OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Introduction: Diabetic Retinopathy (DR) is a common microvascular complication of diabetes mellitus. Optical Coherence Tomography Angiography (OCTA) is a new method for visualizing the microvasculature of the retina and choroid, which is based on detecting the movement of circulating erythrocytes.

Objective: To present OCTA findings in patients with diabetes mellitus with different microvascular changes to diagnose diabetic retinopathy before the onset of clinical signs of the disease, as well as to monitor changes in clinically visible retinopathy, with or without Diabetic Macular Edema (DME).

Methods: In this study, OCTA findings were compared in three groups of selected subjects - 5 patients with Non-Proliferative Diabetic Retinopathy (NPDR) without DME, 5 patients with NPDR and DME, and 5 patients with diabetes but without NPDR and DME.

Results: Patients in all three groups showed decreased vessel diameter (VD) in the foveal, parafoveal, and perifoveal segments of the Superficial Capillary Plexus (SCP) and Deep Capillary Plexus (DCP) and an increase in Foveal Avascular Zone (FAZ).

Conclusion: OCT angiography represents a new technique for visualizing and quantifying vascular changes and is increasingly important in the early diagnosis of subclinical retinopathy, as well as in monitoring existing changes in the retina in people with type 2 diabetes mellitus.

Keywords: diabetic retinopathy, diabetic macular edema, optical coherence tomography angiography

Introduction

Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus (DM) and a leading cause of blindness worldwide. The prevalence of DR among individuals with type 2 DM ranges from 30 to 45% and continues to increase. Data indicate that 60-80% of all patients with type 2 DM will develop DR after 20 years of disease duration.

The first pathological change that occurs in DR is chronic microvascular damage with increased vascular permeability, leading to macular edema. The pathophysiological basis of this is the loss of pericytes, the thickening of the basement membrane, and the loss of smooth muscle cells in the wall of retinal capillaries. Later in the disease's development, retinal ischemia and consequent neovascularization develop.

DR is well-known for its classification into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR has three subgroups: mild, moderate, and severe. Mild NPDR is characterized by microaneurysms alone, while moderate NPDR exhibits microaneurysms along with at least one of the following signs: dot and blot intraretinal hemorrhages, cotton wool spots, hard exudates, and the absence of severe NPDR signs. Severe NPDR is defined by more than 20 intraretinal hemorrhages in all 4 quadrants and/or venous beading like a string of beads in at least two quadrants and/or intraretinal microvascular abnormalities in at least one quadrant, with no signs of PDR. PDR is characterized by at least one of the following signs: vitreous hemorrhage, pre-retinal hemorrhage, and neovascularization of the optic disc or retina.

Optical Coherence Tomography Angiography (OCTA) is a new non-invasive diagnostic method used to quickly detect changes in the capillaries of the retina and choroid[8]. It

DOI: 10.5937/Galmed2306013R

is performed using multiple repeated OCT B - scans of the same location, which detect different signals of reflection from circulating red blood cells in blood vessels[9]. In this way, OCTA detects vascular changes at the level of three capillary plexuses - superficial, intermediate, and deep (superficial capillary plexus within the ganglion cell layer, intermediate between the inner plexiform and inner nuclear layers, and deep between the inner nuclear and outer plexiform layers)[10]. Additionally, OCTA can automatically quantify the size of areas with and without perfusion (flow and non-flow areas), the foveal avascular zone (FAZ), and capillary density (VD)[11, 12]. FAZ is the central avascular zone of the macula where only cones are present[13]. In healthy eyes, it varies[14] between 0.042 and 0.738 mm^2. VD represents the proportion of the surface area of blood vessels relative to the total measured area based on binary images to determine the perfusion of the retinal microvasculature[15].

OCTA is slowly but surely revolutionizing the visualization and diagnosis of changes in DR. The gold standard for this is still fluorescein angiography, but due to its invasiveness and limitations in terms of systemic side effects, numerous scientific studies in the last 10 years have focused on investigating the effectiveness of OCTA as a diagnostic and prognostic tool for DR, especially in cases where changes are not yet clinically visible.

Aim

The presentation of OCTA findings in patients with diabetes mellitus with various microvascular changes, as well as the determination of differences in OCTA parameters in patients with DM, aims to diagnose DR before the onset of clinical signs of the disease and monitor changes in already existing clinically visible retinopathy, with or without diabetic macular edema (DME).

Methodology

This study presents the results of an investigation of 15 patients with type 2 diabetes. Both eyes of all patients (30 eyes) were included in the study and underwent clinical examination by two different physicians using indirect ophthalmoscopy, as well as OCT, based on which they were divided into three groups. The first group consisted of 5 patients (10 eyes) who had no changes on either OCT or clinical examination, and this group was marked as noDRnoDME. The second group of 5 patients (10 eyes) had a finding on the fundus exam consistent with NPDR, but the OCT findings did not indicate the presence of DME. This group was marked as NPDRnoDME. The third group of patients also included 5 patients (10 eyes) with NPDR and DME, and this group was labeled as NPDR+DME.

All patients underwent OCTA imaging of both eyes using a 70 kHz OCT device (RTVue-XR Avanti; Optovue, Inc., Fremont, California, USA) with the AngioVue software. This technology uses a Split-Spectrum Amplitude-Decorrelation Angiography (SSADA) algorithm to detect blood flow in the retinal tissue. The scanning area size was 6x6 mm, and the scanning pattern consisted of two repeated B-scans with 304 raster positions, each B-scan consisting of 304 A-scans. The flow signal is detected by examining the differences or decorrelation between consecutive scans of the same area. The effectiveness of detecting flow signals is improved with the SSADA algorithm, which divides the OCT spectrum into narrower spectral ranges and calculates their average decorrelation. After obtaining the retinal OCTA image, segmentation was performed to visualize individual retinal vascular layers separately[16, 17].

The superficial capillary plexus (SCP) encompasses the vasculature within the ganglion cell layer, while the deep capillary plexus (DCP) encompasses the vasculature on both sides of the inner nuclear layer (INL). The inner boundary of the SCP is 3μm below the inner limiting membrane (ILM), and the outer boundary is 15μm below the inner plexiform layer (IPL). The inner boundary of the DCP is 15 μm below the IPL, and the outer boundary is 70 μm below the IPL[18]. Then, for each layer, the system automatically calculated the vessel density (VD) in the region of the entire macula, as well as the fovea, parafovea, and perifovea, separately. Foveal VD was calculated for a concentric circle with a radius of 0.3 mm centered at the very center of the macula or fovea. Parafoveal VD was calculated for an annular region from 0.3 to 1.25 mm from the center of the macula, and perifoveal VD for an annular region from 1.25 to 1.75 mm from the center of the macula[19]. The software embedded in OCTA automatically calculated the average VD values in SCP and DCP for the entire macula, fovea, parafovea, and perifovea. In addition to VD, the software also automatically obtained the value of the foveal avascular zone (FAZ) area, central macular thickness (CMT), and the percentage of perfused vessels (flow) concerning the total area of vessels in the outer retina (OR) and choriocapillaris (CC). A *One-way Anova* test was used to calculate the differences in these parameters between different groups, and statistical significance was set at a level of 0.05.

Results

The average age of the participants was 68.46 years. In the group without diabetic retinopathy (DR), the average age was 72 years; in the group with non-proliferative diabetic retinopathy (NPDR) and without diabetic macular edema (DME), the average age was 66 years, and in the group with DME and NPDR, the mean age was 67.4 years. There were 9 women and 6 men among the participants, with 4 women and 1 man in the first group, 2 women and 3 men in the second group, and 3 women and 2 men in the third group.

The average CMT in the first group was 250 μm, in the second group 247 μm, and the third group 466 μm. There was a highly statistically significant difference ($p < 0.001$)

between the CMT of the first and third groups, as well as the second and third groups. The average value of FAZ in the group without clinical signs of DR and DME was 0.28 mm^2, in the group with NPDR and without DME 0.249, and in the group with NPDR and DME 0.248. No statistically significant difference was found between these values (p=0.785).

The vascular density in SCP and DCP for all three groups, separated for the whole macula, foveal, parafoveal, and perifoveal ring, is shown in table 1. A statistically significant difference (p=0.016) was found only in the VD value for SCP in the whole macula region, between eyes without DR and eyes with NPDR and DME.

The Flow OR and CC for all three groups are shown in table 2. A statistically significant difference (p=0.001) was found in the flow CC value between the first and second groups, as well as between the first and third groups. An OCTA image showing the foveal avascular zone marked in a healthy eye is shown in Figure 1a, and a patient with non-proliferative diabetic retinopathy in Figure 1b. The finding of OCTA image of the superficial vascular plexus and software-calculated values of VD by regions are shown on a healthy eye on image 2. The findings of OCTA images of the superficial and deep capillary plexus in a patient with DM but without clinically visible signs of DR are shown on images 3a and 3b.

Image 1a. Foveal avascular zone in a healthy eye (FAZ - 0.129 mm^2)

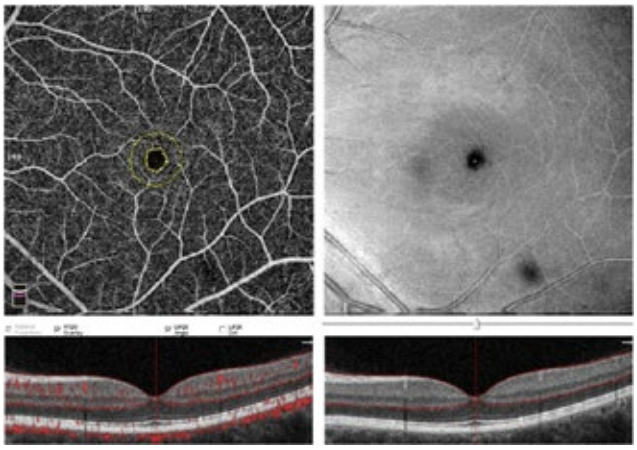
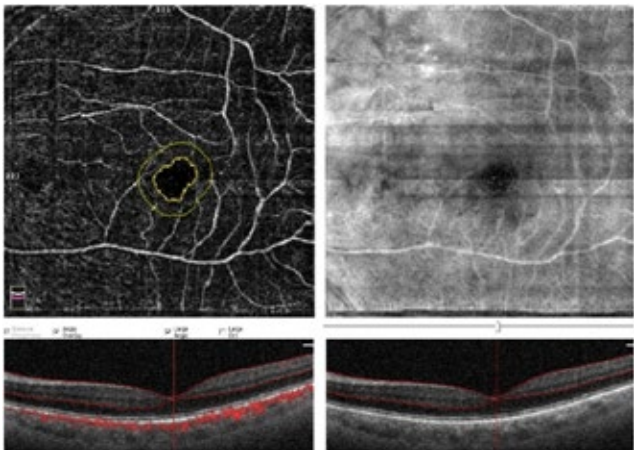
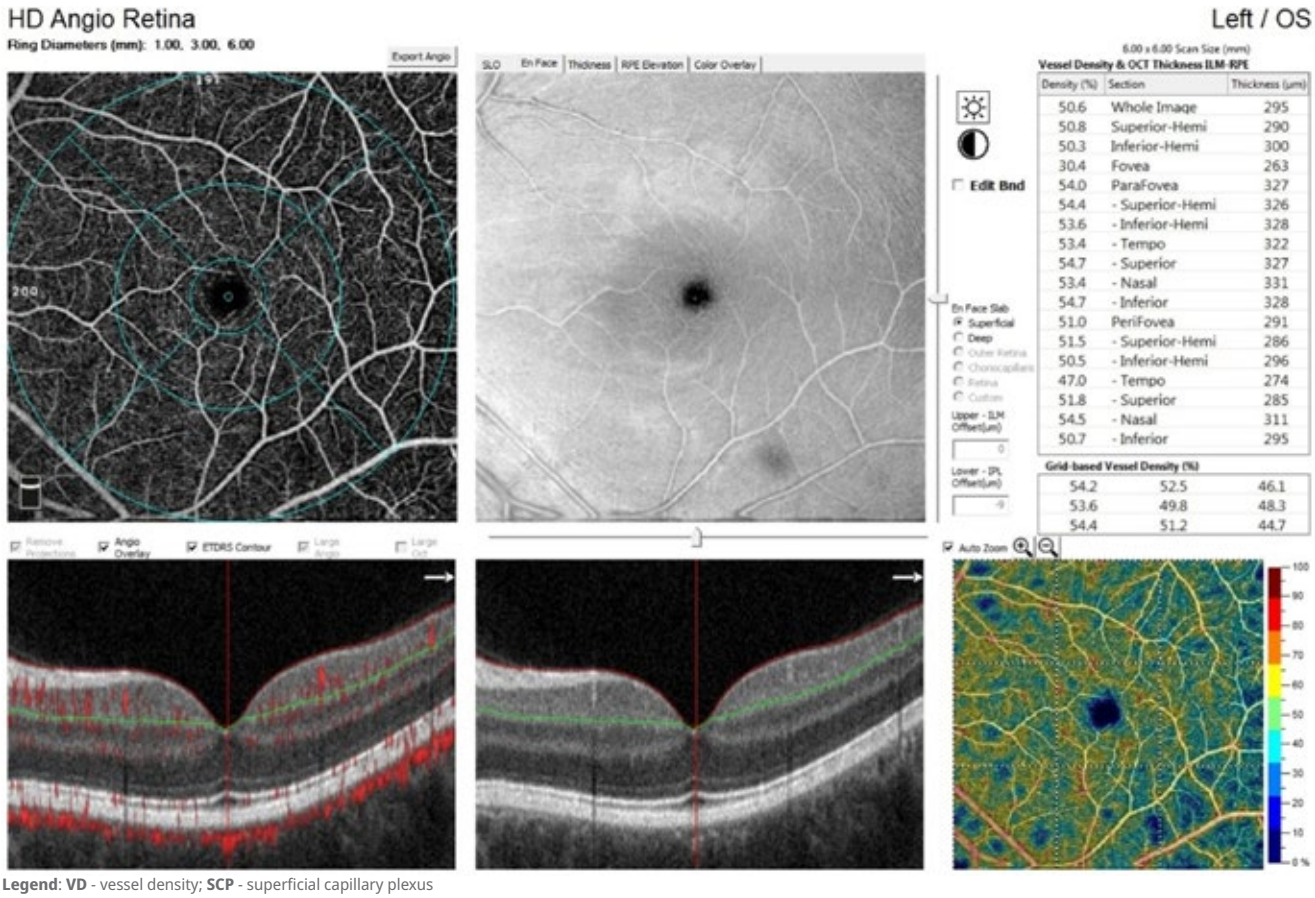


Image 1b. Foveal avascular zone in a patient with NPDR (enlarged FAZ - 0.432 mm^2)



Legend: **NPDR** - Non-Proliferative Diabetic Retinopathy

Image 2. Healthy eye - Capillary density (VD) in the superficial capillary plexus (SCP)



Legend: **VD** - vessel density; **SCP** - superficial capillary plexus

DOI: 10.5937/Galmed2306013R

Table 1. Vascular density in the superficial and deep capillary plexus

VD	Without DR	NPDR without DME	NPDR + DME	p
SCP (macula)	43.85	46.61	43.81	0.375
SCP (fovea)	14.86	21.75	27.56	0.052
SCP (parafovea)	46.48	47.69	44.01	0.270
SCP (perifovea)	44.14	47.63	45.19	0.364
DCP (macula)	44.94	40,94	42.23	0.318
DCP (fovea)	30.2	33.07	31.88	0.689
DCP (parafovea)	51.1	47.14	46.97	0.262
DCP (perifovea)	45.32	41.12	42.95	0.374

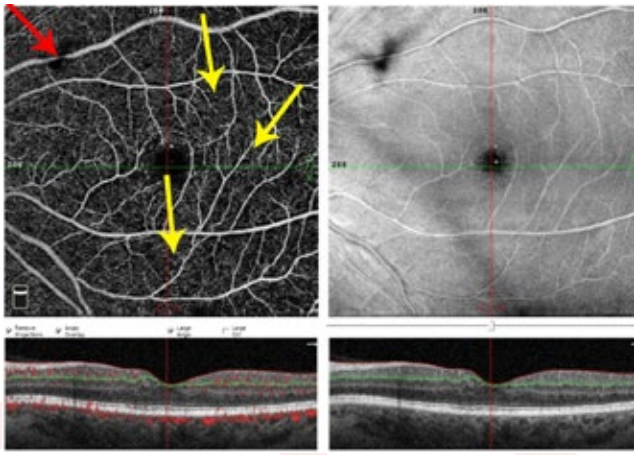
Legend: **VD** - Vessel Density; **SCP** - Superficial Capillary Plexus; **DCP** - Deep Capillary Plexus

Table 2. *Flow* OR and *Flow* CC

	Without DR	NPDR without DME	NPRD + DME	p
Flow OR	1.12	1.042	1.047	0.935
Flow CC	2.05	2.04	1.84	0.001

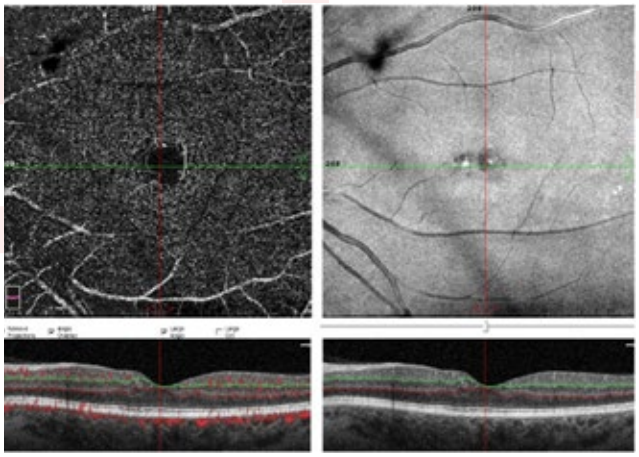
Legend: OR - Outer Retina; **CC** - Choriocapillaris

Image 3a. The superficial capillary plexus in a patient with DM but without DR



Legend: **DM** - *Diabetes mellitus*; **DR** - Diabetic Retinopathy; **FAZ** - Foveal Avascular Zone (The narrowing of the blood vessel and the surrounding ischemic area are marked by the red arrow. Smaller areas of capillary ischemia are indicated by yellow arrows. The image also shows initial enlargement of the FAZ)

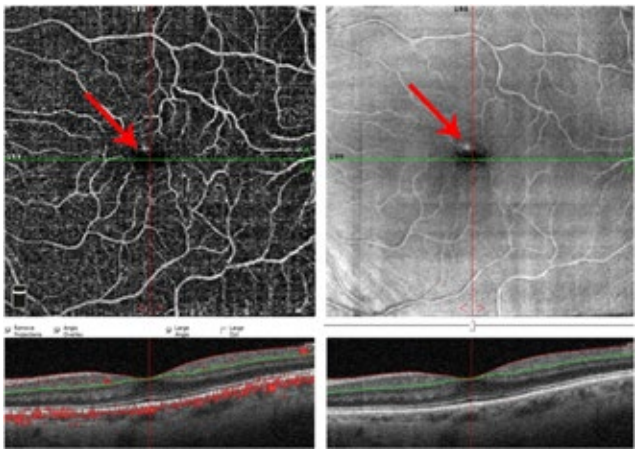
Image 3b. The deep capillary plexus in a patient with DM but without DR



Legend: **DM** - Diabetes mellitus; **DR** - Diabetic Retinopathy; **FAZ** - Foveal Avascular Zone

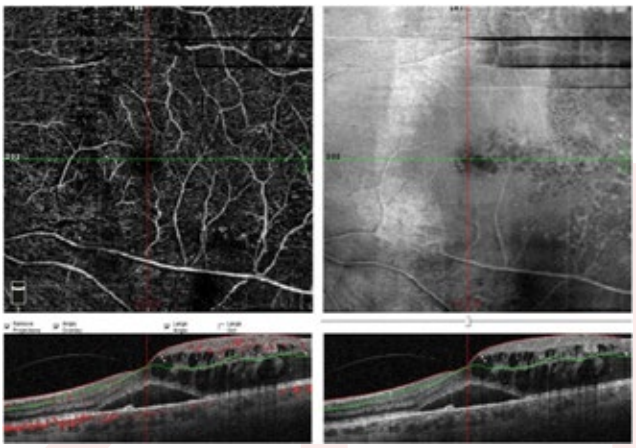
Image 4 shows the superficial capillary plexus in a patient with DM but without clinically detected signs of DR. The OCTA image reveals a microaneurysm that was not identified during the clinical examination.

Image 4. OCTA findings of the superficial capillary plexus in a patient with DM without clinically visible signs of DR



Legend: **DM** - Diabetes mellitus; **DR** - Diabetic Retinopathy (The microaneurysm, not detected during the clinical examination, is marked with a red arrow)

Image 5a. The superficial capillary plexus in a patient with DME



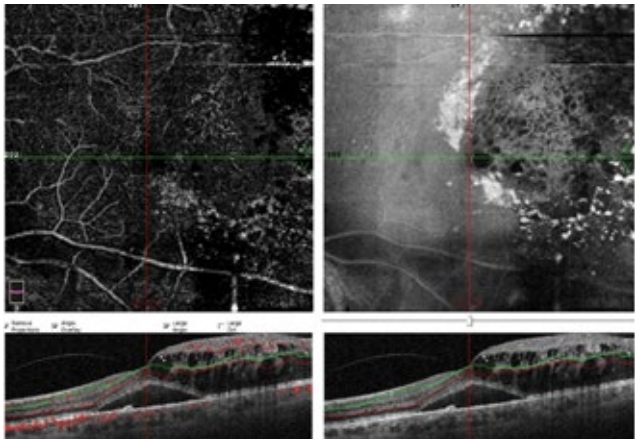
Legend: **DME** - Diabetic Macular Edema

Images 5a and 5b depict the superficial and deep capillary plexus in a patient with diabetic macular edema (DME).

Discussion

The findings of this study indicate that CMT is highest in the group with DME, which is an expected result given the presence of intraretinal fluid leading to macular thickening. The average value of FAZ did not differ between the groups of participants. Moreover, compared to data from other studies, the FAZ area in all three groups of participants corresponds to the values of healthy individuals. Reviewing various articles, it was found that the range of FAZ values in healthy individuals ranges from 0.25 to 0.40 mm^2, in diabetics without DR from 0.34 to 0.54 mm^2, and in diabetics with NPDR[20] from 0.40 to 0.46 mm^2.

Image 5 b. The deep capillary plexus in a patient with DME



Legend: **DME** - Diabetic Macular Edema

When it comes to capillary density, observing the entire macular region in SCP, the study results showed a progressively increasing VD between the groups of subjects. The lowest density was found in subjects without DR changes, slightly higher in those with NPDR, and the highest in those with NPDR and DME. A statistically significant difference was found in these values between the first and third group. These results do not match the findings available in the literature, which show a decrease in VD in the entire macular region in SCP and DCP in those with NPDR compared to those without clinically visible changes in diabetic retinopathy[21]. Such findings could be attributed to the difference in the age of the subjects (the first group had a higher average age of 72 years compared to the average age of subjects in the second and third groups of 66 and 67.4 years). Looking only at the foveal region, Fariba and colleagues did not find a statistically significant difference in SCP between groups without DR and those with NPDR, which is consistent with our results. However, when observing the parafoveal region, the authors found a statistically significant difference between the two mentioned groups[21]. In this study, such differences were not found, and the VD in the NPDR group was slightly higher than in the group without changes (47.69 compared to 46.48).

Many researchers have found a statistically significant decrease in VD in both SCP and DCP in various forms of DR compared to healthy controls[22-24]. Other authors even find this difference between healthy controls and patients with DM without DR[25, 26]. This study did not have a control group of healthy subjects, which is a limitation that should be addressed in future research.

Interesting results were also obtained by Sambav and colleagues, who investigated VD in both capillary layers, but specifically in the parafoveal and perifoveal rings. They concluded that in addition to the statistically reduced VD in the SCP and DCP compared to controls in the NPDR group, the reduction in VD in the DCP was significantly greater than in the SCP ($p < 0.05$), and the reduction in the perifoveal region was greater than in the parafoveal region ($p < 0.05$)[27]. Some authors only investigated VD in the DCP in the parafoveal region and found its reduction compared to healthy controls in the NPDR group, but not in diabetics without DR[28]. Karnevali investigated only diabetics without DR and found a reduction in VD compared to healthy controls, but only in the DCP ($p < 0.05$), while this difference was not statistically significant in the SCP[29]. The contradictory results in the literature are also evidenced by Mershi's study, which did not find a statistically significant difference in values of both FAZ and VD in the SCP, while this difference was statistically significant ($p=0.04$) between patients without DR and healthy controls[30].

The results of this study, which showed a significant reduction in blood flow through the choriocapillaris (flow CC) in the group of diabetic patients with DME compared to the first two groups (without DR and with NDPR but without DME), support the rare findings in the literature. When it comes to blood flow through the choriocapillaris in diabetic patients, research is still in its infancy. Yining et al. investigated flow deficits (FD) in the choriocapillaris, which were increased in the diabetic group compared to the healthy control group. FD was calculated using additional software and represented the proportion of the area with defective blood flow to the overall choriocapillaris region covered by the OCTA image[31]. Similarly, Yaoli et al. found a reduction in choriocapillaris blood flow signal density (CCBFSD) in diabetic patients compared to healthy controls[32]. Felipe et al. also showed a decrease in choriocapillaris perfusion density (CPD) in diabetic eyes compared to healthy controls, including the entire choriocapillaris region covered by the image, as well as the foveal and parafoveal regions[33].

In addition to the mentioned limitation of the lack of a healthy control group, the limitations of the study whose results are presented in this paper include a small number of participants per group, as well as the absence of matching participants by age and gender.

Conclusion

In this study, a significant difference was found in the blood flow in the choriocapillaris between patients without DR and those with changes in DR, with or without DME. These results are important in terms of investigating OCTA as a diagnostic and prognostic tool for diabetic maculopathy. Additionally, a difference was observed in the density of perfusion in the superficial capillary plexus, but in the opposite direction of what was expected, which is most likely due to the average age of the subjects in the examined groups. Given this, this study represents an introduction to planned further research on a larger number of subjects, which will contribute to the view of OCTA as a new technique for visualizing and quantifying vascular changes in terms of early diagnosis of subclinical diabetic retinopathy, as well as monitoring existing changes in the retina in individuals with type 2 diabetes mellitus.

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Declaration of interest statement: None

Received: 26. 02. 2023.
Accepted: 04. 03. 2023.
Online: 01. 06. 2023.