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Original article

Chorioretinal microvascular changes in patients with type 1 diabetes mellitus in the absence of diabetic retinopathy - an OCTA study

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Summary

Introduction. Diabetic retinopathy (DR) is the leading cause of visual impairment in the working-age population. Microvascular changes in the retina occur before clinical signs of DR appear. Optical coherence tomography angiography (OCTA) enables non-invasive visualisation of retinal microvasculature. The aim is to investigate retinal microvascular changes using OCTA in patients with type 1 diabetes mellitus (T1DM) without clinical DR.

Methods. Cross-sectional study of 98 eyes from 49 subjects (29 T1DM patients, 20 healthy controls). All underwent comprehensive ophthalmic examination and OCTA (Cirrus 6000, 3×3 mm angiogram). Superficial capillary density (SCD, mm/mm^2), perfusion density (PD, %), foveal avascular zone area (FAZ, mm^2), central macular thickness (CMT) and macular volume were analysed. Demographic and clinical data were collected.

Results. T1DM patients had significantly higher perfusion density (PD full right: median 38.20% vs. 37.40%, p=0.029). No significant differences were found for other OCTA parameters. FAZ showed a borderline increase in patients with comorbidities (p=0.055). No correlation was observed between OCTA parameters and diabetes duration or HbA1c levels. A positive correlation was found between total daily insulin dose and central macular vascular density. OCTA successfully demonstrated changes in the foveal microvascular zone that are not visible on clinical examination, while all other OCT and OCTA parameters showed no statistically significant difference between groups.

Conclusion. OCTA can detect early microvascular changes in T1DM patients before clinical DR. Comorbidities and glycaemic control may influence OCTA parameters. Longitudinal studies are needed to assess predictive value for DR progression.

Key words: type 1 diabetes, macular microvascular changes, risk factors, OCTA

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Introduction

Diabetic retinopathy is a leading cause of vision loss in working-age individuals. The development of microvascular lesions in diabetes begins with biochemical changes, leading to functional and then anatomical vascular alterations. Retinal microvascular changes occur before the appearance of clinical signs of DR. New technologies have provided better insight into the pathophysiology of DR. OCTA allows non-invasive visualisation of retinal microvasculature without the use of contrast agents [1, 2]. This study aims to investigate retinal microvascular changes using OCTA in patients with type 1 diabetes mellitus without clinical DR, taking into account disease duration, glycaemic control (HbA1c), comorbidities and treatment modality.

Methods

Study design and participants

This observational cross-sectional study included 98 eyes of 49 subjects, divided into two groups: T1DM patients (n=29) and healthy controls (n=20). T1DM patients were further subdivided according to disease duration, comorbidities, HbA1c levels, total daily insulin dose (TDD) and type of insulin therapy (insulin pump vs. basal insulin). The study was conducted at the Clinic for Eye Diseases and the Department of Endocrinology, University Clinical Center of the Republic of Srpska, from October 2024 to March 2025.

All participants underwent a comprehensive ophthalmic examination including fundus photography. OCTA imaging was performed using the Cirrus 6000 (Carl Zeiss Meditec) with a 3×3 mm angiogram. Superficial capillary density (SCD, mm/mm²), perfusion density (PD, %), foveal avascular zone area (FAZ, mm²), central macular thickness (CMT) and macular volume were calculated using automated software. Images with significant artefacts (motion, poor signal, projection artefacts) were excluded from further analysis.

Statistical analysis

Numerical variables showed significant deviation from normal distribution; data are presented as median (interquartile range) and minimum-maximum. Differences between groups were tested using the Mann-Whitney U test, and associations between categorical variables were analysed using the Chi-square test. A p-value ≤0.05 was considered statistically significant.

General participant characteristics

Table 1 summarises the demographic and clinical characteristics of the study population. There were no significant differences in sex distribution between T1DM patients and healthy controls (p=0.343). However, T1DM patients were significantly younger (median 26.0 years vs. 37.5 years, p<0.001) and age category distribution also differed significantly (p=0.013). Median diabetes duration was 15.0 years, with 58.6% of patients having diabetes for >10 years. The majority of T1DM patients used insulin pumps (51.7%) and had HbA1c >7% (58.6%). Comorbidities were present in 75.9% of T1DM patients, with hypertension, hyperlipoproteinemia, PCOS and pulmonary hypertension being the most frequent (37.9%).

OCTA parameters: DM patients vs. healthy controls

When comparing macular vascular parameters between T1DM patients and healthy controls, a statistically significant difference

Table 1. General participant characteristics

Parameter	DM patients (N=29)	Healthy controls (N=20)	Total (N=49)	p-value
Sex				0.343a
Male	11 (37.9%)	5 (25.0%)	16 (32.7%)	
Female	18 (62.1%)	15 (75.0%)	33 (67.3%)	
Age (years), median (IQR), min-max	26.00 (15.00), 19-56	37.50 (12.75), 28-53	31.00 (16.50), 19-56	<0.001b
Age categories				0.013a
19-29	18 (62.1%)	4 (20%)	22 (44.9%)	
30-39	7 (24.1%)	9 (45%)	16 (32.7%)	
40+	4 (13.8%)	7 (35%)	11 (22.4%)	
Diabetes duration (years), median (IQR), min-max	15.00 (9.00), 2-29	NA	NA	NA
Diabetes duration categories		NA	NA	NA
<10 years	12 (41.4%)	NA	NA	
>10 years	17 (58.6%)	NA	NA	
Type of insulin therapy		NA	NA	NA
Insulin pump	15 (51.7%)	NA	NA	
Basal insulin	14 (48.3%)	NA	NA	
Insulin pump duration (years), median (IQR), min-max	4.00 (6.00), 1-16	NA	NA	NA
HbA1c (%), median (IQR), min-max	7.30 (2.90), 6.40-13.10	NA	NA	NA
HbA1c categories		NA	NA	NA
<7%	12 (41.4%)	NA	NA	
>7%	17 (58.6%)	NA	NA	
Complications		NA	NA	NA
Yes	12 (41.4%)	NA	NA	
No	17 (58.6%)	NA	NA	
Type of complication		NA	NA	NA
Polyneuropathy	6 (50%)	NA	NA	
Nephropathy	5 (41.7%)	NA	NA	
Retinopathy	1 (8.3%)	NA	NA	
Comorbidities		NA	NA	NA
Yes	22 (75.9%)	NA	NA	
No	7 (24.1%)	NA	NA	
Comorbidities of interest (HT, HLP, PCOS, PH)	11 (37.9%)	NA	NA	NA
Other comorbidities	18 (62.1%)	NA	NA	
Additional therapy		NA	NA	NA
Yes	18 (62.1%)	NA	NA	
No	11 (37.9%)	NA	NA	

Numerical values are presented as median (interquartile range), minimum-maximum. NA - not applicable; a Chi-square test; b Mann-Whitney U test. HT - hypertension; HLP - hyperlipoproteinemia; PCOS - polycystic ovary syndrome; PH - pulmonary hypertension

was found for perfusion density (PD) full right (p=0.029). T1DM patients had higher values (median 38.20%) compared to controls (median 37.40%). This finding may indicate early adaptive or compensatory microvascular changes. No significant differences were observed for other OCTA parameters (SCD, FAZ, CMT, macular volume).

Correlation with diabetes duration

No statistically significant differences were observed in any retinal microvascular network parameter with respect to diabetes duration. The risk of diabetes-related microvascular and macrovascular complications increases with age and is particularly low before the age of 20 years [11].

Correlation with HbA1c levels

No correlation was found between retinal microvascular network parameters and HbA1c values. This lack of association may be explained by the fact that HbA1c reflects short- to medium-term glucose balance (days to months), whereas OCTA vascular changes represent years of anatomical remodelling.

Impact of comorbidities

Patients with comorbidities of interest (hypertension, coronary artery disease, obesity, hyperlipoproteinemia, etc.) showed a **borderline trend towards larger FAZ** compared to those without comorbidities (p=0.055). FAZ changes and capillary non-perfusion are more common in diabetic patients. Poorer glycaemic regulation tends to reduce parafoveal superficial vessel density [9].

Correlation with insulin dose

A positive correlation was found between total daily insulin dose (TDD) and central macular vascular density. This suggests that OCTA may be a more sensitive biomarker than conventional clinical examinations. High TDD serves as a surrogate for intensive treatment, which has long-term beneficial effects on vascular damage (average TDD: 66.3 units in patients with HbA1c >9% vs. 54.9 units in patients with HbA1c <9%) [6].

OCTA detection of subclinical foveal changes

OCTA successfully demonstrated changes in the foveal microvascular zone that are not visible on clinical examination, while all other OCT and OCTA parameters showed no statistically significant difference between groups [1,9].

Discussion

This study demonstrates that OCTA can detect early microvascular changes in type 1 diabetes patients without clinical signs of diabetic retinopathy. The significantly higher perfusion density in DM patients compared to controls is an intriguing finding. While most previous studies report decreased vessel density in early diabetes, our result may reflect a compensatory phase of microvascular adaptation, possibly due to autoregulatory dysfunction or early inflammation. Mechanistic explanations require longitudinal investigation.

The lack of correlation with diabetes duration and HbA1c levels is consistent with the concept that OCTA captures long-term structural remodelling rather than short-term metabolic fluctuations. Our observation of larger FAZ in patients with comorbidities (borderline significance) aligns with previous reports

that systemic vascular risk factors exacerbate retinal ischaemia.

The positive correlation between total daily insulin dose and central macular vessel density is noteworthy. Intensive insulin therapy is known to reduce long-term complications [6, 8] and may preserve microvascular integrity. However, residual confounding (e.g., better overall diabetes management in pump users) cannot be excluded.

A major limitation of this cross-sectional study is the lack of standardisation among OCTA devices, imaging protocols, analysis techniques and nomenclature, making comparisons with other studies difficult [5]. Future multicentre research should adopt standardised OCTA protocols to confirm the clinical utility of OCTA in detecting early diabetic microvascular changes.

Conclusion

OCTA can detect early retinal microvascular changes in patients with type 1 diabetes before the onset of clinical signs of diabetic retinopathy. Associated comorbidities and poorer glycaemic control may be linked to specific changes in OCTA parameters. Longitudinal studies are needed to determine whether these findings have predictive value for the development and progression of diabetic retinopathy. OCTA parameters cannot be used alone for diagnosis but may aid in risk stratification.

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Ethical approval. The Ethics Committee of the Clinical Centre of Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Mikrovaskularne promjene horioretine kod pacijenata oboljelih od dijabetesa tipa 1 u odsustvu dijabetičke retinopatije - OCTA studija

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Uvod. Dijabetička retinopatija (DR) predstavlja vodeći uzrok oštećenja vida u populaciji radno sposobnog uzrasta. Mikrovaskularne promene na retini nastaju prije pojave kliničkih znakova DR. Optička koherentna tomografska angiografija (OCTA) omogućava neinvazivnu vizualizaciju retinalne mikrovaskulature. Cilj rada bio je ispitivanje mikrovaskularnih promjena retine primjenom OCTA kod pacijenata sa dijabetes melitusom tip 1 (T1DM) bez klinički manifestne DR.

Metode. Studija presjeka obuhvatila je 98 očiju kod 49 ispitanika (29 pacijenata sa T1DM i 20 zdravih kontrola). Kod svih ispitanika urađen je kompletan oftalmološki pregled i OCTA analiza (Cirrus 6000, angiogram 3×3 mm). Analizirani su površinska gustina kapilara (SCD, mm/mm^2), perfuziona gustina (PD, %), površina fovealne avaskularne zone (FAZ, mm^2), centralna debljina makule (CMT) i volumen makule. Prikupljeni su demografski i klinički podaci.

Rezultati. Pacijenti sa T1DM imali su statistički značajno veću perfuzionu gustinu (PD full right: medijana 38,20% naspram 37,40%, p = 0,029). Za ostale OCTA parametre nisu utvrđene statistički značajne razlike. Uočeno je granično povećanje FAZ kod pacijenata sa komorbiditetima (p = 0,055). Nije utvrđena korelacija između OCTA parametara i trajanja dijabetesa niti nivoa HbA1c. Utvrđena je pozitivna korelacija između ukupne dnevne doze insulina i centralne vaskularne gustine makule. OCTA je uspješno prikazala promjene u fovealnoj mikrovaskularnoj zoni koje nisu bile vidljive kliničkim pregledom, dok za ostale OCT i OCTA parametre nije nađena statistički značajna razlika između grupa.

Zaključak. OCTA može detektovati rane mikrovaskularne promjene kod pacijenata sa T1DM prije pojave klinički manifestne DR. Komorbiditeti i glikoregulacija mogu uticati na OCTA parametre. Potrebne su longitudinalne studije radi procjene prediktivne vrijednosti OCTA nalaza za progresiju DR.

Ključne riječi: dijabetes melitus tip 1, mikrovaskularne promjene makule, faktori rizika, OCTA