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ORIGINAL PAPER

Thickness of anterior sclera and corneal layers in systemic sclerosis

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Abstract
Purpose To evaluate the thickness of anterior sclera and corneal layers in patients with systemic sclerosis.
Methods The present cross-sectional study included 41 patients with systemic sclerosis and 41 age- and gender-matched healthy controls. The study and control groups were compared in terms of the thickness of anterior sclera, corneal epithelium, Bowman's layer, corneal stroma, and Descemet's membrane-endothelium complex. The thickness measurements were obtained using the anterior segment module of spectral-domain optical coherence tomography.
Results The thickness of anterior sclera, corneal epithelium, Bowman's layer, and Descemet's membrane-endothelium complex were similar in the patients with systemic sclerosis and healthy controls ($P > 0.05$). Total corneal thickness at the apex was 511.1 ± 33.5 µm in the systemic sclerosis group and 528.4 ± 29.5 µm in the control group ($P = 0.015$). The corneal stroma was thinner in the systemic sclerosis patients compared to the healthy controls ($P = 0.02$).
Conclusions The corneal stroma was thinner in the patients with systemic sclerosis compared to that of healthy controls, while the thickness of the anterior sclera was similar in both groups.

Keywords Systemic sclerosis · Scleroderma · Anterior sclera · Corneal layers

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Introduction

Systemic sclerosis (scleroderma) is a multi-organ disease characterized by vasculopathy and fibroblast dysfunction of the skin and internal organs [1, 2]. The disease mechanisms involve fibrosis, vascular ischemia, and immunologic response abnormality [3]. The pathogenesis of systemic sclerosis is not fully understood yet, but it is accepted that autoimmunity plays a role [4]. Clinical manifestations of systemic sclerosis may vary greatly including disorders of skin, lungs, vascular system, intestines, kidneys, and eyes [1–4].

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The ocular findings of systemic sclerosis include dry eye, corneal abnormalities, astigmatism, eyelid skin changes, anterior uveitis, cataract, retinal microvascular disorders, choroidal thinning, and optic neuritis [5–13]. Corneal abnormalities in systemic sclerosis include thinning of the central cornea, keratoconjunctivitis sicca, steep cornea, and a high corneal resistance factor [11, 14, 15]. Although several studies have reported ocular findings in systemic sclerosis, there is a gap in data regarding the thickness of the corneal layers and anterior sclera.

The present study aimed to evaluate the thickness of the anterior sclera and corneal layers in patients with systemic sclerosis using anterior segment optical coherence tomography (OCT). In addition, dry eye status was assessed by performing the Schirmer 1 and tear breakup time tests. The hypothesis was that the corneal stroma and anterior sclera may be affected in systemic sclerosis, because this disease is associated with abnormal collagen production and the above tissues are mainly composed of collagen. The present study is the first in the literature which investigates the thickness of sclera and individual corneal layers in systemic sclerosis.

Methods

Forty-one eyes of 41 patients with systemic sclerosis and 41 eyes of 41 healthy controls were included in the study. The present study was comparative and cross-sectional and was conducted at a tertiary setting following the approval of the Institutional Review Board. This research was done the principles of the Declaration of Helsinki.

Study population

The study group (systemic sclerosis patients) was diagnosed and initially evaluated in the rheumatology division and was then referred to the eye clinic. The patients were recruited as per the '2013 American college of rheumatology/European league against rheumatism collaborative initiative' classification criteria for systemic sclerosis [16]. The patients in the study and control groups did not have any other systemic or ocular diseases. All participants underwent a standardized ophthalmological examination comprising autorefractometry measurement, visual acuity assessment, slit-lamp biomicroscopy, intraocular pressure measurement with air-puff tonometry, Schirmer 1 test, tear breakup time test, retinal evaluation with direct and indirect ophthalmoscopy, and anterior segment OCT measurements. All subjects had the best corrected visual acuity values of at least 20/20. Exclusion criteria were a history of ocular surgery, systemic diseases other than systemic sclerosis, and any ocular disease except for mild refractive error or low-grade cataract. None of the participants were on dry eye disease treatment before the study. In addition, those wearing contact lenses were also excluded, because contact lenses may affect the studied parameters. The ocular measurements were taken during the same period of the day (between 10:00 and 12:00 a.m.) in order to avoid diurnal variations. The left eye of all subjects was evaluated.

Ocular examination techniques

The anterior segment module spectral-domain optical coherent tomography (ASSDOCT) (Spectralis, version 6.0, Heidelberg, Germany) was used to measure the thickness of the tear film, layers of cornea, and anterior sclera using an add-on lens and the associated software. An add-on lens was integrated to the Spectralis device to measure anterior segment structures.

Measurements of the thickness of the cornea and anterior sclera were performed manually using caliber tools in the Spectralis OCT (Fig. 1). A zoom ranging from 600 to 800% was used to analyze the images. Measurements of the preocular tear film and corneal layers were obtained at the center of the cornea. Anterior scleral thickness measurements were performed at distances of 1 and 3 mm from the limbus (Fig. 2). The conjunctiva was eliminated to measure scleral thickness accurately. Only the temporal sclera was chosen for analysis in all the participants to maintain standardization.

All the corneal and scleral thickness measurements were performed by a single researcher, and all the examinations were performed by an experienced OCT technician. Both the OCT examinations and manual measurements were repeated at least three times, and the highest quality images were selected and used for the statistical analysis. A masked approach is preferred when measuring the thickness of the anterior segment structures to avoid bias.

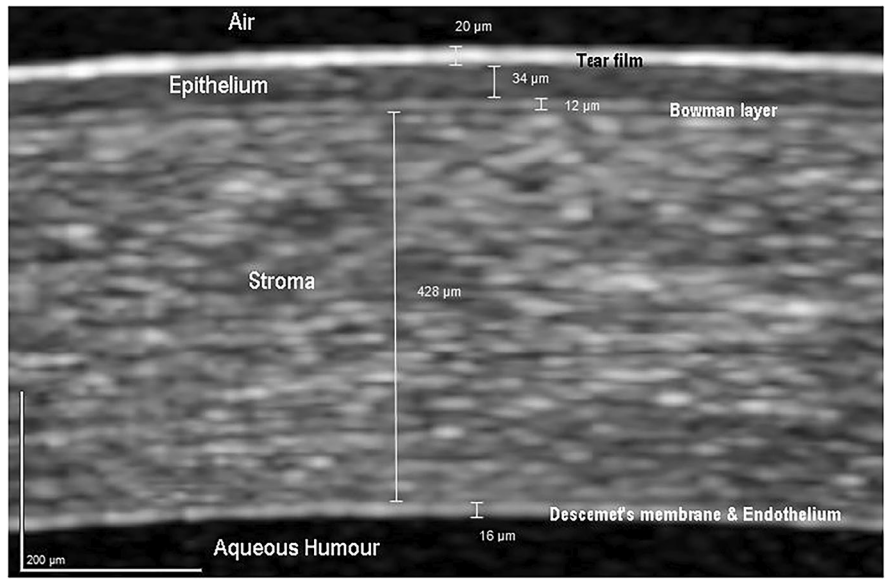

Fig. 1 An example of how the thickness of the preocular tear film and layers of the cornea were measured

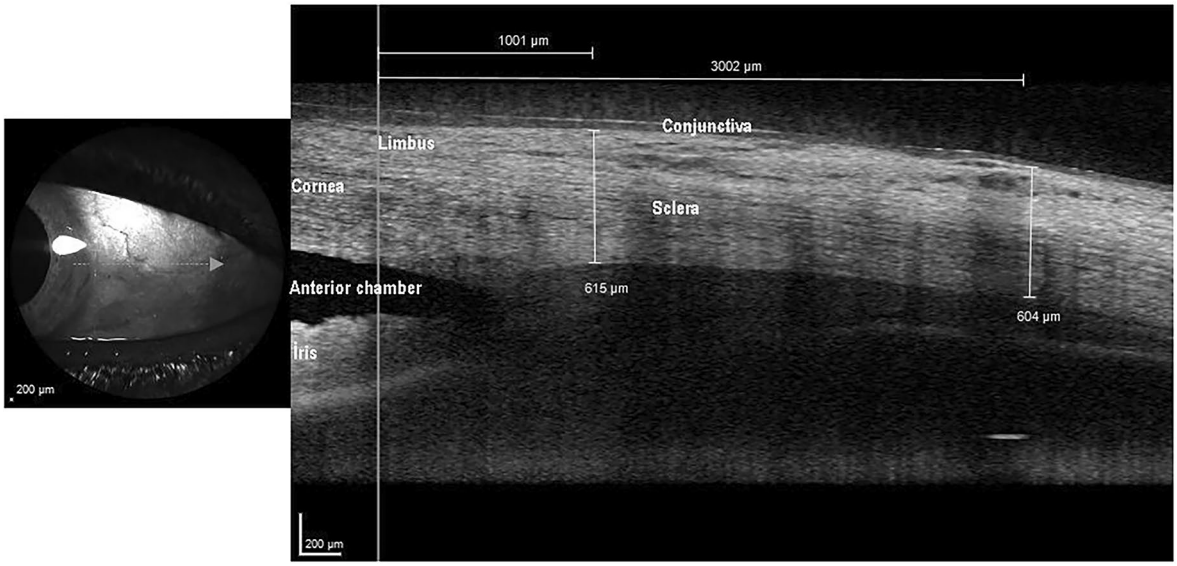

Fig. 2 How to measure anterior scleral thickness

A filter paper of size 35 × 5 mm curved at one end was placed in the lower conjunctival sac following a drop of topical anesthetic to perform the Schirmer 1 test. For correct reading of the Schirmer test, excess tears were removed before starting the test. Tear breakup time was measured by applying a fluorescein drop to the eye and after a few blinks to spread the fluorescein diffusely over the cornea, and the pre-ocular tear film was examined using a slit-lamp biomicroscope in the presence of blue light. Dark areas indicated ruptures of the tear film. Time elapsed since the previous blink was recorded as tear breakup time.

Statistical analysis

The Statistical Package of the Social Sciences (SPSS, version 22.0, Chicago, IL) was used for the

statistical analysis. Only one eye of each participant was selected randomly for the analysis. Differences between groups with P values less than 0.05 were considered statistically significant. An independent sample t test was used to compare the studied parameters between the study and control groups. Pearson's correlation analysis was used to detect associations. The Chi-square test was used for the analysis of categorical values.

Results

A total of 82 participants (41 patients with systemic sclerosis and 41 healthy controls) were included in the present study. The mean ages of the participants in the systemic sclerosis and control groups were 48.0 ± 12.4 years and 49.0 ± 8.9 years, respectively ($P = 0.68$). There were 39 female and two male participants in each group ($P = 1.00$). The refractive error, IOP, and results of the Schirmer 1 test and tear breakup time test in the study and control groups are shown in Table 1. The Schirmer 1 test and tear breakup time test values were lower in the systemic sclerosis patients than those of the healthy individuals ($P < 0.001$).

The thickness of the anterior sclera and corneal layers in the systemic sclerosis and control groups are shown in Table 2. The thickness of the anterior sclera at 1 and 3 mm from the limbus did not differ between the systemic sclerosis patients and healthy controls ($P > 0.05$). Although all the corneal sub-layers were found to be thinner in the systemic sclerosis group than those of the healthy controls, only the corneal stroma was statistically significantly thinner ($P = 0.02$). Total corneal thickness at the apex was 511.1 ± 33.5 µm in the systemic sclerosis group and 528.4 ± 29.5 µm in the control group ($P = 0.015$).

When all the participants were included, the tear film thickness was not correlated with the results of the Schirmer 1 test or tear breakup time test ($P > 0.05$); however, the results of the Schirmer 1 test and tear breakup time test were statistically significantly correlated with each other ($r = 0.71$, $P < 0.001$). The corneal stromal thickness and anterior scleral thickness were correlated with each other in the systemic sclerosis group (at 1 mm from the limbus; $r = 0.37$; $P = 0.02$, and at 3 mm from the limbus; $r = 0.37$; $P = 0.02$) but not in the healthy controls ($P > 0.05$).

Discussion

The results of the present study showed that the thickness of anterior sclera, corneal epithelium, Bowman's

Table 1 The mean values of refractive error, IOP, Schirmer test, and TBUT test results in the systemic sclerosis and control groups

	Systemic sclerosis ($n = 41$)	Control group ($n = 41$)	P value
Refractive error (diopters)	−0.14 ± 0.79	0.13 ± 0.75	0.11
IOP (mmHg)	14.6 ± 2.6	14.2 ± 2.4	0.51
Schirmer 1 test (mm)	6.0 ± 3.6	12.0 ± 5.9	< 0.001
TBUT (seconds)	5.2 ± 2.6	10.9 ± 4.4	< 0.001

IOP intraocular pressure, *TBUT* tear breakup time

Table 2 The mean values thickness values of anterior sclera and corneal layers in the systemic sclerosis and control groups

	Systemic sclerosis ($n = 41$)	Control group ($n = 41$)	P value
Sclera–1 mm from limbus (µm)	595.3 ± 64.1	597.8 ± 62.4	0.86
Sclera–3 mm from limbus (µm)	591.0 ± 61.1	600.3 ± 59.8	0.49
Tear film (µm)	18.6 ± 2.5	19.2 ± 2.2	0.29
Corneal epithelium (µm)	34.0 ± 2.7	34.5 ± 3.4	0.45
Bowman layer (µm)	13.7 ± 1.2	14.1 ± 1.3	0.23
Corneal stroma (µm)	447.8 ± 33.9	464.1 ± 30.0	**0.02***
Descemet's memb. & Endoth. (µm)	15.3 ± 1.4	15.3 ± 0.9	0.93

Memb membrane, *Endoth* corneal endothelium

*Statistically significant

layer, and Descemet's membrane-endothelium complex were similar in the patients with systemic sclerosis and healthy controls, while the corneal stroma was thinner in the systemic sclerosis patients. Since systemic sclerosis is a disease characterized by excessive accumulation of collagen, alterations of the ocular surface structures including the sclera and cornea should be expected, because of the high collagen content in these tissues.

It might be expected to notice alterations in scleral thickness in the patients with systemic sclerosis, because scleral collagen is similar to skin collagen in terms of composition and arrangement [17]. However, we found that the anterior sclera was only slightly thinner (approximately 1%) in the study group compared to the control group, with a statistically insignificant difference. Mabon et al. [18] reported a case of systemic sclerosis with bilateral scleral pit. To the best of our knowledge, this study is the first to evaluate scleral thickness in systemic sclerosis.

There are several reports in the literature involving corneal thickness measurements in systemic sclerosis [19–21]. Gomes et al. [19] found that central corneal thickness decreased by 7.2 µm between the first and second measurements in systemic sclerosis. In another study, it was reported that corneal thickness in patients with systemic sclerosis was similar to healthy individuals in the right eye (534.9, 533.0 µm) and left eye (536.9, 533.1 µm) compared to healthy individuals [20]. Nagy et al. [21] found that pachymetry and corneal volume were significantly lower in the patients with systemic sclerosis than in the healthy individuals. In this study, it was reported that the central corneal thickness in patients with systemic sclerosis was lower in the right eye (547.2, 567.7 µm) and in the left eye (550.6, 566.7 µm) Similar to most of the previous reports, total corneal thickness at the apex was thinner in systemic sclerosis in the present study. We further investigated the layers of cornea and found that the corneal stroma is thinner in systemic sclerosis. This outcome might indicate the alterations in corneal stromal collagen and the ability to maintain water content of the stroma in systemic sclerosis. The mean thickness of corneal epithelium in the previous studies (54.60 ± 4.25, 54.10 ± 2.80 µm) were found to be larger than that of our measurements [22, 23]. That outcome might have occurred due to the elimination of tear film while measuring the epithelium thickness in the present study. Approximately half of the patients (37–79%) with systemic sclerosis suffer from dry eye disease [5]. Tear breakup time and Schirmer 1 test scores were found to be lower in systemic sclerosis. In this study, the mean Schirmer I test values in systemic sclerosis patients were 5.39 mm/5 min, while it was 14.34 mm/5 min in the control group. While the mean tear film breakup time was 5.16 s in systemic sclerosis patients, it was 11.03 s in the control group [24]. Consistent with previous reports (5.3 ± 3.1, 5.9 ± 2.5), our results (6.0 ± 3.6) showed that patients with systemic sclerosis were prone to dry eyes with Schirmer test findings. [24, 25]. On the other hand, the tear film thickness measured via the anterior segment spectral-domain OCT was found similar in the systemic sclerosis patients and healthy individuals in the present study. This outcome might reflect a deficiency of the anterior segment spectral-domain OCT in measuring the tear film thickness. Some technical restrictions might occur in that case since the reflectance is high in the interface of air and tear film.

The present study has several limitations. A longitudinal follow-up study might have enabled us to evaluate the ocular changes over time. Also, the measurements of corneal endothelial cell density, corneal optical densitometry, and corneal hysteresis might have increased the impact of the present study. In terms of clinical importance, the outcomes of the present study may suggest to take into consideration the corneal thickness changes while evaluating corneal refractive surgery candidates or glaucoma suspects in systemic sclerosis.

In conclusion, this study showed that the corneal stroma was thinner in systemic sclerosis, but the thicknesses of the other corneal layers were similar in the patients with systemic sclerosis and healthy individuals. Anterior scleral thickness measurements did not differ in the normal persons and systemic sclerosis patients. The patients with systemic sclerosis showed a tendency to dry eye disease. In patients with systemic sclerosis, studies with larger series are needed to distinguish whether this thinning is due to stromal thinning due to dry eye or if there are different specific mechanisms.

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Declarations

Conflict of interest The author declare that no conflict of interest.

Ethical approval Ethics committee approval was obtained for the study.

Informed consent Informed consent was obtained from all individual participants included in the study.

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