

## Association between objective signs and subjective symptoms of dry eye disease in patients with systemic sclerosis

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**Abstract** The aim of this study was to evaluate the association between clinical signs and symptoms of dry eye disease (DED) in patients with systemic sclerosis (SSc). This cross-sectional observational study included 19 SSc patients and 19 normal subjects with no ocular symptoms or ocular surface disorders. Clinical parameters included tear film break-up time (tBUT), Schirmer I, lissamine green (LG) dye, and tear film osmolarity tests, tear production, and tear secretion flow. For assessment of the dry eye symptoms, the Ocular Surface Disease Index (OSDI) questionnaire was administered to all patients. The following mean values were found in SSc patients: OSDI  $33.6 \pm 19.86$ ; osmolarity of the tear fluid  $310.8 \text{ mOsmol/l} \pm 14.47$ ; tBUT time  $5.158 \pm 2.328 \text{ s}$ ; Schirmer I test  $5.395 \text{ mm/5 min}$ ; LG grading score  $2.026 \pm 0.8893$ ; collected tear fluid volume  $6.397 \pm 2.761 \mu\text{l}$ . The calculated average tear velocity was

$4.654 \pm 1.963 \mu\text{l/min}$ . A significant correlation was found between the OSDI as a subjective parameter and disease duration. Early recognition of dry eye symptoms, a possible extra-intestinal manifestation of SSc, should be included in the check up of the disease to reduce ocular complications. The objective tear functional tests were strongly influenced by individual factors like age and disease duration.

**Keywords** Systemic sclerosis · Schirmer I test · Tear film break-up time · Lissamine green dye · Tear film osmolarity · Tear production · Tear secretion · OSDI

### Introduction

Systemic sclerosis (SSc, or scleroderma) is a rare, chronic, systemic, connective tissue disease of unknown origin characterized by widespread small vessel vasculopathy, immune dysregulation with autoantibody production, and progressive fibrosis. SSc is traditionally divided into two large groups, limited (ISS) and diffuse (dSS), causing a wide spectrum of different functional failures and limitations significantly influencing health-related quality of life [1]. Prevalence and incidence of SSc vary widely across the world. Lower estimates of prevalence (<150 per million) and incidence (<10 per million per year) have been described in northern Europe and Japan, while higher estimates of prevalence (276–443 per million) and incidence (14–21 per million per year) have been reported in southern Europe, North America and Australia [2]. Female predominance is remarkable along with gender differences in incidence and disease activity. The overall female-to-male ratio ranges from 1:1 to 14:1 [3].

SSc affects different organs including the eyes and surrounding tissues, but there are only scarce data available concerning ophthalmological manifestations in the course

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of the disease. Moreover, most of the available data consist of single case reports or small case studies, although ocular expressions occur frequently and decrease the quality of life of these patients [4, 5]. In addition, there are only a limited number of review articles regarding ocular involvement of SSc, since this is a rare disease, not principally affecting ocular tissues [6–8]. One of the most frequent ocular features of SSc is dry eye disease (DED), also known as dysfunctional tear syndrome and keratoconjunctivitis sicca, and other impairments of the lacrimal functional unit (LFU), which has been identified to occur in 37–79% of patients [1, 9]. Depending on its severity, keratoconjunctivitis sicca stands for mucous strands in the precorneal tear film, superficial punctate keratitis, or filamentary keratitis.

Although several studies have found weak or no correlations between symptoms and signs of DED [10–12], complaints in conjunction with DED are the leading causes of patients' visits to eye care units. Efficacy of treatment is assessed by measuring the decrease in the symptoms [13].

SSc abnormalities in the organ of vision are supposed to be the manifestations of systemic complications of scleroderma or adverse effects of the immunosuppressive treatment applied. Ocular signs may occur at any stage of the disease and may involve several ocular tissues [2].

As for ocular concerns of SSc, the assessment of tear physiology, more specifically tear secretion, and tear film stability are the most important.

As there is no definite gold standard diagnostic tool that could reliably diagnose and stage DED in every case [14], different methods were applied to evaluate tear film and tear flow characteristics in SSc patients.

The tests ubiquitously used to help accurately diagnose DED are either subjective (such as questionnaires) or objective [such as tear film break-up time (tBUT)], Schirmer tests, ocular surface dye staining [fluorescein, rose bengal (RB), and lissamine green (LG)], and conjunctival impression cytology) [15, 16]. Objective tests are normally more precise in addressing tear production, flow, and alterations in ocular surface, while questionnaires based on patients' accounts of their symptoms may be misleading and reliable only for follow-up. To investigate the relationship between clinical tests and subjective symptoms of dry eye, the Ocular Surface Disease Index (OSDI) questionnaire (provided by Allergan, Inc. Irvine, CA, USA) [17], perhaps, the most frequently used survey, was administered. This scale is accepted by the US Food and Drug Administration (FDA) for use in clinical trials, since it is based on a clear conceptual framework and there is evidence supporting its psychometric properties [18]. The OSDI questionnaire is a 12-item self-administered PRO (patient-reported outcome) scale including the same five-category Likert-type response option for each item from 0 ("none of the time") to 4 ("all of the time"). The questions asked with reference to a 1-week recall period

measure three subscales of dry eye sensation: ocular discomfort (OSDI-symptoms), which includes symptoms such as gritty or painful eyes; functioning (OSDI-function), which measures limitation in performance of common activities such as reading and working on a computer; and environmental triggers (OSDI-triggers), which measures the impact of environmental triggers, such as wind or drafts on dry eye symptoms. The total OSDI score was calculated according to the questionnaire's algorithm with a total score ranging from 0 to 100 where higher scores point to greater disability. The overall OSDI score determines the ocular surface as normal (0–12 points) or as having mild (13–22 points), moderate (23–32 points), or severe (33–100 points) disease.

The purpose of this study was to evaluate the association between objective clinical signs and subjective symptoms of DED in patients with systemic sclerosis (SSc).

## Patients and methods

### Patients and healthy controls

The study was conducted by the Departments of Ophthalmology and Rheumatology at the University of Debrecen, Debrecen, Hungary. Consecutive patients with SSc diagnosed based on the corresponding international criteria [19, 20] were recruited in the study. None of the patients fulfilled the diagnostic criteria for secondary Sjögren's syndrome, as all patients' SS-A and SS-B laboratory parameters were within the normal range, and none of them took immunosuppressive medications at the time of the tear sampling. All patients involved in this study have undergone an extensive differential diagnostic assessment, which involved serological testing, as well as labial salivary gland biopsy to exclude Sjögren's syndrome. All patients have been followed up long and none has developed secondary Sjögren's during the follow-up period.

Patients and members of the control group did not take any eye drops 2 weeks prior to tear sampling and during study days. Other exclusion criteria were abnormal eyelid position and closure, contact lens wearing, and treatment with corticosteroids.

Patients underwent a comprehensive ophthalmological evaluation, including broad beam examination of the slit lamp to determine the condition of the ocular surface and surrounding tissues, to observe tear film, corneal impairments, conjunctival changes, and eyelids.

The study protocol was approved by the local ethics committee and was in full compliance with Good Clinical Practices (GCP) guidelines of the European Union, and the Declaration of Helsinki (1996). By signing a written informed consent, all patients agreed to have study results regarding

any side effects as well as possible risks and benefits of the study published.

## OSDI

The scoring of the OSDI was performed in accordance with the published guidelines [21]. Before performing any clinical tests, a trained interviewer administered the OSDI questionnaire to each patient. The total OSDI score was then calculated with the help of the following formula:  $OSDI = [(sum\ of\ scores\ for\ all\ questions\ answered) \times 100] / [(total\ number\ of\ questions\ answered) \times 4]$ , and determined on a scale of 0–100, with higher scores representing greater disability.

Then, we performed the following five separate measurements, all on consecutive days, in one room with constant light, temperature, humidity, and airflow, to avoid any ocular surface stress. Ambient temperature was 21 °C and relative humidity was  $60 \pm 3\%$ .

## Osmolarity

Osmolarity was measured in tear samples taken from the lower lateral tear meniscus using the TearLab Osmolarity System (TearLab Corporation, San Diego, CA, USA) [22]. The tip of the pen gently touched the inferior tear meniscus. Approximately 50 nl of tear sample was collected from the inferior lateral tear meniscus of the ocular surface to obtain a reading, as per the manufacturer's recommendation.

## Tear film stability

Three measurements per subject were made (both right and left eye) and the average of the three tBUT values was taken as the mean value. For tBUT measurement, a strip of fluorescein (Haag-Streit, Koenitz, Switzerland) was moistened with a drop of unpreserved, sterile saline solution 0.9% from a single-dose ampule, and this was then used to touch the inferior fornix for a short time with minimal stimulation, and the tear film was observed under cobalt blue-filtered light and wide light. The interval (seconds) between the last complete blink and the first emergence of randomly distributed dry spot was averaged.

## Tear production: Schirmer I Test (ST<sub>I</sub>)

For the estimation of tear production un-anesthetized Schirmer test, the Schirmer I test (ST<sub>I</sub>) was performed using standardized strips of filter paper (Alcon Laboratory, Fort Worth, Texas, USA). Without any use of anesthetic, standard

strips were inserted at the lower lid margin at the junction of the middle and temporal third of both eyes taking care not to touch the cornea. Patients and healthy volunteers were instructed to gently close their eyelids and not to move their eyes for 5 min, and then, the strip was removed and the length of the wet portion was measured (mm/5 min). The average of both side ST values was taken as the mean value.

## Vital staining: Lissamine green (LG) staining

After a resting time of 20 min for LG grading, an LG impregnated paper strip (HUB Pharmaceuticals, Rancho Cucamonga, CA, USA) moistened with a drop of unpreserved, sterile saline solution 0.9% from a single-dose ampule was applied in the lower palpebral conjunctiva. Then, the patients were asked to blink several times, and the test eye was examined under a slitlamp starting with low level of illumination and then gradually increasing the level until the LG dye became most visible in a manner recommended by Foulks [23].

LG grading scores were evaluated according to Bron's scheme (Oxford Grading Charts) using a slit lamp, set at  $\times 16$  magnification with  $\times 10$  oculars with Haag-Streit slit lamp [15, 24]. Grade 0 consisted of 0–9 dots of LG grading on the bulbar conjunctiva (nasal and temporal bulbar conjunctiva graded separately), grade 1 was 10–32 dots, grade 2 was 33–100 dots, and grade 3 was more than 100 dots.

## Tear production and secretion velocity

All samples were collected by the same physician between 11 am and 16 pm. Open eye tears were smoothly collected from the inferior temporal cul-de-sac of both eyes using a capillary micropipette (Haematokrit-Kapillaren, Na-Heparin 3.0 IU/kapillare, 75 mm/60  $\mu$ l, Hirschmann Laborgerate, Eberstadt, Germany), minimizing irritation of the ocular surface or eyelid margin as much as possible. Tear secretion time was measured with a stopwatch until the capillary was filled up or motion of the tear stopped. Tear production was calculated from the lengths of the fluid column in the capillary tube, measured with a vernier caliper, and from the known diameter of the tube. Tear secretion velocity was calculated by dividing the volume of collected sample by time of secretion.

## Statistical analysis

Data of patients and controls were compared by means of an unpaired *t* test with or without Welch's correction (according to the presence or absence of significant difference between variances of data sets, respectively) after verifying the

Gaussian distribution of data with D'Agostino and Pearson as well as Shapiro–Wilk normality tests. Correlation coefficients between variables were calculated with the Pearson method ( $r$ ). For the sake of informative appearance in the figures, linear regression was also performed if there was a significant correlation between the investigated data sets. Data are presented as mean ( $\pm$ SD).  $P$  values less than 0.05 were considered statistically significant. For the statistical analysis, GraphPad Prism 7.02 statistical software was used (GraphPad Software Inc., San Diego, CA, USA).

## Results

17 female and 2 male patients with SSc [age 59.11 (SD  $\pm$  7.73) years] were recruited into our prospective, cross-sectional, observational study, all from the outpatient clinic of the Department of Rheumatology. Most patients had been suffering from SSc for a long time; mean disease duration was 19.79 (SD  $\pm$  11.42) years. We enrolled 19 gender- and age-matched volunteers (17 females and 2 males) [age 53.11 (SD  $\pm$  18.11) years] as healthy controls, who had no history of any autoimmune or ocular surface disorder, or ocular surgery or trauma, or contact lens use. All patients and controls were of Caucasian origin.

The mean OSDI score was 33.6 (SD  $\pm$  19.86) in SSc patients and 12.8 (SD  $\pm$  5.29) in control subjects. The mean osmolarity of the tear fluid was 310.8 ( $\pm$  14.47) mOsmol/l in SSc patients, while 289.9 mOsmol/l (SD  $\pm$  7.36) in controls. The mean tBUT time was 5.16 s (SD  $\pm$  2.33) in the tears of SSc patients and 11.03 s (SD  $\pm$  3.75) in controls,

and the mean Schirmer I test values were 5.39 mm/5 min (SD  $\pm$  3.16) in SSc patients, whereas 14.34 mm/5 min (SD  $\pm$  6.39) in control tears. In SSc patients, the mean LG grading score was 2.03 (SD  $\pm$  0.89) and it was 0.74 (SD  $\pm$  0.71) in healthy volunteers. Duration of tear sample collection ranged between 28 and 158 s. The mean tear production was 6.4  $\mu$ l (SD  $\pm$  2.76) in SSc patients, while it was 14.39  $\mu$ l (SD  $\pm$  9.36) in healthy controls, and the mean calculated tear secretion velocity was 4.65  $\mu$ l/min (SD  $\pm$  1.96) in SSc patients, and 13.04  $\mu$ l/min (SD  $\pm$  6.75) in the control group. Data are represented in Table 1 and Fig. 1.

The results of the correlation analysis are shown in Table 2 and Figs. 2, 3, and 4. In general, the association between the OSDI scores as a subjective parameter and the measured objective clinical test variables was weak. Interestingly, a significant positive correlation was only found between OSDI and disease duration in SSc patients ( $r = 0.6031$ ,  $p = 0.0063$ ). For all other parameters, no significant association was detected.

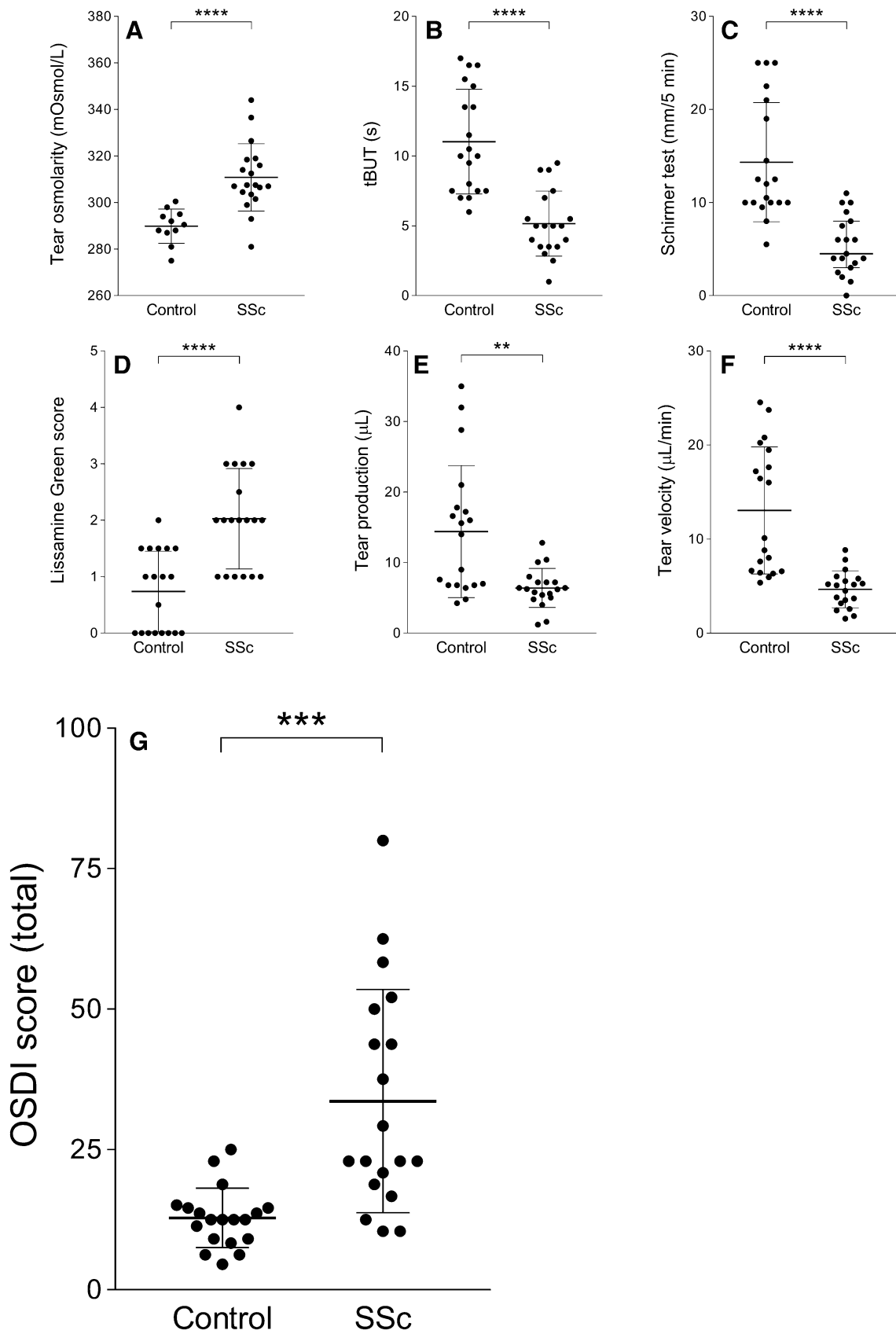
## Discussion

Precorneal tear film is important in maintaining the integrity of the ocular surface, providing a clear vision, and in the defense mechanism of the eye. SSc is a chronic, autoimmune, connective tissue disorder which affects the skin and multiple organs, including the eyes and adnexa. The leading ophthalmological involvement in conjunction with SSc is DED representing a high prevalence.

**Table 1** Data of tear film parameters and OSDI scores of SSc patients and healthy controls

	SSc age (years)	SSc disease duration (years)	SSc tear production ( $\mu$ l)	SSc tear velocity ( $\mu$ l/min)	SSc tBUT (s)	SSc Schirmer test (mm/5 min)	SSc Lissamine green score	SSc tear osmolarity (mOsmol/l)	SSc OSDI total
Mean	59.11	19.79	6.397	4.654	5.158	5.395	2.026	310.8	33.6
Std. deviation	7.731	11.42	2.761	1.963	2.328	3.156	0.8893	14.47	19.86
$P$ value	0.3045	0.1571	0.4408	0.8191	0.6295	0.5426	0.6552	0.3195	0.2892
$P$ value summary	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Control age (years)	Control tear production ( $\mu$ l)	Control tear velocity ( $\mu$ l/min)	Control tBUT (s)	Control Schirmer test (mm/5 min)	Control lissamine green score	Control tear osmolarity (mOsmol/l)	Control OSDI total	
Mean	53.11	14.39	13.04	11.03	14.34	0.7368	289.9	12.8	
Std. deviation	18.11	9.358	6.752	3.747	6.397	0.7143	7.365	5.29	
$P$ value	0.232	0.1689	0.0309	0.0753	0.1883	0.0199	0.5166	0.2386	
$P$ value summary	ns	ns	*	ns	ns	*	ns	ns	

\*  $p < 0.05$



**Fig. 1** Osmolarity (mOsmol/l), tBUT (s), Schirmer I (mm/5 min), LG score, tear production ( $\mu$ l), tear velocity ( $\mu$ l/min), and OSDI values in tears of SSc patients and healthy controls. **a** Tear osmolarity; **b** tBUT; **c** ST<sub>I</sub>; **d** LG; **e** tear production; **f** tear velocity; **g** OSDI scores

**Table 2** Correlations between tear film parameters, OSDI scores, and age together with disease duration in SSc patients and controls

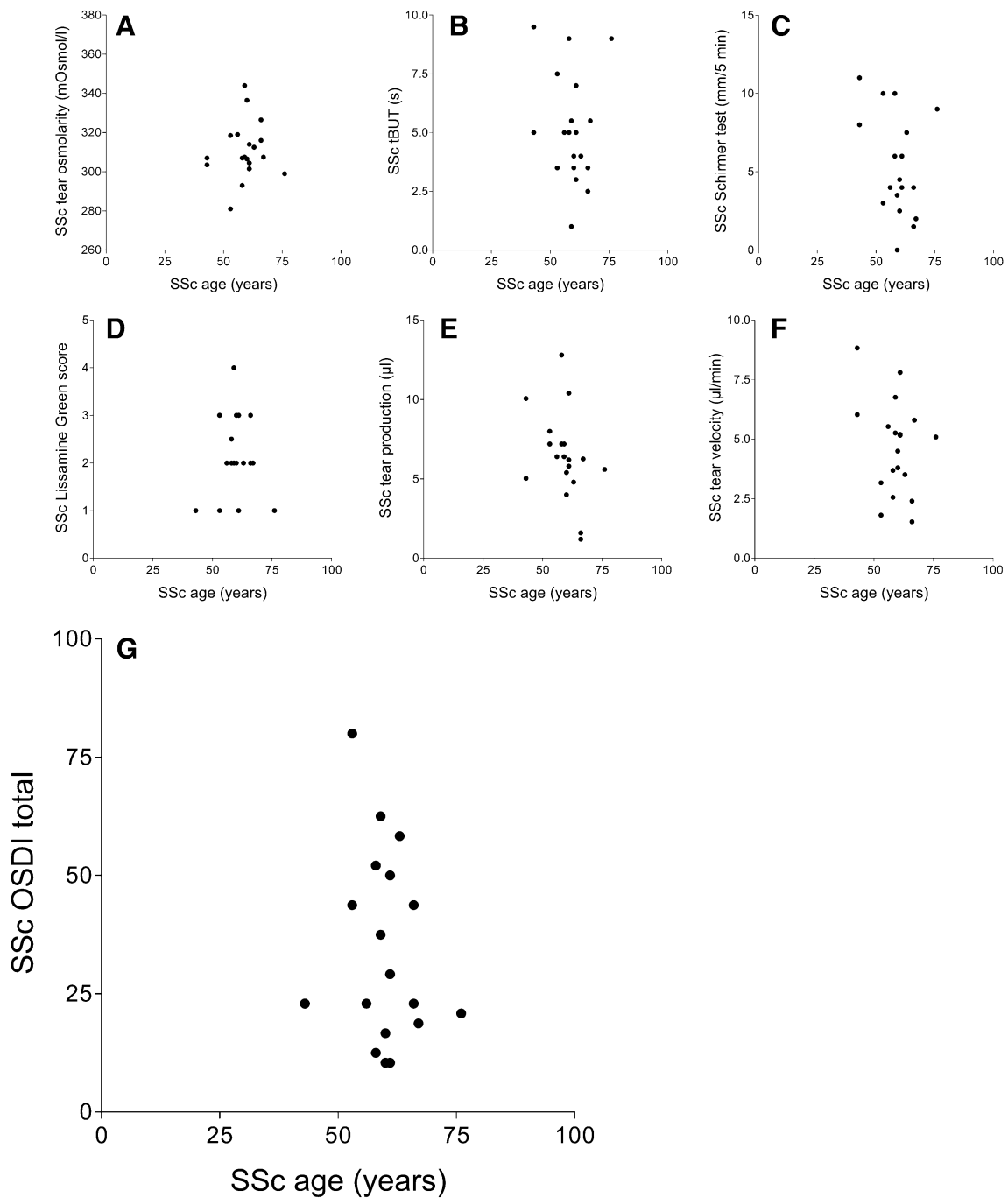
	Control age (years) vs. control tear production ( $\mu$ l)	Control age (years) vs. control Tear velocity ( $\mu$ l/min)	Control age (years) vs. control tBUT (s)	Control age (years) vs. control Schirmer test (mm/5 min)	Control age (years) vs. control lissamine green score	Control age (years) vs. control Tear osmolarity (mOsmol/l)	Control age (years) vs. control OSDI total
r	-0.1901	0.6957	0.653	0.6222	0.6315	0.403	0.201
R <sup>2</sup>	0.03612	0.484	0.4264	0.3871	0.3988	0.1624	0.04039
P (two-tailed)	0.4358	0.0009	0.0024	0.0044	0.0037	0.2191	0.4094
P value summary	ns	***	**	**	**	ns	ns
	SSc age (years) vs. SSc tear production ( $\mu$ l)	SSc Age (years) vs. SSc tear velocity ( $\mu$ l/min)	SSc Age (years) vs. SSc tBUT (s)	SSc Age (years) vs. SSc Schirmer test (mm/5 min)	SSc Age (years) vs. SSc lissamine green score	SSc Age (years) vs. SSc tear osmolarity (mOsmol/l)	SSc Age (years) vs. SSc OSDI total
r	-0.381	-0.2954	-0.1384	-0.3285	0.1652	0.1142	-0.0963
R squared	0.1452	0.08725	0.01914	0.1079	0.0273	0.01304	0.009274
P (two-tailed)	0.1075	0.2195	0.5722	0.1696	0.4991	0.6416	0.6949
P value summary	ns	ns	ns	ns	ns	ns	ns
	SSc disease duration (years) vs. SSc tear production ( $\mu$ l)	SSc disease duration (years) vs. SSc tear velocity ( $\mu$ l/min)	SSc disease duration (years) vs. SSc tBUT (s)	SSc disease duration (years) vs. SSc Schirmer test (mm/5 min)	SSc disease duration (years) vs. SSc lissamine green score	SSc disease duration (years) vs. SSc tear osmolarity (mOsmol/l)	SSc disease duration (years) vs. SSc OSDI total
r	0.2569	-0.2906	-0.03629	-0.06768	0.1099	-0.08834	0.6031
R <sup>2</sup>	0.06601	0.08445	0.001317	0.00458	0.01209	0.007804	0.3637
P (two-tailed)	0.2883	0.2275	0.8828	0.7831	0.6541	0.7191	0.0063
P value summary	ns	ns	ns	ns	ns	ns	**

\*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

The following studies are worth mentioning as they helped us decide on the study design and inclusion–exclusion criteria. In a retrospective study, Sullivan and co-workers studying 344 subjects found correlation between symptoms and only one of the clinical signs of DED, namely corneal and conjunctival staining, while other clinical signs, osmolarity, TBUT, and Schirmer, were disconnected. They were led to the conclusion that symptoms alone are insufficient for the diagnosis and management of DED [25]. Chhadva et al. presented the fact that eyelid laxity may have an impact on both tear parameters, and on OSDI scores, therefore, eyelid laxity was an exclusion criterion in our study [26].

Sahin et al. investigated tear film stability with fluorescein break-up time test (FBUT) and tear production with Schirmer's test with topical anesthesia of 22 SSc patients and found that SSc patients have thinner corneas compared with control subjects. They concluded that coexistence of DED seems to have an additional impact on the thinning of cornea in SSc patients [27]. Gomes and co-workers analyzed the data of objective and subjective signs of DED

in 45 patients suffering from SSc. Their results revealed the fact that DED has a moderate impact on vision-related quality of life in patients with SSc and the subjective symptoms of DED using OSDI questionnaire do not correlate well with objective clinical findings [28]. Stucchi and Geiser described ophthalmic manifestations in 14 patients, 10 females and 4 males suffering from generalized SSc. Although hyposecretion of tears was detected in 11 patients, keratoconjunctivitis sicca and/or Sjögren's syndrome were not found [29]. Horan reported 23 patients, 19 females and 4 males with progressive systemic sclerosis. 47.82% of patients had diminished tear secretion, while keratoconjunctivitis sicca was present in 30.43%, all of them with symptoms due to reduced tear secretion [8]. Wangkaew and co-workers analyzed Sicca symptoms in Thai patients in various rheumatic and autoimmune diseases, and they found 54% ocular sicca symptoms among scleroderma patients [30]. One of the case reports concerning the relationship between SSc and ocular involvements was described by Anand who noticed the use of lubricating solutions in the presence of scleroderma, even



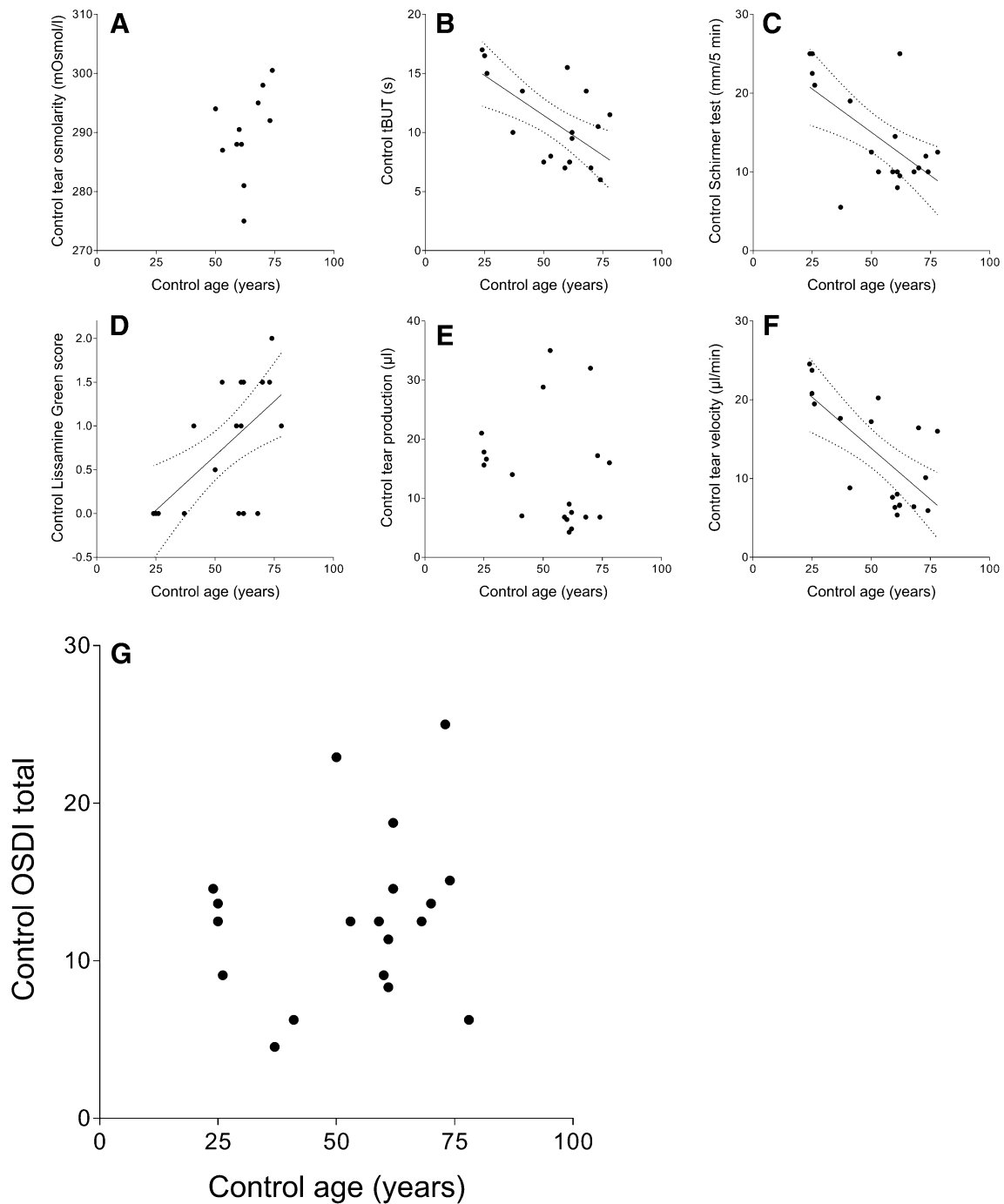
**Fig. 2** Correlation between tear film parameters (**a** tear osmolarity; **b** tBUT; **c** ST; **d** LG; **e** tear production; **f** tear velocity), OSDI scores (**g**), and age in SSc patients. The *continuous lines* show the fit-

ted curves, while the *dotted lines* represent the 95% confidence bands (obtained with linear regression in cases when there was a significant correlation between the data sets)

though the patient presented in the paper did not produce any anterior segment impairment of the eye [31]. Rasker et al. analyzed ocular manifestations of 26 SSc patients and found that 7 of these developed Schirmer’s I test positivity and 6 had abnormal Schirmer’s II test as well. Altogether, the symptom complex of DED was present in 9 SSc patients [32].

Ocular findings in SSc, especially DED, are considered to be caused by fibrosis-related impairment of lacrimal gland secretion affecting the watery layer of the tear film. This along with systemic and progressive vasculopathy typical of SSc due to the rich vascular supply of the conjunctiva and episclera cause additional damage to the ocular surface. Besides fibrosis decreased corneal sensation may also be of





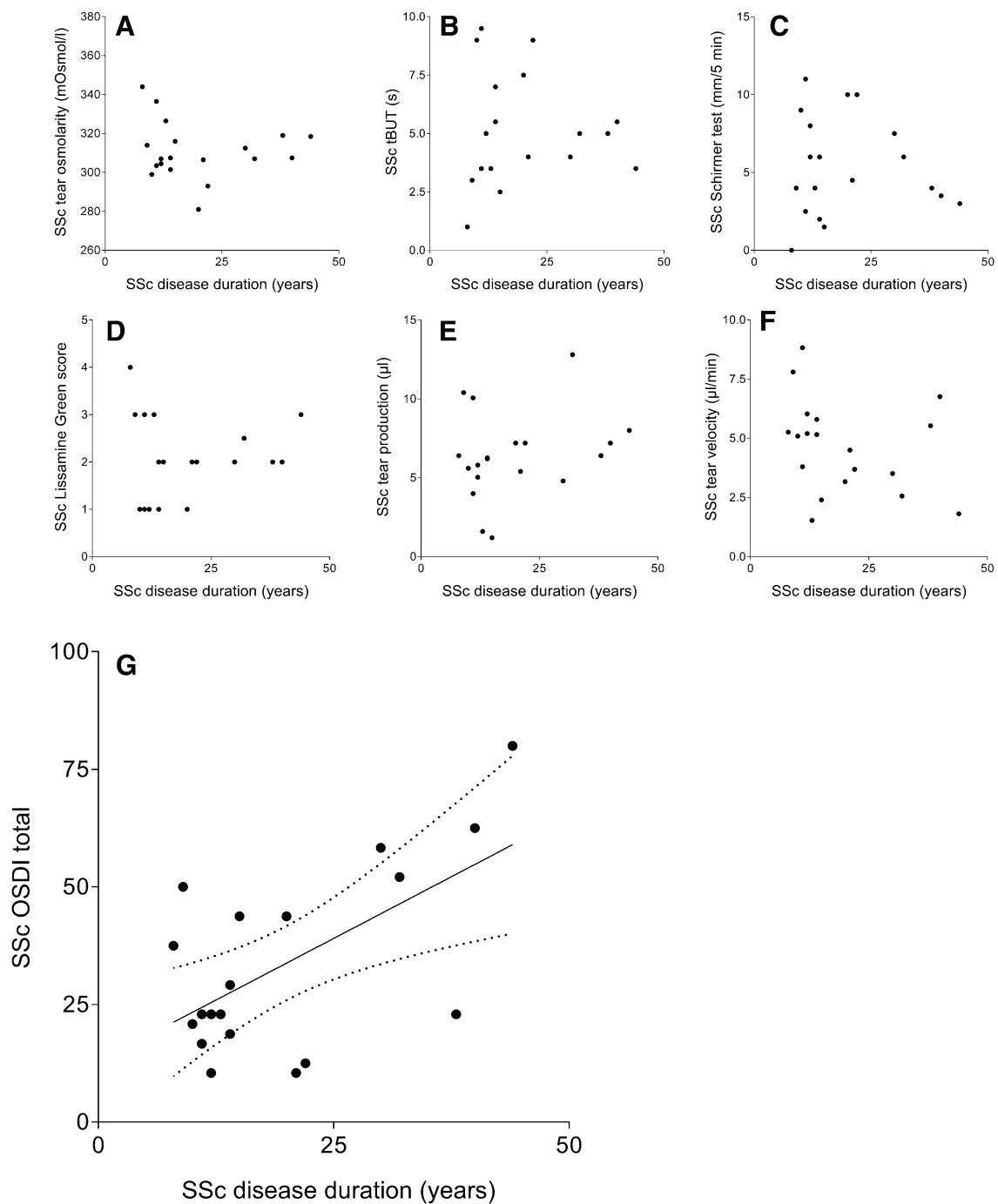
**Fig. 3** Correlation between tear film parameters (**a** tear osmolarity; **b** tBUT; **c** ST<sub>1</sub>; **d** LG; **e** tear production; **f** tear velocity), OSDI scores (**g**), and age in controls. The *continuous lines* show the fitted curves,

while the *dotted lines* represent the 95% confidence bands (obtained with linear regression in cases when there was a significant correlation between the data sets)

importance in severe forms of DED, causing inappropriate feed-back through the ophthalmic nerve to the central nervous system, resulting in less efferent stimulation to the lacrimal gland, consequently reduced tear production [1, 9, 13]. In addition, lipid layer disorder caused by chronic blepharitis and Meibomian gland dysfunction (MGD) can

occur, just as increased evaporation of tears from the ocular surface happens, which is a consequence of restricted eyelid mobility and the consecutive reduced blinking [5]. Comparisons have been drawn between primary Sjögren's syndrome, a prototype of tear deficient DED and DED in SSc, since both diseases are based on primary ductal involvement that





**Fig. 4** Correlation between tear film parameters (**a** tear osmolarity; **b**: tBUT; **c**: ST<sub>I</sub>; **d**: LG; **e** tear production; **f** tear velocity), OSDI scores (**G**), and disease duration in SSc patients. The *continuous lines*

show the fitted curves, while the *dotted lines* represent the 95% confidence bands (obtained with linear regression in cases when there was a significant correlation between the data sets)

suggests similar mechanisms; nevertheless, lymphoid infiltrates are less frequent in SSc. To differentiate between SSc and primary Sjögren's syndrome, a conjunctival biopsy is required. Sjögren's lymphocytic infiltration takes place in the main lacrimal gland, leading to immune-mediated acinar destruction, in some patients to ectopic germinal center

formation in the glands and autoantibody secretion, while in SSc, glandular fibrosis is the etiological component that leads to reduced lacrimal function [33].

Clinicians must be aware of the diverse spectrum of eye and ocular surface involvement in SSc, and include routine evaluations in the care of this multisystem illness. Early

recognition of ocular manifestations can help therapy that will reduce patient discomfort and ocular morbidity, and improve quality of life of patients suffering from this generalized connective tissue disease. Moreover, in patients with ocular manifestations, such as DED, tear analysis is far more informative, and can provide valuable information of the ocular surface; hence, it could help to choose the appropriate treatment, in particular artificial tears or anti-inflammatory eye drops. Although the etiology differs between SSc and Sjögren's syndrome patient groups, lacrimal investigations are crucial diagnostic procedures, which should be introduced in patients with SSc.

In the control group, a significant correlation was found between age and objective tear tests, while in SSc patients, the objective tear functional tests were strongly influenced by individual aspects like age and disease duration factors. The control group, supposed to be made up of healthy persons, spent most of their time also among healthy peers constantly comparing their vision-related quality of life to that of similar individuals; therefore, they are not fagged by the traceable reduction of the tear production and quality parameters based on age. On the contrary, SSc patients, suffering from a rare disease, spent most of their time among similarly aged peers, who are in a relatively better eye condition. Therefore, they are permanently confronted with their imperfections.

To our knowledge, no combined investigation of tear film characteristics and tear velocity investigations has so far been reported in patients with SSc. Based on our investigations, positive correlation was only demonstrated between subjective symptoms of DED and disease duration, which means that patients only consider their symptoms severe towards the end of the disease. This fact draws attention to the significance of DED treatment in SSc patients at an early stage of the disease.

Since DED has been associated with other connective tissue diseases, correlations between incidences of DED and these (SLE, RA, etc.) are also worth investigating, and we are in the process of performing such examinations.

**Authors' contributions** Conception and design of the work: AKB, JH, and PS. Data acquisition and research execution: AR, AN, GS, and ZS. Data analysis and interpretation: RG. Drafting the article: AKB and ZS. Critical revision of the manuscript: PS, AKB

#### Compliance with ethical standards

**Conflict of interest** None of the authors has any potential financial conflict of interest related to this manuscript. No funding was secured for this study. This work has never been published or submitted for publication elsewhere.

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