

Meibomian Gland Dysfunction in Patients with Sjögren Syndrome

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Objective: Changes in the ocular surface of patients with Sjögren syndrome (SS) often are more severe than those in patients with dry eye without SS. This study was conducted to investigate the possible involvement of meibomian gland dysfunction in SS-related ocular surface abnormalities.

Design: A nonrandomized, prospective, clinical study.

Participants: Twenty-seven eyes of 27 consecutive patients with SS (SS group) were studied. Twenty-nine eyes of age- and gender-matched non-SS patients with aqueous tear deficiency (non-SS group) were examined as control subjects.

Intervention: Changes in the ocular surface, tear function, and meibomian gland were examined.

Main Outcome Measures: Tear evaporation rate, meibomian gland expression, and meibography were measured.

Results: Fluorescein and rose bengal staining scores were significantly higher in the SS group than in the non-SS group ($P = 0.0001$). Evaporation of tears was increased significantly in the SS group compared with the non-SS group. There were no significant differences in the rate of tear production between the SS and non-SS groups. Meibography showed that 11 (57.9%) of 19 eyes in the SS group had gland dropout (i.e., histologic destruction of meibomian glands) in more than half of the tarsus. The incidence was significantly higher than that in the non-SS group (5 [18.5%] of 27 eyes; $P = 0.005$).

Conclusions: The results of this study indicate that destruction of meibomian glands and an increase in tear evaporation often are associated with changes in the ocular surface in patients with SS. Severe ocular surface changes in patients with SS may be attributed, in part, to the meibomian gland dysfunction.

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Meibomian glands secrete lipids into tears, and the lipids form an oily layer of precorneal tear film that is responsible for preventing excessive evaporation of tears.¹ Obstruction of meibomian gland orifices causes obstructive meibomian gland dysfunction (MGD). The disorder results in a decrease of lipid supply, which subsequently causes an increase in tear evaporation.^{2,3} We have reported that patients with MGD showed ocular surface abnormalities and experienced ocular discomfort despite having normal tear flow rates.³ We also showed that the incidence of MGD not associated with Sjögren syndrome (SS) was not different between normal subjects and patients with decreased tear production.³

In evaluating changes in the meibomian glands of patients with dry eye, we noticed that the glands often were severely impaired in those with SS. Although desiccation is known to be a major component of SS-related ocular sur-

face abnormalities, patients with SS often exhibit more severe changes in the ocular surface than do patients with dry eye without SS.⁴ We hypothesized, therefore, that MGD may contribute to ocular surface changes in patients with SS. To test this hypothesis, we conducted a prospective, clinical study in patients with SS and in age- and gender-matched non-SS dry eye patients. Tear function tests, including a tear evaporation test, as well as a complete evaluation of the ocular surface and examination of the meibomian glands were performed.

Patients and Methods

We examined a consecutive series of 27 patients with SS (SS group) in a prospective fashion. For the diagnosis of SS, the following four criteria as proposed by Fox et al⁵ were used: (1) objective evidence of keratoconjunctivitis sicca by fluorescein and rose bengal staining; (2) objective evidence of diminished salivary gland flow; (3) presence of lymphocyte foci in minor salivary gland biopsy; and (4) evidence of systemic autoimmune process. Patients were all women who were 52.4 ± 9.2 years of age (mean \pm standard deviation). Twenty-nine patients without evidence of SS and who had both a decrease in tear production (≤ 5 mm in Schirmer's test) and positive vital stainings (fluorescein ≥ 1 or rose bengal ≥ 3) also were examined (non-SS group). Subjects in the non-SS group also were women and were matched in age with those in the SS group (mean age, 54.1 ± 15.6 years). Only the right eye of SS and non-SS subjects was used for analysis. Eyes

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Table 1. Results* of Examinations of the Ocular Surface and Tear Function in the SS and Non-SS Groups: Mean \pm SD

Examination	SS (n = 27)	Non-SS (n = 29)	P
Fluorescein	5.04 \pm 2.79	1.59 \pm 0.91	<0.0001
Rose bengal	4.74 \pm 2.60	1.52 \pm 1.53	<0.0001
Break-up time	2.85 \pm 2.74 (26)	4.48 \pm 3.25 (21)	0.069
Schirmer's test (mm/5 min)	2.67 \pm 1.78	3.24 \pm 1.41	0.18
Clearance	3.41 \pm 1.12	3.43 \pm 1.14	0.94
TFI	35.6 \pm 44.5	41.4 \pm 31.3	0.57
Cotton thread (mm/15 secs)	16.9 \pm 6.54	18.8 \pm 9.11 (24)	0.52

SS = Sjögren syndrome patients; Non-SS = non-Sjögren dry eye patients; TFI = tear function index; SD = standard deviation.

* Number of eyes examined was the same as the number in each group, unless otherwise indicated.

with anterior blepharitis of more than moderate severity or infectious conjunctivitis were excluded from the study.

Most of the patients had been treated with preservative-free artificial tears. A low concentration of topical corticosteroids (0.02% or 0.1% fluorometholone acetate; Flumethoron; Santen Pharmaceutical Co., Osaka, Japan) was used by eight (29.6%) and seven (24.1%) patients, respectively, and antiallergic eyedrops such as 0.4% disodium chromoglycate (Intal; Fujisawa Pharmaceutical Co., Tokyo, Japan) were given to four (14.8%) and five (17.4%) patients in the SS and non-SS groups, respectively. None of the patients had been treated by punctum plug insertion or by surgical occlusion.

After routine ocular examinations, examinations of the ocular surface and tear function were performed by nonmasked observers. Examinations were done in the following order to avoid the influence of one procedure on another with the exception of the tear evaporation test, which was conducted on a separate day: fluorescein and rose bengal staining, measurement of tear break-up time (BUT), Schirmer's test, tear clearance test,⁶ cotton-thread test,⁷ and tear evaporation test.⁸ Cotton-thread test was performed using cotton-thread dyes with a pH indicator (phenol red), which was placed under a lateral portion of inferior palpebral margin for 15 seconds. Length of the wet portion was measured, and the value represents the amount of tears in the inferior cul-de-sac.⁷ For vital staining tests, 2 μ l of a 1:1 preservative-free solution consisting of 1% fluorescein and 1% rose bengal dissolved in saline was used.⁹ Results were assessed semiquantitatively using a 0-to-3 grading scale for fluorescein staining in the cornea and a 0-to-9 scale for rose bengal staining in both the cornea and conjunctiva, according to methods described previously.^{3,9,10} Tear film BUT then was measured three times, and the measurements were averaged.

For the tear function tests, the cotton-thread test⁷ was first performed and then 10 μ l of 0.5% sodium fluorescein with 0.4% oxybuprocaine (Benoxil; Santen Pharmaceutical Co., Osaka, Japan) was applied to the patient's eye. Schirmer's test was performed for 5 minutes. After the application for 5 minutes, tear clearance rate was determined at the same time by evaluating the dilution rate of fluorescein (1, 1/2, 1/4, 1/8, 1/16, 1/32, 1/64, 1/120, 1/256).⁶ The absolute value of the logarithm of the result was used as a parameter for tear dynamics. We calculated the tear function index (TFI) from the results of Schirmer's test divided by that of the tear clearance test since this value was reported to correlate well with the degree of ocular surface change.⁶ The evaporation of tears was measured by the method of Tsubota and Yamada.⁸ The evaporation rate at 40% ambient humidity was used as a representative value.⁸ Because the blinking rate counted when tear evaporation test was variable among subjects, we thought this rate might interfere with the tear evaporation results. Therefore, we measured the evaporation under both normal blinking and forced blinking (i.e., instructing the patients to blink every 5 seconds during the measurement period).

To evaluate the meibomian glands, transillumination observation (meibography) using a fiber-optic device (L-3920; Inami, Co., Tokyo, Japan) was performed in 19 and 27 eyes in the SS and non-SS groups, respectively.^{2,3,11-13} Loss of the visible structure of the meibomian glands (gland dropout) was considered evidence of the presence of MGD since this finding reportedly is a good parameter for MGD-associated ocular surface changes.^{3,14} The degree of meibomian gland dropout was scored as described previously³: grade 0, no gland dropout; grade 1, gland dropout in less than half of the inferior tarsus; and grade 2, gland dropout in more than half of the inferior tarsus. After the meibography, assessment of obstruction in the meibomian gland orifices was conducted. For this assessment, digital pressure was applied on the upper tarsus, and the degree of ease in expressing meibomian secretion (meibum) was evaluated semiquantitatively as follows³: grade 0, clear meibum is easily expressed; grade 1, cloudy meibum is expressed with mild pressure; grade 2, cloudy meibum is expressed with more than moderate pressure; and grade 3, meibum cannot be expressed even with the hard pressure. In some patients, these meibomian gland evaluations were performed on a different day from ocular surface and tear examinations. Eyes with excessive expression of meibum (seborrheic MGD) were excluded from the study.

All data are presented as mean \pm standard deviation. Between-group differences in mean age, tear BUT, Schirmer's test, cotton-thread test, and tear evaporation rate were evaluated by Student's *t* test for nonpaired data. Mann-Whitney's rank-sum test was used to evaluate differences in the results of the fluorescein and rose bengal staining scores, tear clearance test, and TFI. Differences in incidence were evaluated by the chi-square test. A level of *P* < 0.05 was accepted as statistically significant.

Results

Fluorescein and rose bengal staining scores in the SS group were significantly higher than those in the non-SS group (*P* < 0.0001). The BUT was not significantly different in both groups (Table 1). The results of the Schirmer's test were not different between the SS and non-SS groups, both of which were lower than values of nondry eye patients (10.1–11.1 mm/5 minutes).^{4,15} There was no significant difference in results of the cotton-thread test between the two groups, and the values were similar to normal values (17.3–21.0 mm/15 seconds).^{7,15} Tear clearance rate showed slightly decreased values compared with that of normal values (range, 3.71–3.96); however, the difference between the SS and non-SS groups was not statistically significant. Values of TFI (Schirmer's value clearance rate) also were not significantly different between the SS and the non-SS groups.

Results of tear evaporation rate measurements in the SS and non-SS groups are shown in Figure 1. The evaporation rates under both normal and forced blinking were significantly higher in the SS group as compared with those in the non-SS group ($P = 0.0048$ under normal blinking, $P = 0.0017$ under forced blinking).

Meibomian gland dropout (grade ≥ 1) was noted in 16 (84.2%) of 19 eyes in the SS group and 15 (55.6%) of 27 eyes in the non-SS group (Table 2). Incidence of gland dropout was significantly higher in the SS group than in the non-SS group ($P = 0.017$). Some degree of obstruction in meibomian gland orifices was noted in most of the eyes examined (Table 2), and the incidence of severe obstruction (grade 3) was higher in the SS group (7 eyes [38.9%]) than in the non-SS group (3 eyes [11.1%]; $P = 0.028$).

Discussion

Sjögren syndrome is an autoimmune disorder that affects such exocrine glands as the salivary and lacrimal glands. Approximately one tenth of the cases of tear deficiency are attributed to SS.¹⁶ Patients with SS often exhibit more severe changes in ocular surface than dry eye patients without SS.⁴ We also observed significant differences in ocular surface changes between SS and non-SS groups in this study (Table 1). Because results of both tear production and tear clearance tests did not significantly differ between the groups, desiccation alone is unlikely to be responsible for the severe ocular surface abnormalities in patients with SS.

To date, several hypotheses have been postulated as to the mechanism contributing to the SS-related ocular surface changes. Pflugfelder and associates¹⁷ proposed the direct involvement of the conjunctival epithelium as an immunologic target of SS. Support for this hypothesis was provided by Hikichi and associates,¹⁸ who reported that the number of lymphocytes that infiltrated the tarsal conjunctival epithelium of patients with SS was greater than that found in patients without SS. A decrease in reflex tears and in tear components essential for maintaining healthy ocular surface epithelia is an alternate explanation for the pathogenesis of SS-related ocular surface changes.¹⁹⁻²¹

In the current study, we found that the meibomian glands of patients with SS were impaired more severely than the glands of dry eye patients without SS. Although the observ-

Table 2. Semiquantitative Assessment of Meibomian Glands in the SS and Non-SS Groups

	SS (%)	Non-SS (%)	P
Meibography			
Grade 0	3 (15.8)	12 (44.4)	
Grade 1	5 (26.3)	10 (37.0)	
Grade 2	11 (57.9)	5 (18.5)	0.017
Orifice obstruction			
Grade 0	2 (11.1)	5 (18.5)	
Grade 1	2 (11.1)	6 (22.2)	
Grade 2	7 (38.9)	13 (48.2)	
Grade 3	7 (38.9)	3 (11.1)	0.17

SS = Sjögren syndrome patients; Non-SS = non-Sjögren dry eye patients.

ers were not masked, both meibography and digital expression were assessed semiquantitatively. Since gland dropout observed by meibography is considered to represent histologic destruction,¹³ more than half of the patients with SS had destruction of their meibomian glands in more than half of the area examined. We found that the obstruction of meibomian gland orifices correlated less well with ocular surface changes, a finding that agreed with that in our previous study.³ Only the incidence of complete obstruction of gland orifices (grade 3) was higher in the SS group than in the non-SS group (Table 2). Changes in meibography probably represent more severe histologic abnormalities than are observed in changes in gland orifices as suggested in an animal model of MGD.¹³ McCulley and Sciallis²² reported that 35% of patients with aqueous tear deficiency had MGD. It is unclear, however, whether they included patients with SS in their study. In addition, we have found that the incidence of MGD is not significantly different for patients with and without tear deficiency when patients with SS are excluded.³ Taken together, these findings indicate that MGD is associated with dry eye patients, especially those with SS.

We also found that the tear evaporation rate was significantly higher in patients with SS compared to patients without SS. The results of Schirmer's test and the cotton-thread test were similar between the SS and non-SS groups. Therefore, quantitative changes in tears are unlikely to be involved. Dysfunction of meibomian glands causes an increase in tear evaporation.^{2,3} Thus, it seems likely that changes in meibomian glands are responsible for the increased tear evaporation and subsequent worsening of the ocular surface desiccation in SS. To our knowledge, this is the first report to show the possible involvement of MGD in the ocular surface changes related to SS. Alternative explanations can be made for the increased tear evaporation in patients with SS. First, it may be attributed to the instability of tear film. Changes of protein components and goblet cell density in patients with SS have been reported.^{17,23,24} Alterations in tear components may cause unstable tear film and subsequent increase in evaporation. Second, persistent inflammation in the ocular surface also may cause tear evaporation to increase.

Classically, SS affects the exocrine glands, not the sebaceous glands such as the meibomian glands.¹⁶ A few studies

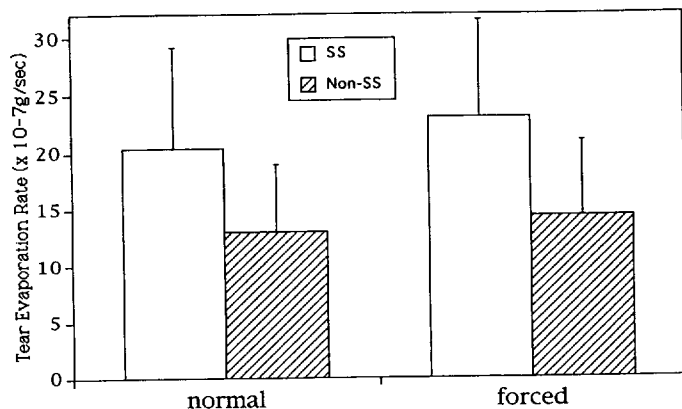


Figure 1. Tear evaporation rates in the patients with Sjögren syndrome (SS) and non-Sjögren dry eye (non-SS) under normal and forced blinking.

have shown, however, the presence of lymphocyte infiltration in the sebaceous glands of the skin in patients with SS.²⁵ Although speculative, it is conceivable that the meibomian gland may be a target organ in SS, as is the conjunctival epithelium. The previously documented lymphocyte infiltration in the conjunctiva of patients with SS^{17,18} may be responsible for the destruction of the meibomian glands since the infiltration comes close to the tarsal conjunctiva with no apparent histologic barrier. Jester et al^{13,14} reported that hyperkeratinization of ductal epithelium at the meibomian gland orifices was an early histologic change in a rabbit model of MGD. The authors also indicated that gland dropout occurred as a consequence of ductal hyperkeratinization. It is well documented that keratinization of ocular surface epithelia occurs in SS.¹⁷ Therefore, it seems reasonable to consider that epithelial keratinization plays a role as mutual pathogenesis of both SS and MGD. Further study is needed to elucidate the mechanism of meibomian gland destruction in patients with SS.

The results of the tear clearance test and TFI in the non-SS group were less than those reported by Xu and associates.⁶ The differences in results probably are because of the difference in patient selection; we selected subjects who had both decreased Schirmer's test values and positive vital staining tests, and the presence of subjective symptoms was not considered. Conversely, Xu and associates recruited dry eye patients who had subjective symptoms plus either decreased Schirmer's test values or positive vital stainings. The mean value of the Schirmer's test in the non-SS dry eye patients was 7.2 ± 6.2 mm in the study of Xu and associates, whereas the value was 3.2 ± 1.4 mm in our study.

However, the cause of SS-related ocular surface changes is multifactorial, and MGD is not responsible for all ocular surface abnormalities. In fact, fluorescein and rose bengal staining scores were still higher in the SS group than in the non-SS group when eyes with grade 2 gland dropout in meibography are excluded (fluorescein; 4.50 ± 2.83 vs. 1.50 ± 1.01 , $P = 0.0002$; rose bengal, 4.00 ± 2.27 vs. 1.27 ± 1.64 , $P = 0.011$). It is likely that alterations in the aqueous and mucin layers as well as in the lipid layer of the tear film contribute to the SS-related ocular surface changes.

In summary, the results of the current study indicate that MGD is involved, at least in part, in ocular surface changes in patients with SS. Close observation of the meibomian glands is necessary in the overall assessment of ocular surface changes in patients with SS. Treatments of MGD such as lid hygiene and the administration of tetracycline may have therapeutic value in these cases.

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