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

Abdulvahit Asik, Semih Bolu, Ilke Direkci, Emre Aydemir and Gozde Aksoy Aydemir

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 ± 67.61 μm in group 1 and 394.42 ± 69.65 μm 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

Received: 29 October 2021; revised manuscript accepted: 27 April 2022.

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. Ocular complications, such as diabetic retinopathy (DR), temporary refractive change, lens opacity, macular edema, and glaucoma have been extensively investigated.

Choroidal vasculature must be structurally and functionally normal for healthy retinal function. 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. Retinal and photoreceptor dysfunction in diabetic eyes occurs

Correspondence to: Gozde Aksoy Aydemir
Ophthalmology
Department, Adıyaman University Education and Research Hospital, 02100 Adıyaman, Turkey.
gzdaksoy@hotmail.com

Abdulvahit Asik
Department of Pediatrics, Adıyaman University Education and Research Hospital, Adıyanan, Turkey

Semih Bolu
Department of Pediatric Endocrinology, Adıyaman University Education and Research Hospital, Adıyaman, Turkey

Ilke Direkci
Emre Aydemir
Ophthalmology
Department, Adıyaman University Education and Research Hospital, Adıyaman, Turkey

Creative Commons Non Commercial CC BY-NC. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
due to abnormal choroidal blood volume. Choroidal vasculopathy may therefore be a precursor to DR. 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.

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. A novel contact tonometer, known as dynamic contour tonometry (DCT) measures IOP independently of the corneal properties.

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.

Patients with any retinal or chorioretinal disease, a history of a systemic disorder, such as insulin resistance, with histories of previous laser photoacoagulation or ocular surgery or ocular trauma, with anterior segment opacities or a refractive error of 1D 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, HbA1c levels, blood lipid profiles, DBP, SBP, and duration of disease were recorded. Patients were divided into two groups based on HbA1c levels. Accordingly, HbA1c levels less than 9 were regarded as good–moderate glycemic control, and levels ≥9% as poor glycemic control.

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 870nm 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 20dB 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...
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 HbA1c 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 $2 \times 2$ 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, HbA1c, 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 $= 12.61 \pm 3.39$ 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 $= 12.90 \pm 3.48$ years), and the patient group consisted of 44 participants, 25 boy and 19 girl (mean age $= 12.35 \pm 3.28$ years). No statistically significant differences were determined
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 mmHg in the type 1 DM patient group and 15.14 ± 2.17 mmHg in the healthy control group ($p = 0.001$). Mean OPA was 1.85 ± 0.34 mmHg in the type 1 DM patient group and 1.65 ± 0.25 mmHg 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).
Correlations between IOP, OPA, CT, GCL, IPL, and RNFL, and age, duration of DM, HbA1c 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 HbA1c values. There were no other statistically significant associations between CT and any other factors.

| Variables       | Mean | SD    | \( p^a \) | 95% CI          |
|-----------------|------|-------|-----------|-----------------|
| Patient         | Control        |       |           | Lower | Upper  |
| Nasal CT        | 282.36 | 70.51 | \(<0.001\) | -123.06 | -68.35 |
|                 | 378.85 | 67.18 |           |       |        |
| Subfoveal CT    | 294.30 | 67.61 | \(<0.001\) | -107.46 | -50.04 |
|                 | 394.42 | 69.65 |           |       |        |
| Temporal CT     | 278.70 | 64.73 | \(<0.001\) | -111.94 | -61.16 |
|                 | 371.81 | 65.78 |           |       |        |
| GCL             | 1.09  | 0.11  | \(0.005\) | -0.09  | -0.02  |
|                 | 1.14  | 0.09  |           |       |        |
| IPL             | .97   | 0.09  | 0.339     | -0.02  | 0.05   |
|                 | .95   | 0.08  |           |       |        |
| IOP             | 16.67 | 2.34  | \(0.001\) | 0.68   | 2.37   |
|                 | 15.14 | 2.17  |           |       |        |
| OPA             | 1.85  | 0.34  | \(0.001\) | 0.09   | 0.31   |
|                 | 1.65  | 0.25  |           |       |        |
| SRNFL           | 115.95| 21.34 | \(0.001\) | -18.83 | -5.05  |
|                 | 127.89| 16.07 |           |       |        |
| NRNFL           | 71.79 | 16.69 | \(0.037\) | -11.35 | -0.35  |
|                 | 77.64 | 13.09 |           |       |        |
| IRNFL           | 118.34| 19.98 | \(0.010\) | -16.63 | -2.36  |
|                 | 127.83| 18.17 |           |       |        |
| TRNFL           | 69.47 | 11.40 | \(0.039\) | -8.00  | -0.22  |
|                 | 73.58 | 9.57  |           |       |        |
| RNFL mean       | 96.46 | 11.69 | \(0.008\) | -10.70 | -2.81  |
|                 | 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.
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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{12} Dimitrova \textit{et al.}\textsuperscript{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.\textsuperscript{14} Similarly, Esmaeelpour \textit{et al.}\textsuperscript{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.\textsuperscript{16} Although Schmidt \textit{et al.}\textsuperscript{17} maintain that choroidal circulation is not affected in adult diabetics with DR, Totan \textit{et al.}\textsuperscript{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.\textsuperscript{19}

\textbf{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.
CT can be affected by choroidal blood flow, and a thinner choroid may indicate damaged choroidal circulation with insufficient blood flow. Regatieri et al. 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. reported similar CT values in diabetic patients to those in healthy controls, and that these were not affected by diabetes duration, HbA1c 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. 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 HbA1c, 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. 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. Another study, by Karti et al., 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.
The patient group was also divided into two subgroups according to HbA1c 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.

**ORCID iDs**

[https://orcid.org/0000-0001-6969-0095](https://orcid.org/0000-0001-6969-0095)

---

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

| Predictors | Unstandardized β | Standardized β | p    |
|------------|------------------|----------------|------|
| HbA1c      | -10.526          | -0.077         | 0.619|
| BMI        | 2.620            | 0.145          | 0.352|

BMI, body mass index; HbA1c, hemoglobin A1c.
Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
Not applicable.

References
1. Gregory JM, Moore DJ and Simmons JH. Type 1 diabetes mellitus. Pediatr Rev 2013; 34: 203–215.
2. Yokota S, Takihara Y, Takamura Y, et al. Circumpapillary retinal nerve fiber layer thickness, anterior lamina cribrosa depth, and lamina cribrosa thickness in neovascular glaucoma secondary to proliferative diabetic retinopathy: a cross-sectional study. BMC Ophthalmol 2017; 17: 57.
3. Hayreh SS. Segmental nature of the choroid vasculature. Br J Ophthalmol 1975; 59: 631–648.
4. Hidayat AA and Fine BS. Diabetic choroidopathy: light and electron microscopic observation of seven cases. Ophthalmology 1985; 92: 512–522.
5. Punjabi OS, Kniestedt C, Stamper RL, et al. Dynamic contour tonometry: principle and use. Clin Exp Ophthalmol 2006; 34: 837–840.
6. Grieshaber MC, Katamay R, Gugleta K, et al. Relationship between ocular pulse amplitude and systemic blood pressure measurements. Acta Ophthalmol 2009; 87: 329–334.
7. Kaufmann C, Bachmann LM, Robert YC, et al. Ocular pulse amplitude in healthy subjects as measured by dynamic contour tonometry. Arch Ophthalmol 2006; 124: 1104–1108.
8. Craig ME, Hattersley A and Donaghuhe K. Definition, epidemiology and classification. In: Hanas R, Donaghuhe K, Klingensmith G, et al. (eds) Global IDF/ISPAD guideline for diabetes in childhood and adolescence. Brussels: International Diabetes Federation, 2011, pp. 8–16.
9. Rewers M, Phoher C, Donaghuhe K, et al. Assessment and monitoring of glycemic control.
10. Nickla DL and Wallman J. The multifunctional choroid. Prog Retin Eye Res 2010; 29: 144–168.
11. Lutty GA, Cao J and McLeod DS. Relationship of polymorphonuclear leukocytes to capillary dropout in the human diabetic choroid. Am J Pathol 1997; 151: 707–714.
12. Burgansky-Eliash Z, Barak A, Barash H, et al. Increased retinal blood flow velocity in patients with early diabetes mellitus. Retina 2012; 32: 112–119.
13. Dimitrova G, Kato S, Tamaki Y, et al. Choroidal circulation in diabetic patients. Eye 2001; 15: 602–607.
14. Querques G, Lattanzio R, Querques L, et al. Enhanced depth imaging optical coherence tomography in type 2 diabetes. Invest Ophthalmol Vis Sci 2012; 53: 6017–6024.
15. Esmæelpour M, Brunner S, Ansari-Shahrezaei S, et al. Choroidal thinning in diabetes type 1 detected by 3-dimensional 1060 nm optical coherence tomography. Invest Ophthalmol Vis Sci 2012; 53: 6803–6809.
16. Willekens K, Rocha R, Van Keer K, et al. Review on dynamic contour tonometry and ocular pulse amplitude. Ophthalmic Res 2015; 55: 91–98.
17. Schmidt KG, von Rückmann A, Kemkes-Matthes B, et al. Ocular pulse amplitude in diabetes mellitus. Br J Ophthalmol 2000; 84: 1282–1284.
18. Totan Y, Akyüz TK, Gülter E, et al. Evaluation of ocular pulse amplitude and choroidal thickness in diabetic macular edema. Eye 2016; 30: 369–374.
19. Frank RN. Diabetic retinopathy. N Engl J Med 2004; 350: 48–58.
20. Ardelen D and Chan CC. Aging is not a disease: distinguishing age-related macular degeneration from aging. Prog Retin Eye Res 2013; 37: 68–89.
21. Regatieri CV, Branchini L, Carmody J, et al. Choroidal thickness in patients with diabetic retinopathy analyzed by spectral-domain optical coherence tomography. Retina 2012; 32: 563–568.
22. Sayin N, Kara N, Pirhan D, et al. Evaluation of subfoveal choroidal thickness in children with type 1 diabetes mellitus: an EDI-OCT study. Semin Ophthalmol 2014; 29: 27–31.
23. Margolis R and Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. *Am J Ophthalmol* 2009; 147: 811–815.

24. Fujiwara T, Imamura Y, Margolis R, et al. Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes. *Am J Ophthalmol* 2009; 148: 445–450.

25. Tan CS, Ouyang Y, Ruiz H, et al. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012; 53: 261–266.

26. Simó R, Stitt AW and Gardner TW. Neurodegeneration in diabetic retinopathy: does it really matter? *Diabetologia* 2018; 61: 1902–1912.

27. Koh VT, Tham YC, Cheung CY, et al. Determinants of ganglion cell-inner plexiform layer thickness measured by high-definition optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012; 53: 5853–5859.

28. Karti O, Nalbantoglu O, Abali S, et al. Retinal ganglion cell loss in children with type 1 diabetes mellitus without diabetic retinopathy. *Ophthalmic Surg Lasers Imaging Retina* 2017; 48: 473–477.