Original Article

Normative optical coherence tomography reference ranges of the optic nerve head, nerve fiber layer, and macula in healthy Saudi children

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ABSTRACT

الأهداف : لتحديد القيم الطبيعية للشبكية والبقعة الصفراء لدى الأطفال السعوديين الأصحاء باستخدام جهاز التصوير الضوئي المقطعي للشبكية، بالإضافة إلى دراسة تأثير الجنس والعمر على هذه القيم.

المنهجية : أُجريت هذه الدراسة الرجعية في مستشفى جامعة الملك عبدالعزيز بجدة في المملكة العربية السعودية من نوفمبر 2022م حتى أبريل 2023م، وشملت الدراسة 135 طفلاً سعوديًا من الفئة العمرية 4 إلى 18 عامًا، حيث تم فحصهم في عيادة طب العيون بمستشفى جامعة الملك عبدالعزيز، وتم الحصول على التفاصيل الديموغرافية والتاريخ المرضي لأمراض العين من سجلاتهم الطبية، وتضمنت المعايير الرئيسية للدراسة قياسات سمك طبقة الألياف العصبية للشبكية، سمك البقعة الصفراء، ورأس العصب البصري.

النتائج : كان متوسط حجم البقعة الصفراء 9.9 مم3 ، متوسط سمك البقعة الصفراء 275.9 مكم، متوسط سمك المنطقة الوسطى الفرعية 240.6 مكم، ولم تكن هناك علاقة ذات دلالة إحصائية بين العمر وقيم البقعة الصفراء بإستثناء البقعة الصفراء الداخلية العلوية، وكان سمك البقعة الصفراء المركزية أكبر لدى الأولاد من البنات، بينما لم يكن هناك فرق في أجزاء طبقة الألياف العصبية للشبكية بين مختلف الفئات العمرية ولم يكن هناك اختلاف في القيم بين الذكور والإناث، وكانت القيم المتوسطة لسمك طبقة الألياف العصبية للشبكية ومساحة القرص ومساحة الحافة وحجم التقعر 93.9 مكم، 2 مم^2 ، 1.6 مم^2، و0.3 مم^3 على التوالي، وكانت نسبة التقعر إلى القرص العمودية 0.4 .

الخلاصة : تم استخدام جهاز التصوير الضوئي المقطعي للشبكية، لإنشاء قيم مرجعية للشبكية والعصب البصري لدى الأطفال السعوديين وذلك للخدمة كمرجع.

Objectives: To use the Cirrus high-definition (HD)-OCT to establish normative data for the macula and optic disc in healthy Saudi children and to examine the effect of age and gender on these parameters.

Methods: This retrospective study was carried out at King Abdulaziz University Hospital (KAUH), Saudi Arabia from November 2022 to April 2023. The study involved 135 full-term and healthy Saudi children aged 4-18 years who were evaluated at the KAUH ophthalmology clinic. Detailed demographic and ocular disease history data were obtained from the patients' medical records. The main outcome measures of the study included measurements of retinal nerve fiber layer (RNFL) thickness, macular thickness, and optic nerve head (ONH).

Results: The mean macular volume was 9.9 mm^3, the mean macular thickness was 275.9 µm, and the mean central subfield thickness was 240.6 µm. There was no significant association between age and the macular values, except for the superior inner macula. Boys had significantly thicker central macula than girls, while the RNFL quadrants were not different between age groups and genders. The mean values for RNFL thickness, disc area, rim area, and cup volume were 93.9 µm, 2 mm^2, 1.6 mm^2, and 0.3 mm^3, respectively. The vertical ratio of cup to disc was 0.4.

Conclusion: Normative values for macular and optic nerve measures among Saudi children were established using the Cirrus HD-OCT device to serve as a reference.

Keywords: thickness, Saudi Arabia, reference, child, database

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Optical coherence tomography (OCT) is a cross-sectional, non-invasive tissue-imaging technology that acquires in vivo high-resolution retinal and optic disc measurements and images via laser light.[1] Optical coherence tomography yields precise quantitative measurements that aid the diagnosis and treatment response or progression follow-up of various eye diseases, including optic neuropathy, glaucoma, and macular disorders, such as macular edema and macular degeneration.[2,3]

Optical coherence tomography can also obtain objective retinal nerve fiber layer (RNFL) and macular measurements at high scanning speeds, making it useful for diagnosing and monitoring ocular diseases in children who can cooperate well enough to hold their gaze during the examination.[4-6] However, the OCT software contains a normative values database only for adults (>18 years); therefore, it would be inappropriate to compare the findings obtained from children with those in the adults' database, as it is suggested that child and adult values might vary.[7] Children typically have a thicker macula than adults.[8] As retinal thickness decreases with age in healthy adults, it is questionable whether child normative values can be extrapolated from those of adults.[9-11] Many studies demonstrated no relationship between RNFL or macular thickness and age.[12,13] Al-Haddad examined 5–17-year-old children in Lebanon and reported that older children had significantly increased macular thicknesses.[14]

Several studies used spectral-domain OCT (SD-OCT) to construct a normative pediatric database of macular thickness and RNFL values, and included participants from different ethnic groups.[9,15] Rothman et al[16] determined that blacks and Hispanic children had significantly thicker superior-temporal sector of RNFL than in whites. The series by Tong et al[17] reported that Black children had thicker RNFL, and larger vertical cup to disc ratio than white children. Accordingly, the macular thickness and RNFL parameters obtained from different ethnicities cannot be generalized to other ethnic populations.[2] A few studies were carried out in Arab countries such as Jordan, Lebanon, and Egypt,[6,13,14] however there is no previous report of normative values among Saudi children. Accordingly, we used SD-OCT to present normative optic nerve and macular parameter values in healthy Saudi children and examined the influence of gender and age on these parameters.

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Methods. This was a single-center retrospective record review conducted at the Department of Ophthalmology, King Abdulaziz University Hospital (KAUH), Jeddah. The study was approved by the Hospital Biomedical Ethical Committee (reference no. 467-22) and was conducted in accordance with the Helsinki Declaration. We reviewed data from children born between 1999 and 2018 who were evaluated at the KAUH ophthalmology clinic. Detailed demographic data, general medical history, and ocular disease history were obtained from the patient medical records database. Given that this was a retrospective study, the requirement for informed consent was waived. The study involved all full-term (gestational age ≥37 weeks) and healthy Saudi children aged 4-18 years, who were classified into 3 age groups: 4-7, 8-12, and 13-18 years. The exclusion criteria were history of ocular conditions such as strabismus, amblyopia, or any retinal or optic disc anomaly; high refractive error, defined as a spherical equivalent (SE) >5.5 D or astigmatism >3 D; and the presence of systemic diseases such as juvenile idiopathic arthritis, diabetes mellitus, inflammatory bowel disease, and sickle cell disease.

Optical coherence tomography scanning procedure. All images were captured using a Cirrus HD-OCT (software version 6.5.0.772; Carl Zeiss Meditec, Inc.). Two scans were acquired: one fovea-centered macular scan (macular cube 512 × 128 protocol) and one optic disc-centered peripapillary scan, where ocular movements were suppressed with an internal fixator (optic disc cube 200 × 200 protocol). The macular thickness parameters were automatically calculated by the Cirrus HD-OCT software and presented according to the 9 areas of the Early Treatment Diabetic Retinopathy Study (ETDRS) grids. The mean thickness, cube volume, and central subfield thickness were noted. The peripapillary RNFL thickness was divided into inferior, superior, temporal, and nasal quadrants. The optic nerve head (ONH) parameters comprised the disc area, neuro-retinal rim area, mean and vertical C/D ratio, and cup volume.

Statistical analysis. Data from the left and right eyes were keyed into Microsoft Excel 2016 and analyzed using the Statistical Package for the Social Sciences version 23 (IBM Corp., Armonk, NY, USA). The study variable characteristics were defined by simple descriptive statistics counts and percentages for the categorical and nominal variables. Continuous variables were reported as the mean and standard deviation (SD). A paired-samples t-test was used to compare the means of 2 variables for a single group, determine the differences between the values of 2 variables for each case, and examine whether the mean differed from 0. One-way analysis of variance (ANOVA) with least significant difference (LSD) as post-hoc test was used to compare means among three or more groups. The tests were carried out assuming normal distribution. Significant predictors were identified with the general linear model (GLM) using the main effect as the model. The null hypothesis was rejected based on a conventional $p<0.05$.

Results. The data of 481 children at the KAUH ophthalmology clinic were evaluated and examined using Cirrus HD-OCT. Following review, only 135 children met the study criteria: 60 (44.4%) girls and 75 (55.6%) boys. Figure 1 depicts the data review process. The children were aged 4–18 years [mean age: 10.19 (SD 4) years]. Forty-nine (36.3%) children, 43 (31.9%) children, and 43 (31.9%) children were aged between 4 and 7 years, 8 and 12 years, and 13 and 18 years, respectively.

Figure 2 presents the macular thickness measurements (mean and SD) for both eyes across the 9 ETDRS grid sectors. The mean macular thickness was 274.4 (SD 20.8) µm for the right eye (n=117) and 275.4 (SD 19) µm for the left eye (n=111). The central subfield thickness was 241.3 µm (SD 31) for the right eye (n=119) and 239.2 µm (SD 34.7) for the left eye (n=112). The cube volume was 9.9 mm^3 (SD 0.7) for the right eye (n=115) and 9.9 mm^3 (SD 0.7) for the left eye (n=110).

The right eye inferior outer quadrant was significantly thinner than that of the left. However, there were no significant differences between both eyes in the other 9 quadrants. The thinnest of the 9 ETDRS areas was the central macula, and the nasal inner segment was the thickest ($p>0.001$). Table 1 lists the mean, median, and percentiles of the macular parameters.

Significant differences were observed for the superior inner macula between the age groups, where the 4–7-year group had significantly thinner measurements compared to the other groups ($p>0.001$). However, no significant differences were observed for the other areas among the age groups.

The independent t-test analysis determined that the boys had a significantly thicker central macula ($p=0.001$) and central subfield than the girls ($p>0.001$) (Table 2).

Retinal nerve fiber layer Measurements. Table 3 depicts the RNFL parameters percentiles. The age groups did not demonstrate differences between the RNFL quadrants. Furthermore, the parameters did not differ between the genders.

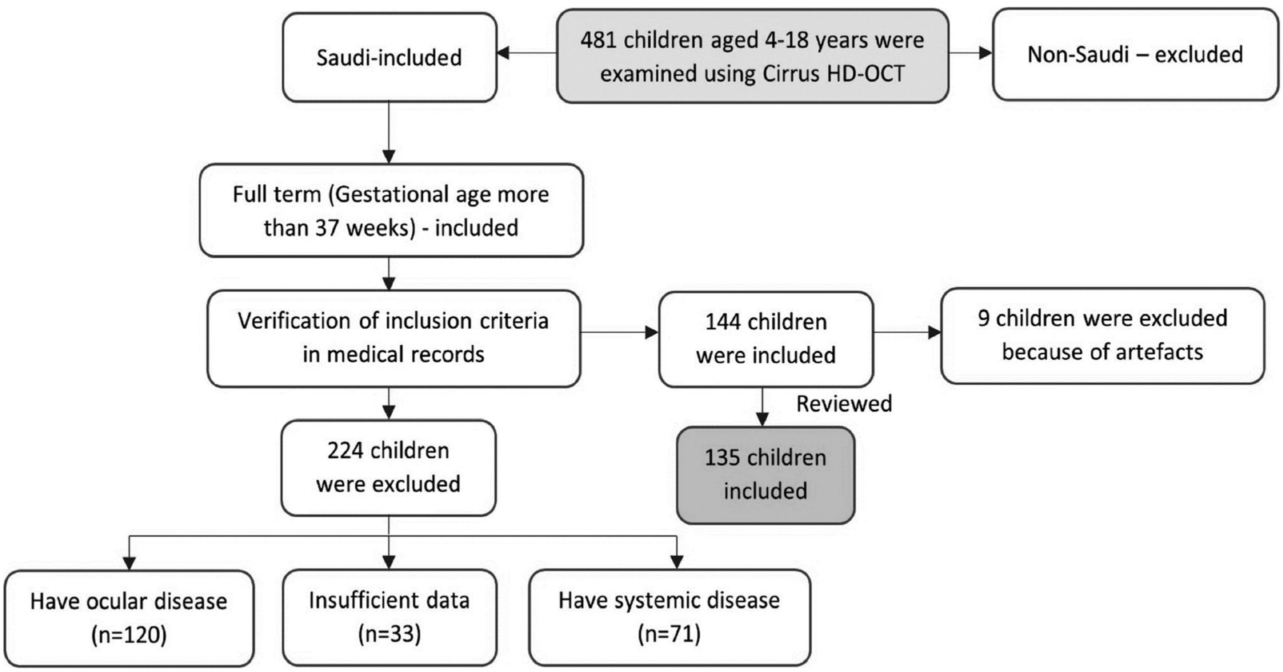

Figure 1 - Flow chart depicting the data review process. HD-OCT: high definition optic coherence tomography

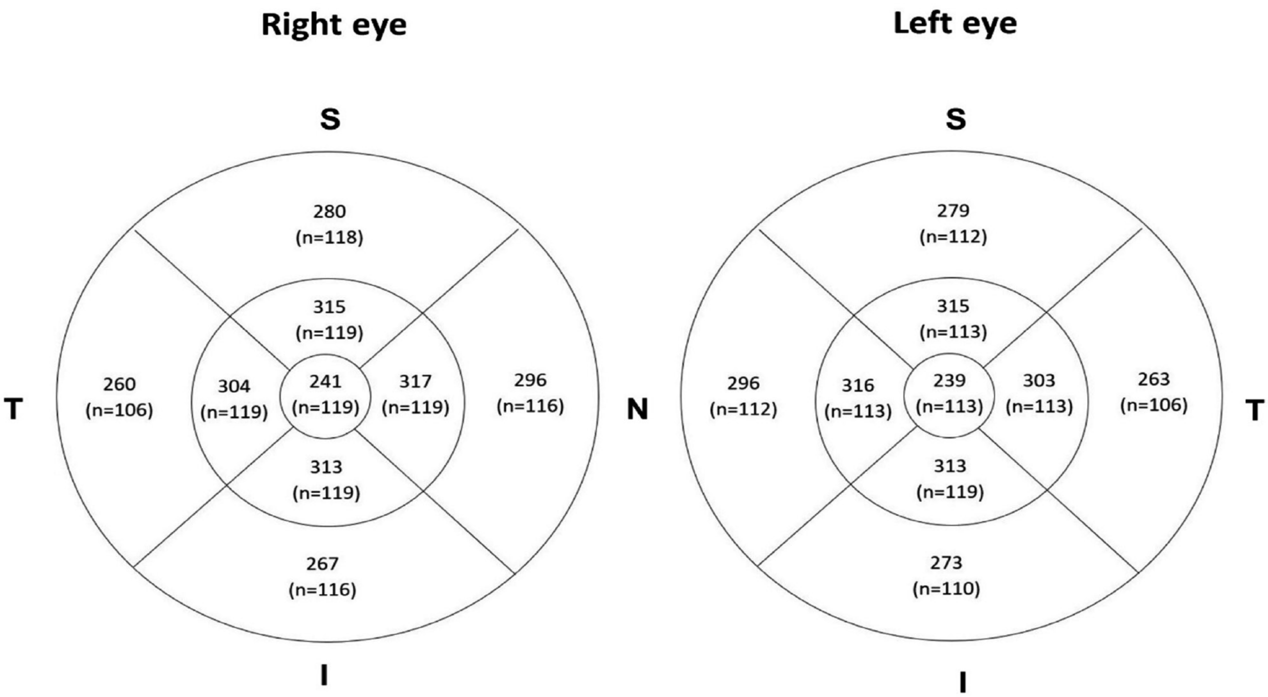

Figure 2 - The mean macular thickness values in the 9 ETDRS for the left and right eyes. I: inferior, S: superior, N: nasal, T: temporal

Table 1 - Percentile of the macular values.

Macular parameter	Mean (SD)	Median (min.–max.)	Percentile			95% confidence interval of the difference	
			25	50	75	Lower	Upper
Cube volume, mm^3	9.9 (0.6)	9.9 (7.4–11.2)	9.5	9.9	10.3	9.8	10
Central subfield thickness, µm	240.6 (28.2)	243 (162.5–304)	221.1	243	258.1	235.2	245.9
Central macular thickness, µm	240 (29)	243 (152.5–304)	221.5	243	259	234.6	245.5
Mean macular thickness, µm	275.9 (17.7)	276 (204–309.5)	264.8	276	287.8	272.6	279.2
Outer circle, µm							
Inferior	269.7 (19.4)	268.50 (190.5–347.5)	259.4	268.5	280.3	266	273.5
Nasal	295.6 (18.9)	296.3 (207.5–335)	286.4	296.3	305.5	292.1	299.2
Superior	279.3 (19.8)	279.5 (190.5–331.5)	268.5	279.5	291.5	275.6	283.1
Temporal	261.57 (19.5)	262.00 (185.5–299.5)	252	262	275	257.6	265.6
Inner circle, µm							
Inferior	312.9 (22.1)	312.5 (206–353)	300.5	312.5	328.5	308.7	317
Nasal	316.3 (20.7)	315.5 (245–357.5)	303	315.5	329	312.4	320.2
Superior	314.9 (22)	313.5 (232.5–357)	302.5	313.5	329.5	310.8	319
Temporal	303.4 (20.5)	302.5 (219.5–345.5)	290.5	302.5	319	299.5	307.2

SD: standard deviation, Min: minimum, Max: maximum

Discussion. In the present study, we used the Cirrus HD-OCT to establish normative data for the peripapillary RNFL, ONH values, macular volume, and macular thickness in healthy Saudi children aged 4-18 years. Additionally, we investigated how these measurements were affected by age and gender.

Table 5 shows mean macular thickness and volume in the pediatric population in our study compared to different studies published in the literature.[3,5,12,14,18-20] The macular values in this study were comparable to those recorded by Gürağaç et al[18] in 3-17-year-old Turkish children, where the mean macular volume obtained with the Cirrus HD-OCT was 9.97 mm^3 as compared to the mean of 9.91 (0.6) mm^3 we recorded. However, we recorded a higher macular volume than Ali et al,[6] who examined Egyptian children aged 6-17 years

Table 2 - Distribution of macular values by gender.

Macular measurement	Male Mean (SD) (range)	Female Mean (SD) (range)	*P*-value
Central macular thickness, µm	248 (27) (153–304)	230 (29) (163–287)	0.001*
Central subfield thickness, µm	249 (26) (198–304)	230 (28) (163–287)	<0.001*
Cube volume, mm^3	10 (0.6) (7.4–11.2)	9.8 (0.6) (8.3–11.1)	0.122
Mean macular thickness, µm	278 (18) (204–310)	273 (17) (230–307)	0.144
Outer circle, µm			
Inferior	270 (20) (191–331)	269 (19) (238–348)	0.851
Nasal	297 (20) (208–335)	294 (18) (246–330)	0.455
Superior	279 (21) (191–319)	280 (18) (225–332)	0.892
Temporal	263 (19) (186–297)	260 (20) (191–300)	0.560
Inner circle, µm			
Inferior	316 (21) (251–353)	309 (24) (206–35)	0.118
Nasal	319 (20) (259–357)	312 (21) (245–358)	0.075
Superior	317 (23) (247–357)	312 (21) (233–357)	0.260
Temporal	306.3 (20) (245–346)	300 (21) (220–338)	0.090

*Significant using independent t-test at <0.05 level. SD: standard deviation

Table 3 - Retinal nerve fiber layer (RNFL) measurement percentiles.

RNFL parameter (µm)	Mean (SD)	Median (min.–max.)	Percentile			95% confidence interval of the difference	
			25	50	75	Lower	Upper
Mean RNFL thickness	93.88 (10.0)	94.50 (67.0–121.5)	88.6	94.5	100.4	92	95.7
RNFL-nasal	69.99 (10.9)	69.50 (46.0–100.0)	61.5	69.5	76.5	68	72
RNFL-temporal	67.07 (11.1)	67.00 (47.5–109.5)	59.5	67.0	72.5	65	69.1
RNFL-inferior	120.25 (16.9)	121.50 (76.0–160.0)	109.5	121.5	131.3	117	123.4
RNFL-superior	119.51 (14.5)	118.50 (90.0–167.5)	108.5	118.5	126.5	116.8	122.2

SD: standard deviation, min: minimum, max: maximum

Table 4 - Distribution of optic nerve head (ONH) values according to age group.

ONH parameter	Mean (SD)	4–7 years Mean (SD)				8–12 years Mean (SD)				13–18 years Mean (SD)				*P*-value
			Percentile 25	50	75		Percentile 25	50	75		Percentile 25	50	75	
Rim area, mm^2	1.6 (0.3)	1.6 (0.3)^A	1.5	1.6	1.7	1.6 (0.3)^A	1.4	1.6	1.8	1.4 ± 0.2^B	1.3	1.4	1.6	0.006[a,b]
Disc area, mm^2	2 (0.4)	2.1 (0.5)^A	1.8	2.0	2.2	2 (0.4)^{AB}	1.6	1.9	2.2	1.8 ± 0.3^B	1.6	1.8	2.0	0.034[a,b]
Cup volume, mm^3	0.3 (1.1)	0.1 (0.2)	0.0	0.1	0.2	0.1 (0.1)	0.0	0.1	0.2	0.5 ± 1.9	0.1	0.1	0.3	0.309
Mean C/D ratio	0.4 (0.2)	0.4 (0.2)	0.3	0.4	0.5	0.4 (0.2)	0.2	0.4	0.5	0.4 ± 0.2	0.3	0.4	0.6	0.150
Vertical C/D ratio	0.4 (0.2)	0.4 (0.2)	0.3	0.4	0.5	0.3 (0.2)	0.2	0.3	0.5	0.4 ± 0.2	0.3	0.4	0.6	0.356

[a]*Capital letters indicate post hoc multiple pairing summary indicator. The presence of the same letter indicates the same measure statistically. Significant using one-way ANOVA at <0.05 level. [b]Post hoc test: LSD.

using the DRI OCT Triton and recorded a value of 7.1 mm^3. This difference might be attributed to the different OCT devices used in these studies, as swept-source (SS)-OCT devices such as the DRI OCT Triton have a longer wavelength and faster image acquisition than SD-OCT devices such as the Cirrus HD-OCT.[21] This supported the findings of Xiong et al,[22] who reported significantly thinner macular thickness in SS-OCT than in SD-OCT. Similarly, Ha et al[23] reported that the mean RNFL measurements were also significantly thinner in SS-OCT as compared to SD-OCT. These studies suggested that the choice of OCT device can affect the macular and RNFL parameter measurements and that it is important to consider the OCT device type when interpreting OCT results. In the present study, the mean central subfield thickness was 240.58 (SD 28.2) µm and the mean macular thickness was 275.90 (SD 17.7) µm. Similarly, a study involving 6–16-year-old Jordanian children that used the Prism SD-OCT, which is from the same manufacturer as the Cirrus OCT, reported comparable mean macular thickness of 277.2 (SD 12.5) µm , central subfield thickness of 246.7 (SD

Table 5 - Mean macular thickness, macular volume and retinal nerve fiber layer thickness in the pediatric population in the literature compared to the results of the current study.

Source	OCT	Population	n	Age (years)	Mean macular thickness (μm) (SD)	Macular volume, mm³ (SD)	Mean RNFL thickness (μm) (SD)
Our study	Cirrus HD-OCT	Saudis	135	4-18	275.9 (17.7)	9.9 (0.6)	93.88 (10.0)
Al-Haddad et al [14]	Cirrus HD-OCT	Lebanese	113	6-17	279.6 (12.5)	10.1 (0.5)	96 (8.7)
Barrio-Barrio et al [12]	Cirrus HD-OCT	Spanish	283	4-17	283.6 (14.08)	10.2 (0.49)	97.4 (9.0)
Gürağaç et al [18]	Cirrus HD-OCT	Turkish	318	3-17	279.27 (12.59)	9.97 (0.44)	96.49 (10)
QUEIRÓS et al [3]	Cirrus HD-OCT	Caucasian	153	4-17	282.26 (11.59)	10.17 (0.41)	97.9 (9.32)
Ali et al [6]	Topcon SD-OCT	Egyptian	50	6-17	276.4 (17.8)	7.84 (0.48)	111.26 (20.46)
Söhnel et al [5]	Spectralis SD-OCT	German	695	4-<19	320.53 (12.29)	8.88 (0.35)	102.88 (8.79)
Krumova et al [19]	SOCT Copernicus REVO SD-OCT	Caucasian	270	6-17	286.7 (9.82)	8.01 (0.28)	117.11 (9.51)

SD: standard deviation, SD-OCT: several studies used spectral-domain, RNFL: retinal nerve fiber layer

16.8) μm and ETDRS grid sector values comparable to ours.[13] Another study in Lebanon that involved children aged 5-17 years reported a mean macular thickness of 279.6 (SD 12.5) μm and central subfield thickness of 249.1 (SD 20.2) μm, which closely matched the values we reported.[14] By contrast, Passani et al[24] examined Caucasian children aged 5–18 years and reported higher ETDRS grid sector values.The variations might be attributed to differences in the OCT device used, where the Heidelberg Spectralis SD-OCT has higher axial resolution than the Cirrus HD-OCT, and to the different ethnicities.[3,25,26] This observation supported the findings of Knight et al,[27] who used the Cirrus HD-OCT and reported that African-Americans had significantly larger optic disc areas and thicker RNFL than Caucasians, while Asians had thinner RNFL than African-Americans and Caucasians. Furthermore, a study that involved participants with different ethnic backgrounds reported significant differences in ONH parameters between ethnic groups, with African-American participants exhibiting larger disc areas and cup volumes and smaller rim areas as compared to other ethnicities.[28] These findings emphasized the importance of considering ethnicity when interpreting OCT measurements. On the other hand, when we compare our macular values with the adult age group, as reported in a study by Al-Zamil W et al[29] on Saudi adults using SD-OCT, the mean macular volume in their study was 8.48 mm³ which lower than our value (9.9 mm³). Central macular thickness was thinner at 229 μm in a middle eastern adult population compared to the central macular thickness reported in our pediatric population at 240 μm.[30] This is the reason which necessitates the need for age- matched normative database for each population and across different age groups.[10]

We observed that age and macular values were not significantly associated, except for the superior inner macula. This observation accorded with several other studies that reported no significant relationship between age and macular values in children, while a significant difference across age groups was observed in Saudi adults (p<0.001) for all macular values except for mean central subfield (p=0.386) and foveal volume (p=0.341).[13,18,29,31]

In agreement with several studies,we observed that boys had significantly a thicker central macula and central subfield than girls, where this gender difference was also evident in a study that involved Saudi adults aged 18-56 years and that used the Cirrus SD-OCT.[6,13,14,18,29] However, a study conducted in Norway divided the sample into ≤43-year and >43-year age groups and determined that the significant difference in macular values ceased to be significant in participants aged >43 years. This finding suggested a potential influence of gonadal hormones in the observed differences, as the decrease in sex hormones that occurs with aging might be involved in reducing the differences in macular thickness between males and females.[32]

In SD-OCT studies that evaluated RNFL thickness in normal children, the mean RNFL thickness as reported by Al-Haddad et al[14] was 95 (SD 8.7) μm and was 96.91 (SD 10.21) μm as reported by Gürağaç et al.[18] In the present study, the mean RNFL thickness was 93.88 (SD 10.0) μm, which was similar to those previous studies. However, this value is lower than that reported by Challa et al[33] in Saudi adults using Swept-source OCT (105.59 μm). This could be attributed to the different OCT device used in their study. Similar to our finding, several other authors reported no significant relationship between age and RNFL thickness.[10,18,19] On the contrary, in adulthood, it has been reported that there is a linear decline in average RNFL thickness that becomes more significant beyond age 50.[10] Additionally, we observed no significant difference between the sexes, which was consistent with the results of Söhnel et al.[5]

The ONH values in the present study were comparable to those reported by Mohammed et al,[4] who used the Cirrus OCT and the study carried out by Challa[33] in Saudi adults using Swept-source OCT. However, our values were lower than those reported by Ali et al,[6] who used the DRI OCT Triton.

The strengths of this study include the broad age range (4-18 years) of the enrolled children and the inclusion of macular, RNFL, and ONH parameters in the Saudi population. This study corroborated the results of other studies that involved Middle Eastern children. Establishing normative reference ranges for OCT parameters in children in various ethnic communities would enhance our capacity to identify pediatric illnesses that affect the macula and optic disc.

The study limitations include the single-center nature of the study and its retrospective design, which might limit understanding of the influence of age on OCT parameters. Furthermore, we did not consider the effect of axial length (AXL) , degree of refractive error and lateral magnification, as Sanchez-Cano et al[34] reported that there is an inversely proportional relationship between axial length (AXL) and retinal image size. Additionally, a systematic review study found a positive correlation between refractive error and average RNFL thickness and central macular thickness, while a negative correlation existed between total macular volume and average macular thickness. However, some studies found no correlation, and ONH measurements did not correlate with the spherical equivalent. The ocular magnification effect may influence these findings, but it might only affect measurements taken laterally or parallel to the retinal plane. Results for macular parameters and the relationship between OCT findings and ocular axial length were inconsistent.[10]

Another limitation of this study is that the sample was from a clinic, which might not accurately represent the Saudi population despite the clinic being a tertiary referral center with patients traveling from various locations to the hospital. Therefore, studies from other regions and involving larger sample sizes would aid the confirmation of our findings.

In conclusion, using the Cirrus HD-OCT, the present study provided normative data on ONH parameters, macular thickness, and RNFL thickness in healthy 4-18-year-old Saudi children. The evaluation of optic neuropathies and macular disorders in Saudi children should be made easier as a result of the established normative values. Given that axial length and refraction both change over time, a longitudinal study would be necessary to better understand their effects on OCT parameters.

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