Structural abnormalities associated with glaucoma using swept-source optical coherence tomography in patients with systemic sclerosis

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ABSTRACT

Purpose Vasospasm represents an early event in systemic sclerosis (SSc). Ocular vasospasm may induce optic nerve head (ONH) damage and has been involved in the pathogenesis of glaucoma, especially normal-tension glaucoma (NTG). We aimed to investigate the presence of structural abnormalities associated with NTG using swept-source optical coherence tomography (SS-OCT) and to correlate the OCT parameters with clinical, capillaroscopy and digital blood flow measures in patients with SSc.

Methods In this cross-sectional study, 40 patients with SSc and 23 age-matched controls were included. The following parameters were measured using SS-OCT: mean and sectoral retinal nerve fiber layer (RNFL) thickness, macular ganglion cell layer complex (GCC) thickness and ONH morphology. Nailfold capillaroscopy (NFC) and digital blood flow measurements using laser Doppler imaging (LDI) were performed in all subjects.

Results Patients with SSc showed a thinner temporal RNFL than the controls (69.23 ± 11.74 versus 83.35 ± 20.19 µm, p=0.001). The other parameters were similar between the two groups. In SSc patients, there was an inverse correlation between the disease duration and the average, superior and inferior RNFL thickness and the GCC thickness and between Raynaud's phenomenon duration and the average RNFL and GCC thickness (p<0.05). NFC and LDI measurements did not show correlations with OCT parameters.

Conclusion A thinner temporal RNFL and the correlation between Raynaud's phenomenon and disease duration and structural abnormalities on OCT suggest the presence of early ganglion cell damage in patients with SSc. Although mild, these findings indicate the need to monitor ocular abnormalities in SSc.

Keywords: Systemic sclerosis, Normal-tension glaucoma, Optical coherence tomography, Retinal nerve fiber layer thickness.
Introduction

Systemic sclerosis (SSc) is a chronic autoimmune rheumatic disease characterized by immune activation, vascular abnormalities and fibrosis of the skin and internal organs. Activation of fibroblasts and dysfunctional repair of connective tissue lead to skin and organ fibrosis of multiple organs, including the lung, heart, kidneys and gastrointestinal tract [1, 2].

Vascular dysfunction, characterized by vasospasm and endothelial activation, represents a central and early event in SSc. In fact, dysregulation of vascular tone control, which is clinically expressed as Raynaud’s phenomenon (RP), is the earliest and most frequent clinical manifestation of SSc and may precede other manifestations of the disease by months or years [3]. In SSc, microvascular endothelial cell injury and progressive proliferation of the intima lead to vessel narrowing and decreased vascular blood flow, leading to chronic tissue ischaemia [4-6]. The morphological abnormalities of the microcirculation can be detected by nailfold capillaroscopy (NFC). Enlarged and giant capillaries, microhaemorrhages and loss of capillaries with formation of avascular areas are the typical abnormalities in NFC [7]. Moreover, the peripheral microvascular damage observed in SSc can also be observed in all affected organs, including the heart, kidneys, and eyes [8].

Glaucoma is a progressive degenerative optic neuropathy characterized by the death of retinal ganglion cells and their axons, with typical changes in the optic nerve head (ONH) and retinal nerve fiber layer (RNFL) and progressive visual loss [9, 10]. Although the level of intraocular pressure (IOP) is an important feature related to the development of glaucoma, other factors, including ocular vasospasm, may induce ONH damage and have been involved in the pathogenesis of glaucoma, especially normal-tension glaucoma (NTG) [10,11].

The diagnosis of glaucoma includes functional evaluation of the visual field and structural documentation of damage of the ONH based on retinography and optical coherence tomography (OCT) examinations [11]. Nonetheless, studies have shown that characteristic visual field defects are detectable when only as many as 30% to 50% of retinal ganglion cells are lost [9]. Thus, documentation of structural damage to the optic nerve is a critical component of the diagnosis of the disease. In this context, several recently developed imaging techniques, such as OCT, particularly its spectral domain variant (SD-OCT), provide more objective and quantitative information about the amount of optic nerve fiber (retinal ganglion cell axon) loss [9]. Swept-source spectral-domain OCT (SS-OCT) is a high-resolution imaging method for the quantitative assessment of the ONH and RNFL that offers several potential advantages in comparison to SD-OCT, including higher imaging speeds, higher detection
efficiencies, improved imaging range, and reduced sensitivity roll-off with imaging depth [12, 13]. A few studies have evaluated ocular glaucomatous abnormalities in patients with SSc using different methods and have shown conflicting results [14-17]. Only one study evaluated the parameters of the optic nerve head and RNFL using SD-OCT in patients with SSc [17]. The authors observed a thinner RNFL in the lower quadrant only in patients with an excavation/vertical disc ratio > 0.5 when compared with the control group and suggested that SSc is a risk factor for the development of NTG [17].

The present study aimed to investigate the presence of structural abnormalities of the ONH, RNFL and macular ganglion cell complex (GCC) using SS-OCT and to correlate the OCT parameters with clinical, capillaroscopy and digital blood flow measures in patients with SSc compared with normal controls.

Patients and methods

Patients

In this cross-sectional study, 40 patients with SSc fulfilling the 2013 ACR/EULAR classification criteria [18] and followed at the Outpatient Clinic of the Rheumatology Division of Escola Paulista de Medicina, Federal University of São Paulo, were consecutively included. Twenty-three age- and sex-matched controls were also included. The control group was selected by inviting patients from the osteoarthritis outpatient clinic, as well as colleagues of the patients included in the study. The study was approved by the local ethics committee of the institution. All participants provided written informed consent before enrolment. Patients younger than 18 years old, with overlapping syndromes with other rheumatic diseases, or with a diagnosis of glaucoma or any other significant ocular pathology were excluded.

Clinical and laboratory assessment

Demographic and clinical data were collected from all patients, including age, sex, RP duration before diagnosis, and disease duration (defined as the onset of the first non-Raynaud’s symptom). Information regarding visceral involvement and the presence of anti-centromere and anti-Scl-70 auto-antibodies was obtained through electronic medical records. The presence of the following clinical manifestations was recorded: telangiectasias, oesophageal dysmotility, digital ulcers, digital pitting scars, and scleroderma renal crisis. Interstitial lung involvement was evaluated by means of pulmonary function tests and high-resolution computed tomography. Pulmonary arterial systolic pressure (PASP) was assessed using Doppler echocardiography. The modified
Rodnan skin score was evaluated in all patients by the same physician on the day of NFC evaluation, as previously described [19]. The SSc patients were also classified into diffuse cutaneous (dcSSc) or limited cutaneous (lcSSc) disease groups [20]. Drug therapy data were collected from all individuals.

Nailfold capillaroscopy (NFC) and the measurement of digital blood flow by means of laser Doppler imaging (LDI) before and after cold stimulus were performed in all subjects in the same week as the ophthalmologic evaluation.

NFC was performed using a stereomicroscope (SZ40, Olympus), with magnification of 10-25 times in both hands excluding the thumb [21]. In brief, the following parameters were evaluated: number of capillaries/mm, the number of giant (10 or more times the normal width of capillary limbs) capillary loops, the number of microhaemorrhages, and the avascular score [7, 22]. The avascular score was determined semi-quantitatively on a scale of 0 to 3. All of the parameters were recorded as the average obtained for all of the analysed fingers.

The blood flow of the cutaneous microcirculation of the fingertips was assessed using LDI (Moor LDI, Moor Instruments, Axminster, United Kingdom). The evaluation was performed at baseline (after resting for 30 min at a room temperature of 24°C ± 1°C) and at 1, 10 and 20 minutes after cold stimulus (performed by immersing both hands in water at 15°C for 60 seconds). The blood flow of the dorsum of the four fingertips of the non-dominant hand (excluding the thumb) was determined by establishing four regions of interest at each fingertip, defined as an area from the proximal interphalangeal joint up to and including the nailbed. The images were recorded using Moor LDI software on a computer for later retrieval and evaluation. The global mean finger blood flow (FBF) of the four fingertips was derived (Moor LDI system software V5.2) and averaged. Blood flow was expressed in arbitrary perfusion units (PUs).

**Ophthalmologic assessment**

All participants underwent complete ophthalmic examination conducted at the Department of Ophthalmology of the Federal University of São Paulo, including (1) best-corrected visual acuity; (2) IOP measurement using Goldmann's tonometry; (3) slit-lamp biomicroscopy; (4) gonioscopy using a four-mirror lens technique; 5) pachymetry for the evaluation of corneal thickness using ultrasonic pachymetry with the SP-3000 pachymeter (Tomey, Phoenix, USA); and (6) dilated fundus examination.

All participants underwent Humphrey visual field (HVF) tests (Carl Zeiss Meditec, Dublin, CA, USA) using the Swedish Interactive Threshold Algorithm (SITA) standard 24-2 strategy. A visual field mean deviation (VF-MD) of < -2 decibels (dB) was
considered significant. Only reliable tests (fixation loss ≤ 33%, false positive rate ≤ 20% and false negative rate ≤ 20%) were included.

**Retina fundus photographs and swept-source optical coherence tomography**

All recruited subjects were dilated to obtain images with the best quality. A commercially available swept-source optical coherence tomography (SS-OCT, Deep Range Imaging OCT Triton, Topcon, Tokyo, Japan) system was used to image both eyes of all subjects. The following parameters were evaluated: average and sectoral RNFL thickness, macular ganglion cell layer (GCL) and inner plexiform layer (IPL) thickness and ONH morphology as previously described [23]. Three-dimensional 6 × 6 mm optic disc cube raster scans with 512 × 256 resolution were obtained with SS-OCT operating at 100,000 A-scan/sec. The average RNFL thickness and the average thickness of the four quadrants (i.e., superior, temporal, inferior, and nasal) were automatically obtained (Fig. 1). The following ONH parameters were measured: disc area (mm²), excavation volume (mm³), rim area (mm²), and vertical cup-to-disc ratio (VCDR). The measurement of the macular ganglion cell complex was performed using the protocol "Glaucoma Analysis-macula" used to create a map with the mean thickness of the GCL + IPL and the total GCL (RNFL + GCL + IPL). Only good-quality images, presenting at least a signal-to-noise ratio greater than 25 dB, were considered for analysis, as suggested by the OCT device manufacturer.

**Statistical analysis**

Demographic and OCT data are presented as the mean and standard deviation (SD) or absolute number and frequency. OCT data from the right eye of each subject were used for analysis. The Kolmogorov-Smirnov or Shapiro test was used to evaluate the distribution of variables. Student’s t tests were used to compare continuous variables with a normal distribution, and the Mann-Whitney test was used to compare continuous variables with a non-normal distribution. For the comparison between qualitative variables, the chi-square test or the Fischer test was used. To analyse the correlation between two variables, Spearman’s correlation coefficient or Pearson’s correlation was used. For the performance of all tests, SPSS (Statistical Package for the Social Sciences) version 25 was used. For all analyses, the significance value was considered as less than 5% (p<0.05).
Results

Forty patients with SSc with a mean age of 51.95 ± 11.18 years and 23 controls with a mean age of 55.00 ± 9.20 years were evaluated. There was a predominance of females in both groups (92.5% in patients with SSc and 82.6% in controls; p = 0.089). Among patients with SSc, the mean disease duration was 11.71 ± 9.89 years, and 40% had diffuse cutaneous SSc. The demographic and clinical characteristics of the patients are summarized in Table 1. Among the medications used by SSc patients, two patients (5%) were currently using corticosteroids, and 17 (42.5%) had previously used corticosteroids (prednisone <10 mg/day). Antimalarials were currently used by 3 patients (7.5%), and 13 (32.5%) had used them previously. Sixteen patients (40%) were using cyclophosphamide, 8 patients (20%) methotrexate, and 5 patients (12.5%) mycophenolate. Calcium channel blockers were currently being used by 22 (55%) of the patients, and sildenafil was used by 9 (22.5%) of the patients.

As expected, nailfold capillaroscopy showed a significantly decreased number of capillaries/mm and a significantly higher number of giant capillaries, microhaemorrhages and avascular score in patients with SSc compared to controls (p <0.001). The mean FBF at baseline and after cold stimulus was also significantly lower in patients with SSc compared to controls (p <0.001) (Table 1).

The visual field evaluation showed significantly lower VF-MD in patients with SSc compared to controls (-2.68 ± 2.28 versus -1.34 ± 1.79 dB, respectively, p=0.032). Visual field defects (VF-MD < -2.00 dB) were found in 18/40 of the patients with SSc and in 7/23 of the controls (p=0.259). A VCDR > 0.3 was observed in 31/40 of the patients and in 15/23 of the controls (p=0.379), and a VCDR > 0.7 was observed in 5/40 of the patients and in 2/23 of the controls (p=0.494).

Patients with SSc showed a thinner temporal RNFL thickness compared to controls (69.23 ± 11.74 µm versus 83.35 ± 20.19 µm, respectively, p=0.001). However, the average RNFL thickness and the thickness of the other quadrants (nasal, superior and inferior) were similar between the two groups. Morphological parameters of the optic disc and the ganglion cell layer complex thickness were also similar between the groups (Table 2). RNFL thickness was similar between SSc patients with visual field defects and those without visual field defects (data not shown).

Data were also compared between patients with diffuse and limited cutaneous SSc. The visual field-pattern standard deviation (VF-PSD) indices were significantly higher in patients with limited SSc than in patients with diffuse SSc (p = 0.027). The cup volume and VCDR were also significantly higher in patients with limited SSc than in patients with diffuse SSc (0.14 ± 0.11 versus 0.08 ± 0.09 mm³, p = 0.005; 0.58 ±
0.19 versus 0.40 ± 0.22, p <0.001, respectively). The average RNFL thickness and the ganglion cell complex thickness were similar between the two groups (Table 3).

In SSc patients, there was an inverse correlation between disease duration and the mean RNFL thickness (R = -0.460; p = 0.003), inferior RNFL thickness (R = -0.353; p = 0.025) and superior RNFL thickness (R = -0.495, p = 0.001), as well as an inverse correlation between RP duration and mean RNFL thickness (R = -0.393; p = 0.012). There was also a significant inverse correlation between the disease duration and RP duration and the mean GCL+ IPL thickness (R=-0.431, p=0.005; R=-0.389, p=0.013, respectively) and total GCL thickness (R=-0.379, p=0.015; R=-0.332, p=0.035, respectively) (Fig. 2). The analysis of capillaroscopy parameters showed no correlation between NFC and OCT measurements (Table 4). The evaluation of a possible correlation between the cutaneous digital blood flow before and after a cold stimulus evaluated by LDI did not show a significant correlation between the variables and the OCT parameters (data not shown).

Discussion

Microvascular abnormalities, including decreased peripheral blood flow and increased levels of endothelin-1, are important features in the pathogenesis of SSc and have also been described in glaucoma [24]. In this context, there is increasing evidence that vascular dysregulation might be involved in the development of glaucomatous optic neuropathy [25-27]. Several vascular dysfunctions, such as autonomic dysfunction, systemic arterial hypotension, migraine, RP, and decreased ocular blood flow, have been described in glaucomatous patients and might result in optic nerve ischaemia and damage [28]. Thus, we investigated the presence of early structural changes that occur in glaucoma in patients with SSc.

In the present study, a significant decrease in the temporal RNFL thickness was observed in patients with SSc compared with healthy controls. Nonetheless, the average RNFL thickness, ganglion cell complex and morphology of the ONH were similar to those of the controls. On the other hand, an inverse correlation was found between disease and RP duration and the mean RNFL thickness and the ganglion cell layer complex thickness, as well as between disease duration and the inferior and superior RNFL thickness. These findings suggest early ocular microvascular dysfunction in patients with SSc.

Several ocular manifestations, including the anterior and posterior segments, have been described in patients with SSc, but most have been reported in a small number of patients and need further investigation [29]. Yamamoto et al. was the first
author to evaluate the frequency of glaucoma in 153 Japanese patients with collagen
diseases, including 41 patients with SSc [30]. The prevalence of NTG and primary
open angle glaucoma was higher only in female patients with collagen disease
compared with healthy women [30]. Of the 41 patients with SSc, one had NTG. More
recently, two studies investigated the prevalence of glaucomatous abnormalities in
patients with SSc [14,15]. In both studies, ocular abnormalities suggestive of
glaucomatous neuropathy defined by a combination of cup/disc > 0.3 and visual field
defects (MD <-2) were found at a higher frequency in patients with SSc. Nonetheless,
the definition of NTG used in these studies is not used in several major studies of NTG
and is not specific for NTG [31]. In our study, we did not find a higher frequency of
patients with SSc with visual field defects or VCDR > 0.3.

Indeed, there is no consensual definition of glaucoma, especially NTG, due to
great variability in the characteristics of the optic disc in normal individuals and the lack
of sensitivity of visual field testing [32, 33]. OCT can provide high-resolution,
reproducible, and quantitative measurement of the optic nerve and retinal layers. In
addition to RNFL thickness, other parameters, including the neuroretinal rim area,
macular ganglion cell layer and inner plexiform layer thickness, can be determined
increasing the sensitivity for the identification of early structural changes and for the
evaluation of disease progression [34, 35]. In the present study, we used for the first
time swept-source OCT, a more recent technology that allows faster and better quality
capture, as well as the evaluation of the RNFL, macular ganglion cell layer and inner
plexiform layer in a single scan [36].

In our study, we observed a significant decrease in the temporal RNFL thickness
in patients with SSc. The mechanisms behind the reduction in the temporal RNFL
thickness in SSc are not entirely elucidated but could be associated with a greater
susceptibility to vasoconstriction or ischaemia in this region. The thinning of the RNFL
in the temporal quadrant can be found in several diseases with optic nerve atrophy,
such as post-neuritic optic atrophy in multiple sclerosis and hereditary and toxic optic
atrophies, and could reveal an early state of optic nerve atrophy [36]. Additionally, it
has been described in patients with migraine, a pathology characterized by episodes of
vasoconstriction and visual dysfunction [37].

Our results are similar to the findings of Sahin-Atik et al., who found no difference
in the parameters of the optic nerve head and average RNFL using SD-OCT in 30
patients with SSc compared to 28 controls [17]. The authors observed only a thinner
RNFL in the lower quadrant in patients with an excavation/vertical disc ratio > 0.5 when
compared with the control group [17], although the excavation/vertical disc ratio cut-off
point > 0.5 is not used to define glaucomatous optic neuropathy in other studies.
The analysis of the parameters of the optic disc morphology showed similar values between patients with SSc and controls. The group of patients with limited cutaneous SSc had a higher VCDR and a higher cup volume, suggestive of damage to the optic nerve head, compared to patients with diffuse SSc. Nonetheless, these values were within the normal ranges, and the significance of these findings should be interpreted with caution.

We found no difference in the measurements of the ganglion cell layer complex between patients with SSc and controls. The assessment of the macular ganglion cell and inner plexiform layer thickness, a measurement that was recently made possible, is useful for the evaluation of structural changes in the internal layer of the retina and provides critical information for the early diagnosis of glaucoma [38]. Only one study has previously evaluated the GCC in SSc and found a thinner average GCC thickness in patients with primary and secondary RP [39]. However, in our study, a negative correlation between disease and RP duration and ganglion cell complex thickness and between disease duration and inferior and superior RNFL thickness was observed, suggesting that a long RP duration with recurrent ischaemia-reperfusion injury could promote ischaemia and damage to the ONH. Further prospective studies are needed to better elucidate this hypothesis.

In the present study, we also originally assessed a possible association between OCT and the structural and functional changes in the peripheral microcirculation using NFC and laser Doppler imaging in patients with SSc. NFC is a widely used method for the assessment of the morphological abnormalities of the microcirculation in SSc. The lack of association with the peripheral microvascular abnormalities evaluated by NFC is in agreement with a previous study with 31 SSc patients in which 7 (23%) patients were diagnosed with glaucoma [16]. As in our study, there was no association between the NFC pattern and the presence of glaucoma [16]. In our study, there was also no association between the peripheral blood flow assessed by LDI and the ocular findings obtained by OCT, indicating that different mechanisms are probably involved in the peripheral vasospasm and the ocular microvascular damage involved in the pathogenesis of NTG.

Our study has several limitations, including the number of study participants, the absence of prospective follow-up to assess a possible development of NTG in patients with early structural changes, and the absence of assessment of serum markers of endothelial injury that could be compared to OCT data.

In conclusion, this is the first study to evaluate different structural parameters using SS-OCT as well as a possible association between peripheral vascular abnormalities and ocular abnormalities associated with glaucoma in patients with SSc.
In the present study, we observed a significant decrease in the thickness of the temporal RNFL in patients with SSc compared to a group of controls. There was also an inverse correlation between disease and RP duration and RNFL thickness and macular ganglion cell complex thickness. These abnormalities, although mild, may indicate the presence of early damage and a high risk for the development of glaucomatous changes in these individuals. Further prospective studies with a larger number of patients are needed to better comprehend the ocular changes present in patients with SSc.

Declarations

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Authors’ contributions: CAT and JS participated in the design of the study, carried out the study, analyzed the data and drafted the manuscript. INFA and EVT conducted experiments and helped to draft the manuscript. TSP and APJr have participated in the study’s coordination and have helped to draft the manuscript. CK supervised the research and drafted the manuscript.

Ethics approval: The study was approved by the local ethics committee and has been performed in accordance with the ethical standards of the Declaration of Helsinki.

Data availability: The data analyzed during the current study are available from the corresponding author upon request.

Consent to participate: All participants provided written informed consent before taking part in the study.

Consent for publication: All authors have agreed to the submission for the article.
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| Variable                                                                 | SSc (n=40)         | Controls (n=23) | p    |
|-------------------------------------------------------------------------|--------------------|-----------------|------|
| Age                                                                     | 51.95 ± 11.18      | 55.0 ± 9.2      | 0.07 |
| Sex (Male/Female), n (%)                                                | 3/37 (7.5/92.5%)   | 4/19 (17.4/82.6%) | 0.089|
| Disease duration (years)                                                | 11.71 ± 9.89       | -               | -    |
| RP duration (years)                                                     | 14.51 ± 11.20      | -               | -    |
| Clinical form (Diffuse/Limited), n (%)                                  | 16/24 (40/60)      | -               | -    |
| Modified Rodnan cutaneous score                                         | 7.63 ± 7.81        | -               | -    |
| Digital ulcers, n (%)                                                   | 16 (40%)           | -               | -    |
| Digital pitting scars, n (%)                                            | 18 (45%)           | -               | -    |
| Telangiectasias                                                        | 20 (50%)           | -               | -    |
| Forced vital capacity (% predicted)                                     | 84.59 ± 20.36      | -               | -    |
| Lung interstitial disease on chest CT, n (%)                            | 27 (67.5%)         | -               | -    |
| PASP on echocardiography (mmHg)                                         | 31.17 ± 11.14      | -               | -    |
| Oesophageal dysmotility, n (%)                                          | 24 (59%)           | -               | -    |
| Scleroderma renal crisis, n (%)                                         | 1 (2.5%)           | -               | -    |
| Anti-centromere, n (%)                                                  | 5 (12.40%)         | -               | -    |
| Anti-Scl-70, n (%)                                                      | 7 (17.50%)         | -               | -    |
| Nailfold capillaroscopy                                                 |                    |                 |      |
| Number of capillaries/mm                                                | 7.38 ± 1.69        | 10.03 ± 0.50    | <0.001|
| Number of microhaemorrhages                                             | 1.96 ± 2.17        | 0.06 ± 0.19     | <0.001|
| Giant capillaries                                                       | 0.38 ± 0.55        | 0.00            | <0.001|
| Avascular score (0 to 3)                                                | 1.29 ± 0.91        | 0.00            | <0.001|
| FBF (PU)                                                                |                    |                 |      |
| Basal FBF                                                               | 291.56 ± 117.99    | 374.07 ± 75.60  | <0.001|
| FBF 1 minute after cold stimulus                                        | 187.50 ± 65.22     | 289.33 ± 84.25  | <0.001|
| FBF 10 minutes after cold stimulus                                      | 218.34 ± 86.26     | 349.51 ± 85.34  | <0.001|
| FBF 20 minutes after cold stimulus                                      | 226.41 ± 90.10     | 348.40 ± 83.72  | <0.001|

The results are presented as the mean ± standard deviation or absolute number and frequency.

CT: computed tomography; FBF: finger blood flow; PASP: systolic pulmonary artery pressure, PU: perfusion units; SSc: systemic sclerosis
Table 2  Ophthalmologic and SS-OCT characteristics among patients with SSc and controls

|                             | SSc (n= 40)     | Controls (n= 23) | p      |
|-----------------------------|-----------------|-----------------|--------|
| Visual acuity logMAR        | 0.079 ± 0.17    | 0.009 ± 0.05    | 0.058  |
| Spherical equivalent (D)    | -0.45 ± 3.03    | 0.07 ± 1.49     | 0.59   |
| IOP (mmHg)                  | 14.73 ± 3.21    | 14.48 ± 2.66    | 0.75   |
| Paquimetry (µm)             | 537.45 ± 33.39  | 540.76 ± 25.99  | 0.69   |
| VF-MD (dB)                  | -2.68 ± 2.28    | -1.34 ± 1.79    | 0.032  |
| VF-PSD (dB)                 | 2.60 ± 1.89     | 2.36 ± 0.98     | 0.98   |

Retinal nerve fiber layer (RNFL) thickness

|                     | SSc (n= 40)     | Controls (n= 23) | p      |
|---------------------|-----------------|-----------------|--------|
| Average RNFL thickness (µm) | 104.58 ± 11.99  | 108.70 ± 12.14  | 0.19   |
| Superior RNFL thickness (µm) | 130.95 ± 17.65  | 129.00 ± 16.67  | 0.66   |
| Inferior RNFL thickness (µm) | 135.33 ± 23.54  | 140.48 ± 17.17  | 0.36   |
| Temporal RNFL thickness (µm) | 69.23 ± 11.74   | 83.35 ± 20.19   | 0.001  |
| Nasal RNFL thickness (µm)   | 82.78 ± 14.13   | 88.22 ± 15.84   | 0.16   |

Morphological parameters of the optic disc

|                     | SSc (n= 40)     | Controls (n= 23) | p      |
|---------------------|-----------------|-----------------|--------|
| Disc area (mm²)     | 2.01 ± 0.56     | 2.51 ± 1.77     | 0.15   |
| Rim area (mm²)      | 1.29 ± 0.52     | 1.46 ± 0.33     | 0.16   |
| Cup volume (mm³)    | 0.13 ± 0.12     | 0.13 ± 0.16     | 0.64   |
| Vertical cup/disc ratio (VCDR) | 0.52 ± 0.18 | 0.49 ± 0.17     | 0.35   |

Ganglion cell layer complex

|                     | SSc (n= 40)     | Controls (n= 23) | p      |
|---------------------|-----------------|-----------------|--------|
| GCL + IPL (mean) (µm) | 64.86 ± 6.47    | 66.43 ± 4.95    | 0.22   |
| Total GCL (RNFL + GCL + IPL) (µm) | 104.56 ± 11.53  | 107.39 ± 8.35   | 0.17   |

dB: decibel; D: dioptries; GCL: ganglion cell layer; IPL: inner plexiform layer; IOP: intraocular pressure; logMAR = logarithm of the minimum angle of resolution; RNFL: retinal nerve fiber layer; SSc: systemic sclerosis; SS-OCT: swept-source optical coherence tomography; VF-MD: visual field-mean deviation; VF-PSD: visual field-pattern standard deviation

Data are presented as the mean ± SD.
Table 3 Ophthalmologic and SS-OCT characteristics among patients with diffuse cutaneous and limited cutaneous SSc

|                           | Limited SSc (n=24) | Diffuse SSc (n=16) | P     |
|---------------------------|-------------------|--------------------|-------|
| Visual acuity logMAR      | 0.06 ± 0.14       | 0.03 ± 0.15        | 0.07  |
| Spherical equivalent (D)  | -0.34 ± 2.57      | 0.20 ± 1.4         | 0.23  |
| IOP (mmHg)                | 15.04 ± 3.09      | 14.06 ± 2.75       | 0.58  |
| Paquimetry (µm)           | 533.57 ± 27.41    | 539.60 ± 45.90     | 0.67  |
| VF-MD (dB)                | -2.66 ± 2.10      | -2.59 ± 2.81       | 0.504 |
| VF-PSD (dB)               | 2.92 ± 2.19       | 2.26 ± 1.62        | 0.027 |
| Retinal nerve fiber layer (RNFL) thickness |                   |                    |       |
| Average RNFL thickness (µm) | 105.87 ±11.13     | 106.77 ± 11.83     | 0.95  |
| Superior RNFL thickness (µm) | 130.49 ± 16.74    | 134.35 ± 20.50     | 0.91  |
| Inferior RNFL thickness (µm) | 137.04 ± 21.73    | 135.35 ± 21.24     | 0.76  |
| Temporal RNFL thickness (µm) | 71.13 ± 12.79     | 74.77 ± 19.20      | 0.91  |
| Nasal RNFL thickness (µm) | 84.64 ± 14.06     | 79.10 ± 11.07      | 0.069 |
| Morphological parameters of the optic disc |                   |                    |       |
| Disc area (mm²)           | 2.04 ± 0.51       | 1.85 ± 0.51        | 0.06  |
| Rim area (mm²)            | 1.29 ± 0.38       | 1.22 ± 0.63        | 0.81  |
| Cup volume (mm³)          | 0.14 ± 0.11       | 0.08 ± 0.09        | 0.005 |
| Vertical cup/disc ratio (VCDR) | 0.58 ± 0.19      | 0.40 ± 0.22        | 0.000 |
| Ganglion cell layer complex |                   |                    |       |
| GCL + IPL (mean) (µm)     | 64.72 ± 7.53      | 65.07 ± 4.44       | 0.68  |
| Total GCL (RNFL + GCL + IPL) (µm) | 104.21 ± 13.11   | 105.10 ± 8.67      | 0.74  |

dB: decibel; D: dioptres; GCL: ganglion cell layer; IPL: inner plexiform layer; IOP: intraocular pressure; logMAR = logarithm of the minimum angle of resolution; RNFL: retinal nerve fiber layer; SSc: systemic sclerosis; SS-OCT: swept-source optical coherence tomography; VF-MD: visual field-mean deviation; VF-PSD: visual field-pattern standard deviation
Data are presented as the mean ± SD
Table 4 Correlation between parameters assessed by nailfold capillaroscopy and SS-OCT in patients with systemic sclerosis

|                          | Number of capillaries/mm | Giant capillaries | Microhemorrhages | Avascular score |
|--------------------------|--------------------------|-------------------|------------------|----------------|
| Average RNFL thickness   | R = -0.214               | R = -0.041        | R = -0.094       | R = 0.204      |
| P = 0.190                | P = 0.802                | P = 0.587         | P = 0.213        |
| Superior RNFL thickness  | R = -0.216               | R = 0.021         | R = -0.104       | R = 0.240      |
| P = 0.187                | P = 0.899                | P = 0.528         | P = 0.140        |
| Inferior RNFL thickness  | R = 0.082                | R = 0.155         | R = 0.139        | R = -0.082     |
| P = 0.621                | P = 0.345                | P = 0.399         | P = 0.082        |
| Temporal RNFL thickness  | R = -0.225               | R = 0.217         | R = -0.209       | R = 0.277      |
| P = 0.169                | P = 0.184                | P = 0.201         | P = 0.088        |
| Nasal RNFL thickness     | R = -0.109               | R = 0.311         | R = 0.279        | R = 0.115      |
| P = 0.507                | P = 0.067                | P = 0.085         | P = 0.484        |
| GCL + IPL (mean)         | R = -0.207               | R = 0.055         | R = -0.030       | R = 0.235      |
| P = 0.207                | P = 0.742                | P = 0.858         | P = 0.151        |
| Total GCL (RNFL + GCL + IPL) | R = -0.165   | R = 0.062         | R = -0.005       | R = 0.172      |
| P = 0.315                | P = 0.706                | P = 0.976         | P = 0.296        |

RNFL: retinal nerve fiber layer; GCL: ganglion cell layer; IPL: inner plexiform layer; SS-OCT: swept-source optical coherence tomography
Figure Legends

Fig. 1 Measurement of the retinal fiber layer (RNFL) thickness using SS-OCT. Circular tomogram of RNFL and RNFL in the 4 sectors (disk) in a healthy control (A) and in a systemic sclerosis (SSc) patient (B), showing decreased RNFL thickness, particularly in the temporal sector, in SSc.

Fig. 2 Correlation between disease duration and the average RNFL thickness ($R = -0.460; p = 0.003$) (a), the superior RNFL thickness ($R = -0.353; p = 0.025$) (b), the inferior RNFL thickness ($R = -0.495; p = 0.001$) (c), the mean GCL+ IPL thickness ($R = -0.431, p = 0.005$) (d), the total GCL thickness ($R = -0.379, p = 0.015$) (e) and between RP duration and mean RNFL thickness ($R = -0.393; p = 0.012$) (f), the mean GCL+ IPL thickness ($R = -0.389, p = 0.013$) (g) and total GCL thickness ($R = -0.332, p = 0.035$) (h).