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Multimodal Retinal Imaging in Patients with Diabetes Mellitus and Association with Cerebrovascular Disease

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Keywords
Diabetes · Diabetic retinopathy · Optical coherence tomography angiography · Ultrawide field retinal imaging · Cerebrovascular disease

Abstract

Introduction: This study aimed to evaluate the association between macular optical coherence tomography angiography (OCT-A) metrics, characteristics of ultrawide field (UWF) imaging, and cerebrovascular disease in patients with diabetes mellitus (DM) with different stages of diabetic retinopathy (DR). ***Methods:*** 516 eyes of 258 DM patients were enrolled in two centers (Milan and Belfast). UWF color fundus photos (CFPs) were obtained with Optos California (Optos, PLC) and graded for both DR severity and predominantly peripheral lesions presence (>50% of CFP lesions) by two independent graders. OCT-A (3 × 3 mm), available in 252 eyes of 136 patients, was used to determine perimeter, area, and circularity index of the foveal avascular zone and vessel density (VD); perfusion density (PD); fractal dimension on superficial, intermediate (ICP), and deep capillary plexuses; flow voids (FVs) in the choriocapillaris. ***Results:*** Out of 516 eyes, 108 eyes (20.9%) had no DR, and 6 eyes were not gradable. The remaining 402 eyes were as follows: 10.3% (53) had mild nonproliferative DR (NPDR), 38.2% (197) had moderate NPDR, 11.8% (61) had severe NPDR, and 17.6% (91) had proliferative DR. A worse DR stage was associated with a history of stroke ($p = 0.044$). Logistic regression analysis after taking into account sex, type of DM, age, DM duration, and OCT-A variables found that PD and VD on ICP were significantly associated with presence of stroke and DR severity. ***Conclusion:*** OCT-A metrics show an association with the presence of cerebrovascular complications, providing potentially useful parameters to estimate vascular risk in patients with DM.

Introduction

Diabetes mellitus (DM) is one of the fastest growing health emergencies of this century, with an expected increase to 783 million worldwide by 2045 [1]. Diabetic

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retinopathy (DR) is the most common microvascular complication of DM [2] and is widely recognized as a reliable marker for DM-related complications in an individual [3]. Evidence suggests that DM patients have a 2- to 4-fold increased risk of stroke and coronary artery disease, with cardiovascular disease being the leading cause of mortality [4–9].

Increasing DR severity has been shown to be associated with an increased risk of stroke [10]. In fact, individuals with DM are more likely to develop small subcortical infarcts or lacunar strokes than those without [11]. A recent meta-analysis from 19 studies involving 45,495 DM patients reported a pooled hazard ratio of 1.62 (1.28–2.06) for the risk of DR and stroke, with a robust correlation only for type 2 DM [12].

The demonstrated relationship between DR and cerebrovascular and/or cardiovascular accident suggests a potential link between microvascular and macrovascular damage [13], where presence of DR indicates that circulation has already been damaged by the hyperglycemic state [3]. Assessing DR severity does not only provide a unique opportunity to directly visualize the morphology of systemic vascular damage in DM [2] but it also represents a non-invasive, repeatable technique that might lead to the eye being considered a novel biomarker of vascular disease risk in asymptomatic DM patients [2].

New technologies, such as ultrawide field (UWF) fundus imaging and optical coherence tomography angiography (OCT-A) allow to grade DR with greater precision. UWF fundus imaging is defined as an image that includes the far periphery of the retina, at a range of 110°–220° [14]. Studies show that lesions outside the standard 7 Early Treatment for Diabetic Retinopathy Study (ETDRS) fields seen on UWF lead to a more severe DR stage in 10–15% of eyes of DM patients [15]. The presence of predominantly peripheral lesions (PPLs) has been linked with an increased risk of DR progression over 4 years, independent of baseline DR severity and HbA1c levels [16]. However, little data are available on whether PPL's presence is associated with cerebrovascular complications and an increased risk of developing stroke or other systemic vascular complications in DM patients.

OCT-A is a fast and non-invasive imaging technique which allows a three-dimensional mapping of the retinal and choroidal vasculature and detailed evaluation of the foveal avascular zone (FAZ) [17]. OCT-A has the advantage of visualizing microvasculature with depth resolution, generating high contrast well-defined images [18] allowing evaluation of the superficial (SCP), intermediate (ICP), and deep (DCP) capillary plexuses.

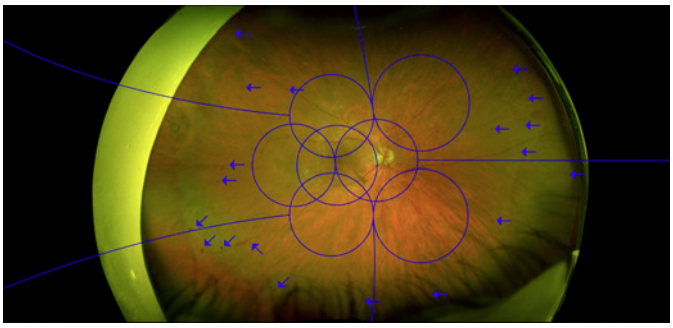


Fig. 1. Ultrawide field color fundus image showing an example of moderate nonproliferative diabetic retinopathy with PPLs, defined as the presence of >50% of lesions outside the Early Treatment for Diabetic Retinopathy Study (ETDRS) fields. The ETDRS seven-field mask was overlaid using Optos Advance (blue circles). Blue arrows point to peripheral retinal lesions.

Previous studies have linked stroke, neurodegeneration, and cognitive dysfunction with retinal findings and OCT-A metrics [19–23]. However, no studies are available on the association between stroke and OCT-A metrics in DM patients. Using retinal images to determine the risk of future systemic morbidity and mortality is an area of considerable interest [13].

The aim of this study was to investigate the association between a history of stroke and the characteristics of OCT-A metrics, DR severity, and the presence of PPL on UWF color fundus photos (CFPs). The former has been evaluated on each of the 3 retinal plexuses and the choriocapillaris (CC) in the macula to determine non-invasive retinal imaging parameters associated with systemic cerebrovascular comorbidity in patients with DM.

Materials and Methods

Altogether, 258 patients with type 1 and 2 DM were recruited at the Retina and Imaging Unit, IRCCS MultiMedica, Milan, Italy and Belfast Health and Social Care Trust, UK The exclusion criteria were as follows: age less than 18 years, presence of other vascular retinal diseases (such as central/branch retinal vein occlusion, central/branch artery occlusion, etc.), unavailable data on systemic history, poor quality OCT-A imaging (signal strength <40). The study followed the tenets of the Declaration of Helsinki with collected written informed consent from all study participants from DR institutional registry after approval by the Institutional Ethics Committee in Milan and the local audit committee in Belfast. For each patient, the following data were collected from medical records: age; duration of DM; type of DM; presence of comorbidities including history of stroke, both ischemic and hemorrhagic and transient ischemic attack; history of cardiovascular disease, including ischemic cardiopathy and myocardial infarction.

UWF Color Photos Grading

UWF-CFP obtained with Optos California (Optos plc, Dunfermline, UK) were graded by two graders independently (SV and RS) according to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales [24]. Before the grading process, the two graders harmonized the gradings, reaching complete agreement. A mask representing the ETDRS seven-field region was overlapped on the UWF-CFP using Optos Advanced option to help identify PPL. PPLs were defined as the presence of more than 50% of lesions outside the 7 standard ETDRS fields (shown in Fig. 1).

OCT and OCT-A Image Analysis

Altogether, 252 eyes of 136 patients underwent OCT and OCT-A imaging with Heidelberg Spectralis (Heidelberg, Germany) in Milan, Italy, using 10 ° × 10 ° macular scan after pupil dilation. Macular volume scan covering 20 ° × 15 ° was used for central macular thickness evaluation and to confirm the presence or absence of diabetic macular edema (DME). The full thickness retinal scan was exported and converted in 320 × 320 pixel format. The converted image was then imported into Image J (version 1.53, provided in the public domain by the National Institutes of Health, Bethesda, MD, USA), where the FAZ was manually drawn to calculate area, perimeter, and circularity index. OCT-A volume scans (10 ° × 10 ° field; 512 B-scans at 6 μm spacing; automatic real-time 5 of SCP, ICP, and DCP were exported and converted in 320 × 320 pixel format for the automatic analysis of the following metrics: perfusion density (PD); vessel density (VD); fractal dimension (FD); and CC slab which was used to estimate flow voids (FVs). All OCT-A images were checked for the quality of signal and the presence of artifacts. Only images with good quality and without artifacts (segmentation, projection, etc.) were included in the analysis.

Projection artifacts due to the presence of cysts in all 3 retinal plexuses were removed according to a previously published image processing method [25]. Briefly, a Gaussian filter was applied to the corresponding en-face SCP, ICP, and DCP images of 3 × 3 mm angio-cubes to reduce the noise; the resulting images were then binarized and dilated. Finally, black pixels due to noise were excluded from the final computation.

The automatic OCT-A image analysis was performed using MATLAB image processing toolbox and custom scripts (version 2020a, MathWorks, Natick, MA, USA). These scripts estimate PD, VD, and FD on SCP, ICP, and DCP, respectively. The FVs were estimated on the CC (shown in Fig. 2).

The PD was estimated on the binarized images. Image binarization was performed by the "imbinarize" MATLAB function. The adopted algorithm was based on an adaptive threshold, achieving a threshold based on the local mean intensity in the neighborhood of each pixel. Then, this threshold was applied to the considered pixel. The threshold computation depended on a parameter called sensitivity, which ranges from 0 to 1. Different values had been carefully considered by expert ophthalmologist who evaluated the binarized images. Thus, the best threshold value has been identified, and it was equal to 0.59.

The binarized image was used to directly evaluate the PD. The area related to the FAZ, manually outlined by an expert ophthalmologist, was excluded from the analysis. Thus, the domain was defined as the set of pixels not belonging to the FAZ area. The PD was computed as follows:

$$PD = \frac{Area_{Perf}}{Area_D} \times 100$$

where $Area_{Perf}$ was the number of white pixels in the binarized image, and $Area_D$ was the total number of pixels belonging to D. VD was computed using the same binarized image as for PD, excluding FAZ here as well. The binarized image was processed by the bwskel MATLAB routine, performing the so-called skeletonization. VD was computed as the percentage of the ratio of the total vessel area (white pixels of the skeletonized image) and the total area belonging to D.

FD used the same skeletonized image and based FD estimation on the box-counting method. It counted the N bidimensional boxes of size R that contain all the white pixels [26]. Then, the FD was computed as follows:

$$FD = \frac{\log\ (N)}{\log\ (R^{-1})}$$

Finally, the FV has been computed by adopting the compensation method proposed by Zhang et al. [27].First, a Gaussian filter of size 3 × 3 to the en-face DCP image was applied, then the filtered image was inverted and subtracted from the DCP one. The output of this phase was the compensation image. This image was then subtracted to the CC, and the mean (I_{mean}) and the standard deviation (I_{SD}) were computed. These two values were then used to binarize the image.

$$I(i,j)_{FV} = \begin{cases} white & if\ I(i,j) - I_{mean} > I_{SD} \\ black & otherwise \end{cases},$$

where $I_{(i,j)}$ was the compensated image.

FVs with a diameter of less than 20 microns were discarded by excluding the binarized image groups of black pixels with 4 or fewer elements. This was done to reflect the 5.7 microns spatial resolution of the instrument. The FV was computed as follows:

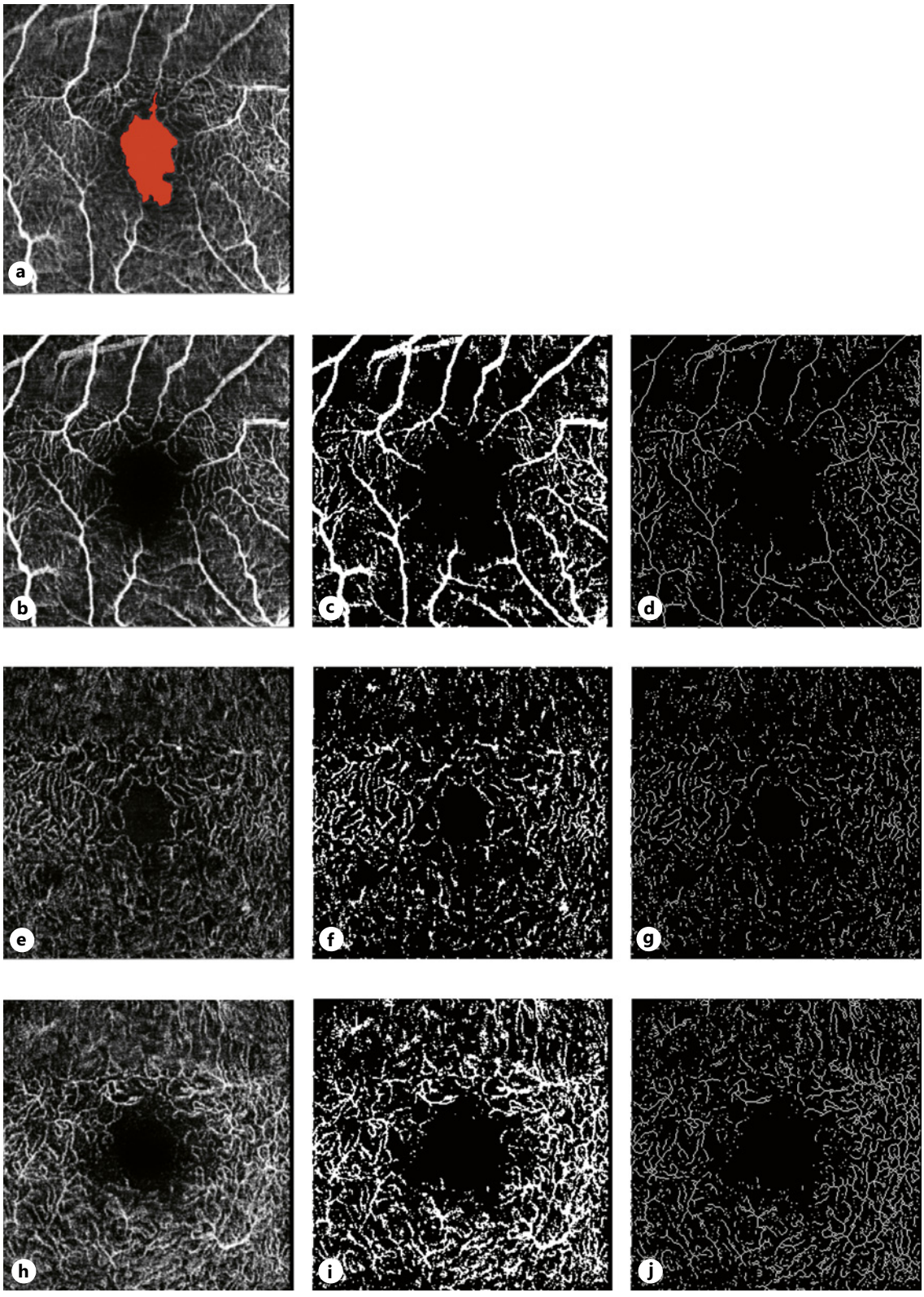
$$FV = \frac{Area_{FV}}{Area_D} \times 100$$

where $Area_{FV}$ was the number of black pixels belonging to groups with more than 4 elements, and $Area_D$ was the domain of the computation.

Statistical Analyses

For continuous variables, the arithmetic mean (±standard deviation) is reported. Categorical variables were reported as experimental frequencies and/or percentages. For all patient-level analysis, the eye with more severe DR diagnosis was used.

The association between DR severity (using the worse eye grade) and clinical variables such as sex, type of DM, presence of PPL, presence of DME, previous history of stroke was assessed in 258 patients using a χ^2 test in 5 × 2 contingency tables. As DM duration and the age were not normally distributed, the association between the DR severity and DM duration and age was assessed using Kruskal-Wallis ANOVA. The presence of significant differences in DM duration for eyes with PPL or DME was assessed using the Mann-Whitney test. One-way ANOVA was used for univariate analysis of OCT-A variables categorized by DR severity. The mean OCT/OCT-A values were compared between eyes with or without PPL and between eyes having DME or not, using a two-sided unpaired *t*-test.



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The association between DR severity and the clinical and OCT-A variables was assessed on a patient basis using an ordinal logistic regression model. The DR severity was considered as the dependent variable; sex and type of DM as categorical predictors; age, diabetes duration, and OCT-A variables as the independent continuous predictors.

The mean OCT-A values were compared between the groups of patients with or without a history of stroke in a univariate analysis using a two-sided unpaired *t*-test. Finally, the association between previous history of stroke and the clinical and OCT-A variables was assessed using a logistic regression. The history of stroke was considered as the dependent categorical variable; sex and DM type as categorical predictors; age, diabetes duration, and OCT-A variables as the independent continuous predictors.

The mean value of OCT-A variables between two eyes was used as the best indicator of OCT-A metric in a single patient to be associated with the presence of stroke. The statistical analyses were performed using Statistica software version 6.0 (StatSoft, Inc., Tulsa, OK, USA), using a two-sided type 1 error rate of $p \leq 0.05$.

Results

Table 1 describes demographic data and clinical features of the enrolled patients. A total of 516 eyes (258 patients) were included in the study of which 58.7% (152) were males and 41.3% (107) were females. The mean age was of 67.1 ± 13.7 years (range, 19–95). 81.9% (212) of patients had type 2 DM, while 18.1% (47) had type 1 DM. Mean duration of DM was 19.1 ± 10.6 years. Positive history of stroke was recorded in 10.4% of DM patients.

On UWF-CFP, 108 eyes (20.9%) did not have signs of DR, 10.3% (53) had mild nonproliferative DR (NPDR), 38.2% (197) had moderate NPDR, 11.8% (61) had severe NPDR, and 17.6% (91) had proliferative DR. Six eyes were not gradable due to poor image quality.

More severe DR was found in patients with type 1 DM, presence of PPL, presence of DME, longer duration of DM, and in younger patients ($p < 0.0001$ for all). A worse stage of DR was associated with a history of stroke ($p = 0.044$) (Table 2). OCT and OCT-A metrics were available for 252 eyes in 136 patients.

In univariate analyses, PD on SCP, FAZ perimeter, area, and circularity index (full retina scan) and FV in CC resulted in being statistically significantly associated with DR severity (Table 3). PD, VD, FD in SCP and FAZ circularity index and FV in CC showed a significant variation in eyes with DME versus eyes without DME (Table 3). No significant differences in OCT-A parameters were found in eyes with and without PPL ($p > 0.47$, for all). A univariate analysis using a two-sided unpaired *t*-test, of OCT-A parameters found a statistically significant borderline decrease for PD (14.6 vs. 17.9, *t* test = 1.87, $p = 0.06$), VD (5.1 vs. 6.4, *t* test = 1.85, $p = 0.06$), and FD (1.35 vs. 1.39, *t* test = 1.87, $p = 0.06$) in SCP in patients with history of stroke versus those without.

The clinical and OCT-A variables were successively inserted as independent variables in generalized linear models to study the association with DR severity (ordinal logistic regression) and the history of stroke (logistic regression). Ordinal logistic regression showed that VD (Wald statistic 9.2; $p = 0.002$) and PD in ICP (Wald statistic 13.1; $p < 0.001$) were the only significant predictors of DR severity.

Logistic regression showed that VD (Wald statistic 6.6; $p = 0.010$) and PD (Wald statistic 5.7; $p = 0.017$) in ICP were the only variables significantly associated with a previous history of stroke. The two generalized linear models are reported in Tables 4 and 5.

Table 1. Demographic data, DR severity by UWF-CFP, and DME on OCT

n = 259 patients	Value±SD or *n*(%)
Female sex	107 (41.3)
Age, years	67.1±13.7
Duration of DM, years	19.1±10.6
Type 2 DM	212 (81.9)
Stroke	27 (10.4)
DR severity on UWF (*n* = 516 eyes)	
No DR	108 (20.9)
Mild NPDR	53 (10.3)
Moderate NPDR	197 (38.2)
Severe NPDR	61 (11.8)
PDR	91 (17.6)
Ungradable	6 (1.2)
Presence of PPL	183 (35.5)
DME on OCT (*n* = 252 eyes)	
DME present	37 (14.7)
DME absent	215 (85.3)

DR, diabetic retinopathy; UWF-CFPs, ultrawide field color fundus photos; DME, diabetic macular edema; OCT, optical coherence tomography; DM, diabetes mellitus; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative DR; PPLs, predominantly peripheral lesions.

Fig. 2. a The original optical coherence tomography angiography (OCT-A) image with the FAZ area marked in red. **b** The original OCT-A image of the superficial capillary plexus (SCP). **c** The binarized SCP image. **d** The skeletonized SCP image. **e** The original OCT-A image of the intermediate capillary plexus (ICP). **f** The binarized ICP image. **g** The skeletonized ICP image. **h** The original OCT-A image of the deep capillary plexus (DCP). **i** The binarized DCP image. **j** The skeletonized DCP image.

Table 2. Tabulation of DR severity (patient level) with history of stroke

	History of stroke, *n* (%)	No history of stroke, *n* (%)	Total
No DR	2 (7.5)	45 (19.5)	47
Mild NPDR	2 (7.5)	21 (9.1)	23
Moderate NPDR	7 (25.9)	94 (40.7)	101
Severe NPDR	5 (18.5)	28 (12.1)	33
PDR	11 (40.7)	43 (18.6)	54
Total	53	231	258

DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative DR.

Table 3. Mean OCT and OCT-A measurements across different DR levels

Total *n* = 252	No DR (*n* = 62)	Mild NPDR (*n* = 34)	Moderate NPDR (*n* = 117)	Severe NPDR (*n* = 19)	PDR (*n* = 20)	*p* value
CMT	275.6 (SD 48.3)	283.1 (SD 39.4)	296.0 (SD 66.8)	315.7 (SD 91.0)	282.1 (SD 31.5)	0.064
PD SCP	20.8 (SD 6.5)	18.5 (SD 5.8)	19.4 (SD 6.1)	21.3 (SD 7.4)	23.8 (SD 7.5)	0.023
FV CC	76.4 (SD 9.4)	78.2 (SD 8.8)	75.7 (SD 10.0)	73.6 (SD13.4)	68.6 (SD 12.9)	0.015
FAZ perimeter	2.6 (SD 0.6)	2.3 (SD 0.6)	3.0 (SD 1.1)	3.3 (SD 1.1)	3.6 (SD 1.4)	<0.001
FAZ area	0.4 (SD 0.2)	0.3 (SD 0.1)	0.4 (SD 0.2)	0.4 (SD 0.2)	0.5 (SD 0.2)	<0.001
FAZ circularity	0.6 (SD 0.1)	0.6 (SD 0.1)	0.6 (SD 0.1)	0.5 (SD 0.1)	0.5 (SD 0.2)	<0.001

DME	Mean		T value	SD		*p* value
	DME absent	DME present		DME absent	DME present	
CMT	281.73	334.62	−5.16	47.38	97.34	<0.001
PD SCP	19.61	23.20	−3.17	6.60	4.71	0.0017
VD SCP	6.96	7.87	−2.04	2.59	1.82	0.0419
FD SCP	1.40	1.42	−2.67	0.06	0.04	0.0081
FV CC	76.32	70.51	3.19	10.39	9.21	0.0016
FAZ circularity	0.58	0.53	2.04	0.14	0.13	0.0425

OCT, optical coherence tomography; OCT-A, OCT angiography; DR, diabetic retinopathy; DME, diabetic macular edema; SD, standard deviation; CMT, central macular thickness; PD, perfusion density; SCP, superficial capillary plexus; FVs, flow voids; VD, vessel density; FD, fractal dimension.

Discussion

In the present bi-center study we report on OCT/OCT-A and UWF color fundus imaging data from the European cohort of patients with different stages of severity of DR and its association to stroke. A more severe stage of DR on UWF-CFP was associated with a history of stroke in the present study. This is in agreement with data reported in the large Australian population cohort, in which people with type 2 DM with moderate NPDR or worse at baseline had a more than 2-fold increase in risk of any subsequent stroke compared with mild NPDR or no DR [10].

The present study documented borderline significant decrease in PD, VD, and FD in SCP in patients with stroke versus those without stroke, using a univariate analysis (two-sided unpaired *t*-test). This may suggest that DM patients with a history of stroke have major modifications of retinal microcirculation. The retina and the brain share similar embryological origin, anatomic, and physiologic characteristics, thus retinal vascular lesions are likely to reflect the presence of similar pathological processes in the cerebral microcirculation [3, 7]. It is known that DR represents an independent risk factor for stroke, suggesting a role of microvascular pathology in the development of stroke in diabetic patients [6]. However, the reason for this correlation has not been defined yet; no studies to our knowledge have investigated the correlation between stroke and OCT-A metrics in DM patients.

Previous studies have found an association between stroke and pathologic vascular findings on fundus

Table 4. Patient's OCT-A parameters associated with DR severity

Ordinal logistic regression	Dependent variable: DR severity	
	Wald statistics	*p* level
Intercept	115.4	<0.001
PD ICP	13.5	<0.001
VD ICP	10.5	0.001

OCT-A, optical coherence tomography angiography; PD, perfusion density; VD, vessel density; FAZ, foveal avascular zone in the full retina; ICP, intermediate capillary plexus.

Table 5. Patient's OCT-A parameters associated with history of stroke

Logistic regression	Dependent variable: history of stroke	
	Wald statistics	*p* level
Intercept	0.01	0.91
PD ICP	5.73	0.017
VD ICP	6.58	0.010

OCT-A, optical coherence tomography angiography; PD, perfusion density; VD, vessel density; ICP, intermediate capillary plexus. The mean value of OCT-A variables between two eyes was selected as the best indicator of OCT-A metric in a single patient.

photography; however, parameters used were qualitative and therefore potentially imprecise. A recent study by Liu et al. [23] reported that VD in SCP and DCP in all macular sectors were decreased in patients with stroke, after adjusting for numerous systemic factors including levels of HbA1c. However, patients with DR were excluded, while the present study aimed to investigate the association between OCT-A metrics and stroke in DM patients with DR, a subpopulation with higher risk of cerebrovascular disease.

FD is the measure of density and complexity of the retinal vascular network [28]. A decreased FD suggests a reduction of the complexity and a rarefaction of the retinal microcirculation [29]. Previous studies have correlated a decreased FD with both stroke and other neurodegenerative diseases [19–22]. Many of these studies, however, calculated FD on fundus photography using different methods. Kawasaki et al. [22] reported that a higher risk of stroke is associated with a reduction in FD on fundus photography. Doubal et al. [30] documented an association between decreased FD calculated on fundus photography and lacunar stoke. DM represents a known risk factor for the lacunar stroke which is considered a specific type of ischemic stroke that occurs when blood flow to one of the small arteries (<1.5 cm) deep within the brain becomes blocked [11].

The logistic regression analysis taking into account patients' clinical and OCT-A variables found that PD and VD in ICP were the only parameters mostly associated with the history of stroke. The results of our study strengthen the hypothesis of an existing association between the entity of retinal damage and the damage of the cerebral circulation in patients with DM; moreover, the results demonstrate the presence of association between OCT-A quantitative metrics and a history of stroke, highlighting that specific OCT-A parameters could be helpful in identifying a subgroup of patients with higher risk of cerebrovascular events. Future studies characterizing the type of stroke with strict control of other risk factors could be helpful in defining more in detail the nature of the association.

The importance of UWF fundus imaging in assessing the severity of DR has emerged recently and has been extensively studied. In fact, UWF-CFP can detect more severe DR in a substantial proportion of patients due to the presence of PPL [15]. Detection of PPL is important due to the greater risk of progression of DR and development of proliferative DR [16]. In the present study, presence of PPL did not show association with stroke; however, more advanced stages of DR (graded on UWF-CFP) were associated with a history of stroke.

OCT-A has been increasingly used for the evaluation of microvascular modifications in patients with diabetes with or without DR. Modifications of the FAZ, including FAZ enlargement, presence of irregular FAZ contour and loss of circularity as well as decreased perfusion and/or VD, and decreased FD have been documented and proposed as signs of macular ischemia associated with DR progression [29–34].

Even if retinal vascular non-perfusion in the macula detected with OCT-A was correlated with increasing severity of DR, evaluated in the periphery [35]; however, in the present study, OCT-A quantitative parameters could predict only approximately 32% (data not shown) of DR severity evaluated on UWF-CFP. These parameters included PD and VD evaluated in the ICP, in a logistic regression analysis.

This may suggest that macular and peripheral modifications in DR may be independent to a certain level and that both UWF imaging and OCT-A may be necessary for better understanding of retinal microvascular modifications due to DM. It remains to be evaluated if the use of wide field OCT-A, evaluating more peripheral microvascular condition in the retina may be better associated with the presence of PPL and severity of DR.

In the present study, the presence of PPL on UWF-CFP was not associated with the presence of cerebrovascular comorbidity, whereas OCT-A quantitative parameters in the macula were associated with the presence of stroke. OCT-A is a new non-invasive tool to quantify retinal and choroidal capillary modifications due to DM and vascular complications in other organs. Thus, future and prospective studies should investigate the ability of OCT-A metrics to predict cerebrovascular events and other systemic comorbidities, such as ischemic cardiopathy in patients with DM. Moreover, development and validation of the automatic algorithms of evaluation of retinal images and implementation in the clinical practice may help in better management of patients with DM and in predicting the risk of systemic vascular comorbidities.

The major limitations of the present study include the limited number of evaluated patients from the cohort for the OCT-A analysis and the lack of longitudinal data. The small sample size did not allow to take into consideration other variables implicated in stroke risk such as diabetic nephropathy stage [36], systolic pressure values [37], BMI [38], and smoking [39]. However, detailed analysis of the available data and the use of sophisticated and already validated methods of OCT-A image analyses should enable to set pilot results that may serve for future larger studies.

Data from the present study should encourage future larger and prospective studies that could strengthen the importance of a multidisciplinary approach together with a multimodal imaging of retinal fundus, automatic evaluation, evaluating both the macula and the far periphery, crucial for better assessing the actual multiorgan disease load on a single patient, thus indicating the best way to approach the patient (reducing the burden and maximizing the beneficial effect).

Statement of Ethics

This study protocol was reviewed and approved by Ethical Review Board IRCCS MultiMedica Ethics Committee, protocol No. 502.2021. Written informed consent was obtained from participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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This research received no external funding.

Author Contributions

Conceptualization and data curation: S. V., R. S., and T. P. Statistical analysis: M.B. Retinal images analysis: S.V., E.T., T. P., and RS. Data collection: S.V., F.F., T.P, R.S., C.L, and L.C. Writing – draft preparation: S.V., F.F, T.P., R.S., P.N., C.L., and L.C. Writing – review and editing: S.V., R.S., T.P., and P.N.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (S.V.) upon reasonable request.

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