The Deterioration of Meibomian Gland Over the Duration of Sjögren Syndrome

Mi Yeon Song

Kim's Eye Hospital

Sung Rae Noh

Kim's Eye Hospital

Kook Young Kim

Kim's Eye Hospital

Kyu Yeon Hwang

Kim's Eye Hospital

Young A Kwon

Kim's Eye Hospital

Kyungmin Koh (✉ kmkoh@kimeye.com)

Kim's Eye Hospital <https://orcid.org/0000-0003-0450-6423>

Research Article

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Abstract

Purpose: To investigate the correlation between Sjögren syndrome (SS) duration and ocular surface parameters in patients with SS-related dry eye.

Methods: We analyzed 108 eyes of 108 female patients with primary SS-related dry eye. Meibomian gland (MG) dysfunction, MG dropout, lipid layer thickness (LLT), partial and total blinking, and partial blinking rate (PBR) were measured using a LipiView® II ocular surface interferometer (TearScience, Morrisville, NC, USA). All patients underwent rheumatoid serologic tests and ocular surface assessments. The ocular surface assessment included the Standard Patient Evaluation of Eye Dryness (SPEED), Schirmer's I test, non-invasive tear break-up time, and grading of corneal/conjunctival staining. The correlations between SS duration and MG dropout rates as well as other ocular surface parameters were determined.

Results: The mean SS duration was 54.1 ± 41.3 months. There was a strong positive correlation between SS duration and MG dropout ($r = 0.766$, $p < 0.001$). The average, maximum, and minimum LLTs showed a weak negative correlation with SS duration ($r = -0.310$, -0.211 , and -0.304 , respectively, $p = 0.014$, 0.028 , and 0.022 , respectively) and MG dropout ($r = -0.191$, -0.326 , and -0.299 , respectively, $p = 0.049$, 0.002 , and 0.009 , respectively). Significant positive correlations were also observed between the SPEED scores and SS duration ($r = 0.303$, $p = 0.042$) and MG dropout ($r = 0.450$, $p = 0.029$).

Conclusions: Longer durations of primary SS-related dry eye were associated with worse MG dysfunction.

Introduction

Dry eye disease (DED) is a chronic disease that results from the destruction of the ocular surface, which leads to tear film instability. Its prevalence increases with age [1]. Evaporative DED is the main subtype of DED, and meibomian gland dysfunction (MGD) is a primary cause of evaporative DED [2,3]. A decrease in the amount or quality of meibum reduces the lipid layer thickness (LLT) and increases the evaporation of the tear film [4].

Sjögren syndrome (SS) is a chronic inflammatory autoimmune disease characterized by diminished lacrimal and salivary gland function following lymphocytic infiltration of these glands [5-7]. The infiltrating cells in glandular elements lead to the secretion of cytokines and the activation of the pathways of interferon-1 and -2. The production of autoantibodies

interferes with muscarine receptors and stimulates destruction [8]. SS may present as a single disease, called primary SS or secondary SS, when associated with other underlying autoimmune conditions such as systemic lupus erythematosus or rheumatoid arthritis [9]. The prevalence of primary SS has been reported to be between 0.1 and 0.8% [10,11]. SS results in aqueous-deficient conditions and manifests with more than moderate dry eye symptoms [12]. The meibomian glands (MGs), namely the sebaceous glands, secrete a lipid coating on the tear film surface of the cornea, which aids in preventing evaporation of the aqueous film [4,13]. The MG in SS-related dry eye patients have been reported to be severely damaged compared with that in those without SS [14,15]. There are many reports on SS and MGD. Prior studies have reported significant destruction of MG and lower non-invasive breakup time in patients with SS [16-18]. Another study compared the patterns in SS-related DED patients by grouping them based on the three-year duration of DED [19]. However, no study has analyzed the patterns of SS-related DED according to the duration of SS. The purpose of this study was to analyze the association between the duration of Sjögren syndrome and ocular surface clinical parameters of DED.

Methods

Subjects

A retrospective, cross-sectional, observational study was conducted at Kim's Eye Hospital, Seoul, Republic of Korea from January 2017 to October 2020. The study adhered to the tenets of the Declaration of Helsinki and was reviewed and approved by the institutional review board at Kim's Eye Hospital, Seoul, Republic of Korea (2021-01-001). The data of the subjects were deanonymized in this study. Due to the retrospective nature of the study, informed consent was waived. A single ophthalmologist diagnosed DED based on the following diagnostic criteria: Standard Patient Dry Eye Evaluation (SPEED) score of ≥ 6 points and non-invasive tear

break-up time (NITBUT) of < 10 seconds [20].YY Age below 20 years, pregnancy or lactation, glaucoma or other concomitant ocular pathologies, ocular history of ocular surgery, ocular injury, ocular infection, using a punctual plug or topical eye drops other than non-preserved artificial tears were excluded. The single investigator handled the LipiView® II ocular surface interferometer (TearScience, Morrisville, NC, USA) (LVII) throughout the study. A single investigator assessed the clinical parameters and SPEED questionnaire scores. Only the test results for the right eye was analyzed.

Sjögren syndrome diagnosis

SS was diagnosed according to the American College of Rheumatology and confirmed by both an ophthalmologist and a rheumatologist [21]. Patients who had at least two of the following three objective features were diagnosed with primary SS: positive serum anti-SSA/Ro and/or anti-SSB/La (or positive rheumatoid factor and antinuclear antibody titer $\geq 1:320$), positive rheumatoid factor and ANA titer $\geq 1:320$), labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score of ≥ 1 per 4 mm², and keratoconjunctivitis sicca with an ocular staining score of ≥ 3 [22,23].

Meibomian gland dropout

All meibography images were acquired from the lower eyelid using the infrared camera system of the LVII. Meibography images were obtained according to the guidelines of the manufacturer. The patients were asked to sit on the chair and lay down their chin and forehead on the indicated resting places, and the image was taken once the MGs were correctly focused. Images with the following characteristics were selected: good image quality, equivalent zoom, and lacrimal point visible with the everted eyelid. The area of MG dropout was calculated using the free-hand selection tool of the ImageJ software (a free open-source image-processing software provided by the National Institutes of Health;

<http://imagej.nih.gov/ij>) [18]. For the measurement with ImageJ, a manual selection of the total area of the everted eyelid was made, followed by a delimitation of the area with MG dropout [24]. The percentage of MG dropout was calculated as the percentage of MG area loss in the entire MG area [25].

Lipid layer thickness

Lipid layer thickness (LLT) is a representative parameter of MG function [26]. The LVII is a non-invasive instrument that uses live digital images of the tear film, measures its lipid component, and calculates blink dynamics [27]. The absolute thickness of the LLT was determined using the LVII by analyzing more than 1 billion data points of the interferometric image. Patients were requested to look into a camera while blinking freely for a 20-second video recording. The participants were also asked not to touch their eyes throughout the imaging. For each measurement, the participants were instructed to rest their heads on the chinrest. The interferometer was operated for its maximum filming time, and the video was instantly analyzed for LLT in nanometers based on interferometric color units (ICUs). The LLT results were transformed from ICUs into nanometers [28,29]. The interferometer offers a non-invasive technique for the estimation of LLT. The LVII assesses the lipid layer thickness using an Interference Color Unit (ICU) score. LVII is capable of direct quantification of LLT [30]. Maximum, average, and minimum LLT values were measured, and the maximum value was 100 nm in all cases.

Blinking Pattern Measurement

The LVII automatically detects and analyzes blink rate and blinking quality through the recorded videos. Participants were asked to blink freely, and the same investigator assessed them throughout the study. The LVII displays the number of full and partial blinks and blink frequencies. Each stage during the blinking cycle was recorded during the examination, and the partial blinks were defined as blinks without the touching of the upper and lower eyelids [31]. This analysis also involved the data on the complete blinking rate and PBR [32].

Dry eye Questionnaire

All patients completed the SPEED questionnaires for evaluating eye discomfort symptoms.

The SPEED scores were graded from 0 to 5 (no symptoms), 6 to 14 (mild and moderate symptoms), and 15 to 28 (severe symptoms) [33,34]. A previous study showed that the SPEED questionnaire was compatible with the Ocular Surface Disease Index (OSDI) [33].

Schirmer's I test

Schirmer's I test without anesthesia was performed using sterile Schirmer strips (I-DEW Tearstrips, Entod Research Cell UK Ltd., London, UK). The standard strips were placed in the midlateral portion of the lower fornix for 5 min. During this procedure, the patients were asked to close their eyes. The length of the wet portion of the strip was recorded in millimeters.

NITBUT

The NITBUT was measured using the IDRA[®] Ocular Surface Analyzer (SBM SISTEMI, Inc., Torino, Italy). The time elapsed between the last blink and the first sign of break-up of the tear film following a ring pattern was documented as the NITBUT. The NITBUT assesses the stability of the tear film by measuring the time from the full blink to the presence of the first disruption of the reflected image on the cornea in seconds.

Ocular staining

Fluorescein staining showed corneal or conjunctival epithelial cell injury [19]. The procedure for scoring corneal and conjunctival fluorescein staining was based on previous reports [35]. The corneal staining was conducted using fluorescein impregnated strips (Haag-Sterit, Bern, Switzerland). The cornea was equally divided into upper, lower, nasal, bitemporal, and middle sections. The score for each section was recorded after staining as follows: 0 = no punctate staining; 1 = less than 5 dots; 2 = between 1 and 3; 3 = whole

staining. The cumulative score for each eye ranged from 0 to 15 [36]. Fluorescein impregnated strips (Haag-Sterit, Bern, Switzerland) wetted with a drop of nonpreserved normal saline was instilled into the inferior conjunctiva. After gentle blinking, the degree of conjunctival staining with total scores ranging from 0 (no staining) to 6 (worst) were measured [37].

Statistical Analysis

The data were analyzed using SPSS software (version 26.0, SPSS Inc., Chicago, IL). The relationship between the measurements was evaluated using Pearson's correlation coefficient analysis and linear regression analysis. The correlation between the values was expressed as a Pearson correlation coefficient (r). Continuous variables were presented as means $\pm$ standard deviation (SD). Statistical significance was set at $p = 0.05$.

Results

One hundred and eight eyes of 108 female primary SS-related DED patients, aged 21–78 years (mean 56.7 years) were enrolled. The baseline characteristics of the study population and the median values for the ocular surface parameters are shown in Table 1. Considering that SS has a robust female predisposition [23], the research involved only female patients, and only the results of the right eye were analyzed.

The mean duration from the time of SS diagnosis was 54.15 ± 41.10 months (range 2–134 months). The mean MG dropout, average LLT, partial and total blinks, and the partial blink rate was $38.55 \pm 25.29\%$, 85.24 ± 21.18 , 5.43 ± 5.20 times per 20 seconds, 10.74 ± 8.05 times per 20 seconds, and 0.52 ± 0.37 , respectively. The mean SPEED questionnaire score was 15.17 ± 5.01 .

The associations between SS duration and other ocular surface parameters in patients with primary SS are shown in Table 2. There was a strong positive correlation between SS

duration and MG dropout ($r = 0.766$, $p < 0.001$, Fig. 1A). The average, maximum, and minimum LLT values showed a weak negative correlation with SS duration ($r = -0.310$, -0.211 , and -0.304 , respectively, $p = 0.014$, 0.028 , and 0.022 , respectively, Fig. 1B) and MG dropout ($r = -0.191$, -0.326 , and -0.299 , respectively, $p = 0.049$, 0.002 , and 0.009 , respectively, Fig. 1C). Significant positive correlations were also observed between the SPEED scores and SS duration ($r = 0.303$, $p = 0.042$, Fig. 1D) and MG dropout rate ($r = 0.450$, $p = 0.029$, Fig. 1E). Schirmer's I test results correlated negatively with the conjunctival staining score ($r = -0.572$, $p = 0.009$, Fig. 1F).

The anti-SSA/Ro, anti-SSB/La, antinuclear antibody, and rheumatoid factor were 72%, 35%, 94%, and 24%, respectively. The results of the serologic test were not statistically significant associations with dry eye parameters.

Discussion

The results of this study showed that a longer SS duration contributed to the worsening of MG dysfunction. DED in SS patients has been classically considered as a result of aqueous Deficiency [38]. However, various studies have reported that SS-related DED patients presented with a significantly thinner lipid layer, shorter NITBUT, and a higher degree of MGD than non-SS-related DED patients. Therefore, it is thought that there are elements of evaporative dry eye associated with MGD in SS-related DED patients [39,16,17,38]. Dry eye in SS patients has been speculated to be due to severe aqueous deficiency, and little attention has been paid to the possibility of evaporative dry eye. This study demonstrated that a longer duration of SS is related to deteriorative changes in MG. This is the first study to evaluate the association between SS duration and ocular surface clinical parameters in patients with primary SS. It is difficult to pinpoint the duration of SS. Approximately one in every ten patients with a significant DED have primary SS, and only one-third have a known diagnosis

at the time they consult the ophthalmologist [40]. It has been documented previously that the incidence of MG dropout and the tear evaporation rates are significantly higher in SS-related aqueous-tear deficient dry eye patients than in non-SS-related dry eye patients [14]. MG is thought to be a special type of sebaceous gland located in the tarsal plates of the eyelids, and MG is also damaged by infiltration of autoreactive lymphocytes, leading to evaporative dry eye [41,42]. The destruction of MGs and an increase in tear evaporation are often associated with changes in the ocular surface in patients with SS. The MGs of patients with SS were more severely impaired than those of dry eye patients without SS [14,39,16].

A previous study showed a negative correlation between NITBUT and meiboscore, but our study did not show any significant association between NITBUT and the MG dropout rate [39]. Based on the principle of interferometry using light reflection in LVII, if aqueous deficiency is severe, the LLT measurement is higher than the actual. However, if SS is prolonged, the damage to the MG becomes irreversible, and, consequently, LLT seems to decrease. LLT is considered to decrease a longer duration of SS is associated with a lower capacity for compensation.

The results of a study indicate that patients with SS have a higher degree of morphological changes in the MG [17]. It has been reported that patients with DED associated with SS have higher MG dropout rates than non-SS DED patients [14,18].

To our knowledge, this is currently the only study that has evaluated the duration of SS and its correlation with ocular surface parameters, including the state of the MG. A study reported on a similar topic cited the failure to observe severe damage to the MG with the increase in the prevalence of SS as a limitation [39].

A longer duration of SS is related to major symptoms and changes in MG. SS is thought to cause inflammation not only in the lacrimal gland but also in the MG, causing damage. Based

on the principle of interferometry using light reflection in LVII, if aqueous deficiency is severe, the LLT measurement is higher than the actual. However, if SS is prolonged, damage to the MG becomes irreversible, and, consequently, LLT seems to decrease.

This study has several limitations. This study on various ocular surface parameters, such as LLT and PBR, failed to evaluate meibum expressibility, meibum quality, mucocutaneous junction shifts, lid telangiectasia, and lid margin irregularity. Since MG dropout and the three above indicators are closely related [43], a study involving the assessment of these parameters will be necessary in the future. The non-inclusion of participants with non-SS-related dry eye is another limitation of this study. Therefore, it is difficult to conclude that the increased MGD observed in the SS group was due to SS or dry eye, and there is the need for further studies including a control group of participants with non-SS-related dry eye.

There are various theories about the relationship between SS and MG dysfunction. A previous study suggested that SS-related ocular surface changes may result in changes in the meibomian glands in patients with SS [14]. Another study reported the presence of lymphocyte infiltration in the sebaceous glands of the skin in SS patients, even though SS affects the exocrine glands and not the sebaceous glands, such as the MGs [44]. The authors also indicated that gland dropout occurred because of ductal hyperkeratinization [45]. It has been documented that keratinization of the ocular surface epithelium occurs in SS [46]. Therefore, epithelial keratinization may play a role in the mutual pathogenesis of SS and MGD [39].

In conclusion, a longer SS duration was associated with worse MG dysfunction. This study also suggests that MGD plays an essential role in SS-related dry eye.

Declarations

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Competing Interests No potential conflict of interest relevant to this article was reported.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board at Kim's Eye Hospital, Seoul, Republic of Korea (2021-01-001).

Informed consent Considering the retrospective nature of the study and the use of deidentified patient data, the written informed consent was waived by the Institutional Review Board of Kim's Eye Hospital, Seoul, Republic of Korea.

Consent to participate Informed consent was waived due to the retrospective nature of the study. Furthermore, this study does not contain any personal information that could lead to the identification of the patient.

Consent to publish Not applicable.

Animal Research Not applicable.

Data Availability More data if necessary are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contribution All authors attest that they meet the current ICMJE criteria or Authorship. MYS, SRN, and KK planned the clinical study, contributed to the conception and design of the study, and the acquisition, analysis, and interpretation of the data. MYS and YAK contributed to the analysis and interpretation of the data. KYK, KYH, SRN, and KK contributed to the conception and design of the study, analysis of data, the drafting of the manuscript and its critical revision for important intellectual content. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the study.

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Tables

Table 1. Demographic data and clinical characteristics of primary Sjögren syndrome dry eye patients.

Variable	Value
Female, n (%)	108 (100 %)
Age, years (range)	56.67 ± 10.21 (21~78)
SS duration, months	54.15 ± 41.10 (2~134)
Clinical evaluation for DED	
SPEED score	15.17 ± 5.01 (6~24)
NITBUT, seconds	2.43 ± 0.82 (1~7)
Schirmer I value, seconds	3.59 ± 1.06 (1~8)
MG dropout rate (%)	38.55 ± 25.29 (4~90)
Antibody status related to SS	
positive serum anti-SSA/Ro, n (%)	78 (72 %)
positive serum anti-SSB/La, n (%)	38 (35 %)
positive antinuclear antibody, n (%)	102 (94 %)
positive rheumatoid factor, n (%)	26 (24 %)
Clinical evaluation about LLT	
Average LLT (nm)	85.24 ± 21.18 (21~100)
Maximum LLT (nm)	94.65 ± 12.32 (43~100)
Minimum LLT (nm)	64.94 ± 26.79 (20~86)
Ocular surface examination	
Corneal staining score (0–15)	6.15 ± 1.57 (3~13)
Conjunctival staining score (0–6)	1.23 ± 0.74 (1~5)
Clinical evaluation about blink dynamics	
Number of partial blinks	5.43 ± 5.20 (0~20)
Number of total blinks	10.74 ± 8.05 (2~28)
Partial blink rate	0.52 ± 0.37 (0~1)

Data are presented as the mean ± standard deviation. DED, dry eye disease. SPEED, standard patient evaluation of eye dryness validated questionnaire (0–28). NITBUT, Non-invasive tear break-up time. TMH, Tear meniscus height. nm, nanometer. Number of partial blinks, number of incomplete blinking per 20 seconds. Number of total blinks, number of total blinks per 20 seconds. MGD, meibomian gland dysfunction.

Table 2. Correlation analysis between Sjögren syndrome (SS) duration and other ocular surface clinical parameters in patients with primary SS.

Parameters	Versus SS duration		Versus MGDR	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age (years)	0.184	0.056	0.133	0.171
SS duration (months)			0.766	< 0.001**
MG dropout rate (%)	0.766	< 0.001**		
Maximum LLT	-0.211	0.028*	-0.326	0.002*
Average LLT	-0.310	0.014*	-0.191	0.049*
Minimum LLT	-0.304	0.022*	-0.299	0.009*
NITBUT	0.071	0.464	0.074	0.447
Schirmer I value	-0.051	0.604	0.009	0.923
Corneal staining score	-0.148	0.127	-0.033	0.738
Conjunctival staining score	0.003	0.974	0.054	0.579
Partial blinks	-0.155	0.112	-0.189	0.064
Total blinks	-0.196	0.069	-0.124	0.073
Partial blinking ratio	-0.171	0.076	-0.128	0.186
SPEED score	0.303	0.042*	0.381	0.029*

r, Pearson correlation coefficient, $-1 \leq r \leq 1$. The correlation was statistically analyzed by linear regression. * indicates statistically significant association ($p < 0.05$). ** indicates statistically significant association ($p < 0.001$). NITBUT, Non-invasive tear break-up time. TMH, Tear meniscus height. nm, nanometer. Partial blinks, number of incomplete blinks per 20 seconds. Total blinks, number of total blinks per 20 seconds. LLT, lipid layer thickness. SPEED, standard patient evaluation of eye dryness validated questionnaire (0–28). MG, meibomian gland.

Figures

Figure 1

Scatterplots of correlation analysis. a Correlation between Sjögren syndrome (SS) duration and meibomian gland (MG) dropout rate. b Correlation between SS duration and average lipid layer thickness (LLT). c Correlation between MG dropout rate and average LLT. d Correlation between SS duration and Standard Patient Evaluation of Eye Dryness (SPEED) score. e Correlation between SPEED score and MG dropout rate. f Correlation between Schirmer's I value and conjunctival stain score.