Original Article

Does Sjogren's syndrome affect only the lacrimal gland in the eye? Time to replace the missing stones

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Purpose: This study aimed to reveal the cause of meibomian gland disease and meibomian gland loss in patients with Sjögren's syndrome (SS) as the leading factor for dry eyes. **Methods:** The study included a total of 30 patients with SS and dry eye symptoms and a control group of 50 age- and gender-matched healthy subjects. The dryness parameters of all the participants were evaluated. At first, meibography was performed to measure meibomian gland loss using noninvasive methods. Later, meibomian gland expression and secretion quality were evaluated using silt-lamp biomicroscopy. Correlations between the measurements were analyzed statistically. **Results:** In patients with SS, MG loss was significantly greater than in the control group (19.7 ± 71%, 12.7 ± 9.6%, $P < 0.001$). All dry eye parameters (tear film breakup time, Schirmer's test score, OSDI, stain score, dry eye disease) were statistically significant in the SS group. There was an extremely negative correlation between upper MB loss and BUT ($P = 0.08$, r: -0.781). There was an extremely positive correlation between upper MB loss and staining ($P = 0.015$, r: 0.739). An extremely negative correlation was determined between sub-MB loss and BUT ($P = 0.18$, r:-0.781), and a moderately positive significant correlation was found between sub-MB loss and staining ($P = 0.031$, r: 0.659). **Conclusion:** The results of this study demonstrated that patients with SS were at a higher risk of being exposed to meibomian gland loss, which directly leads to the severe dry eye symptoms associated with SS.

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Sjogren's syndrome (SS) is an autoimmune, progressive, systemic disease characterized by lymphocytic leakage from some exocrine glands of the body.[1] Atrophy and dysfunction of the gland occur after the infiltration.[2] Sjogren's disease is associated with mild-to-severe dry mouth and dry eye and may be caused by other systemic symptoms.[3] Previously, dry eye associated with SS was thought to be a result of decreased excretion of the aqueous layer in tears, and SS was described as an aqueous inadequate dry eye.[4,5] However, meibomian gland dysfunction (MGD) has also been identified in cases with SS.[6]

The meibomian glands (MG), namely the sebaceous glands, are located in the tarsal plaques of the lower and upper eyelids. There are roughly 30 MG in the upper eyelid and 20 in the lower. MG secrete a lipid coating on the tear film surface of the cornea, which helps to prevent rapid evaporation of the aqueous film following ocular disturbance.[7] Occlusion of the MG orifice causes obstructive meibomian gland disease, which leads to an increase in aqueous evaporation and decreased lipid secretion.[8]

Studies have shown that patients with MGD suffer from ocular surface abnormalities and severe ocular discomfort despite having normal tear flow rates.[9] Changes in the MG of patients with dry eye caused by SS have been reported to be severely impaired compared to those without SS. Therefore, it has been hypothesized that MGD may lead to ocular surface changes in patients with SS, and till date, numerous studies supporting this hypothesis have been conducted.[10] This study aimed to investigate MG loss by applying meibography to patients with SS and to determine whether or not this leads to dry eye.

Methods

Approval for the study was granted by the local ethics committee. All study procedures were applied following the guidelines of the Declaration of Helsinki. Patients were subsequently followed-up at the Training and Research Hospital. Dry eye disease was diagnosed from the presence of symptoms of ocular disturbance such as itching, grittiness, soreness, burning sensation and dryness, and from the Schirmer's test results, tear film breakup time (TBUT), and other ophthalmic assessments. Inclusion criteria were determined as signs and symptoms of dryness ongoing for more than 5 months, low TBUT (<10 sn), and low Schirmer's test score (<10 mm). Patients were excluded from the study if they had

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any corneal or other concomitant eye pathologies, a history of ocular surgery within the last 12 months, eyelash abnormalities, nasolacrimal abnormalities, any systemic diseases such as diabetes mellitus if they had used soft/rigid contact lenses in the previous 3 months, those with smokers used systemic drugs which could potentially affect tear secretion or evaporation (such as benzodiazepines and dopaminergics), were smokers, or females who were pregnant or lactating.

The SS patients were diagnosed by a rheumatologist according to the American-European Consensus Group 2002 modified criteria,[11] which require the presence of at least four of the six criteria clauses, or three of the four objective criteria clauses. The six criteria include objective and subjective ocular dryness, objective and subjective proof of salivary gland involvement, not caused by stimulation of sialography, salivary scintigraphy or salivary flow, the presence of Sjogren-specific antibodies to La (SSB), or Ro (SSA) antigens, or both, and positive minor salivary gland biopsy. None of the SS patients had been treated by surgical occlusion or by punctum spigot insertion. All the control group subjects had a negative history of dry mouth or dry eye discomfort, other eye diseases, systemic disease due to eye involvement, prior surgery, or use of drugs that may affect salivary and lacrimal gland excretion.

The criteria for the MGD study group were used to define MGD.[12] MGD was diagnosed when eyelid margin abnormalities and meibomian gland obstruction were detected. Meibomian gland obstruction was considered to be caused when meibum excretion decreased in one eye and when mild pressure was applied with the thumb to the middle-third region of the upper lid and ≥2 gland orifices appeared to be occluded. Eyelid margin abnormalities were accepted as the presence of at least two of the following in one eye: mucocutaneous junction shifts, ≥2 telangiectasias, and notching.

Ocular surface disease index

Each patient completed a 12-item questionnaire related to ocular symptoms caused by environmental factors during the last 2–4 weeks. Each item was scored from 0 to 4, with a total score ranging from 0 to 100, and higher scores indicating worse disability.[13]

Staining score

The ocular surface was separated into three sections of nasal conjunctival, temporal conjunctival, and cornea to obtain the fluorescein staining score. Each section was evaluated and scored from 0= no staining to 3= severe staining.

Tear breakup time

The tear breakup time (TBUT) was determined by measuring the interval between the instillation of fluorescein and the appearance of the first dry spots on the cornea. The average value was calculated from three consecutive measurements.

Schirmer's test

To evaluate aqueous production, the Schirmer's test was applied with anesthesia. Dryness was accepted as ≤10 mm wetness of the Schirmer paper at 2 min after anesthesia administration.[14]

Noncontact meibography

Noncontact meibography was applied to both the study and control groups using the Sirius (CSO, Florence, Italy) corneal topographic apparatus with the Phoenix-Meibography Imaging software module. The patient was positioned in front of the scanner and both the upper and lower eyelids were measured by the same doctor. The ratio of MG loss (MGL) in all regions was calculated using a special program that allows the user to mark the entire region or the lost regions. After MGL was calculated by the device, it was classified as grade 0 (no MG loss), grade 1 (0–1 / 3 of total MG), grade 2 (1 / 3–2 / 3 total MG), and grade 3 (>2 / 3/total MG).[15]

Statistical analysis

Data obtained in the study were analyzed statistically using the Statistical Package for Social Sciences for Windows (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA). The conformity of data to normal distribution was assessed with the Shapiro-Wilk test. The Student's *t*-test was used to compare the mean of numerical variables between the two groups and the Chi-square test to compare the mean of categorical variables. Pearson's correlation analysis was used to estimate the linear relationship between continuous variables. A value of $P < 0.05$ was considered statistically significant.

Results

The control group consisted of 50 patients (20 males, 30 females, mean age: 41.22 years), and the SS group consisted of 30 patients (3 males, 27 females, mean age: 42.80 years). None of the control group patients used artificial tears, while all of the patients in the SS group used artificial teardrops. In addition to artificial tears, the SS patients applied other procedures to overcome dryness such as autologous serum, lid scrubs, warm compresses, and cyclosporine drops. The duration since diagnosis of Sjogren's syndrome in the SS group ranged from 1 to 12 years.

Meibomian gland abnormalities and loss (%) in the SS group were significantly higher than those in the non-SS group ($P < 0.001$). MG loss was 19.7% (Std ±7.1%) in the SS group and 12.7% (Std ±9.6%) in the control group [Table 1, Figs. 1 and 2]. MGD (presence of meibomian gland occlusion, mucocutaneous junction shifts, telangiectasia, and eyelid margin irregularity) were significantly higher in the SS group compared to the control group ($P = 0.035$).

The median values for the ocular surface disease index (OSDI) questionnaire, staining scores, TBUT, Schirmer scores, and dry eye disease ratios are shown in Table 2. The binomial logistic regression analysis results showed no significant relationship between MBD and disease duration, age, and gender in Sjögren's syndrome patients ($P > 0.05$).

There was a significant negative correlation between upper lid meibomian gland loss and TBUT ($P = 0.08$, r: -0.781). An extremely positive correlation was determined between upper lid MG loss and staining ($P = 0.015$, r: 0.739) [Fig. 3]. There was no significant correlation between upper lid MG loss and OSDI score/Schirmer's test ($P = 0.098$, $P = 0.169$, respectively). An extremely negative correlation was determined between lower lid MG loss and TBUT ($P = 0.18$, r: -0.781), and a moderate positive correlation between lower lid MG loss and staining ($P = 0.031$, r: 0.659) [Fig. 4]. There was no significant correlation between lower lid meibomian gland loss and OSDI score/Schirmer's test ($P = 0.072$, $P = 0.152$, respectively).

Discussion

The results of this study revealed that patients with SS had more MGD findings than those without dry eyes. The

Table 1: Comparison of Meibium gland abnormalities between Sjögren patients and control groups

	Sjogren patients *n*=30	Control patients *n*=50	*P*
MG loss (%) - Mean ± (SD)	19.7±7.1	12.7±9.6	<0.001
MG loss stage	1.33±0.47	0.36±0.53	<0.001
Meibium gland dysfunction (%) *n*	23.3 (7)	6 (3)	0.035
Meibomian gland occlusion (%) *n*	23.3 (7)	6 (3)	91
Telengiectazia (%) *n*	50 (15)	24 (12)	0.033
Mucocutaneous junction shifts (%) *n*	26.7 (8)	6 (3)	0.016
Lid margin irregularity (notching)(%) *n*	30 (9)	8 (4)	0.014

MG: Meibomian Gland, SD: Standard Deviation

Table 2: Ocular surface parameters in the Sjögren patients and control groups

	Sjogren patients *n*=30	Control patients *n*=50	*P*
Tear film breakup time (s) - Mean ± (SD)	9.4±3.4	13.5±3.7	<0.001
Schirmer's test score (mm) - Mean ± (SD)	5.3±2.8	13.7±5.3	<0.001
Ocular symptoms (OSDİ) - Mean ± (SD)	20.1±6.8	6.2±3.6	<0.001
Staining score - Mean ± (SD)	1.4±0.8	0.3±0.5	<0.001
Dry eye disease % *n*	60 (18)	6 (3)	<0.001

OSDI: Ocular surface disease index, SD: Standard Deviation

presence and severity of MGD were assessed by MG occlusion, telangiectasia, lid margin irregularity, and mucocutaneous junction shifts. The distinguishing features of this study are that it has demonstrated MG loss in Sjogren patients with objective methods and explained the correlation with dry eye tests.

SS is an autoimmune disease that affects exocrine glands such as the lacrimal and salivary glands. Approximately a tenth of patients with insufficient aqueous tears are affected by SS. In the past, severe aqueous deficiency was believed to cause dry eye in patients with SS, ignoring the role of evaporative dry eye disease.[16]

MG loss is the most widespread reason for evaporative dry eye.[17] The dysfunction of the MG is characterized by obstruction, stricture, and inflammatory changes (edema, redness, telangiectasia), in addition to qualitative and quantitative changes in the secreted sebum. Strictures of the gland orifices prevent the glands from excreting sebum. Accumulation of meibum in the MG leads to ductal expansion, cystic changes, loss of meibocytes, and ultimately gland damage. Reduced quality of meibum and decrease in meibum volume excreted onto the eye surface leads to changes such as a thinner lipid coating and increased evaporation of the tear film.[18] In a study by Menzie *et al*., a decreased lipid layer was found in tears in SS syndrome and as a result, evaporative dryness was detected.[19] In some studies in SS patients, it has been shown that the evaporative dry eye is linked to MGD and there is the coexistence of aqueous deficient dry eye.[19,20] Patients with SS in the current study were found to have a higher degree of MGD compared to the control group. As a result of the damage to the MGs, the qualitative and quantitative values of the lipid layer of tears decrease, and tear evaporation increases. In the current study, significant correlations were determined between MG loss and TBUT and staining scores. The shortening of TBUT and the increase in staining scores were thought to have been caused by the decreased lipid content of the tears and this view is consistent with previous findings in the literature.[21] Therefore, it can be assumed that the combination of aqueous deficient dry eye and evaporative dry eye exacerbates the dry eye status in SS patients. The current study results were consistent with those of similar studies in the literature.[22,23]

Several hypotheses are explaining the damage to MG caused in SS. Pugfelder *et al*. hypothesized that the conjunctival epithelium have been hypothesized to be the direct immunological target of SS.[24] Hikichi *et al*. found that the number of lymphocytes in the tarsal conjunctival epithelium of patients with SS was higher than in non-SS patients[25] and suggested that disruptive enzymes released from excess lymphocytes in the conjunctiva of SS patients may have damaged the MG as well as conjunctiva cells. According to another hypothesis, MG may be a target tissue in SS since immune cells attack and destroy the MG. However, this hypothesis was not widely supported as the main target of SS is known to be exocrine glands.[26,27] Finally, in another hypothesis, ductal hyperkeratinization in MG has been shown in experimental studies[28,29] and as hyperkeratinization leads to ductal obstruction, which damages MG, it was suggested that epithelial keratinization may play a role in the reciprocal pathogenesis of MSD and SS. In the binomial logistic regression analysis of the current study, a significant relationship was determined between MSD and both lower and upper eyelid MG loss. This was expected because the MGD occurred as a result of damage to the MGs. No significant relationship was determined between age and MGD, which could be attributed to the current study patient group consisting of relatively young patients.

There were some limitations to this study, primarily that the patients in the Sjögren group diagnosed with either primary or secondary SS may also have suffered from MG loss due to a systemic disorder. Another limitation of the study was that non-SS dry eye patients were not included. Therefore, it is difficult to deduce whether the increased MGD seen in the SS group is due to dry eye or SS. Therefore, there is a need for further similar studies with larger and more diverse groups.

Conclusion

In conclusion, the results of this study revealed higher rates of MGD in participants with SS, which likely leads to the

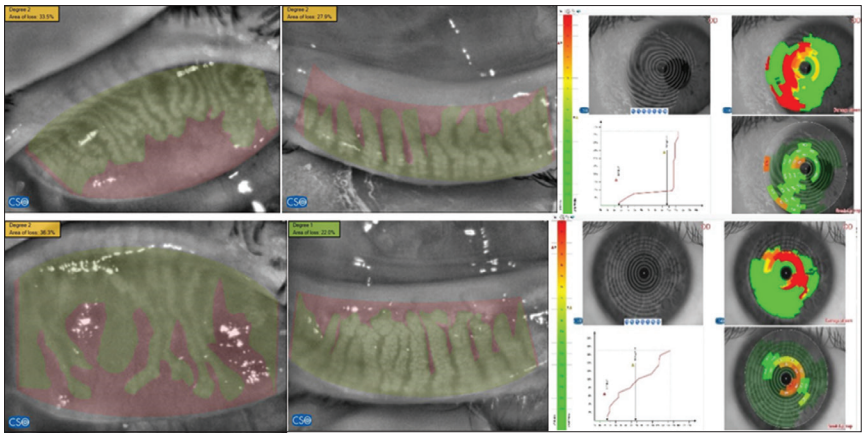

Figure 1: Computer-assisted analysis of meibomian gland morphology in Sjogren's syndrome patients

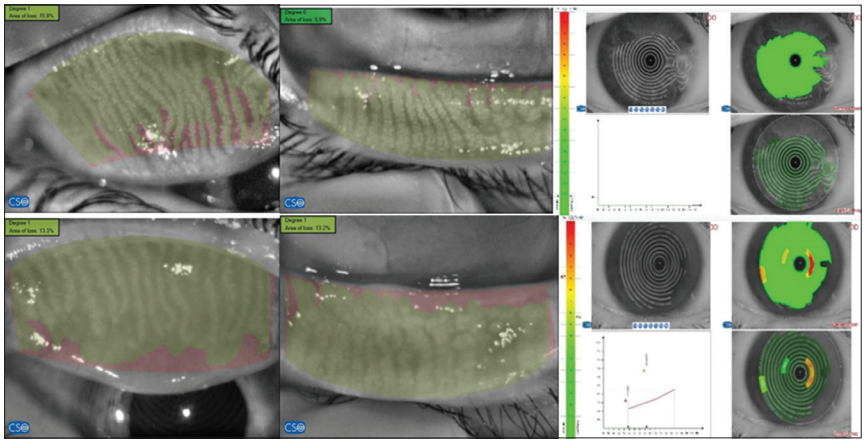

Figure 2: Computer-assisted analysis of meibomian gland morphology in control patients

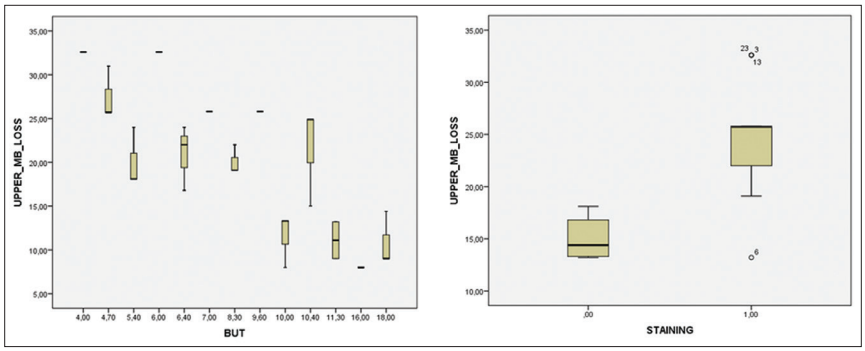

Figure 3: BUT/Staining correlation with loss of upper lid meibomian gland. *MB: Meibomian Gland BUT: Breakup time*

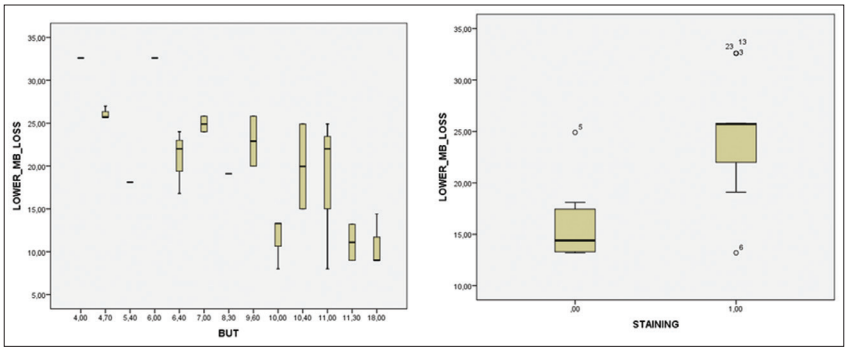

Figure 4: BUT/Staining correlation with loss of lower lid meibomian gland. *MB: Meibomian Gland BUT: Breakup time*

dryness symptoms of SS dry eye patients. This study also contributes to the findings of previous studies by suggesting that MGD plays an important role in causing the severe dry eye seen in SS patients. This study can also be considered of importance in demonstrating the availability of meibography for effortless visualization and evaluation of the degree of MG loss in patients with dry eye. Since the digital rating system is time-consuming in clinical practice, this method used to analyze the physical loss of MG can help to better understand and manage the disease.

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Conflicts of interest

There are no conflicts of interest.

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