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Original Article

Peripapillary Choroidal Vasculature in Pediatric Eyes with Type 1 Diabetes Mellitus

Murat Hasanreisoglu,[1] Cem Kesim,[1] Nur Sena Uzunay,[3] Ayse Yildiz Tas,[1] Melisa Zisan Karslioglu,[1] Afsun Sahin[2]

[1]Department of Ophthalmology, Koc University Faculty of Medicine, Istanbul, Türkiye
[2]Koc University Research Centre For Translational Medicine, Istanbul, Türkiye
[3]Koc University Faculty of Medicine, Istanbul, Türkiye

Abstract

Objectives: Choroidal vasculature change in children with diabetes mellitus is not investigated enough although it could reflect clinical outcome.

Methods: Pediatric Type 1 diabetes mellitus (T1DM) patients and healthy controls were retrospectively evaluated. Peripapillary retinal nerve fiber layer optical coherence tomography (OCT) images of the right eyes were analyzed. Choroidal parameters including total choroidal area, luminal area, stromal area, and choroidal vascularity index were measured through image binarization.

Results: Twenty eyes of 20 patients were compared with 46 eyes of 46 healthy controls. Mean total choroidal area, luminal area, and stromal area were 1.59±0.35, 1.10±0.24, and 0.50±0.13 mm^2 in patients' eyes and 1.52±0.49, 1.05±0.34, and 0.47±0.17 mm^2 in healthy eyes. No difference was found in choroidal vascularity indices between patients and healthy eyes (68.8±3.9% vs. 69.4±4.4%, p=0.521). Temporal choroidal vascularity index was significantly higher than its nasal counterpart in healthy eyes (71.8±5.0% vs. 68.6±4.9%, p<0.001) which was not significant in patients' eyes (70.7±4.0% vs. 68.9±5.1%, p=0.067). Temporal quadrant had the highest choroidal vascularity index score among all quadrants in healthy controls (all p<0.05), whereas no choroidal vascularity index difference between quadrants was detected in patients (p=0.75).

Conclusion: Peripapillary choroidal vasculature has shown subtle sectoral changes which did not reflect the overall peripapillary OCT section in pediatric T1DM patients when compared with healthy controls.

Keywords: Peripapillary choroid, retinal vasculature, type 1 diabetes mellitus, vascularity index

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic autoimmune diseases in childhood. The incidence of T1DM has an increasing trend with an annual estimated rate of 3% worldwide (1,2). The microvascular complications of T1DM usually manifest as retinopathy and choroidopathy in the eye (2-4). As the choroid is a highly vascularized ocular layer responsible for the oxygen and nutrient supply of the retina, the structural and functional changes in the choroid are subject to studies related to vascular involvement in diabetes.

Recent developments in optical coherence tomography (OCT) enable better in vivo visualization of the choroidal vasculature. New techniques including enhanced depth imaging OCT allow acquisition of high resolution images which can more clearly define sclerochoroidal border and cross-sectional choroidal vessels, especially located in Sattler's and Haller's layers than the conventional OCT imaging (5). The improved choroidal images can be further analyzed by image

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Address for correspondence: Murat Hasanreisoğlu, MD. Department of Ophthalmology, Koc University Faculty of Medicine, Istanbul, Türkiye
Phone: +90 545 266 06 55 **E-mail:** drhasanreisoglu@gmail.com

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binarization methods that can measure and quantify total choroidal area, luminal area, and stromal area of the choroid through which measurements a novel biomarker, choroidal vascularity index could be calculated for the assessment of choroidal perfusion (6,7).

Choroidal vascularity index has found a wide clinical application for a multitude of ocular and systemic diseases, (8,9) making it a preferable tool to assess choroidal vascular changes that can occur before and after the onset of retinopathy in diabetic patients (10-12). There are some clinical data concerning choroidal changes in T1DM without diabetic retinopathy in adult population (4). Conversely, choroidal vasculature in pediatric T1DM patients has not been investigated until present. It is possible that early detection of microvascular changes in the choroid could be a determinant of clinical outcomes of these patients. From this point of view, this study aimed to evaluate the peripapillary choroidal vasculature of pediatric T1DM patients.

Methods

Ethics

This retrospective cross-sectional study was approved by the local Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Informed consent for the access and use of clinical data was taken from all participants.

Patient Selection and Data Collection Criteria

The study included pediatric T1DM patients in the 1st year of their diagnosis, and age-matched healthy controls that were admitted to Koç University Hospital, Department of Ophthalmology between June 2017 and January 2021. Patients and healthy controls having no ocular involvement with peripapillary retinal nerve fiber layer OCT scans of adequate quality were included in the study.

All subjects underwent complete ophthalmologic examination including best-corrected visual acuity, slit-lamp examination, applanation tonometry, and fundus examination. Retinal nerve fiber layer OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) imaging was performed with Automatic Real-Time Tracking set to 100 images per acquisition. Retinal nerve fiber layer thickness measurements in average and in four quadrants (superior, nasal, inferior, and temporal) were noted. Patients having other ocular conditions (cataract, glaucoma, high myopia, macular dystrophy, diabetic retinopathy and other retinal vascular diseases, optic neuritis, and papilledema) and those who underwent previous ocular surgery were excluded from the study.

Image Processing and Calculation of Choroidal Parameters

Raw retinal nerve fiber layer images acquired by spectral domain OCT from each T1DM patient and control subject were processed for peripapillary choroidal analysis. A 3.4 mm diameter 360° circular scan centered to the optic nerve head is used. Sclerochoroidal junction is defined as the line that separates the outer border of choroidal vascular layer and the inner border of the sclera. Images with unrecognizable sclerochoroidal junction due to poor image quality were excluded from the study. Semi-automated image binarization techniques were applied using the public domain ImageJ software (ImageJ version 1.52q, National Institutes of Health, Bethesda, Maryland, USA). The OCT image was opened with ImageJ software and a polygon tool was used to select the total choroidal area as the region of interest. The upper boundary was traced along the Bruch membrane line and the lower boundary was traced through the sclerochoroidal junction. The image is then converted to 8-bit format to apply the auto local threshold function of Niblack for binarization. The black and white image is reconverted to red-green-blue format to perform color thresholding and select white pixels representing stromal area. The pixel areas of total choroidal area and stromal area were measured and converted to mm^2, luminal area was calculated by subtracting stromal area from total choroidal area. The choroidal vascularity index is then computed by dividing luminal area with total choroidal area. Retinal nerve fiber layer images without recognizable choroidal borders were excluded from the study. The average and four quadrants (superior, nasal, inferior, and temporal) total choroidal area, luminal area, stromal area, and choroidal vascularity index values were noted for each patient.

Statistical Analysis

Data analysis was performed with SPSS 20.0 software (IBM SPSS, IBM, New York, USA). Shapiro–Wilk test was used to determine normality. Non-parametric tests were performed due to seldomly found normal distribution of variables. Mann–Whitney U-test was performed to compare variables among patients and control subjects. Friedman and post hoc pairwise Wilcoxon signed-rank tests with Bonferroni correction were performed to compare differences between quadrants. Correlations between age, retinal nerve fiber layer measurements, and choroidal parameters were evaluated with Spearman's rho analysis. $P<0.05$ was considered statistically significant.

Results

Twenty pediatric T1DM patients and 46 age-matched healthy controls were enrolled in the study. Patient demographics and clinical characteristics are given in Table 1. Female-to-male ratio was 10:10 in T1DM patients and 13:10 in healthy controls. Mean age was 12.4±3.4 years for the entire study.

Measured retinal nerve fiber layer and choroidal parameters of T1DM patients and healthy controls are given in Table 2. There were no inter-eye differences in both T1DM

Table 1. Demographic and clinical characteristics of the study cases

Parameters	Total	T1DM	Control
Number of cases	66	20	46
Female-to-male ratio	12:10	10:10	13:10
Age (years)	12.4±3.4	12.7±2.3	12.2±3.7
Spherical equivalent (D)	-0.15±1.13	-0.23±1.38	-0.12±1.02

Values are given in mean ± standard deviation, T1DM: Type 1 diabetes mellitus.

Table 2. RNFL and choroidal parameters of the study cases

Parameters	Total	T1DM	Control	p*
RNFL (μm)				
Global	105.5±14.6	105.9±9.4	105.3±16.4	0.34
Superior	129.9±16.5	131.6±12.6	129.2±18.1	0.42
Inferior	136.9±26.7	137.4±16.9	136.7±30.1	0.27
Nasal	77.2±14.9	80.9±13.5	75.6±15.3	0.15
Temporal	77.7±16.6	73.6±7.8	79.5±19.0	0.38
TCA (mm^2)				
Global	1.54±0.45	1.59±0.35	1.52±0.49	0.60
Superior	0.40±0.12	0.43±0.11	0.39±0.13	0.29
Inferior	0.35±0.11	0.35±0.08	0.35±0.12	0.90
Nasal	0.39±0.12	0.40±0.10	0.39±0.13	0.48
Temporal	0.40±0.12	0.42±0.10	0.39±0.13	0.36
LA (mm^2)				
Global	1.07±0.31	1.10±0.24	1.05±0.34	0.53
Superior	0.27±0.08	0.29±0.07	0.27±0.09	0.33
Inferior	0.24±0.07	0.24±0.05	0.24±0.08	0.99
Nasal	0.27±0.08	0.28±0.07	0.27±0.09	0.50
Temporal	0.28±0.09	0.29±0.07	0.28±0.09	0.46
SA (mm^2)				
Global	0.48±0.16	0.50±0.13	0.47±0.17	0.49
Superior	0.13±0.05	0.14±0.04	0.12±0.05	0.16
Inferior	0.11±0.04	0.11±0.03	0.11±0.05	1.00
Nasal	0.12±0.04	0.13±0.04	0.12±0.05	0.59
Temporal	0.11±0.04	0.12±0.04	0.11±0.04	0.44
CVI (%)				
Global	69.3±4.2	68.8±3.9	69.4±4.4	0.52
Superior	68.0±4.6	67.5±4.6	68.3±4.6	0.34
Inferior	69.2±5.2	68.9±4.7	69.4±5.5	0.96
Nasal	68.7±5.0	68.9±5.1	68.6±4.9	0.56
Temporal	71.5±4.7	70.7±4.0	71.8±5.0	0.52

Values are given in mean±standard deviation. *: $P < 0.05$ is considered statistically significant. RNFL: Retinal nerve fiber layer, TCA: Total choroidal area, LA: Luminal area, SA: Stromal area, CVI: Choroidal vascularity index, T1DM: Type 1 diabetes mellitus.

and healthy subjects, therefore, only one eye (right) of each subject was included in the study. No significant difference was found in retinal nerve fiber layer, total choroidal area, luminal area, stromal area, and choroidal vascularity index parameters between T1DM patients and healthy controls (all p>0.05). Table 3 shows interquadrantal differences for measured choroidal parameters and calculated choroidal vascularity index values for both groups. Total choroidal area and luminal area measurements of the inferior quadrants were found significantly lowest among all quadrants for both T1DM patients and healthy controls (all p<0.05). Temporal choroidal vascularity index value was found significantly highest in healthy controls (all p<0.05), whereas no significant choroidal vascularity index difference was found between four quadrants in T1DM patients (p=0.074).

Correlation analysis between age, spherical equivalent refraction, retinal nerve fiber layer, and choroidal parameters are given in Table 4. There was no significant correlation between age, refraction, and choroidal parameters. A weak negative correlation was found between retinal nerve fiber layer and choroidal vascularity index in T1DM patients (r: −0.482; p=0.031) which was not present in healthy controls.

Discussion

The arterial supply of the choroid is provided by lateral and medial (occasionally, superior) posterior ciliary arteries that give branch between 10 and 20 short posterior ciliary arteries piercing the sclera near the optic nerve to join the choroid (13). The choroid is, therefore, mainly supplied by the short posterior ciliary arteries that, after giving blood supply to the retrolaminar section of the optic nerve, make entrance into the choroid from the peripapillary area, with terminal branches reaching the choriocapillaris (14). Evaluation of peripapillary choroidal vasculature with OCT imaging provides valuable information in detecting impairment of both choroidal and prelaminar optic nerve perfusion. Detection of vascular changes that occur before presenting signs of retinopathy is of critical importance to determine the duration of disease in diabetes, which is particularly essential in predicting prognosis of visual function in pediatric T1DM patients.

In the present study, differences in peripapillary choroidal vasculature between pediatric T1DM eyes and healthy controls were investigated. The overall peripapillary choroidal vasculature has shown no significant difference in terms of

Table 3. Interquadrantal differences in choroidal parameters of the study cases

Parameters	p*			
	TCA	**LA**	**SA**	**CVI**
T1DM				
Global[a]	<0.001	<0.001	<0.001	0.75
Post-hoc[b]				
Inferior-superior	<0.001	0.001	<0.001	-
Inferior-temporal	0.013	0.001	0.518	-
Inferior-nasal	0.004	0.020	0.029	-
Superior-temporal	1.000	1.000	0.061	-
Superior-nasal	1.000	1.000	0.850	-
Nasal-temporal	1.000	1.000	1.000	-
Healthy controls				
Global[a]	<0.001	<0.001	0.001	<0.001
Post hoc[b]				
Inferior-superior	0.002	<0.001	0.013	1.00
Inferior-temporal	0.002	<0.001	1.000	0.001
Inferior-nasal	0.013	0.010	0.046	1.00
Superior-temporal	1.000	0.750	0.017	<0.001
Superior-nasal	1.000	1.000	1.000	1.000
Nasal-temporal	1.000	0.074	0.059	0.001

*:Significant results are given in bold characters. P <0.05 is considered statistically significant, a:Friedman test, b:Wilcoxon signed-rank test with Bonferroni correction, TCA: Total choroidal area, LA: Luminal area, SA: Stromal area, CVI: Choroidal vascularity index, T1DM: Type 1 diabetes mellitus.

Table 4. Correlation analysis between age, spherical equivalent refraction, RNFL thickness, and choroidal parameters

Parameters	Age		SE		RNFL	
	rho	p	rho	p	rho	p
T1DM						
TCA	-0.119	0.62	0.227	0.34	0.315	0.18
LA	-0.090	0.71	0.223	0.22	0.177	0.46
SA	-0.114	0.63	0.141	0.14	0.4530	0.04
CVI	0.066	0.07	-0.098	0.68	-0.482	0.03
Healthy controls						
TCA	0.168	0.27	-0.060	0.69	0.249	0.10
LA	0.137	0.14	-0.056	0.71	0.246	0.10
SA	0.213	0.21	-0.077	0.61	0.273	0.07
CVI	-0.240	0.11	0.157	0.30	-0.116	0.44

*: Significant results are given in bold characters. P < 0.05 is considered statistically significant, SE: Spherical equivalent refraction, RNFL: Retinal nerve fibre layer, TCA: Total choroidal area, LA: Luminal area, SA: Stromal area, CVI: Choroidal vascularity index, T1DM: Type 1 diabetes mellitus.

measured total choroidal area, luminal area, stromal area, and calculated choroidal vascularity index between T1DM patients and healthy controls, however, slight differences were observed when four quadrants were analyzed separately. The temporal peripapillary choroid was found relatively more vascularized than the other quadrants in healthy eyes, a finding which was similar to previous studies that assessed peripapillary choroidal vasculature (15,16). Higher choroidal vascularity index measurements in temporal peripapillary quadrant might be attributed to the higher amount of vascular branches that emerges from the choroid to the optic nerve head (17) or the need to compensate higher vascular demand of the macular region. According to the present study, vascular supply in the temporal sector of the choroid was found to be rarer under the level of significance in T1DM patients, an outcome that might be considered as an early finding in favor of diabetes-related ocular disease. Although the inferior peripapillary choroid was found relatively thin for both study groups, vascularity index of this sector remained unchanged. This appearance of the inferior peripapillary choroid might be biased by the optical length differences that the incident light beam of the OCT device underwent. As the fovea is located inferior to the optic nerve on the vertical plane, instructing the patient to a nasal fixation relocates the optic nerve head slightly superior to the center of the image plane. This alignment creates an optical length difference between the peripapillary quadrants of the acquired OCT image that is presented as a sinusoidal section of the peripapillary retina and the choroid, with the elevated and depressed sectors with higher curvatures usually corresponding to the superior and inferior quadrants, respectively.

The choroidal vasculature in both Type 1 and 2 diabetic patients was previously evaluated by several studies, (4,18,19) however, to the best of the authors' knowledge, the choroidal vascular changes in pediatric T1DM patients have not been investigated until present. Aksoy et al. detected a decrease in macular choroidal vascularity index readings in T1DM patients without diabetic retinopathy which they related to disease duration (4). Their study included young adult patients (mean age: 23.6±6.9 years) with 6.2±0.7 years of disease duration. The present study included pediatric cases with earlier onset of disease, this may be the reason that only subtle changes were found on the sectoral basis rather than global scale. It is noted that these changes were found as part of a cross-sectional analysis, therefore, the main outcomes of the present study should be verified with consecutive OCT sections that would be acquired in long-term follow-up.

The main limitations of the present study are its small sample size and the lack of data from macular choroidal area due to its retrospective design. Among the reviewed OCT images of cases, only peripapillary OCT sections with clearly visible sclerochoroidal junction and deep tissue resolution were eligible for the evaluation of choroidal vasculature. There are also common limitations that belong to the methods which are commonly employed for choroidal vascularity assessments such as the observer biases in manual segmentation of the choroid and in recognition of the sclerochoroidal junction in particular. Peripapillary choroidal images are also exclusively affected by the shadow casted by retinal arteries and veins, thus additional contrast enhancement procedures would be of benefit to obtain more accurate binarization re-

sults (20). The peripapillary choroid is usually analyzed with purpose to assess the involvement of the optic nerve head in various ocular and systemic conditions. However, being in proximity to the entrance points of a considerable amount of short posterior ciliary arteries, peripapillary choroid may also be considered as a useful biomarker to investigate the involvement of the ocular choroidal circulation as a whole. Furthermore, single section-based macular and peripapillary analysis of choroidal vasculature should be improved with more topographical approaches that could be powered by wide-field OCT imaging modalities (21,22).

Conclusion

Being in proximity to the entrance points of a considerable amount of short posterior ciliary arteries, peripapillary choroid may also be considered as a useful biomarker to investigate the involvement of the ocular choroidal circulation as a whole and subtle changes in peripapillary choroidal vascularity index might occur in pediatric T1DM patients. The findings of the present study suggest that the assessment of choroidal vasculature might be useful to detect choroidal vascular changes that are present before to any retinal involvement in pediatric diabetic subjects. Future studies with prospective design that includes macular choroidal sections would introduce choroidal vascularity index as an important marker to detect actual time of onset in T1DM patients to assess risk factors and disease progression.

Disclosures

Ethics Committee Approval: The study included pediatric T1DM patients in the 1st year of their diagnosis, and age-matched healthy controls that were admitted to Koç University Hospital, Department of Ophthalmology between June 2017 and January 2021.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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