Retinal microcirculation abnormalities in patients with systemic sclerosis: an explorative optical coherence tomography angiography study.

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KEY MESSAGES

- Microvascular retinal involvement has been poorly studied in patients with systemic sclerosis
- Retinal microvascular abnormalities can be demonstrated in patients with systemic sclerosis by using OCT-A
- OCT-A may represent a novel tool for diagnosis, monitoring and prognosis stratification in systemic sclerosis

ABSTRACT

Objectives: To investigate subclinical or clinical abnormalities in retinal and choroidal vascular plexuses in patients with systemic sclerosis (SSc) by means of optical coherence tomography angiography (OCT-A).

Methods: A total of 20 consecutive SSc patients were recruited and compared to 20 healthy subjects. Quantitative analysis of vessel density (VD), choriocapillaris plexus flow index (CCP-FI) and choroidal vascularity index were performed on OCT-A images in the superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris for all patients. Images were further reviewed by two independent readers for the assessment of qualitative abnormalities, including tortuosity, rarefaction areas, megacapillaries and macular-foveal capillaries (MFC).

Results: The DCP-VD in the whole scan and in parafoveal, superior, inferior, nasal and temporal regions was significantly lower in the SSc group. The CC-FI was significantly higher in SSc patients. When comparing SSc patients with and without digital ulcers (DUs), significantly reduced SCP-VD was demonstrated in the whole, parafoveal, superior, inferior, temporal and nasal regions. No difference in any of the OCT-A parameters was observed when comparing patients with or without interstitial lung disease (ILD). Qualitative analysis of OCT-A revealed at least one abnormality in 95% of patients.

Conclusions: We showed the ability of OCT-A to disclose early ocular vascular abnormalities in patients with SSc. Our results may represent a hypothesis-generating basis for exploring the potential role of OCT-A in diagnosis, monitoring and prognosis stratification in SSc.

KEYWORDS

Systemic sclerosis; optical coherence tomography angiography; vessel density; megacapillary

INTRODUCTION

Systemic sclerosis (SSc) is a multisystem disease characterized by microvascular dysfunction, autoimmunity, and fibroblasts activation [1]. Capillary injury, the earliest pathological feature seen in SSc, drives the remodelling of vessels, migration of smooth muscle cells in intima and obliteration of the lumen[2]. The resulting ischemia-reperfusion injury triggers the release of mediators promoting myofibroblasts differentiation and production of large amount of extracellular matrix (ECM) leading, ultimately, to uncontrolled tissue fibrosis [2]. These events extend beyond the skin, and occur in many tissues such as heart, lungs, or gastrointestinal tract [2].

Ocular involvement, mainly presenting as dry eye, has been described in patients with SSc [3]. Other clinical manifestations include keratoconjunctivitis, changes of eyelid skin, impairment of extraocular muscles, episcleritis, scleritis, uveitis, peripheral ulcerative keratitis, glaucoma, enophthalmos and cataract. On the other side, retinal involvement has been poorly studied although a cross-sectional study reported retinal abnormalities on fundus examination in one third of SSc patients [4].

While capillary abnormalities in patients with SSc are routinely assessed by nailfold videocapillaroscopy (NVC), retinal and choroidal microvessels can be studied in a non-invasive, dye-free way through the novel optical coherence tomography angiography (OCT-A) technique [5, 6]. To date, retinal microvasculature has not been studied in SSc, although its physiological characteristics – high metabolism and oxygen demand – justify a greater vulnerability to ischemic stress as exemplified in diabetic retinopathy. On this basis, aim of the present study was to investigate subclinical or clinical abnormalities in retinal and choroidal vascular plexuses in patients with SSc by means of OCT-A imaging.

METHODS

Patients

Consecutive adult patients with limited cutaneous SSc fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism criteria [7] were recruited.

Exclusion criteria were predefined as follows: a) inadequate pupillary dilation and fixation required for high-quality OCT-A imaging, b) past or current history of retinal diseases (e.g., retinal vascular diseases, vitreoretinal diseases, central serous retinopathy or macular dystrophies), and c) previous eye surgery or laser photocoagulation. Age- and sex-matched healthy hospital staff were used as control group. The study protocol was approved by the local Ethics Committee (Comitato Etico Sezione Area Centro - Regione Calabria – n°37/2018, 22/02/2018). All study procedures were conducted after written informed consent.

Clinical evaluation

The extent of skin involvement was evaluated using the modified Rodnan skin score (mRSS). History of digital ulcers (DUs), or presence of interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), gastrointestinal involvement was recorded as dichotomic variable.

Eye examination

A comprehensive ophthalmologic examination was performed to identify exclusion criteria including measurement of best corrected visual acuity (BCVA), dilated slit lamp anterior segment and fundus biomicroscopy, intraocular pressure (IOP), and structural spectral domain-OCT (SD-OCT).

OCT-A protocol

OCT-A scan was performed on the right eye with a XR Avanti AngioVue (Optovue, Fremont, USA) instrument using a scanning area of 3 x 3 mm centred on fovea. This system employs a split-spectrum amplitude decorrelation angiography (SSADA) algorithm and operates at 70,000 A-scans per second using a light source of 840 nm.

OCT-A Quantitative analysis

The proprietary software segments OCT-A scans into four en-face slabs: the superficial capillary plexus (SCP), the deep capillary plexus (DCP), the outer retinal plexus and the choriocapillaris plexus (CCP) providing an automatically calculated SCP and DCP perfusion density (VD) in the whole image, and in foveal and parafoveal regions. The parafoveal region is further divided into four fields: the superior, inferior, temporal, and nasal quadrants. A flow

index (CCP-FI, mm^2), expressing the area covered by vessels, is automatically calculated from the CCP slab in a circular zone of 3.144 mm^2 of a 3 x 3 mm macular angiogram[8].

Choroidal vascularity index

The choroidal vascularity index (CVI), defined as the proportion of luminal area (LCA) to the total choroidal area (TCA), was calculated from high-resolution SD-OCT images obtained using a RTVue (Optovue, Fremont, USA) instrument using the software IMAGE J (National Institutes of Health, Bethesda, USA) as previously described [9, 10].

OCT-A Qualitative analysis

Two different readers (VG and FF) performed qualitative assessment to identify capillary tortuosity, rarefaction of perifoveal capillaries, and megacapillaries. Megacapillaries were defined as relatively dilated irregular loops or networks of capillaries with a diameter of at least twice of that of the surrounding normal-sized vessels in the DCP of the macular region. Furthermore, the presence of macular-foveal capillaries (MFC) – defined as the presence of intraretinal polygonal or straight vascular nets in communication with the surrounding retinal capillary bed – either complete (total absence of avascularity) or incomplete (few thinner vessels crossing through the macula) was evaluated. Disagreement was resolved by consultation with a third senior reader (AC).

Statistical analysis

Data are expressed as mean ± standard deviation, or number (percentage). The Student's T test was used for comparing means of normally-distributed continuous variables. Pearson's correlation analysis was used to evaluate the relationship between OCT-A parameters and other continuous variables. A two-tailed *p* value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS software, v23.

RESULTS

A total of 20 patients with SSc and 20 control subjects were included. General characteristics are described in Supplementary Table S1. Best corrected visual acuity was 20/20 Snellen equivalent in both groups while IOP was 14.85 ± 2.58 in SSc patients versus 15.15 ± 2.25 in controls (p = 0.71). Three out of 20 SSc patients, but none of the controls, had microhaemorrhages in the retinal periphery seen at the standard fundus biomicroscopy, not affecting the OCT-A acquisition that is performed in the macular region.

No significant difference in the SCP-VD between SSc patients and control subject was observed. Quantitative analysis of OCT-A scans showed that the DCP-VD in the whole scan and in parafoveal, superior, inferior, nasal and temporal regions was significantly lower in the SSc group (Table 1). The CC-FI was significantly higher in SSc patients (Table 1). When comparing SSc patients with and without DUs, significantly reduced SCP-VD was demonstrated in the whole (p = 0.03) parafoveal (p = 0.03), superior (p = 0.04), inferior (p = 0.03), temporal (p = 0.04) and nasal (p = 0.03) regions; no difference was observed in other OCT-A parameters. On the other side, no difference in any of the OCT-A parameters was observed when comparing patients with or without ILD.

In partial correlation analysis accounting for age, mRSS inversely correlated with DCP-VD in the nasal region (R = -0.51, p = 0.02) and with CMT (R = -0.455, p = 0.05) but not with other OCT-A parameters.

Qualitative analysis of OCT-A scans (Table 1) in SSc patients revealed capillary tortuosity in 9/20 (45%) eyes, rarefaction in 13/20 (65%) eyes and megacapillaries in 15/20 (75%) eyes (Figure 1). Complete MFC in SCP was found in 3/20 eyes, while 3/20 eyes had incomplete MFC in SCP. Complete MFC in DCP was found in 3/20 eyes, whereas incomplete MFC in DCP was detected in 3/20 (15%) eyes. In SSc patients 19/20 (95%) eyes showed at least one qualitative abnormality; none of the patients in the control group showed qualitative abnormalities.

DISCUSSION

Despite the incomplete comprehension of its pathogenesis, it is well accepted that SSc starts in the microcirculation network [11]. Posterior eye is one of the most metabolically active tissues in the body and therefore extremely sensitive to capillary injury; despite this, the retinal microvascular involvement in SSc has not yet been investigated.

In this exploratory study, we aimed at evaluating for the first time retinal and choroidal microvasculature by means of OCT-A in patients with SSc and demonstrating a reduced vessel density in SSc patients when compared to age- and sex- matched controls. Capillary density is an important quantitative parameter obtained from NVC [12] and its decline has been shown to correlate with the risk of developing DUs, PAH, skin involvement and autoantibody pattern [13, 14].

Interestingly, despite the explorative design of our study, we found a significant inverse correlation between DCP-VD in the nasal region and the extent of skin involvement. Furthermore, SCP-VD – mainly depicting arterioles and venules – was lower in patients with a clinical history of DUs. Intriguingly, not only capillaries but also small calibre (e.g. digital) arteries abnormalities have been shown in SSc [15] and participate in the vicious circle that culminates in development of DUs [16]. Unfortunately, the small sample size hampered the possibility to further explore the potential correlation between VD and other domains (e.g., PAH) or the association with individual NVC patterns.

On the other hand, we did not find any difference in CVI (the proportion of the luminal to the total choroidal area) when comparing SSc patients and controls, implying a preserved ratio between the vascular and stromal components. At the same time, we have shown a significant increase in the CCP-FI, reflecting the area covered by vessels in the choriocapillaris. Taken together, these data suggest that the choroidal vasculature seems not primarily affected in SSc and perhaps may represent a site where compensatory mechanisms occur in order to counterbalance the increased oxygen demand by the retinal layers secondary to the abnormalities found in the SCP and DCP. On the other side, given the unaltered CVI, it is possible to hypothesize that the increased choroidal vessel area may be accompanied by a consensual increase in the stromal compartment (e.g., inflammatory infiltrate or matrix accumulation).

Even though the emerging importance of quantitative measures, the capillaroscopic diagnosis of SSc is based on the identification of morphological abnormalities, namely megacapillaries or bizarre/ramified capillaries.

To explore the possibility that similar findings may be seen in retinal microvessels, we examined OCT-A images to identify abnormal capillaries resembling what found in NVC. Intriguingly, we found that 19/20 patients had at least one morphological abnormality, 75% of which represented by megacapillaries. Furthermore, 15% of patients showed MCP in either SCP or DCP; this condition, usually associated with defined congenital or acquired retinal diseases[18], is rare in general population and represents an aberrant neovascularization process resulting from microvascular injury as seen in diabetic retinopathy[18].

Identification of megacapillaries, the single morphological abnormality with highest sensitivity and specificity [19], is crucial in capillaroscopic diagnosis. Unfortunately, the lack of an adequate sample size impaired the direct comparison between qualitative assessment of OCT-A and NVC; despite this, it is possible to hypothesize a potential role of OCT-A in identifying scleroderma spectrum abnormalities at least in those patients in which NVC is technically difficult. Moreover, digitally stored images can be fully reassessed independently in contrast with NVC [20].

In conclusion, our results, beyond demonstrating a previously unrecognized subclinical retinal/choroidal involvement in patients with SSc, may represent a hypothesis-generating basis for exploring the potential role [19] of OCT-A for diagnosis, monitoring and prognosis stratification in SSc. Adequately powered studies are needed to evaluate the correlation between OCT-A, NVC findings and the sensitivity to detect highly suspicious abnormalities (e.g., megacapillaries) in those patients with doubtful NVC findings or when the latter is technically difficult.

Data availability

The data underlying this article are available in the article.

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Conflicts of interest

The authors declare no conflicts of interest.

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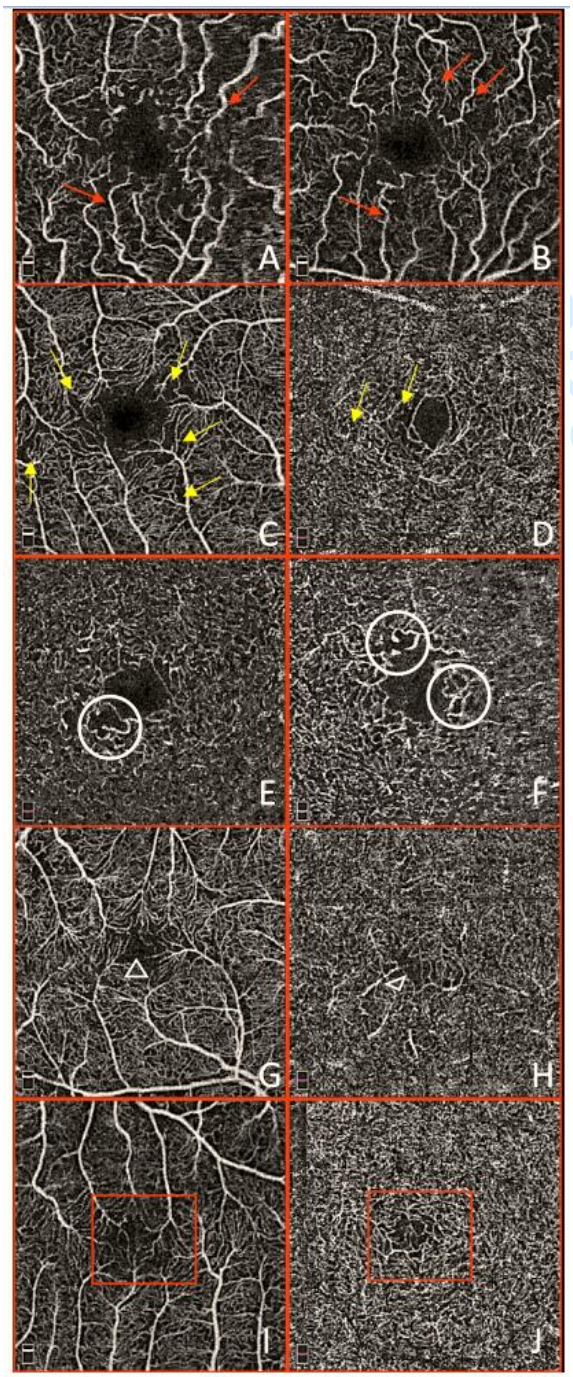
Variable	SSc (n = 20)	Control (n = 20)	*P* value
SCP			
Whole	45.67 ± 5.21	45.64 ± 3.22	0.98
Fovea	24.53 ± 7.82	23.31 ± 3.34	0.53
Para-foveal	48.09 ± 5.19	48.15 ± 3.34	0.97
Superior	48.19 ± 5.21	47.99 ± 3.55	0.89
Inferior	48.00 ± 5.32	48.20 ± 3.48	0.89
Temporal	47.00 ± 4.34	45.83 ± 3.98	0.38
Nasal	47.53 ± 5.59	47.48 ± 3.37	0.97
DCP			
Whole	47.29 ± 3.49	50.81 ± 3.71	0.00
Fovea	35.54 ± 8.14	38.84 ± 4.99	0.13
Para-foveal	49.07 ± 3.02	52.23 ± 3.63	0.00
Superior	49.41 ± 3.21	52.12 ± 3.81	0.02
Inferior	48.72 ± 3.04	52.33 ± 3.59	0.00
Temporal	49.53 ± 3.33	52.54 ± 4.12	0.02
Nasal	49.46 ± 3.10	52.44 ± 3.45	0.01
CMT	269.45 ± 18.100	270.95 ± 19.97	0.80
CCP - FI	2.15 ± 0.11	2.07 ± 0.09	0.01
CVI	66.58 ± 1.13	66.70 ± 1.83	0.80
Tortuosity, n (%)	9 (45)	0 (0)	-
Rarefaction, n (%)	13 (65)	0 (0)	-
Megacapillaries, n (%)	15 (75)	0 (0)	-
MFC in SCP			
Incomplete, n (%)	3 (15)	0 (0)	-
Complete, n (%)	3 (15)	0 (0)	-
MFC in DCP			
Incomplete, n (%)	3 (15)	0 (0)	-
Complete, n (%)	3 (15)	0 (0)	-

Table 1. Quantitative and qualitative analysis of 3x3 OCT-A scans. CCP-FI, choriocapillaris plexus flow index; CMT, central macular thickness; CVI, choroidal vascularity index; DCP, deep capillary plexus; MFC, Macular-foveal capillaries; SCP, superficial capillary plexus; SSc, systemic sclerosis.

Figure 1. Representative images of capillary abnormalities obtained from qualitative analysis of optical coherence tomography angiography (OCT-A) angiograms in patients with systemic sclerosis. A-B: OCT-A images of superficial capillary plexus (SCP) showing capillary tortuosity (red arrows). C-D: OCT-A images of SCP (A) and deep capillary plexus (DPC) (D) showing rarefaction of perifoveal capillaries (yellow arrows) E-F: OCT-A images of DPC showing the presence of megacapillaries (white circle). G-H: OCT-A images of SCP (G) and DPC (H) showing incomplete macular-foveal capillaries (MFC) (white arrow-head). I-J: OCT-A images of SCP (I) and DPC (J) showing complete MFC (red square).



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