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CENTRAL AND PERIPHERAL INVOLVEMENT OF THE RETINA IN THE INITIAL STAGES OF DIABETIC RETINOPATHY

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Purpose: To determine the degree of central microvascular closure using optical coherence tomography angiography in eyes of patients with type 2 diabetes with visible lesions only in the central retina or only in the periphery.

Methods: Cross-sectional study. All 127 eyes underwent ultra-widefield fundus photography 200° examinations with OPTOS California (Optos, Dunfermline, United Kingdom) and Cirrus Angioplex optical coherence tomography angiography 3 × 3 mm acquisitions (ZEISS, Dublin, CA).

Results: Twenty-five eyes showed visible lesions only in the central retina, 57 only in the peripheral retina, and 45 presented visible lesions in entire retina. The group with visible lesions only in the periphery showed definite closure in the superficial capillary plexus in 49% of the eyes, whereas the group with visible lesions only in the central seven-early treatment diabetic retinopathy study fields area showed a definite closure in 64%.

Conclusion: Central capillary closure is already present in the initial stages of diabetic retinopathy even when lesions are only visible in the peripheral retina. Capillary closure in the superficial capillary plexus is three times more frequent than in the deep capillary plexus, demonstrating earlier closure of the superficial capillary plexus. Eyes with visible lesions only in the periphery show a milder form of retinopathy.

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Diabetes mellitus is now regarded as a global epidemic where 90% of all cases are type 2 diabetes. A 2017 report estimates that the worldwide number of individuals diagnosed with diabetes reached 425 million and will increase to 693 million by 2045.[1] As a result, the occurrence of diabetic retinopathy (DR) is also expected to be rapidly increasing. Additional estimates show that a third of the diabetic individuals have manifestations of DR, but only 10% of these will present complications of vision-threatening retinopathy, which may lead to vision impairment or blindness in the working age population.[2] It is crucial therefore, as early as possible, to identify which patients are at risk of progression and development of vision loss in their lifetime.

Diabetic retinopathy vascular changes are usually detected by color fundus photography, but until recently, the field of view of these imaging techniques was restricted to the posterior pole (30–50° of extension). This means that DR angiopathy was mainly detected when macular disease was already installed and consequently when vision loss is at high risk of occurrence. With the advent of ultra-widefield imaging techniques, the retinal area that can be easily documented in just one image increased up to 200°[3] allowing a more accurate evaluation of the entire retinal microcirculation, not only in the macular area but also in the periphery.

Optical coherence tomography angiography (OCTA) allows noninvasive imaging for visualization and quantification of the retinal microvasculature in the superficial and deep capillary networks. It is nowadays essential in the study of retinal vascular diseases like DR to identify ischemia by detecting changes in vessel and perfusion densities.[4,5]

It has been suggested that the identification of peripheral lesions, using ultra-widefield fundus photography (UWF-FP), is associated with more severe disease progression.[6] However, a comparison between peripheral and central vascular changes in the initial stages of diabetic retinal disease is still lacking. It is, therefore, of interest to compare central and peripheral involvement of the retina in the initial stages of DR and their relative relevance. Can predominant central or peripheral involvement be an indicator of different retinopathy subtypes?

In this study, we have examined individuals with type 2 diabetes in a screening setting, looking at the occurrence of visible lesions in the retina and their distribution.

Methods

Study Population

This is a cross-sectional observational study in eyes of patients with type 2 diabetes. The patients included underwent best-corrected visual acuity, intraocular pressure, iCare tonometry, UWF-FP, optical coherence tomography, and OCTA at the Association for Innovation and Biomedical Research on Light and Image within the scope of a screening program for eyes with type 2 diabetes (age mean ± SD: 69.04 ± 10.68 years) that occurred between 2020 and 2022. All patients signed an informed consent, and all study procedures occurred in accordance with the terms of the Declaration of Helsinki.

Eighty-four healthy eyes (age mean ± SD: 69.24 ± 4.47 years) and 127 eyes with type 2 diabetes with DR were considered for this analysis. The following exclusion criteria were applied: 1) presence of vitreomacular traction or epiretinal membrane; 2) presence of age-related macular degeneration, retinal vein occlusion, or other disease that could affect the eye; 3) presence of diabetic macular edema; 4) glaucoma; 5) active intraocular inflammation; or 6) media opacities or other conditions that could compromise the quality of the imagens.

Demographic data and medical history information including diabetes duration, hemoglobin A1c (HbA1c) levels, concomitant medication or treatment for diabetes, blood pressure, systemic diseases such as hypertension, history of strokes or heart attacks, and smoking and alcohol habits were provided by the primary health care units with consent of the patients as part of the established screening program.

Color Fundus Photography

All patients underwent a 200° nonmydriatic UWF-FP with OPTOS California (Optos, Dunfermline, United Kingdom). After acquisition, UWF-FP images were analyzed by the OPTOS Advance Review Software (version 4.3.31). The seven-early treatment diabetic retinopathy study (ETDRS) fields grid was overlaid to the images which were then graded based on the presence and location of retinal lesions: 1) eyes with lesions only in the periphery (outside the seven-ETDRS fields); 2) eyes with lesions only in the central (inside the seven-ETDRS fields); and 3) eyes with lesions in both locations (inside and outside the seven-ETDRS fields).

Optical Coherence Tomography and Optical Coherence Tomography Angiography Acquisitions

Optical coherence tomography Macular Cube 512 × 128 and OCTA Angiography 3 × 3 mm acquisitions (Cirrus HD-OCT 5000, Zeiss, Dublin, CA) were performed in all patients to obtain both structural and vascular information, respectively. Structural optical coherence tomography composed of 128 B scans of 512 A scans were analyzed to extract central retinal thickness—average retinal thickness in the central subfield (500 μm radius circle centered at the fovea) and ganglion cells layer plus inner plexiform layer—average layer thicknesses in the 0.5 mm to 2 mm annulus centered at the fovea. Optical coherence tomography angiography acquisitions consisting of 245 clusters of 4 B-scan repetitions at the same spatial location, where

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each B scan consists of 245 A scans, were acquired and processed by the Carl Zeiss Meditec Density Exerciser (version:10.0.12787) to extract OCTA metrics, namely foveal avascular zone (FAZ) area, FAZ perimeter and FAZ circularity, skeletonized vessel density (SVD), and perfusion density (PD) for the superficial and deep capillary plexi (superficial capillary plexus [SCP] and deep capillary plexus [DCP]). These metrics were only considered for the inner ring (InR) (0.5 mm to 1.5 mm annulus centered at the fovea). Quality assessment for the vascular metrics was performed by an experienced grader. Foveal avascular zone measurements with poor delimitation were discarded from the analysis. In addition, the grader reviewed each InR quadrant for the SCP and DCP and to ensure reliability of the metrics. Criteria for measurement reliability were well-focused capillary networks and absence of cropped scans, vessel duplication, or opaque artifacts. Single low-quality InR quadrants were not considered in the analysis. If more than one InR quadrant was classified as low quality, then all InR measurements for that slab were discarded. The area of capillary nonperfusion was identified by measuring the area of intercapillary spaces calculated using the methodology previously described by our group.[7] This methodology applies morphologic operations to the binary enface slabs of the SCP and DCP to identify abnormal spaces between capillaries.

Statistical Analysis

Statistical analysis was performed using Stata 16.1 (StataCorp LLC, College Station, TX), and P-values < 0.05 were considered statistically significant. Normal distribution was assessed with the Shapiro–Wilk test and graphically verified by histogram. Demographic, systemic, and ocular characteristics continuous variables were summarized as means and corresponding standard deviations. The Mann–Whitney U test was performed to compare the control group with eyes with retinal lesions. The Kruskal–Wallis and all-pairwise post hoc comparisons with Bonferroni correction were used to evaluate the differences between eyes with DR lesions (lesions in periphery, in central seven-ETDRS fields, and in both locations).

Results

One hundred twenty-seven eyes from patients with type 2 diabetes presenting visible lesions in the fundus were included in the analysis. Of the eyes with visible lesions, 25 (20%) showed visible lesions only in central retina (inside the seven-ETDRS fields), 57 (45%) presented visible lesions only in the peripheral retina (outside of the seven-ETDRS fields), and 45 (35%) presented visible lesions in the entire retina, both inside and outside the seven-ETDRS fields (central + peripheral).

Patients' demographic data are summarized in Table 1, comparing patients with DR visible lesions with an age-matched control population.

Location of Diabetic Retinopathy Lesions in Ultra-Widefield Fundus Photography and Systemic Factors

Eyes with visible lesions in the entire retina (central and peripheral) show longer diabetes mellitus duration (18.18 ± 10.95 years, $P = 0.005$) and higher values of HbA1c ($7.67 \pm 1.37\%$, $P = 0.010$) suggesting a more advanced or severe stage of the disease. Higher HbA1c levels ($\geq 7\%$) were also found in eyes showing visible lesions only in the central retina, reinforcing the relevance of metabolic control in relation to the development of central vision-threatening retinopathy (Table 1).

Significant differences in best-corrected visual acuity ($P = 0.001$) were found when comparing eyes with visible lesions in the entire retina (central + peripheral), with eyes showing visible lesions only in the peripheral area (69.67 ± 20.54 letters vs. 81.67 ± 5.85 letters), suggesting an association between the occurrence of central capillary closure and central vision impairment. Regarding ganglion cell layer + inner plexiform layer thickness obtained from structural optical coherence tomography data, representing neurodegeneration, a significant thinning of this layer was observed in all study groups being particularly evident in the group with lesions in the entire retina (central + peripheral), again suggesting this to be a more severe retinopathy subtype.

Location of Diabetic Retinopathy Lesions in Ultra-Widefield Fundus Photography and Optical Coherence Tomography Angiography Metrics

Optical coherence tomography angiography metrics, SVD, PD, and capillary nonperfusion were calculated in all eyes. The individuals with type 2 diabetes showed a significant decrease of SVD and PD and increase of capillary nonperfusion in the InR (central retina) when compared with the control group ($P < 0.001$) (Table 1). This decrease in OCTA vascular metrics in the central macular area is more evident in eyes with both peripheral and central retina affected ($P < 0.001$), suggesting that this lesion distribution is associated with a more advanced stage of microvascular disease of the retina. On other hand, the eyes with visible lesions only in the periphery showed less capillary closure, and higher SVD and PD, indicating that these eyes had less ischemia in the central retina (Table 2).

Table 1. Comparison of Demographic, Systemic, and Ocular Characteristics Between Healthy and DR Groups

	Healthy Eyes	DR Eyes With Visible Lesions Only in the Peripheral Area		DR Eyes With Visible Lesions Only in the Central Area		DR Eyes With Visible Lesions in Both Areas		
	(N = 84)	(N = 57)		(N = 25)		(N = 45)		
	Mean ± SD	Mean ± SD	*P* (vs. H)	Mean ± SD	*P* (vs. H)	Mean ± SD	*P* (vs. H)	*P**
Demographic characteristics								
Age (years)	69.24 ± 4.47	67.12 ± 9.57	**0.040**	68.32 ± 12.47	0.567	71.87 ± 10.59	0.177	0.076
Diabetes duration (years)		12.02 ± 8.49		9.47 ± 6.16		18.18 ± 10.95		**0.005**
Systemic characteristics								
Diastolic blood pressure (mmHg)		77.35 ± 9.81		77.04 ± 8.58		74.86 ± 10.30		0.493
Systolic blood pressure (mmHg)		138.36 ± 14.97		142.65 ± 14.28		131.90 ± 12.56		**0.004**
HbA1c (%)		6.91 ± 0.98		7.43 ± 1.65		7.67 ± 1.37		**0.010**
Ocular characteristics								
BCVA (letters)		81.67 ± 5.85		77.40 ± 13.47		69.67 ± 20.54		**0.005**
IOP (mmHg)		14.98 ± 3.42		16.84 ± 4.17		14.71 ± 3.47		0.082
CRT (μm)	270.52 ± 18.07	264.32 ± 20.48	0.117	265.96 ± 22.98	0.243	265.61 ± 21.05	0.193	0.994
GCL + IPL thickness (μm)	82.53 ± 5.71	79.14 ± 6.50	**0.012**	79.24 ± 7.15	**0.022**	76.57 ± 8.38	<**0.001**	0.244
FAZ area (mm^2)	0.24 ± 0.11	0.25 ± 0.10	0.417	0.24 ± 0.09	0.568	0.26 ± 0.08	0.308	0.833
FAZ perimeter (mm)	2.07 ± 0.49	2.21 ± 0.53	0.248	2.15 ± 0.39	0.461	2.26 ± 0.40	0.067	0.544
FAZ circularity (a.u.)	0.65 ± 0.07	0.64 ± 0.08	0.556	0.65 ± 0.09	0.886	0.62 ± 0.05	0.096	0.407
SVD-InR—SCP (mm^{-1})	22.07 ± 0.69	20.50 ± 1.66	<**0.001**	19.89 ± 1.78	<**0.001**	19.13 ± 1.93	<**0.001**	**0.002**
SVD-InR—DCP (mm^{-1})	16.85 ± 2.03	16.10 ± 2.60	0.059	15.16 ± 2.44	**0.002**	13.67 ± 2.52	<**0.001**	<**0.001**
PD-InR—SCP (a.u.)	0.40 ± 0.01	0.37 ± 0.02	<**0.001**	0.36 ± 0.03	<**0.001**	0.35 ± 0.03	<**0.001**	**0.003**
PD-InR—DCP (a.u.)	0.32 ± 0.03	0.31 ± 0.04	**0.049**	0.29 ± 0.04	**0.002**	0.27 ± 0.04	<**0.001**	<**0.001**
Capillary nonperfusion—SCP (×1,000 a.u.)	12.29 ± 3.69	21.98 ± 11.71	<**0.001**	26.13 ± 13.39	<**0.001**	34.20 ± 15.22	<**0.001**	<**0.001**
Capillary nonperfusion—DCP (×1,000 a.u.)	29.58 ± 10.04	38.82 ± 18.22	**0.001**	42.63 ± 14.20	<**0.001**	52.95 ± 19.46	<**0.001**	<**0.001**

Bold values represent statistically significant alterations with $P < 0.05$ using the Mann–Whitney *U* test to compare healthy control group with diabetic groups with visible lesions, and the *Kruskal–Wallis test and all-pairwise post hoc comparisons with Bonferroni correction were used to compare between diabetic groups.

H, healthy eyes; N, number of participants; BCVA, best-corrected visual acuity; IOP, intraocular pressure; CRT, central retinal thickness; GCL + IPL, ganglion cell layer + inner plexiform layer; FAZ, foveal avascular zone; a.u., arbitrary units.

When comparing eyes with visible lesions only in the peripheral retina (outside of the seven-ETDRS fields) with eyes with visible lesions only in the central retina (inside the seven-ETDRS fields), differences were also identified. Decreased values of PD of SCP were observed only in eyes with visible lesions in the central retina ($P = 0.048$), confirming more advanced central microvascular disease in these eyes (Table 2).

When comparing eyes with visible lesions only in the peripheral retina (outside of the seven-ETDRS fields) with eyes showing visible lesions in the entire retina (central + peripheral), differences in OCTA metrics can be identified in both SVD, PD, and capillary nonperfusion with strong statistical significance differences ($P < 0.001$) in both SCP and DCP. This shows that the eyes with visible lesions in the entire retina (central + peripheral) have a more advanced stage of retinal capillary closure (decrease values of SVD and PD). It is relevant to add that best-corrected visual acuity ($P = 0.001$) is significantly decreased, and hemoglobin A1c ($P = 0.002$) is significantly increased in the eyes with visible lesions in the entire retina, both central and periphery (Table 2).

There is, indeed, also more capillary closure in the DCP, both in SVD and PD, in eyes with visible lesions in the entire retina (central and peripheral) when compared with the eyes with lesions only in the central retina (inside the seven-ETDRS fields). This shows that added peripheral involvement is associated with increased retinal microvascular disease involving the DCP (SVD $P = 0.010$; PD $P = 0.008$). Isolated peripheral involvement is also associated with increased diabetes duration ($P = 0.003$) and lower values of systolic blood pressure ($P = 0.002$) (Table 2).

When evaluating the ETDRS severity level inside the seven-ETDRS fields area, eyes with visible lesions

Table 2. Comparison of Demographic, Systemic, and Ocular Characteristics Between DR Groups

	A. DR Eyes With Visible Lesions Only in the Peripheral Area (N = 57)	B. DR Eyes With Visible Lesions Only in the Central Area (N = 25)	C. DR Eyes With Visible Lesions in Both Areas (N = 45)	*P* (A vs. B)	*P* (A vs. C)	*P* (B vs. C)
Demographic characteristics						
Age (years)	67.12 ± 9.57	68.32 ± 12.47	71.87 ± 10.59	0.705	**0.018**	0.284
Diabetes duration (years)	12.02 ± 8.49	9.47 ± 6.16	18.18 ± 10.95	0.309	**0.010**	**0.003**
Systemic characteristics						
Diastolic blood pressure (mmHg)	77.35 ± 9.81	77.04 ± 8.58	74.86 ± 10.30	0.890	0.240	0.484
Systolic blood pressure (mmHg)	138.36 ± 14.97	142.65 ± 14.28	131.90 ± 12.56	0.333	**0.009**	**0.002**
HbA1c (%)	6.91 ± 0.98	7.43 ± 1.65	7.67 ± 1.37	0.405	**0.002**	0.202
Ocular characteristics						
BCVA (letters)	81.67 ± 5.85	77.40 ± 13.47	69.67 ± 20.54	0.065	**0.001**	0.339
IOP (mmHg)	14.98 ± 3.42	16.84 ± 4.17	14.71 ± 3.47	0.081	0.538	**0.026**
CRT (μm)	264.32 ± 20.48	265.96 ± 22.98	265.61 ± 21.05	0.938	0.923	0.993
GCL + IPL thickness (μm)	79.14 ± 6.50	79.24 ± 7.15	76.57 ± 8.38	0.661	0.111	0.277
FAZ area (mm^2)	0.25 ± 0.10	0.24 ± 0.09	0.26 ± 0.08	0.995	0.544	0.717
FAZ perimeter (mm)	2.21 ± 0.53	2.15 ± 0.39	2.26 ± 0.40	1.000	0.288	0.427
FAZ circularity (a.u.)	0.64 ± 0.08	0.65 ± 0.09	0.62 ± 0.05	0.762	0.266	0.209
SVD-InR—SCP (mm^{-1})	20.50 ± 1.66	19.89 ± 1.78	19.13 ± 1.93	0.162	**<0.001**	0.075
SVD-InR—DCP (mm^{-1})	16.10 ± 2.60	15.16 ± 2.44	13.67 ± 2.52	0.134	**<0.001**	**0.010**
PD-InR—SCP (a.u.)	0.37 ± 0.02	0.36 ± 0.03	0.35 ± 0.03	**0.048**	**0.001**	0.317
PD-InR—DCP (a.u.)	0.31 ± 0.04	0.29 ± 0.04	0.27 ± 0.04	0.154	**<0.001**	**0.008**
Capillary nonperfusion—SCP (×1,000 a.u.)	21.98 ± 11.71	26.13 ± 13.39	34.20 ± 15.22	0.192	**<0.001**	**0.046**
Capillary nonperfusion—DCP (×1,000 a.u.)	38.82 ± 18.22	42.63 ± 14.20	52.95 ± 19.46	0.151	**<0.001**	**0.024**

Bold values represent statistically significant alterations with $P < 0.05$ using the Mann–Whitney *U* test.
N, number of participants; BCVA, best-corrected visual acuity; IOP, intraocular pressure; CRT, central retinal thickness; GCL + IPL, ganglion cell layer + inner plexiform layer; FAZ, foveal avascular zone; a.u., arbitrary units.

only in the central retina showed a similar severity compared with eyes with visible lesions in the entire retina (central + periphery). We can observe, however, that a higher percentage of eyes with visible lesions in the entire retina (central + periphery) have the more severe stages of ETDRS 43 to 47. In the group with visible lesions only in the central retina, six eyes (24%) were classified as ETDRS level 20, 17 eyes (68%) were classified as ETDRS level 35, and two eyes (8%) were classified ETDRS level 43 to 47. Whereas in the group with visible lesions in the entire retina (central + periphery), 11 eyes (24%) were classified as ETDRS level 20, 23 eyes (51%) were classified as ETDRS level 35, and 11 eyes (25%) were classified as ETDRS level 43 to 47 (Table 3).

Definite capillary closure was present in 61% of our type 2 diabetes population (77 of 127 eyes). Eyes with visible lesions only in the periphery showed a definite decrease in SVD of SCP of 49%, whereas eyes with visible lesions only in the central retina showed a definite decrease in SVD of SCP in 64%. Eyes with visible lesions in the entire retina (central and peripheral) showed a definite decrease in SVD of SCP of 73%. Regarding the eyes showing definite capillary closure in both SCP and DCP (20% of our type 2 diabetes population—25 of 127 eyes), 12% had lesions only in the periphery, 8% had lesions only in central retina, and 36% had lesions in both areas (central and periphery) (Table 4).

Discussion

The observations here reported confirm the complexity of DR and the variability of its presentation. Even in the initial stages of diabetic retinal disease, there are eyes that show visible lesions only in the central retina, others only in the peripheral retina,

Table 3. ETDRS Severity Level Inside Seven-Field Area

	Lesions Only in the Central Area (N = 25)	Lesions in Both Areas (N = 45)
ETDRS level 20	6 (24%)	11 (24%)
ETDRS level 35	17 (68%)	23 (51%)
ETDRS level 43–47	2 (8%)	11 (25%)

N, number of participants.

whereas in others the entire retina appears affected simultaneously. Different eyes show different regional distribution of the lesions indicating different patterns of disease presentation.

The seven-ETDRS fields color fundus photography protocol only acquires approximately 30% of the entire retinal surface, i.e., the central 90° of the retinal area. Lesions in the peripheral retina are not assessed or taken into consideration. Silva et al[8] showed that additional lesions were detectable beyond the standard ETDRS fields using UWF-FP. This suggests that DR severity assessment may be underestimated at least in some patients. The authors also suggested that patients with peripheral lesions predominance (mostly microaneurysms and hemorrhages) have a greater risk for progression to more severe stages of the disease compared with people with central lesions only covered by the seven-ETDRS fields.[9] However, the importance of regional distribution is not well understood, and its diagnostic value remains largely unknown.

A study from Bek and Helgesen reported the contribution of lesion distribution to the progression of vision-threatening DR. They describe the association of progression of DR with the early progression of lesions distant from the vascular arcades in a similar manner to hypertensive retinopathy.[10] In this study, we were able to demonstrate that the localization of lesions may be associated with specific risk factors, such as duration of diabetes and HbA1c values, which are considered to play a role in the course of the disease, offering perspectives for improved characterization of different subtypes of the retinal disease progression in diabetes. Different patterns of disease progression may, indeed, be determined not only by local characteristics of the retinal response to diabetes but also by different associated risk factors such as concomitant hypertension or poor glycemic control.

The results here presented were obtained in a screening setting and are, therefore, focused on the initial stages of diabetic retinal disease. We believe that they open new perspectives for characterization, prevention, and more efficient follow-up of diabetic retinal disease.

Correlations between these early retinal disease changes and systemic factors such as age, duration of diabetes, metabolic control as identified by HbA1c values, blood pressure levels, and presence of kidney disease should be looked for in the context of these different subtypes of diabetic retinal microvascular disease. Our results show that, when compared with those having only central lesions, eyes with lesions only in the peripheral retina belong to patients with a longer duration of diabetes. Because the central retina does not show visible lesions despite the longer duration of diabetes, this suggests a milder form of the disease. The observation that eyes with lesions both in central and peripheral retina (inside and outside the seven-ETDRS fields) are associated with higher values of HbA1c may, conversely, be indicative of a more aggressive systemic disease. Diabetes is a multifactorial disorder grouping several conditions generally categorized by a simple diagnostic criterion, hyperglycemia. Clinically distinct subtypes of T2D have been associated with different diabetic complications using clustering approaches of clinical biomarkers.[11]

Our study confirms the existence of these different subtypes of retinopathy and that definite capillary closure of the SCP occurs earlier in the disease process than definite capillary closure of the DCP. The DCP closure seems to be associated with more advanced stages of the disease. Capillary closure of the SCP in the central macula is shown in this study to be present since the initial stages of diabetic retinal disease even in eyes with visible lesions only in the peripheral retina.

Table 4. Characterization of Groups According to Decreases in SVD in SCP and SVD in DCP

	Visible Lesions Only in the Peripheral Area		Visible Lesions Only in the Central Area		Visible Lesions in Both Areas	
Decrease of SVD in SCP ≥ 2SD of healthy controls	28/57	49%	16/25	64%	33/45	73%
Decrease of SVD in SCP ≥ 2SD of healthy controls and decrease of SVD in DCP ≥ 2SD of healthy controls	7/57	12%	2/25	8%	16/45	36%

When comparing eyes with visible lesions in the central retina with eyes with visible lesions in both central and peripheral retina, the differences seem to be associated with involvement of the DCP. Capillary closure of this layer is increased in the eyes that show involvement of the peripheral retina.

Presence of definite capillary closure was identified in 49% of eyes with only peripheral lesions, 64% of eyes with only central lesions, and 73% in eyes with central and peripheral lesions. These results indicate that diabetic eyes with visible lesions only in the peripheral retina may be associated with a milder form of the disease. Capillary closure is an indicator of the degree of ischemia and may be useful to predict severity. It is also of interest to confirm that thinning of the ganglion cell layer + inner plexiform layer (indicative of retinal neurodegenerative disease) is present very early in eyes from diabetic individuals.[12] These neurodegenerative changes seem to occur independently of the topographical location of the retinal microvascular disease.

In conclusion, the topographical distribution of the initial visible lesions observed in the early stages of diabetic retinal disease seems to be relevant to identify different disease subtypes and may in the future allow to predict the risk for more rapid disease progression, thus opening the door for early intervention and prevention of more advanced disease.

Key words: diabetic retinopathy, peripheral retina, ultra-widefield imaging, color fundus photography, OCTA, skeletonized vessel density.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017;128: 40–50.
3. Rasmussen ML, Broe R, Frydkjaer-Olsen U, et al. Comparison between Early Treatment Diabetic Retinopathy Study 7-field retinal photos and non-mydriatic, mydriatic and mydriatic steered widefield scanning laser ophthalmoscopy for assessment of diabetic retinopathy. J Diabetes Complications 2015; 29:99–104.
4. Ribeiro L, Marques IP, Santos T, et al. Characterization of 2-year progression of different phenotypes of nonproliferative diabetic retinopathy. Ophthalmic Res 2022;66:228–237.
5. Marques IP, Alves D, Santos T, et al. Characterization of disease progression in the initial stages of retinopathy in type 2 diabetes: a 2-year longitudinal study. Invest Ophthalmol Vis Sci 2020;61:20.
6. Silva PS, Cavallerano JD, Haddad NMN, et al. Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. Ophthalmology 2015;122:949–956.
7. Mendes L, Marques IP, Cunha-Vaz J. Comparison of different metrics for the identification of vascular changes in diabetic retinopathy using OCTA. Front Neurosci 2021;15: 755730.
8. Silva PS, Cavallerano JD, Sun JK, et al. Peripheral lesions identified by mydriatic ultrawide field imaging: distribution and potential impact on diabetic retinopathy severity. Ophthalmology 2013;120:2587–2595.
9. Silva PS, Dela Cruz AJ, Ledesma MG, et al. Diabetic retinopathy severity and peripheral lesions are associated with nonperfusion on ultrawide field angiography. Ophthalmology 2015;122:2465–2472.
10. Bek T, Helgesen A. The regional distribution of diabetic retinopathy lesions may reflect risk factors for progression of the disease. Acta Ophthalmol Scand 2001;79:501–505.
11. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 2018;6:361–369.
12. Madeira MH, Marques IP, Ferreira S, et al. Retinal neurodegeneration in different risk phenotypes of diabetic retinal disease. Front Neurosci 2021;15:800004.