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ORIGINAL PAPER

Macular spectral-domain optical coherence tomography values and correlations in healthy children

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Abstract
Purpose The aim of this study is to investigate potential correlations between age, gender, spherical equivalent and optical coherence tomography (OCT) retinal parameters among healthy children.
Methods A macular spectral-domain OCT was performed in all patients using a Spectralis® OCT device, and the macular thickness and volume of each of the early treatment diabetic retinopathy study (ETDRS) subfields were analysed.
Results Ninety-four children were enrolled. Mean central macular thickness was 274.968 ± 18.28 μm, while mean central macular volume was 0.216 mm^3. Statistical analysis showed a significant correlation between the factor age and central macular thickness ($F(3,90) = 4.96$, $p = 0.003$, $\eta^2 = 0.14$) and central macular volume ($F(3,90) = 4.98$, $p = 0.003$, $\eta^2 = 0.14$). Statistical analysis showed a significant correlation between the factor gender and macular thickness/volume of several ETDRS subfields. A significant correlation between refractive error and macular thickness/volume was also noted.
Conclusions This study shows significant correlations between macular thickness/volume and the factors age, gender and spherical equivalent. Paediatric spectral-domain optical coherence tomography ranges need further investigations since many significant correlations are still to be confirmed.

Keywords Optical coherence tomography · Paediatric ophthalmology · Retinal imaging · Healthy children · OCT values

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Introduction

Optical coherence tomography (OCT) is an imaging technique that allows a sensitive, detailed and precise study of retina and optic disc. This technology has been developed since in the early 1990s and culminated in 1996 with the commercialization of the Zeiss OCT (Carl Zeiss, Meditech, Dublin, CA), the first OCT device to be available for clinical practice [1–3]. In 2002, the research upon this new technology gave birth to the third-generation time-domain OCT devices (Stratus® OCT, Carl Zeiss, Meditech, Dublin, CA) which obtained a wide diffusion and great commercial success. TD-OCT devices allowed a

useful study of the retina but presented some limitations such as two-dimensional images, slow acquisition time and a low resolution of retinal structures. In order to resolve above-mentioned limitations, the spectral-domain technology (SD-OCT) has been developed during the early 2000s [4]. The SD-OCT allows faster acquisition time, higher resolution (1 μm to 5 μm of axial resolution) and a three-dimensional reconstruction of the examined structures that allows a faster and helpful study of the retina [5–7]. The SD-OCT technique has become an irreplaceable technique in everyday practice and is widely performed for diagnosis and follow-up of several retinal diseases. SD-OCT examination is useful and convenient also thanks to the possibility of comparing patient's examination to a normative reference range database that allows a prompt and sensible analysis of any abnormality. Unfortunately, the reference range of most instruments is based upon normal adults' parameters (subjects of or over 18 years of age) and cannot be profitably used for children. Interest in creating a children-suitable OCT database has been rising since the first publication of Salchow and colleagues [8] and resulted in several studies conducted with both time- [9–11] and spectral-domain [12–18] devices. In spite of the large amount of published clinical series, a normative reference for children's OCT parameters is far to be accomplished. The reason of the present lack of normative parameters is due to the matchless differences that occurred in the above-mentioned studies in terms of technology (spectral domain vs. time domain) and instruments (Stratus® vs. Cirrus® vs. Spectralis®) involved. Among the numerous articles recently published, we found that only few of them employed a spectral-domain technology and that only three used a Spectralis® OCT machine [12–14]. In order to obtain homogeneity with the existing results, we performed similar scanning procedures and employed the same inclusion and exclusion criteria of the cited studies. Compared to the published case series of Yanni, Turk and Pérez-Garcia [12–14], our study confirms some of the already known reference values and suggests some not previously reported correlations.

Materials and methods

Monocentric case series study was performed at the Ophthalmology Unit of Pisa University Hospital (Azienda Ospedaliero-Universitaria Pisana, Department of surgical, medical, molecular pathology and of critical area) upon 94 healthy children between 5 and 18 years of age who underwent routinary ophthalmic evaluation between March and June 2016. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

All the enrolled subjects did not present any systemic or ophthalmic pathology and did not have any family history of ophthalmic diseases. All the subjects were Caucasian race, were born at term, had a best-corrected visual acuity of 20/20 in both eyes and showed a spherical equivalent (SE) error between $\pm$ 4 dioptres with a total astigmatism and < 1 dioptre (measured in cycloplegia). At the slit-lamp examination, none of the subjects showed any anterior or posterior segment abnormality or presented an intraocular pressure > 20 mmHg using a Canon TX-10 tonometer (Canon, Tokyo, Japan). All the subjects enrolled in this study underwent a topographic examination (MODI'02, Costruzione Strumenti Oftalmici, Scandicci, Italy) and a biometry using the IOL Master (Carl Zeiss, Meditech, Dublin, CA) in order to assess anterior chamber depth (ACD) and axial length (AL). Cycloplegia was then performed using cyclopentolate 1% drops that were administered 3 times in 5-min intervals. After the third drop was administered, we waited 20 min before performing an autorefractor keratometer exam using a RM-800 (TOPCON, Tokyo, Japan). All the patients who fulfilled the established refractive parameters (spherical equivalent $\pm$ 4 D, total astigmatism < 1 D) were distributed into 5 groups according to their spherical equivalent error assessed in cycloplegia. The 5 groups are reported below together with the SE error of each group:

- Group 1: SE between $-$ 4 and $-$ 0.75 D.
- Group 2: SE between $-$ 0.50 and 0.0 D.
- Group 3: SE between + 0.25 and + 0.75 D.
- Group 4: SE between + 1.00 and + 1.75 D.
- Group 5: SE between + 2.00 and + 4.00 D.

All subjects were then subjected to a macular and optic disc SD-OCT examination using the Heidelberg Spectralis® OCT device (software version 6.0.9, Heidelberg Engineering, Dossenheim, Germany). The OCT exam has been performed during mydriasis by the same experienced operator. For this study, the macular area has been investigated using the high resolution raster lines 20 × 15 acquisition protocol together with the automatic real-time (ART) function (1.536 A-scans, lateral resolution of 6 µm, average of 25 B-scans). Macular volume of each of the 9 early treatment diabetic retinopathy study (ETDRS) subfields is reported by the device and has been separately recorded (Fig. 1).

Statistical analysis was performed using IBM SPSS Statistics 20 software (IBM, Armonk, NY, USA) applying independent-samples *T* test, ANOVA combined with a post hoc (Bonferroni) statistical test. Right eyes and left eyes have been analysed separately, and since there was no statistical difference between the right eye and the left eye group (independent-samples *t* tests, all $p > 0.17$), we proceeded to analyse the right eye group only.

Results

A total of 105 patients were screened, but 11 were excluded due to excessive refractive error (spherical equivalent > +/4 D); the total number of subjects enrolled was therefore 94 (49 males and 45 females, male-to-female ratio 1:0.92). The two groups (males and females) were matched for age (males 10.29 ± 3.08, females 10.22 ± 3.51, independent-samples *t* test $t(92) = 0.94$, $p = 0.925$). Mean age was 10.5 years, while mean spherical equivalent error was 0.33 ± 1.41 D. Patients were distributed to 4 homogeneous groups according to their age (group 1: 5 to 7 years of age, group 2: 8 to 10 years of age, group 3: 11 to 13 years of age and group 4: 14 to 18 years of age). Macular thickness, macular volume and standard deviation for each of the 9 ETDRS regions (central "C", nasal inner "NI", nasal outer "NO", temporal inner "TI", temporal outer "TO", superior inner "SI", superior outer "SO", inferior inner "II" and inferior outer "IO") are reported in Table 1.

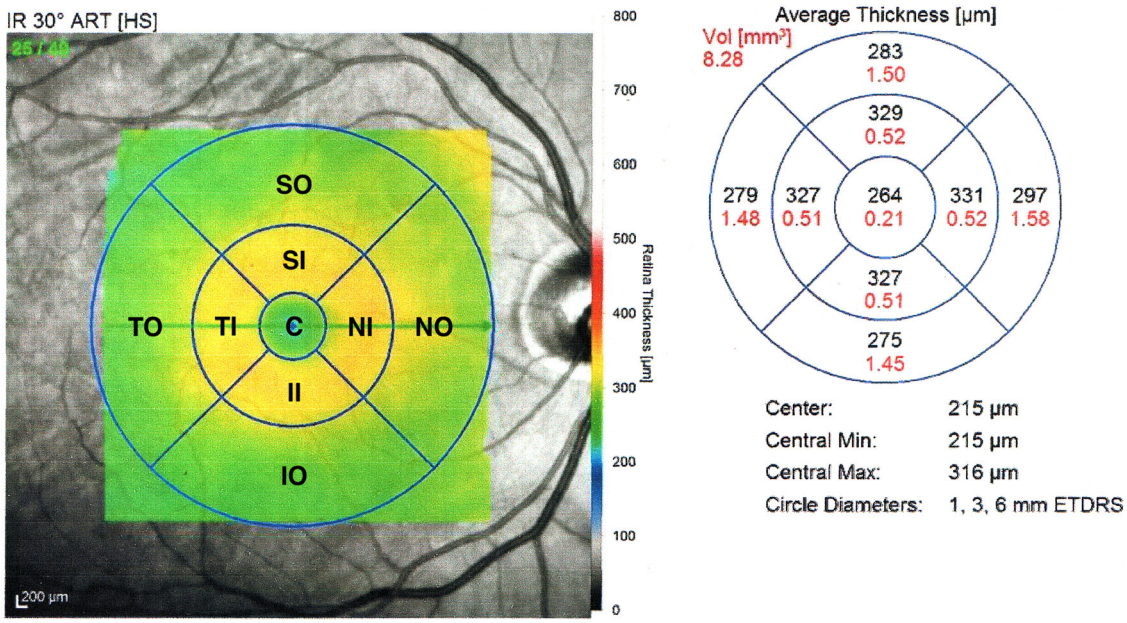

Fig. 1 Macular thickness and volume in each of the 9 early treatment diabetic retinopathy study subfields (central, nasal inner, nasal outer, temporal inner, temporal outer, superior inner, superior outer, inferior inner and inferior outer) as reported by Spectralis® OCT device

Table 1 Macular thickness and macular volume in each of the 9 early treatment diabetic retinopathy study subfields (mean values, percentiles and standard deviation)

	Superior outer	Superior inner	Nasal outer	Nasal inner	Inferior outer	Inferior inner	Temporal outer	Temporal inner	Central
Macular thickness (microns)									
Mean value	312.89	344.15	316.86	346.22	297.90	341.51	288.00	331.55	274.96
1 Percentile	283.00	317.00	272.00	323.00	220.00	304.00	259.00	310.00	234.00
5 Percentile	289.80	324.40	288.60	325.80	269.60	320.80	265.80	313.60	247.80
95 Percentile	344.40	365.40	354.20	371.20	329.00	368.40	313.20	352.40	308.20
Standard Deviation	15.630	13.642	17.745	14.263	18.348	15.436	14.437	12.618	18.275
Macular volume (mm^2)									
Mean value	1.659	0.541	1.680	1.124	1.597	0.536	1.526	0.521	0.216
1 Percentile	1.50	.50	1.44	.51	1.17	.48	1.38	.49	.18
5 Percentile	1.54	.51	1.53	.51	1.43	.50	1.41	.49	.19
95 Percentile	1.83	.57	1.88	.58	1.75	.58	1.66	.55	.24
Standard Deviation	0.0831	0.0215	0.0936	0.6167	0.0977	0.0239	0.0760	0.0200	0.0150

Influence of age

A multivariate ANOVA (age × gender × macular thickness and volume) revealed a significant effect of the factor age for the central macular thickness ($F(3,90) = 4.96$, $p = 0.003$, $\eta^2 = 0.14$) and central macular volume ($F(3,90) = 4.98$, $p = 0.003$, $\eta^2 = 0.14$). The post hoc test (Bonferroni) on central macular thickness parameters showed a significant difference between groups 1 and 3 ($p = 0.004$) and between groups 1 and 4 ($p = 0.021$). For central macular volume, the post hoc test showed a significant variation between groups 1 and 3 ($p = 0.004$) and between groups 1 and 4 ($p = 0.020$).

Finally, a significant positive correlation was found across subjects between age and central macular thickness (Spearman's $\rho = 0.36$, 1,00,000 repetitions, bootstrap permutation test, $p = 0.012$) and between age and central macular volume (Spearman's $\rho = 0.37$, 1,00,000 repetitions, bootstrap permutation test, $p = 0.011$). Central macular thickness and volume among different age groups are summarized in Figs. 2 and 3.

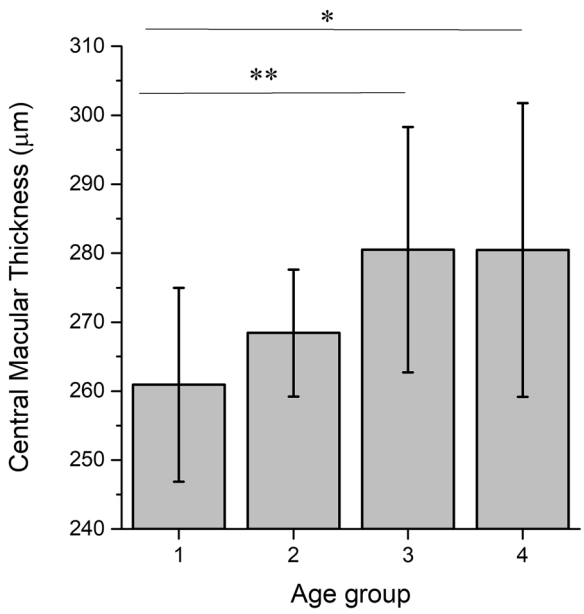

Fig. 2 Central macular thickness among different age groups

Influence of gender

A significant effect of the factor gender was found for the following subfields:

- Inferior inner subfield thickness: $F(1,86) = 6.863$, $p = 0.01$.
- Temporal inner subfield thickness: $F(1,86) = 7.816$, $p = 0.006$.
- Central subfield thickness: $F(1,86) = 10.817$, $p = 0.001$.

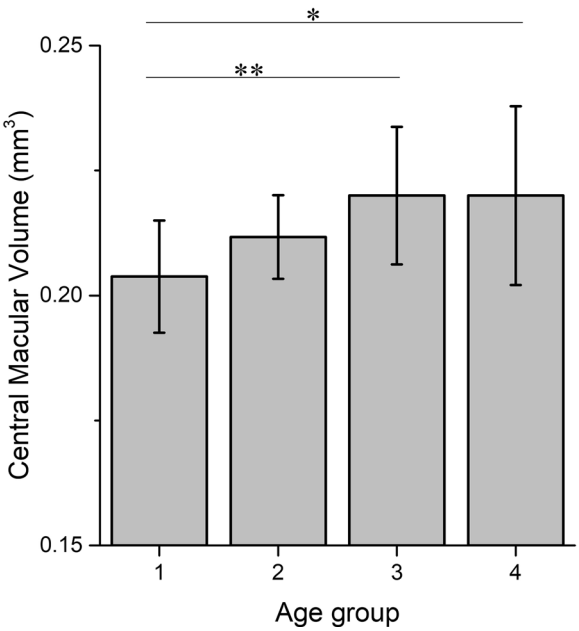

Fig. 3 Central macular volume among different age groups

- Inferior inner subfield volume: $F(1,86) = 7.343$, $p = 0.008$.
- Temporal inner subfield volume: $F(1,86) = 7.339$, $p = 0.008$.
- Central subfield volume: $F(1,86) = 14.036$, $p < 0.001$.

Importantly, no significant interaction was found between the factors age and gender for any of the macular parameters tested (all $p > 0.1$), indicating that the two factors vary independently.

Mean values of macular volume and thickness in the two groups are reported in Tables 2 and 3.

Influence of spherical equivalent

Multivariate analysis of variance (ANOVA 5 × 19) showed a significant difference of macular thickness between the 5 groups in 3 out of 9 ETDRS subfields. Differences in macular thickness were in facts found statistically significant in SO ($F(4,89) = 3.99$, $p = 0.005$), SI ($F(4,89) = 2.90$, $p = 0.005$) and TO ($F(4,89) = 5.45$, $p = 0.001$) subfields. Moreover, post hoc test confirmed significant differences in SO macular thickness between groups 1 versus 4 ($p = 0.035$) and 1 versus 5 ($p = 0.029$). Similar results were also found in the TO subfield where significant differences were found between group 1 versus 4 ($p = 0.014$), 2 versus 4 ($p = 0.002$), 2 versus 5 ($p = 0.036$) and group 3 versus 4 ($p = 0.032$). Linear analysis of the above-mentioned data showed a significant positive correlation between SE and macular thickness of SO (Spearman's index $\rho = 0.41$, $p < 0.001$), SI (Spearman's index $\rho = 0.26$, $p < 0.012$), NO (Spearman's index $\rho = 0.22$, $p = 0.036$), IO (Spearman's index $\rho = 0.32$, $p < 0.002$), II (Spearman's index $\rho = 0.24$, $p = 0.018$), TO (Spearman's index $\rho = 0.41$, $p < 0.001$) and TI (Spearman's index $\rho = 0.25$, $p = 0.012$) ETDRS subfields. Similar results were also found when we analysed the correlation between spherical equivalent and macular volume of each of the 9 ETDRS subfields. Linear analysis showed in fact a significant positive correlation between SE and macular volume of SO (Spearman's index $\rho = 0.41$, $p < 0.001$), SI (Spearman's index $\rho = 0.21$, $p < 0.041$), NO (Spearman's index $\rho = 0.21$, $p = 0.043$), IO (Spearman's index $\rho = 0.33$, $p = 0.001$), II (Spearman's index $\rho = 0.25$, $p = 0.016$), TO (Spearman's index $\rho = 0.42$, $p < 0.001$) and TI (Spearman's index $\rho = 0.21$, $p = 0.004$) ETDRS subfields. Axial length (AL) and anterior chamber depth (ACD) were not recorded for all patients because the collected data tended to show poor acquisition quality probably due to defective instrument software and low patients' compliance. We therefore decided to quit AL and ACD assessment after the first few patients. The already collected data did not anyway show any significant correlation between macular thickness/volume and the factors ACD or AL ($p = 0.08$). Significant linear correlations between macular thickness/volume and spherical equivalent are displayed in Tables 4 and 5. Central macular thickness and volume among different spherical equivalent groups are summarized in Figs. 4 and 5.

Discussion

Regarding central macular thickness this study found a mean value of 274.968 µm which is very similar to the values found by Turk (258.6 µm) [12], Yanni (271.2 µm) [13] and Pérez (263.6 µm) [14]. Mean central macular volume, 0.216 mm^3 in our series, was also found to be very similar to the values found by above-mentioned authors (0.203 mm^3 for Turk and

Table 2 Differences in macular thickness parameters between males and females (mean values, percentiles and SD)

	Sex	Mean value (μm)	SD	1 Percentile	5 Percentile	95 Percentile
Central $p = 0.001$	F	269.911	17.2123	234.00	244.20	304.10
	M	279.612	18.1542	246.00	253.00	314.00
Superior outer $p > 0.05$	F	313.0690	12.54401	283.00	291.30	336.60
	M	310.7941	16.99158	283.00	286.50	356.00
Superior inner $p > 0.05$	F	341.3429	11.41450	322.00	326.60	360.50
	M	344.25	14.558	317.00	322.50	382.00
Nasal outer $p > 0.05$	F	320.2857	15.44168	286.00	290.50	338.20
	M	314.4722	17.76913	272.00	281.50	360.50
Nasal inner $p > 0.05$	F	341.9429	10.69344	323.00	323.90	368.40
	M	344.2500	14.29760	325.00	326.50	375.00
Inferior outer $p > 0.05$	F	295.5484	13.97817	304.00	320.30	360.50
	M	296.6061	18.09858	263.00	269.50	334.50
Inferior inner $p = 0.01$	F	337.667	12.4207	304.00	320.30	360.50
	M	345.041	17.1379	317.00	319.50	381.50
Temporal outer $p > 0.05$	F	284.2286	10.38689	262.00	263.20	307.10
	M	286.7778	14.55455	259.00	266.00	315.00
Temporal inner $p = 0.006$	F	328.089	10.3327	311.00	312.00	346.40
	M	334.735	13.7489	314.00	315.00	360.00

Table 3 Differences in macular volume parameters between males and females (mean values, percentiles and SD)

	Sex	Mean value (mm^3)	SD	1 Percentile	5 Percentile	95 Percentile
Central $p < 0.001$	F	0.211	0.0135	.18	.19	.24
	M	0.220	0.0151	.19	.20	.25
Superior outer $p > 0.05$	F	1.6597	0.06555	1.50	1.54	1.79
	M	1.6471	0.08980	1.50	1.52	1.89
Superior inner $p > 0.05$	F	0.5363	0.01880	.51	.51	.57
	M	0.5408	0.02335	.50	.51	.60
Nasal outer $p > 0.05$	F	1.7069	0.08632	1.52	1.54	1.79
	M	1.6667	0.09411	1.44	1.49	1.91
Nasal inner $p > 0.05$	F	0.5374	0.01738	.51	.51	.59
	M	0.5403	0.02311	.51	.51	.59
Inferior outer $p > 0.05$	F	1.5668	0.07436	1.17	1.42	1.72
	M	1.5706	0.09536	1.39	1.42	1.78
Inferior inner $p = 0.008$	F	0.530	0.0198	.48	.50	.57
	M	0.542	0.0261	.50	.51	.60
Temporal outer $p > 0.05$	F	1.5060	0.05494	1.39	1.40	1.63
	M	1.52	0.07808	1.38	1.40	1.73
Temporal inner $p = 0.008$	F	0.516	0.0163	.49	.49	.54
	M	0.526	0.0220	.49	.50	.57

Table 4 Significant linear correlation between macular thickness and spherical equivalent in the different early treatment diabetic retinopathy study subfields

ETDRS subfield	Spearman's index ρ	p value
Superior outer	0.41	< 0.001
Superior inner	0.26	< 0.012
Nasal outer	0.22	0.036
Inferior outer	0.32	< 0.002
Inferior inner	0.24	0.018
Temporal outer	0.41	< 0.001
Temporal inner	0.25	0.012

Table 5 Significant linear correlation between macular volume and spherical equivalent in the different early treatment diabetic retinopathy study subfields

ETDRS subfield	Spearman's index ρ	p value
Superior outer	0.41	< 0.001
Superior inner	0.21	0.041
Nasal outer	0.21	0.043
Nasal inner	0.23	0.028
Inferior outer	0.33	0.001
Inferior inner	0.25	0.016
Temporal outer	0.42	< 0.001
Temporal inner	0.21	0.004

0.21 mm^3 for Pérez). Regarding the influence of age on central macular thickness and volume, this study suggests a positive correlation between these elements ($p \leq 0.001$ for both central macular thickness and volume). This correlation was also suggested by Yanni [13], Barrio–Barrio [16] and Pérez [14] while is in contrast to the findings of Turk [12], who used a SD-OCT technology, and Zhang [9], who used a TD-OCT technology.

Regarding the influence of gender on macular thickness and volume, Barrio–Barrio found that boys statically have higher values of central macular thickness than girls [16]. In this study, we noticed that boys have higher macular thickness than girls in central ($p = 0.001$), inferior inner ($p = 0.01$) and temporal inner ($p = 0.006$) subfields. Similar results were also found regarding macular volume shown to be higher in boys than in girls in central ($p < 0.001$), inferior inner ($p = 0.008$) and temporal inner

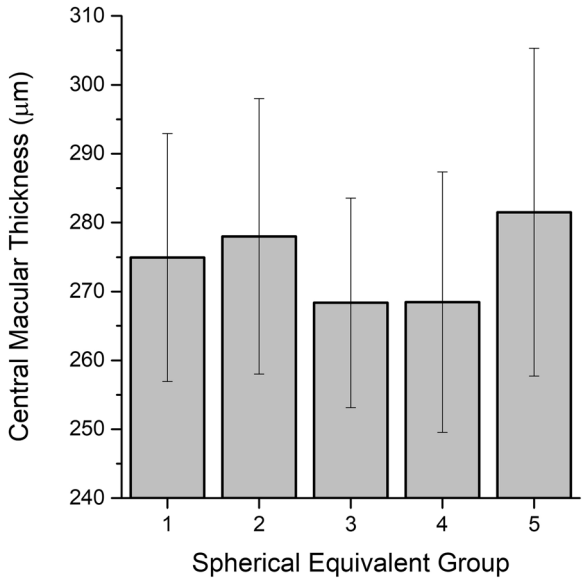

Fig. 4 Central macular thickness among different spherical equivalent groups

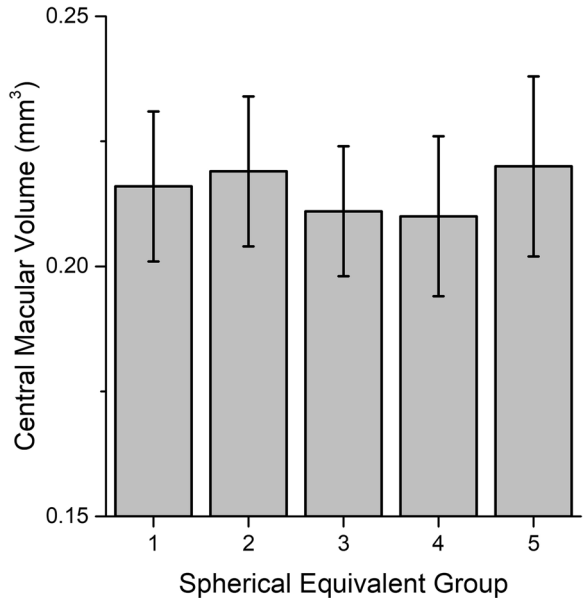

Fig. 5 Central macular volume among different spherical equivalent groups

($p = 0.008$) subfields. The results of this series coincide with those found by Barrio–Barrio [16] who found, in central subfield, higher values of macular thickness/volume in boys than in girls. Despite this concordance, the other cited articles [12, 14] did not notice any correlation between sex and macular

thickness/volume. Larger case series and more overlapping statistical and acquisition procedures are required to clarify this possible correlation.

In our series, we also found a positive correlation between spherical equivalent and macular volume/thickness. Hyperopic patients tend to present a thicker macula and a greater macular volume in several ETDRS subfields (Tables 4, 5). This correlation between SE and macular thickness and volume is not confirmed by the series of Turk, Yanni or Perez-Garcia, while other studies conducted with a TD-OCT [9, 10] described a reduction in central macular volume in myopic eyes together with an increase in perifoveal thickness and volume.

Conclusions

This study suggests a positive influence of age, male sex and hyperopia on macular thickness and volume. Even if the interest upon this topic is very high among the authors, a low number of studies have been published. A larger case series is therefore still needed to better understand the characteristics and the normal reference ranges of SD-OCT in young healthy children.

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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 institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Availability of data and materials All the data used and/or analysed during the current study are available from the corresponding author on reasonable request.

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