A comparison of posterior segment optical coherence tomography findings in full-term and preterm children without retinopathy of prematurity

Claudia J Martínez-Córdoba[1,2], Bernardo A Quijano-Nieto[1,2,3], Claudia L Echeverría-González[2,4], Rosa M Sierra-Bernal[1]

Purpose: Structural differences have been described in the retina of prematurely born children, including increased macular thickness caused by failed migration of the inner retina during development and retinal nerve fiber layer (RNFL) thinning related to low birth weight. The present study aimed to evaluate the differences in macular and RNFL optical coherence tomography (OCT) findings between full-term and preterm children without retinopathy of prematurity (ROP). **Methods:** Thirty-four premature (study group) and 43 full-term patients (control group)—aged 3 to 8 years—were studied. All children underwent a complete ophthalmological exam and OCT of the macula and optic nerve in both eyes to determine macular and RNFL thickness and morphology. Correlation analysis between central macular thickness, age, and visual acuity was also performed. **Results:** Central macular thickness was greater in the study group than in the control group; a difference of 14.2 μm was observed for the right eye ($P = 0.002$) and 12.16 μm for the left eye ($P = 0.019$). The thickness of the parafoveal and the perifoveal zones was consistently greater in the study group. 44.3% of eyes in the study group had mild forms of foveal hypoplasia (grades 1a and 1b) in qualitative description. No correlation between central macular thickness and visual acuity was found. There was no difference in RNFL thickness between both groups. **Conclusion:** Statistically significant structural differences were found in the macula of premature children, with a greater foveal thickness possibly reflecting retention of the inner retina during development, with no repercussion over visual acuity. RNFL thickness was similar in both groups.

Key words: Macular thickness, optical coherence tomography, preterm birth

Premature birth is a well-known risk factor for neonatal morbidity and mortality, affecting multiple systems and organs. Compromised visual pathways and eyes may result in sequelae such as retinopathy of prematurity (ROP), a higher incidence of refractive defects and strabismus, lower stereopsis, and reduced visual acuity of both ocular and neurological etiology.[1-3]

Several studies have identified structural alterations in the posterior segment of patients with a history of preterm birth with and without ROP by optical coherence tomography (OCT). This imaging approach allows for the objective and non-invasive evaluation of morphological characteristics of the macula and the optic nerve, such as increased foveal thickness and retinal nerve fiber layer (RNFL) thinning in prematurely born patients.[4-12]

The thicker macula observed in premature individuals results from alterations in the foveal development. This biological process begins around 24–27 weeks of gestation, continues during childhood, and ends around 3 or 4 years of age. In this process, the inner retina moves centrifugally while the photoreceptors move centripetally to form the physiological foveal depression. Premature patients present retention of the inner retina, especially at the expense of the ganglion cell and the inner plexiform layers, which results in an abnormally thick, hypoplastic fovea.[5,6,9,12-14] In addition, they exhibit altered vasculogenesis that gives rise to foveal avascular zones (FAZs) of smaller diameter with capillaries that cross the fovea, modify its elasticity, and prevent the adequate formation of the foveal depression.[9,12,14] Other macular architecture characteristics have been related as signs of foveal maldevelopment. Mainly, a broad and shallow foveal pit, sometimes reaching absence of foveal depression, and retention of inner retinal layers at the foveola have been found in preterm patients.[14,15] These findings, previously described as foveal aplasia or fovea plana, are now encompassed in the more suitable term "foveal hypoplasia," for which Thomas *et al.* have developed a grading system as follows: grade 1: characterized by retention of inner retinal layers, but outer segment lengthening (OSL) and outer nuclear layer (ONL) widening present (1a: nearly normal foveal pit; 1b: shallow foveal indent); grade 2: as grade 1 but absence of

[1]Ophthalmology and Optometry Department - Hospital Militar Central, Bogotá, [2]Medical and Surgical Specialties Unit - Universidad Militar Nueva Granada, Bogotá, [3]Macula and Retina Institute - Oftalmo Center, Bogotá, [4]Pediatrics and Neonatology Department - Hospital Militar Central, Bogotá, Colombia

Correspondence to: Dr. Claudia J Martínez-Córdoba, Hospital Militar Central – Tv. 3C # 49-02 ZIP– 110231, Bogotá, Colombia. E-mail: claudiajmc25@gmail.com

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foveal pit; grade 3: as grade 2 but absence of OSL; and grade 4: as grade 3 but absence of ONL widening.[14,15]

Other groups have observed RNFL thinning in premature patients with ROP. Both severe ROP stage and previous ablative treatment with laser or cryotherapy have been linked as causes of axonal damage.[4,7,16,17] RNFL thinning has also been reported in patients with low birth weight. It is suggested that babies with higher birth weights have a greater reserve of retinal ganglion cells,[4,7,9] and that hypoxic and inflammatory conditions in the premature patient contribute to neuronal damage.[7]

The objective of this study is to describe the differences in macular and RNFL thickness measured in OCT between children born preterm and at term.

Methods

This cross-section study was developed in accordance with Helsinki Declaration of 1975, as revised in 2000, and to regional regulations. It was approved by the Institutional Research Ethics Committee. Informed consent was obtained from one of the child's parents or caregivers, as well as assent from each child to participate in the study.

For the study group, patients aged 3 to 8 years who had been born prematurely were selected from the institutional Kangaroo Program database through a non-probability convenience sampling. This database included 220 children, 44 of which were not eligible since they were born outside the institution and their clinical data was not available, and 78 lived outside the city at the time of the study. 98 eligible patients were contacted by phone and their caregivers were invited to participate in the study. 22 could not be located, 39 did not accept to participate or did not attend on scheduled dates, 2 did not allow for examination due to poor cooperation and 1 was excluded due to severe neurological impairment precluding fixation. For the control group, patients of the same age group who had been born at term were invited to participate in the study through advertising flyers distributed in the outpatient setting, providing parents or caregivers with the necessary information to register by phone. Patients with media opacity or inability to maintain fixation either due to illness or poor cooperation were excluded. The study group included 34 children, born with a gestational age of 27 to 35 weeks; no patient in this group had a history of ROP. The control group included 43 children born with a gestational age of 36 to 41 weeks. The control group was somewhat older than the study group with an average age of 6.26 years (range: 4–8 years) and 5.03 years (range: 3–8 years), respectively ($P = 0.001$), at the time of the study. All individuals in both groups underwent a complete ophthalmic exam, including best-corrected visual acuity (BCVA) measured in a LogMAR visual acuity chart, biomicroscopy, and fundoscopy. Patients with media opacity, major neurological alterations, or pathologies that prevented them from keeping a fixed gaze were excluded in both groups. All patients had a healthy posterior segment in indirect ophthalmoscopy. Demographic data, gestational age, and weight at birth were recorded from the medical records of all participants and are summarized in Table 1.

Measurements

Macula and optic nerve OCT images were obtained for both eyes of each patient using a Cirrus HD-OCT device (Carl Zeiss Meditec Inc., Dublin, CA). A trained technician, unfamiliar with patient background, performed both macular and optic disc images in a single visit, retaking images with poor signal strength as long as the patient allowed for it. Data collection and statistical analysis were performed by different authors, blinded to patient information except for sex and age. Macular thickness was measured in micrometers (µm) from internal limiting membrane (ILM) to retinal pigment epithelium (RPE) in a 512 × 128 macular cube. HD 5-line raster images were also obtained and analyzed by one of the authors, blinded for all patient data except for eye laterality, who made a qualitative evaluation of foveal architecture describing the presence or absence of foveal hypoplasia according to the grading system proposed by Thomas *et al.*[14,15] Measurements from central, inner, and outer macular ring and macular cube volume are presented in Table 2. RNFL thickness was also measured in µm from a 200 × 200 optic disc cube. Measurements from each quadrant are presented in Table 3. Parameters with signal intensity less than 6/10 were discarded. R (R Core Team version 3.2.3) and Real Statistics Resource Pack version 7.0 were used for conducting statistical analysis. Data distribution was evaluated with the Shapiro Wilk's test, correlation between study variables (central macular thickness, age and BCVA) was evaluated with the Pearson correlation test, and parameters from the study and control groups were compared with the T and/or Mann-Witney U tests; P values less than 0.05 were considered statistically significant.

Results

Macular OCT: Data from 68 eyes in the study group (34 right eyes and 34 left eyes) and 86 eyes in the control group (43 right eyes and 43 left eyes) were analyzed. The average macular thickness was greater in the premature group than in the control group; the difference was statistically significant for the central macular thickness and the macular inner-superior, inner-inferior, and inner-nasal quadrants of both eyes (OU). There were also significant differences for the thickness of the macular inner-temporal, outer-superior, and outer-temporal quadrants of the right eye (OD) and the outer-superior quadrant of the left eye (OS); on the other hand, the difference was consistent but not statistically significant for the inner-temporal, outer-superior, and outer-temporal quadrants of the macula of the OS, the outer-inferior quadrant of the OD, and the outer-nasal quadrant of OU. Macular cube volume was similar for OD in both groups, but somewhat smaller for OS in the preterm group [Table 2]. HD5 Line Raster images were available for qualitative evaluation of foveal anatomy in 67 eyes of the preterm group and 86 eyes of the control group. In the study group, 38 eyes (56.7%) were classified as having a normal foveal architecture, 18 eyes (26.9%) as grade 1a foveal hypoplasia, and 11 (16.4%) as grade 1b foveal hypoplasia. In the control group, 74 eyes (86.1%) were classified as normal, 7 eyes (8.1%) as grade 1a foveal hypoplasia, and 5 eyes (5.8%) as grade 1b foveal hypoplasia. No eyes in either group were found to have grade 2, 3, or 4 foveal hypoplasia. Representative images are provided in Fig. 1.

Optic Nerve OCT: Data from 36 eyes (18 right eyes and 18 left eyes) in the study group and 81 eyes (41 right eyes and 40 left eyes) in the control group were analyzed. The lower sample number resulted from discarding data from eye images

Table 1: Sociodemographic characteristics of patients

Group	n	Sex n (%)	Age at evaluation Mean (range) years	Gestational age at birth Mean (range) weeks	Birth weight Mean (range) g	BCVA Log MAR Mean (range)
Premature	34	Female 16 (47.1) Male 18 (52.9)	5.09 (3-8)	32.5 (27-35)	1769.20 (984-2890)	0.11 (0.0-0.6)
Term	43	Female 21 (48.8) Male 22 (51.2)	6.26 (4-8)	38.89 (36-41)	3155.63 (2240-4450)	0.14 (0.0-0.6)
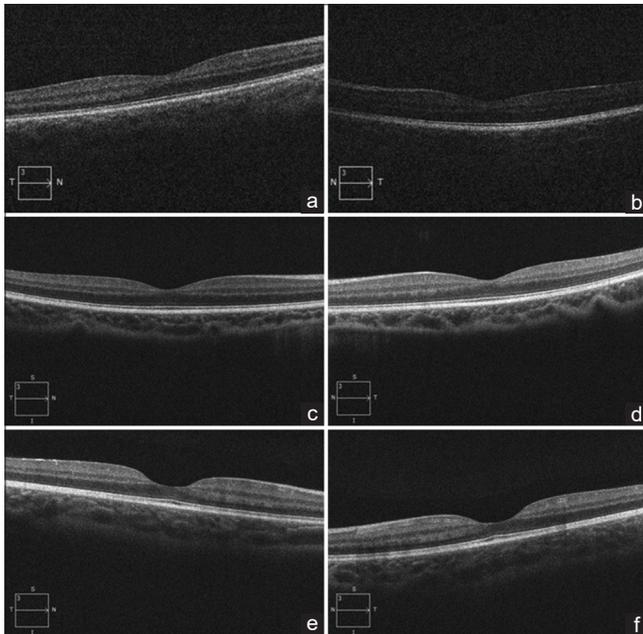
Figure 1: High Definition 5-Line raster images of the central macula of both eyes in a premature patient graded as 1b foveal hypoplasia (top images), a premature patient graded as 1a foveal hypoplasia (central images), and a full-term patient with normal foveal anatomy (bottom images). Right eye (a, c, e), left eye (b, d, f)

that did not reach a signal strength of at least 6/10, mainly due to poor cooperation since the fixation requirements are more demanding for the optic disc cube (longer fixation time and non-central gaze fixation position) than for the macular cube. It is possible that more data were invalid for the study group since it included somewhat younger patients in whom the examination may be more difficult to perform. No differences were observed in the average RFNL thickness or in the RFNL thickness of the different quadrants between the two groups of patients [Table 3].

Visual Acuity: BCVA was similar between the two groups, with an average of 0.11 LogMAR (range: 0–0.6) in the study group and 0.14 LogMAR (range: 0–0.6) in the control group ($P = 0.67$). Pearson test showed no correlation between central macular thickness and visual acuity, with weak positive values in all cases except for the right eye in the control group. There was a small negative correlation between central macular thickness and age in both eyes of the study group, and a small positive correlation between age and visual

acuity in all groups; however, no value reached statistical significance [Table 4].

Discussion

A greater macular thickness was observed in the premature group than in the control (at-term) group, with an average difference in central macular thickness of 14.26 μm in the OD and 12.16 μm in the OS. In other studies conducted in patients of similar ages, differences in macular thickness of 3.8 μm,[11] 6.2 μm,[6] 14 μm,[5] and 14.6 μm[13] have also been found between premature patients without ROP and at-term patients. Previous studies have attributed this finding to the retention of the inner retinal layers during development in premature infants, leading to an abnormally thick hypoplastic fovea,[5,6,9,12,15] for which gestational age is the most significant risk factor, even when adjusted to birth weight or the diagnosis of ROP.[5,9] A small difference in macular cube volume was observed only in the OS, being smaller in the preterm group. A smaller macular cube volume in preterm children without history of ROP has been previously described by Tariq *et al.*,[13] a finding considered to be possibly secondary to the impaired cell migration that occurs during retinal development in preterm babies. However, this difference was only significant when comparing children born before 33 weeks to children born at term, and was not held when comparing individuals with modest degrees of prematurity (33 to 36 weeks) to children born at term[13] implying again the important role of gestational age on retinal development. 43.3% of the eyes in the study group were found to have some grade of foveal hypoplasia, for which retention of inner retinal layers is the hallmark characteristic. This is higher than the frequency found by Thomas *et al.*[14] who reported signs of macular arrested development in 44% of spontaneously regressed ROP and in 27% of preterm infants without ROP. Other microanatomical alterations such as cystoid macular edema (ME) have been described in previous studies in preterm children with[18] and without ROP.[19] No ME was identified in any of the patients in this study; however, it should be taken into account that the aforementioned studies evaluated infants of a much younger age, and, since ME can be a self-resolving condition, it is possible that it may not persist up to the ages here studied.

In this study, no differences in BCVA were observed between the two groups of patients and no correlation between macular thickness and visual acuity was found, despite the relatively large percentage of patients graded as having some kind of foveal hypoplasia. This supports the concept that structural differences do not always

Table 2: Macular thickness in premature and at-term born children, evaluated by OCT

Zone	Eye	Group	Thickness (µm)			P*	P†
			Mean	Max	Min		
Central	OD	Premature	246.52	295.00	196.00	1.000	**0.002**
		Term	232.26	281.00	192.00	0.373	
	OS	Premature	244.63	286.00	191.00	0.531	**0.019**
		Term	232.47	272.00	190.00	0.666	
Macular Cube Volume	OD	Premature	10.21	11.10	9.30	0.251	0.128
	OS	Term	10.04	11.00	8.70	0.511	0.972
		Premature	9.89	11.10	6.10	**0.0001**	
		Term	9.99	11.20	8.80	0.502	
Inner-superior quadrant	OD	Premature	314.79	345.00	243.00	**0.001**	0.323
		Term	311.60	339.00	258.00	**0.016**	
	OS	Premature	313.58	350.00	255.00	**0.003**	0.524
		Term	309.67	353.00	243.00	**0.010**	
Inner-temporal quadrant	OD	Premature	304.88	325.00	257.00	**0.001**	**0.031**
		Term	299.95	325.00	266.00	0.208	
	OS	Premature	302.72	327.00	254.00	0.054	0.325
		Term	299.28	331.00	268.00	0.911	
Inner-inferior quadrant	OD	Premature	309.88	337.00	255.00	**0.004**	0.764
		Term	309.14	340.00	262.00	0.065	
	OS	Premature	309.78	338.00	267.00	0.507	0.323
		Term	305.95	337.00	266.00	**0.050**	
Inner-nasal quadrant	OD	Premature	316.97	350.00	253.00	**0.009**	0.087
		Term	312.63	348.00	271.00	0.273	
	OS	Premature	315.31	350.00	236.00	**0.0001**	0.986
		Term	314.42	346.00	280.00	0.439	
Outer-superior quadrant	OD	Premature	293.61	342.00	248.00	0.769	**0.012**
		Term	281.51	315.00	200.00	**0.0003**	
	OS	Premature	291.93	331.00	239.00	0.491	0.280
		Term	286.05	343.00	247.00	0.160	
Outer-temporal quadrant	OD	Premature	272.97	299.00	241.00	0.717	0.013
		Term	263.76	285.00	227.00	**0.016**	
	OS	Premature	268.61	318.00	241.00	0.297	0.229
		Term	263.20	287.00	228.00	0.228	
Outer -inferior quadrant	OD	Premature	275.55	314.00	244.00	0.173	0.121
		Term	269.53	297.00	225.00	0.135	
	OS	Premature	274.22	309.00	244.00	0.351	0.097
		Term	266.98	295.00	185.00	**0.00005**	
Outer-nasal quadrant	OD	Premature	299.61	331.00	253.00	0.474	0.702
		Term	297.91	346.00	259.00	0.078	
	OS	Premature	301.28	337.00	255.00	0.639	0.671
		Term	298.86	335.00	266.00	0.650	

OCT, Optical coherence tomography; OD, Right eye; OS, Left eye. Significant P values are highlighted in bold; *Shapiro-Wilk's test; †T/Mann-Whitney U test

translate into reduced visual acuity,[8,10] likely because photoreceptor maturation may occur in the absence of foveal depression,[10] and also because the hypoplasia here found was mild (grades 1a and 1b), differing from the behavior of other diseases like albinism or achromatopsia, where low visual acuity can be found in relation to moderate or severe hypoplasia (grades 2,3 and 4).[14,15] One must recall, however, that even in the presence of foveal hypoplasia, lower BCVA in preterm patients can also have non-ophthalmological (i.e. neurological) causes.[1-3,15,19]

No differences in the RNFL thickness were observed between preterm and at-term children, likely because the study group consisted only of patients without history of ROP, supporting that the RNFL thinning probably results either from severe ROP or from direct damage of ganglion cells caused by ablative treatment of ROP.[4,7] Other authors have found differences in the RFNL in low birth weight patients, but this relationship was not upheld after adjusting for gestational age.[7,9] In these cases, an unexpectedly thick RNFL was attributed to the early visual stimulation to which premature patients are exposed,

Table 3: RFNL thickness in premature and at-term born children, evaluated by OCT

Zone	Eye	Group	Thickness (µm)			P^*	$P^\dagger$
			Mean	Max	Min		
Average	OD	Premature	101.83	126.00	82.00	0.149	0.401
		Term	99.56	123.00	73.00	0.771	
	OS	Premature	100.78	123.00	72.00	0.745	0.920
		Term	100.78	123.00	66.00	0.695	
Superior	OD	Premature	131.72	189.00	86.00	0.351	0.187
		Term	124.05	206.00	40.00	0.076	
	OS	Premature	125.22	170.00	56.00	0.440	0.419
		Term	130.53	176.00	87.00	0.941	
Temporal	OD	Premature	69.94	88.00	49.00	0.939	0.054
		Term	65.73	89.00	42.00	0.626	
	OS	Premature	66.28	86.00	45.00	0.309	0.677
		Term	64.70	91.00	49.00	0.202	
Inferior	OD	Premature	136.39	182.00	76.00	0.705	0.958
		Term	135.83	186.00	84.00	0.541	
	OS	Premature	139.72	182.00	83.00	0.775	0.554
		Term	135.23	182.00	56.00	0.074	
Nasal	OD	Premature	69.17	103.00	49.00	0.155	0.303
		Term	73.41	114.00	48.00	0.517	
	OS	Premature	71.56	119.00	45.00	0.280	0.780
		Term	72.40	100.00	47.00	0.790	

OCT, Optical coherence tomography; OD, Right eye; OS, Left eye. *Shapiro-Wilk's test; †T/Mann-Whitney *U* test

Table 4: Correlation between age, central macular thickness, and BCVA*

Group	Eye		Age	Central thickness	BCVA
Premature	OD	Age	1	-	-
		Central Thickness	−0.041	1	-
		BCVA	0.035	0.083	1
	OS	Age	1	-	-
		Central Thickness	−0.013	1	-
		BCVA	0.211	0.014	1
Term	OD	Age	1	-	-
		Central Thickness	0.116	1	-
		BCVA	0.102	−0.052	1
	OS	Age	1	-	-
		Central Thickness	0.042	1	-
		BCVA	0.017	0.356	1

*Pearson correlation values (positive values indicate positive correlation, negative values indicate negative correlation, values of 0 indicate no correlation. Values greater than ±0.5 are considered significant)

which generates neurotrophic factors that reduce the axonal degeneration commonly occurring during the third trimester of gestation.[9]

The present study's limitations include the relatively small sample size, hindering to establish definitive results, for which a larger sample size would be required. There was a small but statistically significant age difference between both groups, and a small negative correlation between central macular thickness and age. Albeit this correlation was not significant, it is possible that central macular thickness was greater in the study group because the patients were somewhat younger, and therefore these results should be interpreted carefully. Another limitation is not having considered other OCT variables, such as FAZs diameter. Particularly, less optic nerve data were included because this evaluation requires more concentration and gaze fixation time, which is a difficult task to achieve for young children. Notwithstanding, the study has several strengths, such as the inclusion of a control group, the analysis only of data with signal intensity greater than 6/10, which increases its reliability, the inclusion of qualitative macular architecture assessment, and the correlation analysis between macular thickness, BCVA, and age.

Conclusion

In conclusion, statistically significant structural differences were observed in the macula of children with a history of premature birth, even without ROP. Specifically, a greater foveal thickness was observed, which could possibly be associated with inner retinal retention during development, which is the hallmark of foveal hypoplasia, present in low grade in a considerable percentage of patients in the study group. However, this difference did not translate into a lower visual acuity; thus, anatomical changes do not always translate into functional outcomes. No differences in RNFL thickness were observed, which is consistent with other studies that have reported thinning in patients with a history of severe ROP but did not identify differences between at-term and preterm individuals without ROP, as those included in the study group.

Conflicts of interest

There are no conflicts of interest.

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