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Retinal Nerve Fiber Layer and Macula Thickness with Spectral Domain Optical Coherence Tomography in Children: Normal Values, Repeatability and the Influence of Demographic and Ocular Parameters

Çocuklarda Spektral Domain Optik Koherens Tomografi ile Retina Sinir Lifi Tabakası ve Maküla Kalınlığı: Normal Değerler, Tekrarlanabilirlik ve Demografik ve Oküler Parametrelerin Etkisi

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ABSTRACT Objective: To determine normal values for retinal nerve fiber layer (RNFL) and macular thickness in children using spectral domain optical coherence tomography (SD-OCT), to assess the repeatability of the SD-OCT measurements and to analyse their correlations with age, gender, refraction and axial length. **Material and Methods:** Healthy children aged 5-17 years were enrolled for this cross-sectional study. All subjects underwent comprehensive ophthalmological examination, cycloplegic refraction and axial length measurement. Thereafter, three consecutive SD-OCT measurements were obtained by the same operator. The mean of three consecutive measurements for each SD-OCT parameter was included in the normal values. Repeatability was calculated by comparing the three consecutive measurements and expressed as an intraclass correlation coefficient. The correlation of all SD-OCT parameters with age, gender, spherical equivalent refraction and axial length were statistically analysed. **Results:** Two hundred two eyes of 202 children (103 females and 99 males) with a mean age of 10.4±3.4 years were included. The mean of average RNFL thickness was 103.9±8.2 (84.3-132) µm. The mean central macular thickness was 257.4± 22.1 (217-329) µm. Intraclass correlation coefficients of repeated measurements were over 0.81 for all evaluated parameters. Males had significantly thicker central macula than females (p=0.013). On multivariate linear regression analysis, spherical equivalent refraction was the only parameter independently effective on average RNFL thickness (p<0.001). **Conclusion:** This study has provided normal values for RNFL and macular thickness measured with SD-OCT in healthy children. The high repeatability of the measurements indicates that SD-OCT can be used reliably in children that are five years and older. Data obtained in this study may be helpful in the assessment of childhood optic nerve and macular diseases with SD-OCT.

Keywords: Child; tomography, optical coherence; macula lutea; retina

ÖZET Amaç: Çocuklarda spektral domain optik koherens tomografi (SD-OKT) ile retina sinir lifi (RSLT) ve maküla kalınlıklarının normal değerlerini belirlemek, SD-OKT ölçümlerinin tekrarlanabilirliğini ve yaş, cinsiyet, refraksiyon ve aksiyel uzunluk ile ilişkilerini saptamak. **Gereç ve Yöntemler:** Bu kesitsel çalışmaya yaşları 5-17 yıl arasında değişen sağlıklı çocuklar dahil edildi. Tüm olguların ayrıntılı göz muayenesi, sikloplejik refraksiyon ve aksiyel uzunluk ölçümleri yapıldı. Sonrasında art arda üç kez aynı görevli tarafından SD-OKT ölçümleri alındı. Normal değerler belirlenirken her parametre için bu üç ölçümün ortalaması alındı. Tekrarlanabilirlik ise bu üç ölçüm karşılaştırılarak hesaplandı ve sınıf içi korelasyon katsayısı olarak ifade edildi. Ayrıca tüm SD-OKT parametrelerinin yaş, cinsiyet, sferik ekivalan refraksiyon ve aksiyel uzunluk ile ilişkileri istatistiksel olarak analiz edildi. **Bulgular:** Ortalama yaşları 10,4±3,4 olan 202 çocuğun (103 kız, 99 erkek) 202 gözü çalışmaya dahil edildi. Ortalama RSLT kalınlığı 103,9±8,2 (84,3-132) µm, ortalama santral maküla kalınlığı ise 257,4±22,1 (217-329) µm idi. Tekrarlanan ölçümlerin sınıf içi korelasyon katsayıları tüm parametreler için 0,81'in üzerinde idi. Erkeklerde santral maküla kalınlığı kızlara göre daha yüksek idi (p=0,013). Çok değişkenli lineer regresyon analizinde, ortalama RSLT kalınlığı üzerinde bağımsız olarak etkili olan tek parametre sferik ekivalan refraksiyon idi (p<0,001). **Sonuç:** Bu çalışma sonucunda, sağlıklı çocuklarda SD-OKT ile RSLT ve maküla kalınlık ölçümleri için normal değerler belirlenmiştir. Ölçümlerin yüksek tekrarlanabilirlik göstermesi SD-OKT'nin çocuklarda beş yaşından itibaren güvenilir şekilde kullanılabileceğine işaret etmektedir. Bu çalışmada elde edilen veriler çocuklarda optik sinir ve maküla hastalıklarının SD-OKT ile değerlendirilmesinde yardımcı olabilir.

Anahtar Kelimeler: Çocuk; tomografi, optik koherens; maküla lutea; retina

The assessment of macular and optic nerve diseases with fundoscopy or visual field testing may be difficult in paediatric patients due to limited cooperation. Spectral domain optical coherence tomography (SD-OCT), which provides high-resolution cross-sectional images and quantitative measurements of retinal structures, may particularly be helpful in the assessment of children, as it is a non-contact and fast method. Measurements obtained with SD-OCT should be compared to normal reference values to differentiate abnormalities. However, built in normative data of SD-OCT devices are for individuals older than 18 years. To overcome this limitation, several reports have provided normal values for paediatric SD-OCT.[1-6] On the other hand, the repeatability and reproducibility of this method in children has been shown in a limited number of studies.[7,8] The purpose of this current study was to determine normal values of retinal nerve fiber layer (RNFL) and macula thickness in a cohort of healthy Caucasian children using iVue 100 SD-OCT and to assess the repeatability of the SD-OCT measurements. The correlations of the SD-OCT measurements with age, gender, refraction and axial length (AL) were also analysed.

MATERIAL AND METHODS

Caucasian children aged 5-17 years were consecutively and prospectively recruited for this cross-sectional study. The study protocol was approved by the local ethics committee and adhered to the tenets of the Declaration of Helsinki. An informed consent was obtained from parents or legal guardians of each child before participation.

All subjects underwent comprehensive ophthalmological examination. Cycloplegic refraction was measured with an autorefractometer (ARK 510A, Nidek, Japan) 20 minutes after instillation of two drops of tropicamide 1% and recorded as spherical equivalent refraction (SER). Axial length was measured with IOL master device (Carl Zeiss AG, Oberkochen, Germany) and the average of ten readings was recorded.

Healthy children with BCVA≥ 20/25 and normal findings on biomicroscopic and fundoscopic examination in at least one eye were included in the study. Exclusion criteria were prematurity, systemic diseases, family history of glaucoma, prior ocular surgery or trauma, amblyopia, strabismus, media opacities, retinal or optic nerve head abnormalities, glaucoma and high refractive errors (spherical error exceeding ±6.00 diopters or cylindrical error >2.50 diopters). Three subgroups were established based on age (5-8, 9-12 and 13-17 year olds).

Spectral domain OCT imaging was performed with iVue100 (version 3.1, Optovue Inc., Fremont, CA, USA). This device uses a scanning laser diode to emit a scan beam with a mean wavelength of 840±10 nm. The scan speed is 26,000 A-scans per second and the axial resolution is 5 μm. The image quality is determined by the scan quality index (SQI) of the device. According to the manufacturer's guidelines, SQI ≥27 for a RNFL scan and SQI≥40 for a macula scan indicates adequate quality.

All SD-OCT measurements were performed through dilated pupils by the same operator. Three consecutive scans of RNFL and macula were obtained from both eyes. For RNFL thickness measurements, nerve fiber optic nerve head scan protocol of the device was used. This protocol measured the circumpapillary RNFL thickness by recalculating data along a circle of 3.45 mm in diameter around the optic disc. The software's automatic detection of the optic nerve head was reviewed and the centring of the scans was confirmed by directly observing the optic disc on the screen. Retinal nerve fiber layer parameters provided by the device software included an average thickness, four quadrant and eight sector thicknesses (Figure 1a). Macular thickness measurements were obtained using the 6x6 mm retina map scan and demonstrated in nine areas of the ETDRS subfield template (Figure 1b).[9]

One eye of each child was included in the study. The left eye was included if the child's right eye had one of the exclusion criteria, inadequate quality scans or scans with motion artefacts. Otherwise, the right eye was used. Children who could

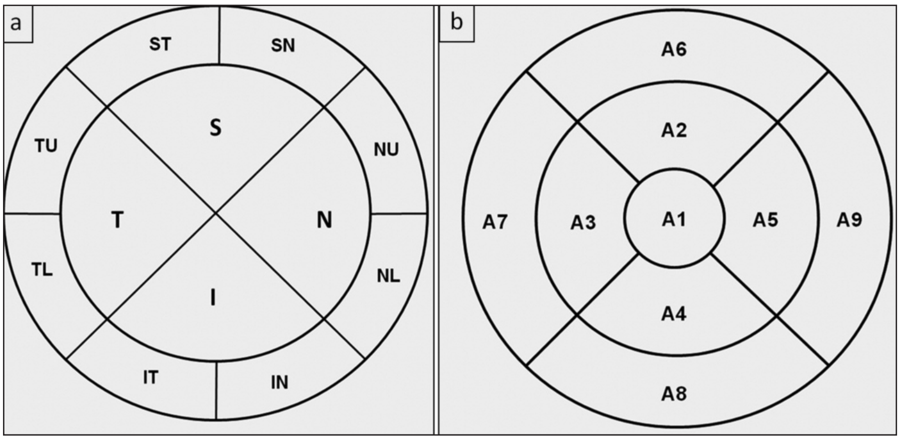

FIGURE 1: (a) Retinal nerve fiberlayer template. S:superior, N:nasal, I: inferior, T:temporal SN: superior nasal, NU:nasal upper, NL:nasal lower, IN:inferior nasal, IT:inferior temporal, TL:temporal lower, TU:temporal upper, ST:superior temporal **(b)** Macular subfield template. Central (A1), inner circle (A2-A5) and outer circle (A6-A9).

not cooperate with the SD-OCT procedure and children whose scans from both eyes were of inadequate quality or had motion artefacts were excluded from the study.

Statistical analysis was performed using SPSS version 22 (IBM corp., Armonk, NY, USA). Data normality was assessed using the Kolmogorov-Smirnov test. For each parameter, the mean value of three adequate quality scans was included in the normal values. Repeatability was calculated using three consecutive measurements and expressed as an intraclass correlation coefficient (ICC). An ICC close to 1.0 is regarded as perfect. ANOVA (Tukey test) and Kruskal-Wallis test were used to compare measurements among the different age groups. Independent sample t-test and Mann-Whitney U test were used to analyse the effect of gender on measured thicknesses. Correlations were analysed using the Spearman correlation analysis. Multivariate linear regression analysis was used to determine the effects of variables on SD-OCT measurements.

RESULTS

Two hundred seventeen children whose parents gave consent were initially enrolled in the study. Fifteen of these children were excluded due to lack of cooperation, motion artefacts or inadequate quality scans. Two hundred two eyes of 202 children (103 females and 99 males) with a mean age of 10.4±3.4 (median: 9.7) were finally included. Table 1 shows the characteristics of the children by age groups (Table 1).

Mean SQI was 64.9±8 for RNFL measurements (range: 41-82, median: 65.3) and 66.2±6.9 (median: 67 range: 40-81) for macula measurements. No significant difference was observed between age groups regarding SQI of RNFL (p=0.836) or macula (p=0.128) scans.

Table 2 shows normal RNFL and macular thickness values in all children and in three age groups (Table 2). Statistically significant correlations (p<0.001) were found between three consec-

TABLE 1: Characteristics of study subjects with regard to age groups.

			Spherical equivalent (D)		Axial length (mm)	
Age (years)	N	(F / M)	Mean ± SD	Range	Mean ± SD	Range
5 - 8	80	37 / 43	0.72 ± 1.51	-3.3 - 4.5	22.7 ± 0.92	20.1 - 24.9
9 - 12	71	43 / 28	-0.01 ± 1.51	-4.3 - 5.9	23.5 ± 1.12	21.8 - 26.9
13 - 17	51	19 / 32	-0.67 ± 2.05	-5.8 - 3.9	23.9 ± 1.05	22.2 - 26.6

N, number of subjects; F/M, female/male; D, diopters.

TABLE 2: Normal values for retinal nerve fiber layer and macular thickness (µm).

	Total		Age: 5-8 (yr)		Age: 9-12 (yr)		Age: 13-17 (yr)		
	Mean±SD	5th-95th percentile	Mean±SD	5th-95th percentile	Mean±SD	5th-95th percentile	Mean±SD	5th-95th percentile	P value
Quadrant RNFL									
I	130.6±14.2	107.5-155.7	130.2±15.8	103.8-161.8	132.9±13.0	111.6-154.3	127.9±13.0	105.7-151.5	0.153
S	126.8±12.2	107.0-148.0	129.2±13.0	106.8-151.1	127.6±10.6	110.4-146.9	122.0±12.0	100.8-147.0	0.003*
N	82.2 ±10.9	65.3-101.0	82.7±11.0	66.2-102.2	84.7±11.2	64.0-104.4	78.2±8.9	63.2-92.9	0.004*
T	76.2± 8.2	63.0-91.4	76.7±7.4	64.8-90.9	77.3±8.7	62.5-92.6	73.8±8.2	60.4-92.1	0.046*
Sector RNFL									
SN	113.6±16.4	89.0-143.4	117.0±17.2	91.0-145.1	115.5±15.6	92.7-145.1	105.9±13.8	86.2-132.0	<0.001
NU	88.2±12.6	68.0-110.0	88.7±13.0	69.0-110.6	91.1±12.6	68.7-111.0	83.6±10.5	63.0-100.1	0.004*
NL	76.3 ±11.0	59.0-96.0	76.9±11.1	61.4-98.0	78.4±11.5	59.8-99.6	72.5±9.0	56.7-86.8	0.011*
IN	115.9±19.8	84.8-151.0	116.9±22.5	82.4-168.2	118.7±18.3	90.3-150.4	110.5±16.5	81.6-142.1	0.067
IT	145.1±16.0	118.3-169.1	143.2±16.3	116.7-165.9	147.0±16.4	114.6-172.5	145.4±14.9	122.0-170.7	0.360
TL	70.3±9.1	57.8-82.7	71.5±10.1	59.9-86.8	70.6±8.1	57.3-82.6	68.3±8.7	54.8-81.9	0.159
TU	81.9±11.5	65.9-105.0	82.1±10.5	66.7-105.0	83.6±12.0	64.9-104.8	79.4±11.9	62.5-110.9	0.137
ST	139.9±14.0	115.0-164.0	141.5±14.1	117.4-164.3	139.6±13.7	114.7-158.9	138.0±14.4	113.2-167.2	0.391
A	103.9±8.2	91.0-118.0	104.6±8.7	89.8-119.1	105.6±7.8	93.1-119.6	100.5±7.0	88.6-114.4	0.002*
Macular subfield									
A1	257.4±22.1	227.0-307.4	255.6±26.0	225.0–321.3	260.5±20.2	230.5-303.5	256.2±17.7	225.6-288.8	0.361
A2	313.5±13.9	290.8-337.1	310.1±14.1	281.0–333.3	317.1±14.4	291.0-341.5	314.0±11.7	293.5-331.8	0.052
A3	299.6±15.5	277.7-323.0	297.1±16.3	277.3–321.3	301.3±15.6	272.5-336.0	301.2±13.8	276.6-323.0	0.190
A4	307.8±15.0	282.0-331.1	303.5±14.8	281.4-325.4	311.0±15.2	283.0-332.5	310.2±13.7	287.9-333.4	0.005*
A5	316.0±15.5	292.8-342.0	312.2±14.6	291.9-340.1	318.1±16.1	292.0-344.5	319.1±14.9	294.5-344.4	0.052
A6	288.7±13.9	267.0-313.1	285.6±13.3	263.7-307.5	292.3±14.2	266.5-315.5	288.2±13.6	269.5-318.9	0.052
A7	280.1±13.8	257.0-303.0	280.7±12.6	258.7-303.0	281.8±15.5	255.5-312.5	276.6±12.7	256.5-298.6	0.114
A8	285.1±15.3	260.0-315.0	285.4±15.1	259.8-310.0	287.6±16.3	255.5-317.5	281.2±13.5	260.5-310.0	0.073
A9	301.7±15.3	277.0-327.1	299.4±14.3	274.6-323.2	304.9±15.7	275.0-333.0	300.9±15.7	279.5-335.3	0.083

I: Inferior; S: Superior; N: Nasal; T: Temporal; SN: Superior nasal; NU: Nasal upper; NL: Nasal lower; IN: Inferior nasal; IT: Inferior temporal; TL: Temporal lower; TU: temporal upper; ST: Superior temporal; A: Average; A1: Central; A2: Inner superior; A3: Inner temporal; A4: Inner inferior; A5: Inner nasal; A6: Outer superior; A7: Outer temporal; A8: Outer inferior; A9: Outer nasal; yr: years.
*p< 0.05.

utive SD-OCT measurements and ICCs were over 0.81 in all RNFL and macular thickness parameters (Table 3).

Average RNFL thickness did not differ between females and males (104.0±8.2 µm vs. 103.8±8.2 µm, p=0.912). Female patients had significantly thicker RNFL in the temporal quadrant (p=0.002), temporal upper (p=0.003) and inferior temporal sectors (p=0.029).

Spearman correlation analysis revealed a significant positive correlation of average RNFL thickness with SER (p<0.001) and a significant negative correlation of average RNFL thickness with AL (p<0.001) and age (p=0.003). On multivariate linear regression analysis, SER was found to be the only independent variable affecting average RNFL thickness (p<0.001) (Figure 2).

Males had significantly thicker central macula than females (260.8±21.1 µm vs. 254.3±22.7 µm, p=0.013). Also, the A2, A3, A4, A8 areas were significantly thicker in males (p□0.05). Among the whole group, the inner circle subfield was significantly thicker than the outer circle subfield (309.3±13.6 µm vs. 294.9±12.3 µm, p<0.001).

In Spearman correlation analysis, all outer circle thicknesses (A6, A7, A8, A9) were positively correlated with SER (p<0.05). Temporal, inferior and nasal outer circle thicknesses (A7, A8, A9)

TABLE 3: Repeatability of retinal nerve fiber layer (RNFL) and macula measurements expressed as intraclass correlation coefficient (ICC) with confidence interval (CI).

	ICC	95% CI	P value
RNFL Quadrants			
I	0.949	0.931 - 0.963	< 0.001
S	0.908	0.876 - 0.933	< 0.001
N	0.848	0.788 - 0.885	< 0.001
T	0.870	0.825 - 0.906	< 0.001
RNFL Sectors			
SN	0.915	0.886 - 0.938	< 0.001
NU	0.865	0.818 - 0.902	< 0.001
NL	0.818	0.754 - 0.867	< 0.001
IN	0.936	0.913 - 0.953	< 0.001
IT	0.884	0.843 - 0.915	< 0.001
TL	0.829	0.769 - 0.875	< 0.001
TU	0.929	0.904 - 0.948	< 0.001
ST	0.859	0.810 - 0.897	< 0.001
Average RNFL	0.973	0.964 - 0.980	< 0.001
Macula subfields			
A1	0.837	0.778 - 0.882	< 0.001
A2	0.917	0.887 - 0.940	< 0.001
A3	0.926	0.899 - 0.947	< 0.001
A4	0.932	0.908 - 0.951	< 0.001
A5	0.925	0.898 - 0.946	< 0.001
A6	0.948	0.929 - 0.962	< 0.001
A7	0.893	0.854 - 0.923	< 0.001
A8	0.920	0.891 - 0.942	< 0.001
A9	0.968	0.956 - 0.977	< 0.001

I: Inferior; S: Superior; N: Nasal; T: Temporal; SN: Superior nasal; NU: Nasal upper; NL: Nasal lower; IN: Inferior nasal; IT: Inferior temporal; TL: Temporal lower; TU: Temporal upper; ST: Superior temporal, A1: Central; A2: Inner superior; A3: Inner temporal; A4: Inner inferior; A5: Inner nasal; A6: Outer superior; A7: Outer temporal; A8: Outer inferior; A9: Outer nasal.

were negatively correlated with AL ($p<0.05$). No significant correlations were found between age and any of the macular parameters.

DISCUSSION

RETINAL NERVE FIBER LAYER THICKNESS

Among this current sample of healthy Caucasian paediatric subjects, an average RNFL thickness of 103.9±8.2 µm was found with iVue 100 SD-OCT. Chen et al. reported an average RNFL thickness of 106.89±12.84 µm with the same device in a population based sample of 2324 Chinese students aged 6 to 17 years.[10] Tsai et al. found an average RNFL thickness of 109.4±10.0 µm with RTVue - an equivalent device with iVue-in another population based study among 470 healthy Chinese school children aged 7 and 12 years.[11] In our study, quadrant thickness distribution of RNFL followed the "ISNT" rule.[12] Chen and Tsai's results differed from ours as they followed SITN and ISTN sequences respectively.[10,11] In all previous SD-OCT studies that have reported RNFL thickness in children, the superior and inferior quadrants were found to be thicker than the nasal and temporal quadrants, congruent with the "double-hump" pattern.[1,3-6,10,11,13,14]

It has been reported in most studies that RNFL thickness decreases with myopia and increases with hyperopia.[3-6,10,11,14] Congruently, we have found SER as an independent variable effecting average RNFL thickness. On the other hand, the correlation of RNFL thickness and AL in children is controversial. While some authors have reported significant negative correlation between RNFL and AL, others have not found any correlation.[1,4,5,10,14] According to our findings, AL was not independently effective on RNFL thickness.

Most of the previous studies have reported that gender is not an effective factor on RNFL thickness.[2-6] However correlation with gender has

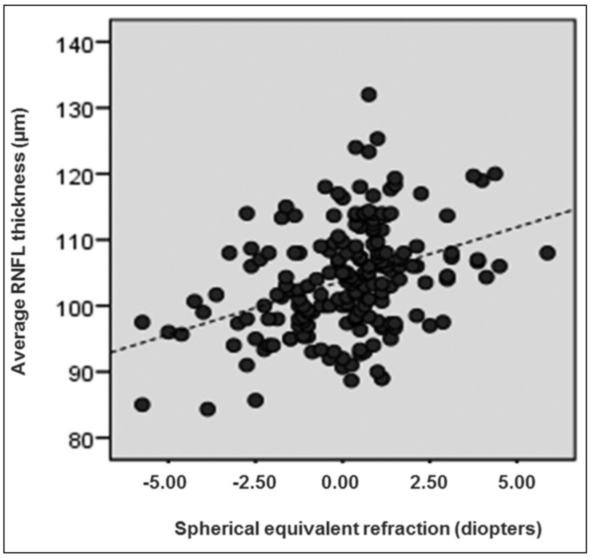

FIGURE 2: Scatter plots of the average retinal nerve fiber layer (RNFL) thickness and spherical equivalent refraction.

been found by some authors. For example, in Rao's study, average RNFL thickness was significantly higher in females.[14] Chen et al. reported greater RNFL thickness in females in the inferior and temporal quadrants.[10] In Turk's study, temporal inferior sector was thicker in females.[1] In the current study, average RNFL did not differ between females and males; but the temporal quadrant, temporal upper and inferior temporal sectors were significantly thicker in females resembling Chen and Turk's results.[1,10]

Age related thinning of the RNFL in adults has been reported by some authors.[15,16] However, in most paediatric studies including ours, age was not found to effect RNFL thickness.[1-6,11,14] It has been suggested in some adult studies that age-related thinning of RNFL starts later in life and the rate of loss is slower in younger ages.[17,18] This may explain the lack of an independent correlation between RNFL thickness and age among children.

MACULAR THICKNESS

The mean central macular thickness (A1) was 257.4±22.1 μm in our study. In all studies reporting normative paediatric SD-OCT data of macular thickness, the thinnest area of the macula was the central area.[1-6,8] Our result was consistent with this finding. Additionally, we found that the inner circle subfield was significantly thicker than the outer circle subfield, which also was congruent with most of the previous studies.[3-6,8]

In children, the effect of age on macular thickness was observed as the younger children having thinner central and inner macula than the older age groups.[2-6] This finding is consistent with continued development of the macula within the preschool period.[19] However, in our study, none of the macular parameters were correlated with age. Similarly, Molnar et al. and Turk et al. could not find such a positive correlation between any of the macular parameters and age. The reason for this might be that Molnar, Turk and the current study did not include children younger than 5 years old.[1,8]

We have found that central macular thickness and inner macular thicknesses (A2, A3, A4) were higher in males. This was congruent with most of the paediatric and adult studies which also have shown that being male is associated with a thicker central and inner macula.[1,3-5,20,21]

It has been hypothesized that with increasing myopia and axial length, the thickness of the inner and outer rings of the macula is decreased due to the mechanical stretching of a similar volume of retina over a larger area.[22,23] Congruent with this hypothesis, we found significant positive correlations between outer macula thicknesses and SER, and significant negative correlations between outer macular thicknesses and AL. Similar correlations were also found by other authors.[3-5]

There are several studies about the repeatability and reproducibility of OCT measurements in children.[7,8,24]Recently, Altemir et al. and Molnar et al. demonstrated good repeatability and reproducibility of SD-OCT (Cirrus) measurements in children.[7,8] In Altemir's study, the ICCs for repeatability were more than 0.82 in all the evaluated parameters. Similarly, Molnar et al. reported ICCs for repeatability ranging between 0.923 to 0.975 in macular areas. In our study, repeatability was also good with high ICCs (>0.81) in all the measured parameters.

A limitation of this study is the small sample size. Also, our data may not be applicable in children with different racial backgrounds. Another limitation is that optical magnification effect was not considered while analysing the data. However, it has been reported that OCT measurements of RNFL and macular thickness are not affected by optical magnification.[24]

As a conclusion, this study provided normative data for RNFL and macular thickness measured with iVue 100 SD-OCT in healthy Caucasian children aged 5 to 17 years. The repeatability of the measurements was good. The normative data provided in this study may help in better interpretation of SD-OCT measurements performed on children. The high repeatability suggests that SD-OCT measurements of RNFL and macula in children are reliable.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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