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Original Article

Optical coherence tomography angiography: a window on systemic sclerosis microangiopathy☆,☆☆

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ABSTRACT

Introduction: Retinal vascular alterations were reported in patients with SSc suggesting a potential role for OCTA in the evaluation of SSc-related microangiopathy. The aim of the study is to evaluate the microangiopathic alterations in the retina of patients with SSc and to evaluate their correlation with the clinical manifestations of the disease and the capillaroscopic findings

Materials and methods: This is a case-control study comparing SSc patients to healthy controls. OCTA acquisition consisted on scans of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) of both the macula and the optic nerve, performed using Canon OCT. Vascular density (VD), vascular length density (VLD), foveal avascular zone (FAZ) and retinal thickness in the fovea and in the perifoveal region were obtained using dedicated software.

Results: 41 SSc patients (11 were VEDOSS) were compared with 20 healthy controls. SSc patients showed reduced VD and VLD values in all areas evaluated both in the SCP and DCP ($p < 0.001$ for both). At the optic nerve level, both VD and VLD values were reduced at the SCP ($p < 0.001$ for both) and DCP levels ($p = 0.009$ and $p < 0.001$). Retinal thickness in the parafoveal region was increased in SSc patients ($p = 0.013$) and correlated with blood flow at nailfold videocapillascopy ($p = 0.030$). VD and VLD at the foveal level in DCP were associated with the presence of avascular areas ($p = 0.018$ and $p = 0.019$) and neoangiogenesis ($p = 0.023$ and $p = 0.025$).

Conclusion: Ocular microangiopathy is present in scleroderma patients since the early stages of the disease and is correlated with capillaroscopic alterations.

1. Introduction

Systemic sclerosis (SSc) is a rare multisystem disease characterized by early microvascular damage that leads to fibrosis of skin and internal organs [1]. SSc-related ocular manifestations have been poorly investigated. Different types of ocular involvement have been reported in patients with SSc: dry eyes, reduced choroidal thickness, astigmatism, posterior subcapsular cataract, increased intraocular pressure, eyelid abnormalities and retinal microcirculatory impairments [2,3]. A recent systematic literature review has reported that the most common ocular manifestations are eyelid skin fibrosis, dry eye disease, and involvement of the posterior segment, especially in the choroidal microvasculature [4,5]. The vascular pathogenesis of systemic sclerosis could lead to hypothesize an alteration of retinal vessels as well, since vasculopathy is

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the main feature of this disease [6,7]. In fact, retinal vascular involvement occurs in approximately 34 to 55 % of patients in SSc [8]. In the last decades optical coherence tomography angiography (OCTA) has emerged as a valuable, innovative tool to detect microvascular impairment of retinal as well as choroidal vessels in patients with SSc. This is a new, non-invasive, high-resolution imaging technique that allows a detailed analysis of retinal microvasculature networks without requiring the injection of intravenous fluorescent dye [9]. Some studies have demonstrated that retinal and choroidal vessels are affected by systemic vasculopathy, leading to optic nerve and endothelial cell damage, choroidal ischemia, macular oedema, and precapillary basement membrane thickening [10–18]. These vascular changes have been reported, in patients with SSc, even in absence of any clinical evidence of retinopathy and early detection of vascular alterations is crucial for both diagnosis and monitoring of disease progression. In addition, a limited number of studies with contrasting results have compared retinal findings with other disease manifestations and nailfold videocapillaroscopy (NVC) alterations [19–25]. In Table 1 studies regarding OCTA in SSs are summarised.

2. Aim

The aim of the present study is to evaluate retinal vasculature perfusion parameters in SSc patients with respect to healthy controls (HC) and to correlate these parameters in relation to capillaroscopic features and other disease manifestations.

3. Materials and methods

3.1. Study design and data collection

This is a monocentric retrospective case-control study of SSc patients and age- and sex-matched HC cohort carried out at the Rheumatology Unit in collaboration with the Institute of Ophthalmology of the University of Modena and Reggio Emilia between January 2025 and June 2025. All patients enrolled gave their informed consent for the study and the OCTA evaluation. The study was performed in conformity with the Good Clinical Practices and the ethical guidelines of the Declaration of Helsinki, and the research project was approved by the local Institutional Ethics Committees (Modena, protocol no. 275/16). A strobe checklist was also use for preparing and writing the present manuscript.

Consecutive patients aged >18 years and classified according to the SSc ACR/EULAR 2013 criteria [26] were included. Very Early Diagnosis Systemic Sclerosis (VEDOSS) patients were diagnosed according to the VEDOSS criteria [27]. The control group included age- and sex-matched non-smoker, healthy volunteers, who consented to OCTA image acquisition. Exclusion criteria both for patients and HC were: underage patients (< 18 years old), active smokers, hydroxychloroquine therapy, underlying malignancies, systemic untreated infections (i.e., HBV, HCV, and HIV), any clinical conditions which could represent a bias for retinal microvascular assessment at OCTA (such as diabetes, severe uncontrolled systemic hypertension, peripheral atherosclerotic disease, coexisting ocular diseases including refraction anomalies such as severe myopia, cataracts, glaucoma or a previous diagnosis of retinopathy, and optical media opacities that could impair the quality of the OCT scans. Both patients and HC underwent a complete ophthalmic examination for both eyes, including OCTA.

3.2. Rheumatologic assessment of SSc patients

Demographic, clinical and laboratory features were recorded from thorough medical chart review for all consecutive SSc patients including the following informations: demographic information (age, sex), tobacco use, disease duration (calculated from the first non-Raynaud symptoms), cutaneous subsets (diffuse cutaneous-dcSSc, limited cutaneous-lcSSc and sine scleroderma-ssSSc), skin involvement

Table 1
Summary of the reports about the use of OCT-A in SSc patients.

Author, year	Study design	Patients	Results
Rommel F, 2021 [13]	case-control	15 SSc vs 15 HC	lower macular volume, lower Sattler's layer thickness, lower Haller's layer thickness, reduced SRP and DRP *Clinical correlation:* correlation between SLT and mRSS as well as HLP and CSURI. FRP correlated positively with SRP and DRP, as well as SRP and DRP with each other. Choroidal substructure analysis revealed signifcant correlation between SLP and HLP. the perfusion values in none of the retinal slabs showed a statistically significant correlation with the perfusion in any choroidal sublayer.
		Subanalysis: SSc patients ⟨ 60 months disease duration vs SSc patients ⟩ 60 months disease duration	Patients with a disease duration >60 months showed a positive correlation between retinal and choroidal malperfusion.
Rothe M, 2019 [12]	case-control	12 SSc vs 12 HC	lower retinal perfusion SRCP and DRCP The macular volume and FAZ in the SRCP and DRCP did not differ. *Clinical correlation:* the perfusion in the FR slab correlated significantly with macular volume as well as mean arterial pressure. BCVA correlated significantly with perfusion in the SRCP as well as the DRCP slab. Perfusion values in either slab did not show any significant correlation with age, disease duration or mRSS.
Hekimsoy HK, 2020 [14]	Case-control	45 SSc vs 12 HC	CMT did not significantly differ between SSc patient and HC SFCT was significantly lower in SSc. No significant difference was found in FAZ. The SCP vessel densities of the whole image, fovea, parafovea and perifovea were significantly lower in patients with SSc. The DCP vessel densities of patients with SSc were not significantly different from those of HC subjects, except for the fovea in which the DCP vessel density was significantly lower in SSc patients. No significant difference in the choriocapillaris

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Table 1 (*continued*)

Author, year	Study design	Patients	Results
			flow area between patients with SSc. *Clinical correlation:* There was no correlation between the duration of the disease and vessel densities in SCP or DCP in patients with SSc.
Ranjbar M, 2019 [11]	Case-control	12 SSc vs 12 HC	Submacular perfusion was significantly reduced in all 3 vascular layers in patients with SSc. In the CC, differences between the SSc group (47.8 %) and the HC (47.0 %) were the smallest; however, they were still statistically significant. In SL, differences between patients with SSc (62.4 %) and healthy matches (59.6 %) were the largest and were highly significant.
			A significantly thinner subfoveal choroid in patients with SSc substructure analysis revealed that only the thicknesses of the SL and HL, but not the thickness of the CC were significantly reduced. *Clinical correlation:* subfoveal choroidal thickness significantly correlated with mRSS. The perfusion values in none of the slabs showed any significant correlation with age, disease duration, or mRSS.
Kok M, 2021 [8]	Case-control	47 SSc vs 44 HC	a statistically significant decrease in both SCP VD and DCP VD in SSc. Superficial Fovea VD significantly was higher in SSc. FAZ assessment tool variables were (FAZ area, FAZ perimeter, foveal density) significantly lower in SSc FAZ in the superficial retinal capillary plexus (Superficial Fovea VD) was significantly higher, FAZ in the deep retinal capillary plexus in SSc patients did not significant differ with HC. In SSc, it was determined that the flow in the 1 mm and 3 mm circular area (Outer Retina 1–3 mm Flow Area) of the outer retinal fold covering the fovea, increased significantly compared to the control group. There was a significant decrease in choroid thickness and choroidal flow (Choriocapillaries 3 mm Flow Area) in SSc. It must be underline that Authors

Table 1 (*continued*)

Author, year	Study design	Patients	Results
			considered not patients but eye, and it could represent a bias for the analysis.
		Subanalysis: lcSSc vs dcSSc	No statistically significant OCTA findings were found
Cerasuolo G, 2022 [23]	Case-control, Poster presentation	30 SSc vs 30 HC	impaired VD at SCP, DCP, FAZP and CC in SSc. *Clinical correlation*: The presence of DU, telangiectasias and ILD was related to reduced VD at FAZP, CC, and DCP. The average capillary density on capillaroscopy showed a positive correlation with VD at FAZP, DCP, and foveal CC and there was also a correlation between CC and both DLco and FVC/DLco
Erturk A, 2023 [17]	Case-control	22 PRP vs 19 VEDOSS vs definite SSc (25 lcSSc and 13 dcSSc)	parafoveal, and perifoveal superficial capillary plexus (SCP) vessel densities (VDs), deep capillary plexus VDs, and whole, inside, and peripapillary VDs were significantly higher in the PRP group FAZ was significantly higher in lcSSc than VEDOSS. Retinal nerve fiber layer VDs were significantly lower in the lcSSc group than in the PRP and VEDOSS. The whole and peripapillary optic disc VDs of the VEDOSS group were significantly higher than in the lcSSc.
Cutolo CA, 2023 [19]	Case-control	32 SSc vs 27 HC	A significant difference emerged between SSc patients and HCs in terms of intraocular pressure (IOP): more specifically, IOP was found higher in SSc than in HCs ($p = 0.006$). No difference was detected in the thickness of the retinal nerve fiber layer (RNFL) between SSc patients and HC. As expected, SSc patients showed significant differences from HCs in all NVC and LASCA variables ($p < 0.01$). *Clinical correlation:* The mean capillary number at NVC directly correlated with the retinal perfusion values of the SVP and DVP. Choroidal thickness resulted significantly higher in Scl70 + and in patients who had previous DU patients with ACA +*y* exhibited a significantly reduced choroidal thickness.

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Table 1 (*continued*)

Author, year	Study design	Patients	Results
			A direct correlation between choroidal thickness and disease duration there was a significant < in all of the perfusion variables, including the superficial vascular plexus, deep vascular plexus, and choriocapillaris. In a logist regression model the perfusion of the CC remained significant in predicting a diagnosis of SSc
		Subanalysis: 22 lcSSc vs 10 dcSSc	reduction of % Choriocapillaris, increment of Choroidal thickness in dcSSc
Küçük MF, 2022 [16]	Case-control	53 eyes of 30 SSc vs 61 eyes of 33 HC	In the multivariate analysis, a decrease in the VDs of the superficial capillary plexus and an increase in the FAZ area, FAZ perimeter and non-flow area were detected in the SSc group compared to the controls While there was a decrease in SFCT, no change was found in CCFA ($p = 0.001$ and $p = 0.902$, respectively). The RPC analysis revealed a decrease in the VDs of all vessels for the entire area and the intradisc area, as well as the VDs of the small vessels for the intradisc area ($p = 0.021$, $p = 0.001$, and $p = 0.003$, respectively). In the ONH analysis, there was an increase in the C/D area ratios and cup volumes, and a decrease in the rim areas and nasal quadrant retinal nerve fiber layer thickness ($p = 0.004$, $p = 0.004$, $p = 0.013$, and $p = 0.032$, respectively).
Mihailovic N, 2022 [22]	Case-control	*Subanalysis:* 7 VEDOSS vs HC	the VD in the OCTA-CC was still significantly reduced
		Subanalysis: 15 definite SSc vs 7 VEDOSS	significantly reduced VD of the RPC in patients with definite SSc
Foti R, 2024 [18]	Case- control	32 SSc vs 9 HC	whole superficial vessel density was comparable between the two groups. significant reduction in the ETDRS superficial vessel density in SSc. The whole deep vessel density was lower in SSc. lower ETDRS deep vessel density in SSc. significant enlargement in FAZ in SSc. average RNFL thickness, GCC thickness and C/D area ratio were comparable. *Clinical correlation:* whole superficial vessel density was negatively correlated

Table 1 (*continued*)

Author, year	Study design	Patients	Results
			mRSS, capillaroscopy score and disease duration. The radial peripapillary vessel density whole was negatively correlated with skin score and disease duration.
Paczwa K, 2024 [25]	Case-control	31 SSc vs 41 HC	In the SSc group, the parafoveal vessel density in DCP was significantly higher in relation to the mean value ($p < 0.0001$) and in each quadrant of the macula ($p < 0.0001$) compared to HC ($p < 0.0001$). *Clinical correlation*: The patients with early scleroderma patterns in capillaroscopy had a larger superficial and deep FAZ ($p = 0.0104$, $p = 0.0076$, respectively) than those with active and late patterns. There was a statistically significant difference in the FAZ when comparing early to active ($p < 0.0001$) and early to late scleroderma patterns ($p < 0.0001$). A statistically significant difference was found in the type of interstitial lung disease and the deep FAZ area ($p = 0.0484$). SSc patients with nonspecific interstitial pneumonia (NSIP) had a larger FAZ than those with usual interstitial pneumonia (UIP) ($p = 0.0484$). Moreover, NSIP cases had a higher parafoveal mean superficial vessel density than those with UIP ($p = 0.0471$).

Legend: subfoveal choroidal thickness (SFCT), as well as the thickness of the choroidal vascular sublayers, such as choriocapillaris (CC), Sattler's layer (SL), and Haller's layer (HL), were measured manually in the EDI-OCT scans. Macular volume (MV) was acquired according to the Early Treatment Diabetic Retinopathy Study (ETDRS) gridSuperfcial retinal perfusion (SRP), deep retinal perfusion (DRP) and full retinal perfusion (FRP), as well as CC perfusion (CCP), were calculated by scoring the percentage of white pixels in relation to the number of total pixels, while for SL perfusion (SLP) and HL perfusion (HLP) the percentage of black pixels was taken into account central macular thickness (CMT),subfoveal choroidal thickness (SFCT), PRP: Primary Raynaud phenomenon.

(evaluated by modified Rodnan skin score (mRSS), telangiectasia, digital ulcers (DU), tendon friction rubs. Moreover the detection of internal organ involvement included: oesophageal and gastrointestinal symptoms (dysphagia, reflux, diarrhoea, abdominal bloating, constipation, malabsorption), hearth involvement, both pulmonary arterial hypertension (PAH) evaluated by right heart catheterization, and arrhythmias, interstitial lung disease (ILD) by pulmonary function tests and high-resolution computed tomography (HRCT), scleroderma renal crisis (SRC) as sudden onset of severe arterial hypertension with acute renal failure.Laboratory findings encompassed: antinuclear antibodies-ANA, anti-extractable nuclear antigens, particularly the SSc-related

autoantibodies, i.e. Hep-2 anticentromere or anti-CENP antigens (CENP), anti-topoisomerase-I (ATA), and anti-RNA polymerase III (ARA)

Previous and current therapies were also collected, categorized as vasoactive/vasodilating drugs (bosentan, ambrisentan, macitentan, sildenafil, tadalafil, iloprost, epoprostenol, PGE1, riociguat, calcium channel blocker), corticosteroids, conventional synthetic disease modifying antirheumatic drugs (csDMARDs, including cyclophosphamide, methotrexate, leflunomide, azathioprine, mycophenolate and cyclosporine) and biological DMARDs (bDMARDs, including rituximab, anti-tumor necrosis factor-α antagonists, tocilizumab and abatacept).

3.2.1. Nailfold videocapillaroscopy (NVC)

NVC was performed using an optical probe, equipped with a 200 × contact lens connected to image analysis software (DATA SYSTEM). The same physician (F.S.) performed NVC examinations for the enrolled participants according to the standardized procedures [28]. According to recent consensus-based definitions, the NVC parameters were defined as following: normal capillaries (hairpin-shaped), non-specific capillary variations of morphology (tortuous or crossing capillaries with branch diameters < 20 μm), dilated capillaries (irregular or homogeneous increase of capillary diameter between 20 and 50 μm), giant capillaries (homogeneously dilated normal shaped loops with a diameter ≥ 50 μm), microhemorrhages (dark lesions attributable to hemosiderin deposit), abnormal shapes (i.e., ramified capillaries, non-convex head of capillaries, neoangiogenesis, originating from a single capillary), and lower capillary density [29–30]. Mean capillary density was calculated assessing the number of capillaries in all the images available divided by the number of images. The degree of capillary density was considered to be 0 when capillaries were >9/mm, 1 for 7–9 capillaries/mm, 2 for 4–6 capillaries/mm and 3 for <4 capillaries/mm. The medium number of capillaries is defined as the number of capillaries in the distal row in a single image / number of images. A semi-quantitative rating scale was adopted to score capillary abnormalities: 1 = < 33 %; 2 = 33–66 % 3 = >66 % of changes on the total number of capillaries/mm. The mean score for each subject was obtained from the analysis of all fingers assessed (31). The rating system for avascular areas (avascularity of the capillary bed) was classified as follows: grade 0 = no obvious avascular areas; grade 1 = mild (one or two discrete areas of vascular deletion); grade 2 = moderate (more than two discrete areas of vascular deletion); grade 3 = severe (presence of large, confluent avascular areas). At the time of capillaroscopy, capillary blood flow was assessed, and the presence or absence of granular flow was recorded. In addition, the visibility of the capillary venous plexus was evaluated using the following scoring system: 0 = not visible, 1 = doubtful visibility, 2 = visible only in restricted areas of the plexus, 3 = clearly visible over a wide area. Finally, patients were distributed into the suitable NVC pattern belonging to the scleroderma pattern: (i) early (few giant capillaries, few hemorrhages, relatively preserved capillary distribution, not obvious loss of capillaries). (ii) active (frequent giant capillaries, frequent hemorrhages, moderate loss of capillaries with some avascular areas, mild disorganization of the capillary bed, absent or some ramified capillaries). (iii) late (irregular enlargement of the capillaries, few or absent giant capillaries, absence of hemorrhages, severe loss of capillaries with confluent avascular areas, severe disorganization of the capillary array, frequent ramified/bushy capillaries). The presence or number of abnormally shaped capillaries (capillaries without the characteristic "U" shape, such as bushy or tortuous capillaries) was recorded. Neoangiogenesis refers to the presence of abnormal capillary shapes, such as bushy, ramified, bizarre, or tortuous capillaries, with irregular morphology and orientation, in areas of capillary loss.

3.3. Ophthalmological assessment

All patients and HCs underwent a comprehensive ophthalmological examination which included best corrected visual acuity (BCVA) measured using the Snellen chart, slit lamp biomicroscopy of the anterior segment, and fundoscopy. Both eyes were examined in all subjects.

3.3.1. Optical coherence tomography angiography

OCTA acquisition consisted of 3 × 3 mm scans of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) both in the macula and in the optic nerve head, which were performed using Canon OCT HS100 (Canon New Zealand Ltd.) through dilated pupils. The OCTA images of the SCP and DCP were binarized and then skeletonized by an integrated image-processing system software. Vessel density (VD), calculated on a binarized image, indicates the percentage of white pixels in the region by percent (%). Then, to represent the vessel length density (VLD) (skeletonization of the image), the software transformed the lines of a binary image into thin lines (1 pixel of thickness), and the value was obtained by dividing the sum of the length of the thin lines in the region by the area by "mm^{-1}". All the above-mentioned image processing and segmentation for the retinal vascular plexuses were performed by dedicated software (OCT-HS100 Angio Expert AX®, RX Capture for OCT-HS100®, Canon, Japan). Ophthalmology specialist, expert in retinal diseases (T.V.), performed a detailed review of the OCTA images. VD and VLD were automatically calculated in a fovea-centred circle area (1 mm diameter around the foveola) and in a parafoveal area (an annular area extending between 1 and 2.5 mm diameter, centred on the foveola) segmented into four quadrants (superior, nasal, inferior, and temporal), and then density parameters were recorded for each of them. Furthermore, the mean values of VD and VLD in the foveal area, in the parafoveal area, and in the whole macular area were recorded in SCP and DCP for each patient. The foveal avascular zone (FAZ) was automatically calculated by the OCT-integrated software for both SCP and DCP. Finally, retinal thickness in the fovea and in the perifoveal region was measured using the automated software of the OCT machine.

3.4. Statistical analysis

Data from the enrolled SSc patients and HCs who met the inclusion criteria were analyzed. The average of the measurements from both eyes was calculated, and the difference between the two groups was tested using a *t*-test for normally distributed variables, or a nonparametric Mann–Whitney test when the normal distribution assumption was not met. Differences in proportions were assessed using chi-squared tests. Linear regression models were fitted to verify the linear association between continuous variables. Box plots were used to graph the distributions of the different groups. Statistical significance was set at $p < 0.05$. All analyses were performed using STATA™ software (version 19).

4. Results

4.1. Descriptive analysis

Based on the abovementioned inclusion criteria, 41 SSc patients were eligible for the study; of them 11 were VEDOSS. Most of the patients were classified as limited cutaneous SSc (19, 46.3 %), with mean age 56.2 ± 12.3 SD years and mean disease duration 9.1 ± 7.7 SD years. Anti-topoisomerase I antibodies (ATA) were positive in 20 patients (48.8 %), while anticentromere antibodies (ACA) in 14 patients (34 %). Interstitial lung disease (ILD) was detected in 46.3 % of cases and PAH on right heart catheterization in 3 patients (7.3 %). Almost all patients (95.1 %) were on vasodilator/vasoactive treatment (at least one), mostly prostacyclins (95.1 %) and 61 % were on immunosuppressive medications (at least one). The mean revEUSTAR-AI was 1.6 ± 1.4. A thorough description of the study population is reported in Table 2. The two groups were similar in age, gender.

NVC was performed on 30 SSc patients, of which 7 patients were VEDOSS. Overall, SSc pattern was identified in 23 patients (76.7 %), with a higher prevalence of an active pattern (12 patients, 52.2 %).

Table 2
Characteristics of the study population.

Parameters	SSc $n = 41$	Definite SSc $n = 30$	VEDOSS $n = 11$	p-value	DU – $n = 26$	DU + $n = 15$	p-value
Age (years), mean (SD)	56.2 (12.3)	56.6 (10.7)	55.1 (16.4)	0.74	55.6 (9.3)	57.9 (11.9)	0.51
ATA, n (%)	20 (48.8)	14 (46.7 %)	6 (54.5 %)	0.73	12 (46.2 %)	8 (53.3 %)	1.00
ARA, n (%)	1 (2.4)	1 (3.3 %)	0 (0.0 %)	1.00	0 (0.0 %)	1 (6.7 %)	1.00
CENP, n (%)	14 (34.1)	9 (30.0 %)	5 (45.5 %)	0.46	10 (38.5 %)	4 (26.7 %)	0.44
Disease duration (years), mean (SD)	9.1 (7.7)	11.6 (7.6)	2.2 (1.3)	<0.001	6.7 (7.6)	13.1 (6.3)	0.009
Esophageal symptoms, n (%)	33 (80.5 %)	28 (93.3 %)	5 (45.5 %)	0.002	19 (73.1 %)	16 (93.3 %)	0.22
gastrointestinal symptoms, n (%)	14 (34.1 %)	14 (46.7 %)	0 (0.0 %)	0.026	4 (15.4 %)	11 (73.3 %)	0.033
lcSSc, n (%)	16 (39.0 %)	16 (53.3 %)	0 (0.0 %)	<0.001	11 (42.3 %)	8 (53.3 %)	1.00
dcSSc, n (%)	14 (34.1 %)	14 (46.7 %)	0 (0.0 %)	<0.001	7 (26.9 %)	7 (46.7 %)	
mRSS, mean (SD)	5.9 (6.2)	8.2 (6.0)	0.0 (0.8)	<0.001	4.7 (6.0)	8.0 (6.1)	0.12
DU, n (%)	15 (36.6 %)	15 (50.0 %)	0 (0.0 %)	0.003	-	-	-
Teleangiectasis, n (%)	24 (58.5 %)	22 (73.3 %)	2 (18.2 %)	0.003	9 (34.6 %)	15 (100.0 %)	0.049
Tendon friction rubs, n (%)	1 (2.4 %)	1 (3.3 %)	0 (0.0 %)	1.00	1 (3.8 %)	0 (0.0 %)	0.43
Arrhythmia, n (%)	4 (9.7 %)	4 (13.3 %)	0 (0.0 %)	0.3	3 (11.5 %)	3 (20.0 %)	0.65
PAH, n (%)	3 (7.3 %)	3 (10.0 %)	0 (0.0 %)	0.55	1 (3.8 %)	2 (13.3 %)	0.54
ILD, n (%)	19 (46.3 %)	19 (63.3 %)	0 (0.0 %)	<0.001	10 (38.5 %)	9 (60.0 %)	0.21
Resting sPAP	24.2 (7.4)	25.0 (8.3)	21.6 (1.9)	0.27	22.4 (5.1)	27.6 (9.8)	0.048
LVEF (%)	62.4 (4.9)	61.8 (5.0)	64.7 (3.7)	0.16	62.0 (5.1)	62.8 (4.7)	0.65
DLCO (%)	64.8 (17.3)	62.1 (17.3)	74.4 (14.6)	0.077	69.8 (16.7)	57.5 (16.1)	0.032
DLCO/ VA (%)	77.7 (16.5)	75.8 (17.0)	85.6 (12.3)	0.16	82.2 (16.0)	71.4 (15.6)	0.052
FVC (%)	102.3 (19.9)	98.9 (20.0)	114.6 (14.4)	0.046	108.6.5 (16.0)	71.4 (15.6)	0.016
FEV - 1 (%)	99.9 (24.7)	96.6 (26.3)	112.2 (12.6)	0.11	103.2 (20.1)	95.2 (30.4)	0.34
Therapy							
Vasodilator or vasoactive treatment (≥1), n (%)	39 (95.1 %)	30 (100.0 %)	9 (81.8 %)	0.067	24 (92.3 %)	15 (100.0 %)	0.52
ERA, n (%)	16 (39.0 %)	16 (53.3 %)	0 (0.0 %)	0.002	6 (23.1 %)	11 (73.3 %)	0.002
PDE5i, n (%)	4 (9.8 %)	4 (13.3 %)	0 (0.0 %)	0.68	0 (0.0 %)	4 (26.7 %)	0.013
Prostacyclins, n (%)	39 (95.1 %)	30 (100.0 %)	9 (81.8 %)	0.067	24 (92.3 %)	15 (100.0 %)	0.52
Immunosuppressive treatment (≥1), n (%)	25 (61.0 %)	23 (76.7 %)	2 (18.2 %)	0.001	13 (50.0 %)	12 (80.0 %)	0.097
Corticosteroids, n (%)	15 (36.6 %)	15 (50.0 %)	0 (0.0 %)	0.003	7 (26.9 %)	8 (53.3 %)	0.11
Biologic DMARDS, n (%)	12 (29.3 %)	12 (40.0 %)	0 (0.0 %)	0.018	6 (23.1 %)	6 (40.0 %)	0.30
Conventional DMARDs, n (%)	12 (29.3 %)	21 (70.0 %)	2 (18.2 %)	0.005	12 (46.2 %)	11 (73.3 %)	0.11
revEUSTAR-AI at baseline, mean (SD)	1.6 (1.4)	2.0 (1.3)	0.3 (0.6)	0.002	0.9 (0.9)	2.5 (1.3)	< 0.001
NVC parameters							
Scleroderma pattern	23 (76.7 %)	19			14 (73.7 %)	9 (81.8 %)	1.00
NVC Scleroderma Pattern Early, n (%)	6 (26.1 %)	6 (31.6 %)	0 (0.0 %)	0.13	5 (35.7 %)	1 (11.1 %)	0.39
NVC Scleroderma Pattern Active, n (%)	12 (52.2 %)	8 (42.1 %)	4 (100.0 %)		7 (50.0 %)	5 (55.6 %)	
NVC Scleroderma Pattern Late, n (%)	5 (21.7 %)	5 (26.3 %)	0 (0.0 %)		2 (14.3 %)	3 (33.3 %)	
Mean capillary density (N/mm2),				0.14			0.002
score 0	9 (30.0 %)	6 (28.6 %)	3 (33.3 %)		5 (26.3 %)	4 (36.4 %)	
score 1	13 (43.3 %)	7 (33.3 %)	6 (66.7 %)		12 (63.2 %)	1 (9.1 %)	
score 2	7 (23.3 %)	7 (33.3 %)	0 (0.0 %)		1 (5.3 %)	6 (54.5 %)	
score 3	1 (3.3 %)	1 (4.8 %)	0 (0.0 %)		1 (5.3 %)	0 (0.0 %)	
number of capillaries, mean/mm	7.7 (2.2)	7.7 (1.9)	7.8 (2.8)	0.89	7.8 (2.2)	7.5 (2.2)	0.74
Giant capillaries, n (%)	23 (76.7 %)	18 (85.7 %)	5 (55.6 %)	0.15	15 (78.9 %)	8 (72.7 %)	1.00
Giant capillaries				0.62			0.50
< 33 %	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)		0 (0.0 %)	0 (0.0 %)	
33–66 %	10 (43.5 %)	8 (44.4 %)	2 (40.0 %)		6 (40.0 %)	5 (62.5 %)	
> 66 %	13 (56.5 %)	10 (55.6 %)	3 (60.0 %)		9 (60.0 %)	3 (37.5 %)	
Avascular areas, n (%)	8 (26.7 %)	6 (28.6 %)	2 (22.2 %)	1.00	4 (21.1 %)	4 (36.4 %)	0.42
Grading avascular areas				0.081			0.81
< 33 %	3 (37.5 %)	1 (16.7 %)	2 (100.0 %)		2 (87.5 %)	1 (25.0 %)	

(*continued on next page*)

Table 2 (*continued*)

Parameters	SSc $n = 41$	Definite SSc $n = 30$	VEDOSS $n = 11$	p-value	DU – $n = 26$	DU + $n = 15$	p-value
33–66 %	5 (62.5 %)	5 (83.3 %)	0 (0.0 %)		2 (12.5 %)	3 (75.0 %)	
> 66 %	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)		0 (0.0 %)	0 (0.0 %)	
Microhemorrhages, n (%)	18 (60.0 %)	13 (43.3 %)	5 (16.7 %)	0.69	13 (68.4 %)	6 (54.5 %)	0.70
Grading microhemorrhages							0.85
< 33 %	10 (55.6 %)	8 (61.5 %)	2 (40.0 %)		8 (61.5 %)	3 (50.0 %)	
33–66 %	8 (44.4 %)	5 (38.5 %)	3 (60.0 %)		5 (38.5 %)	3 (50.0 %)	
> 66 %	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)		0 (0.0 %)	0 (0.0 %)	
Abnormal Morfology capillary (bushy capillaries, ramified, bizarre loops), n (%)	23 (79.3 %)	16 (76.2 %)	7 (87.5 %)	0.65	14 (77.8 %)	9 (81.8 %)	1.00
Abnormal Morfology capillary grading				0.87			1.00
< 33 %	14 (60.9 %)	10 (62.5 %)	4 (57.1 %)		8 (57.1 %)	6 (66.7 %)	
33–66 %	9 (39.1 %)	6 (37.5 %)	3 (42.9 %)		6 (42.9 %)	3 (33.3 %)	
> 66 %	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)		0 (0.0 %)	3 (0.0 %)	
Neoangiogenesis, n (%)	7 (23.3 %)	7 (43.8 %)	0 (0.0 %)	0.071	3 (15.8 %)	4 (36.4 %)	0.37
Neoangiogenesis grading				0.05			0.33
< 33 %	7 (38.9 %)	7 (100.0 %)			3(100.0 %)	4 (100.0 %)	
33–66 %	0 (0.0 %)	0 (0.0 %)			0 (0.0 %)	0 (0.0 %)	
> 66 %	0 (0.0 %)	0 (0.0 %)			0 (0.0 %)	0 (0.0 %)	
Granular flow, n (%)	13 (43.3 %)	8 (38.1 %)	5 (55.6 %)	0.44	8 (42.1.3 %)	5 (45.5 %)	1.00
Visibility of the capillary venous plexus				0.078			0.27
- not visible,	20 (66.7 %)	16 (76.2 %)	4 (44.4 %)		14 (73.7 %)	6 (54.5 %)	
- doubtful visibility	4 (13.3 %)	3 (14.3 %)	1 (11.1 %)		1 (5.3 %)	3 (27.3 %)	
- visible only in restricted areas of the plexus,	4 (13.3 %)	2 (9.5 %)	2 (22.2 %)		2 (10.5 %)	2 (18.2 %)	
clearly visible over a wide area.	2 (6.7 %)	0 (0.0 %)	2 (22.2 %)		2 (10.5 %)	0 (0.0 %)	

Legend: SSc: Sistemic sclerosis; ATA: Anti-Scl-70 antibodies;ARA: Anti RNA polymerase III antibodies; CENP-1: Anti-centromere antibodies; lcSSc: limited skin involvement; dcSSc: diffuse skin involvement; mRSS: modified Rodnan Skin Score; DPS: Digital pitting scar; DU: Digital Ulcers; SRC: Scleroderma Renal crisis; sPAP: systolic pulmonary artery pressure; LVEF: Left ventricular ejection fraction; NVC: nailfold videocapillaroscopy, TFR:Tendon Friction rubs PAH: pulmonary arterial hypertension; ILD: Interstitial lung disease;DLCO: Diffusing Capacity of Lung for Carbon Monoxide; DLCO / VA: Diffusing Capacity of Lung for Carbon Monoxid divided by alveolar volume; FVC: Forced Vital Capacity; FEV – 1: forced expiratory volume in 1 s; ERA: endothelin receptor antagonists; cs DMARDS: Conventional synthetic disease modifying antirheumatic drugs; revEUSTAR-AI: revised EUSTAR Activity Index.
In bold type p-value is <0.05.

4.2. Comparison between SSc patients and healthy controls

82 eyes of 41 SSc patients and 40 eyes of 20 healthy controls (HC) were analyzed and SSc patients were compared with HCs.

Patients showed significantly reduced VD and VLD values in all areas evaluated compared to controls. In particular, both in foveal and in perifoveal region, patients showed significantly reduced VD and VLD values compared to controls both at the SCP and DCP level ($p < 0.001$). Similarly, at the optic nerve level, VD values were significantly reduced both at the SCP and DCP level ($p = 0.009$) as well as the VLD values ($p < 0.001$ for both). See details in Table 3

Differently, FAZ values were not significantly different in patients versus HCs neither at SCP nor DCP ($p = 0.47$ and $p = 0.15$; respectively). Retinal thickness of the parafovea was significantly increased in SSc patients ($p = 0.013$) while no differences were noted regarding the retina thickness of the fovea. Detailed data are reported in Table 3.

4.3. Comparison between definite SSc patients and VEDOSS patients

No significant difference was found by comparing the OCTA parameters of SSc patients with VEDOSS patients, neither at the SCP nor DCP of the macular area and the optical nerve. Similarly, FAZ values were not significantly different in SSc patients versus VEDOSS patients neither at SCP nor DCP. All the detailed data are reported in Table 4.

4.4. Correlation between OCTA values and NVC values

Correlating retinal values with capillaroscopic parameters, the values of foveal VD and VLD in DCP correlate with the presence of avascular areas ($p = 0.018$ and $p = 0.019$; respectively) and neoangiogenesis ($p = 0.023$ and $p = 0.025$; respectively). In addition, the correlation between FAZ DCP and the presence of avascular areas is at the limit of significance ($p = 0.056$). Retinal thickness of the parafovea correlates with granular flow registered at NVC ($p = 0.030$). No other correlations were found between OCTA parameters and NVC parameters, in particular with the presence of megacapillaries, microhemorrhages, neoangiogenesis and granular flow. All the analysis are reported in Fig. 1.

4.5. Correlation between OCTA and disease characteristics

No correlation was found between OCTA values (vascularity and retinal thickness) with PAH and mRSS. Regarding DU, when the analysis was conducted including VEDOSS patients, there was no significant correlation, as shown in supplementary Table 1a. In a subanalysis performed only on the definite SSc patients, a significant correlation was found only for the VD and VLD of the SCD in the left eye ($p = 0.024$ and 0.008 respectively); however, the significance was lost when the analysis was performed on both eyes. A significant correlation was found between foveal retinal thickness and Scl 70 +($p = 0.035$). Detailed data are reported in supplementary Table 2. Detailed data are reported in supplementary Table 3 for PAH and supplementary Table 8 for mRSS.

Correlation was found between whole VD DCP at the optic nerve and disease subtype ($p = 0.021$) Detailed data are reported in supplementary Table 4.

No correlation between vasoactive therapy and vascularization but a significant correlation was found with Retinal thickness both in the fovea and the parafoveal region ($p = 0.050$ and $p = 0.036$; respectively). Detailed data are reported in supplementary Table 5.

A significant correlation was found between the whole optical nerve

Table 3
Comparison between OCTA values in SSc patients and health controls.

		item	SSc $n = 41$ Mean, SD	HC $n = 20$ Mean, SD	p-Value
Macula	Foveal	VD SCP, %	21.4 (3.9)	24.3 (4.3)	**0.009**
		VD DCP, %	14.4 (4.7)	20.6 (6.5)	**<0.001**
		VLD SCP, mm^{-1}	13.8 (2.6)	15.9 (3.3)	**0.008**
		VLD DCP, mm^{-1}	9.6 (3.0)	13.7 (4.9)	**<0.001**
	Perifoveal	VD SCP, %	35.2 (3.1)	38.1 (2.0)	**<0.001**
		VD DCP, %	35.6 (5.2)	40.0 (2.2)	**<0.001**
		VLD SCP, mm^{-1}	22.2 (2.0)	24.7 (1.1)	**<0.001**
		VLD DCP, mm^{-1}	25.2 (3.5)	28.5 (1.3)	**<0.001**
	Whole	VD SCP, %	32.4 (2.9)	35.3 (2.1)	**<0.001**
		VD DCP, %	31.6 (4.8)	36.1 (2.8)	**<0.001**
		VLD SCP, mm^{-1}	20.6 (1.8)	23.0 (1.3)	**<0.001**
		VLD DCP, mm^{-1}	22.2 (3.3)	25.5 (1.9)	**<0.001**
Optical Nerve	Whole	VD SCP, %	46.2 (3.4)	51.3 (3.5)	**<0.001**
		VD DCP, %	26.0 (4.9)	30.4 (5.7)	**0.009**
		VLD SCP, mm^{-1}	20.6 (4.3)	25.9 (2.0)	**<0.001**
		VLD DCP, mm^{-1}	12.9 (3.6)	18.1 (3.6)	**<0.001**
FAZ		SCP, mm^2	0.3 (0.1)	0.3 (0.1)	0.47
		DCP, mm^2	0.4 (0.1)	0.4 (0.1)	0.15
Retinal thickness		Fovea, μm	217.3 (27.1)	204.4 (16.0)	0.14
		Parafovea, μm	346.1 (39.6)	313.1 (28.9)	**0.013**

SSc: Systemic sclerosis; HC: health controls; VD: Vessel density, %; VLD: vessel length density, mm^{-1}; SCP: superficial capillary plexus; DCP: deep capillary plexus; FAZ: foveal avascular zone, mm^2.
In bold type p-value is <0.05.

Table 4
Comparison between definite SSc patients and VEDOSS patients.

		item	**SSc** $n =$ 30 Mean, SD	**VEDOSS** $n =$ 11 Mean, SD	p-Value
Macula	Foveal	VD SCP, %	21.1 (4.0)	22.1 (4.0)	0.50
		VD DCP, %	14.2 (4.7)	14.9 (4.7)	0.71
		VLD SCP, mm^{-1}	13.6 (2.6)	14.3 (2.6)	0.41
		VLD DCP, mm^{-1}	9.4 (3.0)	10.0 (3.1)	0.59
	Perifoveal	VD SCP, %	35.6 (3.0)	34.1 (3.2)	0.17
		VD DCP, %	36.1 (5.0)	34.4 (5.8)	0.36
		VLD SCP, mm^{-1}	22.5 (1.9)	21.6 (2.1)	0.22
		VLD DCP, mm^{-1}	25.5 (3.4)	24.3 (4.0)	0.36
	Whole	VD SCP, %	32.6 (2.8)	31.7 (3.0)	0.37
		VD DCP, %	31.8 (4.6)	30.8 (5.4)	0.54
		VLD SCP, mm^{-1}	20.8 (1.8)	20.1 (1.9)	0.32
		VLD DCP, mm^{-1}	22.4 (3.2)	21.5 (3.5)	0.43
Optical Nerve	Whole	VD SCP, %	45.7 (3.6)	47.6 (2.8)	0.26
		VD DCP, %	25.4 (4.8)	27.8 (5.1)	0.31
		VLD SCP, mm^{-1}	20.3 (4.6)	21.6 (3.8)	0.53
		VLD DCP, mm^{-1}	12.6 (3.8)	13.8 (3.1)	0.48
FAZ		SCP, mm^2	0.3 (0.1)	0.3 (0.1)	0.45
		DCP, mm^2	0.4 (0.1)	0.5 (0.1)	0.53
Retinal thickness		Fovea, μm	213.3 (26.7)	228.5 (26.1)	0.11
		Parafovea, μm	344.6 (34.2)	350.0 (53.5)	0.71

Legend: SSc: Systemic sclerosis; HC: health controls; VD: Vessel density, %; VLD: vessel length density, mm^{-1}; SCP: superficial capillary plexus; DCP: deep capillary plexus; FAZ: foveal avascular zone, mm^2.
In bold type p-value is <0.05.

vascularization and disease duration ($p = 0.05$ for VD SCP; $p = 0.042$ for VLD SCP and $p = 0.019$ for VLD DCP). Detailed data are reported in supplementary Table 6.

A significant correlation was found between the whole optical nerve vascularization and DLCO ($p = 0.049$ for VD SCP). Detailed data are reported in supplementary Table 7.

5. Discussion

In the present study we investigated retinal vasculature and perfusion using OCTA in SSc patients in comparison with HCs correlating OCTA parameters with vascular disease features and capillaroscopic parameters. The most important result of our study is the reduction in both retinal vasculature and perfusion parameters in SSc patients compared to HCs, suggesting that OCTA could represent a valuable tool for the evaluation of microangiopathy in SSc patients.

In particular, patients with SSc showed significantly reduced retinal VDand VLD compared to HCs. This reduction was seen in the central foveal region but also in the perifoveal region and around optic nerve, at both SCPand deep DCP with statistically significant differences (mostly $p < 0.001$). These findings demonstrates that SSc is associated with diffuse retinal microvascular impairment, not limited to one area of the retina and this aligns with the systemic microangiopathy seen in SSc (similar to nailfold capillaroscopy findings).

OCTA has already been proven to be a reliable method for detecting microvascular changes in the retina and the choroid of SSc patients (see Table 1). Retinal vascular involvement has been reported in approximately 34 to 55 % of SSc patients [23,31] and a recent systematic review and meta-analysis including 11 observational studies and counting a total of 366 SSc, confirmed significantly lower SCP and DCP VD in SSc [31]. The vascular alterations highlighted by OCTA could be not only related to intrinsic retinal damage, but an expression of microcirculatory damage characteristic of SSc. In our study, we found a significant impaired retinal vasculature with decreased levels of SCP and DCP density in patients with SSc. This finding is similar to previous studies that reported lower VD of SCP and DCP in patients with SSc that supported decreased blood circulation in eyes due to vasculopathy in SSc [8,11,12,14,17,22,23]. In fact, in SSc, vascular damage affects microvascular circulation, including capillaries and arterioles. These data supported our hypothesis regarding the presence of microvascular ocular involvement in SSc [4,5]. Ocular vascular injury has been detected without any clinical sign of retinopathy in SSc patients, even in early stage of the disease [8]. In fact, in the present analysis, no significant differences were observed in OCTA parameters between patients with established SSc and those classified as VEDOSS. Similarly, FAZ measurements were comparable between SSc and VEDOSS patients at both the SCP and DCP levels, suggesting preservation of central avascular architecture across disease stages. These findings may indicate that retinal microvascular impairment occurs early in the disease spectrum, potentially preceding the development of fully established SSc. The absence of detectable differences between VEDOSS and overt SSc could support the hypothesis that microvascular damage represents an early and possibly foundational event in disease pathogenesis, rather than a progressive change strictly associated with later fibrotic or systemic involvement.

In our study, FAZ area did not differ significantly between SSc patients and HCs.

These finding was initially unexpected and may seem contradictory: if capillary density is reduced we might expect a bigger FAZ as

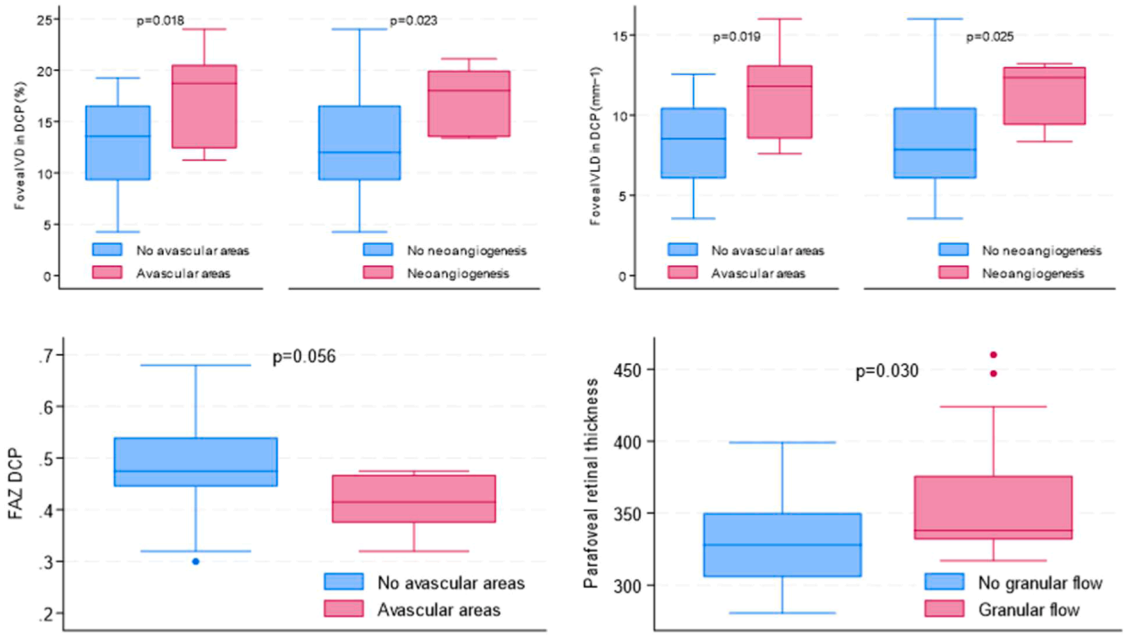
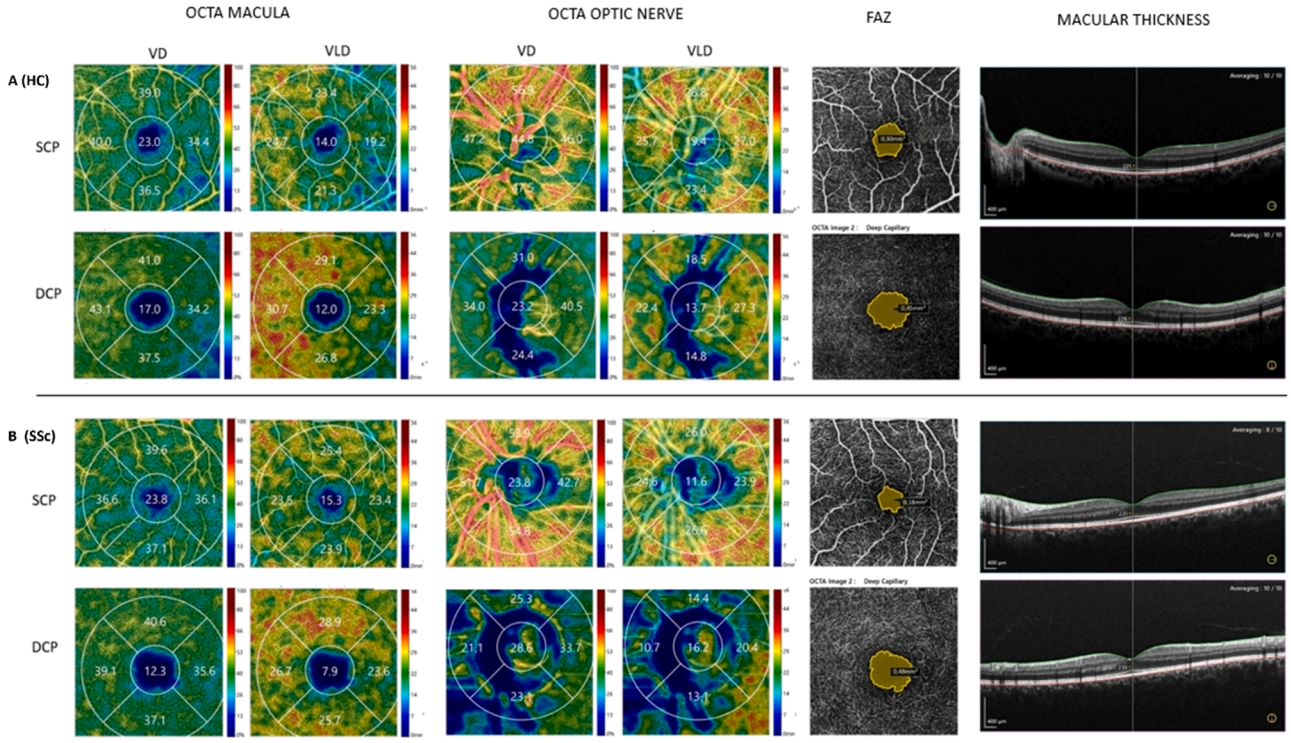


Fig. 1. Optical coherence tomography angiography images of retinal perfusion in the macular area, in the optic nerve head area, of the FAZ and of the macula thickness in a healthy control (A) and in a SSc patient (B). SSc: Systemic sclerosis; HC: health controls; VD: Vessel density; VLD: vessel length density; SCP: superficial capillary plexus; DCP: deep capillary plexus, FAZ: foveal avascular zone.



Legend: VD: vessel density; DCP: deep capillary plexus; VLD: vessel length density; FAZ: foveal avascular zone.

previously found in diabetic retinopathy,hypertensive retinopathy and retinal vascular occlusive disease [32–33]. However, the literature presents contrasting data regarding FAZ measurements in SSc. This different result could arise from an increased outer retina flow area, which covered an increased FAZ area [8]. A possible interpretation can be that FAZ enlargement may be a later-stage phenomenon and that outer retinal flow compensation may mask FAZ changes; moreover, this finding can reflect a chronic low-grade microvascular compromise in SSc rather than acute ischemia. However, FAZ stability does not exclude microvascular disease, and capillary density reduction appears to be a more sensitive early marker of microangiopathy [34]. On this basis, it is possible that FAZ enlargement represents a later-stage phenomenon, whereas capillary rarefaction may occur earlier in the disease process. Another notable finding was the increased parafoveal retinal thickness in SSc patients, despite no difference in foveal thickness. This was an unexpected result of our study and a possible explanation is related to

the presence of a subclinical inflammation with chronic hypoxia-induced remodelling of the retina and vascular dysregulation. However, it has been previously demonstrated that macular thickness could be considered an inflammatory marker in autoimmune diseases with vascular injury [11,18,25]. Several studies showed choroidal and retinal involvement in SSc associated with vascular changes. In particular, Grennan et al. [35] reported hypoperfusion in the choroid layer, which leads to abnormalities in choriocapillaris (CC) and small arterioles in fundus fluorescein angiography. Additionally, Ushiyama et al. [20] identified retinal lesions, including microhemorrhages, hard exudates, and macular degeneration using fundus photography. This vascular damage is believed to be related to mediators such as endothelin-1 and angiotensin II that disrupt choroidal autoregulation and blood flow. A reduction in choroidal perfusion can result in retinal atrophy and reduced retinal thickness [36,37]. Histopathological findings in patients with SSc revealed endothelial cell damage, basement membrane thickening, and absence of pericytes in choroidal vessels [38,39]. This localized retinal thickening may reflect subclinical inflammation or tissue remodelling secondary to chronic microvascular injury reinforcing the concept of SSc as a systemic microangiopathic disease. The absence of central foveal involvement could indicate a degree of anatomical or functional resilience in the most metabolically critical region of the retina.Then, the present analysis demonstrates a significant association between retinal microvascular impairment and NVC abnormalities, further supporting the systemic nature of microangiopathy in SSc. Specifically, reduced foveal VD and VLD at the level of the DCP were significantly associated with the presence of avascular areas and neoangiogenesis on NVC. Patients with these capillaroscopic abnormalities exhibited lower retinal microvascular values compared with those without such findings. This suggests that retinal capillary rarefaction parallels peripheral microvascular damage, particularly in more advanced capillaroscopic patterns characterized by capillary loss and aberrant vascular remodelling. The correlation between FAZ area at the DCP level and the presence of avascular areas on NVC approached statistical significance, suggesting that OCTA alterations reflect the disease progresses and the vascular impairment, as previously reported [18,25]. This correlation could be very interesting because it points out the ineffectiveness of vasodilating therapy on vascular SSc damage and led to future research on the action of vasoactive and/or immunosuppressant on endothelial damage. Although not definitive, this trend may indicate that enlargement of the FAZ could represent a later manifestation of progressive microvascular dropout, in line with more severe systemic capillary loss.

Additionally, increased parafoveal retinal thickness was significantly associated with granular flow detected on NVC. This finding may reflect a relationship between altered peripheral microvascular perfusion patterns and retinal structural changes. One possible explanation is that chronic microvascular dysfunction contributes to tissue remodelling or subtle inflammatory changes within the parafoveal region.

Importantly, no significant correlations were observed between OCTA parameters and other capillaroscopic features such as megacapillaries or microhemorrhages, indicating that retinal microvascular metrics are more closely linked to capillary loss and neoangiogenic remodelling rather than to early or predominantly dilative vascular abnormalities.

Finally in this study, retinal OCTA parameters did not show a consistent association with major markers of systemic disease severity, including PAH and mRSS. Similarly, no significant correlations were observed between retinal vascular parameters or retinal thickness and DU when the analysis included both definite SSc and VEDOSS patients. These findings suggest that retinal microvascular impairment may not directly parallel global clinical severity indices or overt vascular complications when early-stage patients are considered. Differently, some studies reported that impaired perfusion often correlate with mRSS disease severity, duration, capillaroscopic patterns [19], and specific autoantibodies [11,19,22]. Lack of relationship between avascularity zone report on OCTA and NVC with PAH could be related to the limited number of patients enrolled and low number of PAH in this population. Correlation between retinal avascular area and major capillaroscopic alterations (such as avascular rea) could represent a “marker” for those patients with more severe vascular disease. In this sense, OCTA could be considered as a window on scleroderma vasculopathy.

One of the primary strengths of our study lies in the large number of patients included, all of whom are affected by a rare disease. This sizable patient cohort enhances the reliability of our findings. Additionally, the case-control study design provides a robust methodological framework facilitating meaningful comparisons between groups. Then, the meticulous collection of both clinical and capillaroscopic data ensures comprehensive and accurate data for analysis. From a methodological perspective, our study benefits from the fact that ocular assessments and the OCTA examinations were consistently performed by the same operator using the same machine (with identical boundaries and segmentation algorithms), under the same conditions, thus ensuring more homogeneous images collection and analysis.

Some limitations of our study must be considered when interpreting the results. First, the sample size is relatively small, especially for those who performed NVC, this may affect the statistical power of the study. To establish further correlations between OCTA and clinical severity scores, larger and adequately powered studies are needed. Then, this research was conducted at a single- third level center, limiting its generalizability. In addition, most patients were receiving vasoactive treatment so we can hypothesize that some results could be influenced by the effect of this therapy and different results might be observed in patients not undergoing such treatment. Further studies with a prospective design or from large groups with reliable longitudinal data should be performed in the future.

There are some final practical clinical interpretations for ophthalmologist point of view that is important to underline.

Retinal OCTA can detect subclinical microangiopathy in SSc, even in the absence of visible retinopathy or visual symptoms. The retina therefore behaves as a systemic microvascular biomarker, acting as a window into scleroderma-related vasculopathy. The presence of similar retinal vascular alterations in VEDOSS and established SSc suggests that endothelial injury occurs early in the disease course, supporting a potential role for OCTA in screening high-risk patients. For ophthalmologists, these findings indicate that systemic sclerosis leads to early, diffuse retinal microvascular impairment, with OCTA revealing capillary rarefaction that parallels peripheral microangiopathy before clinical retinopathy becomes evident. While the FAZ appears preserved in early disease, parafoveal thickening may reflect subclinical inflammation or retinal remodeling. Overall, OCTA offers valuable pathophysiological insight into systemic vascular dysfunction and represents a promising non-invasive research and monitoring tool, although it does not yet warrant changes in immediate clinical decision-making or serve as a routine marker of disease severity.

In conclusion, this study highlights that ocular microangiopathy is present in scleroderma patients since the early stages of the disease and correlated with capillaroscopic alterations. SSc affects retinal microcirculation, even without obvious ophthalmologic symptoms, with widespread retinal vascular changes involving both superficial and deep vascular layers and showing a parafoveal retinal thickening reflecting a subclinical disease. These data support the concept of early systemic endothelial dysfunction in SSc pathogenesis and that the retina acts as a “window” to systemic microcirculation even without clinical retinopathy suggesting that OCTA may represent a fast and non-invasive marker of systemic microvascular damage. Moreover, for clinical practice, the absence of significant OCTA differences between VEDOSS and established SSc showed that retinal OCTA changes may appear before severe systemic manifestations, and OCTA could represents a potential tool for monitoring disease severity in SSc. Further studies are needed to clarify whether these retinal changes correlate with internal organ involvement, disease duration, or progression, and whether they may

have prognostic value in systemic sclerosis.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The research project was approved by the local Institutional Ethics Committees (Modena, protocol no. 275/16).

Consent

All patients enrolled gave their informed consent for the study and for the gynecological evaluation and the research project

Data and/or code availability

Data available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

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Authorship

As corresponding author, I certify:

All authors have made a substantial contribution to the conception and design, or the acquisition of data, or the analysis and interpretation of data, as well as to the drafting or critical revision of the manuscript, and accept public responsibility for portions of the content.
All authors have seen and agree with the order of authorship as stated on the accepted manuscript and verify that all persons named as authors meet the criteria for authorship.
All authors verify that the manuscript represents valid work.
All authors have reviewed the final manuscript and approve it for publication.
All authors confirm that neither this manuscript, nor any other with substantially similar content by one or more of the same authors, has been published, accepted or is currently being considered for publication elsewhere except as an abstract.
I confirm that all authors have had access to the raw data and that, upon request, will produce the data on which the manuscript is based for examination by the Editor or their assignee.
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I, the corresponding author of this manuscript, certify the above to be true.

Declaration of competing interest

Martina Orlandi, Tommaso Verdina, Filippo Santoro, Mohammed El Alouani, Matteo Gibertini, Mariagrazia Nuara, Alessandra Carobbio, Giorgia Roveta, Amelia Spinella, Marco De Pinto, Giuseppe Querques and Dilia Giuggioli have no conflict of interest to declare.

Supplementary materials

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