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PEDIATRICS

Retinal structural changes in preterm children without retinopathy of prematurity

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Abstract

Purpose The aim of this study was to compare all retinal layers' thickness in full-term and preterm children without retinopathy of prematurity (ROP).

Methods Cross-sectional study including two groups of patients: group 1 children with history of preterm gestation without ROP (gestational age < 37 weeks) and group 2 healthy children with history of full-term gestation. All subjects underwent an ophthalmic examination including spectral domain-optical coherence tomography. After automatic retinal segmentation, each retinal layer thickness (eight separate layers and overall thickness) was calculated in all nine Early Treatment Diabetic Retinopathy Study areas. Demographic, systemic, gestational, and birth data were collected. Generalized additive regression models were used to analyze the data.

Results Fifty-one children (51 eyes) were recruited, 19 full-term and 32 preterm children, mean age at ophthalmic examination of 10.58 (4.21) and 14.13 (3.16), respectively. In multivariable analysis, the preterm group's retinal thickness was significantly decreased in total retina nasal outer sector, ganglion cell layer (GCL), and inner plexiform layer (IPL), specifically GCL temporal outer ($p = 0.010$), GCL superior outer ($p = 0.009$), IPL temporal outer ($p = 0.022$), and IPL superior outer ($p = 0.004$), when compared with full-term group. From the variables compared only with birth head circumference that influenced the models, a non-linear association was identified and consequently modeled with splines through a generalized additive model.

Conclusion This study suggests that preterm children without ROP have structural retinal alterations, mostly in GCL and IPL in outer areas of the macula. Therefore, it is crucial to question gestational history since these retinal changes may be found later in life leading to useless investigation.

Keywords Preterm children · Retinal layer thickness · Optical coherence tomography · Ganglion cell layer · Inner plexiform layer

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Key messages

- Prematurity, even in the absence of ROP can have visual consequences, although this topic has been underestimated by the scientific community.
- This study suggests that preterm children even without ROP still have structural retinal changes, mostly in GCL and IPL in outer areas of the macula.
- Disruption of lateral cell migration of the macula might be the mechanism responsible for these changes observed in prematurity.

Introduction

Prematurity, defined as gestational age (GA) < 37 weeks, is a global concern with an estimated world incidence of about 15 million births per year [1, 2]. Prematurity is associated with multiple comorbidities, such as retinopathy of prematurity (ROP), which has become a major cause of child blindness [1, 3]. For this reason, most frequently, studies have been focusing on visual, cognitive, and neurologic aspects of ROP [4]. Nevertheless, studies suggest that prematurity, even in the absence of ROP, can have visual consequences as they identified a higher rate of decreased visual acuity or increased refractive errors in this group [5–8].

Retinal and vascular development starts around 16 weeks of gestation, normally being completed around 40 weeks [3, 9]. It has been suggested that throughout retinal development, there is a continuous increase in retinal layer thickness [10]. For this normal growth, intra-uterine characteristics such as oxygen, luminescence, hormones, and growth factor levels are essential [9]. This delicate balance is interrupted by premature birth. Thus, even without ROP, retinal development is incomplete, including neuronal differentiation and neurologic tissue migration [3, 11].

Numerous studies, using optical coherence tomography (OCT), have explored the link between prematurity and retinal development. However, the majority of these focused on preterm children with ROP overlooking the possible alterations in preterm children without ROP. In these last ones, conclusions have been slim, as they differ regarding change in choroid, fovea, and macula thickness and function in this population [5, 12, 13]. Some studies reveal that the average thickness of retinal nerve fiber layer (RNFL) of preterm children without ROP might be similar to full-term children [7, 12, 14]. Ganglion cell layer (GCL) and inner plexiform layer (IPL) have been less studied, with contradictory conclusions but a decrease in thickness may be associated with a GA lower than 28 weeks or low birth weight [11, 12].

The aim of this study was to shed light to the possibility of prematurity, in the absence of ROP, as a cause of retinal alterations. In order to investigate this hypothesis, we compared all retinal layers' thickness in full-term and preterm children without ROP. Additionally, we analyzed possible perinatal influence factors.

Materials and methods

Study population

This cross-sectional study included two groups of consecutive children recruited during routine pediatric ophthalmology appointment: group 1 including children with history of preterm gestation (GA < 37 weeks) without ROP and group 2 composed by healthy children with history of full-term gestation (GA ≥ 37 weeks). The inclusion criteria were children (ages 3–17) with ability to cooperate with the study and approved informed consent by the legal guardian. The exclusion criteria were the following: previous eye trauma or surgery, presence of serious congenital anomalies, history of ROP, or ocular diseases other than refractive errors.

Patient demographics and clinical characteristics

We collected demographic, systemic, gestational, and birth data: age, gender, GA, type of birth, birth weight, birth length, birth head circumference, Apgar score at 1st and 5th minutes, and medical history. All participants underwent an ophthalmic examination, which included assessment of best corrected visual acuity, biomicroscopy, and fundoscopy. Lastly, a spectral-domain optical coherence tomography (SD-OCT) was obtained and the right eye of each subject was included in this study.

Spectral-domain optical coherence tomography imaging and layer segmentation

Tomographic images were obtained using the Spectralis® SD-OCT (software version 6.0; Heidelberg Engineering). Only good-quality scans with well-focused images, without overt misalignment, continuous scan patterns without missing or blank areas, without artifacts, and a signal strength better than 20 (40 = maximum) were included in the analyses. The fast macular thickness OCT protocol was performed with measurements 20 × 20-degree raster scans (consisting of 25 high-resolution scans). The automatic real-time function was set to nine frames per B-scan. An internal fixation light was used to center the scanning area on the fovea while the eye-tracking system was activated.

The Spectralis® automatic segmentation software was used to obtain individual retinal layer thickness measurements including overall retinal thickness (RT), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), retinal pigment epithelium (RPE), and photoreceptor layer (PR) as seen in Fig. 1.

Images obtained were read by two ophthalmologists blinded to the patients' diagnosis. High reproducibility and repeatability of the OCT reading were seen during this and previous studies with the same team of ophthalmologists. Segmentation was subject to inspection and manual refinement whenever deemed necessary.

In all layers, the thickness values were calculated for the nine Early Treatment Diabetic Retinopathy Study (ETDRS) macular areas [15]. An ETDRS plot consists of three concentric rings of 1-, 3-, and 6-mm diameter centered at the fovea. The two outer rings are divided into quadrants by two intersecting lines. Each sector was designated central (C), temporal inner (T3), superior inner (S3), nasal inner (N3), inferior inner (I3), temporal outer (T6), superior outer (S6), nasal outer (N6), and inferior outer (I6). The ETDRS grid was positioned automatically by the Spectralis® OCT software, enabling the capture and extraction of the macular thickness values as seen in Fig. 2.

Statistical analysis

Demographics and clinical characteristics of patients were described with frequencies (percentages), mean (SD: standard deviation), or median and interquartile range (IQR: 25th percentile-75th percentile), as appropriate.

To identify the variables which explain the variability of thickness of retinal layers considering full-term and preterm (GA < 37 weeks) infants without ROP, generalized additive regression models were used. The following variables were considered in all the univariable analyses: age, gender, parity, birth weight, length, head circumference, Apgar score 1st and

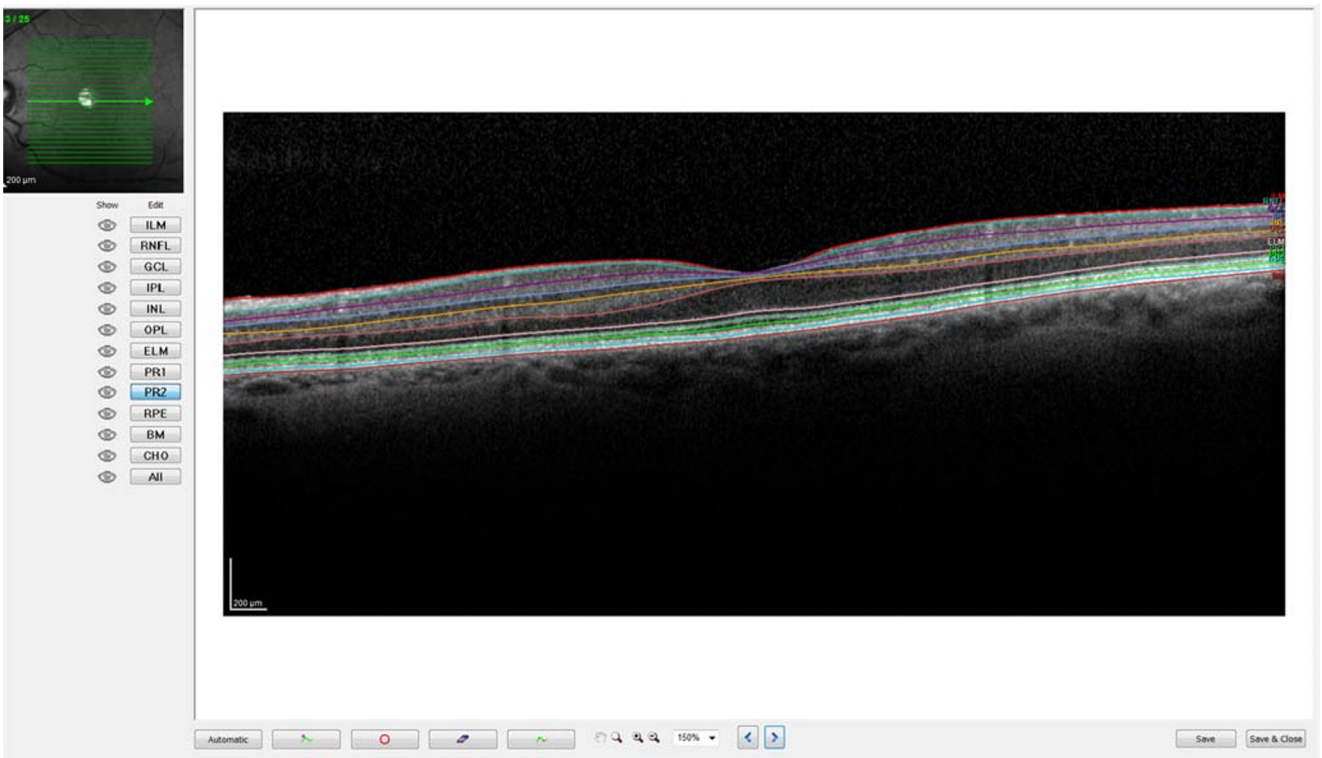

Fig. 1 Retinal layer segmentation

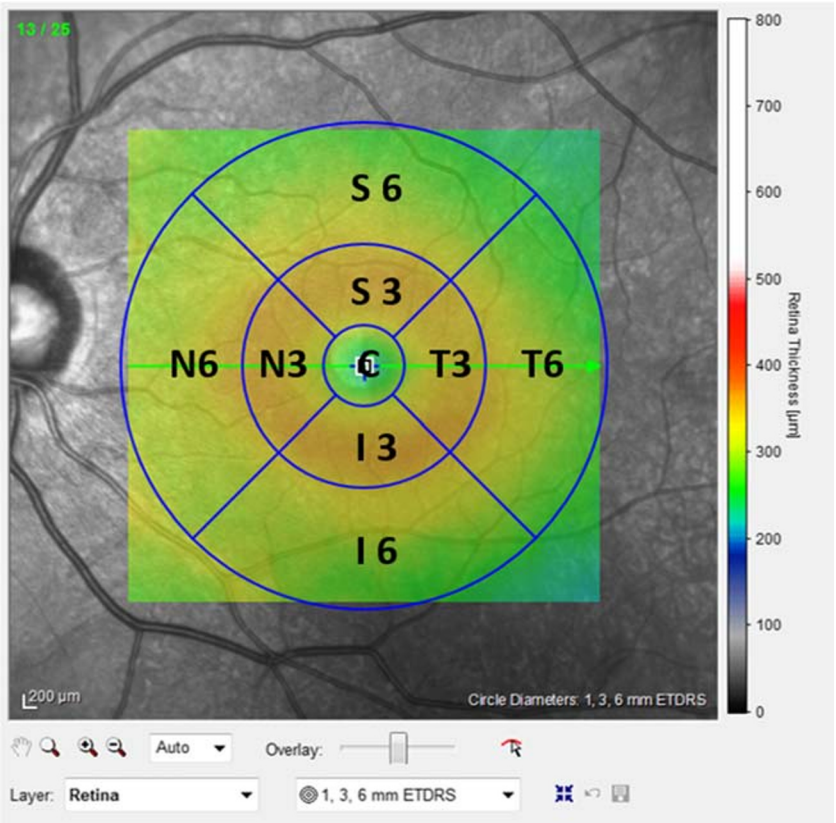

Fig. 2 Representative Spectralis® SD-OCT scans of macular thickness map (ETDRS protocol)

5th minutes, and spherical equivalent; all the variables that attained a p value ≤ 0.25 were considered for the multivariable analysis. For all multivariable models, head circumference was modeled with splines, because a non-linear association with each thickness of retinal layers was identified. Normality assumption of the residuals was verified using Shapiro–Wilk goodness-of-fit test. A level of significance $\alpha = 0.05$ was considered. Statistical analysis was performed using R software (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, year = 2019, http://www.R-project.org.).

Results

Patient demographics and clinical characteristics

A total of 51 children (51 eyes) were recruited, 19 full-term and 32 preterm children. Among the preterm children, 20 were late preterm (GA from 32 to 36 weeks) and 12 early preterm (GA less than 32 weeks). The mean age at observation was 14.13 (3.16) years in the preterm group and 10.58 (4.21) years in the full-term group. Mean GA was 32.16 (2.42) versus 38.89 (1.28) weeks and mean birth weight was 1743 (507) and 3079 (481) g, in the preterm

Table 1 Demographics and clinical characteristics of the patients by group

	Preterm children ($n = 32$)	Full-term children ($n = 19$)	p
Age (years)	14.13 (± 3.16)	10.58 (± 4.21)	0.001
Male gender, n (%)	17 (53.1)	9 (47.4)	0.691*
Gestational age (weeks)	32.16 (± 2.42)	38.89 (± 1.28)	< 0.001
Birth weight (g)	1743 (± 507)	3079 (± 481)	< 0.001
Birth length (cm)	41.53 (± 4.10)	47.78 (± 2.37)	< 0.001
Head circumference (cm)	29.97 (± 2.76)	33.56 (± 1.29)	< 0.001
Apgar score at 1st minute	6.63 (± 2.35)	8.94 (± 0.80)	< 0.001
Apgar score at 5th minute	8.97 (± 1.00)	9.94 (± 0.24)	< 0.001
Caesarean section, n (%)	18 (56.3)	4 (22.2)	0.020*
Spherical equivalent	− 1.27 (± 4.04)	− 1.24 (± 4.46)	0.628

Results are expressed as mean (SD)

*Chi-square test p, remaining p were obtained by Mann-Whitney test p

Table 2 Retinal layer thicknesses (μm)

	Preterm children ($n = 32$)	Full-term children ($n = 19$)	p
Total retina central	284.84 (22.69)	269.63 (19.99)	0.019
Total retina temporal outer	283.72 (12.89)	294.53 (19.03)	0.038
Total retina nasal outer	313.97 (15.10)	326.58 (19.83)	0.030
Total retina inferior outer	288.16 (15.22)	303.32 (24.31)	0.013
GCL temporal outer	35.69 (5.20)	38.79 (2.62)	0.019
GCL inferior outer	33.41 (3.67)	35.37 (3.28)	0.026
IPL temporal outer	31.94 (3.10)	33.74 (2.45)	0.036
IPL superior outer	27.72 (3.13)	29.95 (3.10)	0.017
IPL inferior outer	27.22 (2.98)	29.79 (2.74)	0.004
INL central	20.56 (5.38)	16.84 (3.56)	0.010
OPL central	29.88 (8.47)	24.68 (3.95)	0.016

Results are expressed as mean (SD). p were obtained by Mann-Whitney test p

GCL ganglion cell layer, *IPL* inner plexiform layer, *INL* inner nuclear layer, *OPL* outer plexiform layer

and full-term group, respectively. This data and remaining demographic, clinical, and ophthalmologic characteristics, except retinal layers' thickness of both groups, are summarized in Table 1.

Analysis of retinal layer thickness

An exploratory analysis of the retinal layer thickness in preterm children when compared with full-term children is

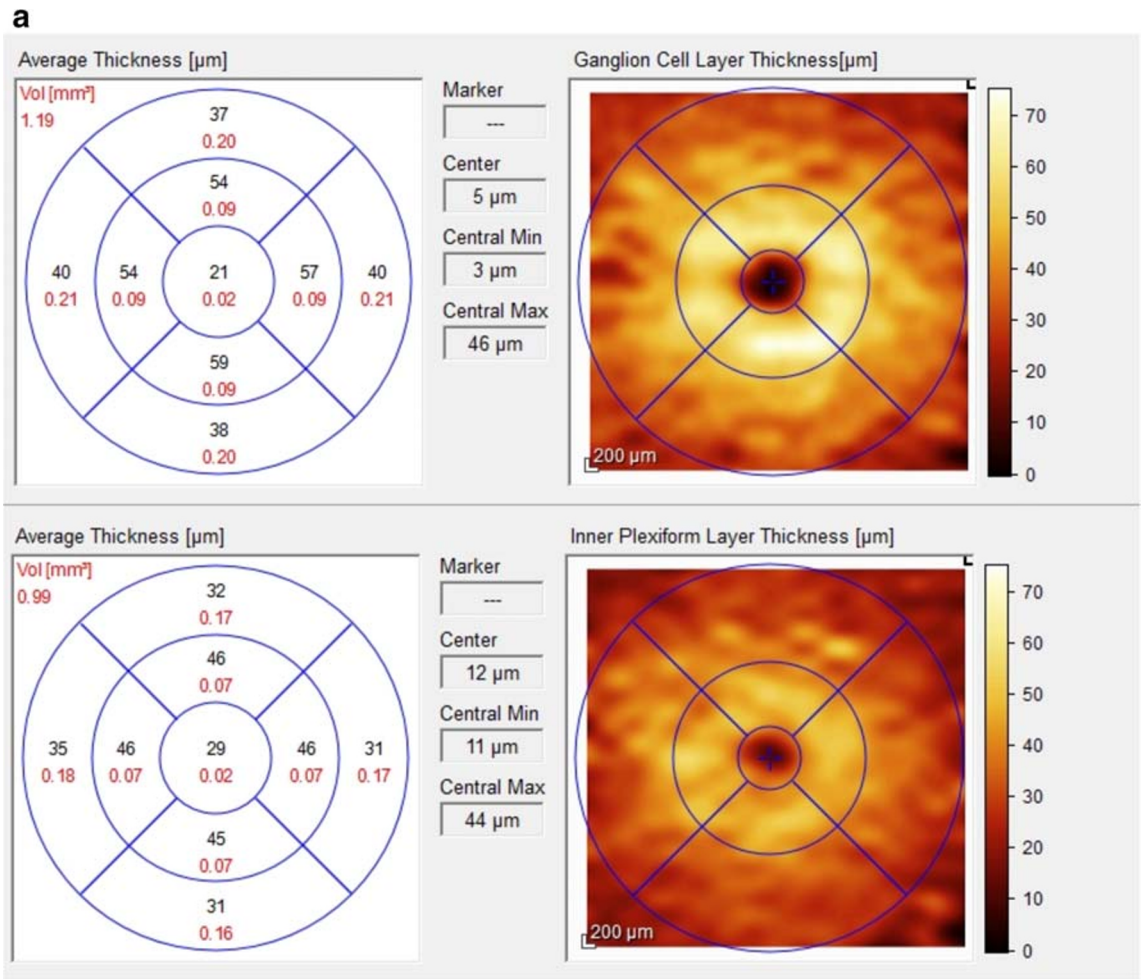

Fig. 3 **a** Example of GCL and IPL thickness profile of a full-term child. **b** Example of GCL and IPL thickness profile of a preterm child

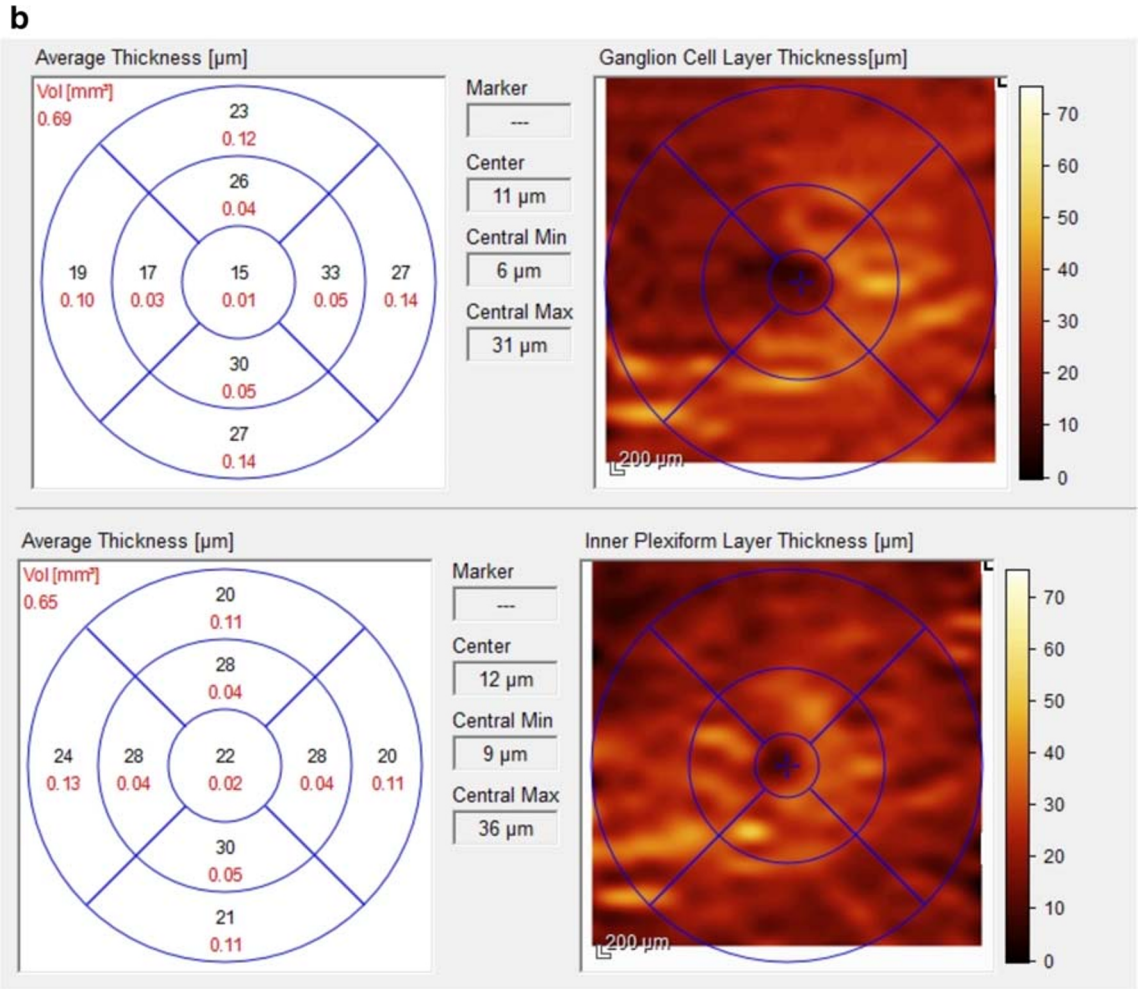

Fig. 3 (continued)

summarized in Table 2. Total retina thickness in the central sector was increased in preterm versus full-term children ($p = 0.019$) and was decreased in three outer areas (temporal, $p = 0.038$; inferior, $p = 0.013$; and nasal, $p = 0.030$). This reduction was also observed in preterm group when compared with full-term group, in GCL and IPL, specifically GCL temporal outer ($p = 0.019$), GCL inferior outer ($p = 0.026$), IPL temporal outer ($p = 0.036$), IPL superior outer ($p = 0.017$), and IPL inferior outer ($p = 0.004$) as can be seen in the clinical example shown in Fig. 3.

In multivariable regression, models were used adjusting for age, gender, parity, birth weight, length, head circumference, Apgar score 1st and 5th minutes, and spherical equivalent. From these variables, only the birth head circumference influenced the models. Thus, a non-linear association was identified between birth head circumference with increased thickness of the total retina nasal outer, GCL (superior outer, temporal outer, and nasal outer) and IPL (superior outer, temporal outer, inferior outer), and consequently modeled with splines through a generalized additive model (Fig. 4).

In these multivariable analyses, the preterm children when compared with the full-term children had thickness reduction in total retina nasal outer sector ($p = 0.018$), in GCL outer sectors: temporal ($p = 0.010$), superior ($p = 0.009$), and in IPL outer sectors: temporal ($p = 0.022$) and superior ($p = 0.004$) as shown in Table 3.

Discussion

Prematurity can cause incomplete retinal development, including neuronal differentiation and neurologic tissue migration [3, 11]. Altered thickness of retinal layer might be a sign of these malformations.

This cross-sectional study used SD-OCT to compare the all retinal layer thickness between 32 prematurely born children without ROP and 19 full-term children. To our knowledge, this is one of the first studies, focusing solely on preterm children without ROP that analyzes each retinal layer and each

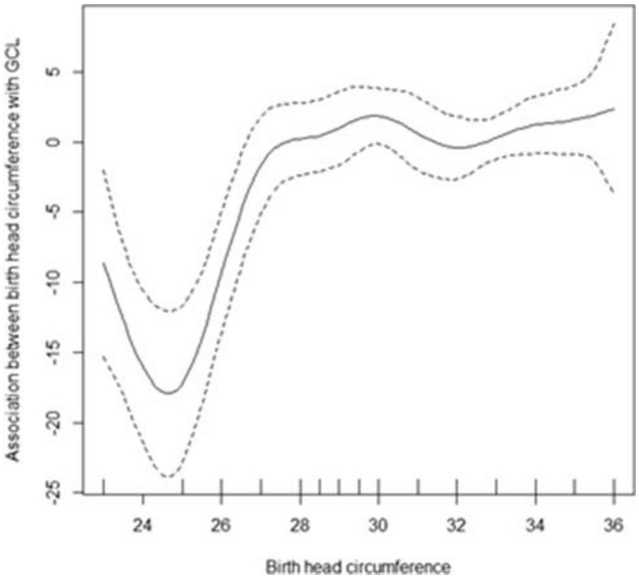

Fig. 4 Influence of birth head circumference (centimeters) in GCL temporal outer layer thickness (black curve) and corresponding 95% confidence intervals (dashed lines), showing a non-linear association

ETDRS macular area. This study suggests that preterm children even without ROP still have structural retinal changes.

Overall, after adjusting for age, gender, parity, birth weight, length, head circumference, Apgar score 1st and 5th minutes, and spherical equivalent and correcting for multiple testing, the current analysis revealed that preterm children compared with full-term children had a significantly thinner total retinal nasal outer, GCL (temporal outer, and superior outer) and IPL (temporal outer and superior outer).

Table 3 Multivariable linear regression model results

Model	Coefficient estimate	*p*	95% CI
Dependent variable: total retinal nasal outer thickness			
Preterm children	− 10.48	0.018	− 18.84 to − 2.13
Dependent variable GCL temporal outer thickness			
Preterm children	− 3.69	0.010	− 6.36 to − 1.02
Dependent variable GCL superior outer thickness			
Preterm children	− 3.49	0.009	− 5.99 to − 0.98
Dependent variable: IPL temporal outer thickness			
Preterm children	− 2.37	0.022	− 4.30 to − 0.43
Dependent variable: IPL superior outer thickness			
Preterm children	− 3.07	0.004	− 5.04 to − 1.11
Dependent variable: IPL inferior outer thickness			
Preterm children	− 2.42	0.039	− 4.64 to − 0.20
Birth length	0.39	0.056	0.00 to 0.77

P values were obtained by generalized additive regression models

GCL ganglion cell layer, *IPL* inner plexiform layer

*Reference category: preterm children group

Very few articles have investigated GCL and IPL differences between preterm without ROP and full-term children. Fieß and colleagues described thinner inner retinal layers (GCL + IPL) in infants with GA ≤ 28 weeks in the inner and outer locations, while not finding any change in GPL + IPL thickness in infants with GA 29–32 weeks [12]. Pueyo et al. found no differences in the average GCL-IPL, fovea, or macula measurements among full-term or preterm in the absence of ROP [11]. Our results differed from these; however, our study was slightly different in design; firstly, it divides inner and outer locations into temporal, superior, nasal, and inferior; secondly, our premature group was mainly composed of late preterms (62.5% of preterm had GA of 32–36 weeks); and finally, we analyzed GCL and IPL layers separately.

The central depression of the fovea is mainly caused by the thinning or absence of the inner nuclear and ganglion cell layers [16]. It is thought that the normal development of inner retinal layers (GCL, IPL) starts from the fovea followed by a lateral cell migration away from this center [4, 16–18]. This migration commences as soon as the GCL of central retina is established (12-week gestation) and occurs continuously throughout the gestation [18]. Studies have suggested that premature birth may disrupt this migration, hypothesizing that this is the reason why there is an increased foveal thickness in preterm children [14]. This might also be the reason for decreased thickness of GCL and IPL mainly found in outer areas, namely temporal outer and superior outer of macula in this study.

Additionally, the only factors that influenced the thinning of the total retina nasal outer, GCL (superior outer, temporal outer and nasal outer) and IPL (superior outer, temporal outer, inferior outer), were the preterm birth and birth head circumference. Unlike some studies, birth weight had no impact on our models regarding any retinal layer [4, 14, 19]. Neither did birth length nor Apgar score at 1st or 5th minutes, this may be due to the fact that our study was mostly composed of late preterms without ROP.

Most studies have focused on the difference between foveal thickness in preterm children with or without history of ROP with full-term children [12, 17, 19–21]. In our study, the same trend of increased foveal thickness for preterm children (none had ROP) was observed (284.84 μm ± 22.69 versus 269.63 μm ± 19.99) although this was only true in univariate analysis [12, 17, 19–21].

Regarding RNFL, our results were aligned with other studies, where the average thickness of this retinal layer was found to be similar between preterm without ROP and full-term children [7].

There was a statistically significant mean age difference between the analyzed preterm group and full-term group, this variable was one of the considered in our multivariable regression, along with gender, parity, birth weight, length, head circumference, Apgar score 1st and 5th minutes, and spherical equivalent.

We are aware that age influences retinal thickness. Although not largely studied, it is thought that increases in total retinal thickness and retinal layer thickness occur from early childhood to adolescence [22]. In this specific study, the preterm group had a higher mean age compared with the full-term group. This according to current knowledge would mean an increase in retinal layers, but the opposite was seen. The preterm group had thickness reduction in total retina nasal outer sector in GCL outer sectors: temporal and superior and in IPL outer sectors: temporal and superior.

Frequently, ophthalmologists are confronted with subnormal OCT values in adolescents or adults, namely regarding GCL thickness. This changes eventually lead to an extensive investigation with new ophthalmologic and neurologic examinations, which ultimately lead to no conclusion. This extensive investigation may lead to patient's anxiety, overdiagnosis, and high costs to healthcare systems. This study reveals that some of these cases in adolescents or adults might be related with history of prematurity even without ROP.

A limitation of our study is its limited sample size and also the lack of longitudinal data. Nonetheless, this study has several strengths, children were all born in the same geographical area, ROP and all comorbidities were excluded in all preterm children, and the analysis was made to all retinal layers in each ETDRS macular area.

In conclusion, preterm children without ROP have thinner outer areas of GCL and IPL, when compared with full-term children. This highlights the importance of questioning gestational history, since these retinal changes may be found later in life leading to useless investigation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the (place name of institution and/or national research committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants and/or legal guardians included in the study.

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