ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2025.2025-2-17

J Clin Res Pediatr Endocrinol

Nailfold Capillaroscopy: A Non-Invasive Tool for Early Detection of Microvascular Alterations in Children with Type 1 Diabetes Mellitus

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What is already known on this topic?

Nailfold capillaroscopy (NC) is a non-invasive and practical method for assessing microvascular structures and has been widely used to detect vascular alterations in various systemic diseases. In type 1 diabetes mellitus (T1DM), microvascular complications such as retinopathy, nephropathy, and neuropathy are well-established consequences of chronic hyperglycemia. However, microvascular structural and functional abnormalities can develop during childhood and adolescence, even in the absence of clinically evident vascular disease. Early detection of these changes is essential for timely intervention and the prevention of long-term complications. Although NC has the potential to identify early microvascular alterations in pediatric T1DM patients, data in this population remain limited. Most existing studies have focused on adults, underscoring the need for further research to clarify the role of NC in early diagnosis, monitoring, and the characterization of diabetes-related microvascular changes in children and adolescents.

What this study adds?

This study demonstrates that microvascular structural and functional abnormalities can develop in children and adolescents with T1DM even before the appearance of clinically evident vascular complications. It highlights the significant association between poor glycemic control, longer disease duration, and capillaroscopic alterations, particularly reduced capillary density. The findings emphasize the potential of NC as a valuable, non-invasive tool for the early detection and monitoring of microvascular changes in pediatric T1DM populations. Early identification of these alterations may facilitate timely interventions aimed at preventing the progression of vascular complications.

Abstract

Objective: Nailfold capillaroscopy (NC) is a non-invasive tool that can detect microvascular changes in the early stages of vascular disease. To assess capillary microarchitecture in children with type 1 diabetes mellitus (T1DM) and its relationship with clinical characteristics, laboratory findings, and glycemic control.

Methods: We included children and adolescents with T1DM, aged 6-18 years, and diagnosed for at least one year and an equal number of age- and sex-matched healthy controls. For all patients with T1DM, data on diabetes duration were collected, and the average annual HbA1c value was calculated for the four measurements made at routine follow-up in the preceeding year. In patients using 24-hour continuous glucose monitoring (CGM) devices, glycemic data from the previous three months were analyzed. The capillaroscopic

Cite this article as: Akın Kağızmanlı G, Aydın T, Yüksek Acinikli K, İşgüder R, Kızıldağ Karabacak Z, Demir K, Böber E, Ünsal ŞE, Abacı A. Nailfold capillaroscopy: a non-invasive tool for early detection of microvascular alterations in children with type 1 diabetes mellitus. J Clin Res Pediatr Endocrinol. [Epub Ahead of Print]

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Received: 27.02.2025
Accepted: 21.05.2025
Epub: 03.06.2025

findings were evaluated by two different researchers with experience in the field of pediatric rheumatology. Capillaroscopic parameters were compared based on glycemic control (HbA1c ≥7.5% vs. <7.5%), disease duration (<5 vs. ≥5 years), time in range (TIR≥70% vs. <70%), and glucose variability (CV≤36% vs. >36%).

Results: The median age of the 55 patients with T1DM was 14.5 (11.3-17.2) years, with a median disease duration of 3.8 (2.3-6.7) years. Compared to controls, patients with T1DM had significantly lower capillary density and more frequent dilated, tortuous, cross-linked, and abnormal capillaries ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.01$, and $p = 0.03$, respectively). Capillary density was significantly lower in patients with poor glycemic control ($p < 0.001$) and those with longer disease duration ($p = 0.02$). A negative correlation was observed between capillary density and disease duration ($r = -0.3$, $p = 0.02$). After adjusting for age, gender, body mass index, and diabetes duration, capillary density remained negatively correlated with average HbA1c ($r = -0.4$, $p = 0.004$). Among CGM users ($n = 22$), capillary density showed a positive correlation with TIR ($r = 0.5$, $p = 0.04$), even after adjustment for confounders.

Conclusion: Children with T1DM exhibited significantly higher microvascular changes, mostly associated with poor glycemic control, compared to healthy controls. NC may be a useful technique for detecting early alterations in the capillary structures of children with T1DM, even in the absence of overt clinical microvascular complications.

Keywords: Diabetic vasculopathy, morbidity, hyperglycemia, insulin, screening

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic metabolic disease that affects the microvasculature as well as other systems. Chronic hyperglycemia causes various molecular and biochemical changes, leading to a chronic proinflammatory process that damages capillaries. These changes become evident in the initial stages of vascular disease, before the development of diabetic macro- and microvascular complications (1,2). Although these complications are uncommon in childhood and adolescence, early vascular functional and structural deterioration may occur during this period (3). Given that the majority of diabetes-related complications typically manifest later in life, the early detection of subclinical vascular changes in childhood offers an important opportunity for earlier intervention. Early identification and appropriate management may delay or even prevent the progression of microvascular and cardiovascular complications, thereby reducing morbidity and mortality (3,4).

Various factors, such as genetics, gender, pubertal stage, duration of diabetes, glycemic control, and lifestyle, play a role in the development of vascular complications. It is important to identify vascular disease in patients with diabetes before the onset of clinically evident complications (3). Different techniques are used to detect early microvascular damage, including Doppler flowmetry, ophthalmoscopy, optical coherence tomography and 24-hour ambulatory blood pressure monitoring (5,6,7). However, these methods have several limitations. For instance, while Doppler flowmetry offers real-time measurement of blood flow, it is limited in its ability to provide structural information about microvessels and may be affected by movement artifacts, making it less reliable in clinical practice (8,9). Ophthalmoscopy, although effective for detecting retinopathy, is restricted to assessing retinal vessels and does not provide a comprehensive view of systemic microvascular health (10). Similarly, 24-hour ambulatory blood pressure monitoring focuses on blood pressure fluctuations but does not directly assess microvascular structure or function. This method can also be costly and impractical for repeated use due to patient compliance issues, and physical activity throughout the day can affect the accuracy of readings (11). In contrast to these techniques, nailfold capillaroscopy (NC) is a non-invasive, simple, cost-effective, and reproducible imaging technique that assesses both quantitative and qualitative characteristics of nailfold microvasculature. It allows for the direct visualization of capillary structure, making it a valuable tool for detecting subtle microvascular changes. In recent years, NC has gained importance for diseases that affect vascular structure and function, such as diabetes, in addition to connective tissue diseases (12).

Few published studies have assessed the effectiveness of the NC method in detecting early vascular disease in children and adolescents with T1DM (5,6,13,14). Moreover, to the best of our knowledge, there is no data available on the use of this technique in clinical practice for patients using a 24-hour continuous glucose monitoring (CGM) system. The objective of this study was to examine the presence of nailfold capillary abnormalities in children with T1DM by comparing them to age- and sex-matched healthy controls.

Methods

Patients

This cross-sectional, single-center study involved patients aged 6–18 years diagnosed with T1DM and followed up in our outpatient clinic for at least a year, along with an equal number of healthy individuals of similar age and sex who were referred to the pediatric endocrinology clinic for various reasons. Diagnosis of T1DM was made according to the criteria of the International Society of Pediatric and

Adolescent Diabetes (15). Children with other types of diabetes, such as type 2 diabetes, maturity-onset diabetes of youth, and secondary diabetes, as well as patients with connective tissue disease or autoimmune diseases, those with traumatic lesions in the periungual fold of the finger, recent infections, or those using medications known to affect microcirculation (e.g., vasodilators, antihypertensive drugs), were excluded from the study. Informed consent was obtained from each patient or their legal guardians.

Clinical Evaluation

A thorough analysis of medical records was conducted retrospectively to collect information such as the anthropometric measurements, physical examinations, duration of diabetes, insulin therapy, use of insulin pumps and CGM devices, as well as the history of diabetes-related complications such as retinopathy, neuropathy, or nephropathy.

Height was measured with a Harpenden stadiometer capable of measuring with an accuracy of 0.1 cm. Body weight was measured in underwear without shoes using an electronic scale (SECA, Hamburg, Germany) to the nearest 0.1 kg. The standard deviation (SD) scores for height, weight, and body mass index (BMI) were calculated using an online tool (Child Metrics), according to the Turkish standards established by Neyzi et al. (16).

Laboratory tests consisted of the most recent measurements of glycated hemoglobin (HbA1c), and fasting lipid profile, which included triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol, as well as urinary albumin creatinine ratio measured from an early morning, fasting urine sample. In addition, the annual mean HbA1c was calculated, and glycemic control was defined based on the mean HbA1c levels. Mean annual HbA1c was calculated by averaging the four most recent measurements made at three-monthly routine follow-up clinic visits. Patients with HbA1c $<7.5\%$ were considered to have good glycemic control, while those with HbA1c $\geq 7.5\%$ were classified as having poor glycemic control. Furthermore, patients with diabetes were divided into two subgroups according to disease duration (≥ 5 years vs. <5 years) when assessing microvascular alterations.

In diabetic patients using CGM devices, the glucose data for the last three months were obtained. Time in range (TIR) was defined as the percentage of readings and time per day within the target glucose range of 70 to 180 mg/dL. Achieving a percentage of over 70% for the time in the target glucose range was accepted as indicating good glycemic control. Glycemic variability [coefficient of variation (CV)] was defined as the percentage fluctuation in blood glucose. The glucose profile was considered stable when CV was $\leq 36\%$. Patient subgroups were created using CGM data based on TIR ($\geq 70\%$ vs. $<70\%$) and CV ($\leq 36\%$ vs. $>36\%$) (17).

Capillaroscopic Evaluation

All patients underwent a comprehensive assessment by two different researchers experienced in the field of pediatric rheumatology. The researchers were blinded to the participants' group status (patients with T1DM or healthy controls) to minimize potential bias and ensure objectivity in the evaluations. Each image was independently evaluated by both observers using the predefined criteria of the European League Against Rheumatism developed in 2020 for the standardization of NC in the evaluation of patients with Raynaud's phenomenon and systemic sclerosis were used for qualitative assessment (18). In cases of disagreement, the images were re-examined and discussed collaboratively until a consensus was reached. However, there were no significant discrepancies between the two assessors. The mean of the two observers' measurements was used for data analysis. This approach was designed to eliminate inter-rater reliability and ensure consistency and accuracy in the final evaluation of the capillaroscopic findings.

To standardize evaluations, capillaroscopy was performed under controlled conditions, following a 15-20-minute rest period at room temperature. Fingers affected by recent local trauma were excluded from the analysis. Images were captured at $200\times$ magnification using the Dino-Lite CapillaryScope 200 Pro/MEDL4N Pro, a validated digital capillaroscopy device, and analyzed with DinoCapture 2.0, version 1.5.49.B software (Dino-Lite Europe, IDCP B.V., The Netherlands). For optimal visualization, a drop of immersion oil was applied to the nail bed to improve image resolution. Each examination involved the assessment of eight fingers, excluding the thumbs, with two distinct images obtained from the midline of each finger.

The capillaroscopic examination consisted of both quantitative and qualitative analyses. A quantitative assessment was performed on images obtained from a 1 mm length area in the distal row of capillaries. This analysis evaluated several parameters, including capillary density, width, and length, intercapillary distance, capillary morphology, and the presence of microhemorrhages and avascular areas. The qualitative analysis included general pattern recognition, where the images were classified as either showing a scleroderma pattern or a non-scleroderma pattern, which could be normal or exhibiting non-specific abnormalities.

"Capillary density" refers to the number of capillaries per millimeter, and ≤7 capillaries per mm indicates a decrease in capillary number. A capillary diameter (arterial, venous, or apical) < 20 µm was considered normal; an increase from 20 µm to 50 µm was classified as an enlarged capillary; and a diameter ≥50 µm was classified as a giant capillary. Giant capillaries have been described as potentially indicative of an underlying scleroderma spectrum disorder. An intercapillary distance of more than 500 µm in the distal row of capillaries was considered an "avascular area." Microbleeding around the capillary appears in dark masses adjacent to the distal row, known as "micro-hemorrhages". Capillaries exhibiting a hairpin shape or a "tortuous" shape in which the afferent and efferent limbs bend but do not intersect, as well as a shape that is "cross-linked" once or twice, were defined as normal capillary morphology. All other shapes were defined as having "abnormal" morphology (Figure 1).

For each participant, 16 images obtained from eight fingers were analyzed for the presence or absence of capillaroscopic parameters, including decreased capillary density, the presence of enlarged or giant capillaries, cross-linked capillaries, tortuosity, abnormal morphology, avascular area, and microhemorrhages. In both groups, capillary abnormalities were defined as the presence of signs in at least two fingers. In addition, capillary density, length, width, and distance between capillaries in each image were measured and calculated as the mean.

Ethics

This study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2023/41-02, date: 20.12.2023) and performed in line with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using the SPSS program for Windows, version 24.0 (IBM Co., Armonk, NY, USA). The data were tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics for categorical variables are presented as a number (%), while continuous variables are reported as a mean ± SD for normally distributed data and as medians with the respective 25-75th percentile (interquartile range) values for non-normally distributed data. Comparisons between categorical variables were conducted using the Pearson chi-square test or Fisher's exact test, as appropriate. The Student's t-test was used to compare normally distributed continuous variables between the T1DM and control groups. The Pearson correlation test was used to assess correlations between capillary density and continuous variables. Then, any correlation was investigated among the identified significant variables after adjusting for age, gender, and BMI. Multivariate linear regression analysis was performed to examine the association between capillary density and potential confounding factors, including age, gender, BMI, duration of T1DM, insulin dose, average HbA1c, and LDL-C and TG levels as independent variables, with capillary density as the dependent variable. A two-sided p-value of < 0.05 was regarded as statistically significant.

Effect Size and Power Analysis

The effect size in this study was calculated based on capillary density, a key parameter in assessing microcirculation. It was determined by calculating the standardized difference between the two means, divided by the SD for the two independent groups (19). The analysis revealed a large effect size (Cohen's d = 1.6), indicating a significant difference in

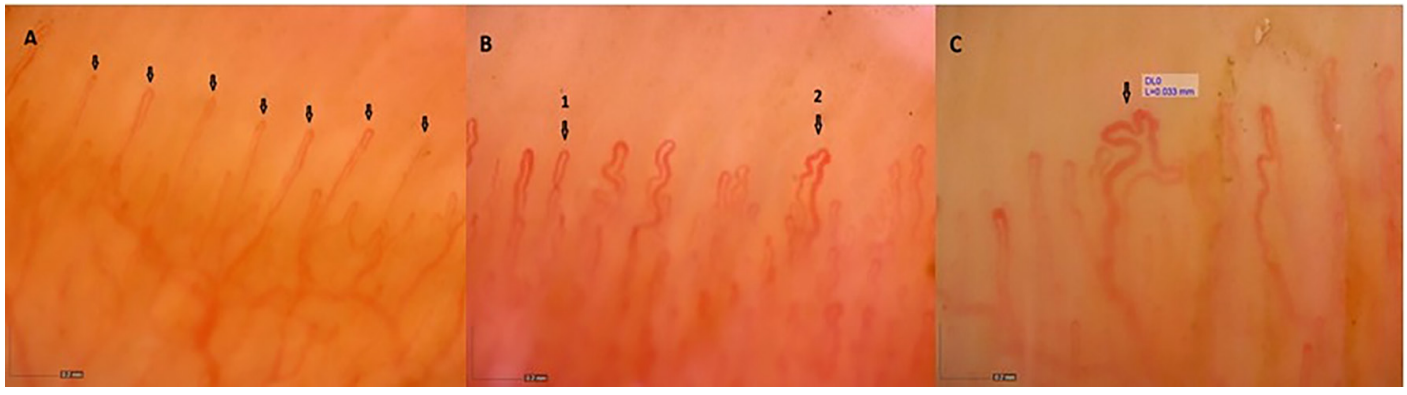

Figure 1. Examples of capillaroscopy findings in the analyzed groups of healthy controls (A and B) and a patient with T1DM (C). **A)** Capillaries with a normal "hairpin" shape; **B)** capillaries that display crossing (1) and tortuosity (2) patterns are considered not indicative of any pathological conditions; **C)** abnormal morphology and enlarged capillary with an increase in capillary diameter (20-50 µm)

T1DM: type 1 diabetes mellitus

capillary density between the T1DM group and the control group. Moreover, a post-hoc power analysis was performed using G*Power (version 3.1.9.4). With 55 subjects in both the T1DM and control groups, and an effect size of 1.6, the analysis demonstrated that the study achieved a statistical power of greater than 90% at a significance level of $\alpha = 0.05$.

Results

The Baseline Characteristics of Study Subjects

The study included 55 patients with T1DM, with a median age of 14.5 (11.3-17.2) years. We compared their data with those of 55 age-matched healthy controls [13.0 (10.2-16.0) years, $p = 0.2$]. The female/male ratio in the control group was 28/27, while it was 24/31 in the diabetes group, demonstrating similar ratios ($p = 0.5$). In addition, the pubertal stage, height, weight, and BMI SD scores were similar between the two groups ($p = 0.5$, $p = 0.8$, $p = 0.4$, and $p = 0.3$, respectively). The clinical and laboratory characteristics of the subjects with T1DM are listed in Table 1.

NC

Table 2 presents the comparison of capillaroscopic parameters between the two groups. Patients with T1DM exhibited a significantly lower capillary density than healthy individuals ($p < 0.001$). In addition, T1DM patients had significantly increased arterial, venous, and apical diameters compared to healthy individuals ($p < 0.001$). Furthermore, in the T1DM group, there were more dilated, tortuous, cross-linked, and abnormally morphological capillaries ($p < 0.001$, $p < 0.001$, $p = 0.01$, and $p = 0.03$, respectively). Moreover, non-specific abnormalities were also more common in the T1DM group ($p < 0.001$).

Capillaroscopic parameters were found to be similar in both male and female patients with diabetes. When the patients were categorized by age (under and 12 years and over), no significant differences were observed in qualitative and quantitative capillaroscopic features, except for larger arterial and apical diameters in the older group ($p = 0.02$ and $p = 0.03$, respectively). Similarly, no significant differences were detected between the prepubertal and pubertal T1DM groups, except for greater apical, arterial, and venous diameters in the pubertal group ($p = 0.03$, $p = 0.01$, and $p = 0.04$, respectively).

Table 3 shows the capillaroscopy findings in patients with diabetes, categorized based on HbA1c levels and disease duration. Patients with poor glycemic control, defined as average HbA1c≥7.5% in the previous year, exhibited significantly lower capillary density compared to those with good glycemic control ($p < 0.001$). Capillary density was found to be negatively correlated with the average HbA1c ($r = -0.5$, $p < 0.001$) (Figure 2). After adjusting for age, gender, BMI, and diabetes duration, the negative correlation between capillary density and average HbA1c persisted ($r = -0.4$, $p = 0.004$). In addition, the group with poor glycemic control demonstrated significantly greater venous diameters ($p = 0.02$). However, all other quantitative parameters, including arterial and intercapillary diameters, as well as abnormal capillary morphology, were similar between the two groups ($p = 0.1$, $p = 0.2$, and $p = 0.7$, respectively).

Table 1. The clinical and laboratory characteristics of the patients (n = 55)

Age, years	14.5 (11.3-17.2)
Female/male, n (%)	24 (43.6%)/31 (56.4%)
Pubertal, n (%)	43 (78.2%)
Family history of T1DM, n (%)	11 (20%)
The presence of DKA	22 (40%)
Duration of T1DM, years	3.8 (2.3-6.7)
The presence of autoantibodies, n (%)	40 (72.7%)
Height, SD score	0.3 ± 1.1
Weight, SD score	0.4 ± 1.3
BMI, SD score	0.2 ± 1.2
Insulin dose, unit/kg/day	0.8 ± 0.2
Treatment with pump, n (%)	6 (10.9%)
The use of CGM, n (%)	22 (40%)
TIR, %	54.3 ± 22.3
CV, %	37.1 ± 6.5
Recent HbA1c, %	8.0 ± 1.4
Average HbA1c, %	8.2 ± 1.4
TC, mg/dL	163.0 (147.0-183.0)
HDL-C, mg/dL	54.0 (47.0-63.0)
LDL-C, mg/dL	90.4 (80.6-107.2)
TG, mg/dL	76.0 (64.0-104.0)
Dyslipidemia, n (%)	5 (9.1%)
Autoimmune thyroiditis, n (%)	2 (3.6%)
Celiac disease, n (%)	4 (7.3%)
Urinary albumin creatinine ratio, mg/g	10.2 (7.5-15.4)
Microvascular complication	
Retinopathy, n (%)	0 (0%)
Nephropathy, n (%)	2 (3.6%)
Neuropathy, n (%)	1 (1.8%)

Data were presented as mean ± standard deviation for normal distribution and median (25-75p) for those not distributed normally.
Reference values: Total cholesterol, 111-202 mg/dL; HDL, 31-68 mg/dL; LDL, 45.6-131 mg/dL; TG, 38-143 mg/dL
T1DM: type 1 diabetes mellitus, DKA: diabetic ketoacidosis, SD score: standard deviation score, BMI: body mass index, CGM: continuous glucose monitoring, TIR: time in range, CV: glycemic variability, HbA1c: glycated hemoglobin, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG, triglyceride

Table 2. Comparative analysis of nailfold capillaroscopy findings between patients with T1DM and the control group

NC parameters	Patients with T1DM (n = 55)	Healthy controls (n = 55)	p
Quantitative			
Capillary density, capillary/mm	6.5 ± 0.5	7.3 ± 0.5	**< 0.001**[a]
Reduced capillary density (< 7/mm), n (%)	45 (81.8%)	15 (27.3%)	**< 0.001**[b]
Capillary length, µm	507.5 ± 75.1	425.5 ± 51.8	**< 0.001**[a]
Arterial diameters, µm	12.3 ± 1.8	10.6 ± 1.3	**< 0.001**[a]
Venous diameters, µm	16.0 ± 2.5	13.4 ± 2.0	**< 0.001**[a]
Apical diameters, µm	16.7 ± 2.9	14.5 ± 2.0	**< 0.001**[a]
Intercapillary diameters, µm	194.6 ± 21.5	178.2 ± 16.1	**< 0.001**[a]
Presence of dilated capillaries, n (%)	26 (47.3%)	0 (0%)	**< 0.001**[b]
Giant capillaries, n (%)	0 (0%)	0 (0%)	-
Tortuosity, n (%)	42 (76.4%)	24 (43.6%)	**< 0.001**[b]
Cross-linked capillaries, n (%)	22 (40%)	10 (18.2%)	**0.01**[b]
Abnormal capillary morphology, n (%)	7 (12.7%)	0 (0%)	**0.03**[b]
Presence of avascular areas, n (%)	0 (0%)	0 (0%)	-
Presence of microhemorrhages, n (%)	0 (0%)	0 (0%)	-
Qualitative			
Pattern, n (%)			
Normal	7 (12.7%)	42 (76.4%)	**< 0.001**[b]
Non-specific abnormalities	48 (87.3%)	13 (23.6%)	

Data were presented as mean ± standard deviation for normal distribution. [a]Student's t-test, [b]Pearson's chi-square test, p < 0.05.
T1DM: type 1 diabetes mellitus, NC: nailfold capillaroscopy

Table 3. Comparative analysis of nailfold capillaroscopy findings based on HbA1c levels in patients with T1DM

NC parameters	Patients with HbA1c < 7.5 (n = 21)	Patients with HbA1c > 7.5 (n = 34)	p	Duration of T1DM < 5 years (n = 33)	Duration of T1DM > 5 years (n = 22)	p
Quantitative						
Capillary density, capillary/mm	6.7 ± 0.4	6.4 ± 0.5	**0.01**[a]	6.7 ± 0.4	6.4 ± 0.5	**0.02**[a]
Capillary length, µm	489.4 ± 85.0	518.6 ± 67.2	0.2[a]	497.1 ± 73.9	523.1 ± 75.9	0.2[a]
Arterial diameters, µm	11.9 ± 1.7	12.6 ± 1.9	0.1[a]	12.3 ± 1.7	12.4 ± 2.1	0.8[a]
Venous diameters, µm	15.0 ± 2.4	16.6 ± 2.4	**0.02**[a]	15.6 ± 2.2	16.6 ± 2.8	0.1[a]
Apical diameters, µm	15.6 ± 2.6	17.4 ± 2.9	**0.02**[a]	16.8 ± 2.9	16.5 ± 2.9	0.7[a]
Intercapillary diameters, µm	189.9 ± 23.2	197.6 ± 20.1	0.2[a]	194.4 ± 21.6	195.1 ± 21.7	0.9[a]
Presence of dilated capillaries, n (%)	6 (28.6%)	20 (58.8%)	**0.03**[b]	13 (39.4%)	13 (59.1%)	0.2[b]
Giant capillaries, n (%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Tortuosity, n (%)	11 (52.4%)	31 (91.2%)	**0.002**[b]	22 (66.7%)	20 (90.9%)	**0.04**[b]
Cross-linked capillaries, n (%)	3 (14.3%)	19 (55.9%)	**0.002**[b]	12 (36.4%)	10 (45.5%)	0.5[b]
Abnormal capillary morphology, n (%)	2 (9.5%)	5 (14.7%)	0.7[b]	2 (6.1%)	5 (22.7%)	0.1[b]
Presence of avascular areas, n (%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Presence of microhemorrhages, n (%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Qualitative						
Pattern, n (%)						
Normal	7 (33.3%)	0 (0%)	**0.01**[b]	7 (21.2%)	0 (0%)	**0.03**[b]
Non-specific abnormalities	14 (66.7%)	34 (100%)		26 (78.8%)	22 (100%)	

Data were presented as mean ± standard deviation for normal distribution. [a]Student's t-test, [b]Pearson's chi-square test, p < 0.05.
T1DM: type 1 diabetes mellitus, HbA1c: glycated hemoglobin

Individuals with poor control showed increased frequencies of dilated, tortuous, and cross-linked capillaries (p = 0.03, p = 0.002, and p = 0.002, respectively). Moreover, non-specific abnormalities were more frequently found in this group (p = 0.01).

Among patients with diabetes, those with a T1DM duration ≥5 years exhibited a significantly lower capillary density than those with a T1DM duration < 5 years (p = 0.02). Capillary density showed a negative correlation with the duration of T1DM (r = -0.3, p = 0.02) (Figure 2). However, after adjustment for age, gender, and BMI, the relationship between capillary density and disease duration became non-significant (p = 0.08). Nevertheless, patients with a longer duration of T1DM displayed significantly higher rates of non-specific abnormalities (p = 0.03).

In the multivariate linear regression analysis (Table 4), capillary density was evaluated as the dependent variable, while adjusting for potential confounders, including age, gender, BMI, duration of T1DM, insulin dose, average HbA1c, LDL-C, and TG levels. The analysis revealed that only average HbA1c levels were significantly associated with capillary density (β-coefficient = -0.358, p = 0.03), indicating that higher HbA1c levels correlated with reduced capillary density. Other variables, including age, gender, BMI, duration of T1DM, insulin dose, LDL-C, and TG levels, did not show significant associations with capillary density (p > 0.05). The overall model explained 29.1 % of the variance in capillary density ($r^2 = 0.291$, p = 0.032), suggesting that glycemic control plays a key role in influencing capillary density.

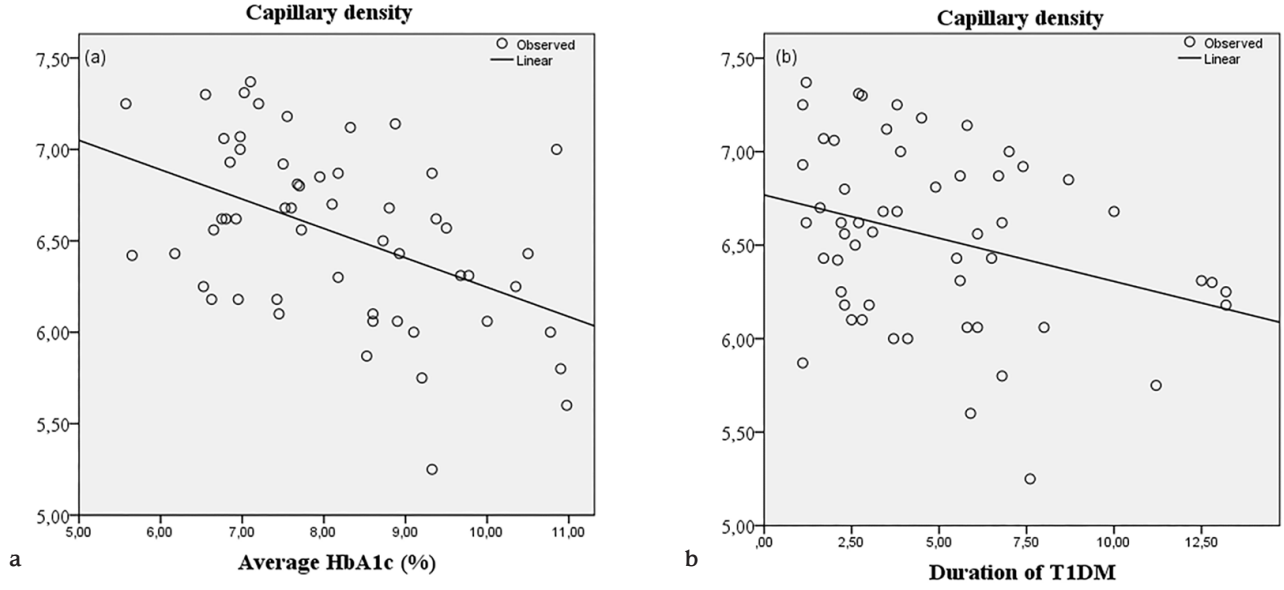

Figure 2. The correlation between capillary density and **(a)** average HbA1c (r = -0.5, p < 0.001), **(b)** duration of T1DM (r = -0.3, p = 0.02)

T1DM: type 1 diabetes mellitus, HbA1c: glycated hemoglobin

Table 4. Multivariate linear regression analysis (dependent variable: capillary density)

Variable	B (95% CI)	SRC (ß)	T	p
Age, years	-0.014 (-0.057/0.030)	-0.111	-0.620	0.5
Gender (female/male)	-0.068 (-0.329/0.193)	-0.071	-0.526	0.6
BMI, kg/m^2	0.011 (-0.031/0.052)	0.100	0.521	0.6
Duration of T1DM, years	-0.015 (-0.063/0.032)	-0.106	-0.657	0.5
Insulin dose, unit/kg/day	-0.418 (-1.014/0.179)	-0.204	-1.409	0.2
Average HbA1c, %	-0.123 (-0.229/-0.016)	-0.358	-2.316	0.03
LDL-C, mg/dL	0.001 (-0.005/0.006)	0.030	0.214	0.8
TG, mg/dL	-0.001 (-0.003/0.002)	-0.083	-0.559	0.6

T1DM: type 1 diabetes mellitus, BMI: body mass index, HbA1c: glycated hemoglobin, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, B: coefficient of regression, SRC: standardized regression coefficient ($r^2 = 0.291$, p = 0.032, Durbin Watson = 1,887), CI: confidence interval

Among the subjects with T1DM, 22 (40%) used CGM devices. The median age of these patients was 13.3 (9.7-15.6) years, with a median disease duration of 3.1 (1.7-5.7) years. Within this group, 16 patients (72.7%) exhibited a TIR of <70%, while 12 individuals (54.5%) showed a CV of >36%. The capillaroscopic characteristics did not show a significant difference between patients with a TIR of ≥70% and those with <70%. Likewise, these findings were similar in both patients with a CV of ≤36% and those with >36% (data not shown). However, there was a positive correlation between capillary density and TIR ($r = 0.5$, $p = 0.01$). This correlation persisted after adjusting for age, gender, BMI, and disease duration ($r = 0.5$, $p = 0.04$), indicating that diabetic children with better TIR had higher capillary density. However, there was no significant correlation between TIR and apical, arterial, or venous diameters ($r = -0.4$, $p = 0.07$; $r = -0.3$, $p = 0.2$; and $r = -0.4$, $p = 0.09$, respectively). Similarly, no significant correlation was present between CV and capillary density, apical, arterial, or venous diameters ($r = 0.02$, $p = 0.9$; $r = -0.2$, $p = 0.3$; $r = -0.08$, $p = 0.7$; and $r = -0.07$, $p = 0.7$, respectively).

Discussion

In the current study, it was found that children and adolescents with T1DM exhibited significant microvascular changes, even in the absence of diabetes-related microvascular complications. In particular, these abnormal microvascular alterations were associated with poor glycemic control and longer diabetes duration. The results of our study are in line with previously reported effects of diabetes on capillary structure and function in both adult and pediatric populations (5,6,14,20). Of note, our study was the first to assess the utility of NC in CGM users and found a positive correlation between capillary density and TIR, suggesting that patients with better TIR had a better microvascular structure.

In the review of the literature, few studies have focused on capillaroscopy changes in children with T1DM. Although a typical diabetic pattern has not yet been identified, these studies have reported characteristic morphological capillaroscopic features in diabetic patients, including reduced capillary density, increased capillary diameter, tortuous and cross-linked capillaries, microhemorrhagic areas, and avascular zones (5,6,12,13,14,21). For instance, in a study involving children and adolescents with T1DM, Hosking et al. (5) identified microhemorrhages and avascular zones as the most frequent microvascular alterations, with patients who had microvascular complications exhibiting more avascular areas on NC. Similarly, Bogusz-Górna et al. (6) reported that the most common lesions among juveniles with T1DM were enlarged, tortuous, bushy, elongated vessels, and hemorrhages. Another study found that diabetic adolescents had a higher prevalence of tortuous, cross-linked, and giant capillaries, as well as avascular areas, compared to healthy controls (14). Furthermore, in a study investigating the relationship between microangiopathic lesions in retinal vessels and capillary alterations in adults with T1DM and T2DM, Barchetta et al. (20) observed that patients with T1DM exhibited more capillaroscopic abnormalities, including reduced capillary density, than those with T2DM. They also noted these changes in nearly 50% of patients with diabetes without retinopathy, indicating early capillary abnormalities (20).Our study confirmed previously published findings that children with T1DM had significantly lower capillary density, increased capillary diameters, and a higher prevalence of dilated, tortuous, cross-linked, and abnormal morphological capillaries compared to healthy individuals. However, microhemorrhagic and avascular areas were not observed. These findings might suggest that alterations in the peripheral microvasculature are associated with end-organ damage in diabetes, even without any microvascular complications. However, it is worth noting that while capillary density is an important parameter of microcirculation, indicating disease severity, capillaroscopic variations, such as tortuous or cross-linked capillaries, can occur in healthy individuals without accompanying damage or symptoms (18,22,23,24,25).

The development of diabetes-related complications is associated with various risk factors, including puberty, elevated HbA1c levels, high glycemic variability, and longer disease duration (3,26,27). Some studies have shown that adolescent girls have a higher incidence of microvascular complications compared to boys (28,29,30). It has been reported that the duration of diabetes before puberty has less influence on complications (31). However, several studies have suggested that individuals who develop diabetes during puberty are at a higher risk of vascular complications compared to those who develop diabetes after puberty (29,32,33). Consistent with previous studies, female patients had a higher frequency of abnormal morphological parameters than male patients in a study evaluating microvascular alterations in diabetic patients (34). Similarly, Kaminska-Winciorek et al. (13) found that an increased number of vessels, indicating possible neoangiogenesis, occurred more frequently in female juveniles with diabetes. In contrast to these earlier studies, the current study found similar structural changes in both male and female patients. Moreover, there were no significant differences observed, except for larger capillary diameters in the pubertal T1DM group compared to the prepubertal group.

Chronic hyperglycemia, along with the accumulation of advanced glycation end products, oxidative stress, and inflammatory cytokines, leads to dysregulation in vascular tone, hemostasis, and intercellular communication, resulting in vascular endothelial damage (35). This endothelial dysfunction, characterized by a pro-inflammatory and pro-thrombotic state, plays a major role in the development of microangiopathy (2,36,37). These mechanisms can explain the capillaroscopic alterations seen in diabetic patients, even before the manifestation of overt vascular complications. Several studies evaluating the relationship between capillaroscopy findings, diabetes duration, and metabolic control have demonstrated increased morphological changes in patients with higher HbA1c levels or longer diabetes duration, further supporting the role of hyperglycemia in driving microvascular damage (5,13,14). However, there have also been conflicting results regarding the association between capillaroscopic abnormalities and disease duration, or glycemic control (6). Abdelmaksoud et al. (14) reported a significant positive correlation between microvasculature changes and longer diabetes duration, as well as poor glycemic control. In another study, Kaminska-Winciorek et al. (13) observed that elevated HbA1c levels were associated with increased dilated capillaries and reduced capillary density. Furthermore, these authors noted that the presence of abnormal capillaries correlated with the duration of diabetes (13). Kuryliszyn-Moskal et al. (35) showed that diabetic adults with poor metabolic control also had severe capillary changes. Once again, they found that the disease duration was longer in patients with severe capillaroscopic changes compared to those with mild or moderate microvascular abnormalities (35). In contrast, Bogusz-Górna et al. (6) found no significant relationship between the presence of capillaroscopic changes and the duration of diabetes or metabolic control.

The current study demonstrated that patients with poor glycemic control had significantly lower capillary density and more dilated capillaries. In addition, patients with a longer disease duration exhibited significantly reduced capillary density. We also found a negative correlation between capillary density and both average HbA1c levels and disease duration. While there was a positive correlation between capillary density and TIR, the capillaroscopic characteristics were found to be similar between CGM users with a TIR of ≥70 % and those with < 70 %. Similarly, there was no significant difference in capillaroscopic findings between patients with a CV of ≤36 % and those with > 36 %. This observation may be attributed to the small sample size of patients evaluated.

Several published studies have demonstrated a close association between capillaroscopic alterations and diabetes-related complications, such as retinopathy, nephropathy, and neuropathy, in both T1DM and T2DM patients (5,36,38,39,40). In one of these studies, Hosking et al. (5) reported a higher frequency of avascular areas in T1DM patients with microvascular complications. Similarly, Chang et al. (41) identified a correlation between diabetic retinopathy and the presence of tortuous, ramified, and dilated capillaries, with these alterations increasing as retinopathy progressed. Abdelmaksoud et al. (14) found that diabetic nephropathy and neuropathy were independently associated with NC changes, with more significant capillary abnormalities observed in patients with vascular complications compared to those without. In addition, Kuryliszyn-Moskal et al. (35) showed abnormal capillaroscopic findings in 81 % of adults with diabetes, noting that more severe changes were present in over half of those diagnosed with microvascular complications.

In the present study, only three patients exhibited microvascular complications: two with albuminuria and one with neuropathy. These patients displayed reduced capillary density and abnormal capillary morphology. However, due to the limited number of patients with complications, a detailed comparison could not be performed. Given that micro- and macrovascular complications are rare in the pediatric population, our findings emphasize the need for long-term follow-up studies. Although most patients did not present with overt complications, the observed capillaroscopic changes, particularly decreased capillary density and abnormal morphology, are suggestive of early subclinical endothelial dysfunction. Considering the progression of diabetic microangiopathy from silent structural alterations to clinically manifest disease, these findings may hold prognostic significance. Identifying microvascular alterations at an early stage may provide a valuable opportunity for timely interventions that could delay or prevent the development of long-term complications, such as retinopathy, nephropathy, and neuropathy.

NC has the potential to be implemented as a routine screening tool in pediatric diabetes care due to its simplicity, non-invasive nature, ease of use, repeatability, low cost, minimal equipment requirements, and ability to provide high-quality images for both qualitative and quantitative assessments of peripheral microvascular abnormalities (12,22). Current clinical guidelines recommend initiating annual screening for microvascular complications, such as retinopathy, nephropathy, and peripheral neuropathy in children with T1DM starting at puberty, or age 11 years, after 2 to 5 years of diabetes duration (3). Within this framework, NC could be integrated into annual routine follow-up visits as a complementary tool, especially in patients with poor glycemic control or longer disease duration. Longitudinal

studies are necessary to further explore the predictive value of early capillaroscopic changes in T1DM patients. However, for NC to be widely adopted as a screening tool, standardized protocols, appropriate clinician training, and further research are required to validate its diagnostic accuracy and prognostic utility in larger patient cohorts.

Study Limitations

The current study has several limitations. First, it was conducted on a relatively small group of diabetic patients and CGM users, which may limit the generalizability of the findings. Future studies with larger sample sizes for both groups could provide more definitive results. Second, as a cross-sectional study, it did not allow for the assessment of the progression of microvascular changes over time. Prospective longitudinal studies are necessary to explore how early capillaroscopic changes relate to long-term clinical outcomes in T1DM patients. Third, inter-rater reliability metrics, such as the intraclass correlation coefficient could not be calculated because individual scoring data from each observer were unavailable; only the averaged values were used in the final dataset. Although factors such as age and pubertal status were considered in subgroup and adjusted analyses, larger datasets are needed to more accurately assess their impact on microvascular structure. In addition, the type of insulin therapy was not evaluated, which may represent another potential confounding factor. Future studies should explore treatment modalities more comprehensively to determine their independent effects on microvascular health.

Conclusion

These capillaroscopic findings in patients with T1DM suggest that microvascular structural and functional abnormalities, primarily associated with poor glycemic control, can develop during childhood and adolescence, even in the absence of clinically evident vascular disease. This highlights the importance of early diagnosis and monitoring of microvascular health in pediatric populations with diabetes. NC may provide valuable data for detecting vascular damage before diabetes progresses and complications arise. Future prospective longitudinal studies with larger sample sizes are needed to determine the role of this method and to better characterize diabetes-related microvascular features in patients with T1DM.

Ethics

Ethics Committee Approval: This study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2023/41-02, date: 20.12.2023).

Informed Consent: Both patients and parents were required to sign the informed consent form to participate in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Gözde Akın Kağızmanlı, Concept: Gözde Akın Kağızmanlı, Tuncay Aydın, Kübra Yüksek Acinikli, Rana İşgüder, Zehra Kızıldağ Karabacak, Korcan Demir, Ece Böber, Şevket Erbil Ünsal, Ayhan Abacı, Design: Gözde Akın Kağızmanlı, Kübra Yüksek Acinikli, Rana İşgüder, Zehra Kızıldağ Karabacak, Ayhan Abacı, Data Collection or Processing: Gözde Akın Kağızmanlı, Tuncay Aydın, Analysis or Interpretation: Gözde Akın Kağızmanlı, Tuncay Aydın, Rana İşgüder, Zehra Kızıldağ Karabacak, Korcan Demir, Ece Böber, Şevket Erbil Ünsal, Ayhan Abacı, Literature Search: Gözde Akın Kağızmanlı, Kübra Yüksek Acinikli, Korcan Demir, Ece Böber, Şevket Erbil Ünsal, Ayhan Abacı, Writing: Gözde Akın Kağızmanlı, Ayhan Abacı.

Conflict of Interest: One of the author of this article, Korcan Demir is member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, he was not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions.

Financial Disclosure: No grants or fellowships were provided to support the writing of this paper.

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