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Original Article

Relationships between Continuous Glucose Monitoring-Derived Glycemic Parameters and Early Retinal Vascular Changes in Children with Type 1 Diabetes Mellitus

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Abstract
Objective: This study investigated relationships between continuous glucose monitoring (CGM)-derived metrics and early retinal vascular changes in children having type-1 diabetes mellitus (T1DM) with no clinically-visible diabetic retinopathy (T1DM-noR).
Methods: Forty-two T1DM-noR patients and 45 healthy children were enrolled. Optical coherence tomography angiography (OCTA) parameters of superficial and deep capillary plexuses (SCP/DCP) were compared between groups. In T1DM-noR group, correlations of OCTA parameters with HbA1c, diabetes duration, time-in-range (TIR), time-in-tight-range (TITR), time-above-range (TAR), glucose-management-indicator (GMI) and coefficient of variation (CV) were examined, followed by adjusted multivariable regressions.
Results: Compared to controls, T1DM-noR group showed significantly reduced SCP and DCP vessel densities in whole retina (p=0.038; p=0.017), fovea (p=0.046; p=0.041), parafovea (p=0.025; p=0.012) and perifovea (p=0.032; p=0.021). In T1DM-noR cases, whole retina, fovea, parafovea and perifovea measurements of SCP and DCP were significantly negatively correlated with HbA1c, diabetes duration, TAR, GMI and CV, but positively correlated with TIR and TITR ($p<0.05$). In multivariable regression, all significant associations in DCP and almost all in SCP remained independent after adjusting for age and diabetes duration ($p<0.05$).
Conclusion: We found that T1DM children had reduced SCP and DCP vessel densities before development of clinically-visible retinopathy. In our study, as TIR and TITR decreased and HbA1c, diabetes duration, TAR, GMI and CV increased, SCP and DCP vessel densities decreased. Our study suggested that reduced densities, independently associated with CGM metrics (especially in DCP), might serve as early indicator of retinal changes in T1DM-noR children, and in such patients, more effective glycemic control should be considered.

What is already known on this topic?
Previous studies showed that children having type-1 diabetes mellitus with no clinically-visible diabetic retinopathy (T1DM-noR) might exhibit some retinal microvascular changes. Until our study, relationships of retinal vessel densities with time-in-range (TIR), time-in-tight-range (TITR), time-above-range (TAR), glucose management indicator (GMI) and coefficient of variation (CV) had not been comprehensively researched.

What this study adds?
T1DM children had reduced superficial and deep capillary plexuses (SCP/DCP) vessel densities before clinically-visible retinopathy. As TIR and TITR decreased and HbA1c, diabetes duration, TAR, GMI and CV increased, vessel densities decreased. Reduced densities were independently associated with these metrics after adjusting for age and diabetes duration, especially in DCP.

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Introduction

Type 1 diabetes mellitus (T1DM) is a chronic metabolic disease (1). The worldwide incidence of T1DM in children and adolescents has increased substantially in recent years (1,2). Over time, T1DM can affect various systems by causing vascular, neurodegenerative and/or structural changes. The involvement of different layers of the eye can lead to visual dysfunction (3,4,5,6,7). Routine traditional screening for diabetic retinopathy is performed by evaluating the dilated fundus using ophthalmoscopy and/or slit-lamp biomicroscopy with appropriate lenses (8). However, this examination method is a subjective process and may be insufficient, particularly in identifying microvascular damage. Therefore, additional imaging methods are required. Fundus fluorescein angiography (FFA) is a helpful diagnostic tool visualizing retinal vessels. However, FFA is a time-consuming and invasive imaging method because of the requirement for intravenous fluorescein dye injection during the procedure (9). Additionally, some systemic side effects such as nausea, vomiting, urticaria, anaphylaxis, kidney failure and/or death may occur due to dye injection (9,10). Moreover, FFA has limited ability to separately visualize superficial and deep vascular structures (4,11). Therefore, non-invasive and more sensitive imaging methods are needed to detect early ocular findings related to diabetes in children and thereby prevent potential visual dysfunction. Optical coherence tomography angiography (OCTA), which has been increasingly used in recent years, is a fast, non-invasive, and objective imaging technique that shows retinal microvascular structures in high resolution (4,9,11). OCTA can also detect microvascular changes at an earlier stage in diabetic patients. It visualizes superficial capillary plexus (SCP) and deep capillary plexus (DCP) of the retina in three dimensions. Furthermore, since OCTA technique does not require intravenous dye injection, it has become an increasingly preferred imaging method for ocular screening and follow-up of diabetic individuals (4,9,11).
Traditionally, blood glucose levels and glycated hemoglobin (HbA1c) measurements have been used for the diagnosis and monitoring of diabetes mellitus (DM) (1,12,13,14). In recent years, however, diabetes technologies, particularly continuous glucose monitoring (CGM) systems, have become increasingly important in the management of T1DM children (2,12,14,15). CGM systems provide detailed information on glucose levels, fluctuations, and patterns, which may facilitate more comprehensive diabetes management (12,13,14,15). CGM-derived metrics, including time in range (TIR), time in tight range (TITR), time above range (TAR), time below range (TBR), glucose management indicator (GMI) and glucose coefficient of variation (CV), have emerged as new glycemic parameters in diabetic cases (12,14,15). To the best of our knowledge, in children having T1DM with no clinically visible diabetic retinopathy (T1DM-noR), correlations of SCP and DCP vessel densities with TIR, TITR, TAR, TBR, GMI and CV have not been comprehensively researched in the past. Therefore, we conducted this study. The aim of our study was to investigate relationships between CGM-derived glycemic parameters and early retinal vascular changes in T1DM-noR children.

Methods

This cross-sectional observational study was performed with approval of our hospital's Ethics Committee (approval number: 2025/05-26) and in accordance with Declaration of Helsinki. Detailed information about the study was provided to all individuals and their families. Written informed consent was obtained from all participants and their legal guardians.
Children and adolescents diagnosed with T1DM who had no clinically visible diabetic retinopathy on fundus examination, and healthy individuals were examined. T1DM was diagnosed according to International Society of Pediatric and Adolescent Diabetes/International Diabetes Federation (ISPAD/IDF) guidelines (1). Forty-two patients (27 females/15 males) aged 9-18 years, with regular clinical follow-up and a DM duration of at least 3 years, receiving multiple daily insulin injections or continuous subcutaneous insulin infusion, using a CGM system, and having CGM data available for the last year, were classified as T1DM-noR group. None of the patients had complications such as neuropathy or nephropathy. In a similar age range and gender distribution to T1DM-noR

group, 45 healthy children and adolescents (28 females/17 males) with no ocular disorders and systemic diseases that could affect retinal structures were classified as healthy group. Exclusion criteria were as follows: participants with a history of ocular surgery or ocular trauma; individuals previously diagnosed with eye disease that could affect retinal structures; those with spherical equivalent measurements outside the range of -1.50 to +1.50 diopters; patients having additional systemic diseases other than T1DM; and individuals using topical and/or systemic medications that could affect ocular structures.

Age and gender characteristics, as well as medical and family histories, were evaluated for all participants. The presence of ocular and systemic diseases was investigated. Individuals' weight, height, body mass index (BMI), BMI-standard deviation score (BMI-SDS), and pubertal stage according to Tanner classification were recorded (16). Body weight was measured without clothing to the nearest 0.1 kilogram (kg) using calibrated balance scale. Standing height was determined to the nearest centimeter using rigid stadiometer. BMI was calculated using the formula: weight (kg) / height (m)². For weight, height and BMI measurements, SDS values were obtained using reference data for Turkish children (17). Levels of fasting blood glucose, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides were measured by standard laboratory methods. HbA1c levels were determined by high-performance liquid chromatography (HPLC) and reported according to National Glycohemoglobin Standardization Program (NGSP) standards. Mean HbA1c was calculated from all available HbA1c measurements obtained during the follow-up period. CGM-derived metrics, including TIR (% of readings within 70-180 mg/dL), TITR (% of readings within 70-140 mg/dL), TAR (% of readings >180 mg/dL), TBR (% of readings <70 mg/dL), GMI (%, calculated as 3.31 + 0.02392 × mean glucose) and CV (%, calculated as 100 × standard deviation of glucose / mean glucose) were noted (12,15). Mean values of CGM-derived metrics were calculated from all available Ambulatory Glucose Profile (AGP) reports obtained during the follow-up period after CGM initiation.

All participants underwent detailed ophthalmological examinations. Best-corrected visual acuity (BCVA) and intraocular pressure values were recorded. Pupillary dilation was achieved with topical ophthalmic solution containing 1% cyclopentolate hydrochloride. Slit-lamp biomicroscopy with 90-diopter lens, autorefractokeratometer (Topcon KR-1, Tokyo, Japan) and OCTA (AngioVue, Optovue, Fremont, California, USA) devices were used to assess ocular structures. OCTA device placed automatically three fovea-centered circles on macular region using density evaluation tool for SCP and DCP. The fovea was defined as a central circular area with a diameter of 1 mm. Foveal avascular zone (FAZ) was described as the avascular region located at the center of the fovea. The parafovea was defined as the annular area encircling the fovea, with inner and outer diameters of 1 mm and 3 mm, respectively. The perifovea was described as the annular region outside the parafovea, reaching an outer diameter of 6 mm (9). The boundary for SCP was extending from internal limiting membrane (ILM) to inner plexiform layer (IPL)-10 µm. The boundary for DCP was extending from IPL-10 µm to outer plexiform layer (OPL)+10 µm (9). Vessel density was calculated as the percentage of the area that was occupied by blood vessels within the region of interest. FAZ area, as well as the vessel densities of SCP (for whole retina, fovea, parafovea and perifovea) and DCP (for whole retina, fovea, parafovea and perifovea), were automatically calculated using the FAZ and vessel density assessment tool. All measurements were obtained between 9:00 am and 11:00 am by the same experienced researcher (BÖ) under identical environmental conditions. For the analyses, the average of three measurements taken with good quality was used. In analyses, only data obtained from the right eye of each participant were evaluated to avoid potential bias arising from inter-eye correlation and to ensure statistical independence of observations. Clinical and laboratory data, as well as OCTA parameters, were compared between the groups. In T1DM patients, correlations of OCTA parameters with HbA1c, DM duration, TIR, TITR, TAR, TBR, GMI and CV were examined. Additionally, multivariable linear regression analysis was performed to determine whether CGM-derived metrics were independently associated with OCTA parameters after adjustment for age and DM duration.

Statistical analyses were made with Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM, New York, USA). Descriptive characteristics were given as mean ± standard deviation (minimum-maximum) values. Categorical data were presented as number and percentage. The normality of data distribution was assessed using Shapiro-Wilk test. Chi-square test was used to analyze categorical variables. In comparisons, independent sample t-test (for normally distributed variables) and Mann-Whitney U test (for non-normally distributed variables) were used. Relationships of OCTA parameters with HbA1c, DM duration, TIR, TITR, TAR, TBR, GMI and CV were evaluated using Spearman correlation analysis, and Spearman correlation coefficients (r) were reported. A multivariable linear regression analysis was also performed. Variables that showed significant associations in univariable correlation analysis ($p<0.05$) were included in the models. OCTA parameters were entered as dependent variables, while each CGM-derived metric was entered separately as independent variable. All models were adjusted for age and DM duration. Standardized regression coefficients (β) and p values were reported for each analysis. P value <0.05 was considered statistically significant.

Results

BCVA of all individuals was 1.0 (20/20). Mean age of subjects was 15.1±2.4 years in healthy group and 14.5±3.2 years in T1DM-noR group (p=0.756). Gender distribution, BMI, BMI-SDS, pubertal stage, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels of the groups were similar (p>0.05). Clinical and laboratory data of the groups were given in Table 1. In T1DM-noR group, mean HbA1c was 8.6±1.4% (range: 6-11.5), mean DM duration was 7.0±2.8 years (range: 3.7-14), and mean glucose level was 192.3±39.8 mg/dL (range: 138.2-318). Mean daily insulin dose was 0.98±0.29 IU/kg/day (range: 0.47-1.69). In T1DM-noR group, mean TIR, TITR, TAR, TBR, GMI and CV were 47.6±16.6% (range: 18.5-84.7), 29.9±12.4% (range: 8.2-57.8), 48.7±17.7% (range: 14.5-81.3), 4.1±2.9% (range: 0.3-11), 7.9±1.0% (range: 6.4-10.9) and 39.8±5.3% (range: 25.5-50.1), respectively.

Mean FAZ area of healthy group was similar to that of T1DM-noR group (p=0.592). When SCP vessel densities were evaluated, compared to healthy group, T1DM-noR group showed significantly reduced values in whole retina (p=0.038), fovea (p=0.046), parafovea (p=0.025) and perifovea (p=0.032). Similarly, when DCP vessel densities were assessed, compared to healthy group, T1DM-noR group had significantly reduced values in whole retina (p=0.017), fovea (p=0.041), parafovea (p=0.012) and perifovea (p=0.021). OCTA parameters of the groups were given in Table 2.

In T1DM-noR group, there were no significant relationships of FAZ area with mean HbA1c, DM duration, TIR, TITR, TAR, TBR, GMI and CV (p>0.05). When SCP and DCP vessel densities were evaluated, in T1DM-noR patients, mean HbA1c was significantly negatively correlated with whole retina (r=-0.222, p=0.032 for SCP; r=-0.279, p=0.010 for DCP respectively), fovea (r=-0.215, p=0.035; r=-0.241, p=0.025, respectively), parafovea (r=-0.226, p=0.031; r=-0.312, p=0.004) and perifovea (r=-0.217, p=0.034; r=-0.268, p=0.015) measurements. Similarly, DM duration was significantly negatively associated with SCP and DCP vessel densities in whole retina (r=-0.201, p=0.041; r=-0.270, p=0.014, respectively), fovea (r=-0.203, p=0.040; r=-0.216, p=0.034), parafovea (r=-0.211, p=0.036; r=-0.289, p=0.007) and perifovea (r=-0.204, p=0.039; r=-0.225, p=0.031). In T1DM-noR cases, as HbA1c and DM duration increased, SCP and DCP vessel densities decreased.

In T1DM-noR subjects, TIR was significantly positively related to SCP and DCP vessel densities in whole retina (r=0.214, p=0.035; r=0.285, p=0.008, respectively), fovea (r=0.231, p=0.029; r=0.273, p=0.013), parafovea (r=0.240, p=0.026; r=0.321, p=0.001) and perifovea (r=0.227, p=0.030; r=0.253, p=0.021). Similarly, TITR was significantly positively correlated with SCP and DCP vessel densities in whole retina (r=0.193, p=0.045; r=0.257, p=0.019, respectively), fovea (r=0.189, p=0.048; r=0.192, p=0.046), parafovea (r=0.202, p=0.041; r=0.265, p=0.016) and perifovea (r=0.199, p=0.043; r=0.208, p=0.037). In T1DM-noR cases, as TIR and TITR decreased, SCP and DCP vessel densities decreased.

In T1DM-noR patients, TAR was significantly negatively associated with SCP and DCP vessel densities in whole retina (r=-0.203, p=0.040; r=-0.261, p=0.017, respectively), fovea (r=-0.195, p=0.044; r=-0.236, p=0.027), parafovea (r=-0.207, p=0.038; r=-0.281, p=0.009) and perifovea (r=-0.200, p=0.042; r=-0.239, p=0.026). In T1DM-noR cases, as TAR increased, SCP and DCP vessel densities decreased. On the other hand, there were no significant relationships of TBR with SCP and DCP vessel densities in whole retina, fovea, parafovea and perifovea (p>0.05). GMI was significantly negatively correlated with SCP and DCP vessel densities in whole retina (r=-0.232, p=0.028; r=-0.274, p=0.012, respectively), fovea (r=-0.212, p=0.036; r=-0.245, p=0.024), parafovea (r=-0.223, p=0.032; r=-0.298, p=0.006) and perifovea (r=-0.219, p=0.033; r=-0.260, p=0.018). Moreover, CV was significantly negatively associated with SCP and DCP vessel densities in whole retina (r=-0.209, p=0.037; r=-0.302, p=0.005, respectively), fovea (r=-0.228, p=0.030; r=-0.256, p=0.020), parafovea (r=-0.230, p=0.029; r=-0.318, p=0.003) and perifovea (r=-0.242, p=0.025; r=-0.251, p=0.022). In T1DM-noR cases, as GMI and CV increased, SCP and DCP vessel densities decreased. Correlation analysis of OCTA parameters with HbA1c level, DM duration and CGM-derived metrics in T1DM-noR group was given in Table 3. Following adjustment for age and DM duration in multivariable models, all of the previously identified significant associations between CGM-derived metrics and OCTA vessel density measurements in the DCP were again found to be statistically significant (β=0.258, p=0.010 for TIR-whole retina; β=0.252, p=0.014 for TIR-fovea; β=0.281, p=0.004 for TIR-parafovea; β=0.230, p=0.024 for TIR-perifovea; β=0.232, p=0.023 for TITR-whole retina; β=0.176, p=0.048 for TITR-fovea; β=0.244, p=0.018 for TITR-parafovea; β=0.191, p=0.041 for TITR-perifovea; β=-0.237, p=0.022 for TAR-whole retina; β=-0.207, p=0.034 for TAR-fovea; β=-0.255, p=0.013 for TAR-parafovea; β=-0.211, p=0.031 for TAR-perifovea; β=-0.249, p=0.015 for GMI-whole retina; β=-0.218, p=0.028 for GMI-fovea; β=-0.256, p=0.011 for GMI-parafovea; β=-0.241, p=0.020 for GMI-perifovea; β=-0.268, p=0.007 for CV-whole retina; β=-0.226, p=0.025 for CV-fovea; β=-0.274, p=0.006 for CV-parafovea; and β=-0.222, p=0.027 for CV-perifovea, respectively). In the SCP, almost all of the previously identified significant associations between CGM-derived metrics and OCTA vessel density measurements again maintained their statistical significance (β=0.189, p=0.042 for TIR-whole retina; β=0.206, p=0.035 for TIR-fovea; β=0.215, p=0.030 for TIR-parafovea; β=0.205, p=0.035 for TIR-perifovea; β=0.180, p=0.047 for TITR-parafovea; β=0.177, p=0.048 for TITR-perifovea; β=-0.185, p=0.045 for TAR-whole retina; β=-0.191, p=0.041 for TAR-parafovea; β=-0.183, p=0.046 for TAR-perifovea; β=-0.208, p=0.032 for GMI-whole retina; β=-0.188, p=0.043 for GMI-fovea; β=-0.196, p=0.038 for GMI-parafovea; β=-0.192, p=0.040 for GMI-perifovea; β=-0.187, p=0.044 for CV-whole retina; β=-0.197, p=0.038 for CV-fovea; β=-0.203, p=0.036 for CV-parafovea; and β=-0.219, p=0.028 for CV-perifovea, respectively). Only a few associations in the SCP remained just above the threshold of significance after adjustment for age and DM duration (β=0.168, p=0.054 for TITR-whole retina; β=0.164, p=0.057 for TITR-fovea; and β=-0.171, p=0.052 for TAR-fovea, respectively).

Discussion

T1DM is one of the most common chronic endocrine and metabolic disorders of childhood and adolescence (1,14). In cases with inadequate metabolic control, T1DM may lead to visual dysfunction by causing progressive microvascular damage over time (3,4,5,8). OCTA, an advanced imaging technique, may provide insights into early retinal microvascular alterations (4,11). Detecting early subclinical changes and subsequently achieving effective glycemic control may be important in preventing diabetes-related vascular complications (3,4,8,14,18). HbA1c has traditionally been used to assess glycemic control in patients with diabetes (1,12,13,14,15). However, HbA1c, as a static average, has limited capacity to reflect glycemic variability and short-term glucose fluctuations (1,12,14,15). So, there seems to be a need for new-generation glycemic indicators in monitoring and clinical management of diabetic cases (12,15). Currently, TIR, TITR, TAR, TBR, GMI and CV are considered novel dynamic glycemic parameters (12,14,15). In diabetic patients, evaluating relationships of glycemic parameters with retinal microcirculation and subclinical changes has become a topic of growing scientific interest (19). Therefore, we conducted this study.

In literature, varying results concerning FAZ area of T1DM-noR children were reported (5,18,20,21,22,23,24). Onoe et al. detected that FAZ area measurements of T1DM-noR cases were significantly greater than those of healthy subjects (20). Similarly, Sherif et al. showed significantly larger FAZ area measurements in T1DM patients compared to healthy controls. They considered that FAZ enlargement in T1DM patients might be associated with disruption of retinal capillary plexuses' integrity over time (21). On the other hand, most authors stated no significant difference in FAZ area measurement between T1DM-noR children and healthy subjects (5,18,22,23,24). We also found that FAZ area values of T1DM-noR group were similar to those of healthy group. The similar FAZ area values observed in our study could be attributed to the fact that early diabetic damage in FAZ region might initially manifest as morphological distortions rather than FAZ area changes (18,25). Additionally, the earliest microvascular alterations may not yet have reached a level sufficient to affect FAZ area, which is mainly devoid of blood vessels, thereby contributing to our findings (26).

Previous studies reported different results regarding SCP and DCP vessel densities in T1DM-noR children (5,18,21,22,23). Demir et al. evaluated only fovea and parafovea measurements of SCP and DCP in T1DM cases. They determined these measurements of T1DM patients to be similar to those of healthy individuals (22). Similarly, Inanc et al. found that in T1DM children, whole retina, fovea, parafovea and perifovea measurements of SCP and DCP did not differ from those of healthy subjects (18). Sherif et al. assessed only whole retina and fovea measurements of SCP and DCP. The authors detected that in T1DM patients, whole retina measurements of SCP and DCP were similar to those of healthy controls. In contrast, they observed significant reductions in fovea measurements of SCP and DCP in T1DM patients compared to healthy individuals (21). On the other hand, Koca et al. showed that T1DM cases had significant decreases in whole retina, parafovea and perifovea measurements of SCP and DCP compared to healthy cases. However, in T1DM children, the authors found no significant change in fovea measurement of the SCP, whereas they determined a significant reduction in that of the DCP compared to healthy cases (5). Kara et al. also stated that T1DM patients exhibited significant decreases in whole retina, fovea, parafovea and perifovea measurements of SCP and DCP compared to healthy individuals (23). Similarly, we found that whole retina, fovea, parafovea and perifovea measurements of SCP and DCP in T1DM-noR children were significantly lower than those of healthy controls. In T1DM patients, the reduction in SCP and DCP vessel densities may be attributed to the damage of retinal capillary endothelial cells and pericytes resulting from cellular-level oxidative stress induced by hyperglycemia (5,22,23). This endothelial cell and pericyte damage was implicated in blood-retina barrier disruption, basement membrane alterations, and capillary occlusion (5,22,23). Based on these findings, we suggested that vessel density measurements might serve as a potential early indicator of retinal microvascular perfusion and capillary changes associated with vascular occlusion in T1DM-noR children (5,18).

In literature, there were varying results concerning relationships of FAZ area with HbA1c level and DM duration in T1DM-noR individuals (18,21,22,25). Some studies reported significant positive correlations of FAZ area with HbA1c and DM duration in T1DM cases (21,22), whereas others found no such correlations (18,25). Similarly, in our study, FAZ area was not associated with HbA1c and DM duration in T1DM-noR children. Additionally, FAZ area was not correlated with TIR, TITR, TAR, TBR, GMI and CV in our study. To the best of our knowledge, since previous studies did not evaluate relationships of FAZ area with TIR, TITR, TAR, TBR, GMI and CV in T1DM-noR children, direct comparison of their findings on this topic with ours could not be made. Early diabetic involvement in FAZ region may first appear as morphological distortions instead of FAZ area changes (18,25). Therefore, FAZ area measurement may not be a sensitive assessment method for detecting early-stage microvascular damage (18,25). In our study, the reason for the lack of significant correlation may be related to the mechanism mentioned above. However, long-term uncontrolled diabetes may cause progressive and more serious microvascular damage during the chronic course of the disease, thus affecting the FAZ area and potentially enlarging it over time (21,22).

Previous studies reported different results regarding relationships of SCP and DCP vessel densities with HbA1c level and DM duration in T1DM-noR children (5,18,22,23,25). Some authors stated that there were no significant associations of SCP and DCP vessel densities in fovea, parafovea and perifovea with HbA1c and DM duration (18,25). In contrast, others found significant negative correlations of SCP vessel densities in whole retina (5,23), fovea (22), parafovea (5,23) and perifovea (5,23) with HbA1c. Moreover, DCP vessel densities in fovea (22) and parafovea (23) were detected to be significantly negatively related to HbA1c. Some studies also showed significant negative associations of SCP vessel densities in whole retina (23), fovea (22,23) and parafovea (23) with DM duration. Furthermore, DCP vessel densities in fovea (22,23) and parafovea (22) were reported to be significantly negatively correlated with DM duration. As far as we know, since previous studies did not evaluate relationships of SCP and DCP vessel densities with TIR, TITR, TAR, TBR, GMI and CV in T1DM-noR children, direct comparison of their findings on this topic with ours could not be made. In our study, whole retina, fovea, parafovea and perifovea measurements of SCP and DCP were significantly negatively correlated with HbA1c, DM duration, TAR, GMI and CV, whereas these measurements of SCP and DCP were significantly positively correlated with TIR and TITR. In other words, we found that as HbA1c level, DM duration, TAR, GMI and CV increased, SCP and DCP vessel densities decreased, while TIR and TITR decreased, vessel densities also decreased. Our multivariable analysis showed that this alteration in vessel density could not be explained merely by chronological age or DM duration and might be independently associated with glycemic control and variability as captured by CGM-derived metrics. Specifically, the persistence of all significant associations in the DCP suggested that capillaries in this deeper plexus might be relatively more susceptible to changes in glycemic control and variability, independently of age and DM duration (4,5,22,23,27). Furthermore, although the SCP was reported to be exposed to higher perfusion pressure and theoretically better regulated, our findings indicated that superficial capillaries might also be sensitive to glycemic fluctuations (22,23,26,27). Therefore, reduced SCP and DCP vessel densities might serve as a potential early indicator of retinal changes in T1DM-noR children, while their independent associations with CGM-derived metrics (especially in the DCP) further supported the role of glycemic control and variability in these early retinal alterations. However, we detected no significant relationships of SCP and DCP vessel densities with TBR. In cases with longer DM duration and higher HbA1c level, the exposure time to serious hyperglycemia may also rise (5,8,22,23). Over time, cumulative effects and fluctuations may lead to progressive capillary narrowing and occlusion, resulting in further expansion of retinal non-perfusion areas (4,5,22,23,28). Compared to the SCP, these changes may be even more pronounced in the DCP because of its vascular architecture, which may render it more vulnerable to hypoperfusion and ischemia (4,5,22,23,27). In our study, we considered that significant associations, which we observed between SCP and DCP vessel densities and the values of HbA1c, DM duration, TIR, TITR, TAR, GMI and CV, might be explained by the mechanisms mentioned above. In literature, the retina was reported to possess various autoregulatory and metabolic compensatory mechanisms that contributed to maintaining retinal function and perfusion during hypoglycemic attacks (29,30,31). Accordingly, adverse effects of hypoglycemia might be compensated to a certain extent by adaptive changes in retinal blood flow and neurovascular responses (29,30,31). In our study, the lack of significant relationships between vessel densities and TBR value may be attributed to these factors.

Study Limitations

There were some limitations in this study. It had a cross-sectional design and a relatively small sample size. There might have been additional undetectable factors affecting retinal vessel density. Future prospective studies with larger sample sizes and longer follow-up periods may provide more comprehensive data regarding the effects of glycemic metrics and DM duration on retinal vessels.

Conclusion

In summary, as far as we know, in T1DM-noR children, our study was the first study comprehensively researching relationships of SCP and DCP vessel densities with CGM-derived TIR, TITR, TAR, GMI and CV. We found that T1DM children had reduced SCP and DCP vessel densities before the development of clinically visible diabetic retinopathy. We also detected that as TIR and TITR decreased and HbA1c, diabetes duration, TAR, GMI and CV increased, SCP and DCP vessel densities decreased. Our study suggested that reduced SCP and DCP vessel densities might serve as a potential early indicator of retinal changes in T1DM-noR children, while their independent associations with CGM-derived metrics (especially in the DCP), regardless of age and DM duration, further supported the role of glycemic control and variability in these early retinal alterations. In such patients, more effective glycemic control should be considered. The combined interpretation of OCTA findings and CGM-derived glycemic metrics might provide complementary information about retinal microvascular status and help identify children who could benefit from closer ophthalmic follow-up.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was conducted with approval of Izmir Tepecik Training and Research Hospital's Ethics Committee (approval number: 2025/05-26), adhering to the ethical principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all participants and their legal guardians.

Footnotes

Peer-review: Externally peer-reviewed.
Authorship Contributions: Surgical and Medical Practices: Bediz Özen, Hakan Öztürk, Emrullah Arslan; Concept: Bediz Özen, Hakan Öztürk, Emrullah Arslan; Design: Bediz Özen, Hakan Öztürk, Emrullah Arslan; Data Collection or Processing: Bediz Özen, Hakan Öztürk, Emrullah Arslan, Müge Nasırlı, Eren Er, Bumin Nuri Dündar; Analysis or Interpretation: Bediz Özen, Hakan Öztürk, Emrullah Arslan, Müge Nasırlı, Eren Er, Bumin Nuri Dündar; Literature Search: Bediz Özen, Hakan Öztürk, Emrullah Arslan, Müge Nasırlı, Eren Er, Bumin Nuri Dündar; Writing: Bediz Özen, Hakan Öztürk, Emrullah Arslan.
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Table 1. Clinical and laboratory data of the groups

Clinical and laboratory characteristics	Healthy group (n=45)	T1DM-noR group (n=42)	p
Age (years)	15.1±2.4 (9-18)	14.5±3.2 (9-18)	0.756[a]
Gender distribution (female/male)	28/17	27/15	0.934[b]
BMI (kg/m²)	20.2±3.1 (14.3-26.4)	20.6±3.6 (15.2-32.7)	0.892[a]
BMI-SDS	0.12±0.85 (-1.59-1.48)	0.13±1.02 (-1.78-3.05)	0.951[a]
Pubertal stage (tanner)	3.5±1.1 (1-5)	3.7±1.2 (1-5)	0.879[c]
Total cholesterol (mg/dL)	166.8±30.5 (96-198)	170.5±42.7 (114-305)	0.453[a]
LDL-cholesterol (mg/dL)	90.7±24.3 (62-125)	93.6±40.9 (41-214)	0.287[a]
HDL-cholesterol (mg/dL)	56.9±11.7 (43-72)	55.8±15.4 (31-92)	0.325[a]
Triglycerides (mg/dL)	98.2±40.3 (41-152)	101.9±54.2 (40-291)	0.276[c]

Descriptive characteristics were given as mean ± standard deviation (minimum-maximum) values
n: Number of cases, T1DM-noR: Type 1 diabetes mellitus with no clinically visible diabetic retinopathy, BMI: Body mass index, kg/m²: Kilograms per square meter, SDS: Standard deviation score, mg/dL: Milligrams per deciliter, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.
[a] Independent sample t-test, [b] Chi-square test, [c] Mann-Whitney U test, p value <0.05 statistically significant.

Table 2. OCTA parameters of the groups

OCTA parameters		Healthy group (n=45)	T1DM-noR group (n=42)	p
Foveal avascular zone (FAZ) area (mm²)		0.26±0.07 (0.08-0.41)	0.27±0.12 (0.11-0.86)	0.592[a]
Vessel density of superficial capillary plexus	Whole retina	50.43±3.06 (44.60-56.21)	49.04±3.11 (42.12-54.09)	**0.038**[b]
	Fovea	21.86±6.37 (11.49-35.28)	19.84±6.23 (11.06-35.12)	**0.046**[a]
	Parafovea	52.97±2.47 (46.91-56.02)	51.38±3.72 (43.01-55.96)	**0.025**[b]
	Perifovea	50.65±2.61 (46.32-56.14)	49.18±3.17 (42.19-55.06)	**0.032**[b]
Vessel density of deep capillary plexus	Whole retina	53.14±5.92 (44.85-59.78)	51.34±5.41 (43.52-58.29)	**0.017**[b]
	Fovea	39.25±6.15 (24.64-52.75)	36.79±6.68 (21.29-52.35)	**0.041**[a]
	Parafovea	57.32±3.71 (48.07-61.82)	55.29±3.96 (45.60-60.51)	**0.012**[b]
	Perifovea	54.75±4.69 (47.84-60.47)	53.04±4.72 (44.62-58.71)	**0.021**[b]

Descriptive characteristics were given as mean ± standard deviation (minimum-maximum) values.
OCTA: Optical coherence tomography angiography, n: Number of cases, T1DM-noR: Type 1 diabetes mellitus with no clinically visible diabetic retinopathy, mm²: Square millimeter
[a] Mann-Whitney U test, [b] Independent sample t-test, p value <0.05 statistically significant

Table 3. Correlation analysis of OCTA parameters with HbA1c level, DM duration and CGM-derived metrics in T1DM-noR group

OCTA parameters		HbA1c level	DM duration	TIR	TITR	TAR	TBR	GMI	CV
Foveal avascular zone (FAZ) area		r=0.081 p=0.408	r=0.071 p=0.524	r=-0.087 p=0.343	r=-0.062 p=0.643	r=0.069 p=0.540	r=0.089 p=0.338	r=0.073 p=0.496	r=0.085 p=0.365
Vessel density of superficial capillary plexus	Whole retina	r=-0.222 **p=0.032**	r=-0.201 **p=0.041**	r=0.214 **p=0.035**	r=0.193 **p=0.045**	r=-0.203 **p=0.040**	r=-0.127 p=0.168	r=-0.232 **p=0.028**	r=-0.209 **p=0.037**
	Fovea	r=-0.215 **p=0.035**	r=-0.203 **p=0.040**	r=0.231 **p=0.029**	r=0.189 **p=0.048**	r=-0.195 **p=0.044**	r=-0.113 p=0.206	r=-0.212 **p=0.036**	r=-0.228 **p=0.030**
	Parafovea	r=-0.226 **p=0.031**	r=-0.211 **p=0.036**	r=0.240 **p=0.026**	r=0.202 **p=0.041**	r=-0.207 **p=0.038**	r=-0.134 p=0.142	r=-0.223 **p=0.032**	r=-0.230 **p=0.029**
	Perifovea	r=-0.217 **p=0.034**	r=-0.204 **p=0.039**	r=0.227 **p=0.030**	r=0.199 **p=0.043**	r=-0.200 **p=0.042**	r=-0.116 p=0.197	r=-0.219 **p=0.033**	r=-0.242 **p=0.025**
Vessel density of deep capillary plexus	Whole retina	r=-0.279 **p=0.010**	r=-0.270 **p=0.014**	r=0.285 **p=0.008**	r=0.257 **p=0.019**	r=-0.261 **p=0.017**	r=-0.169 p=0.073	r=-0.274 **p=0.012**	r=-0.302 **p=0.005**
	Fovea	r=-0.241 **p=0.025**	r=-0.216 **p=0.034**	r=0.273 **p=0.013**	r=0.192 **p=0.046**	r=-0.236 **p=0.027**	r=-0.148 p=0.112	r=-0.245 **p=0.024**	r=-0.256 **p=0.020**
	Parafovea	r=-0.312 **p=0.004**	r=-0.289 **p=0.007**	r=0.321 **p=0.001**	r=0.265 **p=0.016**	r=-0.281 **p=0.009**	r=-0.176 p=0.062	r=-0.298 **p=0.006**	r=-0.318 **p=0.003**
	Perifovea	r=-0.268 **p=0.015**	r=-0.225 **p=0.031**	r=0.253 **p=0.021**	r=0.208 **p=0.037**	r=-0.239 **p=0.026**	r=-0.156 p=0.089	r=-0.260 **p=0.018**	r=-0.251 **p=0.022**

OCTA: Optical coherence tomography angiography, HbA1c: Hemoglobin A1c, DM: Diabetes mellitus, CGM: Continuous glucose monitoring, T1DM-noR: Type 1 diabetes mellitus with no clinically visible diabetic retinopathy, TIR: Time in range, TITR: Time in tight range, TAR: Time above range, TBR: Time below range, GMI: Glucose management indicator, CV: Glucose coefficient of variation.
r: Spearman correlation coefficient, p value <0.05 statistically significant