Retinal Nerve Fiber Layer and Central Corneal Thickness in Patients with Exfoliation Syndrome

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Abstract

***Purpose*:** To evaluate the retinal nerve fiber layer (RNFL) and central corneal thickness (CCT) in patients with exfoliation syndrome (XFS)

***Methods*:** In this comparative case series we measured RNFL thickness and CCT in 30 patients with XFS and in 30 age and sex matched healthy subjects who met the inclusion criteria.

***Results*:** Average RNFL in XFS group were significantly thinner than controls (94.36±8.70 µm vs. 100.80±6.68 µm) (P=0.002). In the analysis with regard to quadrants, no statistically significant reduction in RNFL thickness was found between groups. XFS patients and controls did not differ in CCT measurements (522.90±40.71 µm vs. 517.30±30.50 µm) (P=0.549).

***Conclusion*:** No significant differences in CCT and RNFL thickness in temporal, nasal, superior and inferior quadrants between XFS and controls were observed. However, average RNFL measurements in eyes with XFS showed lower values.

***Keywords*:** Exfoliation Syndrome, Retinal Nerve Fiber Layer Thickness, Central Corneal Thickness

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Introduction

Exfoliation syndrome (XFS) is an age-related disease characterized by the production and progressive accumulation of abnormal fibrillar extracellular material in many intraocular and extraocular tissues.[1-3] Secondary chronic open angle glaucoma associated with XFS or exfoliative glaucoma (XFG) accounts for approximately 25% of all glaucoma and represents the most common identifiable cause of glaucoma.[3] Although elevated intraocular pressure (IOP) represents the main risk factor for loss in retinal nerve fiber layer (RNFL), several reports suggest that pressure independent factors may increase the risk of glaucomatous damage in XFS, such as impaired ocular and retrobulbar perfusion, abnormalities of elastic tissues of lamina cribrosa or exfoliative material itself.[4-8]

Some studies have reported the presence of difference in RFNL thickness measurement between the eyes with the XFS and fellow eyes, normal control eyes and eyes with XFG.[9-11]

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However a recent study found no significant difference between optic nerve head parameters of subjects with XFS and controls.[12]

Concerning central corneal thickness (CCT) in subjects with XFS and XFG; references in literature are conflicting.[13-16] Recent studies recognize CCT as an intrinsic ocular factor in the pathogenesis and progression of glaucoma.[17,18]

In this study, we decided to select subjects with XFS who had normal IOP, diurnal variation <5 mmHg and normal visual field tests and to determine whether there is any differences in RNFL thickness measured by optical coherence tomography (OCT) and CCT between these patients and normal subjects and also to evaluate the possible correlation between CCT and RNFL thickness in them.

Methods

The study adhered to the tenets of the Declaration of Helsinki and approved from the regional medical research ethics committee of Tabriz University of Medical Science. Written Informed consent was obtained by all participants. Participants were recruited in a consecutive-if-eligible fashion from the outpatient glaucoma and screen service of the Nikookari Eye Hospital in Tabriz, Iran. The control group was compromised of healthy volunteers who visited the outpatient service of the aforementioned department.

According to the results of a previous study upon RNFL thickness in patients with pseudoexfoliation,[9] considering α=0.05 and power=80%, statistically the sample size estimated 26 patients. So in this study we enrolled 30 patients for each group.

XFS was defined clinically as the occurrence of biomicroscopically detectable material on the anterior lens capsule or at the pupillary border after pupillary dilation with 1% tropicamide.

All participants underwent a complete ocular examination including autorefractometric measurement (RM-8800-Autorefractometer, Topcon, Tokyo, Japan) uncorrected and best corrected visual acuity (BCVA) testing with Snellen charts, slit-lamp biomicroscopy, dilated fundus examination, gonioscopy, automated perimetry using the 30-2 Swedish Interactive Thresholding Algorithm (SITA) program test strategy with the Humphrey Visual Field Analyzer (Humphrey Instruments, San Leandro, CA, USA), ultrasonic pachymetry (Tomey SP-3000, Tomey, Nagoya, Japan) and an optic disc scan with the OCT device (Stratus OCT-3 , Carl Zeiss Meditec Inc, Dublin, CA, USA). IOP was measured with a calibrated Goldmann applanation tonometry (Haag Streit, Koniz, Switzerland) at 8.00 a.m., 12.00 p.m. and 5.00 p.m. each time, IOP was measured by the same ophthalmologist (V M). Diurnal variations of IOP in all subjects were lesser than 5 mmHg. The mean of 3 recordings was used for analysis.

All participants had the following criteria: IOP<21 mmHg in all measurements, BCVA≥$^{20}/_{40}$ with refractive error not exceeding 3 diopters sphere and 2 diopters cylinder, open angle in gonoscopy, normal visual field tests (glaucoma hemi field test results and pattern standard deviation within normal limits and no characteristic glaucomatous visual field defects) and normal optic disc appearance (defined as having a vertical linear cup-to-disk ratio≤0.3, a neuroretinal rim with no glaucomatous changes such as localized rim loss or slimming of the rim or peripapillary hemorrhages seen ophthalmoscopically).

Eyes with retinal pathology, dense cataracts or with corneal opacities making OCT imaging impossible and eyes previously subjected to intraocular surgery or ocular laser treatment and anti-glaucomatous drug were excluded. Participants were evaluated systematically by an internal medicine specialist, and patients with any signs of systemic disease that might influence the optic nerve head such as uncontrolled diabetes mellitus, sever cardiovascular disease or a history of transient ischemic attack or stroke were eliminated from participation.

Whenever both eyes of the participants met the inclusion criteria, one eye from each patient was randomly selected to be included in the study. Participants who met the inclusion criteria were examined by OCT (Stratus OCT-3, Carl Zeiss Meditec Inc, Dublin, CA, USA). Each eye dilated with 1% tropicamide before scanning. All scans were done using an internal fixation target in the OCT device. The fast RNFL scan protocol

consisted of 3 consecutive 360 degree circular scans with a diameter of 3.4 mm centered on optic disc. Parameters including average thickness of RNFL and average RNFL thickness in 4 quadrants were generated automatically in the analysis report. The average and four-quadrant RNFL thickness data (temporal, superior, nasal, inferior) was collected and compared in both groups. Standard measurement of CCT was performed in the participants by ultrasonic pachymetry (Tomey SP-3000, Tomey, Nagoya, Japan). After instillation of one drop of 0.5% tetracaine the tip of the probe was cleaned with alcohol, dried and then applied lightly to the corneal surface. Four to six measurements were taken and the mean value was calculated automatically and reported. The data was collected and compared in both groups. Pachymetry always precedes applanation tonometry.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences for windows, version 15.0 (SPSS, Chicago, IL, USA). Data were reported as the mean±standard deviation (SD). The independent sample t-test was used to compare the differences between the groups. The correlation between RNFL thickness and CCT in XFS group was analyzed using the Spearman correlation coefficient. A P value of less than 0.05 was considered statistically significant.

Results

Sixty eyes of 60 patients were included in the study; 30 eyes with XFS and 30 control eyes. Table 1 shows demographic and clinical characteristics of all subjects. There were no significant differences between the groups according to gender and age. There were also no significant differences at the mean IOP measurements between both groups. Regarding CCT; no statistically significant differences was found when comparing values of both groups. Although RNFL thickness in XFS group in all quadrants were thinner than controls, no statistically significant differences were found between the two groups. Average RNFL thickness in XFS group was significantly decreased compared with controls (P=0.002), as shown in Figure 1. Moreover no significant correlation was observed between CCT and RFNL thickness in both groups (Table 2).

Table 1. The demographic and clinical characteristic data for the exfoliation syndrome and control group patients

	Exfoliation syndrome (n=30)	Control (n=30)	P
Age (mean±SD)	68.8±7.2	70.2±7.5	0.34
Sex (male/female)	15/15	15/15	-
IOP (mm Hg)	14.07± 2.27	13.07±1.98	0.075
CCT (µm)	522.90±40.71	517.30±30.50	0.549
RNFL thickness (average, µm)	94.36±8.70	100.80±6.68	0.002
RNFL thickness (nasal, µm)	67.40±15.35	70.73±13.31	0.37
RNFL thickness (superior, µm)	112.00±18.77	119.37±13.68	0.08
RNFL thickness (temporal, µm)	74 .00±20.87	83.03±17.95	0.07
RNFL thickness (inferior, µm)	124.07±15.29	130.07±11.62	0.09

IOP: Intraocular pressure, CCT: Central corneal thickness, RNFL: Retinal nerve fiber layer, XFS: Exfoliation syndrome

Table 2. Spearman correlation among central corneal thickness and retinal nerve fiber layer thickness in exfoliation syndrome and control patients

	Exfoliation syndrome		Control	
	r	P	r	P
Nasal	0.0197	0.12	0.0002	0.38
Temporal	0.0701	0.45	0.0000	0.44
Superior	0.1270	0.01	0.1320	0.20
Inferior	0.0220	0.41	0.0016	0.41
Average	0.0009	0.17	0.0020	0.43

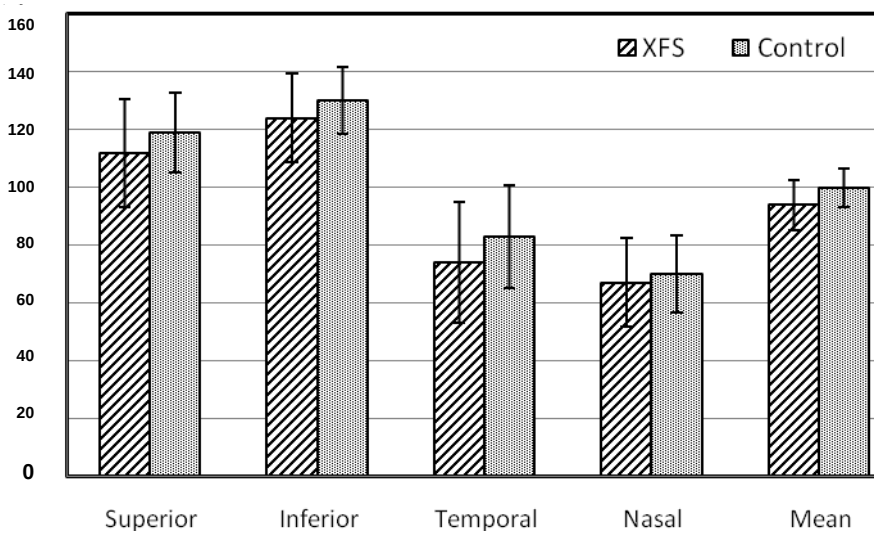

Figure 1. Comparison between retinal nerve fiber layer thickness in all quadrants and average value in both groups

Discussion

Patients with XFS are twice as likely to convert from ocular hypertension to detectable glaucoma.[19] At the time of glaucoma diagnosis, the IOP is higher, diurnal variation in IOP is greater, and initial visual field loss is more advanced.[20] The diurnal fluctuations in IOP was reported to be higher in eyes with XFS and may be responsible for the lower values in RNFL thickness.[21,22] Clinically unilateral XFS is probably never truly unilateral; it is asymmetrical. The cumulative probabilities of patients with unilateral XFS that proceed to bilateral involvement are reported to be between 17-38 percents in 10 years.[23] Instead of comparing the two eyes of persons with clinically unilateral XFS, we compared them with eyes of participants without XFS. Furthermore we excluded patients with XFS and ocular hypertension and great diurnal variation and visual field defect to evaluate the effect of XFS itself in RNFL thickness and CCT.

In our study CCT in XFS eyes did not have any significant difference compared to normal eyes. Concerning CCT in subjects with XFS references in the literature are controversial. Kitsos and colleagues showed that CCT was not affected by the presence of XFS[24] and their results was in agreement with previous studies.[13,25] On the contrary, Inoue and coworkers reported thinner corneas in individuals with XFS compared to controls.[26] Puska and coworkers reported that CCT in eyes with XFS was thicker than CCT found in the other eye of the same patient that did not have XFS.[16]

Consistent with previous studies that showed the CCT was not affected by the presence of XFS[13,24,25]; the results of present study suggested that CCT in XFS was not significantly thinner compared to controls. Nevertheless CCT must be assessed in patients with XFS in order to avoid the underestimation of the IOP.

In this study the CCT was not correlated to the RNFL thickness in our two groups. There are studies that indicate a possible biological link between aspects of the front of the eye that can be measured such as thickness or material properties of cornea and the structure deformability or physiology of the optic disc, lamina cribrosa, and prepapillary sclera.[18,27] But this study showed that such a correlation did not exist between RNFL and CCT in subjects with XFS.

To the best of our knowledge, the correlation between the CCT and RNFL measured by OCT has not been compared between XFS patients and normal subjects and our study is the first one.

Our study demonstrated that average RNFL thickness was significantly decreased in XFS patients, but in comparing quadrants we did not find any significant differences in the

RNFL thickness of healthy non-glaucomatous participants and patients with XFS. Yuksel et al found that RNFL thickness measured by OCT in eyes with XFS decreased segmentally compared with control subjects.[9]

In all types of glaucoma, RNFL thickness loss might occur in a localized pattern which is too small to detect at an early stage and may only become visible with the progression of the disease. The segmental reduction of RNFL in eyes with XFS may be an early sign of glaucomatous damage, as the damage to the RNFL has been shown to precede visual field loss.[28-30]

Grodum et al reported that thinner RNFL measurements may be related with the increasing risk of development of glaucoma in XFS patients.[31] Cankaya and Beyazyidiz in their study found that the thickness and the cross-sectional area of the RNFL were decreased in eyes with exfoliation, but in their study mean IOP of eyes with XFS was higher than controls. Therefore the difference in RNFL thickness might be the result of either the structural alterations or higher IOP.[12] Gumus et al reported that RNFL thickness values measured by scanning laser polarimetry are significantly lower in patients with XFS specially in those showing diurnal variation >5 mmHg.[22]

In our study decreased average RNFL (non-localized) thickness in patients with XFS with normal IOP and diurnal variation without visual field loss suggested that a systemic factor such as blood perfusion or hemodynamic status of RNFL or pseudoexfoliative material itself may be responsible. An impaired ocular vascular regulation is proposed in XFG.[32] Previous studies showed that hemodynamic changes occurred in XFS as well as XFG, when patients were compared with healthy controls. These changes seem to be more prominent in XFG than XFS.[33-35] Our study was limited by the fact that the sample size was relatively small. The sample size and systemic characteristics of subjects may have an influence on the results. Thus, although the results of the present study provide concern about decreased RNFL thickness in XFS patients, independent to the known risk factors such as high IOP and greater variation of IOP, a possible selection bias according to the systemic condition specially cardiovascular and hemodynamic status of patients may account for these results. So further longitudinal or cross-sectional studies with a larger sample size with considering systemic and hemodynamic variables should be performed to confirm these findings.

Conclusion

CCT is not affected by XFS alone, however average RNFL thickness in this syndrome decrease without coincidental glaucoma and this may a predictive factor for occuring more progressive and dangerous glaucoma in these patients.

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