folia medica

Folia Medica 62(2): 338-44
DOI: 10.3897/folmed.62.e46678

Original Article

# Normal Reference Ranges of Optical Coherence Tomography Parameters in Children

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**Received:** 18 Sept 2019 ♦ **Accepted:** 11 Feb 2020 ♦ **Published:** 30 June 2020

**Citation:** Krumova S, Sivkova N, Marinov V, Koleva-Georgieva D, Voynikova D. Normal reference ranges of optical coherence tomography parameters in children. Folia Med (Plovdiv) 2020;62(2):338-44. doi: 10.3897/folmed.62.e46678.

## Abstract

**Aim:** To measure the macular thickness, macular volume and peripapillary retinal nerve fiber layer (RNFL) in healthy Caucasian children using spectral domain optical coherence tomography (SDOCT) and analyze the correlation of these values with age, refraction, and biometric measurements.

**Materials and methods:** In this cross-sectional study, we recruited 270 healthy children (150 female and 120 male) aged 6 to 17 years with no ocular abnormalities. All children underwent a detailed eye examination. The measurements were obtained using a SDOCT device (SOCT Copernicus REVO). Main outcome measures were macular thickness, macular volume and RNFL thickness. Their correlations with age, refractive error, anterior chamber depth (ACD) and axial length (AL) was analyzed. Right eyes of all subjects were selected for analysis.

**Results:** In this study group (mean age 10.70±2.82 years), the average peripapillary RNFL thickness was 117.11±9.15 μm, the central macular thickness was 232.10±15.81 μm, the average macular thickness was 286.70±9.82 μm, and the average macular volume was 8.01±0.28 $mm^3$. The average values for the biometric data were: axial length – 23.16±0.94 mm, anterior chamber depth – 3.64±0.26 mm, the spherical equivalent (SE) value – +0.81±0.58 diopter. Central macular thickness, inner macular thickness (superior, inferior, nasal, temporal quadrants) values, total macular thickness and macular volume were significantly higher in males than in females. We found a positive correlation between central macular thickness, inner nasal macular thickness, outer inferior macular thickness values, and age. Also, we found a significant correlation between the average macular thickness values and the average macular volume values ($p<0.0001$). RNFL measurements did not correlate with age ($p=0.199$). Almost all macular parameters were consistently positively correlated with SE. A significant correlation was also found between the central macular thickness, inner inferior macular thickness, inner nasal macular thickness and the ACD. We found a significant correlation between the average macular thickness, macular volume, inner superior macular thickness, outer macular thickness (superior, inferior, nasal, temporal quadrants) values and the AL.

**Conclusion:** This study found normal reference ranges for RNFL and macular parameters measured by SOCT Copernicus REVO in healthy Caucasian children aged 6-17 years. This normative values could be very useful in early diagnosing and monitoring of optic neuropathy, glaucoma and macular diseases in childhood.

## Keywords

anterior chamber depth, axial length, children, macular thickness, peripapillary retinal nerve fiber layer, spherical equivalent

## INTRODUCTION

The number of children suffering from blindness worldwide is approximately 1.4 million. An estimated 19 million children worldwide are visually impaired.[1,2] To decrease the risk of blindness, it is critical to diagnose children with ROP early and treat the evolving disease before permanent

damage has occurred. Optical coherence tomography is a non-invasive, noncontact method that uses low-coherence interferometry to perform high-resolution cross-sectional imaging of tissue morphologic features, providing an optical biopsy.[3] Spectral domain OCT (the latest generation of the technology) provides higher resolution (up to 5 μm) and decreased acquisition time in comparison to the previous time-domain OCT.[4] This is extremely useful while performing OCT examination in uncooperative children. OCT enables detection of morphological changes in the retina that cannot be seen with traditional ophthalmoscopy. Thus, various macular diseases could be diagnosed at an early stage. Sometimes computer perimetry is difficult to perform in children. Functional losses proven by perimetry correspond to morphological changes evidenced by OCT, as shown in many previous studies.[5-7] Optical coherence tomography makes also possible quantitative measurements of retinal thickness, including the retinal nerve fibre layer thickness. This enables the early diagnosis of juvenile glaucoma as well as the detection of various optic neuropathies. All OCT devices have an integrated normative database only for adult subjects of 18 years and older. Because the OCT data are based on age, it is not appropriate to compare measurements in children with the adult database. There are some published studies for normative database in children obtained by several old OCT devices.[8] So far, no data have been reported about the new generation SDOCT devices (such as SOCT Copernicus REVO). Therefore, we aimed in this study to report the normative values for SDOCT measurements of macular thickness, macular volume and peripapillary retinal nerve fiber layer (RNFL) thickness in children.

## MATERIALS AND METHODS

This study was performed in a high school in December 2018 year. We evaluated 270 eyes from 270 children with no ocular abnormalities except refractive error. This study was performed in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee of the participating center. Written informed consent was obtained from all parents of the children after explaining the imaging modality to them and to the child. Autorefractometry, best-corrected visual acuity, slit-lamp biomicroscopy, dilated indirect fundus examination, and intraocular pressure measurements (using a noncontact tonometer) were conducted. All of the included children were born at term ( ≥ 37 weeks gestational age) and with normal birth weight ( ≥ 2500 g). The inclusion criteria were: best-corrected visual acuity (BCVA) of at least 0.7 (on the Snellen visual acuity scale) in the 6–7-year olds and 0.8 in the older groups, refractive error (in spherical equivalent) within ±5.00 diopters, intraocular pressure ≤ 21 mmHg in both eyes, cup-to-disc (C/D) ratio ≤ 0.4, and C/D ratio asymmetry ≤ 0.2 between the 2 eyes. We excluded patients with a history of intraocular surgery, strabismus, amblyopia, retinal pathology, glaucoma. Patients with history of prematurity, neurologic, metabolic or other systemic diseases were also excluded.

Each subject underwent an initial ophthalmic examination including measurement of the BCVA (Snelen chart), refraction, assessment of ocular motility, anterior segment and fundus. The pupils were dilated with three drops of 1% cyclopentolate at intervals of fifteen minutes, and the cycloplegic autorefraction (UNICOS URK-700 autokeratorefractometer) was assessed 30–35 minutes after the last drop was instilled. The biometric data–AL and ACD were measured using SOCT Copernicus REVO (Optopol Technology SA, Zawiercie, Poland) before cycloplegia, and a mean of ten measurements was used in the analysis. The measurements performed by autorefkeratometer were repeated at least 5 times, and the average value of those measurements was recorded for each eye. In addition, the spherical equivalent refraction values (SE = spherical error + 50% of cylindrical error) were calculated from the average refractive error values for each eye.

### Optical coherence tomography measurements

Images of the macular region were obtained using a SOCT Copernicus REVO (Optopol Technology SA, Zawiercie, Poland). This instrument uses a super-luminescent diode light source with a peak wavelength of 830 nm (bandwidth, 50 nm), providing OCT images with an axial resolution of 5 μm, a transverse resolution of 12 μm to 18 μm, and a scanning speed of 80.000 A-scans per seconds. All included subjects underwent SDOCT examination by a single operator. Internal fixation was used to suppress ocular movements. Multiple measurements were taken and the best centred one with good signal strength was chosen for analysis. The programs used for the present study were 3D scan protocols. The macular thickness data are presented in the nine ETDRS areas (Early Treatment Diabetic Retinopathy Study Research Group 1985) **(Fig. 1)**.[9] The peripapillary RNFL thickness parameters that were automatically calculated by

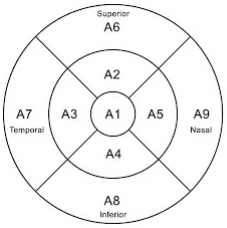


**Figure 1.** Macular thickness for the nine Early Treatment Diabetic Retinopathy Study regions using SOCT Copernicus REVO. **A1** = central, **A2** = inner superior, **A3** = inner temporal, **A4** = inner inferior, **A5** = inner nasal, **A6** = outer superior, **A7** = outer temporal, **A8** = outer inferior, **A9** = outer nasal area. The central subfield (**A1**) measures 1 mm in diameter, the inner (**A2–A5**) and outer (**A6–A9**), 3 and 6 mm, respectively.



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the SDOCT device and divided into regions including inferior, superior, nasal and temporal quadrant thickness.

## Statistical analysis

The data of right eyes of the 270 subjects were analysed using SPSS 19.0. Descriptive statistics were reported as mean and standard deviation. The normality of the distribution of the study sample was assessed by the Shapiro-Wilk test/ Kolmogorov-Smirnov test. Independent two-sample t-test was used to test the difference between the two genders if a normal distribution was present or the Mann-Whitney test otherwise. Correlation analysis and Pearson's correlation coefficients, and Spearman's correlation coefficients were used to evaluate the effect of age, sex, SE and AL on the macular and RNFL thicknesses. P values less than 0.05 were considered to be statistically significant.

# RESULTS

A total of 307 Caucasian children were recruited for this study. Of these, 32 were excluded because of failure to obtain parental consent, and 5 children were excluded because the children did not cooperate during the SDOCT examination. The average age of all 270 children [150 girls (55.6%) and 120 boys (44.4%)] involved in the study was 10.70±2.81 years (range 6-17).

## Measurements

The mean peripapillary RNFL thickness was 117.11±9.15 μm, the central macular thickness was 232.10±15.81 μm, the average macular thickness was 286.70±9.82 μm **(Fig. 2)** and the average macular volume was 8.01±0.28 mm$^3$. For the biometric data: the mean axial length was 23.16±0.94 mm, the mean anterior chamber depth was 3.64 0.26 mm, the mean spherical equivalent value was +0.81±0.58 diopters. **Table 1** shows the axial length, ACD and SE values for the right eyes of all children included in the study.

In the correlation analysis, no significant correlation was found between the ages of the patients and the peripapillary RNFL thickness ($p > 0.05$). Also, no significant correlation was found between sex of the children and NRFL thickness **(Table 2)**. However, there was a significant positive correlation between the age of the patients and AL values ($r = 0.249$,

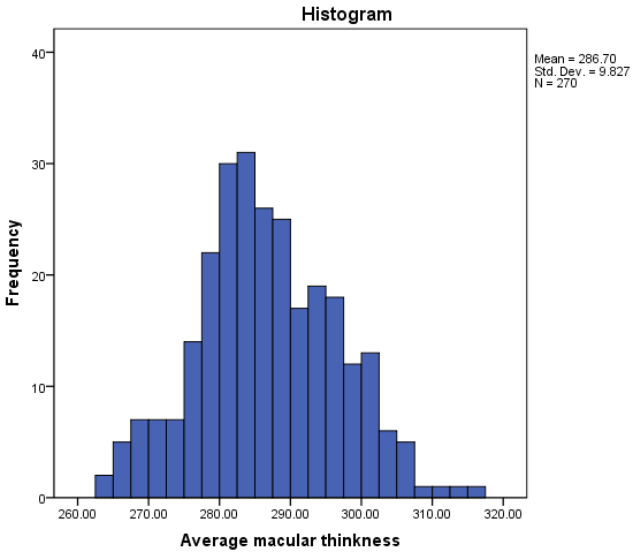


**Figure 2.** Normal distribution of average macular thickness.

**Table 1**. Biometric parameters[a] of healthy pediatric patients

| Measurement | Male (n=120) | Female (n=150) | *p* value[b] | Total (n=270) |
|---|---|---|---|---|
| Anterior chamber depth (mm) | 3.69±0.27 | 3.59±0.26 | 0.006 | 3.64±0.26 |
| Axial length(mm) | 23.46±0.89 | 22.92±0.91 | 0.000 | 23.16±0.94 |
| Spherical equivalent (diopters) | 1.00±0.75 | 0.65±1.10 | 0.000 | 0.81±0.98 |

[a] Mean±SD (normal range); [b] Mann-Whitney Test.

**Table 2**. Average peripapillary retinal nerve fiber layer thickness[a] in healthy children using SOCT Copernicus REVO

| Area | Male (n=120) | Female (n=150) | *p* value[b] | Total (n=270) |
|---|---|---|---|---|
| Superior | 146.42±14.83 | 147.59±14.80 | 0.517 | 147.07±14.80 |
| Inferior | 147.45±14.04 | 149.79±15.16 | 0.194 | 148.75±14.68 |
| Temporal | 79.39±9.11 | 80.27±10.39 | 0.469 | 79.88±9.83 |
| Nasal | 93.98±14.98 | 91.77±14.37 | 0.218 | 92.75±14.66 |
| Total | 116.81±9.04 | 117.36±9.27 | 0.628 | 117.11±9.51 |

[a] Mean±SD (normal range); [b] Independent samples t test.

$p = 0.000$), as well as significant positive correlation between the age and ACD values ($r = 0.165$, $p = 0.007$). In the correlation analysis, a significant negative correlation was found between the SE values of the patients and the ACD ($r = -0.344$, $p < 0.0001$) and AL values ($r = -0.255$, $p < 0.0001$). No significant correlation was found between the SE values and the age ($r = -0.110$, $p = 0.07$). Also, there was a significant positive correlation between the ACD values of the patients and AL values ($r = 0.471$, $p < 0.0001$). We found a correlation between macular parameters and some biometric data. There were significant differences in the average macular thickness and average macular volume between boys and girls. Boys were found to have greater macular thickness than girls in the central macular thickness and inner ring regions **(Table 3)**. There was a significant correlation between the average macular thickness values and the average macular volume values ($r = 0.958$, $p < 0.0001$). In the current study, average inner macular thickness were statistically significantly higher than average outer macular thickness ($r = 0.724$, $p < 0.0001$). Macular thickness in the superior inner, inferior inner, temporal inner, superior outer and inferior outer quadrants were significantly correlated with SE (Spearman correlation analysis, $p = 0.007$, 0.006, 0.024, 0.001, 0.02 respectively). Macular thickness in superior inner, superior outer, inferior outer, temporal outer, and nasal outer quadrants were significantly correlated with AL (Spearman correlation analysis; $p = 0.011$, 0.000, 0.000, 0.000, 0.000, respectively). Also, the average macular thickness and the average macular volume were significantly correlated with AL. In the correlation analysis, a significant correlation was found between the central macular thickness, inner inferior macular thickness and inner nasal macular thickness values of the patients and the ACD (Spearman correlation analysis, $p = 0.008$, 0.046, 0.044, respectively). Significant correlation was found between the NRFL (average NRFL, superior and inferior quadrant) values and the AL, but no such correlation was found between NRFL and ACD.

## DISCUSSION

In this study, we report normative data for NRFL thickness, macular thickness and volume, assessed with SOCT Copernicus REVO in 270 full-term, healthy children aged between 6 and 17 years. Different authors indicate different values of macular parameters because of different OCT devices. In our study, the central macular thickness was 232.1±15.8 μm, unlike that reported by AL-Haddad et al. (249.1±20.2)[10], Turk et al. (258.6±17.2)[11], and Barrio-Barrio et al. (253.9±19.8)[12]. Their results are similar in that they used SD-OCT Cirrus. Pierro et al. (2010), compared the values of macular thickness in adults with different OCT device and found that the macular thickness was the thinnest in SOCT Copernicus.[13] We found the same relationship in children. The mean macular thickness is less at central level, increases in the inner perifoveal ring, and then decreases in the outer perifoveal ring.

The sex comparison of macular parameters in the present study showed that boys had significantly higher macular thickness at the fovea and the four inner quadrants when compared to girls. While significant differences were noted in some quadrants between boys and girls, however, there was no significant difference in average macular thickness and volume. This finding is in agreement with the results reported by Barrio-Barrio et al. and Huynh et al.[12,14] However, Turk et al. does not find a correlation between age and macular thickness and macular volume.[11]

Glaucoma in childhood is a rare disease that occurs asymptomatically with gradual loss of ganglion cells. Diagnosis and follow-up are therefore difficult, especially for children. It is of utmost importance to detect the disease early before functional impairment occurs in the visual field. Therefore, early evaluation of the nerve fiber layer in children will support early detection, follow-up and treatment of the disease. It is therefore reasonable to establish a reference database for children. Turk et al. evaluated 107

**Table 3.** Average macular thickness[a] in the healthy children using SOCT Copernicus REVO

| Area | Male (n=120) | Female (n=150) | *p* value[b] | Total (n=270) |
|---|---|---|---|---|
| A1 | 235.57±15.78 | 229.33±15.33 | 0.01 | 232.10±15.81 |
| A2 | 316.11±11.64 | 312.31±11.33 | 0.07 | 314.00±11.60 |
| A3 | 303.61±10.52 | 297.46±11.23 | 0.000 | 300.19±11.32 |
| A4 | 313.79±10.97 | 309.19±11.35 | 0.01 | 311.23±11.40 |
| A5 | 314.66±11.90 | 310.19±11.98 | 0.03 | 312.18±12.13 |
| A6 | 275.71±11.30 | 277.24±11.68 | 0.278 | 276.56±11.52 |
| A7 | 267.31±10.45 | 264.30±10.99 | 0.23 | 265.64±10.84 |
| A8 | 271.48±11.84 | 271.75±12.07 | 0.85 | 271.63±11.95 |
| A9 | 296.50± 13.11 | 297.01±11.78 | 0.735 | 296.79±12.37 |
| Total | 288.30±9.68 | 285.42±9.78 | 0.16 | 286.70±9.82 |

[a] Mean±SD (normal range); [b] Independent samples t test.



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children between 6 and 16 years of age and found that the mean RNFL thickness was 106.45±9.47 μm.[11] Yanni et al. defined that the mean global RNFL thickness in 83 healthy children aged 5 to 15 years was 107.6±1.2 μm.[15] Barrio-Barrio et al. found that the mean RNFL thickness in 301 healthy white children aged 4 to 17 years was 97.4±9 μm with Cirrus HD-OCT.[12] The average RNFL thickness in our study of healthy Bulgarian children was determined as 117.11±9.15 μm. The quadrant thickness distribution followed the classic "double hump" pattern seen in adults with the thickest being the inferior followed by the superior then nasal and temporal, consistent with the "ISNT rule".[16] However, there are various studies on this matter that reported different variations. The sequence of average RNFL thickness in study by Turk et al. was as follows: inferior superior temporal nasal (ISTN).[11] Leung et al. found that the RNFL thickness decreased from superior to inferior to temporal to nasal (SITN) quadrants, in contradistinction to the ISNT rule.[17] In this study, it was found that the RNFL thickness decreased from the inferior, to superior, to nasal to temporal quadrants, which is in accordance with the "ISNT rule".

In this study, RNFL values were not affected by age in agreement with other reports. Some authors suggested that nerve fiber layer losses happened later in life after the age of 50 years, hence the absence of RNFL correlation with age in children. RNFL thickness evaluation with OCT devices may be used for both research and clinical purposes to diagnose and follow-up the optic neuropathies and diseases that affect the central nervous system, which include traumatic and toxic optic neuropathy, optic neuritis, compressive optic neuropathy, and hereditary optic neuropathies.

A positive correlation between age and central macular thickness was reported by Barrio-Barrio et al.[12] and Al-Haddad et al.[10] After correlation analysis, we were able to find such correlation in the present study. Barrio-Barrio et al. and Al-Haddad et al. found no correlation between macular thickness and spherical equivalent.[10,12] In this study, we also found such a correlation.

Limitations of this work include the mostly uniform ethnic group (Caucasian race) so the effect of race and ethnicity could not be tested. We also excluded patients with high refractive errors and increased cup-to-disc ratios; normative data for these groups were not established.

## CONCLUSIONS

This study established normal reference ranges for RNFL and macular parameters measured by SOCT Copernicus REVO in healthy Caucasian children 6–17 years of age. SDOCT is fast, non-invasive, harmless method that allows repeatability studies. It provides an objective, quantitative evaluation of the structure of the macula and NRFL, which makes the process very suitable for children, where cooperation is limited. This adds another database to the available literature on normative values using other OCT devices and facilitates evaluation of OCT measurements in children with optic neuropathies, glaucoma and macular diseases. Future studies involving pediatric patients to be performed in addition to our study will contribute to the formation of a normative SDOCT database for the pediatric population.

## Acknowledgements

The authors received no specific funding for this study. The authors have no support to report.

## Conflict Of Interest

The authors have no competing interests to declare.

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# Нормальные референсные значения параметров оптической когерентной томографии у детей.

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**Дата получения:** 18 сентября 2019 ♦ **Дата приемки:** 11 февраля 2020 ♦ **Дата публикации:** 30 июня 2020

**Образец цитирования:** Krumova S, Sivkova N, Marinov V, Koleva-Georgieva D, Voynikova D. Normal reference ranges of optical coherence tomography parameters in children. Folia Med (Plovdiv) 2020;62(2):338-44. doi: 10.3897/folmed.62.e46678.

## Резюме

**Цель:** Измерить толщину макулы, макулярный объём и перипапиллярные нейрофибриллярные клубки (RNFL) здоровых детей белой расы с помощью оптической когерентной томографии спектральной области (SDOCT) и проанализировать корреляцию этих значений с возрастом, рефракцией и биометрическими измерениями.

**Материалы и методы:** В этом исследовании мы включили 270 здоровых детей (150 женского пола и 120 мужского пола) в возрасте от 6 до 17 лет без нарушений зрения. Все дети прошли детальное обследование глаз. Измерения проводились с помощью прибора SDOCT (SOCT Copernicus REVO). Основные измерения были в отношении толщины макулы, макулярного объёма и толщины RNFL. Их корреляции с возрастом, рефракционной ошибкой, глубиной передней камеры (ACD) и осевой длиной (AL) были проанализированы. Для анализа были выбраны правые глаза всех участников.

**Результаты:** В этой группе (средний возраст 10,70 ± 2,82 года) средняя толщина перипапиллярной RNFL составила 117,11 ± 9,15 μm, центральная толщина макулы составила 232,10 ± 15,81 μm, средняя толщина макулы составила 286,70 ± 9,82 μm, а средний объём макулы составил 8,01 ± 0,28 мм$^3$. Средние значения биометрических измерений составили: осевая длина 23,16 ± 0,94 мм, глубина передней камеры – 3,64 ± 0,26 мм, значение сферического эквивалента (SE) – + 0,81 ± 0,58 диопитрий. Центральная толщина макулы, значения внутренней толщины макулы (верхняя, нижняя, носовая, височный квадрант), общая толщина макулы и объём макулы были значительно выше у мальчиков, чем у девочек. Мы обнаружили положительную корреляцию между значениями центральной толщины макулы, внутренней толщины назальнй макулы, наружной нижней толщины макулы и возрастом. Мы также обнаружили значительную корреляцию между средними значениями толщины макулы и средними значениями макулярного объёма (p <0,0001). Измерения RNFL не коррелировали с возрастом (p = 0,199). Почти все макулярные параметры находились в постоянной положительной корреляции с SE. Значительная корреляция была



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также обнаружена между центральной толщиной макулы, внутренней толщиной нижней макулы, внутренней толщиной назальной макулы и ACD. Мы обнаружили значительную корреляцию между значениями средней толщины макулы, объёма макулы, толщины внутренней верхней макулы, толщины наружной макулы (верхнего, нижнего, носового, височного квадранта) и AL.

**Выводы:** В этом исследовании были установлены нормальные референсные значения RNFL и макулярных параметров, измеренные с помощью SOCT Copernicus REVO, у здоровых детей белой расы в возрасте 6-17 лет. Эти нормативные значения могут быть полезны для ранней диагностики и мониторинга невропатии зрительного нерва, глаукомы и макулярной болезни у детей.

## Ключевые слова

глубина передней камеры, осевая длина, дети, толщина макулы, перипапиллярные нейрофибриллярные клубки сетчатки, сферический эквивалент