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Evaluation of ocular surface parameters in dogs with and without meibomian gland dysfunction

Dajeong Jeong | **Seonmi Kang** | **Jaeho Shim** | **Eunji Lee** | **Youngseok Jeong** | **Kangmoon Seo**

Department of Veterinary Clinical Sciences, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul, Korea

Correspondence
Kangmoon Seo, Department of Veterinary Clinical Sciences, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Korea.
Email: kmseo@snu.ac.kr

Abstract

Background: Interest in meibomian gland dysfunction (MGD) is growing in veterinary medicine. However, research on MGD in dogs is lacking. The aims of this study were to compare the interferometry grades, tear meniscus height (TMH) and non-invasive tear break-up time (NIBUT) grades between dogs with and without MGD.

Methods: Routine ophthalmic examination, interferometry, NIBUT assessment, TMH measurement and meibography were performed. Age and Schirmer tear test-1 (STT-1) results were compared between the control and MGD groups using Student's *t*-test. Interferometry grades, NIBUT grades and TMH were compared between the two groups using Mann–Whitney *U*-test.

Results: There was no significant difference in age between the two groups ($p = 0.279$). STT-1 ($p = 0.024$), interferometry ($p = 0.004$) and NIBUT grades ($p = 0.012$) were significantly lower in the MGD group than in the control group. No significant difference in TMH values ($p = 0.587$) was observed between the two groups. While the control group included 18 and seven eyes in meiboscore 0 and 1, in MGD group, 12, eight, five and three eyes were included in meiboscore 0, 1, 2 and 3, respectively.

Conclusions: Low interferometry and NIBUT grades were associated with MGD, suggesting decreased meibum and disrupted tear film quality. TMH did not differ between the two groups. Meibography could aid in the diagnosis of MGD in severe cases, although it could not detect early MGD in the dogs in this study.

INTRODUCTION

Meibomian gland dysfunction (MGD) occurs when the meibomian glands are affected by terminal obstruction and qualitative or quantitative changes in meibum secretion.[1] It is a common cause of dry eye disease in humans, accounting for two-thirds of cases.[2] Although reliable statistical data on the prevalence of MGD in dogs are lacking, 70% of ocular surface disease cases are reportedly affected by MGD.[3]

The typical diagnostic methods for MGD include the evaluation of lid margin abnormalities such as thickening, irregularity, displacement of the mucocutaneous junction and plugged meibomian gland orifices.[4–8] However, in the early stage of MGD, lid margin abnormalities may not be detected.[1,9] Nonetheless, it is widely used as a diagnostic tool in human and veterinary medicine owing to its availability. Analyses of meibum quantity and quality can also be diagnostic aids for MGD.[4,10,11] However, they are not commonly used because of their low repeatability.[8,12]

Interferometry facilitates the estimation of lipid layer thickness based on interference patterns using white light.[13] It has been used to diagnose dry eye in human medicine.[14–16] Although a previous study has reported the use of interferometry to assess lipid layer thickness in dogs,[3] few studies have evaluated it as a diagnostic method for MGD in veterinary medicine.

Meibomian gland atrophy can occur in MGD because of increased intraglandular pressure.[17] Numerous imaging techniques have been developed to identify the degree of meibomian gland atrophy.[18–22] Meibography detects meibomian gland atrophy by directly visualising gland structures.[2,4,8,18,19] It is widely applied in human medicine because it reveals the association between anatomical meibomian gland loss and ocular surface diseases or symptoms.[2,11] However, the applicability of

meibography to diagnose MGD in veterinary ophthalmology has not been well studied.

The tear film comprises mucoaqueous and lipid layers; defects in any of these components can affect the ocular surface and tear film, resulting in ocular surface disease. Since lipids secreted from the meibomian glands prevent evaporation and help maintain tear film,[10,11,14,23,24] disruption of the meibomian gland affects tear film. Alterations in tear film quality and quantity can be evaluated with tear film break-up time (TBUT) and tear meniscus height (TMH), which were traditionally assessed using fluorescein dye.[5,11,25,26] Recently, non-invasive measurements of TBUT (non-invasive tear break-up time [NIBUT]) and TMH have been performed using a non-contact device, which is safer in patients at risk of globe perforation or requiring excessive restraint, contraindicating Schirmer's tear test or methods using fluorescein dye.

This study aimed to compare interferometry, NIBUT and TMH between dogs with and without MGD, and identify the degree of meibomian gland atrophy in dogs with MGD.

MATERIALS AND METHODS

Ophthalmic examinations

Medical records of 53 eyes of 35 client-owned dogs were reviewed. Most dogs were presented at Seoul National University Veterinary Medical Teaching Hospital for various ophthalmic diseases or regular check-ups. The other four client-owned dogs were volunteered for ophthalmic examinations. Approval of each owner was obtained prior to the examinations. All dogs underwent routine ophthalmic examinations, including Schirmer tear test-1 (STT-1, Schirmer tear test; Merck Animal Health), rebound tonometry (TONOVET; Finland Oy), menace response, dazzle reflex, slit-lamp biomicroscopy (Topcon-Model SL-D7; Topcon Corp.), indirect ophthalmoscopy (Keeler Vantage Plus; Keeler) and fluorescein staining (Fluorescein Paper; Haag-Streit). Ophthalmic medications were stopped at least 1–2 hours before the examinations. STT-1, rebound tonometry, menace response and dazzle reflex examinations preceded tear film evaluation and meibography by at least 5 minutes. All other ophthalmic tests followed tear film evaluation and meibography.

Eyes with the following conditions were excluded: (1) history of ophthalmic surgery within 3 months; (2) keratoconjunctivitis sicca (KCS, STT value <15 mm/min with clinical signs consistent with KCS); (3) mucous discharge spread over the cornea; (4) repeatedly protruding third eyelid that redistributed tear film; (5) a palpebral fissure so tight that the upper eyelid could not be fully everted for the middle two-thirds; (6) eyelid mass being in contact with the cornea; (7) distichiasis; (8) pigmentation or extensive chemosis of the palpebral conjunctiva; (9) severe corneal lesions, including pigmentation, blood vessels, oedema, facet, granulation tissue, corneal dystrophy/degeneration, or ulcer/erosion; (10) cataract interfering with the interpretation of test results.

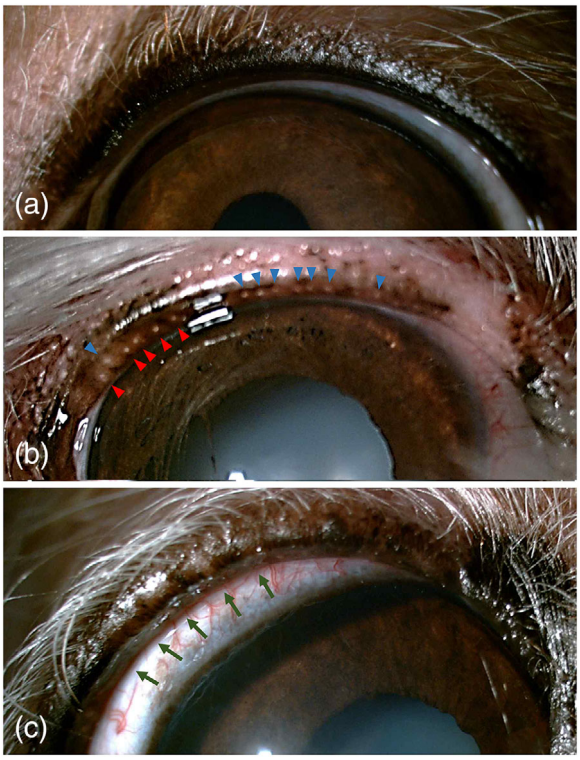

FIGURE 1 Lid margin abnormalities observed with slit-lamp biomicroscopy. (a) Normal eyelid without meibomian gland dysfunction. Lid margin abnormalities consistent with MGD are shown in (b) and (c). (b) Note the plugged gland orifices (blue arrowheads), and retroplaced and plugged orifices (red arrowheads). (c) Thickened lateral eyelid. Note the irregular lid margin (arrows)

The lid margins of all dogs were evaluated using slit-lamp biomicroscopy. Dogs without lid margin abnormalities were enrolled in the control group. MGD was diagnosed in the dogs that satisfied at least one of the following criteria, which was modified from previous studies[4,27] (Figure 1): (1) thick lid margin, (2) irregular lid margin, (3) plugged meibomian gland orifices and (4) retroplaced meibomian gland orifices.

Tear film evaluation and meibography

Interferometry, TMH, NIBUT and meibography were evaluated using an ocular surface analyser (OSA-VET; SBM Sistemi). Interferometry was evaluated based on the observation of lipid layer patterns 2–3 seconds after complete manual blinking with minimal force. As several interferometry patterns could coexist in the same tear film, the grade was assessed for the thickest area of the lipid layer. The classification of the patterns followed the criteria proposed by García-Resúa et al.[28], with an additional grade that indicated no lipid layer within the tear film. A six-point scoring system was used as follows (Figure 2): (1) Grade 0: absence of a lipid layer; (2) Grade 1: grey, marble-like pattern with spaced mesh, with the iris visible through the pattern; (3) Grade 2: grey, marble-like pattern with compact mesh, forming a continuous path; (4) Grade 3:

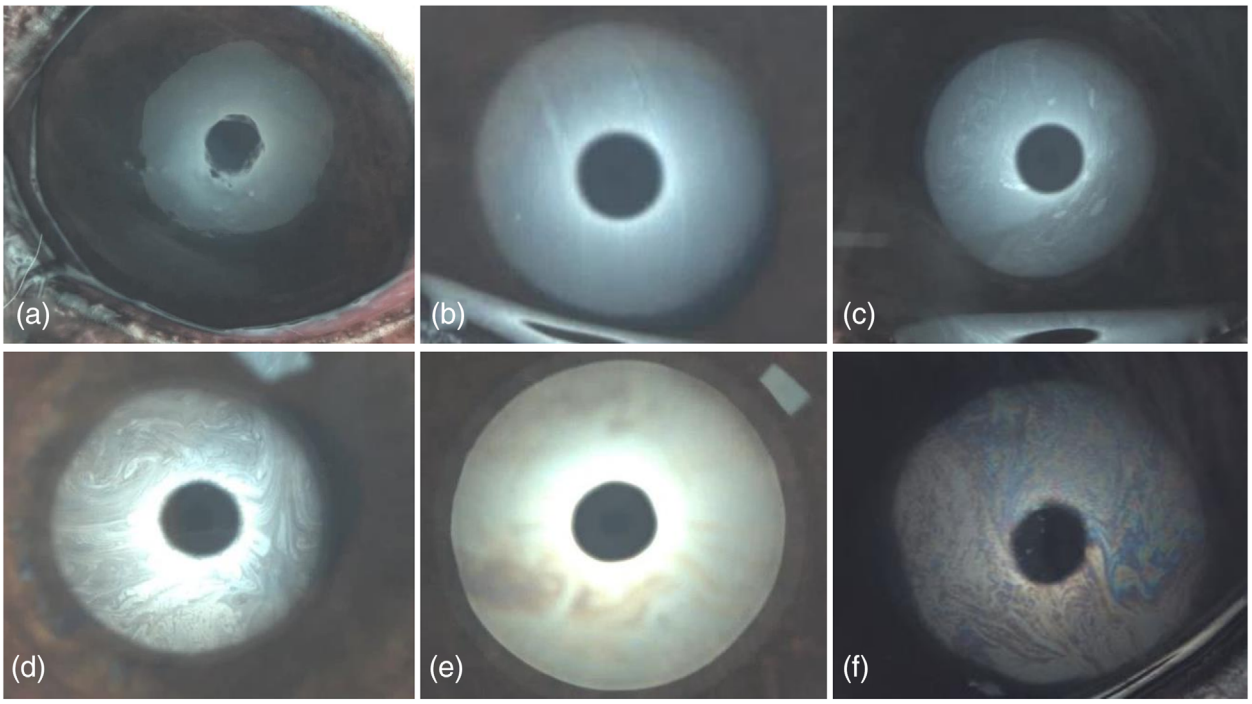

FIGURE 2 Representative images for each grade of interferometry. (a) Grade 0 includes cases of no lipid layer. (b) Grade 1 corresponds to the grey, marble-like pattern with a spaced mesh, with the iris seen through the pattern. (c) Grade 2 corresponds to the grey, marble-like pattern with a compact mesh forming a continuous path. (d) Grade 3 corresponds to the wavy pattern formed by well-defined lines. (e) Grade 4 corresponds to the white bright or yellowish homogeneous pattern with the iris invisible through the pattern. (f) Grade 5 corresponds to the wavy pattern with yellow, brown, blue and purple colours spread

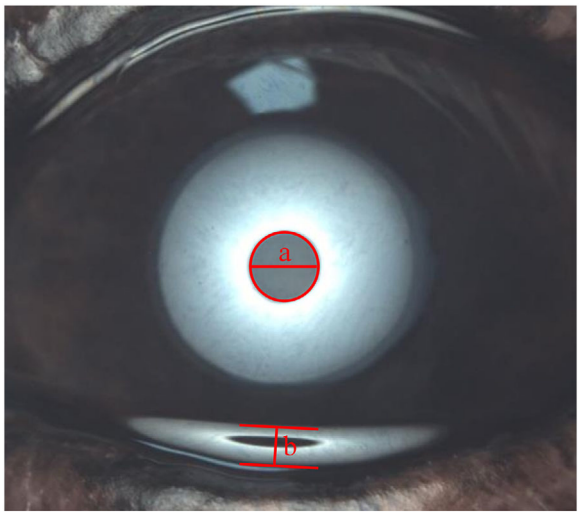

FIGURE 3 Tear meniscus height (TMH) measurement. TMH was calculated by comparing the diameter of the inner circle of reflected light (a) with the distance from the upper limit to the lower limit of the inferior tear meniscus (b)

wave/fluid pattern formed by well-defined lines; (5) Grade 4: white bright or yellowish homogeneous patterns with the iris not visible through the pattern; (6) Grade 5: waves with yellow, brown, blue and purple colours spread.

TMH was defined as the distance between the upper limit and lower limit at the midpoint of the inferior tear meniscus, and it was compared with the diameter of reflected white light by the program equipped within the instrument (Figure 3). The eyelids were not excessively everted for the measurement of TMH. NIBUT was evaluated by measuring the time from eyelid opening to the time point when at least one line on the grid was distorted (Figure 4). If the distorted line was not observed after 20 seconds, the examination was stopped, since it can cause irritation and reflex tearing. The observed values below 20 seconds were subdivided into five groups to reduce observational errors. A six-point grading system was introduced as follows: (1) Grade 1: 0 second ≤ NIBUT < 4 seconds; (2) Grade 2: 4 seconds ≤ NIBUT < 8 seconds; (3) Grade 3: 8 seconds ≤ NIBUT < 12 seconds; (4) Grade 4: 12 seconds ≤ NIBUT < 16 seconds; (5) Grade 5: 16 seconds ≤ NIBUT < 20 seconds; (6) Grade 6: NIBUT ≥20 seconds.

Meibography was assessed through eversion of the middle two-thirds of the upper eyelid. Following the criteria suggested by Arita et al.[20], all eyes were manually scored from 0 to 3 (Figure 5): (1) meiboscore 0, no meibomian gland loss; (2) meiboscore 1, loss of less than one-third; (3) meiboscore 2, loss of more than one-third and less than two-thirds; and (4) meiboscore 3, loss of more than two-thirds. All parameters of tear film evaluation and meibography were evaluated by one operator (Dajeong Jeong) to avoid interobserver differences.

Statistical analyses

The normality of age, STT-1 and TMH was assessed using the Shapiro–Wilk test. STT-1 and TMH were expressed as mean ± standard deviation. Age, interferometry grades and NIBUT grades were expressed as median (range). Mann–Whitney *U*-tests were performed to compare the interferometry grades and NIBUT grades between the control and MGD groups.

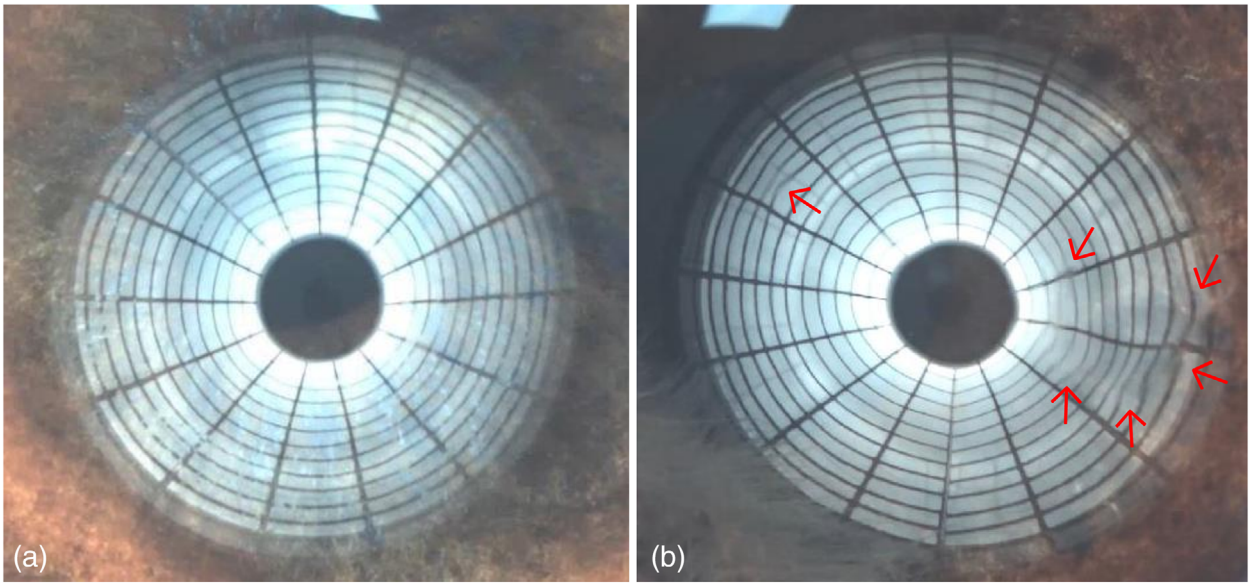

FIGURE 4 Non-invasive tear break-up time measurement. (a) Stable tear film without any distorted spot. (b) Note the multiple spots of tear film break demonstrated as distorted grids (arrows)

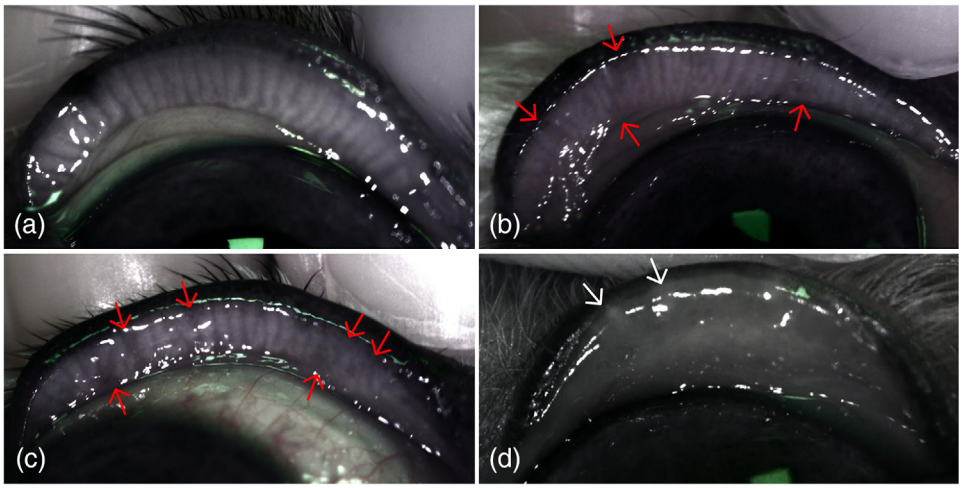

FIGURE 5 Representative images for each meiboscore. The middle two-thirds of upper eyelids were scored. (a) Meiboscore 0 corresponds to the normal meibomian glands without atrophy. (b) Meiboscore 1 corresponds to loss of one-third of the meibomian glands (red arrows). (c) Meiboscore 2 corresponds to loss of more than one-third and less than two-thirds of the meibomian glands (red arrows). (d) Meiboscore 3 corresponds to loss of more than two-thirds of the meibomian glands. Note diffuse meibomian gland atrophy characterised by a generalised darkened area with no normal gland morphology. Remaining glands are filled with dense opaque meibum (white arrows)

TMH with non-normal distribution was also compared between the control and MGD group using Mann–Whitney *U*-test. Age and STT-1 were compared between the two groups using Student's *t*-test.

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Probability values <0.05 were considered statistically significant.

RESULTS

Subject characteristics

Among the 53 eyes of 35 dogs enrolled, 28 eyes of 19 dogs were diagnosed with MGD, and 25 eyes of 17 dogs were classified as the control group based on slit-lamp biomicroscopy. One dog was included in both groups, with each eye in different groups. Dogs in the control group were presented for regular checkup (13/17, 76.5%), cataract (5/17, 29.4%) and glaucoma (1/17, 5.9%). Two of 25 eyes in the control group were receiving topical ophthalmic medications at the time of examinations. One eye was prescribed with flurbiprofen due to subclinical lens-induced uveitis. The other eye was prescribed with combination of dorzolamide and timolol (Cosopt; Santen) due to glaucoma, with well-controlled intraocular pressure. Nineteen of 28 eyes in MGD group were receiving topical ophthalmic medications at the time of examinations. Eyes were being administered different combinations of the following topical ophthalmic medications: cyclosporine

($n = 17$), flurbiprofen ($n = 5$), ofloxacin ($n = 2$), bromfenac ($n = 1$), diclofenac ($n = 1$) and tobramycin ($n = 1$). Cyclosporine was administered for previous transient decrease in STT-1 or tear quality disruption. Flurbiprofen, bromfenac, diclofenac, ofloxacin and tobramycin were administered for treatment of MGD.

The median ages of control and MGD groups were 11 years (range, 3–15) and 9 years (range, 3–13), respectively. Age was not significantly different between the two groups ($p = 0.279$). The subjects included nine neutered females, seven neutered males and one entire female in the control group and 10 neutered females, eight neutered males and one entire female in the MGD group. The seven different breeds in the control group included Poodle ($n = 6$), Maltese ($n = 4$), mixed breed ($n = 3$), and one each of Bichon Frise, Pomeranian, Shih-Tzu and Yorkshire Terrier. Similarly, the eight different breeds in the MGD group included Maltese ($n = 8$), Bichon Frise ($n = 2$), mixed breed ($n = 2$), Pomeranian ($n = 2$), Poodle ($n = 2$), Chihuahua ($n = 1$), Miniature Schnauzer ($n = 1$) and Shih-Tzu ($n = 1$).

Tear film analyses and meibography

The mean STT-1 of the control group (20.0 ± 2.8) was significantly higher than that of MGD group (17.5 ± 4.4) ($p = 0.024$). The median interferometry grades in the control and MGD groups were 3 (range, 0–5) and 2 (range, 0–3), respectively, showing a statistically significant difference ($p = 0.004$). The median NIBUT grades were 3 (range, 1–6) and 2 (range, 1–6) in the control and MGD groups, respectively, showing a statistically significant difference ($p = 0.012$). The mean TMHs in the control and MGD groups were 0.552 ± 0.273 and 0.574 ± 0.410, respectively, showing no statistically significant difference ($p = 0.587$). In the control group, 18 eyes were included in meiboscore 0, and seven eyes in meiboscore 1. In the MGD group, the most common meiboscore was meiboscore 0 (12 eyes), followed by meiboscore 1 (eight eyes), meiboscore 2 (five eyes) and meiboscore 3 (three eyes). The results of the tear film evaluation and meibography are summarised in Table 1.

DISCUSSION

The methods for evaluating meibomian glands include the assessment of lid margin abnormalities, digital expression of meibomian gland secretion, vital staining of the ocular surface, lipid layer interferometry, meibometry and meibography.[2,4,6,11,14–18,27,29,30] Currently, the diagnostic method for MGD varies across ophthalmologists, and there is no established definite diagnostic method for MGD. Slit-lamp biomicroscopy is a simple and non-invasive method to evaluate lid margins and detect plugged meibomian gland orifices, which is pathognomonic for MGD.[4] Therefore, it is a widely used diagnostic method for MGD, utilising the criteria established in various studies in human medicine.[7,31] However, it may overlook early MGD because the condition can occur without alteration in the lid margin morphology, particularly in the early stage.[1,9]

In MGD, the amount and composition of lipids secreted into the tear film are altered[10,31] and can be detected with decreased expressible glands, disrupted meibum quality, or more quantitatively with meibometry.[2,9,17,27] However, because these methods require specialised equipment, lack repeatability,[8,12] and are slightly invasive, they are not easily applied in clinical settings.

Interferometry estimates the thickness of the lipid layer in precorneal tear film by observing specific patterns, based on the fact that the patterns and their flow reflected in the tear film vary depending on the lipid layer thickness.[13] In obstructive MGD, the lipid layer spread over the tear film becomes thinner due to decreased lipid secretion.[32] Interferometry has been reported to be associated with dry eye disease in several human studies.[14–16,33] In the present study, interferometry grades were significantly lower in the MGD group than in the control group, consistent with previous studies. However, it is difficult to diagnose MGD using interferometry alone. It has been reported that some normal eyes might have a thin but stable tear film.[23] Similarly, in the present study, a few eyes with low interferometry grades were included in the control group, as seen in Table 1. Furthermore, another type of MGD with excessive lipid secretion has been reported in human medicine, although not in dogs.[29] In addition, lipid secretion in tear film may be affected by blinking and show diurnal changes.[17,34,35] Therefore, it is recommended to assess interferometry together with tear quality features and ocular symptoms, rather than relying on interferometry alone. As interferometry does not quantify, but estimates tear film lipid layer thickness using reflected patterns, a few grading systems have been introduced to classify these patterns.[16,28,36] However, several patterns can be mixed within one tear film.[28] In this study, interferometry was assessed for the thickest part of the tear film lipid layer. Considering the significant difference between the two groups in this study, changes in the tear film lipid layer thickness could be detected with only the thickest part using the six-point grading system. Therefore, although interferometry alone is not a definitive diagnostic tool for MGD, it can be a useful non-invasive tool for MGD screening.

Meibography detects meibomian gland atrophy. In obstructive MGD, gland atrophy can be observed through palpebral conjunctiva. Some grading systems have been suggested for evaluation of gland morphology with meibography,[19,21,22,30,37] one of which was applied in this study. Several studies in human medicine have reported that meibomian gland atrophy identified by meibography is related to gland function.[2,18,20,27,30,38] However, it remains controversial as a definitive diagnostic method for MGD in

TABLE 1 Statistical characteristics of tear film parameters

Ocular surface parameters	Grade	Control group	MGD group	*p*-Value
STT-1		20.0 ± 2.8[a]	17.5 ± 4.4	0.024[b]
Interferometry grade	0	1	5	0.004[c]
	1	4	6	
	2	6	12	
	3	9	5	
	4	2	0	
	5	3	0	
	Median (range)	3 (0–5)	2 (0–3)	
NIBUT grade	1	1	13	0.012[c]
	2	6	3	
	3	11	7	
	4	2	2	
	5	1	0	
	6	4	3	
	Median (range)	3 (1–6)	2 (1–6)	
TMH		0.552 ± 0.273[a]	0.574 ± 0.410	0.587
Meiboscore	0	18	12	
	1	7	8	
	2	0	5	
	3	0	3	

Note: STT-1 and TMH were described in mean and standard deviation. Interferometry and NIBUT grades were described in median value and range.
Abbreviations: MGD, meibomian gland dysfunction; NIBUT, non-invasive tear break-up time; STT-1, Schirmer tear test-1; TMH, tear meniscus height.
[a]Mean and standard deviation of STT-1 and TMH.
[b]Significant difference between the two groups according to Student's *t*-test.
[c]Significant difference between the two groups according to Mann–Whitney *U*-test.

human medicine, as it may be insufficient to assess meibomian gland function with meibography alone.[2] In veterinary medicine, some studies have utilised meibography to assess gland atrophy in dogs.[3,39] However, no study has evaluated the relationship between meibomian gland atrophy detected by meibography and lid margin abnormalities seen in MGD. MGD starts with hyperkeratinisation of the lid margin. With continued production of meibum, pressure atrophy occurs in the late stage of MGD.[2,17] In the MGD group, almost half of the eyes (12/28 eyes, 42.9%) had no meibomian gland atrophy (meiboscore 0). Meibography was performed only for the upper eyelid because of its greater accessibility, which might have missed the gland loss of lower eyelid. However, it has been reported that meibomian gland atrophy of only the upper or lower eyelid was associated with total gland loss of the upper and lower eyelids.[2,3] Therefore, the distribution of meiboscores in MGD group is thought to be because the degree of atrophy may not reflect the current function of the meibomian gland. Since meibomian gland atrophy occurs in the later stage of MGD, it may not be present in early MGD.[17] However, when severe atrophy is observed, it may be assumed that obstructive hyposecretion with increased intraglandular pressure exists or has previously existed.

The TMH of the MGD group did not differ significantly from that of the control group in this study. However, the mean STT-1 was significantly higher in control group than that of MGD group. There may be two reasons for this. First, the TMH of the MGD group might have been overestimated as, in eyes with MGD, thinned tear film lipid layer increases the tensile strength of tear film.[40] This might have resulted in the tear film flowing down to the inferior tear meniscus by gravity, increasing the TMH of the MGD group. Second, decreased reflex tearing of the MGD group might have influenced the results. While STT-1 measures both basal and reflex tearing, measurement of TMH rarely induces reflex tearing, since it measures the tear quantity non-invasively in a very short time. In meibomian gland diseases, the aqueous phase increases to compensate for abnormalities in the meibum or in response to irritation from ocular surface damage.[24,41] Several human studies revealed that chronic lacrimal stimulation induced by tear quality disruption led to immune-based inflammation of lacrimal gland and neural dysfunction, thus explaining decreased corneal sensitivity and reflex tearing in MGD.[42–44] It has been reported that evaporative tear loss caused by MGD affects the aqueous-deficient dry eye or vice versa in human medicine,[40,45] and this might explain the difference of STT-1 results between the two groups, although the eyes with definite KCS were excluded in the present study.

In the present study, NIBUT grades were significantly lower in the MGD group than in the control

group. Abnormal lipid layer thickness or distribution in MGD affects spreading of tear film, making it easier for tear film to evaporate and, eventually, rupture. These evaporation and tear film rupture events cause ocular surface damage, which makes the cornea hydrophobic, leading to a vicious cycle of further disruption of the tear film.[40] Although all these findings from previous studies were established in human medicine, not in veterinary medicine, the results of this study support that similar mechanisms might work in dogs.

TBUT using fluorescein dye is the representative method for the assessment of tear film stability.[5,11,25,26] However, fluorescein dye itself destabilises the tear film.[25,41] Unlike TBUT, NIBUT is a completely non-invasive method. It assesses tear quality using the tear film as a mirror, to determine whether it homogeneously reflects illuminated light. The results of this study demonstrated the ability of NIBUT to detect changes in tear stability in MGD. Therefore, NIBUT can be a useful tool for the non-invasive evaluation of tear quality.

This study has several limitations. First, the effects of systemic diseases or concurrent ophthalmic diseases were not considered. Also, the effects of ophthalmic or systemic medications were not considered. Eyedrops such as antibiotics, anti-inflammatory drugs and cyclosporine or preservatives included in eye drops could affect the tear film and ocular surface.[46–48] Therefore, further studies are needed that take into account the effects of concurrent systemic or ophthalmic diseases and the use of concurrent medications.

Another limitation of this study is that the diagnosis of MGD was made through a single method only. Although there are several studies in humans that diagnosed MGD only through lid margin abnormalities,[6,7] this might not be sufficient as it could miss the early stage of MGD.[1,9] Recent studies in humans used interferometry, meibography or meibum expression, in combination with lid margin evaluation for the diagnosis of MGD.[4,8] The present study diagnosed MGD via lid margin evaluation only because the utility of interferometry or meibography has not been verified yet and meibometry has been reported to have low repeatability in dogs.[12] Therefore, we recommend that future diagnosis of MGD to be performed by utilising interferometry together with lid margin evaluation, referring to the results of the present study.

Third, the tear film analyses and meibography were performed following STT-1, tonometry, menace response and dazzle reflex, with an interval of at least 5 minutes. It has been reported that an interval of 5 minutes may be sufficient for the examination of tear film, which causes reflex tearing, while more than 10 minutes is recommended to fully replenish the tear film.[49–52] Therefore, further studies with a sufficient time interval are needed.

Lastly, correlation between the interferometry grade and the severity of lid margin abnormalities was not analysed. In the present study, the degree of lid margin abnormalities was not so diverse for each patient within the MGD group, making it hard to classify the severity of lid margin abnormalities. Therefore, further investigation on a larger population is needed to clarify the correlation between the lipid layer thickness and the severity of MGD.

In conclusion, interferometry could be a useful test for MGD screening, presenting decreased lipid secretion. Low NIBUT was associated with MGD in this study, which suggests disruption of tear film quality. TMH was not associated with MGD. Meibography could be aid in the diagnosis of MGD in severe cases, although it could not detect early MGD.

AUTHOR CONTRIBUTIONS

Conceptualisation, data collection, statistical analysis, writing (original draft, review and editing): Dajeong Jeong. *Conceptualisation, statistical analysis, writing (review and editing)*: Seonmi Kang. *Data collection, statistical analysis, writing (review and editing)*: Jaeho Shim, Eunji Lee and Youngseok Jeong. *Conceptualisation, supervision, writing (review and editing)*: Kangmoon Seo.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

FUNDING INFORMATION

The authors received no specific funding for this work.

ETHICS STATEMENT

All procedures were conducted according to the guidelines of and with the approval of the Institutional Animal Care and Use Committee (IACUC) of Seoul National University (SNU-200726-1).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Dajeong Jeong https://orcid.org/0000-0001-6129-2391
Seonmi Kang https://orcid.org/0000-0001-8017-0891
Jaeho Shim https://orcid.org/0000-0002-2179-8950
Eunji Lee https://orcid.org/0000-0003-0313-7494
Youngseok Jeong https://orcid.org/0000-0002-6646-8277
Kangmoon Seo https://orcid.org/0000-0001-6645-7116

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