Clinical Ophthalmology

ORIGINAL RESEARCH

Normative Data of Macular Thickness Using Spectral Domain Optical Coherence Tomography for Healthy Jordanian Children

Hisham M Jammal[1], Rami Al-Omari[2], Yousef Khader[3]

[1]Department of Ophthalmology, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan; [2]Department of Ophthalmology, Faculty of Medicine, Yarmouk University, Irbid, Jordan; [3]Department of Public Health, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan

Correspondence: Hisham M Jammal, Department of Ophthalmology, Faculty of Medicine, Jordan University of Science and Technology, PO Box 1099, Irbid, 21110, Jordan, Tel +962-2-7201000, Fax + 962-2-7095123, Email hmjammal@just.edu.jo

Purpose: To report normative values of macular thickness and volume by spectral-domain optical coherence tomography (SD-OCT) in the eyes of healthy Jordanian children aged 6–16 years and assess the correlation of macular parameters with age, sex, and refractive error.

Patients and Methods: This observational study included 144 eyes of 144 healthy children. All children underwent comprehensive ocular examination and cycloplegic refraction. Average macular thickness, macular volume, central subfield thickness (CST), and macular thickness for all the Early Treatment Diabetic Retinopathy Study (ETDRS) quadrants were obtained using Primus SD-OCT (Carl Zeiss Meditec).

Results: The study group consisted of 68 boys and 76 girls with a mean age (SD) of 10.8 (3.0) years. The mean (SD) spherical equivalent refraction (SER) was 0.56 (1.73) diopters (range: −4.75 to 4.75). The mean of macular average thickness was 277.2±12.5 µm, and the mean of the central subfield thickness was 246.7±16.8 µm. In multivariate analysis, all macular parameters except the central subfield thickness (CST) correlated positively with the SER. Boys had significantly higher CST than girls (p=0.008). None of the macular parameters were correlated with age.

Conclusion: Normative data of macular thickness for healthy Jordanian children were established for sex and age groups using SD-OCT.

Keywords: central subfield thickness, macular thickness, normative data, pediatric OCT, Primus OCT

Introduction

Optical coherence tomography (OCT) is a well-established method for acquiring high-resolution images of the retina and optic disc. Its main advantages include being noninvasive, objective, reliable, with good repeatability and reproducibility[1] in both adult and pediatric populations. Besides providing a morphological assessment of the retina and optic disc, it also provides accurate quantitative measurements that help diagnose and monitor the progression or response to treatment of many retinal pathologies.

Despite the expected difficulties when performing OCT in children, where it requires a certain degree of cooperation and attention, OCT has proven to be well tolerated in children and has many clinical applications in pediatric retinal and optic disc pathologies.[2]

Different OCT machines come preloaded with normative data on retinal parameters for adults (18 years and older) derived from certain ethnic groups, but not for children, and this may limit the value of OCT in the pediatric setup since the diagnosis of early retinal or optic disc pathologies requires knowledge of normal OCT values of the studied tissue. Many published papers reported such normative data on macular thickness and volume in normal children among different ethnic groups using spectral-domain OCT (SD-OCT), and the reported data varied with race and other factors, however, only two reports come from the Middle East.[3,4] To the best of our knowledge, normative macular thickness OCT data for Jordanian children have not been published previously.

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The purpose of this study was to report normative data on macular thickness and volume measured by SD-OCT in normal eyes of healthy children in Jordan and assess its correlation with age, sex, and refractive error.

Materials and Methods

Design and Study Population

An observational study was performed on 144 consecutive healthy Middle Eastern children aged between 6 and 16 years who presented to a comprehensive ophthalmic outpatient clinic in Irbid, Jordan. The study adhered to the tenets of the Helsinki declaration and was approved by the Jordan University of Science and Technology Institutional Review Board. Informed written consent was signed by parents (guardian) of the participating children.

The participating children attended the eye clinic for routine refraction, or for vision screening on the request of parents or school, and were healthy, born term (≥37 weeks gestational age), with no history of systemic metabolic or CNS diseases, no history of ocular abnormalities such as retinal or optic nerve pathology, corneal diseases, strabismus, amblyopia, glaucoma, no history of significant ocular trauma and no history of intraocular surgery. Children were also included if they had monocular best corrected visual acuity of 1.0 in both eyes (Snellen's chart or the Tumbling E chart), normal anterior and posterior segment examination, and no abnormality of extraocular motility and ocular alignment examination.

We excluded children with high refractive errors of more than ± 5 diopters of spherical equivalent refraction (SER), anisometropia >1.5 diopters SER, children with abnormally looking foveal reflex, optic discs with a cup/disc ratio >0.5 (or >0.2 asymmetry between the two eyes), optic disc anomalies such as a tilted disc, and uncooperative children for OCT imaging.

Demographic data was recorded including age, sex, general medical history, and family history of inherited ophthalmic diseases. The children were separated into three groups according to age; group 1: <10, group 2: 10–12, and group 3: >12 years.

Ocular Examination

All participating children underwent a standard ophthalmic examination. Best corrected visual acuity was recorded monocularly using the Snellen's chart or the Tumbling E chart, followed by assessment of ocular alignment, extraocular motility testing, and anterior segment examination with a slit lamp. All children underwent cycloplegic refraction using cyclopentolate 1% eye drops instilled in each eye 10 minutes apart. Cycloplegic refraction was measured 50 minutes after the last drop using an autokeratorefractometer (ARK-1s, Nidek, Aichi, Japan), which provides the median of at least 3 measurements. Astigmatism was recorded as the negative cylinder and spherical equivalent refraction was calculated according to the equation: SER = sphere power +(1/2 cylinder power). Dilated fundus examination was then performed using slit-lamp biomicroscopy and indirect ophthalmoscopy.

OCT Measurement

The Primus SD-OCT machine (Carl Zeiss Meditec AG, Germany, model 200, software version 3.0) was used to acquire macular OCT images through the dilated pupil. It acquires retinal images using a super luminescent diode with a wavelength of 840 nm at a scanning speed of 12,000 A-scans per second and has an axial tissue resolution of 5 μm and a transverse resolution of ≤20 μm. The device has been shown to have good repeatability and reproducibility for both normal and diseased eyes.[5] Additionally, there was a substantial equivalence between the PRIMUS 200 and Cirrus HDOCT Model 4000,[5] and a substantial level of agreement in normative limits between normative databases of Primus 200 and Cirrus for the measurement parameters obtained from a given subject.[6]

The macular thickness analysis scan protocol generates a cube of data through a 6 mm square grid centered on the fovea by acquiring a series of 32 horizontal scan lines each composed of 512 A-scans. The machine displays the thickness measurements over a circular map which is a modified ETDRS (Early Treatment Diabetic Retinopathy Study) Grid and calculates the total macular volume and overall macular average thickness for the ILM-RPE tissue layer over the entire 6 mm square scanned area. The modified ETDRS grid map shows overall average thickness in nine sectors. This circular map is automatically centered on the fovea and is composed of three concentric circles: the central circle with a diameter of 1 mm corresponding to the foveal central 1mm circle, and its thickness is referred to as Central Subfield Thickness (CST), the inner circle, 3 mm in diameter, and the outer circle 6 mm in diameter. Both inner and outer circles are divided into superior, nasal, inferior and temporal quadrants. The macular thickness analysis map obtained by the Primus OCT of the measured and calculated macular parameters is shown in Figure 1.

All OCT scans were performed by a single experienced operator utilizing the same OCT machine and during the same day of conducting ocular examination and cycloplegic refraction. The right eye was scanned first followed by the left eye. Internal fixation light was used, and the procedure carried out in a dim room. Three to four images were taken for each eye and then reviewed individually by the operator. Images with poor signal strength (less than 7/10), poorly centered, those with motion artifacts, and images with dark areas were excluded with the purpose of having at least 2 images with acceptable quality.

The two authors reviewed all images and by consensus, selected the image with the highest signal strength, best centration, and no missing data.

Statistical Analysis

The data from the left eye were used for analysis and were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM corporation, Armonk, NY, USA). The normality of distributions for the measured macular parameters were tested using the Shapiro–Wilk test. Mean (± standard deviation) as well as 5th and 95th percentiles were used to describe the macular parameters. Percentages were used to describe categorical variables. Pearson correlation was used to test the correlation between the measured macular parameters and other variables. The generalized linear model (GLM) multivariate procedure was used for testing the effect of different variables on macular parameters. The GLM Multivariate procedure provided regression analysis and analysis of variance for multiple macular parameters by sex, age, and SER. A p-value of less than 0.05 was considered statistically significant.

Results

The data on the left eyes of 144 children (68 boys and 76 girls) were analyzed. Their age ranged from 6 years to 16 years with a mean (SD) age of 10.8 (3.0) years. A total of 49 (34%) children aged <10 years, 49 (34%) aged between 10 and 12 years, and

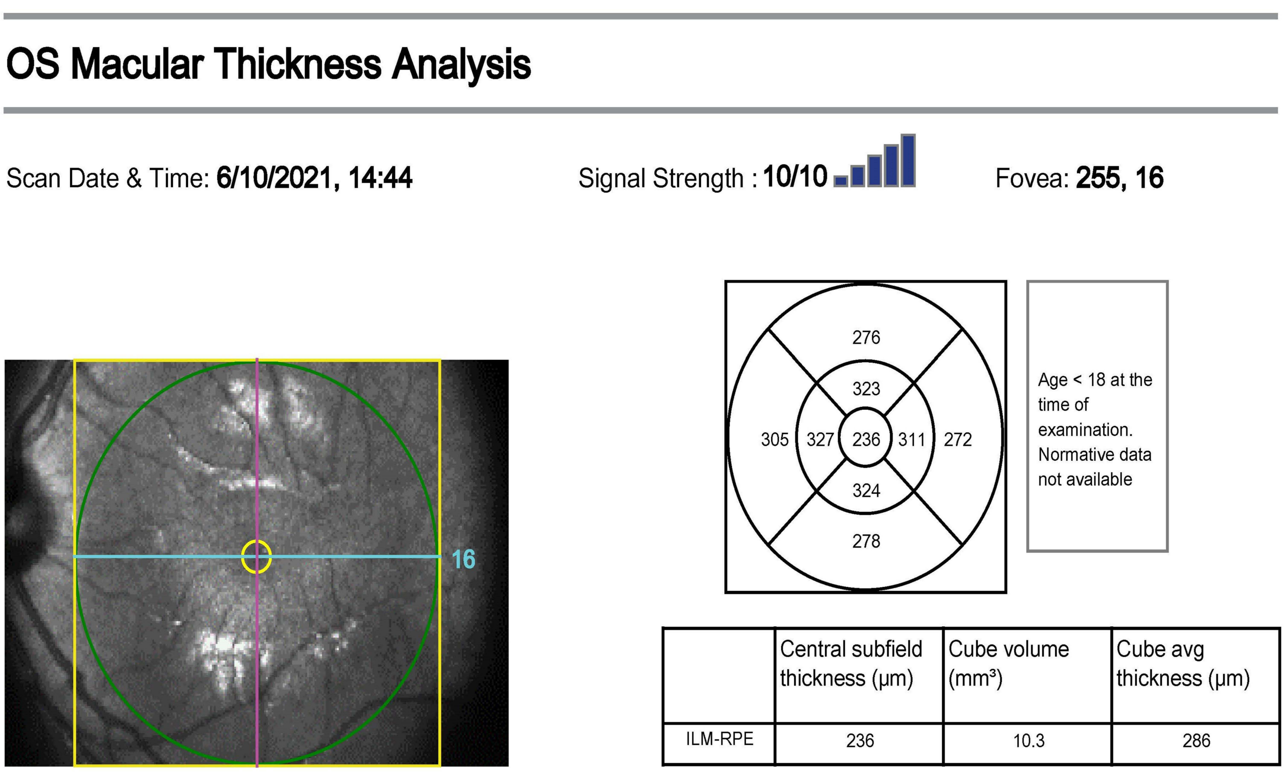

Figure 1 Macular thickness analysis map. Cube volume: macular volume, cube avg thickness: average macular thickness.

46 (31.9%) aged >12 years. The mean (SD) spherical equivalent refraction was 0.56 (1.73) diopters (Range: −4.75 to 4.75). Table 1 shows sex and spherical equivalent refraction according to age groups. The mean of macular average thickness was 277.2±12.5 µm, and the mean of the central subfield thickness was 246.7±16.8 µm. The macular thickness measurements in the 9 ETDRS grid sectors, the average macular thickness, and the total macular volume according to age groups and sex are shown in Table 2.

All the macular measurements, average macular thickness, and the total macular volume were weakly and positively correlated with the SER ($p<0.05$) except the central subfield thickness ($p =0.79$).

Using the GLM Multivariate Analysis (Table 3), age was not significantly associated with all studied macular parameters. There was no significant sex difference in all parameters, except for central subfield thickness. The adjusted mean of central subfield thickness was significantly higher in boys (250.68 µm (95% CI: 246.68, 254.68)) compared to girls (243.06 µm (95% CI: 239.29, 246.84)). As the SER increased, all macular parameters, except central subfield thickness, significantly increased. There was no significant interaction between age, sex, and SER for all macular parameters. The overall sex, age, and SER adjusted means of all macular parameters are shown in Table 4.

Table 1 Sex and Spherical Equivalent Refraction According to Age Groups

Age Group (Years)	Gender (Girls, %)	Spherical Equivalent Refraction		
		Mean (SD)	Range	
< 10	20 (40.8)	1.04 (1.57)	−4.63	4.75
10–12	24 (49)	0.46 (1.70)	−3.88	3.88
> 12	32 (69.6)	0.17 (1.83)	−4.75	4.75

Table 2 Normative Values of Macular Parameters According to Sex and Age Groups

Macular Parameters		Age Group (Years)											
		<10			10–12			>12			Total		
		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile	
			5th	95th		5th	95th		5th	95th		5th	95th
Macular Volume (mm^3)	Male	10.0	9.2	10.6	10.0	9.4	10.9	9.9	9.3	10.5	10.0	9.3	10.7
	Female	10.0	9.4	10.8	10.0	9.2	10.9	9.9	9.1	10.5	10.0	9.2	10.7
	Total	10.0	9.3	10.7	10.0	9.2	10.9	9.9	9.3	10.5	10.0	9.2	10.7
CST (µm)	Male	249	215	278	251	228	270	252	232	280	250	226	274
	Female	240	215	268	248	230	282	242	217	268	243	217	271
	Total	245	215	274	250	228	274	245	218	271	247	218	272
Macular Thickness (µm)	Male	278	255	293	277	262	302	276	258	291	277	257	298
	Female	279	260	298	278	255	303	276	253	292	277	255	297
	Total	278	257	297	277	256	302	276	258	291	277	256	297

(*Continued*)

Table 2 (Continued).

Macular Parameters		Age Group (Years)											
		<10			10–12			>12			Total		
		Mean	Percentile		Mean	Percentile		Mean	Percentile		Mean	Percentile	
			5th	95th		5th	95th		5th	95th		5th	95th
Inner circle													
Superior (µm)	Male	321	294	346	318	302	341	317	296	341	319	294	345
	Female	318	298	342	319	290	341	314	295	346	317	295	346
	Total	320	294	346	319	293	341	315	296	341	318	295	345
Inferior (µm)	Male	318	287	342	315	294	345	318	300	338	317	291	342
	Female	314	286	337	315	292	339	310	285	342	313	285	340
	Total	316	287	340	315	292	345	313	290	338	315	291	340
Nasal (µm)	Male	321	292	347	318	296	344	322	302	341	320	294	344
	Female	315	287	339	319	295	339	314	295	348	316	294	345
	Total	319	292	344	319	295	344	316	296	345	318	294	344
Temporal (µm)	Male	309	281	337	306	286	338	307	289	328	307	284	337
	Female	302	278	327	306	280	338	299	275	326	302	275	326
	Total	306	281	336	306	280	338	301	276	326	304	280	333
Outer circle													
Superior (µm)	Male	276	253	300	275	260	297	271	251	289	275	254	297
	Female	278	256	296	276	249	305	276	259	292	276	250	298
	Total	277	254	298	276	250	303	274	257	292	276	252	297
Inferior (µm)	Male	271	247	294	270	249	298	268	251	282	270	249	294
	Female	275	256	314	267	242	293	268	247	286	270	246	294
	Total	273	249	301	269	246	298	268	247	285	270	247	294
Nasal (µm)	Male	294	269	315	293	275	318	290	267	307	293	270	316
	Female	297	277	319	297	264	328	293	274	319	296	267	321
	Total	295	270	316	295	266	327	292	272	316	294	270	319
Temporal (µm)	Male	262	239	284	259	241	284	258	239	283	260	239	284
	Female	262	239	279	259	240	282	257	236	273	259	239	280
	Total	262	239	283	259	240	284	257	239	273	259	239	283

Abbreviation: CST, central subfield thickness.

Discussion

Optical coherence tomography has become an established and indispensable method for the diagnosis and monitoring of many retinal and optic nerve diseases in the pediatric population, however the technique is still underutilized in this population because of expected difficulties when performing the test and more importantly, lack of normative database.[2]

Table 3 Multivariate Analysis of the Association Between Macular Measurements and Sex, Age, and Spherical Equivalent Refraction

		Regression Coefficient (B)	95% Confidence Interval		P-value
			Lower Bound	Upper Bound	
Macular volume	Sex (male vs female)	0.00	−0.15	0.15	0.983
	Age (Years)	0.00	−0.03	0.03	0.985
	SER	0.07	0.03	0.11	0.002
CST	Sex (male vs female)	7.62	2.06	13.17	0.008
	Age (Years)	0.47	−0.49	1.44	0.335
	SER	0.40	−1.24	2.03	0.632
Average macular thickness	Sex (male vs female)	−0.24	−4.35	3.87	0.909
	Age (Years)	0.01	−0.71	0.72	0.985
	SER	1.96	0.75	3.17	0.002
Inner macular ring					
Superior	Sex (male vs female)	2.27	−2.63	7.18	0.361
	Age (Years)	−0.11	−0.96	0.75	0.807
	SER	2.19	0.74	3.63	0.003
Inferior	Sex (male vs female)	4.45	−0.63	9.53	0.085
	Age (Years)	0.15	−0.73	1.04	0.729
	SER	1.91	0.42	3.41	0.013
Nasal	Sex (male vs female)	4.66	−0.53	9.84	0.078
	Age (Years)	0.32	−0.58	1.22	0.488
	SER	1.89	0.36	3.41	0.016
Temporal	Sex (male vs female)	4.94	−0.15	10.03	0.057
	Age (Years)	−0.12	−1.00	0.77	0.792
	SER	1.62	0.12	3.12	0.035
Outer macular ring					
Superior	Sex (male vs female)	−1.98	−6.26	2.31	0.363
	Age (Years)	−0.04	−0.78	0.71	0.923
	SER	2.64	1.38	3.90	0.000
Inferior	Sex (male vs female)	−0.05	−4.80	4.71	0.984
	Age (Years)	−0.47	−1.29	0.36	0.267
	SER	1.79	0.39	3.19	0.013

(*Continued*)

Table 3 (Continued).

		Regression Coefficient (B)	95% Confidence Interval		P-value
			Lower Bound	Upper Bound	
Nasal	Sex (male vs female)	−3.22	−8.21	1.77	0.204
	Age (Years)	−0.17	−1.04	0.69	0.695
	SER	1.83	0.36	3.30	0.015
Temporal	Sex (male vs female)	0.90	−3.33	5.13	0.674
	Age (Years)	−0.18	−0.91	0.56	0.633
	SER	2.55	1.30	3.79	0.000

Abbreviations: SER, spherical equivalent refraction. CST, central subfield thickness.

Table 4 Sex, Age, and Spherical Equivalent Refraction Adjusted Means of All Macular Parameters

Macular Parameter	Mean*	SE	95% Confidence Interval	
			Lower Bound	Upper Bound
Macular volume (mm^3)	9.978	0.037	9.906	10.051
CST (μm)	246.871	1.376	244.150	249.592
Average macular thickness (μm)	277.202	1.018	275.190	279.214
Inner circle (μm)				
Superior	317.973	1.215	315.571	320.375
Inferior	314.846	1.259	312.357	317.335
Nasal	317.977	1.285	315.437	320.517
Temporal	304.484	1.262	301.990	306.979
Outer circle (μm)				
Superior	275.584	1.062	273.485	277.683
Inferior	269.818	1.178	267.489	272.147
Nasal	294.070	1.235	291.628	296.513
Temporal	259.310	1.047	257.239	261.380

Note: *Adjusted for age, spherical equivalent refraction, and sex.
Abbreviations: SE, standard error of the mean. CST, central subfield thickness.

Although OCT in children proved to be repeatable and reproducible,[1] normative data are still not provided by the OCT manufacturers in their machines for subjects younger than 18 years, and therefore, the provision of such data is still a necessity.[7] The current study reported the normative data for macular thickness and macular volume in a sample of healthy Middle Eastern children from Jordan and examined the effect of sex, age, and refractive errors on these data.

In the current study, the mean of macular average thickness was 277.2±12.5 µm, and the mean of the central subfield thickness was 246.7±16.8 µm. Those measurements were comparable to those reported by studies that used the Cirrus SD-OCT,[3,8–13] which ranged from 271 µm to 289 µm for the macular average thickness, and from 235 µm to 255 µm for the central subfield thickness. In particular, our results for the macular average thickness and CST were very close to those reported by Al-Haddad[3] (279.6±12.5 µm, 249.1±20.2 µm, respectively) in the only study performed using Cirrus SD-OCT on a sample of

Middle Eastern children from Lebanon, with nearly similar age distribution (10.7±3.1 years). Similarly, the means of the inner and outer ETDRS grid quadrants from the current study were comparable to those from the other studies using Cirrus SD-OCT.[3,8–13] Although OCT measurements from different machines cannot be used interchangeably, the Primus SD-OCT machine used in the current study and the Cirrus SD-OCT are both made by the same manufacturer, use the same technology, and both machines provided very similar mean values of macular parameters when a comparative analysis was performed for both machines.[5] The average macular thickness and CST were found to be less in general when compared to those reported by studies conducted using the Spectralis SD-OCT,[14–18] which is known to give higher values due to different measurement algorithms and software used in different machines.[19] It is important to note that the value of comparisons between the current study's results and those of other research may be limited by the influence of age range, refractive error state, type and size of the studied sample, ethnicity, and methodology.

Regarding age, the current study sample involved a wide range of ages but excluded those younger than 6 years for the expected lack of cooperation. We did not find a significant association between age and the measured macular parameters, in line with several previous reports.[12,14,20–24] However, other studies reported a relation between age and the following: CST,[8,9,11,15,17,18,25] specific segmented retinal layers,[26–28] macular volume,[17,18] all macular parameters,[3,13] and CST in black but not white children.[29] These results are variable regarding the measured anatomical area and therefore, cannot be generalized. A longitudinal study design would be preferable for establishing a relationship between age and macular characteristics.

We found a significantly higher CST in boys than girls, but other macular parameters showed no sex difference. Many studies reported a sex difference particularly in CST, with males showing higher values than females,[3,4,8–11,13,21] while other studies reported no difference, and we found no reports showing higher values in females regarding macular parameters. This sex difference is also noted in the adult population,[30,31] however Wexler[31] found that this sex difference became non-significant in subjects older than 43 years and suggested that sex difference in the younger adults (<43 years) is due to gonadal hormonal effect.

The spherical equivalent refractive (SER) error was positively correlated with all the macular parameters measured in this study but showed no correlation with the CST. The results of association between SER and macular parameters from previous research are variable. While positive correlation was reported between SER and various macular parameters in several studies,[3,10,13,18,21,32,33] it is interesting to note that all of these studies, except the study by Huynh et al[32] showed either a negative correlation[10,13,21,33] or no correlation with the CST.[3,18] Additionally, several authors[4,8,12,14,16,17] reported no association between SER and any of the measured macular parameters, including the CST. It is still unclear why the CST remains normal or even thicker with smaller SER, but the explanation by Wakitani[34] seems a plausible one, in which decreased peripheral retinal thickness in myopia may act as a compensatory mechanism to preserve central macular thickness.

The current study has a limitation in that it is single-center, clinic-based rather than multi-center, hospital-based design which would reduce selection bias. Another limitation is that ocular axial length was not measured, and therefore the effect of axial length and ocular magnification could not be assessed.

Conclusion

The current study presented normative data on macular thickness measurements in healthy Jordanian children aged 6–16 years using SD-OCT. In general, these data were comparable to those from the Middle East, and other regions internationally. The effect of age and refraction needs to be further assessed by longitudinal studies as both factors continuously change with time. Finally, we recommend that OCT manufacturers include normative database in their OCT machines through carefully designed, international multicenter studies.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at the Jordan University of Science and Technology (Reference number 26-140-2021). Informed consent was obtained from all subjects (guardians) involved in the study.

Author Contributions

All authors made a significant contribution to the conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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