DOI: 10.14744/eer.2021.63935
Eur Eye Res 2021;1(3):150–155

EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

# Analysis of tear osmolarity, stability and production in systemic sclerosis

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## Abstract

**Purpose:** To analyze tear film characteristics using objective tests in patients with scleroderma or systemic sclerosis (SSc), a rare condition for which there is limited literature data.

**Methods:** This cross-sectional study included 31 SSc patients and a group of age- and sex-matched controls. Tear quantity, stability, and osmolarity were assessed in both groups with Schirmer I test (S1T), fluorescein tear film break-up time (TBUT), and the TearLab Osmolarity System, respectively.

**Results:** There was no significant difference in age or sex between the groups. The median disease duration was 6 (0.83–30) years. Compared to the control group, the SSc patient group showed significantly higher mean tear osmolarity (307.84±5.86 mOsm/L vs. 294.87±8.55 mOsm/L) and lower TBUT (5.68±2.07 s vs. 10.06±1.20 s) and S1T (4.55±2.26 mm/5 min vs. 10.06 ± 1.20 mm/5 min) values ($p<0.001$ for all). Age and disease duration were not significantly correlated with the results of objective dry eye tests in SSc patients, and there were no significant correlations among the test parameters ($p>0.05$ for all).

**Conclusion:** Tear characteristics are affected in SSc, with patients demonstrating decreased tear production, shorter TBUT, and tear hyperosmolarity.

**Keywords:** Dry eye; Schirmer; systemic sclerosis; tear film break-up time; tear film osmolarity.

Scleroderma or systemic sclerosis (SSc) is a rare, progressive autoimmune connective tissue disease that most commonly appears between the fourth and seventh decades and preferentially affects women.[1] Although the pathogenesis of SSc is not fully understood, it is believed to involve an interplay of genetic and environmental factors. This multisystem disease is characterized by defective neovascularization, insufficient remodeling, and diffuse fibrosis following vascular damage caused by aberrant immune activation.[2] SSc is commonly classified as limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc).[3] In lcSSc, sclerosis is limited to the arms and face and is associated with a history of Raynaud's phenomenon; dcSSc, which is reported in approximately half of all cases (40–58%), can cause multiorgan fibrosis, with pulmonary fibrosis and pulmonary hypertension in particular being the main causes of mortality.[4,5]

**Cite this article as:** Mayali H, Erdogan M, Altinisik M, Kurt E, Ilker SS. Analysis of tear osmolarity, stability and production in systemic sclerosis. Eur Eye Res 2021;1:150-155.

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**Submitted Date:** 07.07.2021 **Accepted Date:** 20.10.2021

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Because SSc is a rare condition, involvement of the eye and surrounding tissues has generally been reported as small case series or case reports. Although the most common ophthalmological finding in SSc is eyelid skin fibrosis, SSc has also been associated with glaucoma, choroidal thickness changes, microhemorrhages, hard exudates, and increased vascular tortuosity in the retina, corneal thickness changes, and dry eye disease (DED).[6–10]

DED is thought to occur in SSc patients due to fibrosis of the conjunctiva and lacrimal gland and is seen in 39–77% of cases.[10,11] The lack of a gold standard diagnostic test for DED has demonstrated the need for more diverse assessment methods. For this purpose, in addition to questionnaires about patients' symptoms, tests to assess tear quantity, stability, and composition have been standardized. The Schirmer I test (S1T) and tear film break-up time (TBUT) have long been used to evaluate tear quantity and stability in DED. Measurement of tear film osmolarity (TFO) also gained importance in the evaluation of tear film composition after its role in the pathogenesis of DED was recognized.

Although TFO analysis was initially presented as having gold standard potential in the diagnosis of DED, it did not see widespread acceptance due to the difficulty of obtaining samples with the old techniques used in osmolarity measurement. Using the TearLab Osmolarity System in TFO measurements, the easy sampling technique and ability to measure from sample volumes as small as 50 nL prevents reflex tearing to yield more reliable results.[12] Although TFO measurements are not widely used in clinical practice due to instrument dependence, they are frequently utilized in clinical studies because they have high repeatability and provide objective findings independent of the patient and observer.[13,14] Cut-off values for TFO as a marker of ocular inflammation have not been definitively determined, but high osmolarity values have been shown to be associated with inflammation and dry eye.[12,14] In the Dry Eye Workshop (DEWS) II report, TFO was added to the dry eye diagnostic criteria, with an upper limit of approximately 308 mOsm/L.[15]

The aim of this study was to compare objective data obtained with S1T, TBUT, and TFO tests in SSc patients and a control group. An age- and sex-matched control group was enrolled to minimize individual differences between the study and control groups.

## Materials and Methods

The study was approved by Manisa Celal Bayar University Faculty of Medicine Ethics Committee. A total of 31 women diagnosed as having SSc according to the American College of Rheumatology criteria were included in the study.[16] All 31 patients had lcSSc. Individuals who were age- and sex-matched to the SSc patients, had no systemic disease. The patients in the control and study groups both had not used any eye drops in the past 2 weeks. Exclusion criteria were previous refractive and intraocular surgery, contact lens use, pregnancy, diabetes or hypertension, and high refractive error (>3 diopters [D] spherical and >1D cylindrical). In addition, SSc patients receiving immunosuppressive therapy other than low-dose (<10 mg/day) steroid therapy were excluded. All patients underwent slit-lamp examination and best-corrected visual acuity (BCVA) assessed by Snellen chart. The participants' age, sex, disease duration (for the SSc group), BCVA, and spherical equivalence of refraction were recorded.

Following those assessments, dry eye tests were performed at 30-min intervals to prevent incorrect measurements. The TearLab Osmolarity System (TearLab Corporation, San Diego, CA, USA) was used to measure TFO. As per the manufacturer's instructions, the tip of the probe was gently touched to the inferior lateral tear meniscus and approximately 50 nL of tear film was sampled for measurement.

Tear film stability was assessed using TBUT. For this test, 1 drop of 2% sodium fluorescein (Fluoresceína®, Allergan, Brazil) was instilled into the inferior fornix and the patient was instructed to blink several times. The time from the last blink to the appearance of the first area of tear film break-up was determined using the cobalt blue filter of the slit-lamp. The mean of three measurements was recorded.

Tear production was evaluated by S1T with topical anesthesia. After instilling 1 drop of proparacaine 0.5% (Alcaine, Alcon, Switzerland), a commercially available 5 × 35-mm paper strip (Schirmer strips®, Alcon Laboratory, Texas, USA) was inserted into the inferior fornix. After 5 min, the wetted portion of the paper was measured in millimeters (mm/5 min).

All statistical analysis were analyzed with SPSS version 24.0 (SPSS Inc, Chicago, USA). Only one randomly selected eye per subject was used for statistical analysis. In the present study, unless otherwise indicated, all data were expressed as the mean ± standard deviation (SD). The normality test was performed using the Kolmogorov-Smirnov test. According to distribution pattern, Student's t-test or Mann-Whitney U test were used to compare the groups, and as well as Spearman or Pearson correlation analysis was used to evaluate the association between the parameters.

**Table 1.** Demographic data and baseline characteristics of the groups

| | Systemic sclerosis (Mean±SD; n=31) | Control (Mean±SD; n=31) | p-value |
|---|---|---|---|
| Age (years) | 51±10.14 | 51.39±10.67 | 0.884* |
| Gender (female/male), n | 31/0 | 31/0 | N/A |
| Disease duration (years), median (min-max) | 6 (0.83–30) | N/A | N/A |
| Spherical equivalent (D) | –0.63±1.21 | 0.12±0.94 | 0.122* |
| BCVA (LogMAR) | 0.09±0.12 | 0.07±0.17 | 0.798* |
| Intraocular pressure (mmHg) | 14.25±1.87 | 15.29±2.35 | 0.081* |

BCVA: Best corrected visual acuity; SD: Standard deviation.

**Table 2.** Comparisons of the findings of systemic sclerosis and control groups

| Group | Kolmogorov-Smirnova | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|
| | Statistic | df | Significance | Statistic | df | Significance |
| Tear osmolority | | | | | | |
| Normal | 0.143 | 31 | 0.108 | 0.944 | 31 | 0.104 |
| Systemic sclerosis | 0.102 | 31 | 0.200* | 0.976 | 31 | 0.708 |
| Schirmer test | | | | | | |
| Normal | 0.253 | 31 | 0.000 | 0.795 | 31 | 0.000 |
| Systemic sclerosis | 0.160 | 31 | 0.043 | 0.897 | 31 | 0.006 |
| Break-up time | | | | | | |
| Normal | 0.295 | 31 | 0.000 | 0.837 | 31 | 0.000 |
| Systemic sclerosis | 0.144 | 31 | 0.099 | 0.955 | 31 | 0.213 |

*This is a lower bound of the true significance. Lilliefors Significance Correction.

Power analysis was used to assess the sample (power = 0.80, α=0.05, two-sided test, G power 3.0, Dusseldorf, Germany). A sample size calculation determined that minumum 17 eyes of each group were required to detect a 10 mOsm/L TFO difference with a standard deviation 10 mOsm/L.

## Results

Thirty-one eyes of 31 women with SSc (mean age, 51±10.14 years; range, 26–71 years) were enrolled in this cross-sectional, observational study. The control group included 31 eyes of 31 age-matched healthy women. There were no differences in age, gender, spherical equivalent, BCVA, or IOP between the two groups (p>0.05, Table 1). The median disease duration was 6 years (range, 0.83–30 years). The healthy women in the control group had no history of the ocular surface disease, ocular surgery or trauma, or contact lens use. No signs of severe eyelid thickening were observed in the SSc patients. The demographic data and baseline characteristics of the groups are summarized in Table 1.

The SSc and control groups had mean S1T values of 4.55±2.26 mm and 14.52±3.57 mm, mean TBUT values of 5.68±2.07 s and 10.06±1.20 s, and mean TFO values of

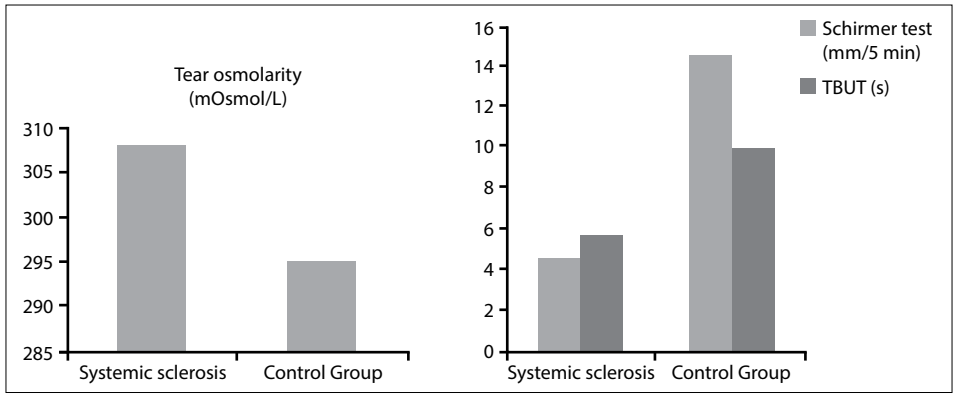


**Fig. 1.** Mean values of tear film osmolarity, schirmer test, tear break up time in systemic sclerosis and control groups.

307.84±5.86 mOsm/L and 294.87±8.55 mOsm/L, respectively. Mean TFO was significantly higher and TBUT and ST values were significantly lower in SSc patients compared to the controls ($p<0.001$ for all; Table 2, Fig. 1).

Among TFO, TBUT, and S1T values, the only significant relationship was a moderate positive correlation between TBUT and S1T in the control group ($r=0.48$, $p=0.01$). SSc duration was not significantly correlated with TFO, TBUT, or S1T values ($p>0.05$ for all).

## Discussion

In this study, we investigated tear film characteristics in SSc patients independently of ocular symptoms by examining S1T, TBUT, and TFO values, and determined that these patients had significantly lower TBUT and S1T values and higher TFO values compared to the control group.

SSc is a rare autoimmune connective tissue disease associated with high mortality and morbidity. Although the etiology of SSc remains unclear, immunologic, mesenchymal, and vascular elements are reported to play a role in its pathophysiology and dysregulated and dysfunctional wound healing is believed to contribute to the development of the disease.[17] SSc has variable clinical presentations, and early signs such as Raynaud's phenomenon and gastroesophageal reflux that are common in the general population may not raise clinical suspicion of SSc. Some SSc patients have inflammatory skin findings, while others may present findings related to the internal organs, such as pulmonary fibrosis, renal failure, pulmonary hypertension, cardiac arrhythmias, and heart failure.[16] While sclerotic skin changes in and around the eyelid are most frequent in SSc patients, the posterior segment and cornea may also be affected, and conjunctival and lacrimal involvement often leads to DED.[1]

There is no gold standard test for the diagnosis of DED, which has a multifactorial pathogenesis, but diagnostic and treatment planning approaches based on tear film layer characteristics have been reported.[18] Determining the volume, stability, and osmolarity of the tear film layer is an important part of ocular surface health and DED evaluation. Although tear meniscus assessment as a measure of tear volume is being incorporated into more diagnostic algorithms for DED, the S1T performed with topical anesthesia is frequently used in ophthalmology practice because it is well standardized, easy to perform, and widely accessible.[15] It was reported that S1T values ≤5 mm/5 min indicates DED with 78% sensitivity and 70% specificity.[19] In the follow-up and evaluation of rheumatology patients, the S1T is used as a diagnostic criterion in connective tissue diseases, especially Sjögren's syndrome.[19] According to the DEWS II, a TBUT <10 s is used to evaluate tear stability as a diagnostic criterion in DED.[20] Although the noninvasive TBUT test is recommended, fluorescein break-up time is most commonly used in clinical practice.[15,19] Tear film instability increases evaporation, resulting in hyperosmolarity and leading to ocular inflammation and DED.[20] The main parameter used to evaluate tear film composition is TFO. Definitive threshold values for the TFO test have not been determined. However, values above 308 mOsm/L or a difference >8 mOsm/L between the two eyes were considered significant in DED[20] and high TFO values have been associated with DED severity.[14]

Previous studies have reported various prevalence rates of dry eye in SSc and a clinical spectrum ranging from mild tear hyposecretion to keratoconjunctivitis sicca.[21,22] In the current study, TFO was significantly higher and TBUT and ST values were lower in SSc patients than in the controls. There was no significant correlation between those parameters in SSc patients or healthy volunteers, and the severity of dryness was not correlated with disease duration in SSc patients. Our findings are similar to those reported by Rentka et al.[23] in one of three studies in the literature evaluating TFO in SSc. Taken together, these results suggest that there is agreement about the coexistence of DED in SSc patients confirmed either by objective or subjective tests which are not correlated with each other.[11,24]

Possible factors that have been implicated in the pathogenesis include lacrimal gland fibrosis, decreased corneal sensation, chronic blepharitis, increased tear evaporation due to decreased eyelid motility, and additional ocular surface damage secondary to vasculopathy in the conjunctiva or episclera.[10,25,26] Indeed, unlike the infiltration of lymphoids and autoantibodies in primary Sjögren's syndrome, glandular fibrosis in the lacrimal gland was shown in SSc tissue specimens.[27]

In a controlled, prospective cross-sectional study by Adiguzel et al.[28] evaluating SSc patients, low TBUT values were observed and there was no relationship between disease duration and objective dry eye tests, similar to our study. Unlike the present study and that by Rentka et al., there were no statistically significant differences in TFO values between the control group and SSc patients in Adiguzel et al.'s study. Similarly, S1T values in SSc patients were similar to the control group. Adiguzel et al. suggested that the difference in findings from Rentka et al. may be related to the younger patients or the exclusion of smoking patients

from the study. In addition, discrepant results in the studies may be related to SSc severity in the cases studied. Gagliano et al.[29] retrospectively examined 60 SSc patients and detected a correlation between their skin scores (Rodnan skin score) and S1T, noninvasive TBUT, and TFO. In that study, TFO values were high (mean: 328.51±23.8 mOsm/L) and disease duration was not associated with noninvasive TBUT, S1T, and TFO but was associated with tear film lipid layer thickness when the tear film layer was evaluated with an ocular surface interferometer. However, they did not include an exclusion criterion related to the use of drugs that may alter ocular surface properties in their study.

Observational and cohort studies have emerged suggesting benefit from currently used immunosuppressive drugs in SSc.[30] There are studies showing regression in skin fibrosis with methotrexate, mycophenolate mofetil, and cyclophosphamide. Considering the inflammatory etiology of DED, we did not include patients using immunosuppressive agents in our study. In this way, we had the opportunity to work with a more homogeneous group in SSc disease. We conducted our study independent of the effects of immunosuppressive drugs on tears.

Similar to other studies in the literature, our patient sample was limited due to the rarity of SSc. All of the SSc patients included were women with lcSSc. This may not reflect the characteristics of SSc ocular findings in dcSSc patients and men, which are reported to be more severe.[31]

The fact that disease severity, corneal sensitivity, corneal staining scores and subjective dry eye tests were not evaluated in SSc patients is a limitation of our study. The ocular findings of SSc disease may vary according to skin score or SSc subgroup.

### Conclusion

In summary, the SSc patients in this study were found to have high TFO and low TBUT and S1T values. Although the cause-effect relationship cannot be clearly demonstrated in cross-sectional studies, we think that dry eye tests should be evaluated in SSc patients. Early detection, follow-up, and treatment of the ocular findings of SSc, a progressive disease that can cause multiorgan involvement, may improve patients' quality of life as well as provide information about the course of the disease. Further controlled, prospective studies on this rare disease are needed to reach a definitive conclusion about how to interpret the data from dry eye tests in terms of SSc.

**Ethics Committee Approval:** This study was approved by Manisa Celal Bayar University Faculty of Medicine Ethics Committee (date: 03.06.2020; number: 20478486-050.04.04).

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: H.M., M.E., M.A., E.K., S.S.I.; Design: H.M., M.E., M.A., E.K., S.S.I.; Supervision: H.M., M.E., M.A., E.K., S.S.I.; Resource: E.K., S.S.I.; Materials: H.M., E.K., S.S.I.; Data Collection and/or Processing: H.M., M.E.; Analysis and/or Interpretation: H.M., M.E., M.A.; Literature Search: H.M., M.E., M.A.; Writing: M.E.; Critical Reviews: H.M., M.A., E.K., S.S.I.

**Conflict of Interest:** None declared.

**Financial Disclosure:** The authors declared that this study received no financial support.

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