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Early microvascular changes in patients with prediabetes evaluated by optical coherence tomography angiography

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Abstract

Background: Timely detection of early microvascular changes in patients with prediabetes could help reduce the likelihood of progression of diabetes-related retinal complications.
Aim: To determine early microvascular changes in patients with prediabetes using optical coherence tomography angiography (OCT-A).
Methods: In this single-center retrospective case-control study, macular OCT-A images of superficial capillary plexus (SCP) and deep capillary plexus (DCP) were analyzed in non-diabetic controls, and prediabetic and diabetic subjects. A quantitative analysis was performed using ImageJ software of the foveal avascular zone (FAZ) area, acircularity index (AI), perfusion density (PD), and vascular length density (VLD).
Results: A total of 94 eyes of 53 patients were included in this study. The global mean age was 57.7 years, 39.6% men and 60.4% women. In SCP, the mean PD was 0.283 ± 0.15, 0.186 ± 0.720, and 0.186 ± 0.07 in non-diabetic controls, and prediabetic and diabetic groups, respectively. The mean VLD was 8.728 ± 3.425 in non-diabetic controls, 6.147 ± 1.399 in prediabetic group, and 6.292 ± 1.997 in patients with diabetes. The comparison of prediabetic patients and controls shows statistical differences between PD and VLD in both plexus SCP ($p = 0.002$ and $p = 0.001$, respectively) and DCP ($p = 0.005$ and $p = 0.002$, respectively). The mean area of FAZ in patients with diabetes and normal individuals was 0.281 and 0.196 mm^2, respectively ($p < 0.001$). AI was higher in the control group (0.87 ± 0.14) and prediabetic group (0.80 ± 0.17) compared to diabetic patients (0.64 ± 0.19). There were no differences in FAZ area and AI between prediabetic and non-diabetic controls.
Conclusion: PD and VLD demonstrated to be early microvascular changes in prediabetic patients evaluated by OCT-A. No alterations of FAZ were evidenced in this group.

Keywords: acircularity index, foveal avascular zone, optical coherence tomography angiography, perfusion density, prediabetes, vascular length density

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Introduction

Diabetes mellitus (DM) is described as 'the epidemic of the 21st century'[1] and is a devastating disease with high socioeconomic burden. It affects at least 347 million people worldwide with an expected increase to 629 million by 2045.[2] In Latin America, the negative effect of DM has also been notable, with prevalence rates that vary ranging from 5.5% to 13.6%.[3]

Diabetes-related complications include diabetic macular edema (DME) and diabetic retinopathy (DR) with an estimated prevalence of 3.2 million by 2020.[4] They represent common causes of preventable visual loss. Research aimed at new standpoints for their timely detection and treatment is essential to reduce their impact.

'Prediabetes' is the term which comprises elevated glycemic levels that do not fulfill the criteria of DM, including impaired two-hour glucose tolerance test (GTT) of 140–199 mg/dL or impaired fasting plasma glucose (FPG) of 100–125 mg/dL or glycosylated hemoglobin (HbA1 C) of 5.7–6.4%. This category represents the state of increased risk to develop DM and cardiovascular diseases compared to age-matched controls.[5] On this account, its prompt recognition is crucial to reduce the likelihood of progression and related retinal complications.

Recent studies have focused on biomarkers in DM. A biomarker is a defining characteristic, measured as an indicator of biological and pathogenic processes or responses to an exposure or intervention.[6] Its identification is valuable as it broadens clinical knowledge, contributing to the best understanding of the pathophysiological mechanisms and providing the basis to predict treatment response.

Several clinical, biochemical, and molecular findings have been described in DM[6] particularly in DR and DME. New technologies in different retinal diseases have emerged, like optical coherence tomography (OCT) and OCT angiography (OCT-A) being tools of diagnosis, monitoring, and prediction of response to treatment.[6–17]

It is well-known that the primary ocular injury target of DM is the retinal microvasculature.[11] Several imaging studies to assess retinal vasculature have been developed, specifically, retinal angiography optimized the value of fundoscopy, motivating the interest in vascular analysis tools, such as the retinal vessel analyzer (RVA)[18] and more recently integrated or nonintegrated analytic software of OCT-A[19] and artificial intelligence[20] that aim to increase the detection of more early changes.

Some studies have showed subclinical microvascular changes at OCT-A in patients with DM without DR, including decreased parafoveal vessel density, enlargement of the foveal avascular zone (FAZ), and capillary non-perfusion.[21–23] Specifically, in type 1 DM, perfusion density (PD) and some structural findings such as retinal nerve fiber layer and ganglion cell complex thickness have also been described.[23,24] To the best of our knowledge, these and other vascular findings have not been evaluated in a prediabetic population.

The prognosis of DR and DME has improved over the last few years due to better imaging technologies and the recognition of imaging features susceptible to early treatment.[13] The establishment of early diagnostic features in patients with prediabetes could reinforce the advances achieved thus far. The present study opens the door to new research under this condition often disregarded despite its relevance, to achieve that, it was proposed to identify early microvascular changes in prediabetes, primarily assessing the role of VLD, PD, and FAZ abnormalities as biomarkers and secondarily seeking to figure out differences in the comparison with non-diabetic controls and patients with diabetes.

Methods

This was a single-center retrospective case-control study was developed from September 2019 to January 2020. The clinical records of all participants were recruited at FOSCAL Internacional clinic, Floridablanca, Colombia and informed consent was obtained from all participants. The study was conducted according to Helsinki declaration principles. This investigation was approved by the institutional revision committee. Approval from ethics committee was not required: according to the 8430 resolution expedited by the Health and Social protection Ministry in Colombia, observational retrospective studies are considered 'without risk'.

Patient eligibility

Inclusion criteria. Individuals of 18–80 years of age were evaluated by OCT-A with the following examinations (carried up to a month earlier to OCT-A): FPG, two-hour GTT, and HbA1C.

All patients were evaluated through a dilated indirect fundus examination by a single retina specialist (J.D.A.) and stereoscopic color fundus photography in seven standard fields (30°) as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group,[25] used to classify diabetic retinopathy and other retinal diseases. In addition, the patients received clinical and paraclinical assessment by a specialist in Internal Medicine and Endocrinology (G.A.P.-S.). Renal and liver function tests (serum creatinine, microalbuminuria levels, and ALT and AST tests measure enzyme) were evaluated.

There were established three groups of evaluation:

Group 1: Non-diabetic controls. Subjects were assigned as non-diabetic controls based on the following criteria: impaired FPG < 100 mg/dL, impaired two-hour GTT < 140 mg/dL and HbA1c < 5.7%.

Group 2: Prediabetic patients. The patient was classified as prediabetic if presented impaired two-hour GTT of 140–199 mg/dL or impaired FPG of 100–125 mg/dL or HbA1c: 5.7–6.4% according to ADA 2020 definition.[5]

Group 3: Diabetic patients. The diabetic patient was defined if it presents of any of the following characteristics: FPG ⩾ 126 mg/dL, two-hour GTT ⩾ 200 mg/dL, HbA1 C ⩾ 6.5%, or symptoms of hyperglycemia, or hyperglycemic crisis plus a random plasma glucose ⩾ 200 mg/dL.[5] Some patients presented non-proliferative diabetic retinopathy according to stereoscopic color fundus photography in seven standard fields (30°) evaluation as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS).

Exclusion criteria

Proliferative diabetic retinopathy: Presence of clinical visible neovascularization, and vitreous or pre-retinal hemorrhage.

Diabetic macular edema: Presence of subfoveal neurosensory retinal detachment, intraretinal cystoid spaces, or mean central subfield thickness > 250 μm.[26]

Macular ischemia: FAZ area enlarging more than 1000 μm in the greatest diameter measured by OCT-A.[27]

Also, other vascular, neurological, and degenerative retinal pathologies (age-related macular degeneration, retinal vascular occlusions, hypertensive retinopathy, glaucoma, pseudophakic macular edema, epiretinal membrane posterior uveitis, and history of vitreoretinal surgery), arterial hypertension, peripheral vascular disease, heart failure, kidney disease, liver disease, carotid atherosclerosis, autoimmune diseases, and acquired immunodeficiency syndrome (AIDS).

Instrument of evaluation

Swept-Source OCT-A, DRI OCT-1 Triton (Topcon, Tokyo, Japan), and IMAGEnet® 6 Digital Imaging System software were used. Only one retina specialist interpreted the images, under the supervision of a second investigator. Automatic segmentation was performed on all images: superficial capillary plexus (SCP), deep capillary plexus (DCP), and, if required, manual segmentation was also performed.

The following variables were analyzed and measured: FAZ area, and acircularity index (AI) of FAZ, PD, and VLD. Quantitative evaluation of OCT-A images of 3 × 3 mm, 6 × 6 mm, and 9 × 9 mm OCT-A maps were used for quantitative analysis. All images were saved and analyzed anonymously and masked. All of these parameters were evaluated using ImageJ software, version 1.51 (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). The SCP slab was segmented from the internal limiting membrane (ILM) + 2.6 μm to the inner plexiform layer (IPL) / internal nuclear layer (INL) + 15.6 μm, whereas the DCP was segmented between IPL / INL + 15.6 μm and IPL / INL + 70.2 μm.

The software of imaging processing (ImageJ analysis)

All images were exported and analyzed with an original resolution of 320 × 320 pixels (lateral resolution of 9.4 μm for 3 × 3 mm images and lateral resolution of 18.7 μm for 6 × 6 mm and 9 × 9 mm). The 3 × 3 mm images were used to statistical calculation. The FAZ profile was delineated manually using the 'hands-free selection tool' on SCP and DCP images, and the software automatically calculated the FAZ area. AI was measured using the following equation: FAZ AI = $4\pi \times$ area / perimeter^2. AI is the expression of the regularity of shape: the closer its value is to 1, the more the shape resembles a perfect circle. Perimeter was defined as the length of the outside boundary of the selection, which is a measure that ImageJ program performed automatically.

The images were converted into 8-bit files, and the 'Otsu threshold method' was applied before performing automatic measurements. Otsu's threshold method uses a bimodal distribution and determines the optimal threshold by minimizing the variance and maximizing the interclass variance. The command used to select this option was 'setAutoThreshold("Otsu dark stack")'. Since the Otsu threshold method is automatic, it was not required to place any numerical parameters.

PD in SCP and DCP was calculated in binarized images as the ratio between the entire perfused

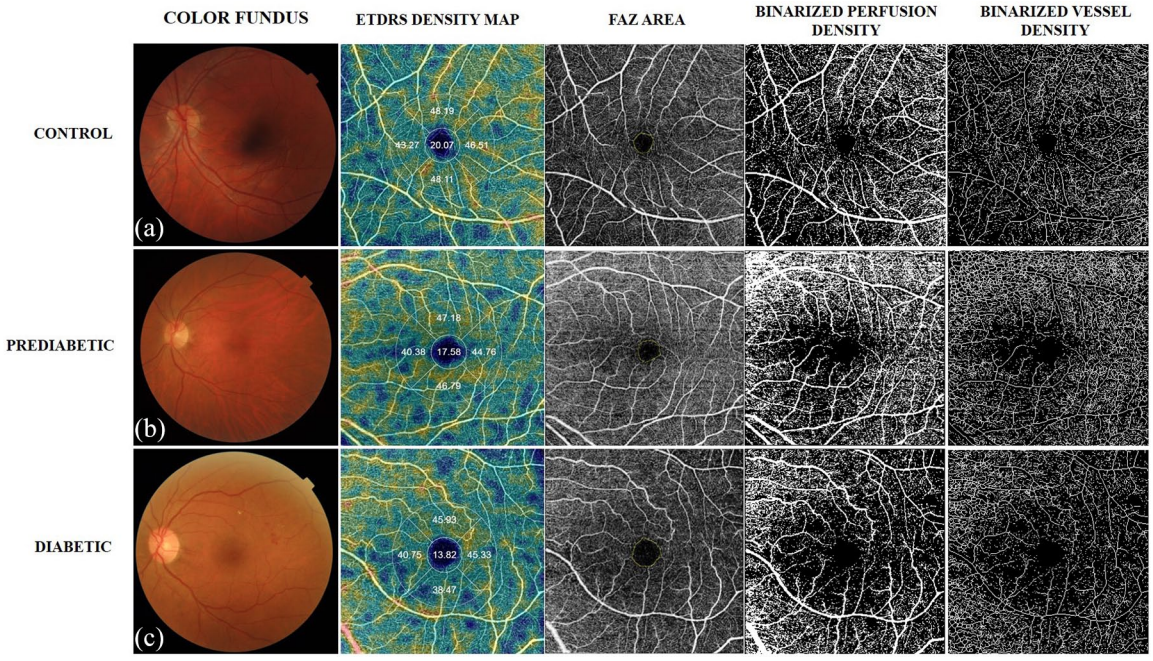

Figure 1. Comparison of different imaging modalities and variables in a non-diabetic control, and prediabetic and prediabetic patients. Images of SCP of a non-diabetic control (a), prediabetic (b) and a diabetic patient (c). The posterior pole (column 1) in the diabetic-control and prediabetic patient is spared, whereas multiple hemorrhages and hard exudates are present in the diabetic patient. The ETDRS density map (column 2), only show the central and paracentral VLD, therefore, binarized images using images by ImageJ software were required to calculate the average VLD (column 5); note the loss of perfusion areas in the prediabetic patient compared to the non-diabetic control. A significant enlargement of FAZ area (column 3) was present only in diabetic patients, compared to prediabetic and non-diabetic controls. The binarized PD images (column 4) present early changes in prediabetic patients.
DM, diabetes mellitus; FAZ, foveal avascular zone; PD, perfusion density; SCP, superficial capillary plexus; VLD, vascular length density.

area in pixels and the total area of the image in pixels; the VLD in SCP and DCP was calculated after skeletonization of the binarized image (Figure 1); it is a measure of the statistical length of moving the blood column. The skeletonization process reduces the entire diameter of the container to 1 pixel; therefore, VLD has the advantage of not being influenced by the vessel's size.

Statistical analysis

Data were obtained from medical records and OCT-A. Descriptive statistics were performed using absolute and relative frequency distribution for qualitative variables, and mean value and standard deviation were used for quantitative variables. The normal distribution of the variables was confirmed with the Kolmogorov–Smirnov test. Chi-square test was used to compare the categorical variables. The ANOVA test was used for multiple comparisons, with the post hoc analysis (Tukey's test). The statistical analysis was performed using SPSS v20.0 statistical software for Windows (SPSS Inc., Chicago, IL, USA), and the statistical significance level was established at $p < 0.05$.

The total sample size calculated for this case-control study was 66, taking into account a power of 80% and a confidence level of 95%.

Results

In total, 94 eyes of 53 non-diabetic controls, and prediabetic and diabetic patients were distributed in three groups. The mean age was 57.7 years, 39.6% ($n = 21$) were men and 60.4% ($n = 32$) were women. Demographic characteristics of all patients are elucidated in Table 1. Three eyes presented non-proliferative diabetic mild diabetic retinopathy in the diabetic group.

The comparison of microvascular changes by OCT-A of 3×3 mm maps between groups was presented in Table 2.

Mean PD presented significant statistical differences between prediabetic and non-diabetic controls in

Table 1. Demographic data of non-diabetic controls, and prediabetic and diabetic patients.

	Global	Non-diabetic controls	Prediabetics	Diabetics	*p*-value
Age, mean ± SD (range)	57.7 ± 13.1 (24.0–80)	50.3 ± 16.1 (24.0–82.0)	58.3 ± 7.2 (44.0–69.0)	63.7 ± 10.2 (41.0–77.0)	< 0.001*
Gender, *n* (%)					
Male	21 (39.6)	7 (13.2)	1 (1.9)	15 (28.3)	< 0.001*
Female	32 (60.4)	13 (24.5)	12 (22.6)	7 (13.2)	
Laterality, *n* (%)					
RE	48 (51.1)	16 (17.0)	13 (13.8)	19 (20.2)	0.967
LE	46 (48.9)	16 (17.0)	13 (13.8)	17 (18.1)	
Number of eyes	94	24	26	28	

LE, left eye; RE, right eye; SD, standard deviation.
*$p < 0.05$.

Table 2. Comparison of microvascular changes by OCT-A in non-diabetic controls, and prediabetic and diabetic patients.

	Global	Non-diabetic controls	Prediabetics	*p*-value*	Diabetics	*p*-value**
Perfusion density (PD) SCP, mean ± SD (range)	0.216 ± 0.01 (0.558–0.705)	0.283 ± 0.15 (0.813–0.750)	0.186 ± 0.720 (0.558–0.345)	0.002	0.186 ± 0.073 (0.651 –0.404)	< 0.001
DCP, mean ± SD (range)	0.196 ± 0.33 (0.03–0.821)	0.258 ± 0.11 (0.753–0.821)	0.186 ± 0.22 (0.659–0.772)	0.005	0.065 ± 0.23 (0.030 –0.120)	< 0.001
Vascular density (VD) SCP, mean ± SD (range)	7.081 ± 2.712 (2.377–18.142)	8.728 ± 3.425 (3.059–18.142)	6.147 ± 1.399 (2.734–8.546)	0.001	6.292 ± 1.997 (2.37–11.060)	< 0.001
DCP, mean ± SD (range)	6.614 ± 2.076 (1.585–12.841)	7.219 ± 1.702 (3.328–10.425)	5.422 ± 1.422 (3.063–8.613)	0.002	6.937 ± 2.437 (1.585–12.841)	0.002
FAZ Area SCP, mean ± SD (range)	0.234 ± 0.084 (0.137–0.780)	0.196 ± 0.031 (0.143–0.275)	0.215 ± 0.041 (0.138–0.302)	0.614	0.281 ± 0.114 (0.137–0.780)	< 0.001
DCP, mean ± SD (range)	0.312 ± 0.108 (0.177–0.733)	0.261 ± 0.039 (0.177–0.359)	0.274 ± 0.044 (0.208–0.401)	0.852	0.388 ± 0.140 (0.209–0.733)	< 0.001
Acircularity index (AI) SCP, mean ± SD (range)	0.76 ± 0.20 (0.20–1.24)	0.87 ± 0.14 (0.59–1.12)	0.80 ± 0.17 (0.53–1.24)	0.233	0.64 ± 0.19 (0.20–1.19)	< 0.001
DCP, mean ± SD (range)	0.76 ± 0.50 (0.20–1.24)	0.86 ± 0.30 (0.50–1.1)	0.79 ± 0.14 (0.52–1.23)	0.07	0.65 ± 0.22 (0.19–1.18)	< 0.001

AI, acircularity index; DCP, deep capillary plexus; FAZ, foveal avascular zone; OCT-A, optical coherence tomography angiography; PD, perfusion density; SCP, superficial capillary plexus; SD, standard deviation; VD, vascular density.
**p*-value calculated comparing non-diabetic controls versus prediabetics. ***p*-value calculated comparing the three groups.

SCP ($p = 0.002$) and DPC ($p = 0.005$). This difference was also present when the control group was compared to the diabetic group ($p = 0.001$).

The mean VLD was statistically lower in diabetic both in SCP and DCP. In the SCP, the mean VLD was minor in non-diabetic controls and prediabetic group compared to diabetic group ($p = 0.001$). The same comparison was observed in DCP ($p = 0.002$). The mean PD and VLD were lower in SCP and DCP in the prediabetic group compared to controls.

The mean FAZ area was 0.196 ± 0.031 mm^2 in the control group, 0.215 ± 0.041 mm^2 in the prediabetic group, and 0.281 ± 0.114 mm^2 in the group of patients with diabetes ($p \leqslant 0.001$). Significant differences were observed in the FAZ area and AI between all groups ($p \leqslant 0.001$) (Figure 1), except in prediabetics versus controls, $p = 0.614$ and $p = 0.233$ to FAZ and AI, respectively. AI was lower in the prediabetic (0.80 ± 0.17) and diabetic (0.64 ± 0.19) groups in comparison with the control group (0.87 ± 0.14).

In both non-diabetic controls and prediabetic group, no qualitatively visible areas of capillary drop-out were observed. In the group of patients with diabetes, this was observed in 8.3%.

Discussion

A comparative structural analysis of microvascular changes occurring in the macular area in non-diabetic controls, and patients with prediabetes and diabetes was performed in the present study. Remarkable alterations of some OCT-A parameters including PD and VLD were revealed. Hypothesized PD and VLD could be considered as early biomarkers of prediabetes.

OCT-A has been an imaging tool of relevance to assess patients with DM,[22,28] allowing the characterization of microvascular findings in early stages of DR and preclinical DR, comprising changes in the FAZ area and decreased average and parafoveal VLD and PD compared to controls.[22–33]

The reproducibility of these variables has been documented in diverse populations of Asia,[21,31] Europe,[32,34] and North America[23] and employing different OCT-A devices as revealed by Vujosevic *et al.*[21] who employed different OCT-A devices as revealed in a comparative study demonstrating the ability of two different SS OCT-A instruments (DRI-Triton Plus and PLEX Elite) to identify the changes of PD and VLD in patients with DM without DR. The main body of evidence is focused on population with an established diagnosis of DM but fails to assess if these findings begin earlier in the disease process. These results highlight the need to establish if these features could serve as biomarkers of microvascular damage in patients with prediabetes.

Decreased PD has demonstrated controversial results in patients with DM without DR. Previous studies have reported the impairment of PD in patients with DR,[21,35] but no significant differences between non-diabetic and diabetic eyes without DR. In contrast, the present study shows a considerable decrease in the PD of SCP and DCP in eyes with prediabetes versus controls. This finding is in agreement with other investigations in samples with diabetes without clinical manifestations of DR.[33,36,37] Recently Khalil *et al.*[36] illustrated in a cross-sectional study using AngioPlex OCT-A a statistical decrement of PD ($p < 0.001$) in patients with type 2 DM. The absence of OCT-A imaging evidence on prediabetic populations precludes a direct comparison and allows only to contrast our results to diabetic patients with no apparent DR. The discrepancy concerning PD among the studies could be attributable to the use of different methods of imaging processing and analytic algorithms which could impact the repeatability and reproducibility of data obtaining. This research has employed ImageJ software version 1.51 and thus future investigations with this and other methods are required.

In essence, decreased PD might be a feature of early microvascular damage in prediabetic status and its presence could concur with the decreased VLD as a result of direct vascular damage of hyperglycemia.

Vessel density also stands as an early marker of microvascular damage in the prediabetic group. Previously, similar results were noticed in patients with DM when compared to non-diabetic patie nts.[22,32,35–37] Some investigations have exclusively demonstrated these vascular changes in DCP of type 1 and 2 diabetic patients without clinical signs of DR,[32] in contrast from the present study which exposes a decreased VLD both in SCP and DCP. This result was also observed by Oliverio *et al.*,[33] who identified the involvement of both plexuses in type 1 and 2 DM without DR and significant differences in FAZ, especially in those with more than 10 years of evolution.

Two postures diverge regarding the compromise of VLD in DCP in patients without clinically evident DR. Some investigators such as Simonett *et al.*[23] and Carnevali defend that DCP is the first to be affected, hence the primary injury occurs at this level. Similarly, the presence of microaneurysms has been initially evidenced in DCP in the early stages of DR.[38] Oppositely, Cao *et al.*[22] and Dimitrova *et al.*[31] have conducted investigations of larger cohorts documenting compromise of both plexus. A noticeable characteristic involved in the

studies of Simonett *et al.*[23] and Carnevali *et al.*[32] corresponded to the fact that all cases presented type 1 DM, whereas patients with type 2 DM were assessed by Cao *et al.*[22] and Dimitrova *et al.*[31] In such manner, it would be hypothesized that type 2 DM is related to the reduction of the VLD in DCP, which could be a subject of debate, thus complementary studies are required. On the other hand, it seems that type 2 DM shows more alterations in the FAZ respect to type 1 DM, as shown by Fleissig *et al.*[39]

PD and VLD could be designated as specific changes in patients with early DR and prediabetes. The deterioration of these parameters could be presented as a consequence of pericytes reduction in small branching vessels resulting in reduced branching complexity of retinal vasculature.[8] Although the development of DR has not been related to the prediabetic state, patients in this category have been linked to and increased risk of cardiovascular disease (RR = 1.13–1.30), coronary disease (RR = 1.10–1.20), stroke (RR = 1.6–1.20), and mortality rates (RR = 1.13–1.32). Many public health policies and in-office physician efforts are directed toward detecting these higher risk patients on which early measures could alter de natural history of disease. The use of a fast non-invasive method such as OCT-A to assess microvascular retinal injury could improve our understanding of the effects of hyperglycemia on retinal plexus and provide a basis to indirectly assess systemic vasculature and organ damage.

Previous studies using OCT-A have identified enlargement of FAZ in DR documenting a high correlation of FAZ area with the severity of the disease.[12] This investigation revealed that in the presence of diabetes, FAZ measurements deviate noticeably from controls. It was demonstrated significant differences of FAZ area and AI between controls and diabetic patients; exhibiting agreement with other studies in the literature,[11,12,30,40] in which these measurements are markedly affected as DR worsens.

Although FAZ has been typically described as circular or elliptical in healthy individuals, it can be altered in the presence of vascular pathology, it can be altered.[30] This study showed decrement of AI in diabetic patients compared to other groups; nonetheless, there were no differences between non-diabetic controls and prediabetics, being consistent with previously described in patients with diabetes without DR.[22,23,32] Therefore, the loss of AI demonstrates to be an early parameter of FAZ changes in DR patients, but not in prediabetics, meaning that FAZ regularity is gradually altered as a hallmark of progression, induced by DM. A preserved FAZ morphology with a decreased DP and VLD in prediabetics could suggest that initial changes of retinal vasculature in response to hyperglycemia could occur in the extrafoveal region.

There are few available data of microvascular changes at OCT-A in states of hyperglycemia without DR. We analyzed prediabetic patients using a SS OCT-A device with a longer wavelength (1050 nm), thus having a better ability to penetrate deeper into the tissues. ImageJ software was a reliable method to image analysis; there it can be used in other studies.

The limitations of this investigation include the small sample size of patients and the lack of homogeneity in the number and some characteristics of groups, particularly the age was significantly different, this could interfere with the interpretation of PD, which decreases physiologically with age,[40] Likewise, a group of patients was evaluated in both eyes, which represents a bias that can lead to limiting the statistical significance of the results, we try to include a greater number of eyes, especially considering that in many patients the pathology can present asymmetrically. Although patients with severe diabetes-related changes such as proliferative diabetic retinopathy and DME were excluded, some patients with mild non-proliferative diabetic retinopathy were included, thus limiting the interpretation of the data, in the comparison of the healthy and prediabetic patients with diabetics. Another critical limitation of current OCT-A devices, is the precision of the segmentation algorithms, particularly in diseases accompanied by significant disruption of retinal layers.

It is expected that the results of this work may contribute in the future to a possible therapeutic impact in patients with systemic complications related to diabetes mellitus. Since the visualization and direct measurement of retinal microvascular changes could be an evaluation gateway for changes that develop in other organs, it could arouse interest among internal medicine and endocrinology specialists in evaluating the use of early therapeutic tools in prediabetes.

We do not propose the results of this research suggest an ophthalmological treatment should be carried out, but rather a surrogate detection, to infer that there may be alterations in other organs, through a non-invasive, safe and affordable examination such as OCT-A.

In brief, OCT-A demonstrates a significant reduction of capillary PD and VLD both in SCP and DCP in eyes with prediabetes. These findings highlight the potential role of OCT-A in early retinal vascular monitoring and quantification in prediabetes.

Conclusion

This study documents early microvascular changes occurring in the macular region of the prediabetic population. Based on these results, we suggest that PD and VLD could be early indicators of microvascular damage in prediabetes, based on the high impact of this disease in diverse cardiovascular events. More extensive longitudinal studies are needed to better understand the extent of microvascular injury in very early hyperglycemic stages.

Author contribution

Study design: JDA, FJA, MMP, RMSA. Data collection: FJA, MMP, GAP, ATH, SJG, EJV, YP. Paper writting: JDA, FJA, MMP, RMSA, IG.

Conflicts of interest statement

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