

# Macular structural characteristics in children with Down syndrome

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## Abstract

**Purpose** This prospective study aimed to investigate macular structural characteristics in children with Down syndrome compared to those in healthy children.

**Methods** Two groups of children (aged 6–16 years) were enrolled: children with Down syndrome (Down syndrome group,  $N=17$ ) and age-matched healthy children who were full-term at birth (control group,  $N=18$ ). Eligible patients had visual acuity of 20/100 or better and gestational age at birth of  $\geq 36$  weeks. Fourier domain optical coherence tomography was used for imaging of the macular retinal structure, and retinal volume scans centered on the macula were obtained. Central subfield thickness (CST) and the thickness of the inner and outer retinal layer regions were analyzed using the instrument's segmentation software. The analysis of data is provided for the right eye only, since there was no significant difference between right and left eyes for either the Down syndrome or control groups.

**Results** Children in the Down syndrome group generally had identifiable retinal structure. The CST for the full retina and inner and outer retinal layers were all significantly greater in the Down syndrome group than the control group (independent  $t$  test, all  $p<0.05$ ). Despite the significantly thicker macula, only about 29 % (5 of 17) of the right eyes of patients with Down syndrome had macular thickness outside the normal range. Visual acuity in the Down syndrome group was not

directly correlated with increased CST ( $t=1.288$ ,  $r=0.326$ ,  $p=0.202$ ).

**Conclusions** On average, CST in the Down syndrome group was greater than that in the control group, suggesting abnormal macular development in children with Down syndrome.

**Keywords** Down syndrome · OCT · Foveal structure · Retina · Visual function · Children

## Introduction

Children with Down syndrome are known to be at increased risk for ocular abnormalities, including significant refractive error, strabismus, nystagmus, and even cataracts [1–5]. Poor optical quality at an early age has implications for retinal and cortical image quality. Visual functions in these children are also often abnormal, including visual, low-contrast, and vernier acuity, and accommodative ability [6–9, 2, 10–12]. The etiology of this poor visual performance associated with Down syndrome is not fully understood.

Foveal development begins around 24–28 weeks after conception [13–15], and fovea continue to mature until children are at least 4 years of age [16, 17]. Eye growth during childhood is a visually guided process, and degradation or alteration of visual input may disrupt growth [18]. Numerous studies have evaluated the effects of early abnormal visual experience in relation to macular thickness in children with strabismic and anisometropic amblyopia [19–24]. Despite the obvious ocular problems, in light of the unique challenges of retinal imaging in children, there are few reports on retinal structure in children with Down syndrome. We occasionally see case reports on Down syndrome children with bilateral macular coloboma [25], optic disc elevation, or other retinal abnormalities [26–28]. Although there are published reports

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discussing these issues, much of the current data are considerably variable. For example, Stirn et al. noted that among a total of 65 Down syndrome children who visited their hospital, 32 % suffered from abnormalities of the retinal vessels, foveal hypoplasia, or retinal pigment epithelium hyperplasia [29]. Fimiani et al., however, reported retinal anomalies in only 6 % of 157 Italian children with Down syndrome [30]. As such, it is uncertain whether abnormalities in retinal structure are common in these children, or whether it is simply that our knowledge of the foveal structure in children with Down syndrome is extremely limited.

Optical coherence tomography (OCT) is an increasingly employed non-invasive and high-resolution imaging technique that offers the potential to quantitatively and objectively evaluate the tissue architecture of the fovea. In the present study, using Fourier domain optical coherence tomography (fdOCT), we investigated retinal macular structural features in children with Down syndrome (Down syndrome group) compared to those of age-matched healthy children (control group).

## Methods

The institutional review board of Indiana University approved this research protocol as well as the Health Insurance Portability and Accountability Act (HIPAA)-compliant forms. Informed consent was obtained from the subjects' parents, and assent was obtained from subjects over 7 years of age. The ocular conditions of all participants were diagnosed and continually cared for by pediatric ophthalmologists at Indiana University School of Medicine.

### Participants

Two groups of children aged 6 to 16 years were enrolled: Down syndrome group ( $N=17$ ) and control group ( $N=18$ ).

**Inclusion criteria in the Down syndrome group** Participants were born with Down syndrome, with the diagnosis of Down syndrome usually reported by a primary care physician before the patient was recommended to our ophthalmologists. Down syndrome can be diagnosed during pregnancy or after birth. For children born with Down syndrome, there is a common blood test to determine the number of the baby's chromosomes. Prenatal screenings/diagnostic tests can take place during pregnancy in order to determine the likelihood of the child being born with Down syndrome. Gestational age at birth of all participants was over 36 weeks.

**Inclusion criteria in the control group** We enrolled healthy age-matched children who were full-term at birth as the control group. Because Down syndrome patients often have

hyperopia [1–5], we allowed several age-matched children with hyperopia to be enrolled in the study, as well as children with emmetropia. The control group had a range of spherical equivalents ( $-1.75$  D to  $6.5$  D) similar to that in the children with Down syndrome.

**Exclusion criteria** Children with glaucoma, cataracts, corneal transplant, or co-existing ocular or congenital infections were excluded.

### Study procedures

At the time of retinal imaging, a cycloplegic refraction was performed using streak retinoscopy. Refraction was recorded as the spherical equivalent (SEQ, the sum of the sphere power and half of the cylinder power). Visual acuity (VA) was measured with Snellen letters.

### Imaging procedures

Macular thickness was measured using high-resolution fdOCT (iVue; Optovue Inc., Fremont, CA, USA). Two or three macular volume scans across the fovea were obtained for each eye, and the volume scan with the highest signal-to-noise ratio was selected. Average sectional total thickness was automatically determined by the instrument's software using a modified Early Treatment Diabetic Retinopathy Study (ETDRS) circle grid (center, middle, and outer rings of 1, 2, and 3 mm, respectively). The instrument's segmentation software was used to calculate the thickness of a central subfield 1 mm in diameter, and the thickness of the inner and outer retinal layer regions were measured. The sectional thickness of the total, inner, and outer retinal layer regions of the middle ring (superior, nasal, inferior, and temporal sections) were also measured and compared to those of the control group. The inner layers included the retinal nerve fiber layer, ganglion cell layer, inner plexiform layer, and inner nuclear layer (INL), while the outer layers comprised the outer plexiform layer (OPL), outer nuclear layer, photoreceptor inner segment layer, photoreceptor outer segment layer, and retinal pigment epithelial layer. The dividing line for the inner versus outer layer regions was between the INL and OPL.

### Sample size

The sample size was planned to provide 0.80 power  $1-\beta$  with  $\alpha=0.05$  to permit detection of  $\geq 10$   $\mu\text{m}$  interocular difference in macular thickness. A value of 10  $\mu\text{m}$  was chosen, as coefficients of repeatability for macular thickness measured by fdOCT in eyes with healthy retinas have been reported at 1.0 to 3.5 %, or up to about 9.5  $\mu\text{m}$  [31, 32]. Interocular differences in macular thickness of  $0.0\pm 13.4$   $\mu\text{m}$  as measured by

fdOCT have been reported for children 6–17 years of age [21]. Using this standard deviation, we determined that a sample size of 16 in each group was sufficient.

### Data analysis

Central subfield thickness (CST) was compared between the two groups using an independent *t* test. In addition, we compared our data with the normative control data of healthy children published by Wu et al. [33].

### Results

The demographic characteristics of children are reported in Table 1. All children in the Down syndrome group showed identifiable retinal structure, including a foveal pit. A sample picture from each group is presented in Fig. 1a and b. Because of similarities between the right and the left eyes, we reported results only for the right eye.

### Retinal thickness

CST and sectional average thickness for the full retina are summarized in Table 2. CST for the full retina was significantly greater in the Down syndrome group ( $281 \pm 17 \mu\text{m}$ ) than the control group ( $246 \pm 21 \mu\text{m}$ ; independent *t* test,  $t=5.90$ ,  $p<0.001$ ). After Bonferroni correction, all regions immediately surrounding the full retina CST were significantly thicker except for the temporal section. The CST for the inner and outer retinal layers were both significantly greater in the Down syndrome group as well (independent *t* test,  $t=4.34$ ,  $p<0.001$ ; independent *t* test,  $t=3.33$ ,  $p=0.002$ ) (Table 2).

When compared to control patients in the study published in Wu et al. [33], the results are similar. The CST of the full

retina for the right and left eyes was again significantly greater in the Down syndrome group (right eye:  $t=5.9$ ,  $p<0.001$ ; left eye:  $t=5.38$ ,  $p<0.001$ ). For the right eyes, approximately 29 % of patients (5/17) in the Down syndrome group were outside the normal range (normal range provided by the control group or Wu et al. [33]).

We also compared CST of the right eyes to CST of the left eyes in the Down syndrome group, and no significant interocular difference was found (paired *t* test,  $t=0.253$ ,  $p=0.802$ ).

### Qualification of foveal pit depth

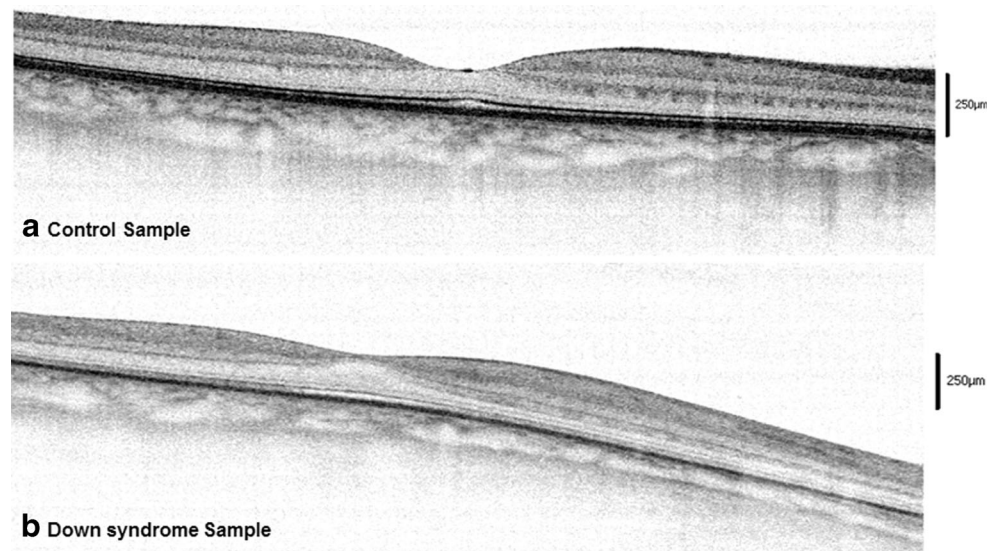
Because the total thickness in the central subfield and the superior and nasal sections of the Down syndrome group were thicker than those of the control group, we used a simple method to qualify foveal pit depth. We subtracted the total thickness of the CST from the four surrounding sections (superior, nasal, inferior, temporal) to estimate foveal pit depth. Except for the inferior section, the sectional thickness differences between surrounding sections and CST in the Down syndrome group were significantly lower than those in the control group, indicating that the depth of the foveal pit was shallower in the Down syndrome group (Table 3).

### Correlation of CST with visual acuity and SEQ

Since many patients with Down syndrome suffer from poor visual acuity, we investigated the correlation between visual acuity and CST values. Our results demonstrate no significant correlation between visual acuity and CST ( $t=1.288$ ,  $r=0.326$ ,  $p=0.202$ ). Furthermore, there was no significant correlation between spherical equivalent (SEQ) and CST in patients with Down syndrome ( $r=0.087$ ,  $p=0.740$ ).

**Table 1** Demographic distribution and characteristics of Down syndrome and control groups. Statistics are described as “mean $\pm$ SD, (minimum–maximum)”

Characteristics	Down syndrome group ( $N=17$ )	Control group ( $N=18$ )
Sex (M/F)	9/8	10/8
Age at imaging (years)	11.0 $\pm$ 3.1, (6–16)	9.6 $\pm$ 3.4, (6–15)
Race		
White	14	15
African American	2	2
Hispanic	1	1
Gestational age (weeks)	38.6 $\pm$ 1.8, (36–40)	39.9 $\pm$ 0.25, (39–40)
Spherical equivalent (D)	2.2 $\pm$ 2.5, (–1.5 to 6.75)	1.5 $\pm$ 2.3, (–1.75 to 6.5)
Visual acuity (logMAR)	(OD) 0.36 $\pm$ 0.16 (OS) 0.42 $\pm$ 0.15 (0.10–0.70)	(OD) 0.08 $\pm$ 0.07 (OS) 0.12 $\pm$ 0.11 (0.0–0.30)



**Fig. 1** **a** OCT image from the right eye of a healthy 11-year-old full-term child from the control group. The full retina central subfield thickness (CST) is 235  $\mu\text{m}$ , and visual acuity was 20/20 at the time of testing. This child had a spherical equivalent of 0.75 D and a normal retina. The foveal pit and central thickness were normal. **b** OCT image from the right eye of

a 13-year-old patient born at 38 weeks of gestational age with Down syndrome. CST is 281  $\mu\text{m}$ , and visual acuity was 20/65 at the time of testing. The patient had a spherical equivalent of  $-1.5$  D and the full retina was significantly thicker as compared to the control group

In addition, we compared the correlation of visual acuity and SEQ to that of CST in our control group. Again, there was no significant correlation between CST and visual acuity ( $t=0.518$ ,  $r=0.163$ ,  $p=0.518$ ), and there was also no significant correlation between SEQ and CST ( $t=1.407$ ,  $r=0.366$ ,  $p=0.135$ ).

## Discussion

This prospective study evaluated the characteristics of macular retinal structure in children with Down syndrome and compared them with an age-matched and spherical equivalent-

**Table 2** Mean retinal thickness (in  $\mu\text{m}$ ) in sectional areas of the right eye

	Down syndrome group ( $N=17$ )	Control group ( $N=18$ )	Wu et al. 2012 control ( $N=47$ )	t value	p value
<b>Full retina</b>					
Central CST	281 $\pm$ 17	246 $\pm$ 21	247 $\pm$ 21	5.90	<0.00001 <sup>a</sup>
Total superior	326 $\pm$ 17	309 $\pm$ 28	315 $\pm$ 16	2.96	0.006 <sup>a</sup>
Total nasal	331 $\pm$ 15	312 $\pm$ 16	317 $\pm$ 14	3.63	0.001 <sup>a</sup>
Total inferior	324 $\pm$ 19	304 $\pm$ 15	302 $\pm$ 45	2.93	0.006 <sup>a</sup>
Total temporal	314 $\pm$ 20	300 $\pm$ 13	299 $\pm$ 14	2.44	0.022
<b>Inner layer</b>					
Central	95 $\pm$ 15	76 $\pm$ 12		4.34	0.0002 <sup>a</sup>
Superior	114 $\pm$ 17	129 $\pm$ 14		-2.21	0.035
Nasal	123 $\pm$ 20	131 $\pm$ 19		-1.03	0.308
Inferior	119 $\pm$ 19	121 $\pm$ 14		-0.37	0.714
Temporal	126 $\pm$ 16	119 $\pm$ 8		1.58	0.127
<b>Outer layer</b>					
Central	185 $\pm$ 16	170 $\pm$ 12		3.33	0.0024 <sup>a</sup>
Superior	211 $\pm$ 25	180 $\pm$ 14		4.13	0.0004 <sup>a</sup>
Nasal	207 $\pm$ 29	182 $\pm$ 17		2.92	0.007 <sup>a</sup>
Inferior	205 $\pm$ 30	183 $\pm$ 13		2.35	0.028
Temporal	190 $\pm$ 24	180 $\pm$ 10		1.41	0.172

<sup>a</sup> Significant difference between the two groups after Bonferroni correction

**Table 3** Qualification of foveal pit depth (in  $\mu\text{m}$ ) of the right eye

Sectional difference in total thickness	Down syndrome group	Control group	<i>t</i> value	<i>p</i> value
Superior (Superior – Central)	45±20	64±14	3.27	0.003 <sup>a</sup>
Nasal (Nasal – Central)	50±18	67±12	3.31	0.002 <sup>a</sup>
Inferior (Inferior – Central)	43±22	58±18	2.21	0.03
Temporal (Temporal – Central)	33±21	53±16	3.18	0.003 <sup>a</sup>

<sup>a</sup>Significant difference between the two groups after Bonferroni correction

matched control group. We are not aware of similar reports in the literature. Although most eyes remained within the published normal range, CST values for children in the Down syndrome group were significantly greater than those in the control group. The thicker macula was also attributable to a thicker central subfield in both the inner and outer retinal layers. Our results suggest that an OCT finding of an apparently thicker macula in the Down syndrome group does not necessarily correlate with degraded visual acuity, which is consistent with previous reports describing a lack of association between macular thickness and visual acuity [15, 34, 35, 36].

We previously found that children with retinopathy of prematurity had a thicker fovea due to arrested foveal development by preterm birth [15]. Macular thickness is generally greater in children with congenital and developmental cataracts, particularly in those with unilateral cataracts [37]. In this study, although the gestational age of children in the Down syndrome group was over 36 weeks, and there was no involvement of severe visual deprivation such as cataracts, their CST measurements were significantly greater, suggesting a potential association between Down syndrome and macular abnormalities. Thicker macular structure may be a primary pathology related to the disorder. Stirn et al. reported the presence of foveal hypoplasia or retinal pigment epithelium hyperplasia in 32.2 % of patients with Down syndrome [29]. Our data showed that thickening could result from both inner and outer layers, which agrees with this report. However, Laguna et al. investigated retinal morphology structure in a mouse model of Down syndrome and reported that only the inner layers contributed significantly to retinal thickening [38]. Furthermore, a significantly shallower foveal pit, which is often demonstrated in foveal hypoplasia [36], was present in the Down syndrome group compared with the control group.

Our study had a few limitations. First, in the Down syndrome group, we excluded children with visual acuity worse than 20/100, significant nystagmus, or previous cataract surgery. The 20/100 visual acuity cut-off was determined based on our previous experiments and the patients' ability to fixate. We have found that many patients with visual acuity over 20/100 are unable to fixate on the target presented in the iVue recording device. More severe macular abnormalities may be associated with those children who were excluded. Aside from

central retinal thickening, our data showed no gross alterations in retinal structural organization. Although we occasionally see case reports of abnormalities of the macula (e.g., bilateral macular coloboma [25]) or optic disc (e.g., unilateral morning glory optic disc anomaly [27]), we observed no such abnormal retinal structures in our sample. Wu et al. conducted a study in 47 normal full-term children, similar in age to those in our study, using the same brand of OCT (OptoVue) as was used in our study, and which provided a normal range (fifth percentile was 205  $\mu\text{m}$  and 95th percentile was 289  $\mu\text{m}$ ) [33]. Based on these values, approximately one-fourth of Down syndrome patients had a CST beyond the normal range.

Second, axial length was not measured in our study. Although axial length can affect CST results [39], we do not think it would have affected the results of this study, for two reasons. 1) We chose spherical equivalent-matched control subjects. On average, axial length is shorter in children with Down syndrome, similar to children with hyperopia. Approximately 80 % of patients with Down syndrome are hyperopic, and their spherical equivalent is correlated with axial length [40]. 2) According to Odell and colleagues [39], after adjusting for shorter axial length, our data should demonstrate an even thicker central subfield in the Down syndrome group. In other words, adjusting for axial length confirmed our conclusion that CST was significantly different between the two groups. Considering that most OCTs in the clinic do not provide axial length adjustment, we presented our major results with unadjusted axial length measurements for general reference. Because OCT is widely available to ophthalmologists as part of their clinical practice, our findings may help clinicians differentiate foveal abnormalities associated with Down syndrome versus abnormalities for other reasons. For example, a thicker central subfield may frequently be seen in patients with Down syndrome.

Third, due to software limitations, we were not able to report more details on the individual layers or foveal contours in children with Down syndrome. This limitation will be addressed in future studies that characterize the individual layers in order to provide a deeper understanding of abnormalities in retinal structure in this population.

## Conclusions

Patients with Down syndrome had significantly greater CST values compared to the control group. In general, both the inner and outer layers contributed to the thicker central subfield. Although patients with Down syndrome tend to suffer from degraded vision, an OCT finding of an apparently thicker macula in a pediatric Down syndrome patient does not necessarily correlate with poorer visual acuity.

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**Conflict of interest** All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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