	70.0 ± 17.7	76.4 ± 9.3	0.89
Minimum GCL+IPL (µm)	60.7 ± 27.9	58.3 ± 22.4	61.7 ± 17.4	0.82
Cental macular thickness (µm)	253.3 ± 35.8	258.5 ± 43.4	255.1 ± 29.9	0.52

Abbreviations: **XFS:** exfoliation syndrome, **XFG:** exfoliation glaucoma, **GCL+IPL:** ganglion cell layer+inner plexiform layer
Bold values indicate significant p-values.

statistically significant (p=0.12). (Figure 2).

In XFS group, we detected weakly positive correlations of average GCL+IPL thickness and minimum GCL+IPL thickness with CT (R= +0.23, R=+0.21 respectively, p=0.15, p=0.19), and we found no correlation between average GCL+IPL thickness and minimum GCL+IPL thickness with CMT (R=0.03, R=0.01 respectively, p=0.81, p=0.94). In XFG patients, average GCL+IPL thickness and minimum GCL+ IPL thickness showed weakly negative correlations with CMT (R= -0.22, R= -0.18 respectively, p=0.08, p=0.15), but there was no correlation between GCC parameters and CT measurements (R= -0.12, R= -0.09 respectively, p=0.32, p=0.52). There was a weakly positive correlation between CT and average RNFL in XFS patients (R=+0.25, p=0.23) whereas no significant correlation was found in XFG group (R= -0.11, p=0.20).

We also explored if there was a relationship between MD scores and mean choroidal thickness. No links were found in any group (Figure 3).

DISCUSSION

Exfoliation syndrome and glaucoma are age-related disorders characterized by deposition of white-gray microfibrillar material on multiple ocular and extraocular structures.[6] The presence of exfoliation material in the choroidal vasculature may interfere with the circulation and lead to ischemia.[7] Recent studies showed that both ocular and choroidal blood flow in patients with XFS has been reduced.[6]

Recently Mohamed et al. demonstrated that XFS was associated with a thinner retinal nerve fiber layer compared to healthy volunteers.[8] In 2019 Alay et al. [9] reviewed 24 patients with unilateral XFS and 20 patients with bilateral XFS and found no difference in RNFL thickness compared to control group. In our series, the mean RNFL thickness was found to be significantly thinner in XFG group. In our XFS patients; a weak positive correlation was detected between the average RNFL and CT. This suggests that choroidal thinning may accompany the early course of disease in XFG patients who begin to lose nerve fiber. One can predict that measurable changes in the choroidal thickness may be another early structural glaucoma damage finding.

Ganglion cell parameters have been proven useful in the assessment of RNFL in examining especially the myopic patients and or patients with peripapillary atrophy in preperimetric stages.[10] In 2015 Eltutar et al. [11] have reviewed 35 patients with XFS and demonstrated that average GCL+ IPL thickness was significantly thinner than the control subjects. In our study, both XFS and XFG groups had clinically thinner minimum and average GCL+ IPL thicknesses compared to healthy patients. We also detected weak positive correlations of average GCL+IPL thickness and minimum ganglion GCL+IPL thickness with CT in XFS patients.

Prskalo et al.[12] evaluated macular thickness in XFS and XFG and demonstrated that the mean macular thickness in unilateral XFS was higher than of bilateral XFG but lower than control group. In the present study, we did not observe any change in CMT measurements between 3 groups. Prior

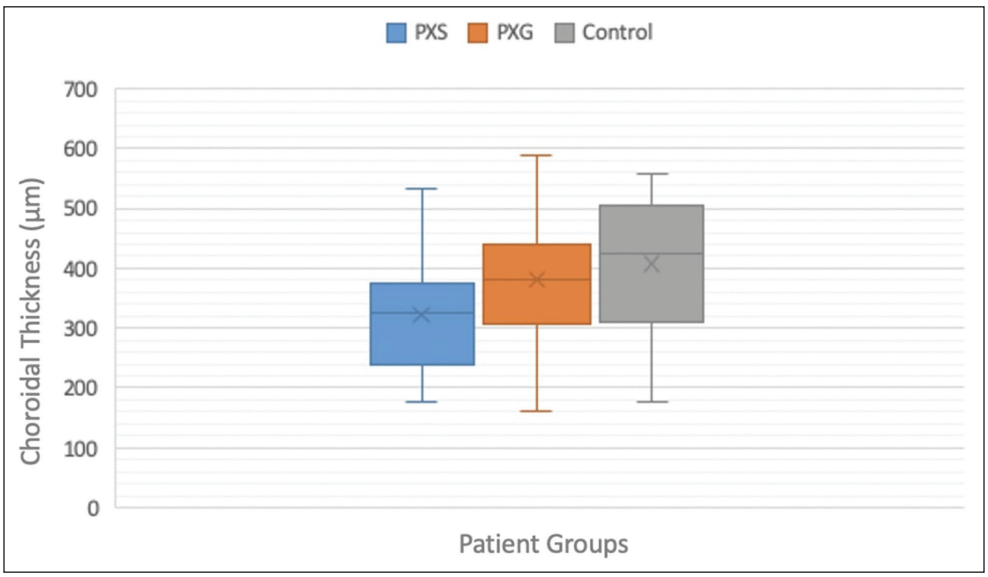

Figure 2. *Evaluation of correlations of macular choroidal thickness and central macular thickness with ganglion cell complex parameters in exfoliation patients. Distribution of mean choroidal thicknesses by diagnostic groups.*

Abbreviations: **MD:** mean deviation, **XFS:** exfoliation syndrome, **XFG:** exfoliation glaucoma.

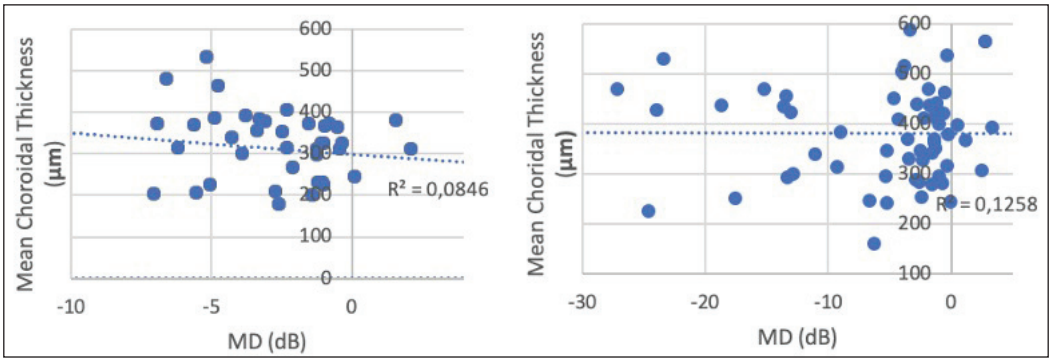

Figure 3. *Evaluation of correlations of macular choroidal thickness and central macular thickness with ganglion cell complex parameters in exfoliation patients. The scatter plots demonstrating the association between mean choroidal thickness and MD in eyes with XFS (left) and XFG (right). Linear R^2 for the models are provided.*

Abbreviations: **MD:** mean deviation, **XFS:** exfoliation syndrome, **XFG:** exfoliation glaucoma.

finding of a decrease in the mean CMT in XFG could be due to the fact that prior study's groups differed statistically according to age; the oldest being bilateral XFG, followed by unilateral XFS and control group. So measuring CMT in older patients perhaps does not provide as direct information as one may ask. We suggest that CMT may not be an indicator of progression in exfoliation patients.

In our study, the mean CT in XFS was significantly thinner than XFG and control. Although eyes with XFS had the thinnest choroid, choroidal thickness was clinically comparable in XFS, XFG and healthy controls. In the published literature, several studies presented choroidal thinning in patients with XFS and XFG whereas Moghimi et al. and You et al. have reported that presence of exfoliation did not alter CT.[5,13-15] In the present study, the mean CT in XFS was significantly thinner than XFG and control. Although eyes with XFS had the thinnest choroid, choroidal thickness was clinically comparable in XFS, XFG and healthy controls. Studies evaluating the choroidal structure in healthy cases have demonstrated that the choroid is thickest in subfovea in subfoveal region and gets thinner as it moves away from the foveal zone. Different findings from these studies may have originated as choroidal thickness measurement is examiner dependent. It has been previously reported that glaucomatous damage can occur in a significant proportion of normotensive patients with XFS.[14] Relatively thicker choroid in XFG group compared to XFS may signal the effect of treatment. So it may be proposed that choroidal changes can reverse in exfoliation patients after glaucoma treatment.

Study limitations include manual measurement of choroidal thickness and cross-sectional nature of the study. A longitudinal project would demonstrate the effects of exfoliation on choroidal anatomy timewise. Study strengths are utilizing an age-matched control group and hence eliminating possible confounders between cases and control.

In the present study, we found that in XFG group choroid was thicker compared to XFS. This may be related to the reversibility of this situation with treatment in early phases. Therefore, choroidal imaging may be a sensitive examination method for the detection of early organic damage in glaucoma. Choroidal thickness may increase after treatment in patients with exfoliation. Further studies are needed to better understand the association between choroid and exfoliation.

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