Effect of Prematurity on Foveal Development in Early School-Age Children

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• PURPOSE: To evaluate the foveal development in preterm children with optical coherence tomography and OCT angiography.
• DESIGN: Retrospective cohort study.
• METHODS: This study included children aged 6-8 years who were born prematurely and who did not receive retinopathy treatment. They were evaluated between September 2018 and July 2019, categorized according to gestational age (GA) (group I: GA ≤30 weeks; group II: GA between 31 and 34 weeks), and compared with full-term children (group III). Central foveal thickness (CFT), inner retinal thickness (IRT), outer retinal thickness (ORT), subfoveal choroidal thickness (CT), temporal and nasal CT, foveal avascular zone (FAZ) diameter, and vessel densities of superficial (SCP-VD) and deep capillary plexuses (DCP-VD) of the foveal and parafoveal areas were examined in detail.
• RESULTS: The study included 126 eyes of 63 patients (group I: 40 eyes; group II: 46 eyes; and group III: 40 eyes). In group I, CFT, IRT, ORT, foveal SCP-VD, and foveal DCP-VD were significantly greater than those in the other groups, and temporal CT and FAZ diameter were significantly lower ($P < .05$). GA showed a significant negative correlation with CFT, IRT, ORT, foveal SCP-VD, and foveal DCP-VD and a significant positive correlation with subfoveal CT, temporal and nasal CT, and FAZ diameter ($P < .05$).
• CONCLUSION: The morphological and vascular foveal structures in early school-age children who were born premature were different from those of full-term children. These differences were correlated with GA and more pronounced in those with GA of ≤30 weeks. (Am J Ophthalmol 2020;219:177–185. © 2020 Elsevier Inc. All rights reserved.)

THE FOVEA IS THE PORTION OF THE HUMAN RETINA critical for high visual acuity and color vision. Its early development begins at fetal week 12 and continues into childhood. Foveal cones develop into elongated cells and by 4-6 years of age, the long inner and outer segments can be observed in the retina. These processes are fully developed before 10 years of age, when the fovea displays all adult characteristics.[1]

At birth, peripheral retinal vascularization has not been completed in premature infants. Features such as incomplete peripheral retinal vascularization and macular region underdevelopment have been noted as a result of prematurity.[2] The macula in preterm infants can appear normal by indirect ophthalmoscopy; however, their foveal anatomy differs significantly from a full-term infant.[3] The fovea has an immature appearance with a shallow foveal pit, persistent inner retinal layers at the foveal center, and thin outer retinal layers in premature infants.[4] Optical coherence tomography (OCT) is an accurate imaging method to evaluate macular anatomy.[5] Persistent inner retinal layers at the foveal center and a shallow or absent foveal pit have been demonstrated in OCT studies of preterm children.[6–8]

OCT angiography (OCTA) is a noninvasive imaging method for visualization of the retinal vascular network.[9] Recently, a few studies reported foveal microvascular anomalies in children with retinopathy of prematurity (ROP) by OCTA.[10,11] However, these studies evaluated patients who previously underwent laser photocoagulation or anti–vascular endothelial factor (anti-VEGF) treatment.[12–14]

In this study, we evaluated early school-age children who were born prematurely and who did not receive retinopathy treatment. We examined the foveal and parafoveal areas in detail with OCT and OCTA. We aimed to evaluate the effect of prematurity on morphologic and vascular developments of the fovea and parafovea. We also investigated the relationship between gestational age (GA) and the vascular and morphologic structures of the fovea and parafovea.

METHODS

• STUDY PARTICIPANTS: This study was approved by the local human research ethics committee and was conducted in accordance with the tenets of the Declaration of Helsinki (2125/2018). Written informed consent was obtained from all the participants' parents or guardians.

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This retrospective cohort study included children 6-8 years of age who were preterm at birth and who had not received retinopathy treatment. These participants were evaluated between September 2018 and July 2019. As neonates, all participants were treated in our neonatal intensive care unit. The GA and birth weight (BW) of the subjects were documented. Patients were categorized into 2 groups according to GA (group I: ≤30 weeks; group II: 31-34 weeks), and their results were compared with those of full-term children (group III: ≥37 weeks GA). Group III consisted of healthy volunteers with a best corrected visual acuity (BCVA) of 20/20 using the Snellen chart and with no evidence of ocular disease in either eye.

Complete ophthalmologic examinations were performed for all participants by the same retina specialist (S.T.D). The non-cycloplegic refractive errors measured (Topcon KR-800 Auto Kerato-Refractometer, Tokyo, Japan) in the eyes were converted to spherical equivalent (SE) as the sum of the sphere value plus one-half the cylindrical value. Device calibration was performed daily, and at least 5 measurements were taken of each eye. The mean values were recorded. Examinations performed on patients included the BCVA according to the Snellen chart, and anterior and posterior segment examinations. Refractive errors noted in the subjects were checked with BCVA examination. Axial length (AL) measurements were performed using noncontact optical biometry (NIDEK Optic Biometry, AL-scan, Japan).

Children were included in the study if they had a BCVA of 20/20, normal macular aspect on fundoscopy, no history of retinopathy treatment, ability to fixate on the light target, and could maintain a stable head position during image capture.

Exclusion criteria included eyes with abnormal posterior pole findings, corneal opacities or cataracts that affected the media and prevented detailed imaging, cases without a BCVA of 20/20, children previously treated for retinopathy, patients with high refractive errors (including myopia, hyperopia, and astigmatism of >3 diopter [D]), the presence of ocular, systemic, or neurologic diseases, and children who could not cooperate with the examination, or those in whom poor imaging quality was obtained (signal strength index <6/10).

• **OPTICAL COHERENCE TOMOGRAPHY MEASUREMENTS:** *Retinal thickness measurements*. Spectral-domain OCT (SD-OCT) imaging (AngioVue, Optovue, Fremont, CA) was performed without sedation in pupils that had been previously dilated (using tropicamide 0.5% and phenylephrine 2.5% eye drops). Because the measurements from the right and left eyes of each participant were different from each other, both eyes of all subjects were examined. The foveal center was defined as the location at which the foveal pit was deepest. The measurements were made in the following areas: a 1- × 1-mm circle on the fovea, and a 3- × 3-mm annulus in the parafoveal region. The parafoveal area was examined in the nasal, superior, temporal, and inferior quadrants. The same observers (M.K., M.D.) carried out all measurements.

The values of central foveal thickness (CFT), inner retinal thickness (IRT), outer retinal thickness (ORT), parafoveal nasal retinal thickness (RT), parafoveal superior RT, parafoveal temporal RT, and parafoveal inferior RT were measured automatically. The CFT was measured as the distance from the deepest point of the foveal pit to the inner border of the retinal pigment epithelium (RPE). The IRT was defined as the area between the inner border of the outer plexiform layer and the internal limiting membrane within the central fovea. The ORT was defined as the area between the inner border of the outer plexiform layer and the inner border of the RPE within the central fovea.

Choroidal thickness measurements. Choroidal thickness (CT) was defined as the distance between the base of the RPE and choroidoscleral boundary. To exclude diurnal variations, all examinations were performed at the same time of day (12-2 PM). Each measurement was performed at the subfoveal and 0.75 mm and 1.5-mm nasal (N1CT, N2CT) and temporal (T1CT, T2CT), respectively, to the fovea using the manual calipers provided with the software of the device.

• **OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY MEASUREMENTS:** *Foveal avascular zone diameter*. All eyes were examined by AngioVue OCTA (AngioVue, Optovue) with a scan of 3 × 3 mm centered on the fovea. The foveal avascular zone (FAZ) is an area on the central fovea that is free from retinal capillaries. The FAZ area (in mm^2) was determined from the en face OCTA images. The FAZ diameter was automatically calculated using the nonflow mode in each image of the auto-segmented retina.

Vessel density. The automated segmentation of the superficial capillary plexuses (SCP; slab from the internal limiting membrane to the inner plexiform layer) and deep capillary plexuses (DCP; slab from the inner plexiform layer to the outer plexiform layer) were obtained using the manufacturer's built-in software. Automatic segmentation was controlled by the investigators. The density of the vessels (%) of the autosegmented SCP and DCP was also measured automatically by the vessel density (VD) mode. The foveal and parafoveal areas were also measured automatically; a 3- × 3-mm circle as the whole image, a 1- × 1-mm circle of the fovea, and a 3- × 3-mm annulus of the parafovea. The parafoveal area was examined in the nasal, superior, temporal, and inferior quadrants.

Flow area in the outer retinal and choriocapillaris layer. The automated segmentation of the outer retina (OR; slab from the outer plexiform layer to RPE) and the choriocapillaris

TABLE 1. Distribution of Age, Sex, Gestational Age, Birth Weight, Axial Length, and Spherical Equivalent of All Groups

	Group I (n = 20) n (31.7%)	Group II (n = 23) n (36.5%)	Group III (n = 20) or n (31.7%)	*P* Value
GA (wk), mean ± SD	28.7 ± 1.6	32.4 ± 0.9	39.7 ± 0.7	**< 0.001**[a]
BW (g), mean ± SD	1040 ± 253	1740 ± 212	3197 ± 333	**< .001**[a]
Age (y), mean ± SD	7.0 ± 0.8	7.0 ± 0.8	7.0 ± 0.8	.870[a]
Sex, n (%)				
Female	26 (65)	24 (52.2)	22 (55)	.461[b]
Male	14 (35)	22 (47.8)	18 (45)	
Axial length (mm), mean ± SD	22.5 ± 0.9	22.4 ± 0.6	22.6 ± 0.9	.321[a]
Spherical equivalent (D), mean ± SD	0.44 ± 0.7	0.24 ± 0.88	0.38 ± 0.5	.055[a]
Zone of ROP				**< .001**[a]
1	2	0		
2	17	6		
3	1	16		
Stage of ROP				**< .001**[a]
0	1	15		
1	11	8		
2	8	0		

BW = birth weight; D = diopter; GA = gestational age; ROP = retinopathy of prematurity.
Statistically significant *P* values were given in boldface.
[a]Kruskal-Wallis (Mann-Whitney U) test.
[b]χ^2 test.

(CC; slab 29-49 μm under the RPE) were obtained using the manufacturer's built-in software. Automatic segmentation was controlled by the investigators to prevent misalignments. The flow area (in mm^2) of the OR and CC layers was also measured automatically by flow mode.

• **STATISTICAL ANALYSIS:** Mean, SD, and ratio values were used to describe statistics of the data. Distribution of variables was measured using the Kolmogorov-Smirnov test. Analysis of variance (Tukey test), Kruskal-Wallis test, and the Mann-Whitney U test were used for analysis of quantitative independent data. The χ^2 test was used to analyze independent data. Pearson's and Spearman's correlations were used for correlation analysis. Correlation coefficients (r value) of 0.2-0.4, 0.4-0.6, 0.6-0.8, and >0.8 were considered to be weak, mild, moderate, and strong correlations, respectively. SPSS 22.0 program (SSPS, IBM, Armonk, NY) was used in the analyses.

RESULTS

A TOTAL OF 126 EYES IN 63 PARTICIPANTS WERE ELIGIBLE FOR inclusion: 40 eyes in the ≤30 weeks' GA group (group I); 46 eyes in the 31-34 weeks' GA group (group II), and 40 eyes in the full-term children group (group III: ≥37 weeks' GA). The distribution of age, sex, GA, BW, AL, SE, zone of vascularization, and maximum stage of ROP of the patients is shown in Table 1. There was a significant difference between the groups with respect to BW and the zone of vascularization and maximum stage of ROP ($P < .001$). A positive correlation was found between GA and BW. There were no significant differences in the mean age, sex distribution, mean AL, and SE among the groups ($P > .05$).

• **OPTICAL COHERENCE TOMOGRAPHY MEASUREMENTS:** *Retinal thickness measurements*. The mean CFT, IRT, ORT, parafoveal temporal RT, parafoveal superior RT, parafoveal nasal RT, and parafoveal inferior RT values of the groups are shown in Table 2 (Figure A) Tthe mean RT parameters decreased gradually from group I to group III. The mean CFT, IRT, and ORT of group I were significantly higher than that of other groups. The mean CFT of group II was significantly higher than that of group III ($P < .05$). The mean nasal parafoveal RT of groups I and II was significantly higher than that of group III ($P < .05$). The differences in the mean nasal parafoveal RT between group I and group II were not significant ($P > .05$). The mean parafoveal temporal, superior, and inferior RTs were not significantly different among the groups ($P > .05$).

Choroidal thickness measurements. The mean subfoveal CT, N1CT, N2CT, T1CT, and T2CT values of the groups are shown in Table 2 (Figure B). The mean all CT parameters increased gradually from group I to group III.

TABLE 2. The Optical Coherence Tomography and Optical Coherence Tomography Angiography Findings of All Groups

Location	Group I (n = 40 eyes) (mean ± SD) or n (31.7%)	Group II (n=46 eyes) (mean ± SD) or n (36.5%)	Group III (n = 40 eyes) (mean ± SD) or n (31.7%)	*P* Value
CFT (μm)	29 ± 15.4[a,b]	249.3 ± 16.6[c]	240.9 ± 21.9	**< .001**[d]
IRT (μm)	75.2 ± 14.6[a,b]	71.7 ± 12.3	69.0 ± 13.1	**.011**[d]
ORT (μm)	184.5 ± 14.3[a,b]	178.1 ± 13.7	172.1 ± 11.5	**< 0.001**[d]
Parafoveal temporal RT (μm)	304.3 ± 12.8	301.9 ± 19.2	298.4 ± 11.5	.078[d]
Parafoveal superior RT (μm)	315.8 ± 11.4	315.8 ± 19.5	313.6 ± 13.5	.344[d]
Parafoveal nasal RT (μm)	317.2 ± 12.1[b]	316.1 ± 20.4[c]	302.6 ± 48.5	**.006**[d]
Parafoveal inferior RT (μm)	313.6 ± 13.7	312.1 ± 19.8	308.2 ± 11.1	.097[d]
Subfoveal CT (μm)	318.9 ± 58.7	320.5 ± 63.6	339.2 ± 55.1	.163[d]
N1CT (μm)	302.2 ± 60.5	306.4 ± 67.4	327.8 ± 56.1	.140[e]
N2CT (μm)	271.6 ± 60.8	271.9 ± 69.0	294.7 ± 61.1	.165[e]
T1CT (μm)	313.4 ± 51.6[b]	313.5 ± 53.7[c]	336.2 ± 52.0	**.038**[d]
T2CT (μm)	301.5 ± 50.7[b]	301.5 ± 59.7[c]	326.4 ± 59.5	**.018**[d]
FAZ (mm^2)	0.16 ± 0.09[a,b]	0.22 ± 0.09	0.28 ± 0.13	**< .001**[e]
Foveal SCP-VD (%)	24.4 ± 6.3[a,b]	21.3 ± 5.3	20.6 ± 6.8	**.014**[d]
Parafoveal SCP-VD (%)	50.8 ± 3.1	50.9 ± 3.1	50.8 ± 3.8	.907[d]
Parafoveal temporal SCP-VD (%)	49.2 ± 3.6	49.7 ± 2.9	50.3 ± 3.1	.303[d]
Parafoveal superior SCP-VD (%)	51.7 ± 3.1	52.1 ± 3.6	51.4 ± 3.1	.286[d]
Parafoveal nasal SCP-VD (%)	49.78 ± 4.2	49.79 ± 3.6	50.76 ± 3.0	.550[d]
Parafoveal inferior SCP-VD (%)	52.27 ± 3.3	51.79 ± 3.8	51.82 ± 3.7	.823[d]
Foveal DCP-VD (%)	40.52 ± 6.5[a,b]	37.53 ± 5.9	35.30 ± 8.6	**.006**[d]
Parafoveal DCP-VD (%)	54.98 ± 3.6	55.08 ± 3.8	54.44 ± 3.9	.563[d]
Parafoveal temporal DCP-VD (%)	55.49 ± 3.3	55.90 ± 3.3	55.30 ± 3.1	.328[d]
Parafoveal superior DCP-VD (%)	55.26 ± 4.5	54.95 ± 4.7	53.75 ± 4.3	.209[d]
Parafoveal nasal DCP-VD (%)	55.25 ± 3.80	55.68 ± 3.95	54.33 ± 3.92	.198[d]
Parafoveal inferior DCP-VD (%)	54.16 ± 4.37	54.16 ± 4.66	53.53 ± 4.61	.597[d]
Outer retina flow area (mm^2)	0.63 ± 0.44	0.71 ± 0.42	0.63 ± 0.35	.512[d]
Choriocapillaris flow area (mm^2)	2.18 ± 0.13	2.16 ± 0.12	2.18 ± 0.11	.572[d]

CFT = central foveal thickness; CT = choroidal thickness; DCP-VD = vessel densities of deep capillary plexuses; FAZ = foveal avascular zone diameter; IRT = inner retinal thickness; N1CT = choroidal thickness 0.75 mm nasal to the fovea; N2CT = choroidal thickness 1.5 mm nasal to the fovea; ORT = outer retinal thickness; RT = retinal thickness; SCP-VD = vessel densities of superficial capillary plexuses; T1CT = choroidal thickness 0.75 mm temporal to the fovea; T2CT = choroidal thickness 1.5 mm temporal to the fovea.

Statistically significant *P* values were given in boldface.

[a]Group I versus group II; $P < .05$.

[b]Group I versus group III; $P < .05$.

[c]Group II versus group III; $P < .05$.

[d]Kruskal-Wallis (Mann-Whitney U test).

[e]Analyis of variance (Tukey test).

The mean T1CT and T2CT were significantly lower in group I and group II than that in group III ($P < .05$). The mean T1CT and T2CT were not significantly different between group I and group II ($P > .05$). The mean subfoveal CT, N1CT, and N2CT values were not significantly different among the groups ($P > .05$). In all groups, the mean CT values were arranged as follows: subfoveal CT > T1CT > N1CT > T2CT > N2CT.

• **OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY MEASUREMENTS:** *Foveal avascular zone diameter*. The mean FAZ values of the groups are shown in Table 2 (Figure C). The mean FAZ diameter increased gradually from group I to group III. In group I, the mean FAZ diameter was significantly lower than those in the other groups ($P < .05$). The mean FAZ diameter was not significantly different between group I and group II ($P > .05$).

Vessel density. The mean foveal SCP-VD, parafoveal SCP-VD, foveal DCP-VD, and parafoveal DCP-VD values of the groups are shown in Table 2 (Figure D). The mean foveal SCP-VD and foveal DCP-VD decreased gradually from group I to group III. In group I, the mean foveal SCP-VD and foveal DCP-VD were significantly lower than those in the other groups ($P < .05$). There was no

TABLE 3. The Correlation Data Between Gestational Age and Birth Weight and Optical Coherence Tomography and Optical Coherence Tomography Angiography Findings.

	GA (wk)		BW (g)	
Location	r	*P* Value	r	*P* Value
CFT (μm)	−0.439	**.000**	−0.381	**< .001**
IRT (μm)	−0.290	**.001**	−0.248	**.005**
ORT (μm)	−0.395	**.000**	−0.348	**< .001**
Parafoveal temporal RT (μm)	−0.171	.055	−0.178	**046**
Parafoveal superior RT (μm)	−0.056	.532	−0.074	.413
Parafoveal nasal RT (μm)	−0.233	**.009**	−0222	**.012**
Parafoveal inferior RT (μm)	−0.124	.165	−0.141	.115
Subfoveal CT (μm)	0.176	**.048**	0.202	**.023**
N1CT (μm)	0.239	**.007**	0.229	**.010**
N2CT (μm)	0.214	**.016**	0.218	**.014**
T1CT (μm)	0.216	**.015**	0.248	**.005**
T2CT (μm)	0.196	**.028**	0.216	**.015**
FAZ (mm^2)	0.474	**.000**	0.414	**< .001**
Foveal SCP-VD (%)	−0.317	**.000**	−0.276	**.002**
Parafoveal SCP-VD (%)	0.053	.554	−0.005	.953
Parafoveal temporal SCP-VD (%)	0.147	.100	0.101	.258
Parafoveal superior SCP-VD (%)	−0.018	.845	−0.063	.481
Parafoveal nasal SCP-VD (%)	0.094	.303	0.047	.609
Parafoveal inferior SCP-VD (%)	−0.047	.600	−0.109	.225
Foveal DCP-VD (%)	−0.353	**000**	−0.301	**.001**
Parafoveal DCP-VD (%)	−0.124	.165	−0.085	343
Parafoveal temporal DCP-VD (%)	−0.102	.257	−0.077	.389
Parafoveal superior DCP-VD (%)	−0.165	.066	−0.144	.107
Parafoveal nasal DCP-VD (%)	−0.096	.295	−0.084	.357
Parafoveal inferior DCP-VD (%)	−0.103	.251	−0.064	.478
Outer retina flow area (mm^2)	0.083	.357	0.096	.283
Choriocapillaris flow area (mm^2)	−0.086	.339	−0.100	.267

BW = birth weight; CFT = central foveal thickness; CT = choroidal thickness; DCP-VD = vessel densities of deep capillary plexuses; FAZ = foveal avascular zone diameter; GA = gestational age; IRT = inner retinal thickness; N1CT = choroidal thickness 0.75 mm nasal to the fovea; N2CT = choroidal thickness 1.5 mm nasal to the fovea; ORT = outer retinal thickness; RT = retinal thickness; SCP-VD = vessel densities of superficial capillary plexuses; T1CT = choroidal thickness 0.75 mm temporal to the fovea; T2CT = choroidal thickness 1.5 mm temporal to the fovea.

Spearman correlation analysis.

Statistically significant *P* values were given in boldface.

significant difference between group I and group II ($P > .05$). The mean parafoveal SCP-VD and parafoveal DCP-VD were not significantly different among the groups ($P > .05$).

Flow area in the outer retinal and choriocapillaris layer. The mean outer retina flow area and choriocapillaris flow area values of the groups are shown in Table 2. The mean outer retina flow area and choriocapillaris flow area were not significantly different among the groups ($P > .05$).

• **CORRELATION OF GESTATIONAL AGE AND BIRTH WEIGHT WITH OTHER VALUES:** The correlation of data between GA and BW and between the OCT and OCTA values are shown in Table 3. There was a significant negative correlation between GA and CFT, IRT, ORT, parafoveal nasal RT, foveal SCP-VD, and foveal DCP-VD ($P < .05$). There was a significant positive correlation between GA and FAZ diameter, subfoveal CT, N1CT, N2CT, T1CT, and T2CT ($P < .05$).

There was a significant negative correlation between BW and CFT, IRT, ORT, parafoveal nasal RT, parafoveal temporal RT, foveal SCP-VD, and foveal DCP-VD ($P < .05$). There was a significant positive correlation between BW and FAZ diameter, subfoveal CT, N1CT, N2CT, T1CT, and T2CT ($P < .05$).

• **OTHER CORRELATIONS:** There was a significant negative correlation between FAZ diameter and CFT, IRT,

ORT, foveal SCP-VD, and foveal DCP-VD (all $P < .001$; $r = -0.774$, -0.721, -0.452, -0.788, and -0.881, respectively). In addition, there was a significant positive correlation between CFT and foveal SCP-VD and foveal DCP-VD (all $P < .001$; $r = 0.616$ and 0.707, respectively).

DISCUSSION

THIS STUDY WAS A CROSS-SECTIONAL QUANTITATIVE comparative study that examined morphologic and vascular parameters of the fovea in early school-age children who were premature at birth and who were previously untreated for retinopathy compared with children born full-term. This comparison was made using OCT and OCTA. The RT, CT, FAZ diameter, and VD of the foveal and parafoveal areas were evaluated in detail. The analysis of foveal morphology in this study showed a significantly higher CFT, IRT, ORT, parafoveal nasal RT, foveal SCP-VD, and foveal DCP-VD but a significantly lower FAZ diameter and temporal CT in preterm children compared with full-term control subjects. There was a significant negative correlation of GA and BW with CFT, IRT, ORT, parafoveal nasal RT, parafoveal temporal RT, foveal SCP-VD, and foveal DCP-VD, whereas a significant positive correlation was found when GA and BW were compared with FAZ diameter, subfoveal CT, and temporal CT.

Histologic studies demonstrated that macular development begins at approximately 24 weeks of GA.[1,15] The foveal pit begins to develop at 24-27 weeks.[16] The process of foveal maturation includes centripetal displacement of photoreceptors and centrifugal displacement of inner retinal layers. Photoreceptor differentiation with outer segment elongation occurs almost entirely after birth and continues until nearly 4 years of age.[8] Preterm birth causes a failure of the inner retinal neurons to migrate away from the fovea and an elevated outer nuclear layer ratio.[17] OCT has allowed macular abnormalities to be recognized in ROP and to assist in the understanding of the underlying pathogenesis.[18] OCT studies showed a thick outer nuclear layer and retention of the retinal ganglion cell layer, inner plexiform layer, and inner nuclear layer at the fovea of patients with ROP.[19–21] Publications indicated the presence or absence of correlation between GA and retinal thickness.[7,19,22] In our study, CFT, IRT, ORT, and parafoveal nasal RT were significantly thicker in early school-age children who were born prematurely compared with those born full-term. There was a significantly negative correlation of GA and BW with CFT, IRT, ORT, and parafoveal nasal RT. All cases in this study had foveal pit cystoid spaces, and none had intraretinal cystoid spaces, dome-shaped foveal elevation, or deterioration of outer retinal layers. In contrast to previous studies, we found that the ORT and parafoveal nasal RT were thicker in premature children. Thicker CFT, IRT, ORT, and parafoveal nasal RT may be a marker of prematurity.

The outer neuroretina is known to consume large amounts of oxygen.[23] Therefore, the choroid supplies increased blood flow to the outer retina.[24] In contrast to an increased foveal thickness, a marked reduction in central and temporal CT was demonstrated in patients with ROP.[21,25,26] Erol et al.[27] measured subfoveal CT in preterm infants at 36 weeks and full-term infants at 42 weeks GA, and 51% of the patients in this study had cystoid macular edema. They observed that the nasal CT was significantly thicker than the temporal CT in premature infants. Anderson et al.[26] reported that there was no correlation of subfoveal CT with GA and BW. In our study, temporal CT was significantly thinner in early school-age children who were born prematurely compared with those born full-term. Although subfoveal CT and nasal CT were thinner, there were no statistically significant differences. The CT was similar in group I (≤30 weeks GA) and in group II (31-34 weeks GA). In contrast to the study by Erol et al., temporal CT was found to be greater than nasal CT in this study. The difference between these studies might be due to the age range of patients and the presence of cystoid macular edema. There was a significantly positive correlation of GA and BW with subfoveal CT, temporal CT, and nasal CT.

VEGF plays an important role in the growth of retinal vessels into the fovea, but angiostatin inhibits vascular ingrowth.[28] The balance between VEGF and angiostatin is the key point in maintaining the FAZ area. Thus, an increased level of VEGF may disrupt the balance, resulting in a small or absent FAZ in children with ROP.[14] In the literature, a smaller or absent FAZ diameter was reported in children born prematurely compared with control subjects.[14,17,29] With OCTA, Chen et al.[14] demonstrated the presence of higher foveal vascular density in patients with ROP with a history of anti–vascular endothelial factor agent treatment. They found a significant positive correlation between foveal VD and foveal thickness. In addition, GA and BW were both significantly correlated with FAZ area and foveal VD. Balasubramanian et al.[30] compared preterm children who underwent laser treatment with untreated preterm children and control groups. They published similar results to previously described studies. However, Nanobe et al.[11] showed that there was no difference in VD in the fovea of children with a history of ROP that required treatment, whereas parafoveal VD was lower. In our study, early school-age children who were born prematurely had a smaller FAZ diameter and higher foveal VD of SCP and DCP compared with full-term children. There was no difference in the parafoveal VD. There were no cases in which the FAZ diameter could not be measured. There was a significant relationship between FAZ diameter and both RT and foveal VD. Also, there was a significant positive correlation between CFT and foveal VD. We found a significant negative correlation of GA and BW

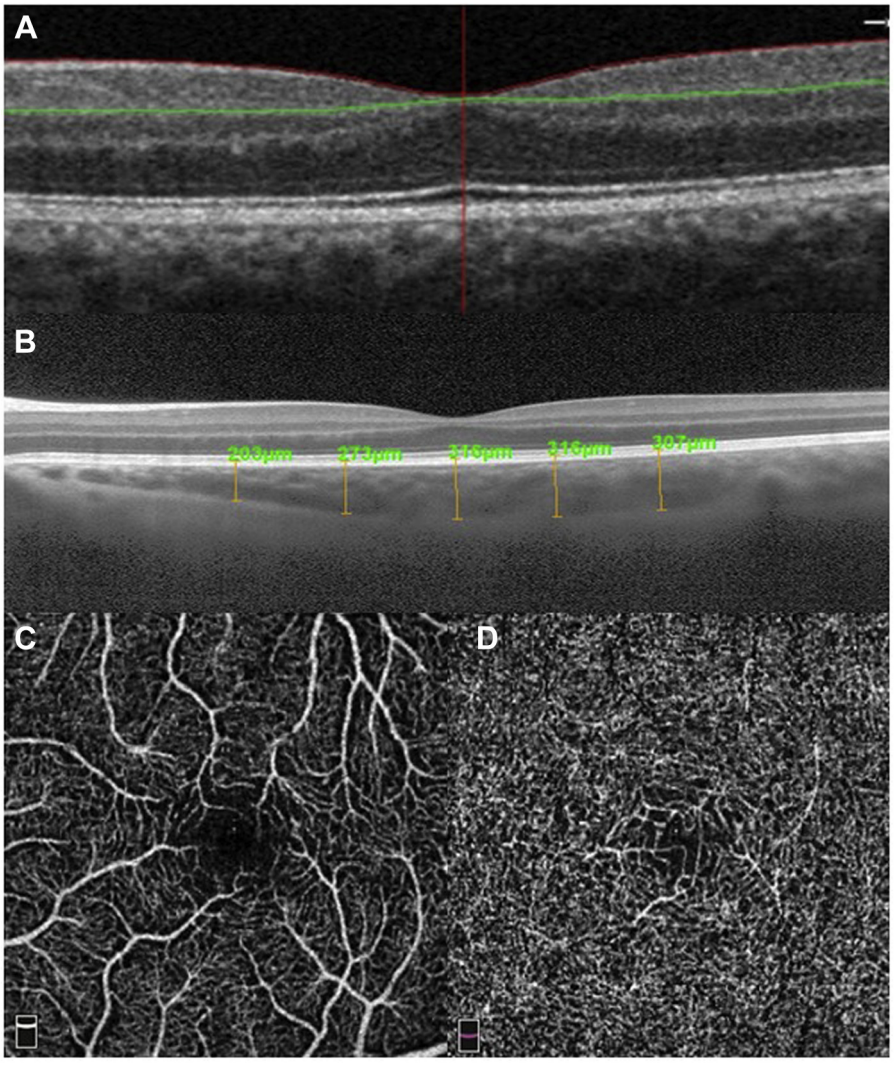

FIGURE. Examples optical coherence tomography and optical coherence tomography angiography images of patients demonstrate measurement of central foveal thickness, choroidal thickness, and the foveal avascular zone. A. Macula optic coherence tomography image of a 7-year-old girl born at 28 weeks' gestational age. The green line shows the separation of the inner and outer retina. B. Subfoveal, nasal, and temporal choroidal thickness measurements of a 6-year-old boy born at 32 weeks' gestational age. C. Foveal avascular zone image in the superficial capillary plexus of a 7-year-old girl born at 27 weeks' gestational age. D. Foveal avascular zone image of the same case in the deep capillary plexus.

with foveal SCP-VD and foveal DCP-VD, whereas a significant positive correlation was found with FAZ diameter.

There are many valuable conclusions that can be gained from our study. In contrast to other studies in the literature, we evaluated only early school-age children who were born prematurely and not treated for retinopathy. Patients who underwent laser photocoagulation and anti-VEGF were excluded. There were no amblyopia cases, the SE values were low, and there was no difference between ALs. There are publications in the literature in which SE and AL affected OCTA vascular parameters. A negative correlation between vascular parameters and AL and SE was also reported.[31,32] There were no factors that could affect the OCT and OCTA data. Therefore, the groups were homogeneously distributed. This study also discussed the correlation between RT and foveal microvascular anomalies. Furthermore, we assessed the changes according to GA and BW.

There were some limitations to our study. First, the study included a limited number of patients. Second, our study was a retrospective study. Third, we did not perform subgroup analysis according to the ROP zone and stage. Fourth, because the data were not necessarily the same between the eyes, we used the data from both eyes of an individual, which might have affected the results.

In conclusion, the OCT and OCTA are useful noninvasive methods to evaluate the morphology and vasculature of the fovea and the parafovea in early school-age children who were born prematurely. Even if fundus examination

appears normal, morphologic and vascular differences may exist between the fovea and parafovea of early school-age children who were born prematurely and those who were born full-term. These differences are more pronounced in the fovea compared with the parafovea. The morphologic and vascular structure of the fovea correlated with GA and BW. Future studies with a larger sample size will be needed to understand the clinical significance of structural and vascular characteristics in the fovea of untreated prematurely born children.

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