Analysis of Spectral-Domain Optical Coherence Tomography in Preterm Children: Retinal Layer Thickness and Choroidal Thickness Profiles

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Purpose. To compare retinal layer thickness and choroidal thickness profiles in preterm and full-term children using spectral-domain optical coherence tomography (SD-OCT).

Methods. We performed horizontal and vertical SD-OCT crosshair scans through the fovea with and without an enhanced depth technique in 31 premature and 30 full-term children. Retinal layer and choroidal thicknesses were measured at various locations including the fovea and 1.0 and 3.0 mm nasal, temporal, superior, and inferior to the fovea. After adjusting for age and the child's axial length, we compared retinal layer and choroidal thicknesses at the measurement points.

Results. Total retinal thickness and outer nuclear layer (ONL) thickness at the foveal center in preterm children (256.00 ± 30.71 μm, 141.87 ± 28.75 μm, respectively) were larger than those in full-term children (217.57 ± 10.64 μm, 101.22 ± 10.90 μm, respectively, $P < 0.001$). Gestational age at birth was inversely correlated with both total retinal and ONL thicknesses ($P < 0.001$). Choroidal thickness 3.0 mm temporal to the fovea in preterm children (283.75 ± 60.47 μm) was significantly less than that in full-term children (339.89 ± 90.32, $P = 0.010$). Retinopathy of prematurity staging showed a marginal inverse correlation with choroidal thickness 3.0 mm temporal to the fovea ($P = 0.053$). Visual acuity in preterm children was not correlated with retinal thickness or choroidal thickness.

Conclusions. Our SD-OCT data demonstrated an increased total retinal thickness and ONL thickness at the foveal center and decreased choroidal thickness 3.0 mm temporal to the fovea in preterm children. Further studies are needed to better understand the association between these structural changes and visual functions in preterm children. (*Invest Ophthalmol Vis Sci.* 2012;53:7201–7207) DOI:10.1167/iovs.12-10599

The visual system is one of the last systems to develop structurally and functionally in human fetuses.[1] Vasculogenesis begins in the central retina 24 to 28 weeks after conception, and the peripheral retina is vascularized at 40 weeks.[2] The differentiation and maturation of the fovea and macular retinal layers begin 24 to 27 weeks after conception and continue until 8 months of age.[3–5] Foveal development includes centrifugal migration of inner retinal neurons away from the fovea and the continuation of the centripetal migration of cone cell nuclei toward the foveal center.[2] Preterm birth immensely changes the infant's environment, and evidence suggests that this could lead to the disruption of normal retinal development and function. The most common retinal defect associated with preterm birth is a vascular disorder called retinopathy of prematurity (ROP), which can cause enormous ocular complications associated with neovascularization. Studies suggest that ROP can cause both peripheral and central retinal visual disorders, as demonstrated by defective cone and rod functions.[6,7] Recent studies using optical coherence tomography (OCT) have revealed that preterm children have thicker central maculae than that of children born at term, regardless of the presence of ROP.[8,9] Another recent study has shown that premature birth is associated with the failure of inner retinal layers to migrate away from the fovea, resulting in increased foveal thickness in patients with ROP.[10]

In contrast to an increased foveal thickness in patients with ROP, markedly deficient vascularity in the central choroid and choriocapillaries was recently reported as an important contributor to central photoreceptor compromise in the oxygen-induced retinopathy animal model of ROP.[11] Choroidal vascular involution can cause decreased oxygen and nutrient delivery to the outer retina. This decreased perfusion can affect photoreceptor signal generation or lead to the loss of overlying photoreceptors. However, to the authors' knowledge, there have been no published reports on choroidal development in human prematurity.

In our study we compared retinal layer and choroidal thickness profiles in preterm and healthy, full-term children using spectral-domain OCT (SD-OCT) with and without an enhanced depth technique. We discuss distinct foveal morphology and choroidal thickness profiles in preterm children compared with those in full-term children.

Methods

This prospective study was performed at a single center according to the tenets of the Declaration of Helsinki. The protocols used in this study were approved by the Institutional Review Board of the Samsung Medical Center, and written informed consent was obtained from either the patients or their legal guardians before enrollment.

Our study involved two groups of children aged 4 to 10 years old: 31 preterm children and 30 healthy, full-term children, who visited the pediatric ophthalmology clinic for routine ocular examinations between October 1, 2011 and March 31, 2012. Inclusion criteria for preterm children included birth before 35 weeks gestational age. All preterm children had previously received ROP screening starting at 5 weeks old and repeated at least every other week. ROP screening

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continued until the retina was fully vascularized or, in the case of children with ROP, until ROP had resolved completely. The criterion for the treatment of ROP was stage 3 disease in at least four contiguous clock hours, even in the absence of plus disease. Inclusion criteria for the full-term children included birth at term and normal birth weight. These children have participated as normal healthy children in the study of choroidal thickness in healthy children in the same department. Only children older than 4 years of age were included, because younger children were unable to cooperate with the OCT examination. Exclusion criteria included a history of stage 4 or stage 5 ROP, previous eye trauma, previous eye surgery, or the inability to cooperate with the OCT examination. Only right eyes were included in the study. We classified stages 1 to 2 ROP as mild and stage 3 ROP as severe, even in children who received laser treatment.

All subjects underwent full ophthalmologic assessments, including visual acuity testing, cycloplegic refraction, slit-lamp biomicroscopy, and fundus examination. Refractions were performed using retinoscopy after the instillation of 1% cyclopentolate and 0.5% tropicamide. Ocular axial length (AXL) was measured using interferometry (IOLMaster; Carl Zeiss Meditec, La Jolla, CA). Horizontal and vertical OCT crosshair scans were performed with SD-OCT (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany), which provided 40,000 A-scans per second with 7 μm optical and 3.5 μm digital axial resolution. We obtained horizontal and vertical SD-OCT scans through the fovea, consisting of 512 A-scans per line, in each patient. An internal fixation target was used, and the patient's opposite eye was covered during scanning. Enhanced depth imaging OCT was conducted in every patient according to a previously described method.[12,13] The choroid was imaged by positioning an OCT camera close enough to the eye to obtain an inverted image. All of the measurements in the current study were performed using a 1:1 micrometer image. Using a commercial software package (Heidelberg Eye Explorer software, version 1.7.0.0; Heidelberg Engineering GmbH), the thicknesses of the eight retinal layers were measured manually from OCT images without an enhanced depth technique as previously described. The eight retinal layers measured included the retinal nerve fiber layer (RNFL), the ganglion cell layer plus the inner plexiform layer (GCL+IPL), the inner nuclear layer (INL), the outer plexiform layer (OPL), the outer nuclear layer (ONL), the inner segment of the photoreceptor layer (IS), the outer segment of the photoreceptor layer (OS), and the retinal pigment epithelium (RPE).[14] Choroidal thicknesses were measured manually via enhanced depth images. Subfoveal choroidal thickness was defined as the distance from the hyperreflective line of the subfoveal Bruch's membrane to the innermost hyperreflective line of the subfoveal choriosclera interface. Each measurement was performed at the fovea and 1.0 and 3.0 mm nasal, temporal, superior, and inferior to the fovea (Fig. 1). Two observers blinded as to whether the child was preterm or full-term performed the measurements twice for all subjects, and the mean value of the two measurements was used for analysis.

Statistical analyses were performed using an analytical software package (SAS software, version 9.2; SAS Institute, Inc., Cary, NC). The thickness of each retinal layer and choroidal thickness profiles were compared in preterm and full-term children using a mixed model, adjusting for time, tester, the patient's AXL, and the patient's age at the time of examination. Correlation between retinal layer and choroidal thicknesses and multiple factors including gestational age at birth, birth weight, ROP stage, and laser treatment were also analyzed using a mixed model, adjusting for time, tester, the patient's AXL, and the patient's age at the time of examination. Due to multiple testing, the resultant P values were corrected using Bonferroni correction. Interobserver variability and intraobserver repeatability were analyzed using an intraclass correlation coefficient (ICC) in a mixed model: excellent ICC $\geq$ 0.75; good ICC $\geq$ 0.4; poor ICC $<$ 0.4. A Student's t-test was used to compare gestational age at birth, birth weight, age at examination, spherical equivalent refractive error, and visual acuity between preterm and full-term children. Pearson's χ^2 test was used to compare sex between the two groups

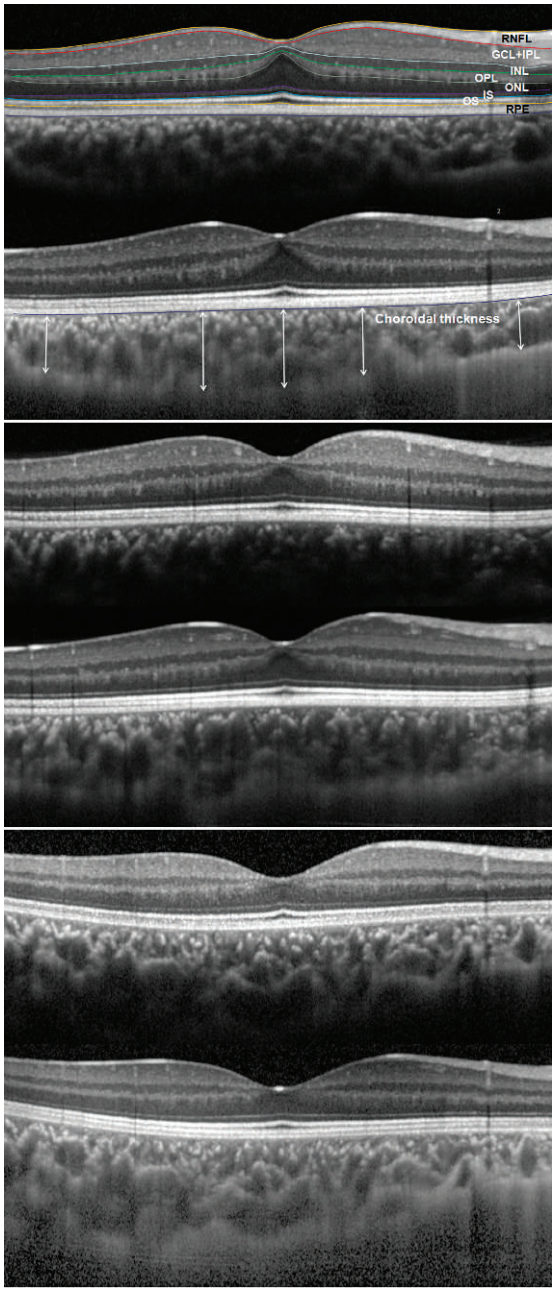

Figure 1. 1:1 pixel views of horizontal optical coherence tomography scan images showing the method of retinal layer thickness and choroidal thickness measurement and representative images in preterm and full-term children. Each thickness was measured at the fovea and 1.0 and 3.0 mm nasal, temporal, superior, and inferior to the fovea. (Actual measurements for analysis in the study were done using 1:1 micron image.) *Top*: 6-year-old boy born at 25 weeks gestational age, with regressed stage 3 retinopathy of prematurity after laser treatment. *Middle*: 5-year-old boy born at 30 weeks gestational age, with regressed stage 3 retinopathy of prematurity after laser treatment. *Bottom*: 6-year-old boy born at term.

Results

Of the 33 preterm children that enrolled, 31 were used for the analysis of retinal layer thickness and choroidal thickness. Two were excluded because of poor scan image quality. Of the 31 full-term children that enrolled, 30 were used for the analysis of retinal layer thickness and choroidal thickness. One full-term

Table 1. Demographic and Clinical Description of the Preterm Children and Children Born at Term

Variable	Preterm, $n = 31$ Mean ± SD	Full-Term, $n = 30$ Mean ± SD	*P* Value
Gestational age at birth, wk	28.00 ± 3.57	≥37	
Birth weight, kg	1.19 ± 0.50	≥2.5	
Age at testing, y	6.06 ± 1.69	6.17 ± 1.44	0.337*
Sex, male/female	17/14	>18/12	0.797†
Refractive error, Diopters	−1.27 ± 4.03	−0.41 ± 1.44	0.003*
Retinopathy of prematurity, *n*	22		—
Mild, stages 1, 2	5		—
Severe, stage 3	17		—
Laser treatment, *n*	17		—

* *t*-test.
† Pearson's χ^2 test.

child was excluded because of a technical error in measuring AXL. Baseline characteristics of the children including demographics, gestational age at birth, birth weight, age at testing, refractive error (described by spherical equivalent), history of ROP, stage of ROP, and laser treatment for ROP are shown in Table 1. The mean refractive error of preterm children was −1.27 ± 4.03, slightly more myopic than full-term children, among whom the mean refractive error was –0.41 ± 1.44 ($P = 0.003$). Table 2 compares visual acuity and disc RNFL thickness. Significant differences were observed between the preterm and full-term children in terms of visual acuity and disc RNFL thickness. LogMAR (logarithm of the minimum angle of resolution) visual acuity was significantly worse in preterm children (0.22 ± 0.23) compared with that in full-term children (0.03 ± 0.06, $P < 0.001$). Nasal and superior disc RNFL thicknesses were significantly smaller in preterm children (nasal, 53.15 ± 15.96 μm and superior, 105.78 ± 29.99 μm) compared with those in full-term children (nasal, 64.10 ± 15.50 μm, $P = 0.012$ and superior, 122.14 ± 23.28 μm, $P = 0.026$).

Retinal Layer Thickness

Table 3 shows the thickness of nine different retinal layers. The central total macular thickness and ONL thickness were significantly larger in preterm children than those in full-term children, even after the child's age and AXL were taken into account. The mean total retinal thickness at the foveal center was 256.00 ± 30.71 μm in preterm and 217.57 ± 10.64 μm in full-term children ($P < 0.001$). The mean ONL thickness at the foveal center was 141.87 ± 28.75 μm in preterm and 101.22 ± 10.90 μm in full-term children ($P < 0.001$). There were no significant differences between preterm and full-term children in other retinal layer thicknesses including RNFL, GCL+IPL, INL, OPL, IS, OS, and RPE layer at the foveal center or at 1.0 and 3.0 mm nasal, temporal, inferior, and superior to the foveal center. We performed a correlation analysis between baseline patient parameters and the thicknesses of the total foveal central layer and ONL at the foveal center. This analysis revealed that gestational age at birth was inversely correlated with both total retinal and ONL thicknesses at the foveal center ($t = -4.34$, $P < 0.001$ and $t = -4.52$, $P < 0.001$, respectively) (Figs. 2, 3). Birth weight, ROP stage, and laser treatment were not significantly correlated with total retinal and ONL thicknesses at the foveal center.

Choroidal Thickness

Table 4 shows choroidal thickness measured at nine locations. The choroidal thickness 3.0 mm temporal to the fovea in preterm children (283.75 ± 60.47 μm) was significantly smaller than that in children born at term (339.89 ± 90.32, $P = 0.010$) after adjusting for the patient's age and AXL. However, there were no significant differences between choroidal thicknesses at the other locations in preterm and full-term children. Our correlation analysis between baseline factors and choroidal thicknesses showed that ROP stage had a marginal inverse correlation with choroidal thickness 3.0 mm temporal to the fovea ($t = -2.53$, $P = 0.053$). Other parameters including gestational age at birth, birth weight, and laser treatment were not significantly correlated with choroidal thickness.

Visual Acuity, Retinal Layer Thickness, and Choroidal Thickness

Preterm children had significantly reduced visual acuity compared with that in full-term children (logMAR, 0.22 ± 0.23 vs. 0.03 ± 0.06, $P < 0.001$). Visual acuity in preterm children was not correlated with total retinal thickness, all the intraretinal layer thicknesses, or choroidal thickness at the foveal center and locations 1.0 and 3.0 mm from the foveal center.

Table 2. Descriptive Statistics (mean ± SD) and Statistical Comparisons of Visual Acuity and Disc Retinal Nerve Fiber Layer Thickness in Preterm Children and Children Born at Term

Variable	Preterm, $n = 31$ Mean ± SD	Full-Term, $n = 30$ Mean ± SD	*P* Value*
LogMAR visual acuity	0.22 ± 0.23	0.03 ± 0.06	<0.001
Disc RNFL thickness, μm			
Total	91.93 ± 19.24	96.34 ± 15.83	0.272
Temporal	86.33 ± 30.29	77.21 ± 15.31	0.168
Nasal	53.15 ± 15.96	64.10 ± 15.50	0.012
Superior	105.78 ± 29.99	122.14 ± 23.28	0.025
Inferior	121.52 ± 28.47	121.10 ± 21.02	0.747

* *t*-test.

Table 3. Comparisons of Mean Retinal Layer Thicknesses in Preterm Children and Children Born at Term Adjusted by Age at Examination and Axial Length

Variable	Preterm, $n = 31$ Mean ± SD	Full-Term, $n = 30$ Mean ± SD	*P* Value*
Thickness (μm)			
Foveal center			
Total	256.00 ± 30.71	217.57 ± 10.64	<0.001
ONL	141.87 ± 28.75	101.22 ± 10.90	<0.001
IS	29.05 ± 3.05	29.95 ± 3.72	0.676
OS	39.51 ± 4.46	39.47 ± 4.21	1.000
RPE	42.90 ± 7.14	43.03 ± 3.75	1.000
Inner locations†			
Inner temporal			
Total	331.77 ± 45.72	333.90 ± 15.45	1.000
RNFL	19.02 ± 3.43	17.67 ± 2.19	0.452
GCL+IPL	84.18 ± 13.22	82.20 ± 11.18	1.000
INL	36.03 ± 6.37	33.42 ± 5.48	1.000
OPL	36.77 ± 12.60	37.38 ± 7.43	1.000
ONL	63.27 ± 17.20	63.57 ± 12.30	1.000
IS	24.21 ± 2.78	24.87 ± 3.65	1.000
OS	27.05 ± 2.83	27.15 ± 3.35	1.000
RPE	40.97 ± 3.97	40.85 ± 3.09	1.000
Inner nasal			
Total	344.69 ± 48.74	345.65 ± 17.90	1.000
RNFL	22.40 ± 5.22	21.27 ± 4.15	1.000
GCL+IPL	92.02 ± 16.38	88.00 ± 13.62	1.000
INL	40.56 ± 6.40	36.83 ± 5.45	0.153
OPL	44.40 ± 17.22	38.33 ± 12.24	0.587
ONL	52.56 ± 17.52	60.23 ± 14.04	0.086
IS	23.88 ± 2.96	24.25 ± 3.12	1.000
OS	26.95 ± 2.71	26.67 ± 2.91	1.000
RPE	41.29 ± 3.73	41.70 ± 3.34	1.000
Inner superior			
Total	347.82 ± 49.23	355.62 ± 13.79	1.000
RNFL	30.11 ± 6.29	31.25 ± 5.75	1.000
GCL+IPL	94.27 ± 18.22	93.12 ± 12.36	1.000
INL	41.24 ± 7.04	39.50 ± 4.71	1.000
OPL	41.97 ± 16.19	45.62 ± 13.93	1.000
ONL	50.02 ± 16.41	49.53 ± 15.66	1.000
IS	22.08 ± 2.73	22.63 ± 3.08	1.000
OS	24.73 ± 2.94	24.90 ± 3.52	1.000
RPE	40.36 ± 3.42	41.43 ± 3.11	1.000
Inner inferior			
Total	352.69 ± 24.32	348.78 ± 13.20	1.000
RNFL	31.33 ± 6.23	30.45 ± 5.94	1.000
GCL+IPL	97.52 ± 13.59	91.02 ± 11.23	0.886
INL	40.59 ± 5.65	37.63 ± 5.62	0.396
OPL	43.50 ± 12.65	49.83 ± 12.49	0.626
ONL	47.40 ± 15.67	43.35 ± 12.69	1.000
IS	22.50 ± 2.45	23.17 ± 3.12	1.000
OS	24.47 ± 2.58	25.70 ± 3.74	1.000
RPE	40.31 ± 3.92	40.97 ± 3.23	1.000
Outer locations‡			
Outer temporal			
Total	279.42 ± 24.45	274.35 ± 13.35	1.000
RNFL	18.82 ± 6.30	18.85 ± 3.49	1.000
GCL+IPL	65.71 ± 10.58	63.62 ± 6.60	1.000
INL	31.84 ± 5.54	29.08 ± 4.37	0.562
OPL	28.06 ± 5.96	28.68 ± 5.97	1.000
ONL	46.66 ± 8.61	45.08 ± 6.29	1.000
IS	20.02 ± 2.54	20.98 ± 2.75	0.294
OS	21.35 ± 3.77	21.15 ± 2.48	1.000
RPE	41.52 ± 4.55	41.42 ± 3.77	1.000
Outer nasal			
Total	306.40 ± 34.53	302.47 ± 57.85	1.000
RNFL	52.94 ± 13.70	57.85 ± 9.85	1.000
GCL+IPL	62.42 ± 11.14	56.00 ± 7.45	0.494
INL	30.08 ± 6.57	27.80 ± 3.80	1.000
OPL	30.39 ± 7.38	30.05 ± 6.94	1.000
ONL	45.40 ± 9.37	42.65 ± 6.98	1.000
IS	19.18 ± 2.49	20.03 ± 3.03	0.785
OS	21.28 ± 3.16	21.85 ± 2.42	1.000
RPE	38.56 ± 4.02	39.62 ± 3.67	1.000
Outer superior			
Total	291.46 ± 28.20	291.97 ± 18.84	1.000
RNFL	46.74 ± 11.83	52.50 ± 11.41	0.639
GCL+IPL	52.73 ± 10.73	51.13 ± 10.33	1.000
INL	27.89 ± 4.88	25.02 ± 4.28	1.000
OPL	26.31 ± 5.49	26.70 ± 5.53	1.000
ONL	50.37 ± 8.55	47.65 ± 6.27	1.000
IS	19.98 ± 2.46	20.75 ± 2.51	0.904
OS	21.24 ± 2.80	21.77 ± 2.44	1.000
RPE	40.26 ± 3.91	39.80 ± 2.80	1.000
Outer inferior			
Total	279.11 ± 20.93	275.45 ± 14.65	1.000
RNFL	51.68 ± 9.45	53.85 ± 11.28	1.000
GCL+IPL	49.84 ± 8.67	45.40 ± 5.69	0.666
INL	25.92 ± 4.28	24.73 ± 5.55	1.000
OPL	25.13 ± 4.95	26.87 ± 5.85	1.000
ONL	41.34 ± 6.30	39.42 ± 6.52	1.000
IS	19.16 ± 3.32	20.32 ± 4.30	1.000
OS	18.90 ± 3.65	19.35 ± 3.11	1.000
RPE	40.13 ± 5.13	41.12 ± 3.36	1.000

* Mixed model adjusting for time and tester. *P* values were corrected by Bonferroni's correction due to multiple testing.

† 990 to 1000 μm away from foveal center.

‡ 2990 to 3000 μm away from foveal center.

The ICC of the intraobserver repeatability was more than 0.4 in measuring each retinal layer thickness at the foveal center, 1.0 mm from the foveal center, and 3.0 mm from the foveal center. The ICC of the interobserver repeatability was more than 0.4 in measuring retinal layer thickness at every location except the total retinal layer at the inner nasal location, the RNFL at the inner superior location, the INL at the inner temporal and outer superior locations, the IS at the inner and superior outer locations, and the OS at the inner temporal, superior, and outer superior locations.

Discussion

Retinal Layer Thicknesses

Our analysis of retinal thickness showed an increased central macular thickness at the fovea in preterm children compared with that in full-term children. This result agrees with recent studies on the subject, which has revealed thicker central maculae in preterm children compared with those in full-term children.[8–10] We also observed significantly thicker ONL in preterm children compared with that in full-term children. Our results are in agreement with the previous findings by Yanni et

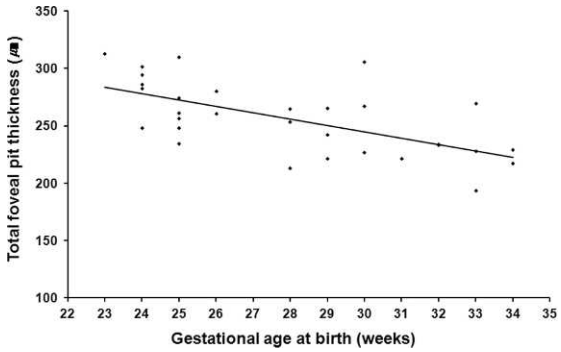

Figure 2. Scatterplot showing the relationship between gestational age at birth and total foveal pit thickness (mixed model adjusting for time and tester with adjustment for the patient's AXL and age at examination, $t = -4.34$, $P < 0.001$).

al.,[9] who reported that the GCL+IPL and the ONL were significantly thicker in preterm children, but other retinal layer thicknesses were not significantly different between preterm and full-term children. Hammer et al.[15] also reported ONL and inner retinal layers were significantly thicker in preterm children than those in full-term children. Wang et al.[10] reported that inner rather than outer retinal layers contributed to differences in retinal thickness between preterm and full-term children. However, we did not observe a significant change in inner retinal layer thickness in preterm children in our study. This study discrepancy may have resulted from differences in the methods of measurement, software, or differences in patient profiles such as age or axial length.

Previous studies have shown that shallow foveal pits in preterm children are correlated with gestational age at birth.[8,10] This has been explained by a failure of the inner retinal layers to migrate away from the fovea in preterm children. Preterm birth at 24 to 28 weeks gestational age has been proposed as a critical period associated with a failure of the normal migration of inner retinal layers away from the fovea, resulting in increased foveal thickness.[10] Our study also found that gestational age at birth was correlated with an increased total retinal thickness and ONL thickness at the foveal center. However, we did not identify a specific gestational age at birth that was related to increased central macular thickness and ONL thickness at the fovea. Central macular thickness and ONL thickness at the fovea were inversely correlated with gestational age at birth and continuously decreased as gestational age increased. This pattern was similar to previously reported patterns by Akerblom et al.[8] This suggests that foveal maturation continues until at least 34 weeks gestational age and preterm birth at any point during this period can cause retinal layers to fail to migrate.

Figure 3. Scatterplot showing the relationship between gestational age at birth and ONL thickness at the foveal center (mixed model adjusting for time and tester with adjustment for the patient's AXL and age at examination, $t = -4.52$, $P < 0.001$).

Table 4. Comparisons of Mean Choroidal Thicknesses in Preterm Children and Children Born at Term Adjusted by Age at Examination and Axial Length

Variable	Preterm, $n = 31$ Mean ± SD	Full-Term, $n = 30$ Mean ± SD	*P* Value*
Thickness, μm			
Foveal center	316.28 ± 74.08	343.10 ± 79.83	0.410
Inner locations†			
Inner temporal	361.78 ± 67.88	348.64 ± 83.41	0.333
Inner nasal	286.47 ± 82.04	304.33 ± 85.81	0.965
Inner superior	319.23 ± 81.39	346.16 ± 81.30	0.410
Inner inferior	313.54 ± 70.98	336.38 ± 82.93	0.639
Outer locations‡			
Outer temporal	283.75 ± 60.47	339.89 ± 90.32	0.010
Outer nasal	198.29 ± 76.99	187.38 ± 66.84	1.000
Outer superior	290.27 ± 82.16	326.14 ± 77.35	0.165
Outer inferior	290.26 ± 78.74	309.15 ± 81.01	0.895

* Mixed model adjusting for time and tester. *P* values were corrected by Bonferroni's correction due to multiple testing.
† 990 to 1000 μm away from foveal center.
‡ 2990 to 3000 μm away from foveal center.

Our finding that retinal layer thicknesses were not associated with visual acuity agrees with previous reports.[9,10] Recent studies of foveal hypoplasia analyzing retinal layer structure and thickness using SD-OCT have shown better agreement between foveal structural abnormalities and visual acuity than retinal layer thickness and visual acuity.[16,17] Visual acuity was abnormal in many children in this study, but a mixed model analysis failed to find a significant association between visual acuity and foveal structure. Previous studies using multifocal electroretinography have reported that even in mild ROP, the most pronounced functional deficits were found in central regions.[18] Of particular relevance was abnormal cone function,[6] which contributed to disorders of color discrimination,[19] defective central rod function and associated dark adaptation,[7,20] and increasingly recognized foveal dysplasia.[21–23] There is a possibility that foveal structural abnormalities in preterm children have different effects on visual function than in patients with foveal hypoplasia. However, it is also possible that we simply could not detect the effect of macular structural abnormalities on visual function because the severity of foveal structural abnormalities in preterm children is much less than that in patients with foveal hypoplasia. In that case, an association between foveal structural abnormalities and visual acuity in preterm children could be detected by a more sensitive and unique test of visual function such as electrophysiologic testing and contrast sensitivity testing.

Choroidal Thickness

We observed significant thinning of the choroid 3.0 mm temporal to the foveal center in preterm children. To the authors' best knowledge, this is the first study to identify the effect of preterm birth on human choroids using OCT. Several studies have measured choroidal thickness using ultrasonography in patients with ROP.[24–26] These studies have reported choroidal thickening in 18% to 30% of patients with ROP; however, the subjects of these studies were patients with advanced stages of ROP. These findings may have represented prephthisical change.[24] Preterm birth significantly changes the

infant's environment, and it can lead to the disruption of normal development in multiple organs. It is not unexpected that preterm birth would affect choroidal vasculature in addition to retinal vessels. Vrabec et al.[27] reported extensive atrophy of the choroidal vasculature in children with ROP. They reported histopathologic findings in children born at 28 weeks gestational age who developed ROP that progressed to threshold disease in one eye. However, patients were treated with cryotherapy before they were studied, and the findings may have been related to the treatment rather than to ROP itself. Choriocapillary degeneration, a distinct form of ischemic retinopathy secondary to diabetes, has also been observed in humans.[28] Another possible explanation for the difference in choroidal thickness between preterm and full-term children may be myopic progression in preterm children. Correlations between choroidal thickness, AXL,[29–31] and age[30,31] are well documented. Choroidal thickness is known to be inversely correlated with AXL and age. Myopic progression is one of the most commonly encountered problems in older children who were born prematurely. Several studies have shown that the prevalence of myopia correlates with increasingly severe ROP.[32–34] However, ocular biometry and the mechanisms of refractive error in preterm children are somewhat different from those in full-term children. Anterior segment components are thought to contribute more to myopic progression than to posterior segment components in preterm children.[33,35–37] Some studies have shown that AXL may be increased in preterm myopic children,[38,39] whereas other studies have reported that AXL was shorter in preterm children with myopia compared with that in normal controls.[34,36–38] In this study, every analysis was performed after adjustments for AXL and age, to avoid the confounding effects of these factors on thickness measurements. In addition, given the previous findings that anterior segment components are more responsible for refractive errors in preterm children, the possibility that myopic progression in preterm children could affect choroidal thickness may be low. Nevertheless, we hypothesized that choroidal thinning as a part of myopic progression might have occurred faster at the outer temporal aspect of the choroid than in other parts of the choroid in our patients. In that case, adjustments for AXL alone may not have been enough to correct for the effects of myopic progression. However, recent studies in highly myopic patients have revealed a thicker choroid at the temporal aspects when compared with the fovea than subfoveal choroidal thickness,[40] contrary to normal eyes.[13,41] Regarding these results, normal myopic patients do not have prominent choroidal thinning at the temporal aspects of their choroid. The only well-established fact at the current time is that choroidal thinning was observed at the outer temporal aspect of the choroid, and the amount of choroidal thinning was more than expected based on myopic progression measured by AXL. The change had a marginally significant correlation with the stage of ROP, but not with gestational age or laser treatment. It may be another pathologic change related to the progression of ROP rather than to myopic progression. However, we could not rule out the possibility that the change was associated with the unique pattern of structural change seen in myopic progression in preterm children.

The outer neuroretina is known to be highly metabolically active[42] and consumes large amounts of oxygen. Choroid supplies more blood flow to the retina, per unit weight, than any other tissue.[43] A marked involution of the central choroid and choriocapillaries, the exclusive circulatory supply of nutrients and oxygen to the outer retina, was recently reported as an important contributor to central photoreceptor compromise in the oxygen-induced retinopathy animal model of ROP.[11] Choroidal abnormalities in preterm children may explain central disorders of the retina, as attested by defective cone and rod functions in ROP.[6,7]

Although the use of only a single institution may limit the power of this study's conclusions, this study confirmed previous findings of foveal structural abnormalities in preterm children and it is the first to report on the choroidal thickness profile of preterm children. Further studies with larger patient populations and different forms of visual function testing, including electrophysiology testing, may confirm our findings and more clearly reveal the association between visual functions and structural abnormalities in the fovea and choroid of preterm children.

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