Analysis of peripapillary choroidal thickness in primary open angle glaucoma.

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Abstract

Glaucoma is the second leading cause of blindness worldwide. It is estimated that Primary Open Angle Glaucoma (POAG), by far the most common type of glaucoma, will affect 79.76 million people aged 40-80 years by 2040. The underlying mechanism of POAG is still unclear. Although increased Intraocular Pressure (IOP) is the main risk factor, multiple studies have shown that reduced perfusion to Optic Nerve Head (ONH) may have a role in development and progression of Open Angle Glaucoma (OAG).

Keywords: Open angle glaucoma, Primary open angle glaucoma, Optic nerve head, Intraocular pressure.

Accepted on 28 May, 2021

Introduction

Glaucoma is the second leading cause of blindness worldwide. It is estimated that Primary Open Angle Glaucoma (POAG), by far the most common type of glaucoma, will affect 79.76 million people aged 40-80 years by 2040 [1]. The underlying mechanism of POAG is still unclear. Although increased intraocular pressure (IOP) is the main risk factor, multiple studies have shown that reduced perfusion to Optic Nerve Head (ONH) may have a role in development and progression of Open Angle Glaucoma (OAG).

Choroid is a highly vascular layer which supplies most of the blood flow of the retina and prelaminar part of ONH [2]. The decreased and increased choroidal thickness in patients having POAG by histologic studies, respectively.
Postmortem changes and processing artifacts may affect the morphology of choroid in such studies [3]. Imaging technologies such as fluoresce in angiography and laser Doppler flowmetry which don't have these drawbacks also have shown delayed and decreased blood flow to ONH.

Newer imaging methods like Enhanced Depth Imaging (EDI) and Swept Source (SS) Optical Coherence Tomography (OCT) have provided high resolution *in vivo* cross-sectional images of choroid [4]. Recent studies have applied these methods for measurement of Choroidal Thickness (CT) in peripapillary and macular regions of glaucoma patients [5]. These studies had mixed results. The purpose of this study is to compare peripapillary CT in POAG and healthy control eyes using EDI-OCT [6].

Materials and Methods

In this observational cross-sectional study 61 eyes of 54 patients having POAG and 37 eyes of 34 healthy subjects were enrolled. Eyes in the POAG group were recruited among newly diagnosed patients of glaucoma clinic of Farabi Eye Hospital and eyes in the control group were chosen among healthy volunteers. Tenets of declaration of Helsinki were adhered in this study and ethics committee approval of Tehran University of Medical Sciences was granted.

All eyes underwent thorough and comprehensive ophthalmic examination including, measurement of best corrected visual acuity, slit-lamp biomicroscopy, tonometry by Goldmann applanation tonometry, gonioscopy, dilated funduscopy, measurement of the Central Corneal Thickness (CCT) by pachymetry (Tomey Corporation, Nagoya, Japan) and ocular biometry (IOLMaster, Carl Zeiss Meditec). Achromatic standard automated perimetry using central 24-2 Swedish Interactive Threshold Algorithm (Humphrey Visual Field Analyzer; Carl Zeiss-Meditec Inc., Dublin, CA) and circumpapillary RNFL scanning by Heidelberg Spectralis OCT (Heidelberg Engineering, Inc., Dossenheim, Germany) were performed in all eyes.

Eyes that were included in this study had spherical refraction within the range of ± 5 diopter and cylindrical correction in the range of ± 3 diopters, best corrected visual acuity ≥ 20/60 and no history of diabetic retinopathy, retinal photocoagulation, age related macular degeneration, inflammatory eye disease, media opacity and intraocular surgery except cataract extraction. Age under 18 years old and absence of two consecutive reliable visual fields (fixation loss >20%; false positive >15%) were considered as exclusion criteria.

The diagnosis of POAG was made by presence of typical glaucomatous optic neuropathy (diffuse enlargement of the optic disc cup or focal notch in neuroretinal rim) and associated visual field defects, an open angle by gonioscopy and IOP>21 mmHg or ≤ 21 mmHg on topical medications without secondary causes. The eyes in control group had normal appearance of ONH, IOP ≤ 21 mmHg and an open angle by gonioscopy. Anderson criteria were used for confirming glaucomatous perimetric defects [7] and presence of an abnormal glaucoma hemifield test, three contiguous non-edge points with p<5% in pattern deviation plot with at least one point having p<1% or a p<5% for pattern standard deviation considered as glaucomatous. All eligible eyes had two consecutive reproducible visual fields.

EDI SD-OCT

All eyes in this study underwent peripapillary Retinal Nerve Fiber Layer (RNFL) scanning by Heidelberg Spectralis SD-OCT (Heidelberg Engineering; Spectralis software version 5.3.2) after pupillary dilation. Peripapillary RNFL thickness measurements were done by using a circle with diameter of 3.5 mm centered on ONH [8]. Images with quality score <20, uneven illumination, poor centration and segmentation excluded from analysis. Images in which the posterior border of choroid was not delineable were also excluded.

Measurement of choroidal thickness

For measurement of choroidal thickness, the choroid in B-scan which is represented as a strip by the device was manually outlined. The inner and outer boundaries were outlined at the base of Retinal Pigment Epithelium (RPE) and choroidoscleral junction, respectively. Choroidoscleral junction is a hyperreflective layer between large vessels of the choroid and sclera. The measurements were done by Heidelberg Eye Explorer software (HEYEX™ Heidelberg Engineering, Dossenheim, Germany) globally and in temporal, superotemporal, superonasal, nasal, inferonasal, inferotemporal sectors [9].

Statistical analysis

The distribution of numerical data was tested for normality using the Shapiro-Wilk test. Student's t test was used to compare patient level demographic continuous variables between POAG and glaucoma subjects [10]. Categorical variables were compared using Fisher's exact test. Mixed-effects models were used to compare ocular parameters between groups. Models were fit with ocular measurements as dependent variables and diagnostic group as a fixed effect. Eye level measurements were nested within subject to account for the fact that eyes from the same individual are more likely to have similar measurements [11]. Models for choroidal thickness were adjusted for age, sex and axial length. univariate linear mixed model was used to explore the factors that are associated with choroidal thickness. Multivariable models were built to adjust for age, gender, axial length and factors with P<0.15 in univariable model. Given the collinearity of the visual field MD and RNFL, separate models were fitted and the coefficients of association for each model were reported. Statistical analyses were performed using STATA v. 15.0 (StataCorp, College Station, TX). The alpha level (type I error) was set at 0.05.

Results

61 eyes of 54 patients having POAG and 37 eyes of 34 healthy subjects were enrolled in POAG and control groups respectively, with respect to the inclusion and exclusion criteria. The mean age was similar between POAG eyes (68.6 ± 10.8 years) and control group (69.1 ± 6.4 years) (P=0.827).

POAG group had more proportion of male (P=0.056), higher IOP (P<0.001) and worse visual field MD compared to control group (-7.8 ± 6.4 vs. 0.2 ± 1.3 dB, P<0.001). However, there was no significant differences in refractive error (P=0.873), CCT (P=0.935), and axial length (P=0.385) between POAG and control groups (Table 1).

	Control	POAG	P value
No (eye)	34(37)		
Age(years)	69.1 ± 6.4	68.6 ± 10.8	0.827
Gender(M/F)	17/20	40/41	0.056
Refractive error SE (D)	0.1 ± 1.5	0.2 ± 1.4	0.873
IOP (mmHg)	13.5 ± 2.6	17.6 ± 6.9	<0.001
CCT (µm)	536.2 ± 43.6	537.1 ± 39.1	0.935
Axial length (mm)	23.3 ± 0.8	23.5 ± 0.9	0.385
Visual field MD (dB)	0.2 ± 1.3	-7.8 ± 6.4	<0.001

Table 1. *D: Diopter, IOP: Intraocular Pressure; CCT: Central Corneal Thickness; MD: Mean Deviation, SE: Spherical Equivalent.*

The eyes in POAG group had thinner RNFL globally (70 ± 14 µm vs. 95.4 ± 8.7 µm) and in superotemporal (88 ± 22.9 µm vs. 122.4 ± 18.6 µm), superonasal (77.8 ± 25.6 µm vs. 111.4 ± 21.9 µm), nasal (57 ± 14.6 µm vs. 77.8 ± 11 µm), inferonasal (79.5 ± 23.1 µm vs. 118.7 ± 20.3 µm) and inferotemporal (86 ± 29.7 µm vs. 132 ± 17.6 µm) sectors (P<0.001). RNFL thickness in temporal sector was not significantly different between POAG and control groups (58.3 ± 14.8 µm vs. 61.4 ± 11.4 µm) (P=0.277) (Table 2).

	Control group (Mean ± SD)	POAG group (Mean ± SD)	P-value
Global RNFL (µm)	95.4 ± 8.7	70 ± 14	<0.001
Temporal RNFL (µm)	61.4 ± 11.4	58.3 ± 14.8	0.277
Superotemporal RNFL (µm)	122.4 ± 18.6	88 ± 22.9	<0.001
Superonasal RNFL (µm)	111.4 ± 21.9	77.8 ± 25.6	<0.001
Nasal RNFL (µm)	77.8 ± 11	57 ± 14.6	<0.001
Inferotemporal RNFL (µm)	132 ± 17.6	86 ± 29.7	<0.001

Table 2. *RNFL thickness in temporal sector was not significantly different between POAG and control groups.*

Global peripapillary CT was 131.7 ± 50.6 µm in POAG group and 158.6 ± 47.7 µm in control group, which was significantly lower in POAG group (P=0.016). CT in temporal (131.5 ± 53.4 µm vs. 167.9 ± 51.6 µm), superotemporal (141.3 ± 59 µm vs. 176.2 ± 51.7 µm), superonasal (143.8 ± 60 µm vs. 170.1 ± 46.5 µm), inferonasal (112.2 ± 48.7 µm vs. 137.7 ± 55.9 µm) and inferotemporal (110.3 ± 47.9 µm vs. 139.8 ± 56.4 µm)

sectors was lower in POAG group than control group (P=0.003, P=0.006, P=0.029, P=0.030 and P=0.014, respectively). After adjusting for age, sex and axial length the difference remained significant globally and in temporal, superotemporal and inferotemporal sectors (P=0.047, P=0.006, P=0.040 and P=0.038, respectively) (Table 3).

	Control group (Mean ± SD)	POAG group (Mean ± SD)	P-value	Adjusted P-value
Global choroid (µm)	158.6 ± 47.7	131.7 ± 50.6	0.016	0.047
Temporal choroid (µm)	167.9 ± 51.6	131.5 ± 53.4	0.003	0.006
Superotemporal choroid (µm)	176.2 ± 51.7	141.3 ± 59	0.006	0.04
Superonasal choroid (µm)	170.1 ± 46.5	143.8 ± 60	0.029	0.109
Nasal choroid (µm)	156.8 ± 52.7	138.6 ± 58.3	0.139	0.337
Inferonasal choroid (µm)	137.7 ± 55.9	112.2 ± 48.7	0.03	0.139
Inferotemporal Choroid (µm)	139.8 ± 56.4	110.3 ± 47.9	0.014	0.038

Table 3. *Adjusted for age, gender and axial length.*

In univariate regression analysis age was negatively correlated with global peripapillary CT (β=-2.31, P<0.001). There was a positive correlation between global peripapillary CT and visual field MD (β=1.43, P=0.048) and global RNFL thickness (β= 0.74, P=0.008). In multivariable analysis older age, thinner RNFL (β=0.67, P=0.008, model 1), and the worse MD (β=2.06, P=0.002, model 2) associated with thinner choroid (Table 4).

	Global peripapillary choroidal thickness					
	Univariate model		Multivariable model 1		Multivariable model 2	
	β ± SE	P value	β ± SE	P value	β ± SE	P value
Age (per 1 year older)	-2.31 ± 0.46	<0.001	-2.28 ± 0.48	<0.001	-2.58 ± 0.49	<0.001
Gender (M/F)	-2.52 ± 12.17	0.837	-4.02 ± 10.65	0.706	-2.92 ± 10.42	0.780
Axial length (per 1 mm longer)	0.50 ± 7.97	0.95	-	-	-	-
CCT (per 1 µm thicker)	0.03 ± 0.13	0.842	-	-	-	-
IOP (per 1mmHg higher)	0.87 ± 0.82	0.293	-	-	-	
VF MD (per 1 DB higher)	1.43 ± 0.72	0.048	-	-	2.06 ± 0.66	0.002
Global RNFL (per 1 µm thicker)	0.74 ± 0.27	0.008	0.67 ± 0.25	0.008	-	-
Model r1: 0.23 Model r2: 0.24						

Table 4. *Global peripapillary choroidal thickness.*

Discussion

Various studies have shown that factors other than IOP may have a role in pathophysiology of POAG [12]. One of these factors is disturbed blood supply to the ONH that can lead to development and progression of glaucomatous optic neuropathy. Choroid is a highly vascularized tissue and is responsible for perfusion of optic nerve specially in the prelaminar region [13]. Histologic assessment of choroid in patients having POAG are contradictory and have found increased or decreased CT in comparison to age-matched healthy subjects. Also studies that have applied imaging modalities like radiofrequency, doppler flowmetry and flourscein angiography have mixed results. By using EDI function of SD-OCT, CT could be measured in detailed cross sectional images of choroid [14].

In our study eyes in POAG group had lower CT globally and in all sectors except nasal sector. As previous studies have shown CT decreases by increasing age and axial length [15]. Gender comparison had a borderline significance in categorical analysis. So, after controlling age, gender and axial length, eyes in POAG group had lower CT globally and in temporal, superotemporal and inferotemporal sectors. Interestingly, this finding supports vascular theory of POAG and is in concordance with glaucoma tendency to damage neuroretinal rim in supero and inferotemporal sectors.

Previous studies have applied different methods and imaging modalities for measurment of peripapillary CT. There is no difference in peripapillary CT between OAG and normal subjects or OAG suspects [16].
But there are multiple studies which have shown thinner peripapillary CT in OAG or Normal Tension Glaucoma (NTG).

The study evaluated peripapillary and macular CT by SD-OCT and swept source OCT (SS-OCT) in normal and POAG subjects. In measurments that were done by SD-OCT in their study, there was no significant difference in peripapillary CT between POAG and normal eyes. But when measurments were done by SS-OCT, POAG eyes had thicker peripapillary CT in all quadrants except inferior quadrant. They attributed

this finding to medications and reduced IOP in treated patients. But the IOP reduction in glaucomatous patients didn't result in greater CT in inferior quadrant [17]. We also showed a lower CT in supero and inferotemporal sectors, which are common locations for glaucomatous damage. So, the results of our studies confirms each other.

Similar to previous investigations, in the present study there was a negative correlation between age and global CT in univariate regression analysis [18]. But there was no significant correlation between axial length and global peripaillary CT, probably because of low standard deviation and low dispersion of axial lengths. In the two multivariable models that were constructed by controlling for age and gender, visual field MD and global RNFL thickness were positively correlated with global CT. This finding means that more functional or structural damage in POAG is in correlation with lower peripapillary CT.

The peripapillary CT between healthy controls and patients with controls and patients with Focal, Diffuse, and Sclerotic Glaucomatous Optic Disc Damage. They found a negative correlation between sclerotic ONH damage and peripapillary CT in OAG (POAG, pseudoexfoliative and pigmentory glaucoma). Although the correlation between peripapillary CT and focal or diffuse ONH damage was not significant, their study showed a correlation between particular type of structural damage and peripapillary CT [19].

Our study has several limitations. First, we used EDI SD-OCT as imaging modality. In this imaging system inner and outer boundaries of choroid could be unclear and difficult to outline. SS-OCT systems can provide better visualization of choroidoscleral junction and applying these system for measurement of CT should be more accurate. Second, this study had a cross sectional desing and precedence of CT change or ONH damage could not be detected. Third, because of small sample size we didn't categorize POAG eyes according to severity [20]. So, we suggest future studies with larger sample size, prospective design and newer imaging techniques for evaluation of the role of choroid in glaucoma.

Conclusion

In conclusion, the present study demonestrated that in eyes having POAG, peripapillary CT is significantly lower regionally and globally compared to healthy controls. Older age and more severe glaucoma were associated with thinner choroid in these eyes. Based on anatomical measurements, the choroid seems to be significantly altered in POAG patients in Iranian population. Future studies investigating the choroidal vascular flow are indicated to confirm the role of the choroid in the pathophysiology of open-angle glaucoma.

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