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Changes in ocular pulse amplitude and posterior ocular structure parameters in type 1 diabetic children without diabetic retinopathy

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Abstract

Background: It is important to determine changes in posterior ocular structures in the early period before retinopathy develops in pediatric patients with type 1 diabetes mellitus (DM).

Objective: To evaluate inner plexiform layer (IPL), ganglion cell layer (GCL), and retinal nerve fiber layer (RNFL) thicknesses, as well as the relationship between choroidal thickness (CT) and ocular pulse amplitude (OPA) in type 1 diabetic children without diabetic retinopathy (DR).

Design: A prospective observational study.

Methods: Group 1 ($n = 44$) consisted of pediatric patients with type 1 DM without DR, and Group 2 ($n = 65$) of pediatric control subjects. Both intraocular pressure (IOP) and OPA were measured using a dynamic contour tonometer. CT, IPL, GCL, and RNFL were all measured using spectral domain optical coherence tomography (OCT).

Results: The mean IOP and OPA values were 16.67 ± 2.34 and 1.85 ± 0.34, respectively, in group 1, and 15.14 ± 2.17 and 1.65 ± 0.25 in Group 2 ($p = 0.001$ for both). The mean subfoveal CT value was $294.30 \pm 67.61\,\mu m$ in group 1 and $394.42 \pm 69.65\,\mu m$ in Group 2 ($p < 0.001$). The mean GCL and RNFL values were 1.09 ± 0.11 and 96.46 ± 11.69, respectively, in group 1, and 1.14 ± 0.09 and 101.73 ± 9.33 in Group 2 ($p = 0.005$ and $p = 0.008$, respectively).

Conclusions: IOP and OPA values were higher, and CT, GCL, and RNFL values were lower in children with type 1 DM during the early stages than in the healthy control group. These findings suggest that CT may be a marker of retinal involvement in children with type 1 DM without DR.

Keywords: choroidal blood flow, choroidal thickness, dynamic contour tonometry, EDI mode OCT, ocular pulse amplitude, type 1 diabetes mellitus

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Introduction

Type 1 diabetes mellitus (DM), a chronic metabolic disease, develops as the result of an autoimmune breakdown of the beta cells that produce insulin in the pancreas.[1] Ocular complications, such as diabetic retinopathy (DR), temporary refraction change, lens opacity, macular edema, and glaucoma have been extensively investigated.[2]

Choroidal vasculature must be structurally and functionally normal for healthy retinal function.[3] Spectral domain optical coherence tomography (SD-OCT) with conventional light sources using 'enhanced depth imaging'-OCT (EDI-OCT); which can be used to conduct a clear assessment of the choroidal structures. Histopathological studies have shown that numerous choroidal disorders, such as choroidal microaneurysms, choroidal vascular occlusion, polypoidal choroidal vasculopathy, and choroidal neovascularization, may affect the pathogenesis of DR.[4] Retinal and photoreceptor dysfunction in diabetic eyes occurs

due to abnormal choroidal blood volume. Choroidal vasculopathy may therefore be a precursor to DR.[4] Ocular pulse amplitude (OPA) is an indirect indicator of choroidal perfusion and reflects the ocular blood flow corresponding to the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Measurements of choroidal thickness (CT) provide data about choroidal blood flow.[5]

OPA represents the pulsatile waveform that forms with the passage of blood through the eye and is a marker, albeit an indirect one, of choroidal perfusion. OPA has been defined as the difference determined between systolic intraocular pressure (IOP) and diastolic IOP.[6] A novel contact tonometer, known as dynamic contour tonometry (DCT) measures IOP independently of the corneal properties.[7]

The aim of this study was to evaluate and correlate OPA and CT measurements in children with type 1 DM and a healthy control group to indirectly evaluate choroidal blood flow. A secondary aim was to determine differences in the inner plexiform layer (IPL), ganglion cell layer (GCL), and retinal nerve fiber layer (RNFL) between the groups.

Methods

Study population and design

One hundred nine cases (51 women and 58 men) referred to the ophthalmology clinic by the Pediatric Endocrinology Department between May 1, 2019 and December 1, 2019 were evaluated.

The study population consisted of 65 healthy cases (the control group) and 44 cases with type 1 DM without DR (the study group). Patients diagnosed with type 1 DM, between 6 and 18 years of age, and referred from the Pediatric Endocrinology Department were included in the study. Diagnosis of type 1 DM was based on International Diabetes Federation/International Society for Pediatric and Adolescent Diabetes (IDF/ISPAD) guidelines.[8]

Patients with any retinal or chorioretinal disease, a history of a systemic disorder, such as insulin resistance, with histories of previous laser photocoagulation or ocular surgery or ocular trauma, with anterior segment opacities or a refractive error of 1 D or more were excluded from the study. Patients with poor-quality OCT images as the result of eye movement, in addition to media opacities or poor fixation were also excluded. The same exclusion criteria were also applied to age- and sex-matched healthy children constituting the control group.

The examination performed in this study was conducted on a randomized eye of each participant. Age, sex, HbA_{1c} levels, blood lipid profiles, DBP, SBP, and duration of disease were recorded. Patients were divided into two groups based on HbA_{1c} levels. Accordingly, HbA_{1c} levels less than 9 were regarded as good–moderate glycemic control, and levels $\geq 9\%$ as poor glycemic control.[9]

Patient examination protocol and study measurements

Detailed ophthalmological examinations, including slit-lamp biomicroscopy, dilated fundus, and best-corrected visual acuity (BCVA), were performed on all members of the patient and control groups.

SD-OCT (Spectralis OCT®; Heidelberg Engineering, Heidelberg, Germany) was used to measure CT, IPL, GCL, and RNFL. The SD-OCT system employed a super-luminescent diode at a wavelength of 870 nm to supply 40,000 A scans/s. It had a 7-lm axial and 14-lm lateral optical resolution. The images were acquired in high-resolution OCT mode, with a 3.9-lm axial and 6-lm lateral digital resolution, and a 38-ms/B-scan acquisition time. Only those scans with a good signal strength, comprising a signal-to-noise ratio of 20 dB or higher, were included in the analysis. Eight scans which exhibited low signal strength were eventually excluded. On the horizontal scans, CT measurement was performed manually at 500 µm nasally as well as 500 µm temporally from the central fovea. The EDI-OCT measurements for each participant were performed within the same time period (from 9 to 11 a.m.). For this study, images needed to be captured as close to the fovea as possible. It was therefore decided to visualize the macula at the thinnest point, since even a small difference in positioning might have an effect on the thickness value determined.

Subfoveal CT was defined as being the length measured perpendicularly between the outer surface of a hyper-reflective line of the retinal pigment epithelium (RPE) and the inner margin of

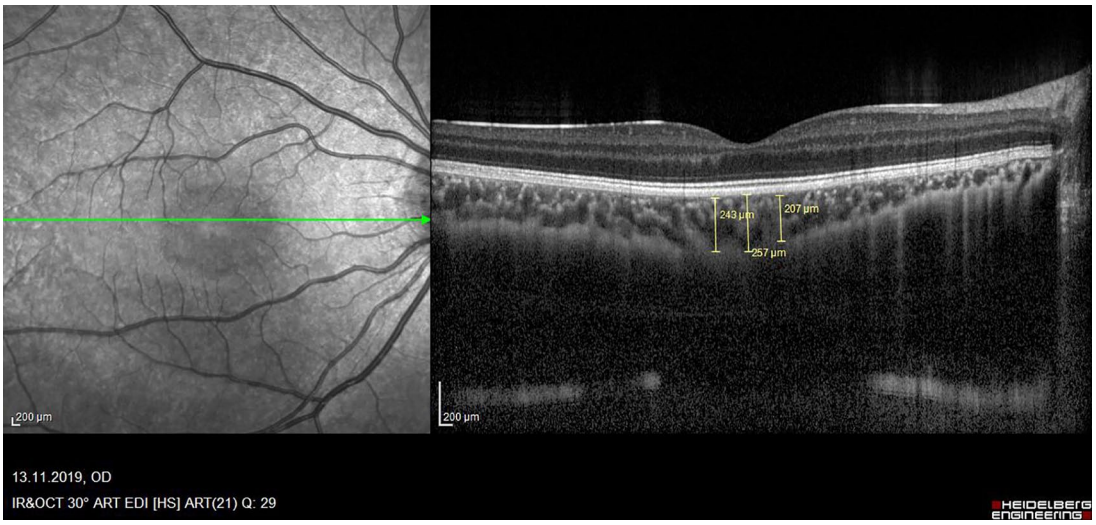

Figure 1. An example of choroidal thickness (CT)* in a patient.
*CT was measured three times in the subfoveal area at a distance of 500 µm from the macula and in the nasal and temporal areas, and the mean value was recorded.

the chorioscleral junction (Figure 1). All measurements were taken by two independent examiners blinded to the study. The mean values of these examiners' measurements were then used in the analysis.

Mean RNFL thicknesses in the four quadrants (superior, nasal, inferior, and temporal) were calculated automatically.

OPA values of the same eye were included in the study. A Pascal DCT device, purchased commercially from Swiss Microtechnology (Bern, Switzerland), was used to obtain IOP and OPA values. The measurements were taken with the subject seated at the slit-lamp after a 5-min rest period.

The mean of three good quality measurements was used for all tests. OPA readings 1 and 2 were employed for quality scores.

The HbA_{1c} values and fasting glucose levels of patients with Type 1 DM were also measured. SBP and DBP were both measured 10 min prior to CT measurement. BP was measured using an Omron M2 HEM-7121-E automatic digital BP device (Tokyo, Japan) following a rest period, and was analyzed three times at 10-min intervals. Blood specimens were collected from all children after 12-h fasting. Blood lipid levels were calculated using a Beckman Coulter DXC 800/USA biochemical analyzer.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows 25.0 software (Armonk, NY, USA), at a statistical significance level of 0.05 (p-value). The Kolmogorov–Smirnov test was used to evaluate the normality of numerical variables with skewness–kurtosis values. As the variables exhibited normal distribution, a t test was applied to compare independent group values. Pearson's chi-square test in a 2×2 grid was used to compare variation between categorical variables. Pearson's correlation coefficient was employed in the analysis of relationships between mean CT, GCL, IPL, RNFL, IOP, OPA, and duration of diabetes, and SBP, DBP, HbA_{1c}, and body mass index (BMI) in child patients. Bland–Altman plot analyses were also performed using MedCalc version 12.3 (MedCalc Software, Ostend, Belgium) software. Univariate regression analyses were conducted to analyze the association of subfoveal CT with the systemic variables among patients' eyes.

Results

One hundred nine patients, between 6 and 18 years in age (mean age = 12.61 ± 3.39 years), 58 boys and 51 girls, were included in the study. The control group consisted of 65 participants, 33 boys and 32 girls (mean age = 12.90 ± 3.48 years), and the patient group consisted of 44 participants, 25 boy and 19 girl (mean age = 12.35 ± 3.28 years). No statistically significant differences were determined

Table 1. Characteristics of the type 1 diabetes patient group.

	Group	*n*	Mean ± *SD*	*P*[a]
BMI-SD	Patient group	44	0.01 ± 1.09	.624
	Control group	65	0.10 ± 0.49	
HbA_{1c}	Patient group	44	9.82 ± 1.95	<**0.001**
	Control group	65	5.15 ± 0.33	
Systolic blood pressure, mm Hg	Patient group	44	106.70 ± 8.55	0.274
	Control group	65	104.58 ± 10.88	
Diastolic blood pressure, mm Hg	Patient group	44	66.25 ± 7.55	0.208
	Control group	65	64.38 ± 7.81	
Total cholesterol	Patient group	44	164.75 ± 43.63	<**0.001**
	Control group	65	128.29 ± 8.94	
HDL	Patient group	44	50.52 ± 9.57	0.914
	Control group	65	50.70 ± 6.40	
LDL	Patient group	44	87.23 ± 33.48	0.473
	Control group	65	90.99 ± 10.76	

p-value for the comparison of clinical characteristics in patient and control groups; bold denotes *p*-values with a statistical significance.
BMI-SD, body mass index standard deviation; HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Independent *t* test.

between the patient and control groups in terms of age or sex ($p > 0.05$). Descriptive statistics for mean HbA_{1c} levels, duration of diabetes, SBP and DBP, and lipid levels in the patient and control groups are shown in Table 1. Mean BCVA was 0.94 ± 0.03, while the mean spherical equivalent (SE) was 0.68 ± 0.35 D in the type 1 DM patient group. In the control group, mean BCVA was 0.98 ± 0.02 and mean SE was 0.62 ± 0.34 D. No significant difference was observed between the groups of mean BCVA or SE ($p = 0.25$ and $p = 0.17$, respectively). The mean axial length in the type 1 DM patient group was 23.3 ± 0.62 mm, compared with 23.4 ± 0.85 mm in the healthy control group. This difference was not statistically significant ($p = 0.42$).

Mean IOP values were 16.67 ± 2.34 mm Hg in the type 1 DM patient group and 15.14 ± 2.17 mm Hg in the healthy control group ($p = 0.001$). Mean OPA was 1.85 ± 0.34 mm Hg in the type 1 DM patient group and 1.65 ± 0.25 mm Hg in the healthy control group ($p = 0.001$). Mean subfoveal CT was 294.30 ± 67.61 µm in the type 1 DM patients and 394.42 ± 69.65 µm in the control group ($p < 0.001$). RNFL measurements and GCL values differed significantly between the patient and healthy control groups ($p < 0.05$). CT, GCL, IPL, IOP, OPA, and RNFL measurements are shown in detail in Table 2.

When the type 1 DM patients were classified on the basis of their metabolic control (MC) levels, 61.4% of the patients were assigned to the poor MC group, and 38.6% were placed to the good–moderate MC group.

IPL, IOP, and OPA were higher in the poor MC group than in the good–moderate MC group ($p < 0.05$), while GCL, CT, and RNFL were lower ($p < 0.001$) (Table 3).

Table 2. Comparison of diabetes patients and the control group in terms of ocular measurements.

Variables		Mean	*SD*	*p*[a]	95% CI	
					Lower	Upper
Nasal CT	Patient	282.36	70.51	**<0.001**	−123.06	−68.35
	Control	378.85	67.18			
Subfoveal CT	Patient	294.30	67.61	**<0.001**	−107.46	−50.04
	Control	394.42	69.65			
Temporal CT	Patient	278.70	64.73	**<0.001**	−111.94	−61.16
	Control	371.81	65.78			
GCL	Patient	1.09	0.11	**0.005**	−0.09	−0.02
	Control	1.14	0.09			
IPL	Patient	.97	0.09	0.339	−0.02	0.05
	Control	.95	0.08			
IOP	Patient	16.67	2.34	**0.001**	0.68	2.37
	Control	15.14	2.17			
OPA	Patient	1.85	0.34	**0.001**	0.09	0.31
	Control	1.65	0.25			
SRNFL	Patient	115.95	21.34	**0.001**	−18.83	−5.05
	Control	127.89	16.07			
NRNFL	Patient	71.79	16.69	**0.037**	−11.35	−0.35
	Control	77.64	13.09			
IRNFL	Patient	118.34	19.98	**0.010**	−16.63	−2.36
	Control	127.83	18.17			
TRNFL	Patient	69.47	11.40	**0.039**	−8.00	−0.22
	Control	73.58	9.57			
RNFL mean	Patient	96.46	11.69	**0.008**	−10.70	−2.81
	Control	101.73	9.33			

Bold denotes *p*-values with a statistical significance.
CI, confidence interval; CT, choroid Thickness; GCL, ganglion cell layer; IOP, intraocular pressure; IPL, inner plexiform layer; IRNFL, inferior retinal nerve fiber layer; NRNFL, nasal retinal nerve fiber layer; OPA, ocular pulse amplitude; RNFL, retinal nerve fiber layer; *SD*, standard deviation; SRNFL, superior retinal nerve fiber layer; TRNFL, temporal retinal nerve fiber layer.
[a]Independent *t* test.

Correlations between IOP, OPA, CT, GCL, IPL, and RNFL, and age, duration of DM, HbA_{1c} values, SBP, DBP, and BMI are shown in detail in Table 4.

The regression model in Table 5 shows that OPA was significantly ($p < 0.05$) associated with HbA_{1c} values. There were no other statistically significant associations between CT and any other factors

Table 3. Comparison of ocular measurements in diabetes patients in terms of metabolic control levels.

Variables		Mean	*SD*	*p*[a]
Choroid thickness (mean)	Good–moderate diabetes	305.64	78.80	0.031
	Poor diabetes	263.92	45.51	
GCL	Good–moderate diabetes	1.14	0.08	0.008
	Poor diabetes	1.06	0.11	
IPL	Good–moderate diabetes	.92	0.06	0.002
	Poor diabetes	1.0	0.09	
IOP	Good–moderate diabetes	15.54	2.77	0.010
	Poor diabetes	17.38	1.73	
OPA	Good–moderate diabetes	1.67	0.29	0.007
	Poor diabetes	1.95	0.33	
RNFL (mean)	Good–moderate diabetes	100.47	9.54	0.015
	Poor diabetes	91.52	12.36	

p-values with a statistical significance.
GCL, ganglion cell layer; IOP, intraocular pressure; IPL, inner plexiform layer; OPA, ocular pulse amplitude; RNFL, retinal nerve fiber layer; SD, standard deviation.
[a]Independent *t* test.

(Table 6). Bland–Altman plot analyses were also performed to determine the mean difference between the CT measurements (Figure 2).

Discussion

To the best of our knowledge, this is the first study to compare the relationships between OPA and CT in pediatric patients diagnosed with type 1 DM without DR. CT decreased significantly while OPA increased significantly in the patient group.

Providing blood and nutrient support to the outer retinal layers is one of the functions of the choroid.[10] Narrowing of the choroidal arterioles, atrophy of the choriocapillaris, as well as capillary dropout have been histopathologically demonstrated by means of choroidal examination of eyes with DR.[11] The relationship between diabetes and retinal blood flow has been investigated in various studies, although inconsistent results have been reported. Although there have been some reports of increased retinal blood flow in patients with DM without DR or with only minimal DR,[12] Dimitrova *et al.*[13] reported decreased retinal and choroidal blood flow in DM patients both with and without DR. Studies have evaluated CT in adult DM groups. One study found significantly lower mean subfoveal CT in a type 1 DM group compared with a healthy control group. That study also reported no significant difference in subfoveal CT values in diabetic patient groups both with and without DR.[14] Similarly, Esmaeelpour *et al.*[15] found that subfoveal CT was significantly lower in type 1 DM patients relative to a control group.

OPA measurement permits the indirect analysis of choroidal perfusion. The effect of diabetes on OPA has previously been investigated, although in only a few studies.[16] Although Schmidt *et al.*[17] maintain that choroidal circulation is not affected in adult diabetics with DR, Totan *et al.*[18] observed decreased choroidal blood flow in patients diagnosed with diabetic macular edema. In the present research, and in contrast to adult studies, both IOP and OPA values were higher in children diagnosed with type 1 DM compared with the healthy control group. This may be explained by the hypothesis that pericyte loss caused by chronic hyperglycemia leads to vascular tone irregularity and hemodynamic changes.[19]

Table 4. Pearson correlations between patient group values.

Variables	Duration of diabetes	SBP	DBP	HbA_{1c}	BMI
CT mean	−.143	−.335	−.115	−.079	−.119
GCL	.100	−.204	**−.297****	.005	.039
IPL	−.076	−.181	**−.341*****	−.096	−.033
IOP	−.015	−.193	−.046	−.142	−.064
OPA	.003	−.205	−.046	−.148	**.303***
RNFL mean	.160	−.088	−.154	−.115	.044

BMI, body mass index; CT, choroidal thickness; DBP, diastolic blood pressure; GCL, ganglion cell layer; HbA_{1c}, hemoglobin A1c; IOP, intraocular pressure; IPL, inner plexiform layer; OPA, ocular pulse amplitude; RNFL, retinal nerve fiber layer; SBP systolic blood pressure.
*Significance level was accepted as <0.05. **Significance level was accepted as <0.01. ***Significance level was accepted as <0.001.

Table 5. Linear regression analyses of systemic factors associated with ocular pulse amplitude.

Predictors	Unstandardized β	Standardized β	*p*
HbA_{1c}	0.297	0.421	0.**004**
BMI	0.025	0.269	0.057

Bold denotes *p*-values with a statistical significance.
BMI, body mass index; HbA_{1c}, hemoglobin A1c.

CT can be affected by choroidal blood flow, and a thinner choroid may indicate damaged choroidal circulation with insufficient blood flow.[20] Regatieri *et al.*[21] showed a significant decrease in CT in adult patients with diabetic macular edema, and reported that decreased CT correlates with the degree of DR. In another study, including children with type 1 DM, Sayin *et al.*[22] reported similar CT values in diabetic patients to those in healthy controls, and that these were not affected by diabetes duration, HbA_{1c} levels, or age. In contrast to Sayin *et al.*, in the present study, we observed a decrease in CT in the children with type 1 DM compared with the healthy control group. This finding suggests that microvascular dysfunction caused by chronic hyperglycemia in children with type 1 DM adversely affects choroidal blood supply. CT can be affected by numerous factors, such as age, refractive error, and diurnal variation.[23–25] To minimize the effect of these variables, the patients in the type 1 DM and the healthy control groups were all matched for age and sex, and measurements were taken during the same time periods. We observed no relationship between CT and HbA_{1c}, duration of DM, BMI, or BP. Additional studies are now needed to identify the factors associated with CT in type 1 DM in the pediatric age group.

DR is a complex complication of diabetes in which retinal neurodegeneration plays an important role.[26] Early morphological changes have been examined in studies using OCT in adult patients with DM, although inconsistent results have emerged. One study comparing type 1 DM patients without DR to a healthy control group reported no significant alteration in GCL–IPL thickness.[27] Another study, by Karti *et al.*,[28] investigated retinal morphological changes in children with type 1 DM and reported that retinal ganglion cells were affected in the early stages of type 1 DM, followed by RNFL thinning in the peripapillary region due to axonal losses at subsequent stages. In the present study, significant differences were observed in GCL, IPL, and RNFL between children with type 1 DM without DR and the control group. This demonstrates that the choroid can change without affecting the retina and that diabetic choroidopathy can be a precursor of DR.

Table 6. Linear regression analyses of systemic factors associated with choroidal thickness.

Predictors	Unstandardized β	Standardized β	*p*
HbA_{1c}	−10.526	−0.077	0.619
BMI	2.620	0.145	0.352

BMI, body mass index; HbA_{1c}, hemoglobin A1c.

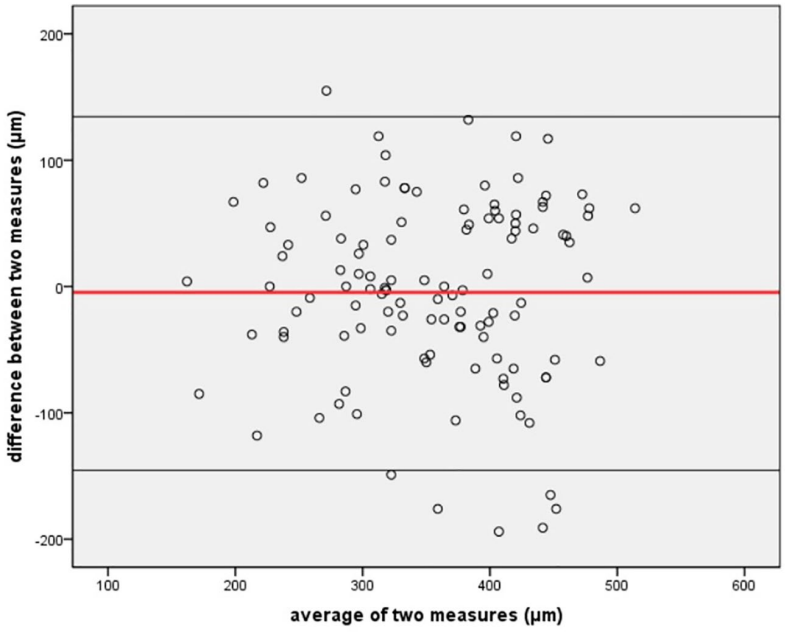

Figure 2. Bland–Altman plot for differences of choroidal thickness measurements between observers. The *x*-axes of the plots show the difference between them, the *y*-axes show the average of them.

The patient group was also divided into two subgroups according to HbA_{1c} levels, with 61.4% of patients in the poor MC group and 38.6% in the good–moderate MC group. The study results were more pronounced in the poor MC group. IPL, IOP, and OPA values were higher in the poor MC group than in the good–moderate MC group, while GCL, CT, and RNFL values were lower.

As described above, previous studies have measured CT and OPA in adults with DM, but these have not been examined in the type 1 DM pediatric patient group. To the best of our knowledge, this is the first study to do this. One contribution of this study to the literature is that patients were classified depending on good–moderate or poor MC. More severe exposure to chronic hyperglycemia in the pediatric patient population may have resulted in the more pronounced results determined in the poor MC group.

There are several limitations to this study, one being the relatively small sample size. Another was the narrow patient age range. In order for this study to be generalizable, the patient groups should be expanded to include more age groups with type 1 DM patients in future studies.

In conclusions, the results of this study demonstrated an increase in IOP and OPA values in children with type 1 DM without DR. We also observed a decrease in GCL and RNFL thickness values in children with type 1 DM compared with the healthy control group. Our results suggest that microvascular dysfunction develops even in the early period of childhood diabetes, and that autoregulatory mechanisms become involved to establish normal choroidal perfusion in these patients.

Ethics approval and consent to participate

This observational, prospective study was approved by the ethical committee of Adıyaman University Education and Research Hospital (Adıyaman, Turkey; approval no. 2019/3-20—approval date: April 16, 2019), and was performed in line with the principles of the Helsinki Declaration. Written informed consent was obtained from the parents or legal guardians of the patients.

Consent for publication

Not applicable.

Author contribution(s)

Abdulvahit Asik: Data curation; Formal analysis; Investigation; Resources; Software.

Semih Bolu: Conceptualization; Formal analysis; Methodology.

Ilke Direkci: Data curation; Formal analysis; Supervision; Validation.

Emre Aydemir: Data curation; Project administration; Software; Visualization; Writing – review & editing.

Gozde Aksoy Aydemir: Conceptualization; Data curation; Supervision; Validation; Writing – original draft.

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Conflict of interest statement

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Availability of data and materials

Not applicable.

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