



Effect of Refractive Status on Peripapillary Retinal Nerve Fiber Layer Thickness and Vascular Density: A Prospective Optical Coherence Tomography Angiography-Based Study

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Abstract

Background: There have been different reports of the retinal nerve fiber layer (RNFL) thickness in myopic and hyperopic patients in optical coherence tomography (OCT)-based studies. This study was conducted to evaluate the correlation between vascular density of the optic nerve head and refractive errors in healthy subjects using OCT-angiography (OCTA).

Methods: In a prospective interventional case series, 47 healthy subjects were enrolled consequently. The target spherical equivalent was -1.00 to +1.00, -1.00 to -6.00, and +1.00 to +4.00 in the emmetropia group (A), myopia group (B), and hyperopia group (C), respectively. The astigmatism was less than 3.00 diopters in all patients. The thickness of the retinal nerve fiber layer (RNFL), the vascular density of the optic nerve head (ONH), and the peripapillary area were measured. Statistical independent samples t-tests were used to evaluate between-group differences and the hyperopia group (group C) was considered as the reference group.

Results: Eighty-eight eyes from 47 patients were included. Twenty-five eyes (28.4%) were emmetropic, 27 eyes (30.7%) were myopic, and 36 eyes (40.9%) were hyperopic. The mean rim area was significantly lower in myopic eyes than in hyperopic eyes (1.64 vs. 1.80, $P=0.039$). Although the lowest mean of RNFL thickness was observed in myopic eyes, the difference between groups was not statistically significant. The nasal radial peripapillary capillaries (RPC) were significantly lower in myopic eyes versus hyperopic (49.04 vs. 52.72, $P=0.006$). There was not any significant difference between the mean of RPC capillary inside the disc.

Conclusion: The vascular density in the RPC area was significantly lower in myopic eyes than in hyperopic and emmetropic eyes.

Keywords: Myopia, Hyperopia, Emmetropia, Optical coherence tomography angiography, Refractive error, Optic nerve head vessel density, Retinal nerve fiber layer thickness

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Introduction

Refractive errors are one of the most common causes of visual impairment in the world and the second leading cause of blindness after cataracts (1). Uncorrected refractive errors are responsible for 123.7 million people with

visual impairment in the world. Different types of ocular changes have been reported in refractive errors. In myopic patients, thinning of the retinal nerve fiber layer (RNFL), macular atrophy, chorioretinal atrophy, and thinning of the

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↑What is “already known” in this topic:

In myopic patients, thinning of the retinal nerve fiber layer (RNFL), macular atrophy, and chorioretinal atrophy have been reported using OCT-based studies. On the other hand, higher thickness of RNFL has been reported in hyperopic patients.

→What this article adds:

We found a significant reduction in the vascular density of the peripapillary area in myopic eyes using OCT-Angiography-based examination. Our study determined a significant decrease in nasal radial peripapillary capillaries (RPC) in myopic eyes compared to hyperopes and a significant increase in RPC in hyperopes compared to emmetropes and myopes.

retina have been reported. On the other hand, higher thickness of RNFL has been reported in hyperopic patients (2-5). Previous studies have evaluated the changes in macula and RNFL in patients with different refractive errors (2-5); but most of them focused on patients with myopia.

Optical coherence tomography angiography (OCTA) is a non-invasive, non-contrast, three-dimensional imaging technique to visualize large vessels as well as microvasculature of the retina and optic nerve head (ONH) (6-8). In this study, OCTA examined RNFL thickness and ONH vascular density. The central retinal artery and the posterior ciliary artery supply the ONH, and the radial peripapillary capillaries (RPC) are the main capillaries near the ONH (9). OCTA automatically divides RPC density into the peripapillary and the inside optic disc area (10).

The purpose of this study was to evaluate RNFL thickness and ONH vascular density in healthy patients with myopia, hyperopia, and emmetropia and to evaluate the relationship between refractive errors with RNFL thickness and ONH vessel density.

Methods

This prospective comparative study was carried out at the ophthalmology department of Rassoul Akram Hospital, Tehran, Iran. The control and subjects were selected from patients who requested a routine ophthalmologic examination. Informed consent was obtained from all of the enrolled subjects. The study was approved by the ethics committee of the Iran University of Medical Sciences (IR.IUMS.REC 1396.32197). Patients were categorized into three groups based on their refractive errors: myopic patients, hyperopic patients, and emmetropic patients. Inclusion criteria were generally healthy volunteer patients with age more than 18 years old with myopia, hyperopia, or emmetropia. The target spherical equivalent was -1.00 to +1.00, -1.00 to -6.00, and +1.00 to +4.00 in the emmetropia group (A), myopia group (B), and hyperopia group (C), respectively. The astigmatism was less than 3.00 diopters in all patients. Exclusion criteria were patients with a history of ocular diseases such as uveitis and ocular surface infec-

tion, those who have a history of any kinds of ocular surgeries, including intra-ocular or extra-ocular surgeries, pregnant or nursing mothers, and patients with diabetes.

All patients underwent a complete ocular examination, including best-corrected visual acuity (BCVA), comprehensive slit lamp examination, and Goldmann applanation tonometry. Measurement of axial length (AL) was carried out using the IOLMaster 700 (Carl Zeiss Meditec, Dublin, CA). All patients were examined by OCTA (RTVue-XR, AngioVue; Optovue, Fremont, CA, USA). The OCTA system has a scanning speed of 70000 A-scans per second. The radial peripapillary capillary (RPC) imaging was centered on the optic nerve head with a scan size of 4.5×4.5 mm. The optic disc OCTA scan was performed using volumetric scans in an area of 4.5×4.5 mm centered around the optic disc. The flow density of the elliptical annulus area considering from the inside annulus to 1mm outward, was then separately calculated in six regions (nasal, inferior-nasal, inferior-temporal, superior-temporal, superior-nasal and temporal) which was compatible with the Garway-Heath Map. High-quality images with (SSI) >40 were selected for the study. Two authors (AM and NA) checked all the images for any kind of OCT and OCTA errors, including segmentation errors, before consideration for analysis.

Statistical analysis

Data analysis was performed using SPSS software version 22 (IBM Corp, Armonk, NY, USA). Statistical independent t-tests were used to evaluate between-group differences and the hyperopia group (group C) was considered as the reference group. Mean and standard deviation were used to analyze continuous variables, and the categorical variables were summarized as numbers (percentages). The *P*-value of less than 0.05 was considered statistically significant.

Results

Eighty-eight eyes of 47 patients were investigated. Twenty-five eyes (28.4%) were emmetropic (group A), 27 (30.7%) were myope (group B), and 36 (40.9%) were hyperope (group C). The mean age of participants was 45.41

Table 1. Clinical and demographic characteristics of 47 subjects

Variable	Group	P-Value
Gender	Emmetropic	8(68%)/17(32%)
Male/Female (N%)	Myope	14(51.9%)/13(48.1%)
	Hyperope	28 (77.8%)/8(22.2%)
Age (Years) (Mean/SD)	Emmetropic	43.6(8.6)
	Myope	42.63(16.88)
	Hyperope	48.75(11.26)
Seq (Mean/SD)	Emmetropic	0.05(0.45)
	Myope	-1.95(0.83)
	Hyperope	1.79(0.71)
Va (Logmar) (Mean/SD)	Emmetropic	0(0)
	Myope	0(0)
	Hyperope	0.1(0.24)
Iop (Mmhg) (Mean/SD)	Emmetropic	16.96(3.56)
	Myope	15.21(2.21)
	Hyperope	15.83(2.52)
Al (Mm) (Mean/SD)	Emmetropic	22.63(0.67)
	Myope	24.39(1.34)
	Hyperope	23.06(0.71)

N: Number, SEQ: Spherical equivalent, VA: Visual acuity, IOP: Intraocular pressure, AL: Axial length, mean/SD: mean/Standard deviation. The hyperopia group was considered as reference group in two-by-two independent t-test comparison.

(± 12.83) years. Table 1 shows the clinical and demographic information of patients by group. No significant difference was found regarding age and gender between groups. The mean spherical equivalent was significantly different between groups ($P < 0.001$ for all pairwise comparisons). Results showed that AL was significantly higher in myopic eyes in comparison with emmetropic and hyperopic eyes ($P = 0.002$ and $P < 0.001$, respectively). No remarkable difference between emmetropic and hyperopic groups was detected concerning AL. The mean intraocular pressure (IOP) did not vary significantly between groups.

In Table 2, the OCT and OCTA values are presented. The

mean rim area thickness was significantly lower in myopic eyes in comparison with hyperopic ones (1.64 vs. 1.80, adj- p -value=0.039). Cup to disc (C/D) ratio and cup volume mean values were higher in myopic eyes, but the differences were not significant. Although the mean values were lower in the hyperopic group regarding C/D vertical ratio and C/D horizontal ratio, this difference was not statistically significant. The mean disc area did not vary remarkably among groups. RNFL peripapillary average has the lowest mean in myopic eyes. In hyperopic eyes, the mean of RNFL thickness was the lowest in the nasal section and highest in the temporal section. In the inferior section,

Table 2. Quantitative findings of OCT and OCT-A examinations in 47 subjects

OCT and OCT-A measures	Emmetropic (mean/SD) N=25 eyes	Myope (mean/SD) N=27 eyes	Hyperope (mean/SD) N=36 eyes
C.D.Area.Ratio	0.18(0.13) P=0.364	0.23(0.17) P=0.158	0.14(0.13)
C.D.Vertical.Ratio	0.43(0.19) P=0.242	0.43(0.29) P=0.260	0.32(0.25)
C.D.Horizontal.Ratio	0.36(0.17) P=0.257	0.37(0.25) P=0.230	0.27(0.21)
Rim.Area	1.73(0.46) P=0.745	1.64(0.36) P=0.039	1.8(0.29)
Disc.Area	2.12(0.44) P=0.922	2.16(0.32) P=0.440	2.11(0.3)
Cup.Volume	0.07(0.07) P=0.849	0.12(0.16) P=0.207	0.05(0.07)
RNFL.Peripapillary (Average)	112.24(13.09) P=0.432	107.59(10.32) P=0.194	111.17(12.03)
RNFL.Superior.	137.24(11.92) P=0.763	124.74(14.37) P=0.083	131.97(15.27)
RNFL.Inferior.	140.24(29.68) P=0.745	135.33(17.83) P=0.813	134.92(19.56)
RNFL.Temporal.	73.08(7.23) P=0.153	72.12(10.39) P=0.662	68.89(11.24)
RNFL.Nasal	102.24(14.24) 0.0803	99.96(18.91) P=0.139	109.11(24.00)
RPC.Capillary.Whole.pre %	49.58(3.39) P=0.529	47.99(2.96) P=0.047	49.93(3.24)
RPC.All.Whole.pre	56.50(3.71) P=0.162	51.56(5.54) P=0.077	54.22(5.38)
RPC.Capillary.Inside.Disc.	48.12(5.7) P=0.833	49.46(4.4) P=0.639	47.65(4.16)
RPC.All.Inside.Disc.pre	58.26(5.98) P=0.651	54.46(8.12) P=0.323	54.67(7.06)
RPC.Capillary.Peripapillary.pre	51.92(3.55) P=0.742	51.05(3.47) P=0.209	52.46(3.72)
RPC.All.Peripapillary.pre	58.65(3.74) P<0.001	52.98(6.8) 0.037	55.91(6.52)
RPC.Capillary.Superior.Hemi.pre	52.85(2.31) P=0.948	51.81(3.37) P=0.209	53.13(3.33)
RPC.All.Superior.Hemi.pre	59.67(2.70) P<0.001	53.40(7.13) P=0.065	56.26(6.75)
RPC.Capillary.Inferior.Hemi.pre	50.90(5.49) P=0.638	50.27(4.11) P=0.288	51.69(4.56)
RPC.All.Inferior.Hemi.pre	57.55(5.26) P<0.001	52.53(6.54) P=0.019	55.53(6.37)
RPC.Capillary.Superior.pre	52.64(2.93) P=0.767	52.00(3.85) P=0.334	53.36(4.67)
RPC.Capillary.Inferior.pre	51.92(8.71) P=0.918	52.15(4.78) P=0.903	52.22(5.50)
RPC.Capillary.Temporal.pre	53.28(3.96) P=0.083	51.73(4.45) P=0.617	51.72(3.74)
RPC.Capillary.Nasal.pre	49.96(4.61) P=0.072	49.04(4.18) P=0.006	52.72(6.28)

Mean/SD: mean and standard deviation, RPC: radial peripapillary capillaries, RNFL: Retinal nerve fiber layer. The RNFL and RPC unit is in microns. The hyperopia group was considered as reference group in two-by-two independent t-test comparison.

RNFL thickness has the lowest mean in emmetrope eyes. In the superior section, the mean of RNFL was varied among groups. However, none of the mean values regarding RNFL thickness, in total and by sections, were not significantly different between groups.

There was a statistically significant difference between the mean values of myopic and hyperope eyes regarding RPC capillary (47.99 in myopic vs. 49.93 in hyperopic eyes, $\text{adj-}p\text{-value}=0.047$, Table 2). Also, the mean of RPC capillary was significantly higher in hyperopic patients compared with myopic eyes in the nasal section (49.04 vs. 52.72, $\text{adj-}p\text{-value}=0.006$, Table 2). No significant difference was found in superior, inferior, and temporal sections regarding RPC capillary density (Table 2). Also, the mean of RPC capillary was nearly the same in the hemi-inferior section in all groups (Table 2). There was not any significant difference between the mean of RPC capillary inside disk, RPC.all.inside disk and RPC capillary peripapillary densities among three groups (Table 2).

As it is presented in Table 2, RPC had a lower mean in the myope group in comparison with emmetropes (56.50 vs. 51.56, $\text{adj-}p\text{-value}=0.004$). In superior and inferior hemi-sections, the mean of RPC was higher in emmetropic in comparison with hyperopic eyes (57.55 vs. 55.53, $\text{adj-}p\text{-value}<0.001$ in inferior hemi-section and 59.67 vs. 56.26, $\text{adj-}p\text{-value}<0.001$). Also, in the inferior hemi-section, the mean of RPC was significantly lower in myopic eyes than in hyperopic eyes (52.53 vs. 55.53, $\text{adj-}p\text{-value}=0.019$). RPC peripapillary was significantly higher in emmetrope eyes in comparison with hyperopes (58.65 vs. 55.91, $\text{adj-}p\text{-value}<0.001$). Also, RPC peripapillary was significantly lower in myopic eyes than in hyperopes (58.65 vs. 55.91, $\text{adj-}p\text{-value}=0.037$).

Discussion

In this prospective comparative study, we compared RNFL thickness, ONH vascular density, and AL in healthy myopic, hyperopic, and emmetropic eyes and found significant differences in vascular density of the nasal sector of RPC. This study determined a significant decrease in nasal RPC in myopic eyes compared to hyperopes and a significant increase in hyperopes compared to emmetropes and myopes. Our aim in this study was to compare vessel density of ONH in low hyperopic and myopic patients. We evaluated RNFL thickness and vessel density in our patients and compared them with normal patients. We used OCTA to compare microcirculation in patients with different refractory errors. With the help of OCTA, direct evaluation of the inner disc and radial peripapillary capillary plexus is possible. OCTA is a noninvasive vascular imaging technology that helps us to have information about the microcirculation of the retina without using intravenous dye.

High myopia with AL of more than 26 mm is associated with chorioretinal atrophy, retinal vessel, and macular changes. Salehi et al. showed that high myopic patients had a significantly lower mean of RNFL and macular thickness (11). Forty-seven studies with a total of 12223 eyes, including 8600 cases and 3623 non-cases, are included in this meta-analysis. They found that in comparison to controls,

highly myopic eyes had a significantly lower value for mean macular thickness, macular GCC, macular GC-IPL, parafoveal, perifoveal, foveal, foveolar, RNFL, and pRNFL thickness. Also, they showed that average peripapillary RNFL thickness was not significantly different between low myopes and controls. When compared to controls, eyes with hyperopia manifested thicker peripapillary RNFL on average as well as inferior segments. However, differences in the other segments were insignificant. On the other hand, some studies showed higher RNFL thickness in hyperopic patients (12). Interestingly, in most studies, temporal RNFL did not differ significantly between high myopic eyes and controls. The thinnest subsector was the inferior quadrant which corresponds to the greater reduction of vascular density in this area, which was reported by several studies. Temporal peripapillary RNFL was even thicker in high myopes, although superior, inferior, and nasal RNFL was thinner in high and moderate myopes than controls, merely similar to average RNFL (11). It should be noted that in myopic patients, optic disc tilt can be a possible cause of nasal RPC thinning. Hua Fan and colleagues have analyzed the macula's retinal vascular density in three groups, including 30 highly myopia, 33 moderate myopia, and 28 control eyes. The superficial and deep retinal vascular density of the macula were lower in high and moderate myopia than in the control eyes group (3).

Lim et al. in Singapore Malay eye study observed an association between narrower retinal arterioles and venules and longer AL and more myopic refraction (13). Also, in another study by Lim et al. on 85 eyes with myopia, hyperopia and emmetropia, lower arterial oxygen saturation was found in myopic eyes (14). In a study by Veisi Oner et al. (15), RNFL thicknesses were obtained from 35 myopic, 30 emmetropic, and 33 hyperopic subjects. Veisi et al. found that RNFL thicknesses were thinner in myopic eyes in all sectors except in the upper and lower nasal sectors (15). Retinal NFL thickness values, except for lower and upper nasal sectors, were thinner in the myopic eyes than in the hyperopic eyes, as reported by Oner et al. They found that average RNFL thickness and the RNFL thicknesses of the supratemporal, superonasal, inferotemporal, and lower temporal sectors were significantly different between the myopic and emmetropic eyes. Also, the average RNFL thickness and the RNFL thicknesses of the upper temporal and inferonasal sectors were significantly different between the hyperopic and emmetropic eyes. In comparison, in our study, RNFL thickness was lower in myopes in all sectors (compared to emmetropes and hyperopes), although the difference in thickness was not significant.

The main basic mechanism is the detection of motion contrast by flowing blood vessels. OCTA has a helpful signal processing named split-spectrum amplitude-decorrelation angiography (SSADA). This technique splits the OCT signal into different spectral bands and increases the number of useful image frames (16). With the help of OCTA, direct evaluation of the inner disc and radial peripapillary capillary plexus is possible. AL can affect OCTA images. Hyperopic patients have shorter AL, which may result in a smaller retinal area being scanned in comparison with the

defined area. This effect may be visa versa in myopic people. As mentioned earlier, vessel density in the nasal part of the optic nerve in myopic patients was lower compared with emmetropic and hyperopic eyes. Axial elongation of the eye may lead to thinning of the retina and a subsequent decrease in oxygen demand and also vascular density.

A Chinese study found a significant decrease in the average RNFL thickness in high myopia and a significant decrease in the superior and inferior RNFL thickness in moderate myopia, compared to emmetropia (17). Also, there are other previously published studies that have shown decreased vascular density in the peripapillary capillary network layer of highly myopic eye that is consistent with our results (18). Our study has its own limitations, and the most important ones is the small sample size and narrow age range of our participants. In the future, studies with larger sample sizes and including patients from different age groups and multiple races should be considered.

Conclusion

In conclusion, in this study, we observed a significant reduction in the vascular density of the peripapillary area in myopic eyes and in the nasal region. We determined a significant decrease in nasal RPC in myopic eyes compared to hyperopes and a significant increase in hyperopes in comparison to emmetropes and myopes.

Authors' Contributions

Conceptualization: AM, NA.

Methodology: AM, NA, SCH, NN

Clinical investigation: AY, NA, AMF

Data analysis: SCH, NA

Writing—original draft preparation: AMF, AY, NA

Writing—review and editing: AM, NA, NN.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all of the enrolled subjects. The study was approved by the ethics committee of the Iran University of Medical Sciences (IR.IUMS.REC 1396.32197).

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Conflict of Interests

The authors declare that they have no competing interests.

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