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ORIGINAL PAPER

Evaluation of early retinal vascular changes by optical coherence tomography angiography in children with type 1 diabetes mellitus without diabetic retinopathy

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Abstract

Purpose To evaluate macular and peripapillary vascular changes by optical coherence tomography angiography (OCTA) in children with type 1 diabetes mellitus (T1DM) without diabetic retinopathy (DR).

Methods This study included 46 patients with T1DM and 46 age-sex matched healthy subjects. All participants were evaluated in terms of macular and optic disk parameters by using AngioVue. Foveal avascular zone (FAZ) area, macular and optic disk vessel density (VD) were analyzed. The correlation of these parameters with metabolic factors such as disease duration, mean hemoglobin A1c (HbA1c), insulin-like growth factor 1 (IGF-1) standard deviation score (SDS), homocysteine (Hcy) level, body mass index (BMI) SDS and daily insulin dose was also investigated in T1DM group.

Results No significant difference was found in FAZ area and optic disk radial peripapillary capillary (RPC) VD comparing diabetic and control groups. In all macular regions, VD was significantly lower in T1DM versus control group both in superficial capillary plexus (SCP) and deep capillary plexus (DCP). None of the metabolic parameters was correlated with FAZ area and optic disk RPC-VD. Vascular density in SCP was negatively correlated with mean HbA1c and positively correlated with IGF-1 SDS. Homocysteine level was negatively correlated with DCP-VD in all areas.

Conclusion In children with T1DM without clinically apparent DR, VD in SCP and DCP was decreased and OCTA is a valuable imaging technique for detecting early vascular changes. The metabolic parameters such as mean HbA1c, IGF-1 SDS and Hcy affect the macular VD in diabetic children.**Trial registration number:** 2011-KAEK-2, 2021/4, **Trial registration date:** 02.04.2021.

Keywords Children · Diabetic retinopathy · Homocysteine · Optical coherence tomography angiography · Type 1 diabetes mellitus · Vessel density

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Introduction

Diabetes mellitus (DM) is a chronic endocrine and metabolic disease with a characteristic sign of hyperglycemia that occurs as a result of insufficiency in insulin production or its effect; diagnosis is made based on characteristic clinical findings (polyuria, polydipsia, weight loss) accompanying admission blood glucose measurements [1, 2]. In a meta-analysis and review study published in 2020, it was seen that the prevalence and incidence of type 1 diabetes increased worldwide [3]. Approximately, 96,000 children under the age of 15 are diagnosed with type 1 diabetes annually worldwide [4].

Diabetes mellitus is known to predispose to microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications in the long term. These complications are seen at an earlier age, especially in poorly controlled diabetes. Screening for diabetic retinopathy (DR) is recommended from the age of 11 years (formerly 10 years). Annual screening is recommended for children with type 1 diabetes from the fifth year in those diagnosed in the prepubertal period and from the second year in those diagnosed in the pubertal period. In terms of retinopathy screening, ophthalmologist examination is performed by biomicroscopic examination and fundus evaluation in the dilated eye, and in recent years, optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) have also been carried out [5, 6].

Optical coherence tomography angiography is a light based on rapid, non-invasive and reliable imaging technique that allows us to evaluate all vascular layers of the retina separately without dye injection. In addition to a high-quality images of retinal vascular structure without leakage, quantitative parameters such as foveal avascular zone and perifoveal capillary vascular density can be evaluated with the OCTA. In recent years, early vascular changes have been reported with OCTA in the absence of clinical signs of DR [7–11].

Therefore, we aimed to evaluate the early vascular changes in T1DM patients without clinically apparent DR in this study. We also examined whether disease duration, mean hemoglobin A1c (HbA1c), insulin-like growth factor 1 (IGF-1) standard deviation score (SDS), Hcy level, body mass index (BMI) SDS and daily insulin dose have a predictive value on OCTA parameters.

Materials and methods

Study population

This prospective comparative study was conducted in the Pediatric Endocrinology and Ophthalmology Clinic of Afyonkarahisar Health Sciences University and organized in accordance with the ethical standards settled by the Ethics Committee of Faculty of Medicine, Afyonkarahisar Health Sciences University. All of the study procedures were performed in accordance with the Declaration of Helsinki. Informed consent was obtained from patients and their parents.

In childhood and adolescence, diabetes mellitus is diagnosed with the classical findings specific to diabetes (polyuria, polydipsia, weight loss) and blood glucose measurements [12]. The group we included in our study consisted of diabetics who required intensive insulin therapy in the post-diagnosis period and had diabetes-specific autoantibodies (GAD, IA2, IAA, ZnT8) positive at presentation and low c-peptide levels. Inclusion criteria for the T1DM group were as follows:

- Those who were 11 years and older with a diabetes duration of 2 years and/or above.
- Cases diagnosed in the prepubertal period and followed with the diagnosis of type 1 diabetes mellitus for more than 5 years, since puberty and prepubertal diabetes duration affect the risk of developing diabetic retinopathy.
- Absence of clinically visible DR at dilated fundus examination.

The age- and sex-matched control group consisted of healthy children without systemic or ocular disease who applied to the ophthalmology clinic for refractive problems or routine control. The exclusion criteria for both groups were as follows: spherical or cylindrical refractive error greater than $\pm$ 3 D, history of ocular trauma or surgery, systemic diseases affecting posterior segment of eye, glaucoma, uveitis, optic nerve diseases, use of topical or systemic medications (except insulin in T1DM group), significant media opacity and poor fixation.

As an anthropometric assessment, weight, height, BMI percentiles and SDSs, puberty stage, and duration of diabetes of the patients with T1DM were recorded. The state of puberty was evaluated according to tanner staging. Stage 1 was considered prepubertal, stage 2

and later was considered as pubertal/postpubertal. The puberty stage of diabetic participants was in stage 2 or later. In terms of glycemic control, the average level of those with at least two HbA1c measurements per year in the last two years was included, expressed as mean HbA1c. Twenty-four-hour urine microalbumin levels of the patients in the study group were obtained from previous records. Microalbuminuria was not detected in the last control in diabetic individuals. Renal function tests (urea and creatinine), systolic and diastolic blood pressures were normal in the diabetic group. Hemoglobin A1c, serum IGF-1 and Hcy levels of diabetics were evaluated. For percentile and SDS calculations of anthropometric data, evaluation was made according to CDC between the ages of 2–20 growth reference data and childmetrics online calculation program was used [13]. IGF-1 SDS was calculated according to age- and gender-specific reference data [14]. Serum Hcy was measured enzyme-linked immunosorbent assay (ELISA) and HbA1c level was measured using electro-chemiluminescence immunoassay (ECLIA) technique by using appropriate commercial kits (Cobas 8000 e602 analyzer, Roche Diagnostics, Mannheim, Germany), and IGF-1 was measured using immunoturbidimetric method (Cobas 8000 c502 analyzer, Roche Diagnostics, Mannheim, Germany). The daily insulin dose was calculated by dividing the sum of basal and bolus insulin doses by body weight.

All participants performed a comprehensive ophthalmologic examination including best corrected visual acuity by decimal system, intraocular pressure measurements, anterior segment biomicroscopy, dilated fundus examination and OCTA (RTVue XR Avanti; Optovue, Inc. Fremont, CA) measurements. OCTA measurements were obtained by the same experienced examiner on the same day with examination after pupil dilatation. The right eye of each participant was evaluated to avoid intra-individual bias, and scans with image quality score greater than 7 were used for analysis.

OCTA measurements

OCTA scans were obtained by the AngioVue Imaging System version 2018.0.0.18 (RTVue XR Avanti; Optovue, Inc. Fremont, CA) using split-spectrum amplitude decorrelation angiography (SSADA) and projection artifact removal algorithm. The AngioVue Imaging System is a spectral domain system which detects motion in blood vessel lumen by measuring the variation in reflected OCT signal amplitude between consecutive cross-sectional scans and can acquire 70,000 A-scans per seconds. In addition to the structural assessment of the retinal microvascular structure device allows us to provide quantitative data such as flow and non-flow area, foveal avascular zone (FAZ) and vessel density (VD).

In this study, 6 × 6 mm central macular imaging size was used to measure FAZ and VD of the superficial and deep vascular complex. Automatic segmentation was used for measurements, and the segmentation results were manually checked. For the superficial capillary plexus (SCP) layer, the borders were defined as internal limiting membrane and 9 μm below the inner plexiform layer. The layer between 9 μm below the inner plexiform layer and 9 μm above the outer plexiform layer was confined as deep capillary plexus (DCP) layer. 6 × 6 mm macular scan is based on an Early Treatment Diabetic Retinopathy Study (ETDRS) grid centered on the macula. Accordingly, the macula is divided into 3 concentric rings with a diameter of 1, 3 and 6 mm, and these rings are described as fovea, parafovea and perifovea, respectively, both on superficial and deep vascular plexus. Vessel density was defined as the percentage of the area occupied by the vessels on both SCP and DCP. The FAZ area was determined on the en face OCT imaging and automatically calculated as mm^2.

Optic disk radial peripapillary capillary (RPC) network measurements in small vessels were evaluated with 4.5 × 4.5 mm optic disk scans. RPC vessel density in whole image, inside disk and peripapillary area was measured automatically and recorded as percentage.

Statistical analysis

In statistical analysis, mean, standard deviation, minimum and maximum values of numerical data were calculated. Categorical data were expressed as frequency and percentage (%). Shapiro–Wilk test was used to evaluate normality assumption. Furthermore, data with kurtosis and skewness values in the range of −1.5, + 1.5 were accepted as showing normal distribution. Levene test was used to evaluate the homogeneity of variances. Student's *T* test was used to

evaluate the difference in the mean between the groups when the parametric test assumptions were provided, and the Mann–Whitney *U* test was used if the parametric test assumptions were not met. In order to show the relationship between the groups, Pearson correlation analysis was used in the groups with normal distribution, and Spearman correlation analysis was used if they did not show normal distribution. Statistically, a p value of < 0.05 was considered significant. SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) software program was used for all analyzes.

Results

Forty-six eyes of 46 patients with T1DM and 46 eyes of 46 age- and sex-matched healthy children were included. There were 20 (43.5%) males and 26 (56.5%) females, and the mean age was 14.4 ± 2.5 years (range, 9–18 years) in both groups. In diabetic group, the mean disease duration was 6.9 ± 3.1 years (range, 3–14 years) and mean HbA1c was 8.69 ± 1.27% (range, 6.14–11.7). The mean IGF-1 SDS was −0.45 ± 1.26 and ranged between −2.9 and + 4.5. Homocysteine level was 8.37 ± 2.73 µmol/l (range 4.2- 16.4). All of the diabetic patients BMI z scores ranged between −2.0 and + 2.1 SDS and the mean value was 0.20 ± 1.11. The mean daily total insulin dose was 1.09 ± 0.22 u/kg (0.72–1.56).

The signal quality of OCTA was 8.67 ± 0.60 and 8.65 ± 0.56 in T1DM and control groups, respectively, and there was no difference between the groups ($p = 0.86$). There was statistically no significant differences between the groups with regard to FAZ area ($p = 0.40$). The mean values and comparison of SCP vascular density is shown in Table 1. At the SCP, diabetic children revealed a significantly decreased VD compared to control subjects in all macular areas except fovea.

Whole and all sectorial VD in DCP was significantly lower in subjects with diabetes than in controls, except in the perifoveal inferior hemifield. (Table 2). None of the optic disk parameters was statistically significantly different between the groups (Table 3).

Table 4 shows relationship between VD and disease duration, mean HbA1c, IGF-1 SDS, Hcy, BMI SDS and daily insulin dose. None of these parameters was correlated with FAZ area and optic disk RPC-VD. Mean HbA1c was negatively correlated with SCP-VD in whole, parafoveal and perifoveal regions ($p = 0.003$, $p = 0.002$ and $p = 0.009$ respectively) (Fig. 1). There was a significant positive correlation between IGF-1 SDS and VD in SCP as shown in scatter plot graphic ($p = 0.005$, $p = 0.01$ and $p = 0.003$ for whole, parafoveal and perifoveal regions respectively) (Fig. 2). DCP-VD in all areas was negatively correlated with Hcy level ($p = 0.01$, $p = 0.03$ and $p = 0.01$ for whole, parafoveal and perifoveal regions) (Fig. 3). BMI SDS and daily insulin dose were not significantly correlated with vascular density.

Table 1 Comparison of superficial capillary plexus vessel density between two groups

	T1DM Group	Control Group	*p*
FAZ area	0.262 ± 0.009	0.247 ± 0.079	0.40
Whole image	51.03 ± 2.56	52.67 ± 2.35	0.000
Superior-Hemi	49.32 ± 2.59	52.39 ± 2.43	0.000
Inferior- Hemi	49.47 ± 2.65	52.96 ± 2.41	0.000
Fovea	22.03 ± 6.15	23.97 ± 6.45	0.14
Parafovea	51.97 ± 3.67	55.66 ± 2.28	0.000
Superior-Hemi	52.23 ± 3.61	55.81 ± 2.22	0.000
Inferior-Hemi	51.70 ± 3,91	55.48 ± 2.63	0.000
Temporal	51.57 ± 3.63	55.34 ± 2.08	0.000
Superior	52.96 ± 4.04	56.64 ± 2.81	0.000
Nasal	51.30 ± 3.74	55.06 ± 2.75	0.000
Inferior	51.97 ± 4.45	55.61 ± 2.89	0.000
Perifovea	49.80 ± 2.47	53.14 ± 2.37	0.000
Superior-Hemi	49.67 ± 2.52	52.90 ± 2.44	0.000
Inferior-Hemi	49.91 ± 2.51	53.37 ± 2.44	0.000
Temporal	46.35 ± 2.65	49.89 ± 2.32	0.000
Superior	49.90 ± 2.83	52.83 ± 2.89	0.000
Nasal	52.88 ± 2.49	56.27 ± 2.60	0.000
Inferior	50.18 ± 2.89	53.53 ± 2.74	0.000

FAZ Foveal avascular zone, *T1DM* Type 1 diabetes mellitus

Discussion

In DR, endothelial cells and pericytes loss, the blood-retinal barrier are disrupted, ocular ischemia and capillary occlusion occur and eventually lead to the classic ocular manifestations of the disease including

Table 2 Comparison of deep capillary plexus vessel density between two groups

	T1DM Group	Control Group	*p*
Whole image	53.71 ± 4.31	56.82 ± 4.54	0.001
Superior-Hemi	53.65 ± 4.45	56.29 ± 4.71	0.007
Inferior- Hemi	53.12 ± 4.39	57.41 ± 4.71	0.000
Fovea	38.16 ± 6.02	42.20 ± 5.54	0.001
Parafovea	55.64 ± 3.62	59.16 ± 3.65	0.000
Superior-Hemi	55.83 ± 3.53	59.51 ± 3.47	0.000
Inferior- Hemi	55.88 ± 3.41	58.83 ± 4.06	0.000
Temporal	56.47 ± 3.14	60.13 ± 3.40	0.000
Superior	55.30 ± 4.20	59.34 ± 3.60	0.000
Nasal	56.41 ± 3.45	59.34 ± 4.01	0.000
Inferior	55.27 ± 4.09	57.83 ± 5.49	0.01
Perifovea	55.33 ± 4.65	58.63 ± 4.82	0.001
Superior-Hemi	55.20 ± 4.66	58.27 ± 4.77	0.002
Inferior- Hemi	55.30 ± 4.90	57.65 ± 10.10	0.16
Temporal	56.28 ± 4.08	59.83 ± 3.79	0.000
Superior	55.11 ± 5.0	57.55 ± 5.21	0.02
Nasal	54.62 ± 5.19	58.13 ± 5.79	0.003
Inferior	54.96 ± 5.56	58.99 ± 5.63	0.001

T1DM Type 1 diabetes mellitus

Table 3 Comparison of optic disk radial peripapillary capillary small vessel density

	T1DM Group	Control Group	*p*
Whole image	49.08 ± 3.18	49.28 ± 1.99	0.57
Inside disk	54.87 ± 4.78	54.11 ± 3.77	0.40
Peripapillary	50.16 ± 3.46	50.66 ± 2.74	0.44
Superior-Hemi	50.06 ± 3.94	50.67 ± 2.92	0.40
Inferior- Hemi	50.25 ± 3.28	50.63 ± 3.01	0.56

T1DM Type 1 diabetes mellitus

hemorrhages, cotton wool spots, lipid exudates, and even neovascularization. Direct hyperglycemia, many angiogenic stimulators and inhibitors, advanced glycation end products play a role in pathogenesis. The retina allows us to evaluate macro- and microvascular end organ damage in T1DM easily and non-invasively. In recent years, the introduction of OCTA, which is a non-invasive imaging method that does not require dye injection, into our daily practice enabled us to detect some retinal microvascular changes earlier.

Recent studies reported that enlarged FAZ area was a sign of early ischemia and a predictive of DR severity and progression [15, 16]. There are studies reporting that the FAZ area expands as the duration of diabetes increases [17]. In our study although the FAZ area was larger than controls, the difference was not statistically significant. Similarly, some studies concluded that FAZ area was not different in the absence of clinically visible DR [18, 19]. Conversely, some studies reported that the FAZ area is significantly larger in both SCP and DCP even without clinical signs of DR [9, 20].

Vascular density is another valuable indicator that provides information about capillary occlusion. In the literature, studies evaluating vascular density in type 1 diabetes have reported controversial results. Scarinci et al. concluded that the microvascular change in the DCP might be a reliable biomarker to evaluate the clinical progression of DR in mild clinical signs of non-proliferative DR without macular edema [21]. Simonett et al. also shown that while there was no difference in SCP-VD, a decrease in DCP vascular density occurred initially [22]. In a study including 25 T1DM patients without DR by Carnevali et al., the decrease in VD has been shown in only DCP [7]. Our study reveals a significant reduction in VD on both SCP and DCP (except perifoveal inferior hemifield) in children without clinically visible DR. Similar to our study, Kara et al. showed a decreased vascular density in both SCP and DCP [18]. Mameli et al. also demonstrated a decrease in vascular density in all regions except fovea [11]. In contrast to our study, Demir et al. and Gołębiewska et al. demonstrated that vascular density in DCP and SCP was not different from the control group [8, 23].

Initially, diabetic retinopathy was defined as a pure microvascular disease, while it has complex pathogenetic mechanisms such as microglial cell activation, ganglion cell loss, progressive neurovascular unit degeneration, pericyte depletion and low-grade chronic inflammation [24–26]. The literature is controversial in the optic disk as well as in FAZ area and macular VD. A study concluded that VD was decreased and vessel morphology was changed in peripapillary area and these findings were correlated with RNFL thinning in patients without DR [27]. In a study by Kara et al., decreased VD in whole and peripapillary area was shown [18]. In our study, we observed that there was no significant difference

Table 4 The correlation between SCP and DCP vessel density with disease duration, mean HbA1c, IGF-1 SDS, homocysteine, BMI SDS and daily insulin dose in diabetic group

		SCP			DCP		
		Whole	Parafovea	Perifovea	Whole	Parafovea	Perifovea
Disease duration	r	−0.21	−0.28	−0.18	−0.12	−0.12	−0.12
	p	0.16	0.06	0.22	0.42	0.39	0.39
HbA1c	r	−0.42	−0.44	−0.38	−0.28	−0.16	−0.26
	p	0.003	0.002	0.009	0.06	0.26	0.08
IGF-1 SDS	r	0.41	0.36	0.43	0.27	0.24	0.24
	p	0.005	0.01	0.003	0.06	0.10	0.09
Homocysteine	r	−0.06	−0.14	−0.07	−0.34	−0.31	−0.36
	p	0.66	0.34	0.63	0.01	0.03	0.01
BMI SDS	r	0.01	0.14	−0.008	−0.14	−0.001	−0.09
	p	0.92	0.32	0.95	0.34	0.99	0.52
Daily insulin dose	r	0.08	0.10	0.13	−0.007	0.03	−0.06
	p	0.57	0.47	0.37	0.96	0.81	0.67

DCP Deep capillary plexus, *SDS* Standard deviation score, *SCP* Superficial capillary plexus

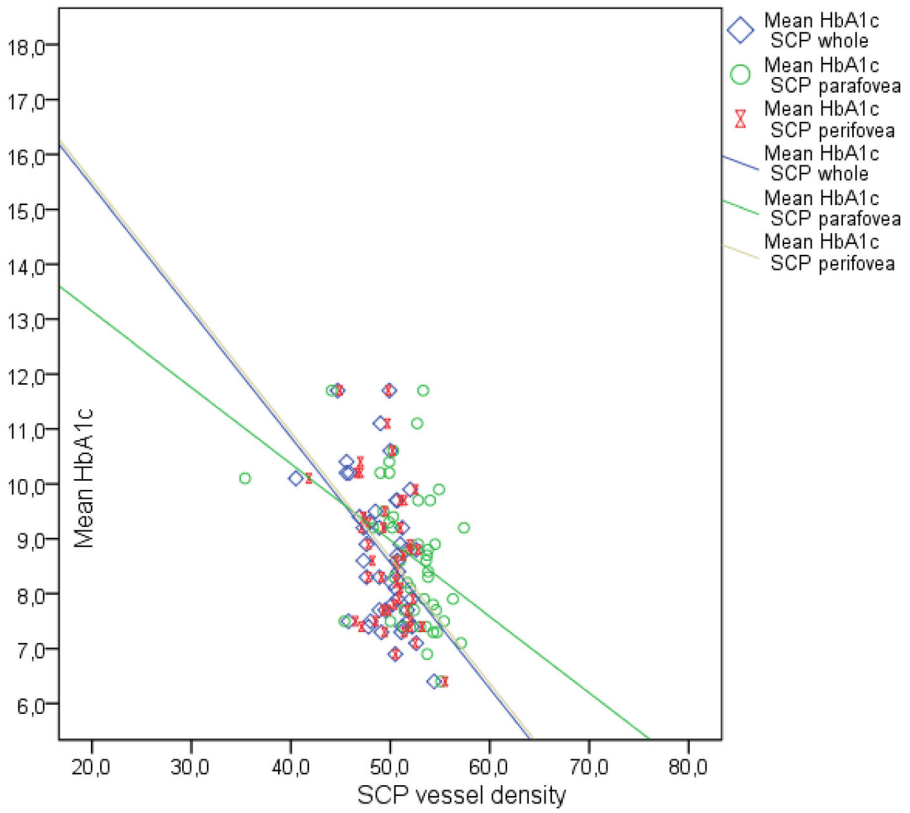

Fig. 1 Correlation between SCP vessel density and mean HbA1c in whole, parafovea and perifovea regions

between the groups in terms of optic disk RPC-VD. Consistent with our study, Li et al. reported no significant difference between groups in VD of optic disk center, inner and outer rings [10].

Glycated hemoglobin (HbA1c) is the most commonly used laboratory screening test in the diagnosis and follow-up of diabetes mellitus. Older age, puberty, female gender, increased body mass index, prolonged

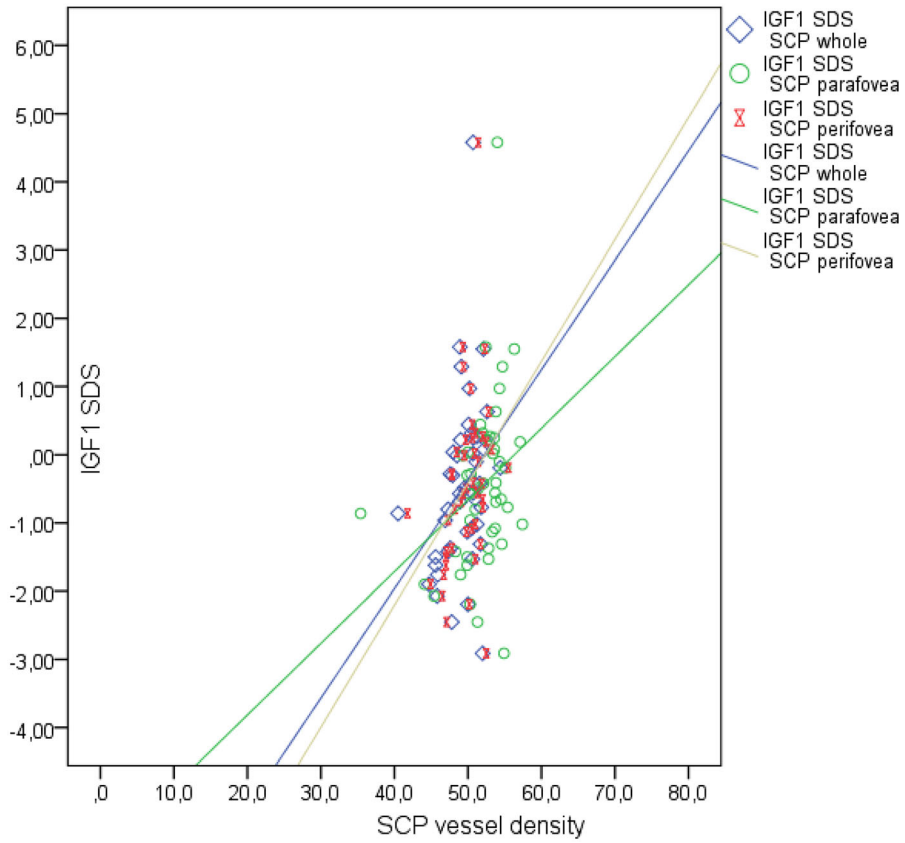

Fig. 2 Correlation between SCP vessel density and IGF-1 SDS in whole, parafovea and perifovea regions

diabetes duration, high blood pressure, dyslipidemia and family history of vascular complications are described as other risk factors for retinopathy [28–34].

In this study, we evaluated disease duration, mean HbA1c, IGF-1 SDS, Hcy level, BMI SDS and daily insulin dose to better understand the physiopathological mechanisms that lead the development of retinal vascular changes in T1DM. Disease duration was no effect on any of the OCTA parameters such as FAZ area, macular VD and RPC-VD in both SCP and DCP. Some other studies also revealed no correlation between disease duration and FAZ area and VD [7, 10]. Therefore, we suggest that other pathogenic factors instead of disease duration may lead to decrease in vascular density. On the contrary, some studies have shown a negative correlation between duration of disease and VD and FAZ area [8, 18]. We found that while mean HbA1c had no effect on the DCP, it was negatively correlated with the decrease in the all regions of SCP-VD. Some recent studies also showed that elevated HbA1c decreased the SCP-VD [18, 23].

Insulin-like growth factor-1 is little peptide hormone that has a critical role in growth and cellular proliferation and binds to its own receptor as well as to homologous insulin/IGF-1 hybrid receptors. IGF-1 and IGF binding proteins are expressed throughout the retina in vascular, neuronal and glial cells, and are altered in response to hyperglycemia and hypoxia [35]. In a study conducted in patients with type 1 diabetes mellitus aged between 8 and 25 years, it was stated that the severity of DR was inversely related to serum IGF-1 levels and that low IGF-1 levels are an indicator to be used in the closer follow-up of diabetic retinopathy and strict management [36]. In our study, there was a statistically significant positive correlation between IGF-1 SDS and VD in SCP.

Homocysteine is an amino acid that has an inflammatory effect, activates proinflammatory signaling pathways, increases reactive oxygen metabolites and

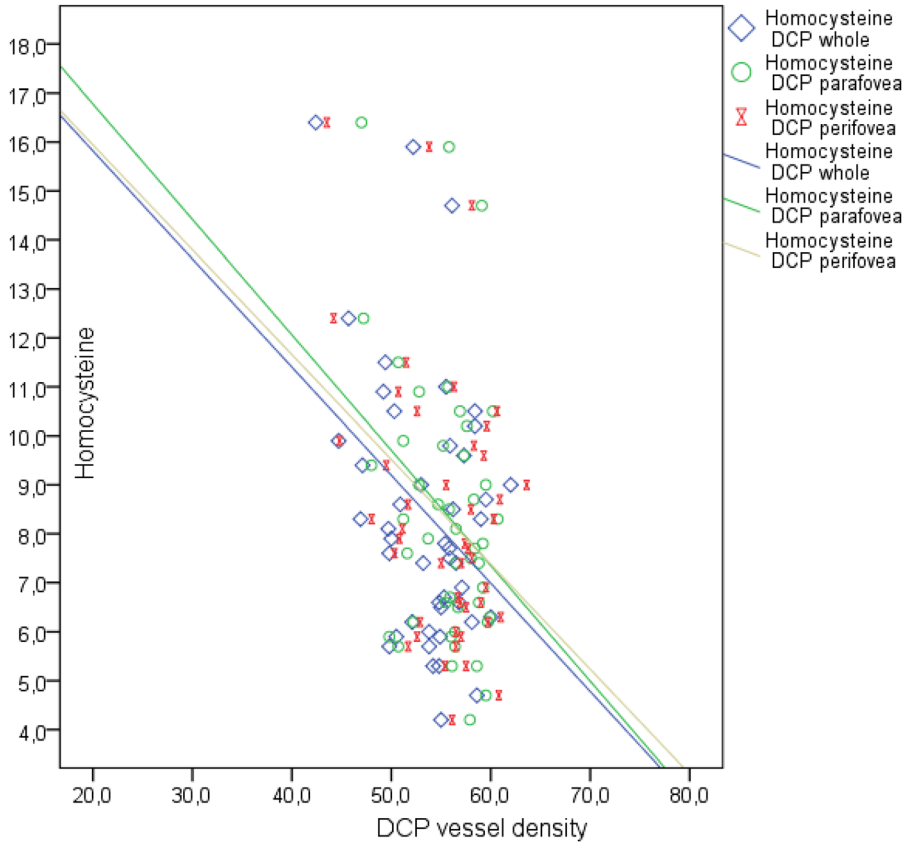

Fig. 3 Correlation between DCP vessel density and homocysteine level in whole, parafovea and perifovea regions

reduces the formation of glutathione peroxidase [37–39]. It has been shown that these effects may lead to endothelial dysfunction. As Hcy is used as a biomarker in vitamin B12 deficiency; in some studies, it has been shown to be a better marker of cardiovascular risk than cholesterol [40]. Homocysteine level increased in diabetic patients in the serum, vitreous and retina. A study reported that Hcy is a biomarker for screening of early DR and early detection of patients at risk of developing DR and even may be used as a therapeutic target for DR in the future [41]. In a meta-analysis examining the relationship between Hcy and type 1 diabetes, increased Hcy was found in those with DR and nephropathy compared to those without any complications [42]. We demonstrated a statistically significant negative correlation between Hcy level and DCP-VD in all macular regions. According to our current knowledge, this is the first study in the literature evaluating the effect of IGF-1 and Hcy level on vascular density measured by OCTA.

We concluded that BMI SDS and daily insulin dose were not significantly correlated with vascular density. Consistent with current study, it has been reported that BMI was not associated with parafoveal vessel density and the amount of basal insulin or insulin per breakfast were not correlated with OCTA parameters [43, 44].

Major limitations of this study are as follows: relatively small sample size, using 6 × 6 macular scan for FAZ evaluation and lack of qualitative assessment of microvascular structure. The main strength of this study is evaluation of metabolic parameters such as Hcy and IGF-1 which are biomarker for the progression of DR.

Conclusion

In summary, this study documents early macular microvascular structure changes in children without clinical visible DR, and OCTA is a valuable imaging

technique for detecting early vascular changes. Metabolic parameters such as mean HbA1c, IGF-1 and Hcy affect OCTA parameters. It may be beneficial to closely follow diabetic children with elevated HbA1c and Hcy levels and low IGF-1 levels in terms of development of DR. Further studies are required to fully understand the role of OCTA in the diagnosis of early DR and the systemic risk factors predisposing to the DR.

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Availability of data and material All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Competing interest The authors declare that they have no competing interests.

Ethical approval The study was organized in accordance with the ethical standards settled by the Ethics Committee of Faculty of Medicine, Afyonkarahisar Health Sciences University.

Consent to participate (Ethics) Informed consent was obtained from patients and their legal guardians.

Consent to Publish (Ethics) All the authors mentioned in the manuscript have given consent for submission and subsequent publication of the manuscript.

Clinical Trials Registration The study was organized in accordance with the ethical standards settled by the Ethics Committee of Faculty of Medicine, Afyonkarahisar Health Sciences University.

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