

Retinal Nerve Fiber Layer Thickness and Macular Ganglion Cell Evaluation in Unilateral Amblyopia using Optical Coherence Tomography

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Abstract

The aim of the current study is to evaluate retinal nerve fiber layer (RNFL) thickness, macular parameters and ganglion cell thickness (GCL+) in unilateral anisometropic amblyopic eye in relation to the normal healthy fellow eye and control one using spectral domain optical coherence tomography (SD-OCT). This study included 56 eyes of 28 cases aged from 8-30 years old subdivided into: 20 amblyopic eyes of patients with unilateral anisometropic amblyopia (group A), 20 sound fellow eyes of the unilateral anisometropic amblyopic patients (group B) and 16 emmetropic eyes of normal non amblyopic control (group C). Anisometropic amblyopic patients further subdivided according to refractive error into hypermetropic, myopic, and astigmatic amblyopic subgroups. All cases underwent detailed ophthalmic examination including visual acuity by Snellen's chart, cycloplegic refraction, ocular motility and alignment test, slit lamp biomicroscopy, intraocular pressure, fundus examination and OCT imaging by SD-OCT. Regarding peripapillary RNFL thickness, macular parameters including (central macular thickness (CMT), average macular thickness and macular volume), and GCL+ thickness, there was no significant difference among the amblyopic, fellow eyes, and normal eyes of non-amblyopic group, $P > 0.05$. By further analysis to compare subgroups according to the refractive error between amblyopic and their fellow eyes, peripapillary RNFL thickness revealed a significant increase in amblyopic eyes of hypermetropic (mean $121.750 \pm 8.647 \mu\text{m}$) and astigmatic subgroups (mean $111.888 \pm 7.043 \mu\text{m}$) compared with their fellow eyes (116.125 ± 8.509 and 107.333 ± 6.480) respectively, but it was significantly thinner in myopic amblyopic eyes (mean $81.333 \pm 23.352 \mu\text{m}$) than that of their fellow eyes (mean 110.00 ± 17.578). CMT revealed a significant increase in myopic amblyopic eyes (mean $199.00 \pm 26.851 \mu\text{m}$) compared with their fellow eyes (mean $191.00 \pm 26.00 \mu\text{m}$). Other OCT parameters did not significantly differ between amblyopic and their fellow eyes in different subgroups. OCT parameters including peripapillary RNFL thickness, macular parameters, and GCL+ thickness showed no significant difference among the amblyopic, fellow eyes, and normal eyes of non-amblyopic group. Hypermetropic and astigmatism amblyopic eyes showed increased peripapillary RNFL thickness than their fellow eyes, while myopic amblyopic eyes had decreased peripapillary RNFL thickness than their fellow eyes. CMT revealed a significant increase in amblyopic eyes of the myopic anisometropic subgroup compared with their fellow eyes.

Keywords: Amblyopia, Spectral domain optical coherence tomography.

1. Introduction

Amblyopia is a developmental ocular disorder characterized by a decrease in best corrected visual acuity (BCVA) to less than 6/9 of snellen's optotype in one or both eyes or by two or more lines difference in Logarithm of minimum angle of resolution (Log Mar) optotype between two eyes at first years of life. It occurs due to abnormal visual experience during critical period of visual development, with no ocular abnormalities [1, 2].

It is considered a socioeconomic disorder with a prevalence of 2-4 % of general population [3].

Amblyopia can be classified into stimulus deprivational, strabismic, anisometropic, and bilateral ametropic amblyopia [4]. Amblyopia mainly result from abnormal visual stimulation early in life which induces cell shrinkage and anatomical changes in the LGN layers and visual striate cortex connected with amblyopic eye, and therefore, cells of the primary visual cortex lose their ability to respond to stimulation of amblyopic eye [5].

Optical coherence tomography (OCT) is a noninvasive and non-contact technique that provides high-resolution cross sectional imaging of retinal layer. With the advances in OCT technique, it is possible to get more detailed information about retinal involvement in amblyopia. The use of SD-OCT has become the mainstream, as it has better spatial resolution and higher

scan speed than time domain optical coherence tomography (TD-OCT) types [6].

Many studies examined the amblyopic retinal thickness using OCT and the degree of retinal involvement accompanying amblyopia is controversial. Some of these studies reported no differences between amblyopic and their healthy normal fellow eyes [6-10], whereas others reported significant differences between amblyopic and healthy eyes [11-15].

The aim of this study was to investigate peripapillary RNFL thickness, macular parameters, and GCL+ thickness in amblyopic eyes in comparison to their normal fellow eyes and normal eyes of non-amblyopic cases.

2. Subjects and methods

2.1 Subjects

The study was performed at the outpatient clinic of ophthalmology hospital, Benha University, as a prospective comparative highly selective cross-sectional study from July 2017 to May 2020. Informed consent for the examinations was obtained from each patient or one of their parents.

The study included 56 eyes of 28 cases aged 8–30 years old subdivided into 3 groups, Group A: included 20 amblyopic eyes of patients with unilateral anisometropic amblyopia, Group B: included 20 sound

fellow eyes of the anisometric amblyopic patients, and Group C: included 16 emmetropic eyes of normal non amblyopic control.

Inclusions criteria: Amblyopic patients and control non amblyopic subjects aged from 8 to 30 years old., unilateral anisometric amblyopic patients with BCVA difference of ≥ 2 lines on Snellen's chart between the amblyopic and fellow eyes, anisometropia with cycloplegic spherical equivalent (SE) difference ≥ 2.0 diopters between the two eyes, the BCVA of fellow sound eyes and normal eyes of non-amblyopic subjects were ≤ 0.1 log MAR.

Exclusion criteria: Systemic disease as diabetes mellitus and hypertension, neurological disorders, ocular disease that may affect RNFL (e.g. Diabetic retinopathy), optic nerve disease such as glaucoma, ocular media opacities (e.g. corneal opacity, or cataract), nystagmus, history of ocular surgery, and previously treated amblyopic patients.

2.2 Methods

All subjects enrolled in this study underwent all ophthalmologic examination including visual acuity assessment by Snellen's chart, cycloplegic refraction, ocular motility test, cover-uncover test and alternate cover test, slit lamp examination of anterior segment, intraocular pressure, fundus examination, and OCT measurement.

All OCT scans were performed using a spectral domain OCT (Topcon 3D OCT-2000 FA, Japan "version 8.30.) with infrared [840 nm] and $< 5 \mu\text{m}$ axial resolution for measuring peripapillary RNFL thickness, central macular thickness (CMT), average macular thickness, macular volume, and ganglion cell layer plus inner plexiform layer (GCL+) thickness.

2.3 Statistical methods

All statistical analysis of the collected data were performed using Statistical Package for Social Science (SPSS), IBM SPSS Statistics for Windows, and Version 25.0. Armonk, NY: IBM Corp. Statistical methods were used to analyze the results of the present study depend on the type of obtained data. Qualitative data were described as number and percentage. Quantitative data were described using

arithmetic mean with standard deviation (SD) as mean \pm SD, and range. One-way ANOVA followed by Tukey's test were used to compare the OCT parameters among 3 main groups (Amblyopic "group A", fellow "group B" and normal control eyes "group C"). Paired t-test was used to assess the statistical significance and compare between the two eyes of amblyopic patients (amblyopic eyes and their fellow eyes) in subgroup analysis. In all statistical tests, level of significance of 0.05 was used, P-values < 0.05 were considered to be statistically significant and vice versa.

3. Results

Table (1) Comparison between group (A),(B),and(C) regarding the OCT parameters.

The current study was conducted on 56 eyes of 28 cases subdivided as: 20 anisometric amblyopic eyes of patients with unilateral anisometric amblyopia (group A), 20 sound fellow eyes of the amblyopic patients (group B), and 16 emmetropic eyes of non-amblyopic control (group C). The mean age \pm SD of amblyopic cases was 18.35 ± 8.87 years old, and the mean age of normal control cases was 20.40 ± 7.50 years old, 40% males and 60% female of group(A) and (B), 37% male and 63% female of group(C).

Mean BCVA by log MAR were 0.757 ± 0.169 for group (A), 0.108 ± 0.090 for group (B), and 0.00 ± 0.00 for group (C).

By further subdivision of 20 amblyopic eyes according to SE refractive error, 8 were hypermetropic amblyopic eyes, 3 were myopic amblyopic eyes, and 9 were astigmatic amblyopic eyes. The mean BCVA by log MAR in hypermetropic amblyopic subgroup were 0.748 ± 0.152 and 0.157 ± 0.063 in the amblyopic and fellow eyes, respectively, in myopic amblyopic subgroup were 0.867 ± 0.231 and 0.060 ± 0.104 in the amblyopic and fellow eyes, respectively, and in astigmatic amblyopic subgroup were 0.729 ± 0.172 and 0.080 ± 0.095 in the amblyopic and fellow eyes, respectively. A significant differences were found between amblyopic and fellow eyes in the 3 subgroups regarding BCVA.

No significant difference was observed among group (A), (B), and (C) regarding peripapillary RNFL thickness, CMT, average macular thickness, macular volume and GCL+ thickness Table(1).

With comparing the amblyopic eyes versus the fellow eyes according to SE refractive error Table(2), an increased peripapillary RNFL was observed in both the hypermetropic amblyopic eyes and astigmatic amblyopic eyes compared with their fellow, (P-value < 0.05), whereas myopic amblyopic subgroup showed a significantly thinner peripapillary RNFL in the amblyopic eyes than their fellow eyes (P= 0.044) Fig (1).

With comparing CMT, no significant difference were detected in both hypermetropic and astigmatic subgroups of the amblyopic eyes compared with their fellow eyes, while the CMT was found to be significantly thicker in myopic amblyopic eyes than their fellow eyes (P=0.005) Fig (2). Regarding GCL+ thickness, no significant difference were detected between amblyopic and their sound fellow eyes in any anisometric subgroups (p-value > 0.05) Fig (3).

4. Discussion

Amblyopia may cause some anatomic alterations in the retina. OCT offered reliable and accurate cross-sectional imaging of the retinal structure and evaluation of the retinal changes accompanying amblyopia. However, evidences for direct retinal changes in amblyopia remain controversial [9, 16]. In the current study we compared the peripapillary RNFL thickness, macular parameters, and GCL+ thickness of amblyopic eyes (group A) with that of fellow normal eyes (group B) and normal control eyes of non-amblyopic subjects (group C) using SD-OCT.

OCT parameter	Group (A) (mean±SD)	Group (B) (mean±SD)	Group (C) (mean±SD)	P-value
Peripapillary RNFLT (µm)				
Superior	130.05 ± 18.729	130.05 ± 12.378	126.533 ± 13.399	0.749
Inferior	132.30 ± 27.654	137.30 ± 15.898	136.20 ± 17.407	0.743
Average	111.10 ± 17.165	111.25 ± 9.716	108.80 ± 10.625	0.837
Macular parameter				
CMT(µm)	191.50 ± 16.863	191.35 ± 16.887	187.40 ± 12.603	0.704
Average macular thickness (µm)	271.46 ± 14.725	274.61 ± 11.854	275.32 ± 7.201	0.586
Total macular volume (mm ³)	7.712 ± 0.427	7.795 ± 0.269	7.778 ± 0.205	0.698
Average GCL+ (µm)	69.05 ± 10.092	71.75 ± 4.876	73.4 ± 2.197	0.173

RNFLT, retinal nerve fiber layer thickness; CMT, central macular thickness; GCL+, ganglion cell layer plus inner plexiform layer; OCT, optical coherence tomography.

Table (2) Comparison between amblyopic and fellow eyes of refractive subgroups regarding the OCT parameters.

OCT parameter	Amblyopic eyes (mean±SD)	Fellow eyes (mean±SD)	P-value
Average peripapillary RNFL (µm)			
hypermetropia	121.750 ± 8.647	116.125 ± 8.509	0.002**
myopia	81.333 ± 23.352	110.00 ± 17.578	0.044*
Astigmatism	111.888 ± 7.043	107.333 ± 6.480	0.035*
CMT (µm)			
hypermetropia	184.125 ± 9.372	191.00 ± 26.000	0.072
myopia	199.00 ± 26.851	191.00 ± 26.000	0.005**
Astigmatism	195.555 ± 18.007	188.555 ± 14.248	0.132
Average GCL+ (µm)			
hypermetropia	74.125 ± 4.015	73.750 ± 4.166	0.598
myopia	50.666 ± 14.153	65.00 ± 5.567	0.257
Astigmatism	70.666 ± 4.716	72.222 ± 3.492	0.071

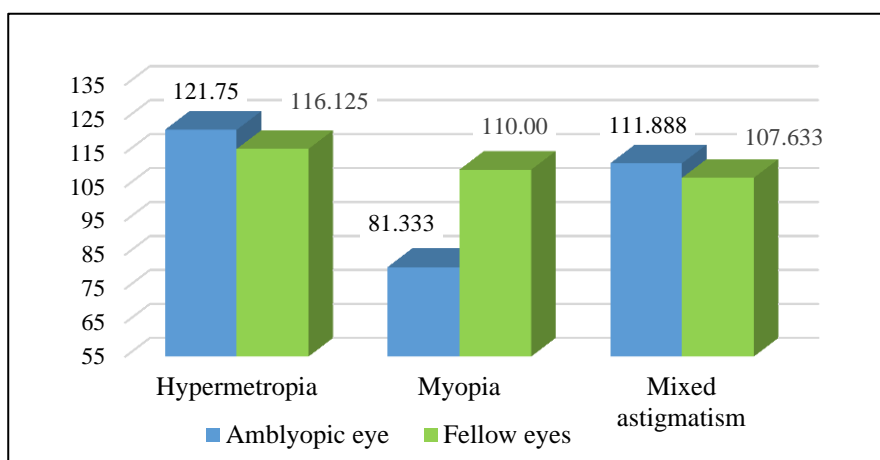


Fig (1) Bar chart indicating the comparison between amblyopic eyes and their fellow eyes in the three groups of anisometropia regarding average peripapillary RNFL thickness.

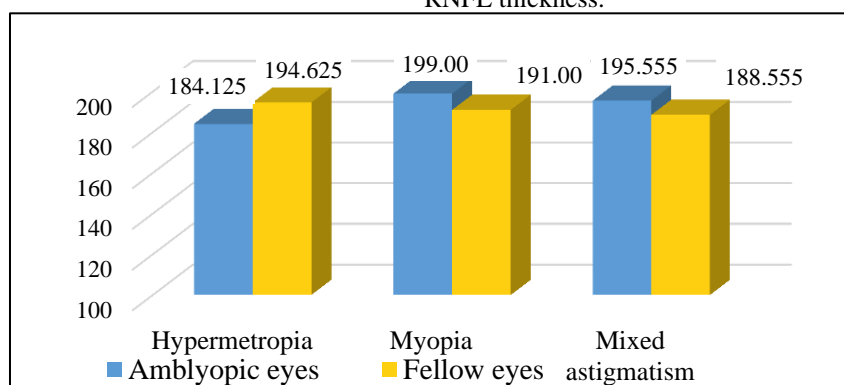


Fig (2) Bar chart indicating the comparison between amblyopic eyes and their fellow eyes in the three subgroups of anisometropia regarding CMT.

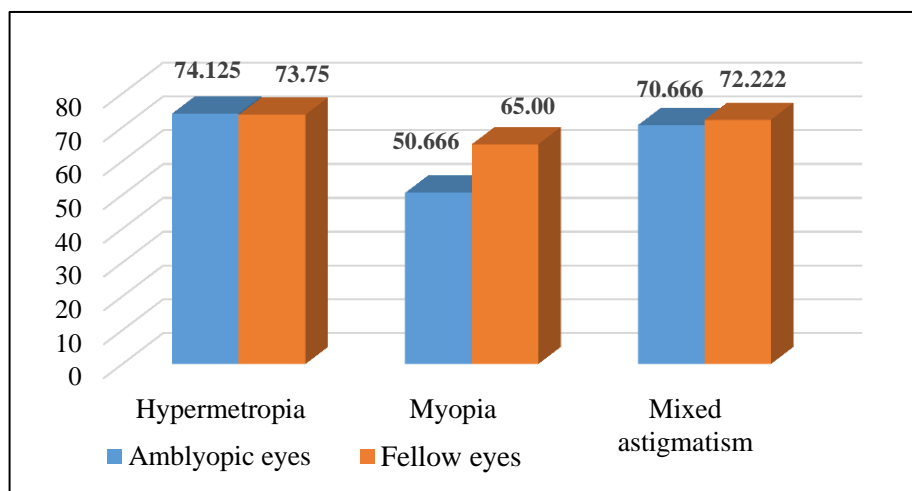


Fig (3) Bar chart indicating the comparison between amblyopic eyes and their fellow eyes in the three subgroups of anisometropia regarding GCL+ thickness.

This comparison revealed no significant difference in all OCT parameter among group A, B, and C. The results of this study corroborate a previous OCT studies. Wang and Taranath concluded 14 patients aged 5-10 years with hyperopic anisometric amblyopia and found no significant difference between amblyopic and their fellow eyes regarding peripapillary RNFL thickness, CMT, and macular volume. The mean of RNFL thickness was $103.4 \pm 12.0 \mu\text{m}$ and $103.4 \pm 17.2 \mu\text{m}$ in amblyopic and fellow eyes, respectively. The mean of macular thickness was $256.2 \pm 26.8 \mu\text{m}$ and $255.1 \pm 22.9 \mu\text{m}$ and the mean of macular volume was 10.3 ± 0.8 and $10.2 \pm 0.7 \text{mm}^3$ in amblyopic and fellow eyes, respectively [7]. Thirty six patients with unilateral amblyopia including strabismic and anisometric amblyopia (5-23 years old) and 32 emmetropic non amblyopic cases (4 -24 years old) were included in the study carried out by Firat and colleagues who reported that the mean peripapillary RNFL thickness, macular thickness, and GCC did not significantly differ among the eyes [8]. Additionally, the study by Abdulhaffar and colleagues concluded no significant difference in peripapillary RNFL, CMT, or GCL+ between amblyopic and their fellow eyes [16].

In contrast to the results yielded by the current study, other studies found a significant difference in the retinal layer thickness between amblyopic and normal eyes. In instances, Kasem and Badawi found a statistically significant increase in the CMT ($196.2 \pm 50.03 \mu\text{m}$) and RNFL thickness ($97.00 \pm 11.60 \mu\text{m}$) in the amblyopic eyes compared with their fellow eyes as the mean were $167 \pm 12.76 \mu\text{m}$ of CMT and $78.50 \pm 13.05 \mu\text{m}$ of peripapillary RNFL thickness in 64 patients aged 7-32 years old with unilateral amblyopia [15]. Similarly, El-Hifnawy et al. included 20 patients aged 15-40 years old with unilateral amblyopia and reported an increase in CMT in the amblyopic eyes ($288.65 \pm 22.61 \mu\text{m}$) versus their fellow eyes ($281.1 \pm 22.6 \mu\text{m}$). They found also an

increase in the mean thickness of the RNFL of the amblyopic eyes ($33.03 \pm 3.816 \mu\text{m}$) compared with their normal fellow eyes ($30.76 \pm 3.75 \mu\text{m}$). In the other hand, they found statistically significant decrease in the thickness of the GCL+ of the amblyopic eyes ($36.38 \pm 5.27 \mu\text{m}$) compared with their fellow eyes ($39.09 \pm 6.19 \mu\text{m}$) only at the outer macular circle [14]. Alotaibi and Enazi enrolled 93 patients with unilateral amblyopia aged 5-12 years old and concluded that the mean RNFL thickness was significantly increased in the amblyopic eyes ($112,16 \mu\text{m}$) versus the fellow eye ($106 \mu\text{m}$), but the macular thickness revealed no statistically significant difference ($P = 0.195$) [12]. Park et al. reported a significant thinning of the GCL+ in the amblyopic eye than their fellow eyes in 20 unilateral amblyopic patients aged 4-19 years old, while no significant difference was obtained regarding total macular thickness between amblyopic and their fellow eyes [17]. Kavitha et al. enrolled 60 children aged 5-18 years old (30 anisometric amblyopia patients and 30 non amblyopic subjects) and found the macular thickness was greater in amblyopic eyes ($286.9 \pm 6.52 \mu\text{m}$) than their fellow eyes ($240 \pm 10.45 \mu\text{m}$) and normal eyes of normal cases ($239.8 \pm 4.294 \mu\text{m}$), while the difference in mean RNFL thickness between amblyopic eyes ($100.87 \pm 6.24 \mu\text{m}$) and fellow eyes ($100.5 \pm 2.895 \mu\text{m}$); and normal eyes of non-amblyopic cases ($98.63 \pm 4.723 \mu\text{m}$) statistically not significant.

By applying further analysis in the present study to compare RNFL thickness in anisometric amblyopic eyes versus the fellow eyes according to SE refractive error, a significant increase was observed in both hypermetropic amblyopic eyes ($121.75 \pm 8.65 \mu\text{m}$) and astigmatic amblyopic eyes ($111.89 \pm 7.04 \mu\text{m}$) compared with the fellow eyes of the same subgroup ($116.12 \pm 8.51 \mu\text{m}$ and $107.33 \pm 6.48 \mu\text{m}$, in hypermetropic and astigmatic group respectively). In contrast, myopic amblyopic subgroup showed a significantly thinner

peripapillary RNFL in the amblyopic eyes than their fellow eyes, mean was 81.33 ± 23.35 and 110.00 ± 17.58 μm in amblyopic and fellow eyes, respectively. The study carried out by Wu and colleagues included 72 children aged 5-16 years with hyperopic anisometric amblyopia, and detected that the mean peripapillary RNFL thickness in the amblyopic eyes (113.9 ± 7.2) was significantly thicker than that of the fellow eyes ($109.2\pm 6.9\mu\text{m}$). The current study corroborated with two other studies by Tekin et al. [18] and Abdulghaffar et al. [16], which have documented a thinner RNFL in myopic amblyopic eyes than their fellow eyes.

In this study, when comparing amblyopic eyes with their fellow eyes according to SE refractive error regarding CMT, only myopic amblyopic eyes yielded a significant thicker CMT in amblyopic eyes than that of fellow eyes, mean CMT was 199.00 ± 26.851 and 191.00 ± 26.00 μm in amblyopic and fellow eyes, respectively.

Pang and colleagues reported the same result. They found a thicker CMT in the amblyopic eyes ($203.58\pm 18.33\mu\text{m}$) of 31 patients compared to their normal fellow eyes (191.00 ± 15.76 μm) [19]. Zhao and colleagues investigated changes in macular thickness associated with high myopia and reported that with an increase in myopia degree, CMT increased [20]. This can be attributed to the vitreous traction on fovea due to stretching of the sclera as a result of elongation of axial length in highly myopic eyes [21].

In contrast to our result in the current study, Singh et al. [9] and Abdulghaffar et al. [16] reported no significant difference in CMT of the amblyopic eyes in any refractive subgroup (hypermetropia, myopia, and astigmatism) compared with their fellow eyes.

B applying further analysis in the present study to compare GCL+ thickness in anisometric amblyopic eyes versus the fellow eyes according to SE refractive error, we did not find any significant difference between amblyopic and fellow eyes in any of anisometric subgroups. The current study was consistent with the study carried out by Abdulghaffar and colleagues [16]. They did not report any significant difference between amblyopic and fellow eyes in any anisometric subgroups. Mean GCL+ in amblyopic and fellow eyes in hypermetropic, myopic, and astigmatic subgroups were 80.85 ± 3.48 and 80.85 ± 3.48 , 80.50 ± 7.14 and 80.50 ± 4.89 , 81.36 ± 4.31 and 80.84 ± 5.76 μm in three subgroups, respectively.

The discrepancy in results of those mentioned previously studies may be attributed to the study design like the retinal structures that were measured and the different versions of OCT devices that were used for the studies and the use of different algorithms between OCT devices. Other factors which affected the OCT measurements presumably were the different patient's age, different number of participants, and biodiversity in races [8].

The limitations of this study was a relatively small sample size, which restrict the classification of the participants into subgroups according to the age, gender, severity of amblyopia (mild, moderate, or severe). We couldn't also divide the participants into persistent and

recovered amblyopia. Therefore, further studies with larger number of amblyopic patients are needed.

The relatively broad age range (8–30 years old), and inclusion of normal control non-amblyopic subjects in the present study are considered the points of strength because the amblyopic patients may have similar but less severe abnormalities in the fellow eyes.

5. Conclusion

The measured OCT parameters including peripapillary RNFL thickness, macular parameters including (CMT, average macular thickness, and macular volume), and GCL+ thickness showed no significant differences in amblyopic eyes (group A) as compared to normal fellow eyes (group B) and normal eyes of non-amblyopic subjects (group C).

However, by further secondary analysis to compare subgroups according to SE refractive error, peripapillary RNFL thickness revealed a significant increase in hypermetropic and astigmatic amblyopic eyes compared with their fellow eyes but it was significantly thinner in myopic amblyopic eyes than their fellow eyes. CMT revealed a significant increase in myopic amblyopic eyes only compared with their fellow eyes. Other OCT parameters did not show a significant difference between amblyopic and their fellow eyes in different subgroups.

However, more studies with greater number of patients are required to confirm these findings.

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